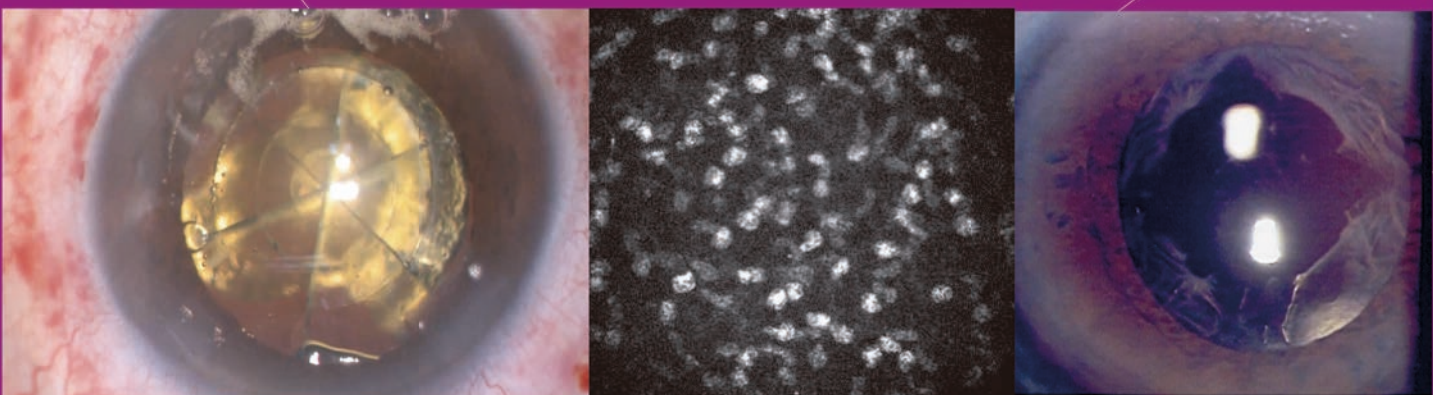


# LASER

## Manual In Ophthalmology

FUNDAMENTALS AND  
LASER CLINICAL PRACTICE

Editors: José Henriques, Ana Duarte, Teresa Quintão





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# FOREWORD

Ocular photocoagulation was first used in 1949 by Gerd Meyer-Schwickerath with xenon-arc photocoagulation. This method was effective for many years especially in the treatment of vascular diseases of the retina and retinal anomalies. It was used for approximately 15 years to treat many ocular conditions. The discovery of the laser in 1960 provided for an extremely precise source of monochromatic light with a range of wavelengths and impulses such that different types of absorption could be induced within the target tissues with the resulting desired effect on ocular tissues.

Dr. José Henriques and colleagues have compiled an extensive work on the possible applications of laser treatment on ocular tissues today. In the first chapters the fundamentals, technology and interaction of lasers on ocular tissues are described.

There then follows a detailed description of the application of laser in the anterior segment, in cases of corneal neovascularisation, iridotomy, iridoplasty, goniotomy and trabeculoplasty. A section is also dedicated to suture lysis with laser. Of special note are the chapters dedicated to Q-switched Nd:YAG laser and the use of femtosecond lasers in cataract extraction.

The use of lasers in different vascular retinopathies is discussed in detail with a particular consideration to diabetic retinopathy and other retinal vascular conditions. Also note worthy is the section dedicated to the advantages of lasers in oculoplastic surgery in treating and correcting different anomalies.

In the diagnostic section the application of lasers in corneal aberrometry, laser Doppler flowmetry, corneal confocal microscopy, pupilometry are reviewed with a special mention in the chapters dedicated to the use of OCT in the study of the retina.

The last section of the book is dedicated to security, maintenance and installation requirements. The book closes with a look to the future at the possible application of laser technologies in Ophthalmology yet to come.

Without any doubt this great work on lasers in ophthalmology covers an important area of Ophthalmology of change and growth. It is the product of the cooperation of well known experts in different fields in the knowledgeable hands of Dr. José Henriques, Dr. Ana Duarte and Dr. Teresa Quintão in the book "The Laser Manual in Ophthalmology - Fundamentals and Laser Clinical Practice".

**Borja Corcóstegui**

Medical Director of IMO Instituto Microcirurgia Ocular  
Barcelona- Spain



# PREFACE

This manual is the fulfilment of a dream that has been present for years. SPILM's (Portuguese Medical Laser Society) objective was to produce a written document to complement the Medical Laser Courses given over the last two decades. SPILM has run in Portugal seven courses in medical laser and trained 200 doctors in the specialized use of medical laser, 120 of whom were ophthalmologists.

This **Laser Manual in Ophthalmology** is the result of the effort, knowledge, dedication and generosity of 129 authors and co-authors, mainly Portuguese but 17 from other countries (Brazil, Italy, Sweden, United Kingdom and USA). A large number of clinical centers and physics laboratories in Portugal and worldwide have also been involved and committed to this voluntary project. A perspective of laser physics, interaction of laser with biological tissues, the clinical applications on different areas in Ophthalmology and an overview of the diagnosis application and aspects of risk management for laser use can be found in the 95 chapters of this book.

This work is also the result of the cooperation of three Portuguese scientific societies: SPILM – Portuguese Medical Laser Society, SPO – Portuguese Society of Ophthalmology and GER – Portuguese Retina Study Group and corresponds to a profitable commitment to training in Ophthalmology.

Training in medical laser is essential so that doctors can integrate laser physics with medical knowledge in order to perform surgery most effectively. One should treat the right tissues, the right pathology, using the appropriate laser settings: at the right time, with the right laser fluency, pulse, duration and wavelength, so as to achieve the best outcome in a scenario of efficiency, secure environment and patient satisfaction. This is what people expect from medicine and the doctor must be able to respond to patient's needs. This is accomplished by training and knowledge of lasers and its capabilities. Another field of laser use is as diagnosis tools. The reader can find several chapters about the use of image technologies based on laser.

This voluntary teaching and training has been carried out with the firm conviction that the greatest benefits can be achieved by sharing. The authors and co-authors of this book are committed to sharing their knowledge with the medical community freely and voluntarily as they are highly conscious that they should give back to society what they have received.

We are very happy to be able to launch this **Laser Manual in Ophthalmology - Fundamentals and Laser Clinical Practice** and we hope that its reading will be for each reader a pleasure, providing a feeling of enrichment and increase in knowledge and an opportunity to improve their care to patients. This has been our goal when we were preparing this work for you.

Views expressed in this publication are those of the author(s) and contributors and do not necessarily reflect those of SPILM – Portuguese Medical Laser Society, SPO – Portuguese Ophthalmic Society or GER – Portuguese Retina Study Group.

**Fernando Chiotte Tavares** and **José Henriques**

(Past and present Presidents of the SPILM – Portuguese Medical Laser Society)

The last few decades have been marked by major technological developments. Lasers are in the forefront of such developments and Ophthalmology is among the medical fields that has most benefited from the new avenues opened by the use of laser technology.

The understanding of interaction between laser radiation and the ocular tissues led to the use of lasers in the diagnosis and treatment of a variety of ocular diseases including the leading vision-threatening diseases: diabetic retinopathy, age-related macular degeneration, glaucoma and cataract. Ophthalmology, which has pioneered many medical advances, was the first medical specialty to use the lasers for therapeutic purposes.

In addition to therapy, lasers were instrumental in the diagnosis and prevention of many vision-threatening diseases. The word laser, by itself, captures our imagination and evokes an advanced and futurist technology. The permanent developments in this area leave us with the feeling that we are living the future now.

Lasers are in fast and constant evolution, allowing for applications in diagnosis and therapy which are, increasingly, more efficient and precise. These remarkable advances were only possible due to persistent, integrated and coherent interdisciplinary approaches. These interdisciplinary efforts are well illustrated by the valuable contributions of all the authors of this book.

I am greatly honored to have contributed to this book, which opens new horizons for future developments in ophthalmology due, not in a small measure, to the quality and diversity of the various contributing authors. It was, therefore, with great pleasure that I accepted the invitation to write one chapter as well as the introduction to this book. It is a remarkable reward to contemplate the new developments in the frontiers of knowledge, that are presented in this book and that, ultimately, aim at the greater benefit of patients. All the chapters in the book share the common challenge of shedding light in a complex subject and bringing the reader current with new developments, in a manner which can be easily understood, while remaining scientifically and technically rigorous.

It was with great pleasure and satisfaction that I read this book which is superbly written and organized. I felt marveled with the organization and contents of the 95 chapters of this book. From the scientific fundamentals of laser technology, to its application in diagnosis and prevention of ocular pathologies, this book is an excellent example of the remarkable work and extraordinary progress that has been achieved in this critical area.

I urge all ophthalmologists to read this remarkable work.

In a time dominated by unprecedented amounts of information and data, it is extremely challenging to establish new landmarks in research. However, given its quality and relevance, I believe that this book will easily become a reference. The reader will feel immediately captivated by the variety and complexity of the different topics but also by the quality of the research work that underlies each topic.

This book leads us to consider how the world, as we know it, is likely to change in the near future and how our current difficulties will pale in comparison with the future challenges that we will need to face soon. Meanwhile, we can all enjoy this fascinating and intriguing work, produced by a new generation of creative ophthalmologists and researchers. As with all collective endeavors, this book is better appreciated having into consideration the uniqueness of each individual contribution as it adds to the richness of a diverse and complex work.

**Maria João Quadrado**

(Presidente of the SPO - Portuguese Society of Ophthalmology)

The **Laser Manual in Ophthalmology – Fundamentals and Laser Clinical Practice** is the kind of book that comes in and fills a gap in ophthalmological publications, in the second decade of the 21<sup>st</sup> century, a time of great changes in the diagnosis and treatment of many eye diseases.

The use of laser is in fact essential for the diagnosis and treatment of the most common eye diseases despite the emergence of new treatments. In the last years new lasers have been introduced into clinical practice for diagnosis and innovative treatments and they are permanently being updated.

I strongly believe that a better understanding of laser properties, laser techniques and laser capabilities for diagnosis and treatment in ophthalmology is essential for the best care to our patients. The **Laser Manual in Ophthalmology** is the answer to this need and I strongly believe that it is a huge and successful challenge.

The book is organized into 18 sections with 95 chapters and over 500 pages, starting with the laser mechanisms and ending with the future perspectives. Different authors from different countries give us an updated, comprehensive and rigorous view about how different lasers operate in different tissues and pathologies. They describe the laser mechanisms and efficacy in oculoplastic surgery, in laser surgery on the cornea, iris, pupil, lens, posterior capsule, vitreous, posterior hyaloid, retina and choroid, as well as the laser technique and effectiveness for the diagnosis and/or treatment of many ocular diseases such as glaucoma, diabetic retinopathy, vein occlusion, central serous chorioretinopathy, choroidal tumors, macular telangiectasia, ocular ischemic syndrome, drepanocytosis or Coats' disease.

In fact, it is a great and updated contribution of its editors, coordinators and all authors for the ophthalmic community. And in the end, this means that we now have a great opportunity to update our knowledge in this field and that our patients will have a better chance to preserve their sight.

**Rufino Silva**

(President of the Portuguese Retina Study Group)





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The editors of this book would like to thank all the authors, coordinators and editorial team for their collaboration. This voluntary participation reveals a true commitment to medical science, clinical practice improvement and ultimately to patients.

To all our non-Portuguese collaborators and their teams, namely to Professor Victor Chong, Professor Edoardo Midena, Professor Francesco Bandello, Professor Daniel Lavinsky, Professor Daniel Pallanker, Professor José Augusto Cardillo, Dr. André Borba Silva, Dr. João Carlos Simão and Dr. Camila Gordilho, a special acknowledgment for their contribution to this project.

The manual would have never happened without the inspiration and enthusiasm of the founders of our scientific society – SPILM (Portuguese Medical Laser Society), including the former President Dr. Fernando Chiotte Tavares and Dr. Pedro van Zeller, member of the scientific council. Their laser knowledge and teaching, and their link to the Moorfield's school (namely with Dr. Peter Hamilton and Professor John Marshall) guided the therapy of thousands of patients with retinal diseases in the last 40 years, and encouraged the following generations to study, investigate and understand the science and practical application of laser in ophthalmology. Also, a particular reference has to be made to Professor Manuel Ribau Teixeira, director of the five previous Post Graduate Medical Laser courses, and to whom the manual owes its basic structure. To all, we would like to express our gratitude for their pioneering.

The editors would like to mention the work of the President of the scientific council of the SPILM, Professor Carlos Marques Neves, and the other members of this council, Professor Joaquim Neto Murta, Professor Rufino Silva and Dr. João Nascimento, and express our appreciation for their work as coordinators of some book sections. To the other sections coordinators, namely to Professor Luís Abegão Pinto, Dr. Miguel Trigo, Dr. Pedro Menéres, Dr. Vítor Rosas, Dr. Ana Fernandes Fonseca, Dr. Susana Teixeira, Dr. João Cabral, Dr. Luís Gonçalves, Dr. Helena Prior Filipe, Professor Amândio Rocha Sousa and Professor Marco Dutra Medeiros, the editors would like to express as well their gratitude for their work.

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We are also very grateful to the President of the SPO (Portuguese Society of Ophthalmology) Professor Maria João Quadrado and to the President of GER (Portuguese Retina Study Group) Professor Rufino Silva, for their cooperation with SPILM and their scientific support to this work.

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The editors

José Henriques, Ana Duarte, Teresa Quintão



# I. The Essential

## 1. Fundamentals of

# LASER radiation

Properties, radiometric units and glossary



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### INTRODUCTION

A laser is a device that produces and amplifies a special type of light. The word *laser* is an acronym that stands for *light amplification by stimulated emission of radiation*, a description of the physical process through which this light is generated. The nature of this process and the special properties of laser light are intimately connected. Nowadays, lasers are fundamental tools in a number of fields, from medicine and biotechnology to telecommunications, automotive production, materials processing and scientific research. They are fundamental components of daily devices such as CD and DVD players, laser printers and fiber optic modems.

Although the first practical laser was demonstrated by Theodore Maiman (1927-2007) in 1960, the idea of stimulated emission goes back to pioneering work undertaken by Albert Einstein (1879-1955) in 1917. While working on the interplay between light and matter and how the two could achieve thermal equilibrium, Einstein made use of the concept of the *photon* – a finite amount of energy in the form of light, proposed by Max Planck (1858-1947) in 1900 – in his new theory. Together with the already well known processes of light absorption and spontaneous emission, this approach led to the establishment of stimulated emission, of a new form of light-matter interaction that is at the root of the laser.

It took time for physicists to recognize the potential of stimulated emission to generate a new form of light, and then it took them more time to find the adequate optical materials and techniques to realize it in practice. This explains the gap of more than forty years between the original idea and the first realization of the laser. Once the secret was unlocked, laser technology progressed at an astonishing pace.

Lasers are available in a wide range of parameters, such as low or high powers, short or long pulses, and colors covering the whole visible spectrum and beyond. A laser may fire a single pulse or a repetitive train of bursts of light,

and the laser device may be as small as an electronic chip or as large as a piece of furniture (or even large, in the case of ultrapowerful laser chains). Many different optical media may be used as laser light sources, and many techniques may be used to provide energy to a laser. For these reasons, laser technology may appear intimidating at first to an outsider. It is certainly reassuring to know that the basic principles at the heart of most lasers are the same, only changing in the way they are implemented in practice. Becoming familiar with these fundamentals will surely provide us with a valuable insight towards understanding their more advanced features, operation and applications. In this chapter we introduce the basic concepts related to the properties of laser light, its generation, and the main components of a laser device. In doing so, we aimed at keeping the descriptions and the definitions simple and compact, avoiding a mathematical treatment. We also eliminated a multitude of minor details and advanced concepts that are unnecessary in a short introduction to the physics and technology of lasers from the viewpoint of medical professionals. The interested reader will be able to find much more thorough discussions in the references provided at the end of the chapter<sup>1-5</sup>.

The chapter ends with two sections that can be helpful as a quick reference, the first one on radiometric quantities, units and their definitions, and the second one containing a glossary of the most common terms related to laser science.

### 1 PROPERTIES OF LASER LIGHT

We will start by briefly discussing the main distinguishing features of laser radiation and how it is different from ordinary light. Later we will relate them to the nature of the process of laser generation.

#### 1.1 DIRECTIONALITY

One of the most striking features of laser light is that it has the shape of a narrow beam that can remain apparently unchanged as it propagates (Figure 1). It

# 1. Introduction

remains essentially parallel to the travelling direction over very long distances, a property that makes it useful for measuring lengths with great precision. Laser beams are even used to measure the distance from the Earth to the Moon thanks to a set of special mirrors left behind by the astronauts of the Apollo 11 mission, which are capable of reflecting back a beam fired from the Earth. By converting the travel time into length, scientists are able to calculate this distance within an accuracy of a few centimeters.



Figure 1. Light and laser show. The thin beams across the image are laser light, whereas the beams emanating from near the center are ordinary light. The laser beams remain focused and intense, while the others spread and become less bright as they move upwards. (Photo: Ronald Tagra)  
[Creative Commons: <https://flic.kr/p/ft5FeE>]

## 1.2 MONOCHROMATICITY

Another characteristic that makes laser light especially appealing is the fact that it can be highly monochromatic, that is, it can consist of a very pure, single color radiation. This is in great contrast to ordinary light sources, either natural or artificial, which are multicolored in nature, or at the least consist of a range of frequencies. For instance, sunlight contains all the visible colors of the rainbow, in addition to (invisible) ultraviolet and infrared. The same is true for a typical household light bulb. An energy saving lamp or a fluorescent lamp exhibit narrower spectral emission lines. Colored light emitting diodes (LED) have a very narrow spectral bandwidth ranging from a few to a few tens of nanometers. But the spectral bandwidth of a common helium-neon laser, emitting red light with a wavelength of 632.8 nm, is measured in *thousandths* of nanometers.

It should be mentioned however that being monochromatic is a possible but not a strict requirement for laser light. In fact, when laser radiation is produced in the form of very short light pulses it can become very polychromatic, and even be comparable to the sources mentioned above.

## 1.3 COHERENCE

Probably one of the most useful properties of laser light is its high degree of coherence. When comparing two sources of light, we call them coherent if they oscillate with a fixed phase relative to each other. As a comparison, imagine two perfectly synchronized swimmers, advancing side by side while performing the same periodic motion. With coherent light one can perform experiments and

measurements involving the properties of the phase, such as using interferometry to measure tiny displacements, or for creating holograms.

Lasers exhibit two types of coherence:

- longitudinal coherence (along the propagation axis) is related to the temporal properties of the laser beam, allowing us to concentrate laser light in time in the form of very short laser pulses;
- transverse coherence (perpendicular to the propagation axis) is related to its spatial properties, allowing us to concentrate laser light in space in the form of tiny, bright, focused spots of light, almost close to a wavelength in diameter.

These are two remarkable properties that are exclusive to laser light. Coherence is also related to the two properties discussed above, directionality and monochromaticity.

## 1.4 BRIGHTNESS

It is easy to observe that laser beams are typically very bright. Although other light sources can be bright as well, they are typically extended in space, and the light spreads apart as it moves away from the source. On the other hand, as mentioned above, laser light is concentrated in a narrow, parallel beam. When focused, the energy per unit area of even a modest laser reaches very high levels, capable of altering the state or causing damage to surfaces. While this property makes them useful for medical purposes, it also makes them potentially dangerous to work with. It is a common requirement for users to wear protective equipment such as goggles with specially colored filters when handling lasers, in order to avoid damage to the eyes, which can be serious and potentially irreversible.

## 2 RADIOMETRIC QUANTITIES AND UNITS

In this section we list some of the main parameters that are commonly used to quantify and characterize the distribution of light (or electromagnetic radiation in general), including laser light. This is a useful reference guide since the same laser beam may be characterized by different parameters depending on which property one wishes to emphasize for a given application.

## 2.1 Base units

Quantity	Unit name	Unit symbol	Description
Radiant energy	Joule	J	Energy of light
Radiant energy density (or dose)	Joule per cubic meter	$J\ m^{-3}$	Radiant energy per unit volume
Power or radiant flux	Watt	W	Radiant energy emitted, reflected, transmitted or received, per unit time
Irradiance*	Watt per square meter	$W\ m^{-2}$	Power received by a surface per unit area
Radiosity*			Power leaving a surface per unit area
Radiant exitance*			Power emitted by a surface per unit area (i.e. The emitted component of radiosity)
Radiant exposure (or fluence)	Joule per square meter	$J\ m^{-2}$	Radiant energy received by a surface per unit area, or irradiance of a surface integrated over the time of irradiation

\* In laser literature these quantities are commonly called "intensity", with the context providing the distinction between each use.

## 2.2 Spectral units

Quantity	Unit Name	Unit Symbol	Description
Spectral flux	Watt per Hertz	$W\ Hz^{-1}$	Radiant flux per unit frequency
Spectral irradiance	Watt per square meter per Hertz	$W\ m^{-2}\ Hz^{-1}$	Irradiance of a surface per unit frequency
Spectral radiosity			Radiosity of a surface per unit frequency
Spectral exitance			Radiant exitance of a surface per unit frequency
Spectral exposure	Joule per square meter per Hertz	$J\ m^{-2}\ Hz^{-1}$	Radiant exposure of a surface per unit frequency

## 2.3 Intensity units

Quantity	Unit Name	Unit Symbol	Description
Radiant intensity	Watt per steradian	$W\ sr^{-1}$	Radiant flux per unit solid angle
Spectral intensity	Watt per steradian per Hertz	$W\ sr^{-1}\ Hz^{-1}$	Radiant intensity per unit frequency

## 2.4 Radiance units

Quantity	Unit Name	Unit Symbol	Description
Radiance	Watt per steradian per square meter	$W\ sr^{-1}\ m^{-2}$	Radiant flux emitted, reflected, transmitted or received by a surface, per unit solid angle per unit projected area
Spectral radiance	Watt per steradian per square meter per Hertz	$W\ sr^{-1}\ m^{-2}\ Hz^{-1}$	Radiance of a surface per unit frequency

## 3 LASER GLOSSARY

### Absorption

Type of interaction between light and matter in which a photon is absorbed and its energy is transferred to the atoms, ions or molecules of the medium, moving them to an excited state. In the context of the laser process, the excitation of the gain medium leading to population inversion usually takes place by absorption of the pump radiation.

### Bandwidth

The width of the optical spectrum of a light source, normally expressed in submultiples of the meter (wavelength units) or multiples of the Hertz (frequency units). Many laser types are monochromatic such that their bandwidth is very narrow.

### Coherence

Two waves are said to be coherent when they remain perfectly synchronized as they propagate. This means that the phase difference between their oscillations remains constant. Laser light is strongly coherent in space and in time, enabling the generation of very tight, intense focused spots of light and of ultrashort, ultrapowerful laser pulses.

### CW (mode)

Acronym that stands for continuous wave i.e. an electromagnetic wave of constant frequency and amplitude. The light emitted by a laser operating in CW mode is therefore approximately monochromatic and of constant power. The other emission mode consists of periodic pulses of light, and it is called *pulsed mode*.

### Energy

One of the main parameters that can be used to characterize a laser beam, energy is stored in the electromagnetic field and travels at the speed of light. It is a measure of the capability of light to induce changes when interacting with matter, such as raising the temperature, melting, ablating and cutting. (*See the previous section on radiometric quantities and units*)

### Excited state

In an atom, ion or molecule, this stands for any energy configuration that is not the ground state, so by definition its energy is higher. When, for example, an atom in the ground state absorbs light energy through the process of absorption, it moves temporarily towards an excited state. After an interval characterized by the decay time, the atom may return to the ground state, releasing a new photon by spontaneous emission.

### Frequency

Temporal period of the sinusoidal wave that represents the oscillations of the electric field of light. Monochromatic (i.e. single color) light has a single frequency, whereas polychromatic (multi-colored) light exhibits different frequencies. The vacuum frequency of visible light ranges between approximately 430 terahertz (border between red and infrared) and 770 terahertz (border between violet and ultraviolet). The frequency of light is an intrinsic property that does not depend on the medium, so it is

the same for vacuum and inside any optical material.

### Gain

In an amplifier, gain denotes an increase of the energy through amplification. In a laser amplifier the gain happens within the gain medium and it corresponds to the multiplication of photons through coherent amplification. Under the condition of population inversion, the gain (stimulated emission) can exceed the loss (absorption) in the medium, and laser light is emitted.

### Gain medium

One of the key components of a laser, the gain medium is the material chosen for the laser process i.e. where the energy exchanges leading to laser emission take place. These exchanges include the excitation of the gain medium through pumping and the coherent amplification of light through stimulated emission.

### Ground state

In an atom, ion or molecule, it stands for the lowest possible energy state. For instance, in an atom this corresponds to the optimized distribution of its electrons by the different orbitals such that the overall energy attains the lowest possible value.

### Intensity

A commonly used term to denote the amount of power per unit area, although formally incorrect (see the previous section for more information). Together with energy and power, intensity may be considered one of the main parameters that characterize a laser beam in terms of its form of interaction with matter.

### Laser

A device that emits light through processes of coherent optical amplification, based on the principle of stimulated emission. Laser light has a set of unique properties: it is highly directional, coherent, bright and can be strongly monochromatic.

### Lifetime

The typical time that characterizes a spontaneous emission transition, that is, how long an atom will stay in a given excited state before moving (decaying) to a lower energy one.

### Monochromatic

The property of light consisting of a single wavelength, or in practice of a very narrow range of wavelengths. Laser light can be almost perfectly monochromatic.

### Photon

An extremely small, unit amount of energy in the form of light. Interactions between light and matter take place through exchanges of energy that are multiples of the photon energy. The energy of a given photon is proportional to its frequency.

### Population inversion

A specific, transitory state of matter in which the density of atoms in a high energy state exceeds the density of

atoms in a low energy state. This contradicts Boltzmann's law for matter in thermal equilibrium, but it is a mandatory condition for laser action to happen.

### **Power**

One of the main parameters that characterize a laser beam, representing the amount of energy delivered per unit time. Power can be constant, as in a CW beam, or variable, as in a pulsed laser. In the latter case one must also distinguish between average and instantaneous power. (*See the previous section on radiometric quantities and units*)

### **Pulsed mode**

The light emitted by a laser operating in pulsed mode consists of short bursts, or pulses, of light. This can be achieved in several ways, from modulating the pump source or the transmission of the optical resonator to periodically blocking the output light, among others. Operation in pulsed mode is important because it allows the energy to be concentrated in very short packets, which can last as little as less than one billionth of a second. The interaction between light and matter in the pulsed mode is strongly dictated by the pulse duration.

### **Pumping**

Pumping is the process through which energy is initially supplied to the gain medium in a laser, enabling it to move to an excited state such that population inversion is achieved. Once this happens, the probability is that stimulated emission overcomes absorption, and the gain medium becomes a coherent amplifier.

### **Refractive index**

Each optical medium may be characterized by a dimensionless number that describes how light propagates, called the refractive index. For instance, the refractive index of vacuum is 1, and the refractive index of water is 1.33. This means that light in water (*i*) travels 1.33 times more slowly than in vacuum and (*ii*) the wavelength of light is 1.33 times smaller. Rigorously, the refractive index of media other than vacuum is frequency dependent. The refractive index is also at the origin of the bending of light rays at the boundary between different optical media.

### **Resonance**

A resonance, in simplified terms, is a specific frequency of a system, such as an atom or a molecule, at which it can interact with light, either absorbing or emitting it.

### **Optical resonator**

One of the fundamental building blocks of a laser, the optical resonator is an arrangement of mirrors (and possibly other optical elements) that makes light circulate in a closed loop, forcing it to cross the gain medium in each pass, becoming amplified in this process. The simplest implementation of an optical resonator consists of two plane mirrors, parallel to each other, separated by some distance, with the gain medium in between.

### **Spectrum**

The spectrum of a laser, or any light source in general,

is the arrangement of frequencies that are present in it. Specifically, the spectrum provides information about how the energy is distributed over all the frequencies present in that source. The spectrum can be displayed by using measurement devices known as spectrometers.

### **Spontaneous emission**

Type of interaction between light and matter that results in the emission of a photon. The energy of the photon corresponds to the energy difference between the initial and the final states of the transition that took place in the atom, causing it to move (to decay) to a lower energy state. Each transition has a typical decay time.

### **Stimulated emission**

Type of interaction between light and matter in which a photon interacts with an excited medium, stimulating it to decay to a lower energy level. This only takes place when the energy difference between the initial and final states matches the energy of the photon. In these conditions a replica photon is emitted, having the same wavelength, direction and phase of the original photon. Stimulated emission is the core principle of laser action, since it allows the coherent amplification of light.

### **Wavelength**

Spatial period of the sinusoidal wave that represents the oscillations of the electric field of light. Monochromatic (i.e. single color) light has a single wavelength, whereas polychromatic (multi-colored) light exhibits different wavelengths. The vacuum wavelength of visible light ranges between approximately 0.39 micron (border between violet and ultraviolet) and 0.7 micron (border between red and infrared). Inside an optical medium these values are smaller by a factor equal to its refractive index.

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# 1. The Essential 2. Fundamentals of LASER radiation

The generation of laser light. Components of a laser system



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## 1 THE GENERATION OF LASER LIGHT

In order to understand how a laser works, we will first take a look at the fundamental physical principles underlying the interaction of light and matter (that is, solids, liquids or gases). From this we will derive the main concepts, such as coherent amplification, population inversion and pumping. This will be achieved essentially in a qualitative way, trying to avoid a more complete mathematical formalism as much as possible. As mentioned earlier, readers interested in deepening knowledge of these topics may find more information in the references provided.

Our current understanding of the way light and matter interact is rooted in the quantum theory of light, put forth by Planck, Einstein and others in the early 20<sup>th</sup> century. According to this theory, for any interaction between light and matter, the amount of energy exchanged is always an integer multiple of a fundamental unit of energy. Think of a commercial transaction as an analogy: when you purchase something with cash, the price that you pay must be an integer multiple of a fundamental unit, such as the smallest coin available in a given currency. For instance, in the case where the smallest unit is a cent, the amount of money exchanged can never include the fraction “half a cent”, because such a fraction does not exist.

The fundamental unit of light is called a *photon*. The amount of energy represented by a single photon is not a fixed unit however; instead, it depends on the color of the light, according to the expression

$$E = h\nu$$

Here  $E$  is the energy (in Joules),  $h$  is the frequency of the light (in Hertz) and  $\nu$  is called Planck's constant, with a value of about  $6.626 \times 10^{-34}$  Joules times second. The energy of a blue photon is therefore about one and a half times larger than that of a red photon, because their frequencies have the same ratio. Since Planck's constant has a very small value, the energy of an individual photon

is extremely small. Exchanges between light and matter in daily life phenomena involve a huge number of photons, and their individual nature is not discernible. However, at the atomic and molecular level, photons and quantum theory are supreme. In this realm, we can imagine photons behaving as tiny *particles of light*, carrying an energy given by the expression above. We can attribute the macroscopic properties of light to the photons, and therefore we can say that the photons in a laser beam are directional, monochromatic and coherent.

Quantum theory also tells us that at the microscopic level, matter is organized in such a way that it can only occupy discrete energy levels. For instance, let us consider the fundamental building block of matter – the atom. It consists of a positively charged nucleus surrounded by a cloud of negative electrons, organized into orbits (Figure 1). When the total energy of the atom is at its lowest possible value (the so called *ground state* of the atom), its electrons are distributed following specific rules over a number of discrete energy levels, separated from each other by precise gaps. Here again, the quantum concept of integer steps appears. When energy is supplied to the atom, electrons will “climb” one or more steps into a higher energy level, moving away from the nucleus. Such an atom is called *excited*. When they move down to a lower level, the atom loses energy, emitting a photon (Figure 2). There are no transitions to “half-levels”.

The expression above also places a restriction on whether light and matter will interact. Specifically, for a photon of energy  $E$  such interaction is only possible if the internal constituents of matter – its atoms, ions, molecules and so on – are organized in such a way that they exhibit two distinct energy levels separated by a gap  $E$ . If this condition is verified, three different types of interaction can take place: *absorption*, *spontaneous emission* or *stimulated emission*. For simplicity, we will use the case of the energy levels of an atom, although the following definitions also apply for other types of energy levels in matter.

## 2. Fundamentals of laser radiation

For simple atoms with a low number of electrons, the available energy gaps – and therefore, possible photon frequencies for interaction – are probably limited. However, for multielectron atoms, complex molecules, amorphous media and in general matter with a very large number of energy levels, the possibilities of interaction are greatly enhanced.

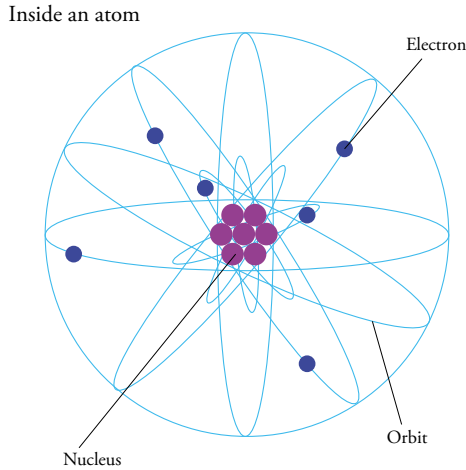


Figure 1. Simplified model of an atom.

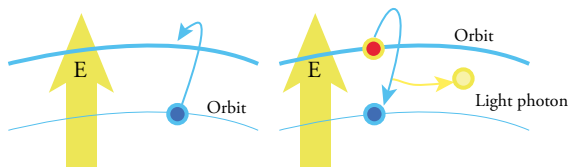


Figure 2. Energy exchanges in an atom.

### 1.1 ABSORPTION

One way to supply energy to an atom and cause it to become excited is to use a beam of light with the correct frequency. When such a beam is shone on a sample of matter, given the tremendous number of atoms and photons involved, eventually an interaction will take place. Let us then look at a single atom-photon interaction. In the case where the atom is in the ground state, one of its electrons will move to another level such that the difference between the final and initial energies is  $E$ . Since the photon has given its energy to the atom, allowing this process to happen, it vanishes - we call this process *absorption*. The frequency of the absorbed photon is called a resonance of the atom.

As described above, simple atoms with few electrons will typically exhibit a small number of discrete resonances, called absorption lines. For more complex systems, the number of resonances increases and can take the form of absorption bands, or even a continuum.

### 1.2 SPONTANEOUS EMISSION

An atom does not stay forever in an excited state, and after absorbing energy from a photon it will eventually

release it. The time that this takes is characteristic of the atom in question and of the transition involved, but is typically very, very short, ranging from  $10^{-8}$  to  $10^{-11}$  seconds (one hundred-millionth to one hundred-billionth of a second), and is called the *lifetime*. In this process, the electron spontaneously moves, or *decays*, to a lower energy level. It may decay to a still excited yet more stable level of lower energy or it may return to the ground state. As a consequence of this, energy is released in the form of light: a photon is emitted, the energy of which equals the difference between the energies of the starting and ending levels. Since this mechanism took place without any intervention external to the atom, it is called *spontaneous emission*. The emitted photon may have the same energy as the original one (in the case where the starting and ending levels exchanged roles between absorption and emission) or lower (in the case where the ending level is still another excited level). In the first case, it is important to note that absorption followed by spontaneous emission will generate a new photon that travels in a random direction, and it is not coherent with the original one. They can have the same color, but their phase and travel directions will very likely be different. Laser light that is absorbed and then emitted spontaneously loses its coherence properties.

### 1.3 STIMULATED EMISSION

While formulating his theory for light-matter interaction, Einstein found that a new type of atomic emission was not only possible, but indeed necessary. Let us start with an excited atom, that is, one which has already absorbed energy, possibly from a photon, corresponding to a given energy gap. As discussed above, this atom will eventually decay through spontaneous emission. However, what happens if a similar photon strikes the atom before that happens, that is, while it is still in the excited state? It cannot be absorbed, since the previous photon has already filled that role. Instead, the presence of this photon, the frequency of which corresponds to an atomic resonance, stimulates the atom to perform the opposite process, that is, to decay emitting a photon. Because this process is triggered by the external photon, it is called *stimulated emission* (Figure 3).

The amazing feature of this kind of emission is that the properties of the newly emitted photon match those of the driving one: they have (naturally) the same frequency, travel in the same direction and are coherent. One can say that stimulated emission is a process for cloning photons.

### 1.4 COHERENT AMPLIFICATION

In normal matter, the probability for stimulated emission to happen is very low, making it very difficult to observe. Indeed, after Einstein's proposal of the process not much attention was devoted to it. Only in the 1930s was it recognized as a method for achieving coherent amplification, that is, increasing the number of photons while preserving coherence. We have already seen that one instance of stimulated emission will lead to a pair of similar photons. As they propagate inside a medium, they may find a pair of excited atoms and replicate themselves, leading to four equal photons. If this process is repeated

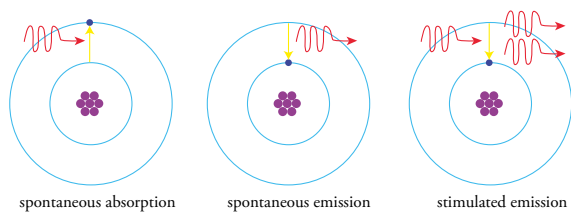


Figure 3. Schematic of the mechanisms of absorption, spontaneous emission and stimulated emission. Note that in the latter we have amplification: one photon goes in, two photons come out.

many times, the number of cloned photons will grow geometrically, leading to a vast army of light particles with the following properties:

- Because they have the same energy, they are monochromatic;
- They travel along the same well-defined direction, creating a narrow beam of light;
- They are mutually coherent;
- If the number of photons is very large, the beam will be very bright.

We have just described the properties of laser light as described in Section 1! It should now be clear why the word *laser* stands for *light amplification by stimulated emission of radiation*.

### 1.5 MATTER IN THERMAL EQUILIBRIUM

Above, we mentioned that stimulated emission is hard to observe in normal matter. In order to understand this, let us picture ourselves for a moment as photons travelling inside a medium. If it is filled with atoms that have a resonance corresponding to our frequency, our fate can be twofold: (i) interact with a nonexcited atom and vanish through absorption, or (ii) interact with an excited atom and replicate. Which process is more likely to happen? By simple probabilistic reasoning, one may conclude that absorption will dominate if the number of nonexcited atoms is higher, since the likelihood of being absorbed increases in that situation.

Through a similar reasoning, for stimulated emission to become dominant it is required that the number of excited atoms is higher. However, this simple statement violates one of the fundamental laws of physics stated by Ludwig Boltzmann (1844-1906): in thermal equilibrium, the probability of finding an excited atom is lower than the probability of finding a nonexcited one; and the higher the energy of the excited state, the lower the probability. In other words, matter tends to self-organize so as to favor the lowest energy distribution, avoiding high-energy states. Unfortunately, that is exactly the opposite of what is required to achieve stimulated emission. This means that photons interacting with matter in thermal equilibrium will be absorbed, as a general rule. Laser light requires a disruption of this natural balance.

### 1.6 POPULATION INVERSION

Enabling stimulated emission and coherent amplification requires achieving an unnatural state of matter: if we only consider atoms occupying two different energy

levels, more high energy atoms than low energy ones are required. Since this contradicts Boltzmann's law for matter in thermal equilibrium, it is a clear hint that we must create a non-equilibrium situation. When this situation is created, we say that these atoms exhibit *population inversion* between the two energy levels. This is a mandatory condition for laser action to happen.

### 1.7 PUMPING

In order to temporarily induce population inversion in a gain medium, energy must be supplied to it. This is a very important stage in any laser and is called *pumping*. At the microscopic level it consists of supplying energy to atoms so that the high-energy ones increase and the low energy ones decrease. However, it can be shown mathematically, or reasoned intuitively, that using photons with the same energy both for pumping (that is, creating the conditions for amplification) and for stimulated emission (that is, to experience the amplification) is not only inefficient, but in fact impossible. In other words, laser action cannot be achieved if only lower and upper energy levels are involved. At least one other higher energy level is required.

We have therefore two major laser configurations (Figure 4), which can be succinctly described as follows:

- *Three-level laser* – atoms are pumped from the ground state level to a high energy level, decaying after a short time to the stable upper laser level. Laser action takes place between this level and the ground one.
- *Four-level laser* – atoms are pumped from the ground state level to a high energy level, decaying after a short time to the stable upper laser level. Laser action takes place between this level and a lower laser level. From this, atoms decay very quickly to the ground state.

Four-level lasers have a more favorable configuration because atoms in the lower laser level can be quickly removed to the terminal ground state level, making population inversion easier.

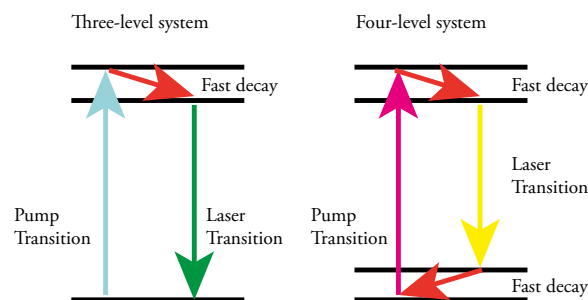


Figure 4. Schematic of three- and four-level lasers. The black horizontal lines represent energy levels.

## 2 COMPONENTS OF A LASER SYSTEM

There are many different types of lasers, but at the root of virtually every one we may find at least three common elements: the gain medium, the optical resonator, and the pump source. These may assume different configurations for each type of laser, so a comprehensive description is outside the scope of this book. Instead we will concentrate on the general role played by each of these elements.

### 2.1 GAIN MEDIUM

The material chosen for the laser process, i.e. where the energy exchanges leading to laser emission take place, is called the *gain medium*, or the *active medium*. These exchanges include the excitation through pumping and the coherent amplification of light through stimulated emission. The gain medium can be in a solid, liquid or gas state. In the first case it has a given geometrical shape, such as a cylinder; in the latter two cases it is enclosed in a chamber with transparent windows. Solid-state lasers are very popular, and the gain medium can be a doped glass or crystal (a transparent, inert medium with a given percentage of the active ions) or a semiconductor. There is a wide variety of media capable of exhibiting laser action, and typical examples will be discussed in Chapter 3.

### 2.2 OPTICAL RESONATOR

Let us imagine a collection of coherent photons traversing through a gain medium. As they do so, each photon will multiply itself many times, and at the end they will emerge as an amplified beam of coherent light. However, it is very likely that the gain medium still contains a very large fraction of excited atoms, which could be used to increase the energy of this coherent beam even more. In other words, crossing the gain medium just once is a very ineffective approach, since it wastes a large amount of the energy stored in the excited atoms.

So how can we achieve more than one pass? Simply by using mirrors that reflect the beam upon itself. In fact, when enclosing the gain medium between two parallel mirrors – a setup called *optical resonator* – the photons can perform a virtually infinite number of passes and their energy can grow as long as the state of population inversion is predominant. However, this approach would be ineffective given that no light emerges from such a mirrored box. For this reason, the typical arrangement for an optical resonator consists of using the following:

- One fully reflective mirror (reflecting close to 100 % of the incident photons);
- One partly reflective mirror (reflecting a little below 100 %, such as 90-95 % of the photons).

The optical resonator is responsible for the very well-defined direction of laser beams. As photons travel back and forth between the mirrors, they define a privileged axis. Photons travelling at an angle to that axis will eventually be lost by failing to be reflected at one of the mirrors. But photons travelling parallel to that axis will multiply and contribute to the overall beam (Figure 5).

In reality the mirrors composing an optical resonator are generally curved, instead of flat, for a question of additional stability. This has an important effect on the beam shape and intensity distribution. If you measure the brightness of a typical laser beam at different points across its aperture, you will find that (i) the distribution is circularly symmetric about the central axis and (ii) it decreases as you move away from the axis, such that if you plot the brightness versus radial distance you will obtain a kind of bell-shaped curve known as a Gaussian curve. This property will be discussed in detail in the following chapters.

### 2.3 PUMP SOURCE

Everything discussed above is only possible if adequate

energy is provided to the gain medium. For both three-level and four-level lasers, this energy must be greater than the energy of the laser photons (Figure 4). The pump energy is absorbed, leading to population inversion. In order that this process happens efficiently, we must take advantage of other resonances, which means that the pump source must be carefully selected to match a given gain medium.

There are different types of pump sources, although light sources or electric currents are commonly used. In a very typical configuration for solid-state lasers, the gain medium consists of a cylindrical rod placed inside a coated chamber and surrounded by cylindrical flash lamps. Each time a current is discharged through the flash lamps, they emit a bright, short flash of light. Some of the spectral emission lines of the lamps will match the absorption lines of the gain medium and excite its laser active atoms or ions. The remaining light will not be optically absorbed, instead raising the temperature of the medium. For this reason, and although very popular, flash lamp pumping is not particularly effective and requires suitable cooling mechanisms.

A more effective choice is to use light that specifically targets the required absorption lines. This can be accomplished by using an external laser that generates monochromatic light of a higher frequency.

With this we conclude the description of the fundamental physics and processes which are common to virtually all lasers. From here onwards one must consider the specific gain media, resonators and pump sources that are used for a given laser device, and from the many combinations of which stems the amazing variety that composes the field of laser technology.

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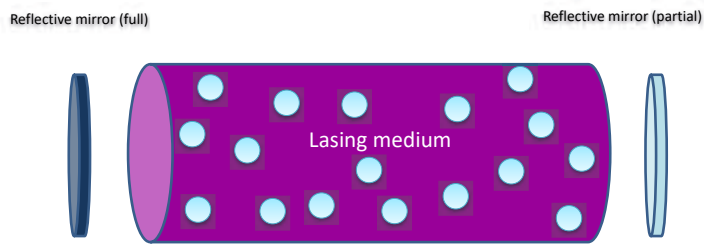


Figure 5 a): Lasing medium at ground state

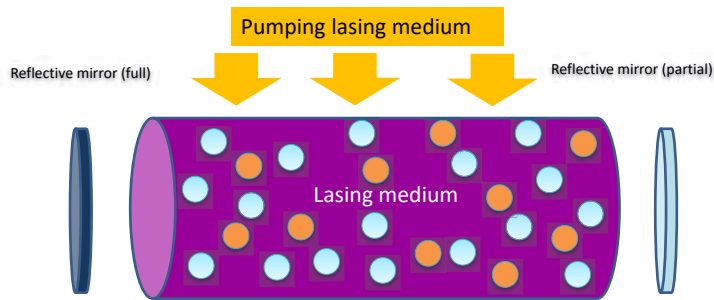


Figure 5 b): Population inversion

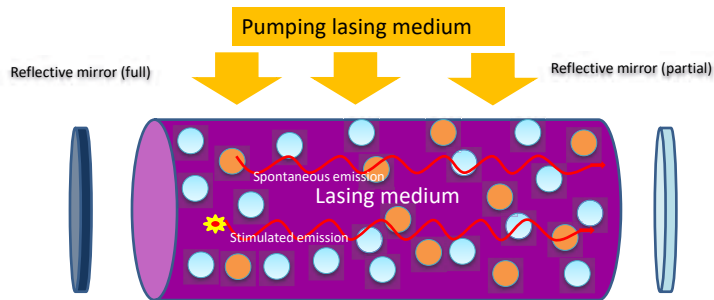


Figure 5 c): Spontaneous emission and the first stimulated emission

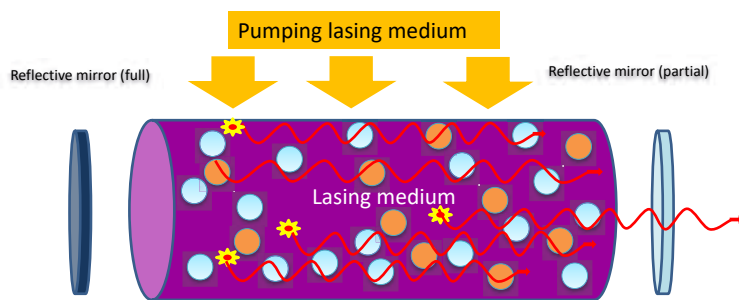


Figure 5 d): Stimulated emission growing

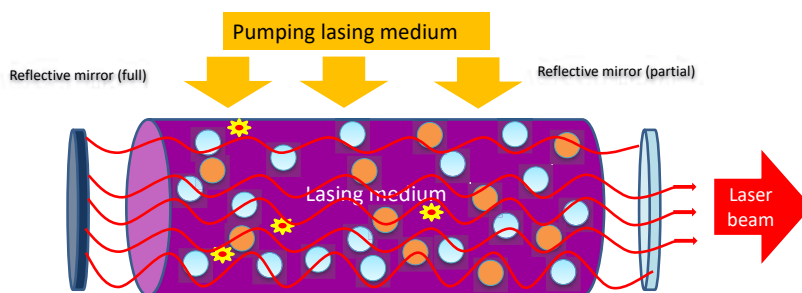


Figure 5 e): All waves are lined up in phase and there is coherent light emission




-  Atom in ground state
-  Excited atom
-  Stimulated emission atom

Figure 5. Laser light building up inside an optical resonator. The left mirror is fully reflective and the right one is partly reflective. The privileged axis for stimulated amplification is perpendicular to both mirrors.





# I. The Essential

## 3. LASER technology-

### various types of

### medical LASER



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The first laser was invented in May, 1960, by Theodore Maiman, to experimentally demonstrate the stimulated radiation emission from a ruby crystal at Hughes Research Laboratories in Malibu, California. Since then, many other materials have been used as the active medium (lasing medium or gain medium) in the development of a large number of lasers.

Lasers are grouped into solid-state lasers, liquid lasers and gas lasers. These are further divided into subcategories. For example, gaseous lasers may be comprised of atoms, ions or molecules, and solid-state lasers can be doped insulators (crystals) or semiconductors. Finally, there are still Free Electron Lasers (FEL), in which the active medium is neither a gas nor a liquid nor a solid but an electron beam from a particle accelerator. Although these lasers are very promising due to their tunability and extremely large range of emission wavelengths, from microwave to x-ray, the requirement of a large-scale facility is a major limitation on their medical applications. For this reason, we will not discuss this type of laser any more but an interested reader can find more information in the references at end of the chapter.

#### 1.1. GAS LASERS

The three main types, which include most gas lasers, are usually classified as atomic, ionic and molecular. Excimer lasers, due to their specificity and broad use in laser medicine practice, will be discussed separately. We will also briefly discuss other gas lasers, which are less used in medical applications, such as metallic vapor and chemical lasers.

##### 1.1.A - ATOMIC LASERS

The pumping of these lasers is usually carried out through

an electric discharge (Figure 1). This type of pumping system is an electronic current flowing into the lasing gas. As a medical laser example that uses an atomic gas as an active medium, we have the helium-neon laser (HeNe). This active medium consists of a mixture of helium and neon at a ratio of 8:1<sup>1</sup>. The amplification by stimulated emission of light is given by the electronic energy levels of atoms of neon (lasing species) and the helium atoms in the mixture are only responsible for the energy transport from the electronic current to the neon atoms.

##### 1.1.B - ION LASERS OF RARE GASES

The most common ion lasers are argon and krypton. This type of laser is different from atomic lasers for use as an ion-active medium gas. The most common medical laser that uses a gas of ions as a lasing medium is the argon ion laser, often called argon laser. The active medium of the laser is single charged positive argon-ion gas obtained from the electric discharge of the pumping system similar to the atomic lasers. There are also argon and krypton lasers doubly ionized which are less efficient which emit light in the ultraviolet range.

Typically, these type of lasers are characterized by simultaneously emitting several lines (different wavelengths) in the visible spectrum with very high continuous power in (about 50 W).

##### 1.1.C - MOLECULAR LASERS

Just as with atoms and ions, molecules may also have multiple discrete energy levels. In the case of molecules, this energy is connected to the vibrational mode of the molecule or molecule rotation according to an axis of symmetry.

Radiative transition (by absorption or emission of photons) occurs between the molecular excited states in the same

### 3. Laser technology-various types of medical laser

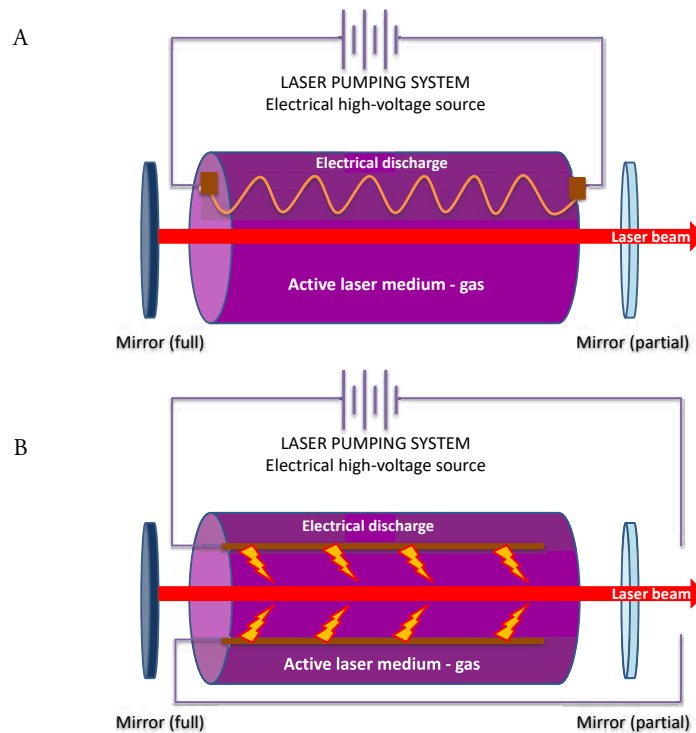


Figure 1. An electric discharge gas laser pumping may be applied (A) longitudinally along the laser axis, or (B) transversely perpendicular to the laser axis.

way as the atomic or ionic states. The energy involved in the transition between vibrational states of the molecules are typically smaller than between those for atomic or ionic states. The emission consists of less energetic photons, in other words, longer wavelengths (typically in the infrared region of the electromagnetic spectrum). However, these lasers produce very high output power due to the huge flow in the emission of these photons.

Invented in 1960 by Dr. C.K.N. Patel, the carbon dioxide laser (CO<sub>2</sub> laser) is currently the most common medical laser that uses a gas in molecular form as its active medium. This gas consists of a mixture of 10% -15% carbon dioxide (lasing species gas), 10% -20% nitrogen (pumping system transport gas), with the remaining 65% -80% helium (heating sink gas which facilitates the final transition in a four-level system – see previous chapter) exerting a total pressure, normally, around 0.008 to 0.02 atm.

Once again, the most common mechanism for pumping these lasers is a DC electric discharge along the gas tube. However, other forms are quite common for pumping these lasers, such as millisecond duration electrical pulses, radio-frequency waves and transverse electric discharge. The latter allows the operation of these lasers with the gas at atmospheric pressure. These lasers are called TEA Lasers (*Transversely Excited Atmospheric pressure*) and are characterized by the emission of very intense short pulses<sup>2</sup>.

#### 1.1.D - EXCIMER LASERS

The name "excimer laser" refers to an entire class of lasers

with a wide variety of medical applications. An excimer is an excited diatomic molecule (excited dimer). This type of short life diatomic molecules is formed from two rare gaseous atoms or, more often, by an atom of a rare gas together with an atom of the halogen class. This type of diatomic molecule, which exists only in an excited state, emits ultraviolet radiation when it dissociates into its constituent atoms. Examples of excimer lasers are: argon fluoride (ArF), krypton fluoride (KrF), xenon fluoride (XeF), xenon chlorine (XeCl), etc...

The pumping system of these lasers is identical to the CO<sub>2</sub> TEA mentioned in the previous section. The energy is deposited in the gas and through an intense electric discharge of short duration (tens to hundreds of nanoseconds) applied transversely to the laser axis. The electrons collide with the noble gas atoms (e.g. argon, krypton, xenon) by changing from a stable electronic configuration into an unstable configuration, which allows a momentary connection with a halogen atom (e.g. fluorine, chlorine). The laser stimulated emission occurs when this excited diatomic molecule dissociates into its constituent atoms. As there are no diatomic molecules in their lowest energy state, the existence of any molecule in the excited state is already a population inversion situation.

#### 1.1.E - METAL-VAPOR LASERS

Metal-vapor lasers are hybrids, since they are neither atomic or ionic but rather have characteristics of both. For example, in the case of a helium-cadmium laser, the



active medium consists of a plasma tube with helium gas which, during operation, due to the electronic current, evaporates the metal cadmium present in one of the discharge electrodes. After that the lasing process is very similar to the HeNe laser discussed above.

### 1.1.F - CHEMICAL LASERS

A chemical laser utilizes two highly reactive gases to form a molecule which becomes a lasing species. An example of a chemical laser is the hydrogen fluoride (HF) where the active medium is a gas mixture of hydrogen and fluorine that reacts chemically producing HF molecules in an excited state. The laser radiation is emitted in the transition between the vibrational excited state to the ground state of the molecule, this will be located in the band of the spectrum with the smaller level of energy, infrared.

### 1.2. - LIQUID LASERS (DYE LASER)

The active medium of a laser liquid is called an organic dye (Rhodamine 6G, Rhodamine B, etc.) dissolved in ethanol or ethylene glycol (liquid solvent). In a dye laser, the active medium is optically pumped by other lasers (argon, Nd: YAG, excimer, ...) or flash lamps which may issue many wavelengths from infrared to ultraviolet. Despite their tunability and amplification broadband (useful for generating ultrashort pulses – see Chapter 5) they have fallen into disuse due to the high level of maintenance that such types of lasers need.

### 1.3. - SOLID STATE LASERS

There are two types of lasers which use an active medium in their solid state: the laser doped insulator (crystal) and the semiconductor laser. However, the latter type has a very different type of operation from the former, so it is normally treated completely separately and the predominant solid-state lasers are only the lasers with doped insulators.

#### 1.3.A - LASER DOPED INSULATOR OR SOLID-STATE LASER (CRYSTAL)

The active medium of this kind of laser is a non-conductive solid, based on a crystalline or a glass material, which is doped and as such responsible for the laser emission.

In a solid-state laser, the active species is an ion immersed in the matrix of another material – usually named the host. A variety of crystals and glasses can become a host if they meet the following criteria: transparency, easy production (ease of growing the crystal) and with good thermal conduction.

The most used crystals contain YAG (*yttrium-aluminum-garnet*) and other synthetic crystals (ruby, sapphires, etc.). Silicates, phosphates and other kind of glasses can also serve as hosts. In commercial lasers, the active species is an impurity introduced during the crystal production, reaching 1% of the final composition.

There are other common host materials for neodymium: YLF (yttrium lithium fluoride, 1047 and 1053 nm), YVO<sub>4</sub> (yttrium orthovanadate, 1064 nm), and glass. A particular host material is chosen in order to obtain a desired combination of optical, mechanical, and thermal properties. The active species in this solid state laser is locked inside the matrix of the insulating material making it impossible to

become excitable by an electric discharge through the active medium. Optical pumping is the only practical solution, assuming that the crystals are transparent to the radiation that the lasing species emits and absorbs. In opposition to gaseous lasers, the absorption band in the active solid state is large due to the crystal matrix properties. This allows the use of pumping by flash lamps, characterized by a large spectral emission with reasonable efficiency.

As illustrated in figure 2, there are two configurations for optical coupling between a flash lamp and the active medium (crystal rod). The flash lamp can be coiled around the crystal rod (cylindrical crystal) and placed in the center of a reflector cylinder in a way that all the light emitted by the flash lamp hits the crystal (figure 2). This system was used in the first designed laser, the ruby laser. In an alternative configuration, the flash lamp is straight-lined and parallel with the crystal rod (each one placed at the focal points of an involving elliptical reflector). In addition, in this way, most of the light emitted by the flash lamp reaches the solid crystal<sup>3</sup> (Figure 2).

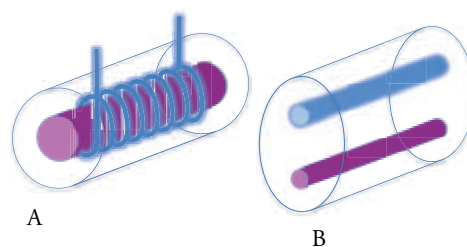


Figure 2. (A) Cylindrical ruby crystal with a coiled flash lamp inside a circular reflecting camera. (B) Flash lamp aligned with the crystal, each one directed to a focal point inside an elliptical reflecting camera.

As electric current passes through the flash lamp, it will produce a bright light impulse. Approximately 30% of this light will be absorbed by the lasing species inside the crystal leading to the population inversion. The remaining 70% of the energy is not absorbed, becoming a source of heat in the crystal. In fact, heat dissipation is a very common problem with this kind of laser. To overcome this situation, solid lasers are operated in a pulsed emission mode instead of a continuum emission mode.

These flash lamps are not very efficient in converting electrical energy to light. In this way, the most efficient laser, pumped by flash lights, has a conversion rate of about 1%. It is possible to increase efficiency by limiting the optical pumping to the absorption band of the lasing species. Unfortunately, most short band light sources are very inefficient. An important exception to this rule is the diode laser (semi-conductive). These lasers are becoming an important source for pumping solid-state lasers. Other solid-state lasers have absorption bands that make pumping by flash lamps or diode lasers ineffective. Thus, these lasers could only be pumped by another laser in a solid or gaseous form, limiting their global efficiency and increasing their cost.

### 3. Laser technology-various types of medical laser

The Nd:YAG laser (*Neodymium: yttrium-aluminum-garnet*) is the solid state laser with a doped crystal that has the most significant medical applications. The active medium of the Nd:YAG laser is a colorless crystal rod with chemical formula  $Y_3Al_5O_{12}$  (known as *yttrium-aluminum-garnet* = YAG). In this crystal rod, 1% of the yttrium atoms are substituted by neodymium ions with electric charge of +3 that are the source of laser light (lasing species). The solid YAG crystal is the host, forming the base for the neodymium ionic impurities. The population inversion is achieved through optical pumping (flash lamp or diode laser) that is absorbed by YAG crystal neodymium ions. The absorption of the pumping photonic energy will excite the neodymium ions to an unstable energy level. The ion will rapidly release a photon decaying to a metastable energy level. The transition to a lower energy level will occur by stimulated emission, responsible for the laser light. Finally, the transition from this energy level to the initial level (fundamental level) is rapidly achieved by spontaneous emission, depopulating the lowest energy level of the laser transition necessary for the population inversion.

Finally, it is important to point out two other types of solid-state lasers due to their uniqueness and potential future application that are the femtosecond and fiber lasers. Femtosecond lasers are lasers that emit radiation pulses in the sub-picosecond range, normally tens or hundreds of femtosecond, ( $10^{-15}$  of a second, see chapter 5). In order to be able to generate such ultra-short pulses the active medium (or gain medium) has to have a very broad spectral emission band. Several solid-state materials can be used (Nd:glass, Er:silica fiber and others) but the most suitable choice is Ti:sapphire, which can produce laser pulses a few femtoseconds long. Its extreme emission bandwidth is possible due to the strong coupling between the electronic energy levels with the lattice vibration of the crystal structure. The fiber laser has the particular property of a very long active medium (hundreds of meters of optical fiber roll), which leads to high amplification and great optical power output. The pumping system of the fiber lasers is possible by using a laser radiation optical pump (usually diode laser) transmitted in the outer-core layer of the fiber that excites the active medium in the inner-core.

#### 1.3.B - LASER MADE OF SEMICONDUCTING MATERIALS (DIODE LASER)

These lasers are very different from the ones we have already discussed. In terms of electrical conductance, the semiconductor materials are situated between metals (excellent electrical conduction) and isolating materials (poor conduction). Semiconductors can be clustered into two groups: the intrinsic semiconductors (silicium and germanium) and the extrinsic semiconductors (formed by adding doping impurities to the intrinsic semiconducting materials).

There are two kinds of semiconductors: the n-type, which contains a chemical impurity from group V of the Periodic Table of Elements (such as phosphorus and arsenic); and the p-type, containing a chemical impurity from group III of the Periodic Table (Aluminum, Gallium or Indium). The success of the semiconductor industry

comes from the capacity to grow these crystals with very precise quantities of doping atoms, which determines the electrical conductivity of the final material.

When combining a p-type semiconductor with an n-type semiconductor, this forms a semiconductor diode or a p-n junction. In this junction, the excess electrons from the n-type can recombine with the "holes" on the p-type (holes are places where there is one electron missing in the connection between the atoms of the semiconductor). This recombination releases energy which, under certain circumstances, can be in the form of photons<sup>1</sup> (Figure 3). The processes of emission, absorption and stimulated emission occur in these materials in the same way as they occur in every atomic and molecular system. The active medium of the diode laser is a semiconductor crystal of gallium-arsenic (GaAs) or similar chemical elements, such as GaAlAs, InGaAs or AlGaInP. The diode laser has the size of a salt grain (Figure 4). An electric current passes through a sandwich of p-type and n-type semiconductors producing light emission. Stimulated emission and absorption are two competing processes. At a certain level of electric current, the rate of the emitted and absorbed photons is equal. When this threshold is passed, stimulated emission prevails and the population inversion is achieved making laser action possible. When two reflecting surfaces to create an optical resonant cavity are included in the structure, the diode works as a micro-laser<sup>4,5</sup>.

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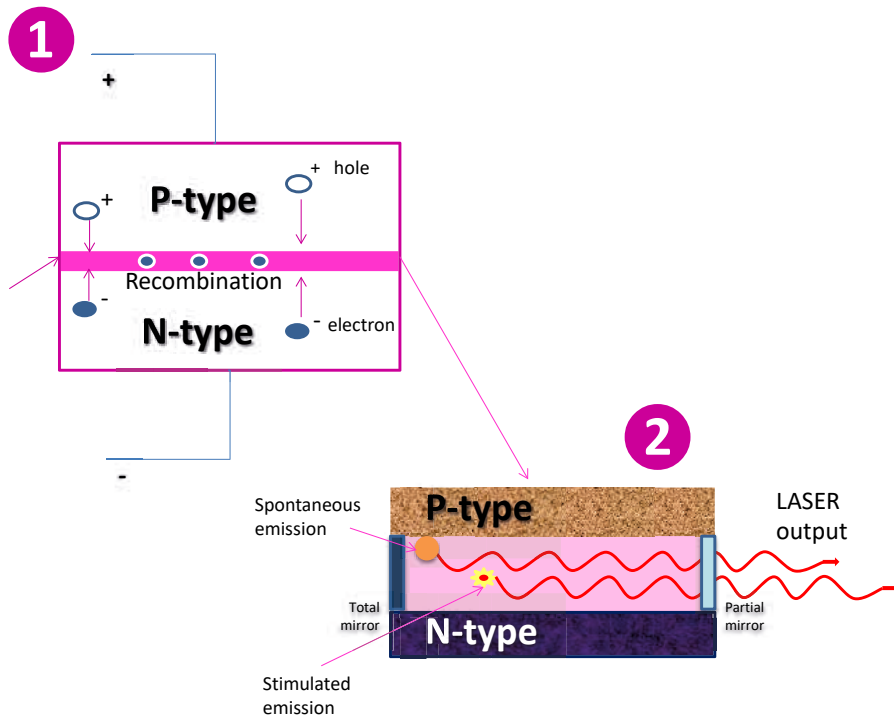


Figure 3. Diode laser operation (simplified): direct tension produces a current and the recombination of electrons between gaps; emission stimulated in the most active level.

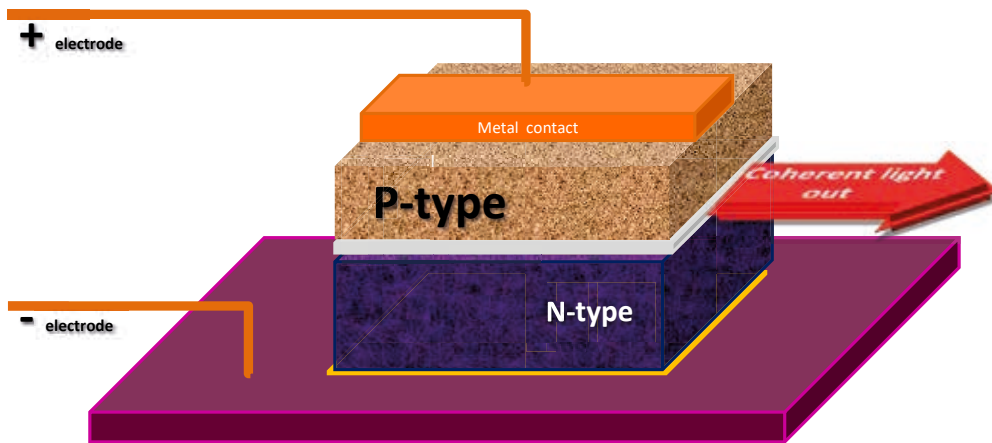


Figure 4. Schematic drawing of a semiconducting laser.



# I. The Essential

## 4. LASER classification

### based on wavelength



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The wavelength of a laser ( $\lambda$ ) is one of the most important parameters to choose from when selecting a medical grade laser, as the suitable choice of a particular laser wavelength can determine how deep the radiation will penetrate into a specific biological tissue.

The wavelength of the laser is closely connected to its active medium characteristics<sup>1</sup>. As has been shown in the previous chapter, the wavelength of the radiation emitted by a laser is fundamentally determined by the transition between energy levels through stimulated emission.

The most important lasers and their emission wavelengths are shown schematically in Figure 1 (note: wavelength scale is logarithmic not linear).

Lasers can emit radiation across the electromagnetic spectrum, ranging from the ultraviolet (UV) and visible to the infrared. This laser emission parameter allows us to classify a particular laser as ultraviolet, visible or infrared based on its specific wavelength. It is based on this model of classification that we propose to enumerate various medical grade lasers in the following sections. As units of wavelength measurement, we will use the nanometer ( $1 \text{ nm} = 10^{-9} \text{ m}$ ) and the micrometer ( $1 \mu\text{m} = 10^{-6} \text{ m}$ ).

#### 1 INFRARED LASERS

These are the lasers, the wavelength ( $\lambda$ ) of which is higher than the red part of the visible spectrum. According to their

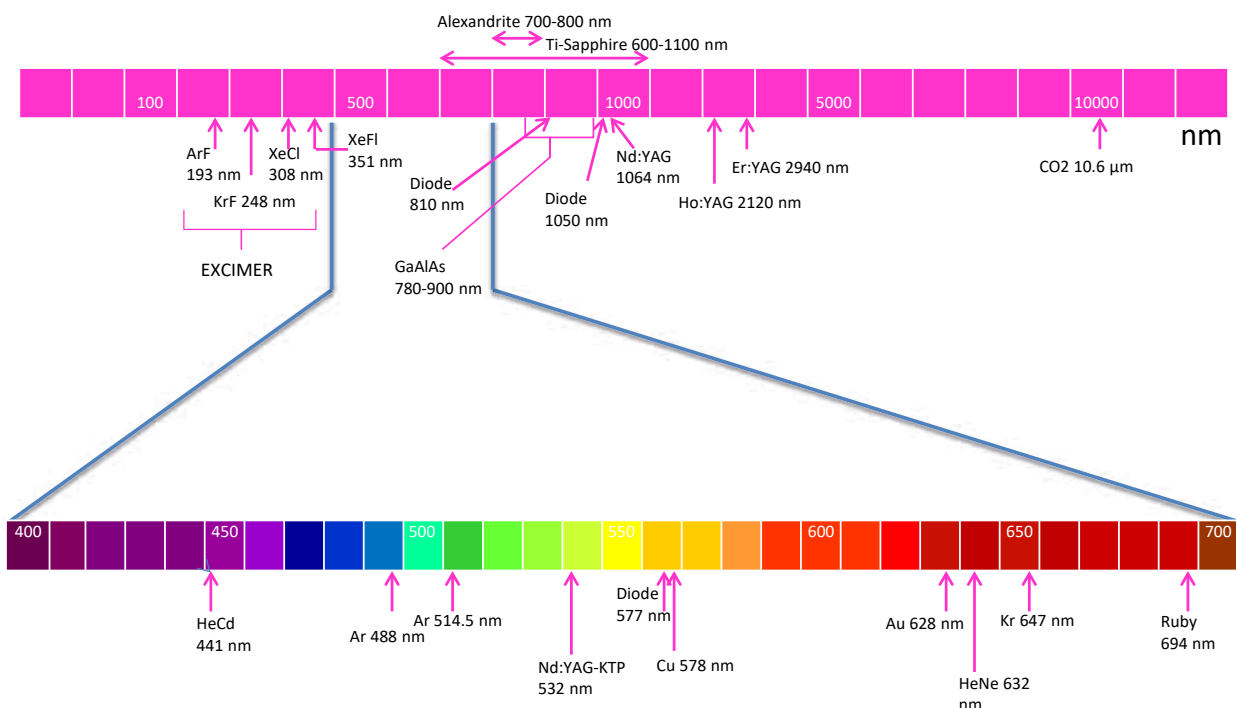


Figure 1. The most important lasers and their emission wavelengths.

## 4. Laser classification based on wavelength

characteristics, lasers can further be subdivided into near-infrared ( $700 \text{ nm} \leq \lambda \leq 3 \text{ }\mu\text{m}$ ), mid- and far-infrared lasers ( $\lambda \geq 3 \text{ }\mu\text{m}$ ). Molecular and gaseous active medium lasers usually fall within this last group because there is little difference between the vibrational states of a molecule, giving rise to low energy, and high wavelength photons.

In this group, the CO<sub>2</sub> laser is by far the most used laser, by physicians, preferably emitting in the 10.6  $\mu\text{m}$  wavelength. However, there are other lasers such as CO ( $\lambda = 5 - 6 \text{ }\mu\text{m}$ ), chemical lasers like the HF ( $\lambda = 2.6 - 3.0 \text{ }\mu\text{m}$ ), and the solid state laser Er:YAG ( $\lambda = 2.94 \text{ }\mu\text{m}$ ) – these latter two can be considered to belong to the near infrared group. However, we have chosen to group them together as they share a wavelength highly absorbed by tissues, due to their water content – a feature which makes them particularly attractive for surgical use.

Medical grade lasers, well inside the near infrared band, comprise the solid state laser, such as the Ho:YAG ( $\lambda = 2.1 \text{ }\mu\text{m}$ ), Nd:YAG ( $\lambda = 1.064 \text{ }\mu\text{m}$ ), Alexandrite and Ti:sapphire and semiconductor lasers (GaAlAs).

In this group we would like to highlight the Nd:YAG laser due to its wide use in medical practice.

### 2 VISIBLE LASERS

The visible band ( $400 \text{ nm} < \lambda < 700 \text{ nm}$ ) is very narrow when compared with the whole of the electromagnetic spectrum. However, we can further subdivide it into its main colors, red, green and blue. As shown in Figure 1, right at the start of the red visible spectrum, we find the Ruby laser (694 nm), and others include the krypton ion laser (647 nm) and the HeNe (633 nm). Both can emit bands with other wavelengths in different regions of the spectrum; krypton and argon ion lasers in particular have the ability to simultaneously emit strong bands across all parts of the visible as well as in the ultraviolet spectrum. Table 1 presents a complete list of the wavelengths of ionic lasers.

The argon ionic laser was once frequently used in the Ophthalmology field but has gradually been replaced by the Nd:YAG-KTP (532 nm - green-yellow) and diode laser (577 nm – yellow)<sup>2</sup>.

Table 1. Wavelengths available for Argon and Krypton ion lasers in the visible spectrum

Argon(nm)	Krypton(nm)
528.7	647.1*
514.5*	568
501.7	530
496.5	
488.0*	
476.5	
457.9	

\*line of higher output power.

Argon mainly emits in the blue-green area of the visible spectrum (488 nm and 514.5 nm). Blue has long been out of use due to a known macular absorption of xanthophyll pigment, by both patient and physician, despite the proper use of protection filters. During the 1980s and 90s it was largely utilized, particularly the green band (514.5 nm), to a point that whenever anyone mentioned retinal laser it was assumed that reference to the Argon laser was being made, even after it was largely replaced by the Nd:YAG-KTP (532 nm). The Nd:YAG-KTP has an important wavelength in the green part of the visible spectrum (532 nm) corresponding to the Nd:YAG second harmonic.

This radiation derives from the non-linear phenomenon of harmonic generation in the KDP or KTP crystal. These crystals, as we shall further consider, have the ability to double the Nd:YAG laser frequency, thereby reducing the wavelength by half.

Finally, in the blue part of the visible spectrum, beyond some of the weakest bands of the Argon, there is the metallic vapor laser HeCd.

Other kinds of laser, which preferentially emit in the visible spectrum, are the liquid dye lasers that have the singular ability to continuously run all the visible spectrum. This is due to the wider wavelength band of the active medium of the dye, which added to the possibility of putting together multiple dyes, completely covers all visible spectrum wavelengths.

In everyday clinical Ophthalmology, it is no longer used but it continues to be useful in the field of Dermatology.

### 3 ULTRAVIOLET LASERS (UV)

In this higher energy band ( $\lambda \leq 400 \text{ nm}$ ) there is clearly a dominating family of lasers – the excimer lasers. All of these (apart from those that do not contain oxygen in their active medium) emit in wavelengths lower than 350 nm.

Table 2 shows a list of the most used excimer lasers and their respective wavelengths. Other lasers emitting in the UV band are the gas lasers. Their wavelengths usually correspond to the secondary bands of ionic and metal vapor lasers, such as the argon laser – various bands from 363.8 nm to 275.4 nm; the krypton laser - 356.4, 350.7 and 337.4 nm; the HeCd laser - 325 nm and the Au laser – 312 nm. Lastly, two other wavelengths should be mentioned regarding the UV spectrum - 354.7 and 266 nm – corresponding respectively to the third and fourth harmonic of the Nd:YAG. As has been previously stated, this can only happen with the use of KDP or KTP crystals through a non-linear mechanism of harmonic generation by tripling and quadrupling the frequency of emitted laser radiation.

### 4 TUNABLE LASERS

There are lasers that can emit at several different wavelengths. When these lasers allow the operator to select the emission wavelength, one can say that the laser is tunable. To allow the operator or laser user the choice of wavelength, there are several techniques that involve changes both inside and outside the laser optical cavity. Next, we discuss two of the main techniques for controlling laser emission wavelength: tuning and selection of lines and generation of harmonics. Another technique is the parametric oscillator,



Table 2. Some excimer lasers and their wavelengths

Excimer	Wavelength (nm)	Excimer	Wavelength (nm)
ArFl	193	F2	157
KrF	248	Kr2	146
XeF	351	Xe2	172
XeCl	308	KrCl	222
ArO	558	KrO	558
XeO	558		

based on parametric amplification, which is a nonlinear phenomenon with theoretical concepts which are rather complex and beyond the scope of this manual, and it is not our current aim to detail this here.

#### 4.1 TUNING AND SELECTION OF LINES

The laser transition model that occurs between two well-defined energy states is too simplistic. In many cases the transition may occur simultaneously between two or more quantum energy states, leading to several types of laser emission. One of these emission types, distinctive of molecular and chemical lasers, is emission into a series of transitions with very narrow spacing. In these molecules, the primary vibrational transition is accompanied by changes in multiple rotational states, so it is possible that these lasers emit in many lines (wavelengths). In some cases, such as the dye laser and some solid-state lasers (the Ti:sapphire), these lines are so close to each other that they create a continuum band, which provides the ability to continuously tune the emitted wavelength<sup>3</sup>.

Another type of emission involve lasers that can emit in a family of transitions simultaneously. This type of emission, very common in ion lasers (argon, krypton, ...), can be designed to emit a single line or to produce a multi-line emission.

Usually, the wavelength can be changed by rotating the dispersive element of wavelengths (a prism or diffraction

grating that is placed either between the mirrors of the cavity or replacing one of those mirrors) so that only one wavelength is aligned with the resonant laser cavity for each position. This method (see Figure 2) is often used to tune dye and CO<sub>2</sub> lasers and to produce a single line in argon and krypton ion lasers<sup>4</sup>.

#### 4.2 GENERATION OF HARMONICS

As mentioned previously in this chapter, we can change the laser wavelength through nonlinear interaction of light with matter. This interaction can generate harmonics which are frequency multiples of the fundamental laser light, or integer fractions of the wavelength (it should be recalled that frequency is inversely proportional to wavelength;  $\omega \propto 1/\lambda$ ). Despite having already reached the 28th harmonic of the 1064 nm of the Nd:YAG laser, for most applications only the second, third and fourth harmonic are produced, because of energy losses. The generation of harmonics is a valuable technique since it can expand the area of wavelengths so that high-power lasers may principally emit in the visible and the ultraviolet areas. As previously seen for the most common case of harmonic generation, an Nd:YAG laser can emit at 532 nm with the second harmonic (green) and at 355 nm and 266 nm with the third and fourth harmonics, respectively (ultraviolet). Doubling the frequency of a dye laser can also achieve a tunable ultraviolet radiation. Moreover, doubling the output frequency of the GaAlAs semiconductor laser, we obtain a blue laser light<sup>4</sup>.

The doublers (harmonic generators) of laser frequency consist of a nonlinear crystal. As a laser beam passes through the crystal, nonlinear interactions between the beam and the material generate an electromagnetic wave at twice the frequency of the laser. To achieve maximum efficiency, the crystal characteristics must correspond precisely to the laser wavelength. This is relatively simple for a single frequency laser such as the Nd:YAG laser; but for tunable lasers such as dye lasers, it is always necessary to adjust the crystal whenever the laser wavelength is changed. There are many nonlinear crystals, with the best known being the dihydrogen potassium phosphate (KDP)

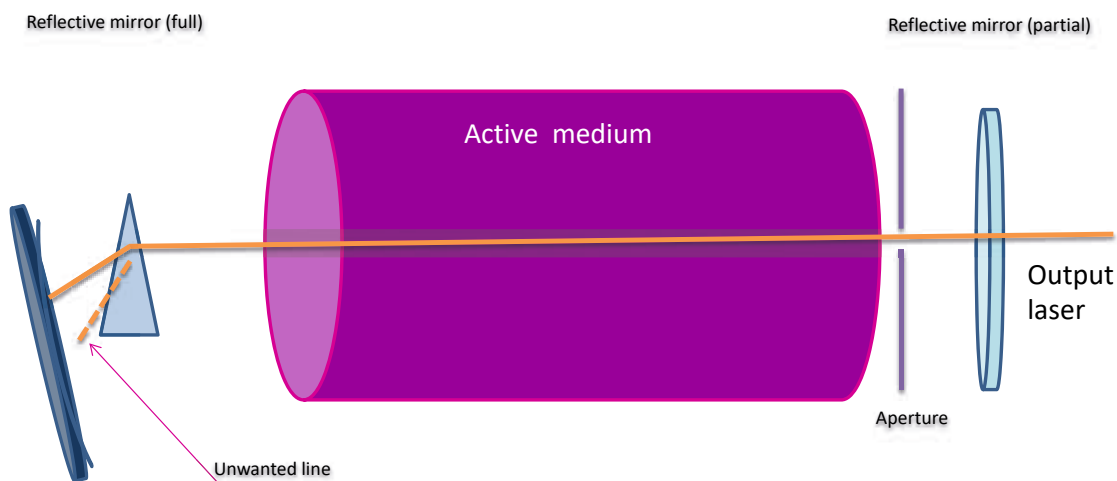


Figure 2. A singular line may be selected using a prism (or other wavelength dispersive devices) placed within the resonant cavity.

## 4. Laser classification based on wavelength

and potassium titanyl phosphate (KTP), but others are also very important such as ammonium dihydrogen phosphate (ADP), lithium borate (LBO) and barium borate (BBO). The magnitude of the nonlinear effect is proportional to the square of the incident laser intensity. Therefore, high power lasers are required to generate harmonics with reasonable efficiency. Often, in order to increase the power level of the crystal, this is put into the laser cavity. However, the doubler crystal can either be placed within the cavity as outside of it. For the generation of the third and fourth harmonics using nonlinear crystals, a multistep process is used. The third harmonic is produced generating the first and the second harmonic ( $2\omega_0$ ). Thereafter, the second harmonic is mixed with the fundamental wavelength ( $\omega_0$ ) in another nonlinear crystal, in order to add the two frequencies, thereby generating the third harmonic ( $2\omega_0 + \omega_0 = 3\omega_0$ ). To produce the fourth harmonic, the beam obtained by the second harmonic generator again goes to another doubler crystal thus quadrupling the fundamental frequency ( $2(2\omega_0) = 4\omega_0$ ).

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# I. The Essential

## 5. Temporal emission

### mode of the LASER



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The temporal behavior of the beam is one of the most critical parameters of laser emission when choosing a laser for medical applications. Moreover, the duration of the laser emission is determinant in the type of interaction that it establishes with biological tissue.

Some lasers emit continuous radiation, maintaining a continuous flow of photon emission, so they are called *continuous-wave* (CW) lasers<sup>1</sup>. Other lasers emit radiation in pulses, and they are called pulsed lasers. Some of the pulsed lasers can emit very short pulses (sub-picoseconds (ps)  $<10^{-12}$ s) and some others emit long pulses (milliseconds). The number of pulses delivered per second is designated as repetition rate. This rate can vary from a very low repetition ( $<1$  pulse per second) up to very high repetition rates ( $>10^9$  per second, or  $>$  gigahertz (GHz)).

Next, we will discuss two methods for laser emission, continuous (CW) and pulsed. As regards the pulsed laser, there are several types of lasers, depending on the system used to create the pulses: gain switching, Q-switching, cavity dumping and mode-locking.

#### CONTINUOUS LASERS (CW)

The lasers can operate in *continuous-wave* mode emitting radiation continuously virtually forever. Bearing this in mind, any laser emission that lasts more than a second is considered *continuous wave*. Although this consideration does not seem very correct from the human point of view, from the physical point of view it is perfectly legitimate, because as long as the laser emission attains a steady state of operation lasting a second, it may be considered as CW. As previously explained, a laser is an optical oscillator comprising of an amplifier (pumped active medium) and of a resonant cavity (two parallel mirrors facing each other). A small amount of radiation is amplified, while passing through the active medium by stimulated emission, and is then reflected back through the amplifier by the cavity mirrors. These mirrors compel the radiation to oscillate back and forth indefinitely until it reaches a

very high concentration level. At this point, a saturation of the amplification gain is achieved, limiting the signal growth. This amplifier saturation occurs when the power of the radiation keeps increasing, leading to a decrease in the available gain. The stable laser emission condition is reached when the amplifier gain is reduced until it evens the losses of the cavity, as well as the radiation emitted by the laser itself (Figure 1)<sup>2,3</sup>. At this point, the gain only compensates the losses and the cycle of amplification and feedback is repeated without changing the steady-state oscillation and the laser emission output remains constant. If we keep the process in this state for a significant period of time ( $> 1$  second) we shall have a laser in *continuous-wave* emission mode.

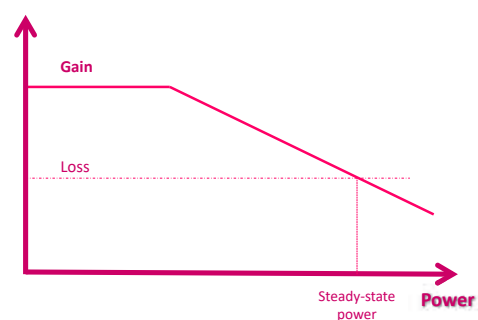


Figure 1. If the gain is greater than the losses, the oscillation in the cavity starts. The amplifier saturates and its gain decreases. The condition for stability is met when the gain equals the loss.

#### PULSED LASERS

For various reasons, many types of lasers can only be made to operate in a pulsed mode. For example, many solid-state lasers must be operated in pulsed mode, due to the need for heat dissipation due to the non-absorbed pump energy. In other cases, the internal physics responsible for laser emission requires the laser to work in pulsed mode.

## 5. Temporal emission mode of the laser

Some of these cases are due to the short lifetime of the population inversion, caused by the rapid decay process in the excited state (such as in excimer lasers) or a rapid increase in the fundamental state population (as in the ruby laser). Furthermore, in the case of high pressure gas lasers, the pulse duration is limited by the inevitable instabilities in the electric discharge pumping the gas. It is normally desirable to vary the "natural" time of a laser pulse. Sometimes, the aim is to broaden the pulse in time. But, in most applications, the aim is to shorten it, in order to be able to extract the highest peak power and the best temporal resolution.

The most direct method for obtaining pulsed laser light is by using a CW laser in combination with a switch or modulator (*shutter*), which only lets light pass for short periods of time. This simple but problematic method has two disadvantages: it is an inefficient system because it wastes the laser power whenever it is blocking the light; and the peak power cannot exceed the stabilized power at the CW source, as illustrated in Figure 2 (a)<sup>3</sup>.

More efficient schemes to create pulsed laser emission modes are based on turning the laser itself on and off, by means of an internal modulation process of the laser emission. This laser modulation process is designed in a way that the energy is stored during the time when there is no laser emission, so that it may later be released, during the emission of radiation towards the exterior of the cavity. The energy can be stored inside the resonant cavity, in the form of radiation that is periodically freed, or it may be stored in the active medium in the form of inverted population, that is occasionally released whenever the system is allowed any oscillation within the

resonant cavity. These schemes make it possible to generate high peak power short pulses, much higher than the power obtained by a CW laser, as can be seen in Figure 2 (b).

The four most common and widespread methods can be used for internal modulation of the laser light. These methods give rise to four types of pulsed laser emission that are designated as *gain switching*, *Q-switching*, *cavity dumping* and *mode-locking*. We shall now further discuss these types of pulsed laser emission.

### A) GAIN SWITCH LASER

This method is based on a very direct approach for modeling the process of laser emission. The gain of the laser amplification is controlled by the turning on and off the pumping system of its active medium (Figure 3)<sup>3</sup>. For example, with the ruby pulsed laser, the pumping (flash lamp) is turned on periodically for brief periods of time, in a sequence of electrical pulses. While the pumping system of the active laser medium is turned on, the amplification gain, within this medium, exceeds the cavity losses, providing laser light emission. This emission is characterized by light pulses, which last the duration of the active medium pumping. The maximum peak power according to this method is limited to the balance between gain and losses through the cavity in a manner analogous to the functioning of continuous lasers.

### B) Q-SWITCH LASER

In this system, the laser emission is cut by a periodic increase in losses in the resonant cavity, with the aid of a modulated absorber inserted inside the laser cavity (Figure 4)<sup>3</sup>. As such,

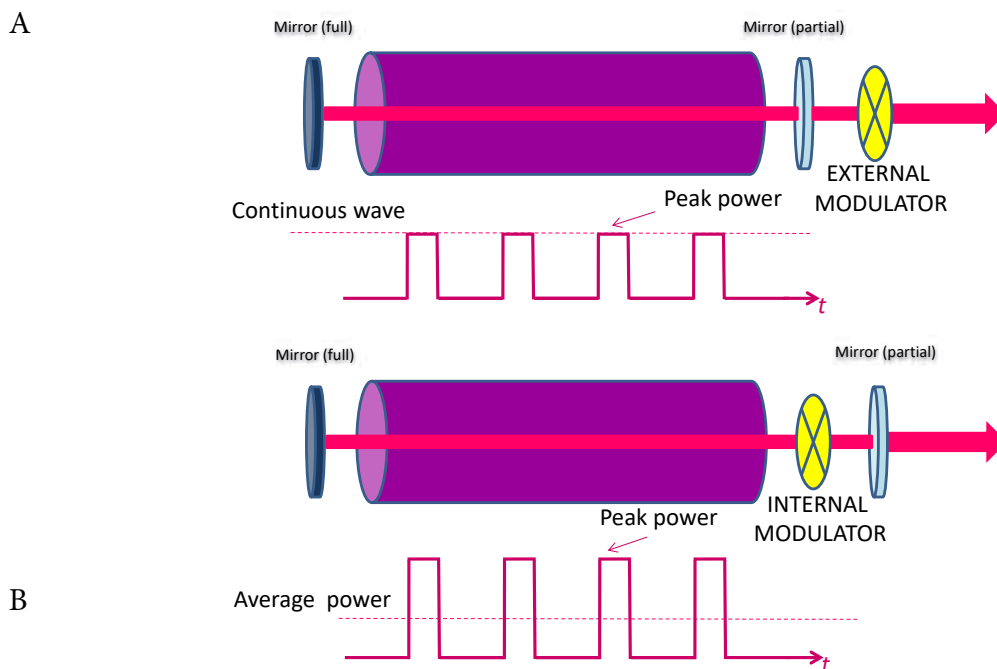


Figure 2. Comparison of output pulse lasers with (A) an external modulator and (B) an internal modulator.

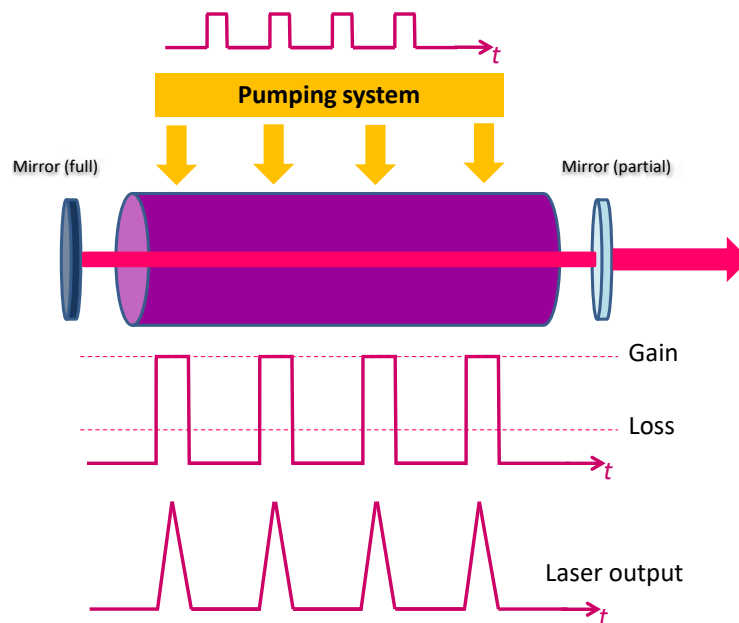


Figure 3. Pulses of a gain switching pulsed laser.

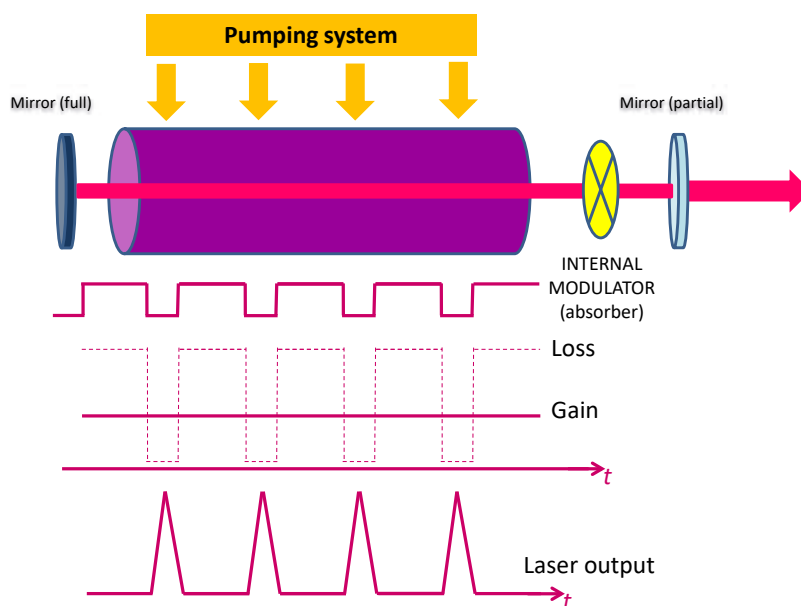


Figure 4. Q-switching.

the Q-switch mode is, basically, a switch linked to losses. During this period of time, when there is no laser emission, due to the losses originated within the cavity, the pumping system continues to inject energy. The latter will keep on being stored in the active medium in the form of an inverted population accumulation. When losses are reduced during laser emission, a large amount of accumulated population inversion is rapidly released, thus generating a very intense pulse of light (which is usually short).

In order to better understand where the name Q-switching came from, we will explain this process of pulsed laser emission by considering the cavity quality factor, Q. Like any oscillator, the laser cavity has a Q quality factor that measures the loss or gain in a cavity. This factor is defined as:

$$Q = \text{Stored energy per passage} / \text{dissipated energy per passage}$$

Typically, the Q factor in a laser cavity is constant. If this Q

## 5. Temporal emission mode of the laser

factor is kept “artificially” low, adding an optical element that will greatly increase the losses in the cavity, the energy will gradually be accumulated in the active medium of the laser, because the energy per passage is almost totally dissipated and there is no radiation oscillation inside the cavity. If, suddenly, this artificial loss is removed, we get a high Q factor cavity and, at the same time, a large amount of population inversion. This way, a high power light pulse is produced with a duration of a few nanoseconds up to hundreds of nanoseconds, from which all the energy accumulated in the active medium will be emitted. This rapid switch of the Q factor in the cavity is called Q-switching.

There are three basic ways to achieve Q-switching, as shown in Figure 5<sup>2</sup>. One consists in using a mirror or prism rotating at the rear mirror location (opposite the output mirror) in the laser cavity. Another way is related to the insertion of a modulator inside the cavity. The third way consists of inserting a non-linear absorbent element in the cavity, which becomes transparent, when a certain amount of energy is attained inside the cavity. The first two techniques are called active Q-switching because they require active control of the system. On the other hand, the third technique is considered passive because, unlike the previous ones, it does not require any sort of control.

The Q-switch performance with a rotating mirror happens as follows: most of the time the mirror is not aligned with the output mirror of the cavity, thereby preventing radiation oscillation. Periodically, this rotating mirror passes the point at which it becomes properly aligned, causing the sudden increase of the Q factor in the cavity, and producing a Q-switched laser pulse. The technique using an optical modulator, which is the most common in Q-switch lasers, blocking one of the cavity mirrors. When the modulator switches to the transparent state, the light can oscillate between the mirrors of the cavity, thereby generating a Q-switch laser pulse. Typically, these modulators are electro-optic or acousto-optic devices.

As for the passive Q-switching, a material with non-linear absorption characteristics is inserted into the laser cavity (typically one cell of a dye solution). This material is highly absorbent when submitted to low levels of light output, thereby blocking, as in the previous case, one of the cavity mirrors. When the pumping energy is pulsed, there is an increase in the light intensity inside the cavity. This light intensity attains such a level that the non-linear absorbent material becomes saturated. At this point, this element becomes transparent, the Q factor soars and the Q-switch laser pulse is produced. This operating mode

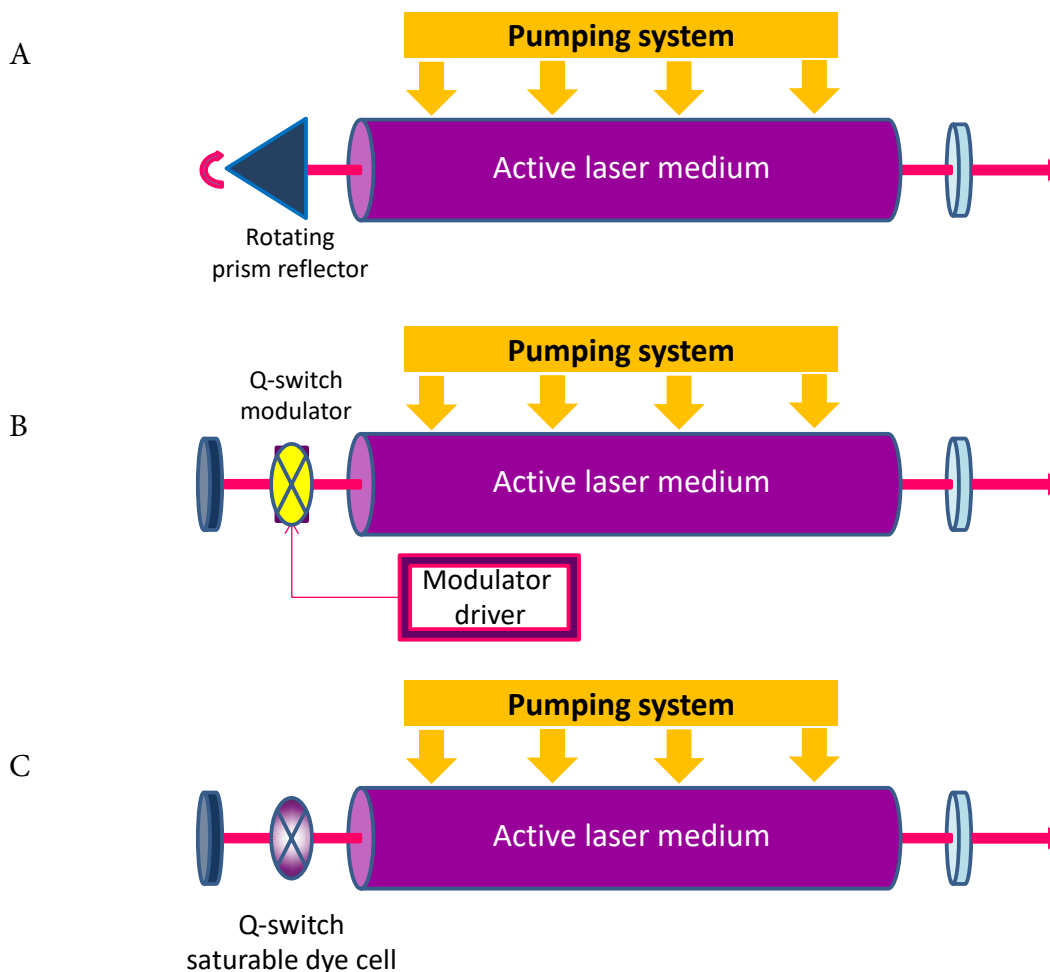


Figure 5. Various types of Q-switch lasers used: (A) rotating mirror or prism; (B) active modulator; (C) saturable dye cell (passive).

of the passive Q-switch is restricted in its use to pulsed pump lasers only. Typically, this method is used in solid-state lasers pumped by flash lamps, such as ruby and Nd:YAG lasers.

The non-linear absorption principle of the passive Q-switches is very simple. The absorption of this material is entirely due to an energy transition between two states of the element of which it is composed (dye molecule). As the light intensity inside the cavity increases, more and more dye molecules absorb light, making the transition into an excited state in which they can no longer absorb any more. These excited molecular states can decay via spontaneous emission, but from a certain time onwards the number of molecules in the excited state will be equal to the number of those in an unexcited state. At this stage, there is as much emission as absorption, so this element will not be able to absorb any more radiation, and we may say it has reached saturation.

The Q-switch pulsed lasers do not increase the pulse energy, but instead they concentrate this energy in a shorter pulse. In this manner, they reach very high peak powers (gigawatts), higher than those normally possible with other pulsed lasers. An inherent limitation to Q-switching is that it only works in the cases of active media, capable of storing energy for a longer period of time than the duration of the Q-switch pulse. This circumstance arises from the fact that the lasing species is responsible for the accumulation of energy, while maintaining its excited state. This is only possible if the lifetime in this excited state is relatively long. Thus, not all

active laser media can emit radiation in the Q-switch mode.

### C) LASERS WITH CAVITY DUMPING

This technique is based on the accumulation of light radiation (rather than on population inversion) in the cavity, which is then fully released, when the laser pulse emission takes place. In spite of achieving a similar result, this technique is quite different in principle from the previous Q-switch technique. The main difference lies in the fact that the energy storage is kept not in the active medium but in the resonant optical cavity. The issuance of the laser pulse occurs when the cavity loses the accumulated radiation. In this case, the modulation of these losses is obtained by the deflection of the radiation out of the cavity or allowing it to pass through the output mirror, rendering it suddenly transparent (Figure 6)<sup>3</sup>. This cavity dumping system behaves like a bucket that keeps on storing water, coming from a tap in a steady stream with its bottom being removed all of a sudden, releasing all the accumulated water at once. As far as this analogy is concerned, the resonant cavity is represented by the water bucket, the tap represents the constant pumping, water acts as the accumulated radiation (photons) and the bucket bottom represents the system, which expels all the radiation - stored up until that moment - from the cavity. The two total reflecting mirrors do not allow the light to flow away from the resonant cavity during the storage. This results in a resonant cavity with almost negligible losses, which causes the flowing power boost inside the

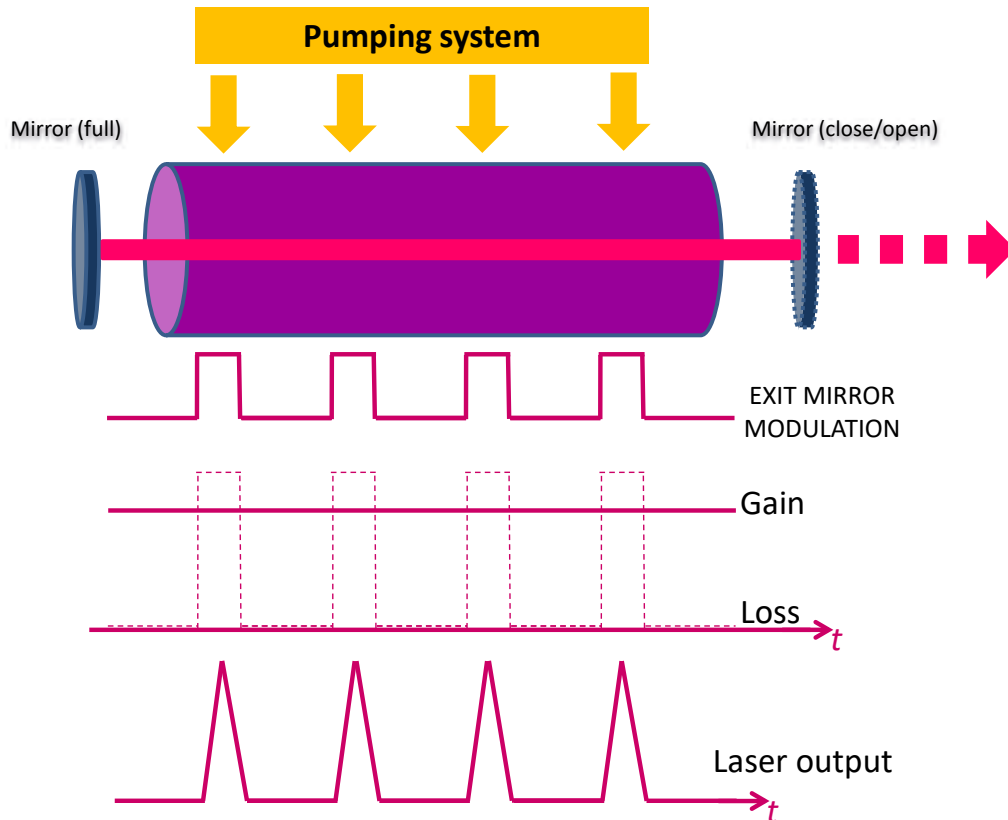


Figure 6. Cavity dumping. The output mirror is removed releasing all the radiation stored up in the cavity.

## 5. Temporal emission mode of the laser

laser. This intense flowing-power may be removed from the cavity by a deflection process. The result is a powerful pulse lasting nearly the same time needed for the light to make 1-round-trip in the cavity.

Usually, the cavity dumping system occurs in two ways. One is based on an acousto-optic deflector placed in the cavity, and whenever it is activated it deflects light away from it, thus producing the laser pulse. Another approach, also widely used, involves an electro-optic modulator and a polarizing beam splitter. When the modulator is turned off, the linearly polarized light remains in the cavity without being affected by the beam splitter. However, when the modulator enters into action, the polarization of the light passing through it undergoes a rotation process and is then reflected outwards, away from the cavity, by the polarizing beam splitter.

This cavity dumping system can be used in continuous CW lasers, in which energy cannot be stored in the excited levels of the active medium and, therefore, the Q-switch system cannot be used. Cavity dumping can also be combined together with other pulsed laser emission modes, such as the Q-switch and the mode-locking (blockage of modes) to produce pulses with particular characteristics.

The cavity dumping of a continuous CW laser can generate pulses of the order of tens of nanoseconds and at a megahertz-level repetition rate. Typically, these pulses are shorter than the Q-switch ones and the repetition rate is higher displaying, however, a lower peak intensity.

### D) MODE-LOCKING LASERS

Pulses in the picosecond ( $10^{-12}$  s) and femtosecond ( $10^{-15}$  s) regime can be generated by the mode-locking process. A

very simplistic view of the pulses of a laser in mode-locking is to imagine a group of photons attached to each other and moving as a block, while oscillating inside the laser cavity. Each time this group strikes the semi-transparent mirror output, part of the photons will be emitted as an ultra-short pulse. Next, the remaining photon group in the cavity make a round-trip, before once again hitting the output mirror, emitting another pulse<sup>3</sup>. Therefore, the pulses are temporally separated by an oscillation time in the cavity given by  $2d/c$ , in which  $d$  corresponds to the cavity length and  $c$  represents the speed of light.

The mode-locking technique is quite distinct from the three previous ones. Here the pulsed laser emission is obtained by coupling modes in the laser cavity and locking their phases between themselves. A laser can oscillate on many longitudinal modes with frequencies that are equally distant by means of the spacing modes  $\nu_f = c/2d$ . This frequency separation, as far as the modes are concerned, corresponds to the wavelengths that are submultiples of the laser length in the cavity  $2d$ , that is to say, the wavelengths multiplied by an integer ( $n = 1, 2, 3, \dots$ ) are equal to the laser length in the cavity  $n\lambda = 2d$ , according to which  $\lambda$  is the wavelength of the longitudinal mode  $n$  in the optical cavity (Figure 7). A resonant optical cavity has infinite modes of oscillation, but a laser only interacts with those which fall within the spectral band of the emitted radiation, that is to say, within the zone of radiation frequencies that the active medium is able to amplify by stimulated emission (Figure 8)<sup>3</sup>.

Although these modes normally oscillate independently (known as free modes) by means of an external action, we can couple them and keep them together in phase. Then, these modes can be viewed through what is known

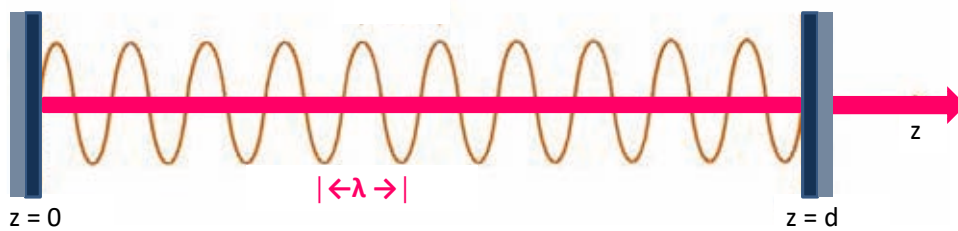


Figure 7. A resonant cavity mode showing a  $\lambda=2d/20$  wavelength.

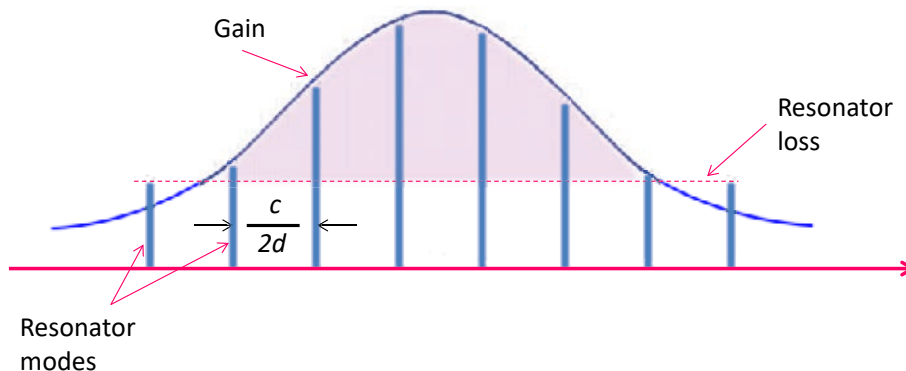


Figure 8. The modes in the cavity that are covered by the spectral bandwidth of the laser gain.

in mathematics as the components of a Fourier series expansion of a periodic signal in time obeying:  $Tf = 1/vf = 2d/c$ , which consists of a pulse train. The period of this pulse train, as mentioned earlier, is equal to the time an oscillation takes in the resonant cavity. In fact, the radiation of a mode-lock laser can be viewed as a short pulse of photons, being reflected back and forth between the cavity mirrors (Figure 9)<sup>3</sup>.

If we have a large number of  $M$  locked modes in phase, they form a giant short pulse that oscillates back and forth in the cavity. The pulse duration of  $t_p$  is a factor  $M$  times smaller than an oscillation period in the cavity  $t_p = 2d/c / M$ . Let us proceed with the issue of how to lock modes in a way that they all share the same phase. This can be achieved with the help of a switch or modulator placed within the resonant cavity. Supposing an optical switch is located within the laser cavity, blocking the light all the time, except when the pulse is about to cross it. In this way, it will only remain open for its passage (Figure 9). As the pulse itself can pass through the optical switch, it will not be affected by its presence and the pulse train keeps on going uninterruptedly. In the absence of mode-locking, the individual modes display different random phases in their fluctuations. If, accidentally, the phases of the modes coincide, the sum of the oscillating radiation of the modes will form a giant pulse, which will not be affected by the optical switch. Any other combination of the phases of the modes would form a distribution of radiation that is totally or partially blocked by the switch. Thus, in the presence of the optical switch, only the modes which are in phase with it, and so in phase with the others, will be able to oscillate in the cavity and so emit light. The mode-lock laser is held on

until the coincidence of the phases of the ways happens, but once the occurrence begins they always remain in phase. The modulation may either be active, changing the transmission of an electro-optical modulator, for example, or it may be passive as a result of a saturation effect similar to the one mentioned about the passive Q-switching device. Here, the oscillation can only occur when the phases of modes are added to form an intense pulse to saturate the non-linear absorber which will thereby let it pass.

The mode-locking requires a laser to oscillate on many longitudinal modes. Therefore, this method is not valid for many gas lasers with narrow spectral lines. However, it can be used with respect to argon ion and krypton lasers, solid-state crystal lasers, semiconductor lasers and dye lasers (which, as we have already seen, have an unusually broad spectral band). The pulse duration is inversely proportional to the number of laser modes and, hence, the spectral width of the laser emission. Therefore, broad spectral gain width lasers can generate ultra-short pulses of the order of femtoseconds ( $10^{-15}$  s), such as the Ti:sapphire solid-state lasers<sup>4</sup>.

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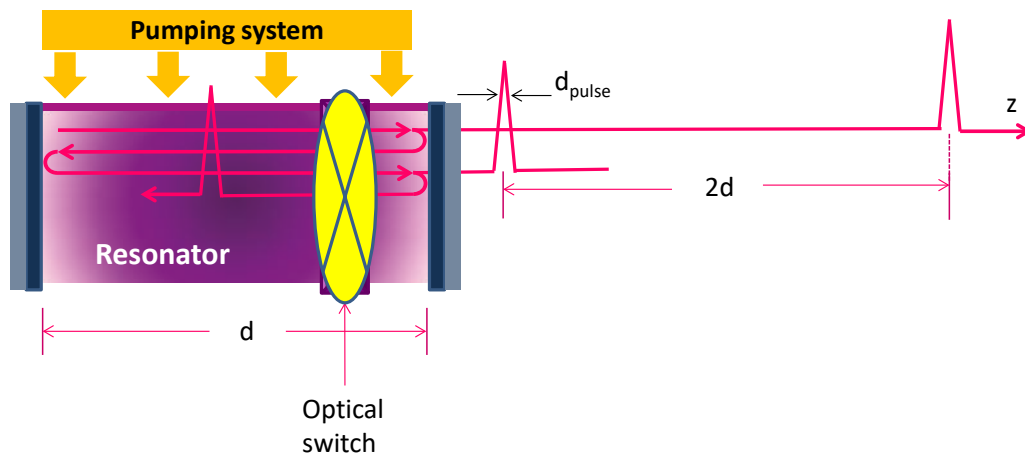


Figure 9. The mode-locked laser pulse is reflected to and fro between the mirrors in the resonant cavity. Each time it reaches the output mirror, a short pulse is transmitted. The transmitted pulses are separated by the distance  $2d$ . The optical switch only opens when the pulse hits it, letting it pass through. Any other wave pattern suffers heavy losses and is prevented from oscillation.





# I. The Essential

## 6. Beam shape



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One of the most important laser parameters in medical applications has to do with the cross-beam shape and its propagation. This parameter reflects the laser beam quality and is given by the transversal distribution of intensity. This distribution is the result of transverse modes in the laser resonant cavity, in the same way that the longitudinal modes are related to the frequency (wavelength) of the laser<sup>1-4</sup>.

### TRANSVERSE LASER MODES (TEM)

The spatial distribution of the emitted light from a laser depends on the resonant optical cavity geometry and the shape of the active medium. So far in this discussion, we have ignored the cross space effects, assuming that the optical resonant cavity was formed by two mirrors arranged in parallel planes, infinitely extended, and the space between them was completely filled by the active medium. Bearing in mind this idealistic geometry, we would have a laser beam output infinitely wide and uniform (plane wave) to propagate along the optical axis of the cavity. It is quite obvious that, in addition to this, mirrors cannot be infinitely extended and the active medium does often does not fill the entire space between them, as a flat mirror cavity is extremely sensitive to misalignments. This type of cavity is considered marginally stable. For stable resonant cavities, there must exist a certain focus of radiation inside the cavity and, for this to happen, the most common process is the use of concave spherical mirrors. The condition for an operational stable resonant cavity is reached when a light beam, which, though not perfectly aligned with the optical axis of the cavity, is continually reflected in the mirrors, remaining inside the laser cavity. The use of concave spherical mirrors is the most common way to satisfy this stability condition.

If one or more curved (non-flat) mirrors are used in the cavity, the wavefronts (imaginary surface of equal phase) will no longer be flat (as in the case of a plane wave) and will have a finite radius of curvature, in order to match the curvature of the mirrors (Figure 1)<sup>1</sup>.

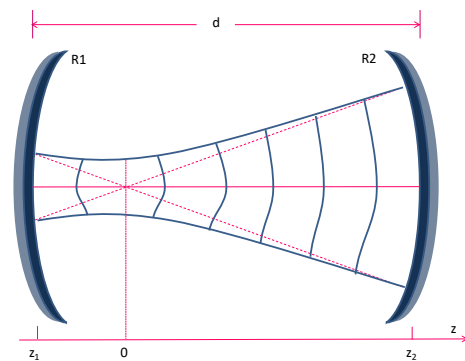


Figure 1. A Gaussian beam with wavefronts that match the curvature of the concave mirrors of the cavity.

This is the condition that will define the transversal distribution of the beam intensity inside the cavity. There are various solutions to this condition and we call them transverse electromagnetic modes of the cavity (TEM – *Transverse Electromagnetic Modes*). Mathematically, these transverse modes are, no more, no less than the mathematical functions that are the solution to a differential equation, which is called the paraxial Helmholtz equation, which physically describes the functioning of this type of resonant cavity.

Figure 2 provides an illustration of the transverse distribution of these functions, called Hermite-Gaussian functions. Terminology exists for each type of distribution given by these functions, which are the transverse modes  $TEM_{lm}$ , where each pair of indices ( $l$ ,  $m$ ) defines the transverse mode and its spatial distribution. The  $TEM_{00}$  mode is simply called the Gaussian beam. Higher index modes, or a combination of them, form the Hermite-Gaussian beams. If we carefully observe the distributions shown in Figure 2, we will see that these indices are, no more, no less than the number of nodes (intensity zero) that appear in each of the directions of the laser beam cross-section. In most applications, the  $TEM_{00}$  mode, i.e. the Gaussian beam, is the most desirable, however, multimode beams can usually be

# 6. Beam shape

more powerful, because they cover the whole active medium section more evenly. Although these multimode beams are of inferior quality when compared to the Gaussian beam, this commitment “quality versus energy” can be acceptable for certain applications<sup>1</sup>.

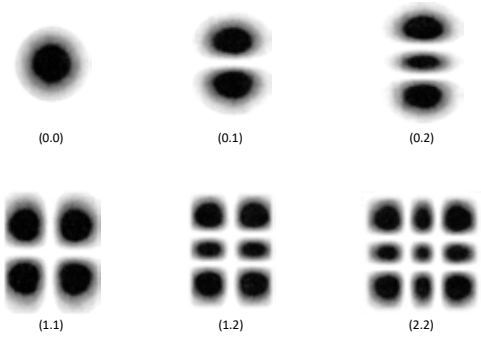


Figure 2. Distribution of intensities of a few Hermite-Gaussian bundles on a transverse plane. The pair of indices (l, m) is indicated for each of the transverse modes.

The standards of different transverse modes discussed earlier are visible only in the so-called *near field*, which means close to the laser output. However, when the beam is transmitted in space, the distribution becomes increasingly uniform, due to the divergence of the beams. So away from the laser, in the so-called *far field*, the non-uniformity of the transversal distribution beam is smoothed.

The intensity distribution of these modes is not merely a mathematical curiosity. It is extremely important for laser-tissue interaction and, in particular, for laser surgery. If we want a small focal point to become powerful enough to vaporize tissue, without affecting the adjacent tissue, this focal point must be the smallest possible. In order to efficiently achieve focusing and high power densities, it is usually advantageous to use a Gaussian beam (TEM<sub>00</sub>).

### GAUSSIAN BEAM (TEM<sub>00</sub>)

For most applications, the geometric properties of beam diameter and its divergence are more important than the structure of the modes. Thus, the Gaussian beam through transverse mode TEM<sub>00</sub> is usually the most desirable for medical applications and other applications as well. The distribution of intensity for this mode is given by the following<sup>1</sup>:

$$I(r) = I_0 e^{-2\frac{r}{w^2}}$$

Where r is the radial distance and I<sub>0</sub> is the maximum intensity in the center.

This is called the Gaussian beam because its shape is given by the mathematical Gaussian function. The schematic graph displaying this function is shown in Figure 3<sup>3</sup>.

The Gaussian beam power is obtained by integrating the distribution of intensities in a particular area. Thus, 90% of the total beam power is contained in a circle of radius w centered within the beam. The quantity D = 2w is,

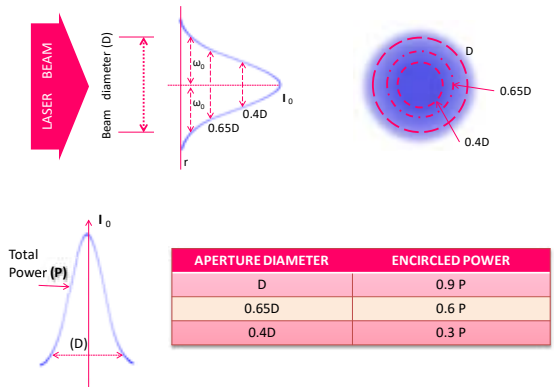


Figure 3. The Gaussian laser beam: intensity distribution.

therefore, designated as the beam diameter (Figure 3). As the beam propagates, its diameter increases. This phenomenon is called the beam divergence (Figure 4)<sup>3</sup>.

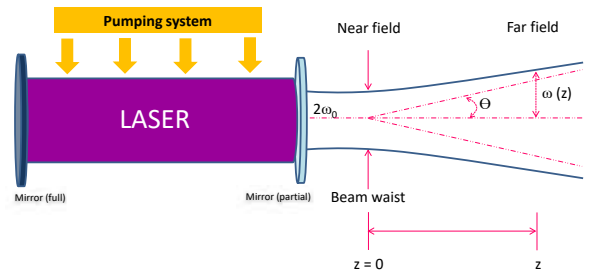


Figure 4. The Gaussian laser beam: divergence.

Normally, there is a special plane at which the beam diameter is minimal, called the *beam waist*, the radius of which is w<sub>0</sub>, and it is usually located inside the laser cavity or very close to it. If z is the distance along the axis of propagation from this focal point (w<sub>0</sub>), then the beam radius can be calculated by the following formula<sup>1</sup>:

$$w(z) = w_0 \left[ 1 + \left( \frac{z}{z_0} \right)^2 \right]^{1/2}$$

In which  $z_0 = \frac{\pi w_0^2}{\lambda}$  where we can see the focus depth (also called the Rayleigh distance) of the Gaussian beam with wavelength λ.

From here we can say that for distances away from the focal point (z >> z<sub>0</sub>) the beam divergence θ (half of the divergence angle) is given by the following equation:

$$\theta = \frac{\lambda}{\pi w_0}$$

This is schematically illustrated in Figure 4, in which θ is measured in radians and the total beam divergence is given by 2θ. As this ratio indicates, the beam divergence can be reduced by using a larger aperture for the laser

output, to increase the beam diameter at the focus point ( $2w_0$ ), or by changing to radiations of shorter wavelength. A Gaussian beam of a *CO2* laser, in the same circumstances, is typically ten times more divergent than a Gaussian laser beam for a *Nd:YAG* laser, due to the wavelength of the *CO2* laser ( $\lambda = 10.6 \mu\text{m}$ ), which is ten times higher than the *Nd:YAG* laser ( $\lambda = 1.064 \mu\text{m}$ ).

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# I. The Essential

## 7. Output energy and power

Units of measurement of the LASER beam and LASER utilization parameters



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The laser emission parameters, which are relevant to medical applications, are related to the amount of output radiation that a laser can emit from its cavity. The two physical quantities that characterize the amount of radiation are laser energy and power.

Energy in Physics is usually defined by the capacity to produce work. The energy of a luminous radiation can be defined by the sum of the energy of the photons (quanta or light particles) that compose it. Each photon has an associated energy  $E = h\nu$ , where  $h$  is Planck's constant and  $\nu = c/\lambda$  is the frequency of the photon that has a wavelength  $\lambda$  ( $c$  is the speed of light in vacuum). Because laser emission is monochromatic (with a single wavelength), the energy of the emitted radiation is directly proportional to the number of output photons. The unit of measurement for energy more frequently used in the world of lasers is the joule (J).

On the other hand, power ( $P$ ) is defined by the energy ( $E$ ) released per unit time ( $t$ ),  $P = E/t$ . The unit of measurement most commonly used to characterize this quantity is the watt (W), so one watt is equivalent to one joule per second. Bearing in mind the number of photons, the power of a laser is given by the flux of photons emitted by that laser. The power specified by a laser manufacturer is quite different from that specified by the manufacturer of common lightbulbs. The power of a common lightbulb is given by the consumed electric power and not by the luminous power that it irradiates. In lasers what is usually specified is the power of the emitted radiation, although they also convert electrical energy to light.

These concepts can also be applied to pulsed lasers. A pulsed laser emits a series of pulses of duration  $\tau$  and the repetition rate  $f$  is given by the number of pulses per second. Therefore, the interval of time between each pulse is  $T=1/f$ . If each emitted laser pulse has an energy  $E_{pulse}$ , the power during the time of emission is  $P = E_{pulse}/\tau$ . This pulse power is called peak power. The average power

is, however, given by the sum of the energy of the pulses emitted during one second, in other words, the pulse energy is divided by the period of repetition  $P_{average} = E_{pulse}/T$ .

In pulsed lasers with high peak power, given by short pulses, and with a low repetition rate, such as the *Nd:YAG* for example, we should not talk about laser power but rather about pulse energy. In these cases, which are very frequent in solid-state lasers, the average power is very low in relation to the peak power of the laser pulse. So, it is more natural in this kind of laser to separately specify the pulse energy, duration and repetition rate to characterize the emitted radiation. On the other hand, for continuous CW lasers or pulsed lasers with very high repetition rates, the quantities used to characterize the laser output radiation are the power or average power, respectively. In Tables 1 and 2, we can see the typical powers of various medical continuous and pulsed lasers, as well as the main parameters of laser emission<sup>1-6</sup>.

The output power of commercial continuous CW lasers ranges from milliwatts to tens of kilowatts. These powers are also comparable to the average powers of pulsed lasers. Typically, these powers are generally limited by the energy transfer processes. In gas lasers, the kinetic processes necessary to keep the population inversion and the stimulated emission may be unsustainable for great volumes and/or pressures. In solid-state lasers, heat dissipation may create major problems, as we have already stated. Until now, the highest continuous or average registered powers, about two megawatts, were produced by chemical lasers with military purposes. Another power record is the peak power of a pulsed laser. These lasers, called ultra-intense, have a pulse duration of the order of subpicoseconds and can reach peak powers higher than Petawatts ( $10^{15}$ W). This kind of laser is being developed not only with military purposes in mind but also for research in several branches of Physics: inertial fusion, particle acceleration, X-ray generation, etc. In Portugal,

## 7. Output energy and power

Table 1. Properties of Continuous Lasers (CW)

Laser (general)	Wavelength	Laser medium	Maximum power
HeCd	325.0 nm	Gas	50 mW
	442.0 nm		150 mW
Ar ion	488.0 nm	Gas	20 W
	514.5 nm		
Kr ion	413.1 nm	Gas	5 W
	530.9 nm		
	647.1 nm		
Dye (Ar pumped)	400-1000 nm	Liquid	2 W
HeNe	632.8 nm	Gas	50 mW
GaAlAs	750-900 nm	Semiconductor, single laser,	100 mW
		array of lasers	10 W
Nd:YAG	1060 nm (1.06 $\mu\text{m}$ )	Solid state	600 W
HF	2600-3000 nm	Chemical	150 W
	(2.6-3.0 $\mu\text{m}$ )		
CO <sub>2</sub>	10600 nm (10.6 $\mu\text{m}$ )	Gas	100 W

Table 2. Properties of Pulsed Lasers

Laser (general)	Wavelength	Laser medium	Pulse duration	Maximum energy (J per pulse)	Maximum repetition rate (Hz)	Maximum average power (W)	
Excimer	193 nm	ArF gas	5-25 nsec	0.5	1000	50	
	249 nm	KrF gas	2-40 nsec	1	500	100	
	308 nm	XeCl gas	1-300 nsec	1.5	500	150	
	351 nm	XeF gas	1-30 nsec	0.5	500	30	
Dye: Ar pumped	400-1000 nm	Liquid dye	3-50 nsec	0.1	100	10	
flash pumped	350-1000 nm	Liquid dye	0.2-30 $\mu\text{sec}$	50	50	50	
Metal vapor	628 nm	Au vapor	15 nsec	$10^{-4}$	$10^4$	1	
Semiconductor (AlGaAs)	750-1550 nm	Single junction	0.2-2 $\mu\text{sec}$	$10^{-4}$	$10^4$	0.1	
		Array of lasers	2-200 $\mu\text{sec}$		100	1	
Nd:YAG	1.06 $\mu\text{m}$	Solid	10 nsec	1	20	20	
Er:YAG	2.94 $\mu\text{m}$	Solid	200 $\mu\text{sec}$	2	20	30	
HF	2.6-3 $\mu\text{m}$	Chemical	50-200 nsec	1	20	3	
CO <sub>2</sub> pulsed	10.6 $\mu\text{m}$	Gas	10 $\mu\text{sec}$ - 10 msec	5	1000	100	
		waveguide	Gas	1 $\mu\text{sec}$	0.01	5000	50
		TEA	Gas	20 nsec - 10 $\mu\text{sec}$	150	1000	30

we have one of these lasers at the *Instituto Superior Técnico* and it can reach multi-terawatts ( $>10^{12}\text{W}$ ), with a pulse duration of hundreds of femtoseconds and with a repetition rate of one shot (pulse) every two minutes. Currently, the highest peak power operating lasers already exceed the Petawatt (1000 terawatts) level.

### LASER UTILIZATION PARAMETERS FOR MEDICAL APPLICATIONS

Besides the laser emission parameters, which characterize the output of the emitted radiation of a laser, there are other parameters that characterize the way a laser beam is applied, for example, in laser-tissue interaction. We can call them Laser Utilization Parameters, and they are the following: exposure surface, power density (or irradiance), radiant exposure (or fluence), radiant energy density (or dose) and exposure time<sup>2,3</sup>.

Because of its small divergence, we may consider that a light beam emitted by a laser is parallel. At its output, the beam diameter is defined by the beam opening, as we have seen before. However, aided by focusing elements, such as lenses and curved mirrors, we can easily change the shape of the beam, increasing or decreasing its diameter and divergence, according to its application. By changing the beam diameter, we are basically molding the area of action of the laser beam in the object in which it is being applied (biological tissue, in the case of medical lasers). This area is called the **exposure surface** and is defined by the *transversal section of the laser beam when it hits the interaction zone*. This parameter is fundamental to determine power and energy densities. The ratio of the emitted power ( $P$ ) to the exposure surface area ( $A$ ) is called the **power density or irradiance ( $I$ )**. The unit commonly used to measure the power density  $I = P/A$  is  $\text{W}/\text{cm}^2$ .

A laser beam may operate intermittently or the laser power applied to a given surface may vary with time. The *total applied energy divided by the exposure surface area* is called the **radiant exposure or fluence**. The unit in which radiant exposure is measured is  $\text{J}/\text{cm}^2$ . This is one of the most important parameters for laser therapy, as we will see later. If, besides the exposure surface, we take into account the depth to which the radiation penetrates a tissue, we can define a volume where the laser radiation is deposited. The laser energy delivered, divided by this volume, is called **radiant energy density or dose** and the usual unit is  $\text{J}/\text{cm}^3$ .

All of the relevant effects with medical application in laser/tissue interaction can be obtained with radiant exposure (fluence) between  $1 \text{ J}/\text{cm}^2$  and  $1000 \text{ J}/\text{cm}^2$ . This is relatively surprising because the power density (irradiance) itself may vary more than fifteen orders of magnitude.

Therefore, only one parameter is important to distinguish and control all these effects, which is the *duration of exposure to the laser radiation in the tissue*, also simply called the **Exposure Time**.

To illustrate this, in Figure 1 we have a map of logarithmic scales with the five basic types of laser-tissue interaction. In the ordinate axis we have the irradiance in  $\text{W}/\text{cm}^2$ . The abscissa axis represents the exposure time in seconds. Two diagonal straight dashed lines show constant densities of energy at  $1 \text{ J}/\text{cm}^2$  and  $1000 \text{ J}/\text{cm}^2$ , respectively. According to the graph,

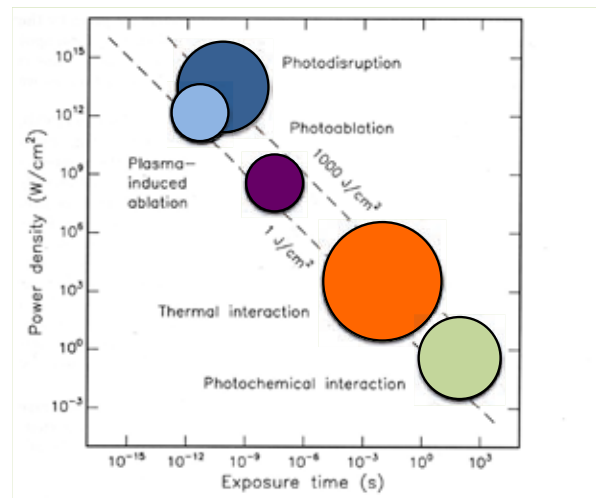


Figure 1. Map of laser-tissue interactions. The circles only give an approximate estimate of the associated laser parameters.

the time scale may be divided into four sections: CW exposures of  $> 1 \text{ s}$  for photochemical interactions, from 1 minute to  $1 \mu\text{s}$  for thermal interactions, from  $1 \mu\text{s}$  to  $1 \text{ ns}$  for photoablation, and  $< 1 \text{ ns}$  for plasma-induced ablation and photodisruption. The difference between these latter two interactions is determined by different radiant exposures. The reciprocal correlation between irradiance and exposure time clearly demonstrates that the same energy density is necessary to obtain any of the interaction types. Therefore, the exposure time is the main parameter in laser utilization that characterizes the different mechanisms of laser-tissue interaction<sup>1-6</sup>.

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# I. The Essential

## 8. LASER-tissue interaction

# Photothermal Effects



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### INTRODUCTION

Thermal effects are particularly associated with the absorption properties of biological tissues and occur as a stepwise process<sup>1</sup>. At the molecular vibration-rotation level, the absorption of a photon promotes the molecule to an excited state (absorption), which is followed by inelastic collisions with some partner molecules of the surrounding medium, leading to the deactivation of the excited molecule and the simultaneous increase in the kinetic energy (deactivation) leading to a temperature increase<sup>1,2</sup>.

Photothermal effect laser tissue interaction occurs when laser energy is absorbed by the target tissue and converted into heat. The effect depends on the magnitude and the rate of temperature elevation<sup>1-4</sup>.

Photothermal effects consist of a large group of laser tissue interaction types, which cause local temperature elevation. According to the peak value, specific laser-tissue interaction effects can occur: hyperthermia, photocoagulation, vaporization, carbonization or melting<sup>1</sup>.

### PHOTOTHERMAL LASER TISSUE INTERACTION

Laser parameters and optical properties of biological tissues determine if photothermal effects predominate when laser light interacts with biological tissues. The extension and type of lesion are also influenced by the thermic properties of tissues<sup>1</sup>.

#### A) LASER PARAMETERS

Several laser parameters need to be taken into account in order to achieve a particular photothermal effect:

- Wavelength
- Power Density or Irradiance
- Exposure Time
- Spot Size
- Repetition Rate

**Wavelength** of the beam determines how effectively

will laser radiation be absorbed and scattered and consequently how deep it will penetrate into the tissue.

**Power Density** – all effects medically relevant are achieved at power densities between 1 J/cm<sup>2</sup> and 1000 J/cm<sup>2</sup>.

**Exposure Time** is the duration of laser radiation and a key parameter determining the type of laser interaction with biological tissues. This can be broadly considered to be a thermal as well as a non-thermal effect. The “1 μs rule” postulates that laser pulse durations that are longer than 1 μs are often associated with measurable thermal effects, whereas exposures of less than 1 μs will become negligible. Only shorter laser pulses allow other types of interactions<sup>1,2,5</sup> (Figure 1).

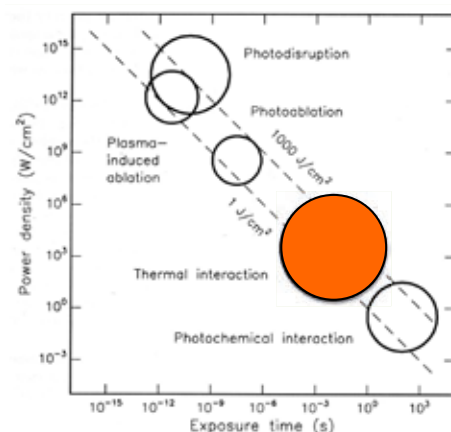


Figure 1. Laser-tissue interactions. Influence of Exposure Time and Power Density (adapted from Niemz<sup>1</sup>).

**Applied intensity** is the ratio between power density and pulse duration. Changes in spot diameter, pulse duration and repetition rate result in different power densities<sup>1</sup>.

## 8.LASER-tissue interaction Photothermal Effects

### B) OPTIC CHARACTERISTICS OF BIOLOGICAL TISSUES

When biological tissues are exposed to laser light, several effects occur as a result of their optical properties:

- Reflection and refraction
- Absorption
- Scattering

**Refraction** can play an important role when irradiating transparent tissues, such as the cornea.

As the absorption coefficient and the scattering coefficient are relevant optical properties of opaque tissues, refraction assessment becomes impossible.

**Absorption** is mainly associated with the presence of free water molecules, pigments and other macromolecules in biological tissues. As an important biological tissue constituent, water molecules play a central role in the effects of laser-tissue interaction. The absorption coefficient is associated with the laser radiation wavelength and its absorption by water molecules. Water is a dominant absorber in the infrared range of the spectrum as opposed to the visible spectrum and ultraviolet range. There is an absorption peak at 3  $\mu\text{m}$  related to symmetric and asymmetric vibrational modes of water molecules. The Er:YAG (2940 nm) and Er:YSGG (2780 nm) lasers typically represent these thermal lasers. Ho:YAG lasers also have a similar absorption peak of water (2120 nm) (Figure 2). Similarly, a thermal absorption peak is seen at 10.6  $\mu\text{m}$ , corresponding to the CO<sub>2</sub> laser wavelength.

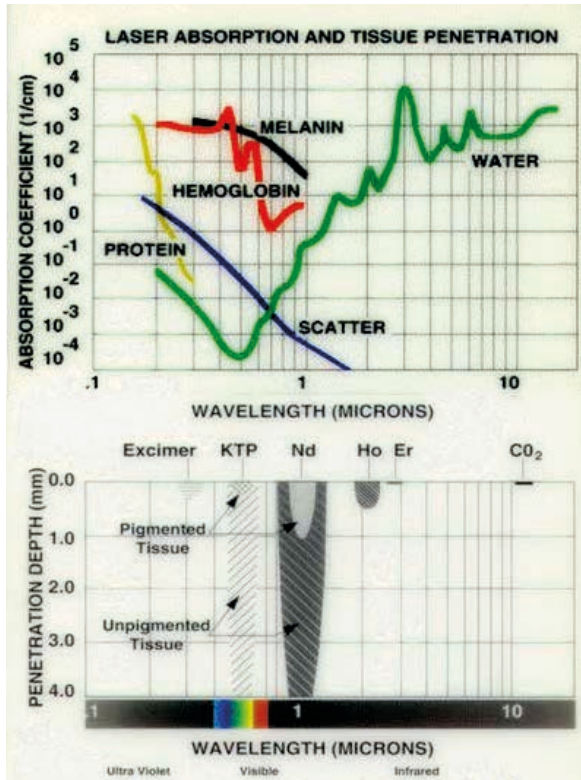


Figure 2. Absorption coefficients and optical penetration depth of water molecules and other tissue components correlated with several laser wavelengths. Courtesy of Coherent-Lumenis.

**Scattering** is the dominant mechanism by which light is homogeneously distributed within tissues<sup>1,2,6</sup> (Figure 3).

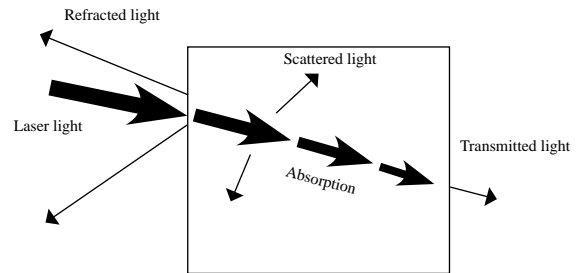


Figure 3. Interaction Laser (light) –Tissue (matter) (adapted from Niemz<sup>1</sup>).

### THE THREE STAGES OF THE PROCESS OF TISSUE HEATING AND THERMAL EFFECT

Three steps are described in the heating process and tissue damage (Figure 4):

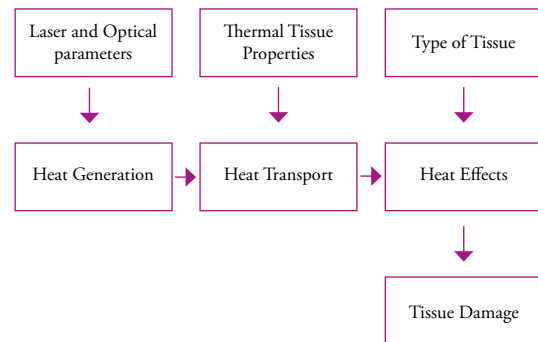


Figure 4. Photothermal interaction model (adapted from Niemz<sup>1</sup>). Heat generation is dependent on laser and optical parameters. Heat transport is dependent on thermal tissue properties. The effects of heat in tissues are dependent on each type of tissue and the characteristics of its biological pigments: melanin, hemoglobin, xanthophyll, water and, possibly, others. These are all responsible for heat absorption.

1. **Optical stage** - heat is generated by a process of photonics energy absorption by molecules. This absorption causes molecular excitation (collision with adjacent molecules) corresponding to kinetic energy and vibration (Figure 4). During photothermal laser interaction (Figure 5), the absorbed photons that have been converted into heat, increase local tissue temperature.

Tissue transmission or penetration depends on the absorption and scattering coefficients of biological pigments, which act as endogenous absorbers. Hemoglobin, melanin and xanthophyll are pigmented targets for laser irradiation. There is a selective absorption by pigmented tissue structures, such as melanosomes, the pigmented retinal epithelium and red blood cells.

Pigments may also be artificially introduced into tissues as it is done in photodynamic therapy (PDT) where the edges of the blood vessels are artificially pigmented with a protein containing indocyanine green dye, which

selectively absorbs the optical energy of a near-infrared diode laser (810 nm).

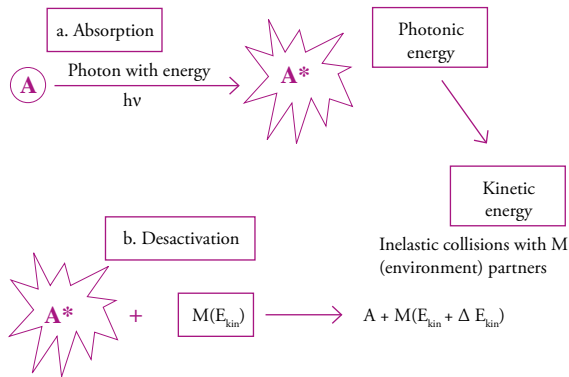


Figure 5. Photothermal effect – optical stage.

2. A **thermal or heat transport stage** follows, responsible for cooling the primary heat source and heating neighboring tissues. The heat diffusion from the irradiated target to a surrounding area is dependent on the thermal properties of tissues, in particular the thermal diffusion coefficient and thermal capability. In biological tissues which are rich in water, the thermal diffusion coefficient approaches that of water. At this stage the resulting heated volume is bigger than the primary heat source.

So as to minimize unwanted thermal damage to the surrounding ocular tissue during laser treatments, the selected irradiance wavelength needs to be preferentially absorbed by the target tissue. In order for this to happen, the laser exposure duration needs to be shorter than the thermal relaxation time of the tissue.

3. Finally, during the **thermal denaturation stage**, the effects are visible in the tissues which, as we shall see below, are essentially dependent on heat generation<sup>7</sup>.

### EFFECTS OF BIOLOGICAL TISSUE HEATING

A model describing the thermal effects on biological tissues should include several parameters and, within certain limits, predict the distribution of temperature inside tissues<sup>7-10</sup>. This relationship between heat and lesions is studied with the mathematical model of Arrhenius, as will be seen in chapters 33 and 34.

Irradiance wavelength, exposure time and absorption coefficient are key parameters in achieving laser-tissue thermal interaction effects. As we have seen, heat transport is characterized by heat conductivity and heat capacity whereas heat effect depends on the tissue type and temperature achieved in the tissue (Figure 3).

Heat diffusion is negligible during nano or picosecond laser pulses, whereas longer exposure durations will produce significant tissue damage. A high repetition rate of laser pulses can provoke an additional increase in temperature if the heat transport is less than the rate of heat generation<sup>1</sup>. Several photothermal effects can be originated by different heat magnitudes in the irradiated tissue<sup>2,4,11</sup> (Figures 6 and 7).



Figure 6. Photothermal effects.

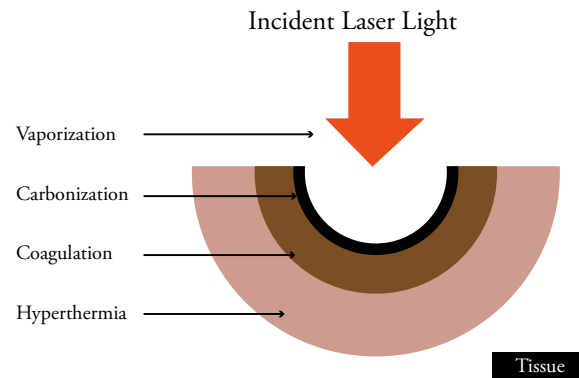


Figure 7. Schematic representation of the laser thermal effect on biologic tissues. See description on the text.

Effects lower than coagulation may be useful in bio stimulation, which was not included in the figure because it is usually categorized as a photo biochemical effect<sup>2</sup>. This is a new field of research, particularly regarding the retina, as we shall see in the section dedicated to laser in the human retina. Assuming the normal body temperature of 37°C, elevations lower than 10°C, occurring in minutes or seconds, usually cause cell damage/death but do not cause any structural alterations to tissues<sup>1,3,8,10,12</sup>.

### 1. HYPERTHERMIA

Temperatures of approximately 41°C cause a sequence of effects. Firstly, membrane and cytoplasmic cell proteins undergo conformational alterations due to cleavage of hydrogen bonds induced by increasingly violent molecular vibrations as temperature increases. Secondly, protein molecules change shape and lose their role within the cells. When this protein is an enzyme (whose catalytic functions depend crucially on its conformation) and starts to deform, reaction rates within the cells slow down. Small increases in temperature can cause apoptosis (cell necrosis) as a result of these effects<sup>1-3,6,11</sup>. The cellular organelles can be damaged and a repair process will be started<sup>3</sup>.

### 2. COAGULATION

At approximately 45°C, collagen optical scattering increases, the tissue whitens and collagen softens and gelatinizes. Denaturation is the structural change that happens in complex molecules such as proteins, DNA and RNA. Coagulation is associated with denaturation and structural tissue disorder.

The coagulation stage is only achieved by raising the temperature to 60°C<sup>1</sup>. When the temperature reaches 62°C, this typically results in cell death<sup>14</sup>.

Photocoagulation requires a short exposure to a high temperature to cause cellular death, irreversible tissue structure damage and visible tissue effects, such as a change in color (Figures 7 and 8). This results in a scattering increase, with absorption nearly maintained and a consequent laser

beam reduced penetration depth. Scattering is useful when significant amounts of tissue need to be photocoagulated and is also a useful tool for minimally invasive surgery in Oncology (retina, brain, prostate, liver or uterus)<sup>1,2,6</sup>. Photocoagulation of the retinal vascular disease, like in



Figure 8. Coexistence of several thermal effects in laser scars post retina photothermal treatment. Fresh photocoagulation lesion (black arrow) and previous healed photocoagulated lesions (white arrow).

microaneurysm occlusion, uses blood as a chromophore whereas laser trabeculoplasty and panretinal photocoagulation use melanin to achieve their effects. Photocoagulation offers a therapeutic effect at exposure times of around milliseconds to half a second and irradiance up to 10 W/cm<sup>2</sup>. Formerly, Argon lasers were the most common laser sources used. Nowadays, double frequency Nd:YAG 532 nm lasers or diodes emitting in the visible spectrum are being used<sup>1,3,14</sup>.

### 3. VAPORIZATION

Water molecules in cells and extracellular fluid boil at 100°C temperatures or higher. As water vaporizes, there is a volume expansion, micro explosions and expelled, thermally decomposed tissue fragments. The water vapor generated carries away the excess of heat and prevents further temperature increases in the adjacent tissue.

Lasers, such as CO<sub>2</sub> laser and Er:YAG laser, typically use this effect<sup>1,2,6</sup> as does the double frequency Nd:YAG 532 nm laser if applied at short impulse duration and high power, creating a localized, rapid increase in temperature at or above 100°C.

### 4. CARBONIZATION

Longer pulse durations cause extreme heat and tissue carbonization. This is usually undesirable and associated with inadequate selection of laser parameters and/or a faulty technique<sup>1,2,6</sup>.

Beyond 300°C, melting occurs resulting in a cooled and melted substance. As with carbonization, melting can happen with almost any type of laser if sufficient power density and exposure times are applied<sup>1,6</sup>.

### SUMMARY

Continuous wave (CW) lasers and pulsed lasers can generate photothermal interaction. The location and extension of each thermal effect depends on the temperature achieved locally after laser exposure. Critical temperature is determined by exposure time and exposure energy, volume and duration, which should be judiciously selected. Carbonization, vaporization and coagulation are irreversible effects associated with irreparable damage. Hyperthermia can be reversible. Exposure durations<sup>1,2,6</sup> are generally comprised between 1 μs to 1 min and power densities between 10 W to 10<sup>6</sup> W/cm<sup>2</sup>.

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# I. The Essential g.LASER-tissue interaction

## Photoablation



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Photoablation is defined by the direct breaking of molecular bonds by high energy UV photons. It is a very “clean” ablation, associated with audible report and visible fluorescence. The excimer lasers – ArF, KrF, XeCl and XeF – are typical lasers with a pulse duration of 10 to 100 nanoseconds and energy power of  $10^7$  to  $10^{10}$  W/cm<sup>2</sup>. Refractive corneal surgery is the main clinical application.

Photoablation was first described by Srinivasan *et al.* in 1982<sup>1</sup>. They identified this phenomenon as ablative photodecomposition (APD), describing it as tissue decomposition when exposed to high intensity laser radiation. Then, in 1983, Srinivasan collaborated with Stephen Trokel, an ophthalmic surgeon, in using APD for a cornea surgery<sup>2</sup>.

In the 1980s, it was discussed whether the effect was photochemical<sup>1</sup> (defended by Srinivasan in 1982) or photothermal<sup>3,4</sup> (advocated by Andrew *et al.* in 1983 and Brannon *et al.* in 1985). Today it is accepted that photoablation means photodecomposition by UV light and that it is a distinct mechanism from the photochemical or thermal process.

### EXCITATION, DISSOCIATION AND EJECTION OF TISSUE FRAGMENTS

Considering two atoms A and B that are bonded by a common electron, the absorption of a photon promotes both atoms at an excited state, following which its dissociation occurs. This event occurs if the photon energy is greater than the binding energy. Photoablation can be summarized as a two-stage process<sup>5</sup>:

- Excitation:  $AB + h\nu \rightarrow (AB)^*$
- Dissociation:  $(AB)^* \rightarrow A + B + E_{kin}$

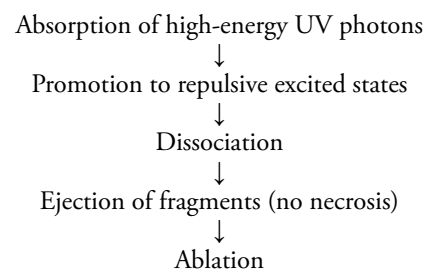


Table 1 shows the dissociation energies of some chemical bonds. Table 2 depicts the photonic energy of different wavelengths.

Table 1. Dissociation energies<sup>5</sup>

Type of bond	Dissociation energy (eV)
C=O	7.1
C=C	6.4
O-H	4.8
N-H	4.1
C-O	3.6
C-C	3.6
S-H	3.5
C-N	3.0
C-S	2.7

Table 2. Wavelengths and photon energies<sup>5</sup>

Laser type	Wavelength (nm)	Photon energy (eV)
ArF	193	6.4
KrF	248	5.0
Nd:YLF (4 $\omega$ )	263	4.7
XeCl	308	4.0
XeF	351	3.5
Argon ion	514	2.4
Nd:YLF (2 $\omega$ )	526.5	2.4
He-Ne	633	2.0
Diode	800	1.6
Nd:YLF	1053	1.2
Nd:YAG	1064	1.2
Ho:YAG	2120	0.6
Er:YAG	2940	0.4
CO <sub>2</sub>	10600	0.1

Comparing the two tables, one can conclude that only the UV light photons – typically excimer lasers – have sufficient energy to dissociate those bonds. Thus, photoablation mechanisms are limited to applications of UV light.

In thermal interaction, photon energy is not high enough for the molecule to reach a repulsive state. The absorbed energy promotes the molecule to a vibrational state and through non-radiative relaxation. Therefore, the absorbed energy is dissipated into heat. Even if we were considering a process of multiphoton absorption, so that it would be possible to achieve  $h\nu$  energies  $>3.5$  eV, the radiation  $h\nu <3.5$  eV would be responsible for warming the surrounding structures associated with consequent thermal effect, which is not the case in this effect with 193 nm radiation<sup>5</sup>. The ablation depth is predictable and proportional to the pulse energy, without the occurrence of thermal phenomena, making this type of ablation so advantageous.

Nowadays, the main clinical application of photoablation is refractive surgery: correcting myopia, astigmatism and hyperopia through cornea modeling.

Experimental models of this technique are made in synthetic organic polymers such as PMMA (polymethyl methacrylate) and Teflon. However, ensuing models also apply to non-homogeneous organic materials.

The expulsion energy of photoablation decomposition is equal to the photon energy in excess relative to the binding of chemical bonds. The ejecting products of ablation of the excimer laser have been analyzed in several studies.

Srinivasan *et al.* (1982)<sup>1</sup> and Brannon *et al.* (1985)<sup>4</sup> identified a mixture of single atoms (C, N, H, O), molecules (C<sub>2</sub>, CN, CH, CO) and stable fragments (MMA-monomers, HCN, benzene). Their great absorption by organic polymers limits penetration, resulting in a small volume of tissue with multiple fragments near the surface. The high pressure applied in such a short space contributes to the ablation and ejection of irradiated material. This type of laser, because of its unique characteristics mentioned above, constitutes a good option for ablation and tissue cutting.

## ABSORPTION OF UV RADIATION IN THE CORNEA

The absorption of energy UV in the cornea occurs for wavelengths lower than 300 nm. As water has no significant absorption at these wavelengths, it is the proteins, primarily collagen (70%), that are responsible for the absorption and therefore the effect of ablation. This effect occurs in the peptide bonds C-C, reaching a maximum effect around 190 nm. Another structure that is absorbent of UV radiation is the nucleic acid, which is mainly located in the epithelium and glycosaminoglycans.

## PHOTOREFRACTIVE KERATOPLASTY

There are numerous surgical options to change the corneal surface modeling the curvature: radial keratotomy, keratomileusis, keratophakia and epikeratophakia. The ablation of the cornea was first demonstrated by Trokel *et al.* (1983)<sup>2</sup> in bovine corneas using a radiation of 193 nm. The achieved ablation was 1  $\mu$  per 1 J/cm<sup>2</sup>. The laser damage was limited to the area of impact with no thermal effects.

Puliafito *et al.*<sup>6</sup> demonstrated the effects of the radiation on corneas of enucleated eyes with radiations of 193 and 248 nm, and determined the minimum fluency necessary for ablation, respectively 46 mJ/cm<sup>2</sup> and 58 mJ/cm<sup>2</sup>. Analyzing it under an electron microscope, stromal side effects were identified at 0.1 to 0.3  $\mu$ m from the limits of ablation, for the wavelength of 193 nm. These side effects at the cutting edges were explained as being tissue fragments which were not ejected from the area of impact or a thermal effect. Kerr-Muir *et al.*<sup>7</sup> calculated that the excimer ablation is 10 times more uniform than when using a diamond knife.

The major concern with this radiation is its potential mutagenic and carcinogenic effects related to interaction with DNA, cell death, mutagenesis, carcinogenesis, interference with protein synthesis and DNA, cell division and delay in changes in the permeability and motility. Nuss *et al.*<sup>8</sup> have shown that unscheduled DNA synthesis was not increased in rabbit corneas irradiated with 400 mJ/cm<sup>2</sup>/pulse. Kochevar<sup>9</sup> explains this lack of effect with the fact that the cell wall proteins are responsible for absorbing the radiation.

Numerous factors may explain the lack of side effects of this radiation, 1) the depth of absorption is only 3.1  $\mu$ m resulting in a small amount of incident energy deposited in a small volume of tissue; 2) the pulses are short (10-20 ns) preventing the diffusion of heat; 3) the low vascularization of the cornea (epithelium), the avascularity of the stroma (glycosaminoglycans) and the large endothelial repair capacity<sup>5</sup>.

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# I. The Essential

## 10. LASER-tissue interaction

# Photodynamic Therapy



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### INTRODUCTION

From the moment lasers were invented by Maiman in 1960<sup>1</sup>, there have been ongoing investigations on the possible effects of laser interaction with the tissues, which can be classified into: 1) photochemical effects; 2) photo-thermal effects; 3) photoablative effects; 4) plasma induced ablation; and 5) photodisruption effects. The factors that influence these photobiological effects are<sup>2</sup>:

1. **Optical characteristics of tissues:** a) reflection coefficient, b) absorption coefficient and c) dispersion coefficient, which together determine the total light transmission to the tissue for a given wavelength; d) thermal properties (heat conduction and 'heat capacity') should be taken into account due to the production of photothermal effects.

2. **Properties of Laser light:** 1) wavelength; 2) exposure time; 3) applied energy or radiant energy (joule); 4) spot size; 5) power i.e., delivered energy per time unit (watt) and power density or irradiance (watt/cm<sup>2</sup>) i.e., power per area unit of the beam laser.

3. Among the various **Parameters of Laser Light**, the most important are the exposure time and power density (irradiance – amount of power per unit area). Thus, for exposure times longer than 1 sec in continuous mode and low irradiance, the photochemical effect is obtained. As the irradiance increases and the exposure time decreases, the remaining effects will be: photothermal ( $t < 1$  min to  $1 \mu\text{s}$ ), photoablation ( $< 1 \mu\text{s}$  to  $1$  ns) and for  $t < 1$  ns, plasma induced ablation and photodisruption (Figure 1). The circles represented in this diagram give only a rough estimate of the effects obtained and cannot be accurately separated. For example, the parameters used for a photochemical or photoablation treatment might influence the production of heat with the consequent thermal effect. The application of laser in biological tissues is conditioned by their heterogeneity, consisting of a complex of molecules, cells, extracellular, organic pigments and 60% of water.

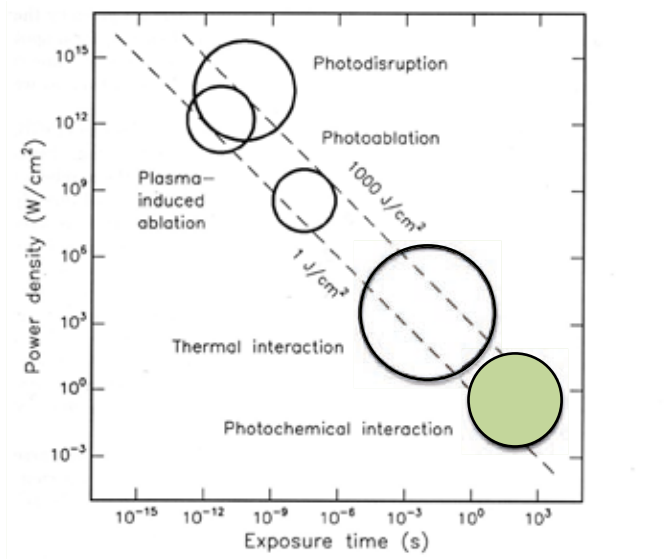


Figure 1. Relationship between power density and exposure times and the laser-tissue interaction (modified by Boulnois 1983<sup>3</sup>).

### PHOTOCHEMICAL EFFECT – PHOTODYNAMIC THERAPY (PDT)

The first application of photodynamic took place in 1903<sup>4</sup>, when Tappeiner and Jesionek treated skin cancer through exposure to sunlight after applying eosin. However, only with the development of hematoporphyrin derivate (HPD) by Schwarz *et al.* in the 1950s<sup>5</sup> did the modern PDT emerge, with further developments in the 1970s<sup>6</sup>, assisted by the use of laser light and optical fiber technology, capable of accessing *inside-body* injuries. The laser light allows the use of enough energy to treat small superficial tumors in cavity organs accessible with endoscopy<sup>2</sup>. In order to obtain destruction of a tumor cell, or other

non-tumor cells, using PDT, three components are needed: 1) a chromophore - photosensitizer (PS), which after administration is captured selectively by the target cells; 2) light with a selected wavelength -  $\lambda$  (chosen on the basis of PS absorption spectrum), and with appropriate energy (corresponding to energy differences between energy levels) to induce the desired photochemical effect. The PS will only be activated in the place where the light is focused; and 3) oxygen. The photochemical effect occurs with low power densities and long action times. The tissue penetration depth varies with the optical characteristics of each tissue and also inversely with its wavelength.

The electrons of organic molecules, including the PS, are in their ground state (level of lower energy), and paired with opposite spins (singlet state). With the absorption of light (Figure 2) an electron changes its position in the electronic cloud without changing their spin, moving to a higher energy level, which is unstable, and later declining to a level of less energy (most often the fundamental state). This decay can occur by: 1) Heat release; 2) Light emission; or 3) Moving to an intermediate stage (not the fundamental state) - **triplet state** - where there is a reversal of the excited spin (partial loss of power).

The decline from this stage is slower, also in the form of heat or light emission - phosphorescence, or by hydrogen atom or electron transference to a substrate (not oxygen) **reaction type I**, with subsequent formation of radicals that act as oxidants, subsequent reaction with oxygen molecules leading to the formation of a superoxide anion and hydrogen dioxide); or **type II reaction** with energy transfer to oxygen molecules and formation of singlet oxygen (oxygen radicals). It is thought that the latter is responsible for the underlying reaction to PDT effect.

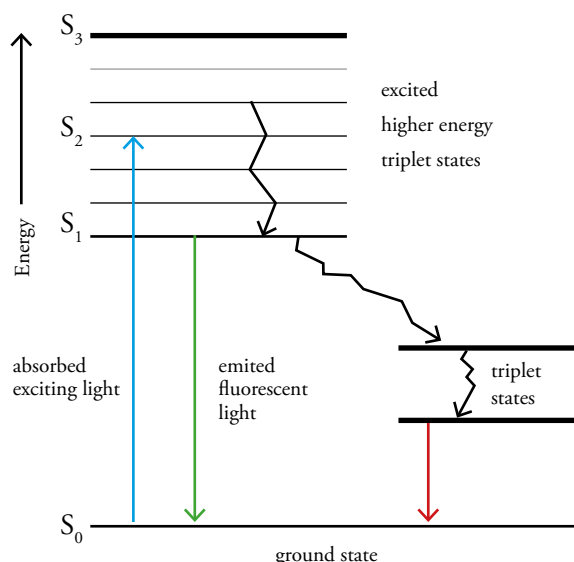


Figure 2. Molecular excitation and decays by Jablonski<sup>7</sup>.

This singlet oxygen molecule, with short half-life time, is an extremely cytotoxic reagent causing oxidation of amino acids, nucleic bases, and adjacent lipidic chains, accounting for the effects that lead to cell death (rupture of the plasma membrane and intracellular organel-

les membrane) - irreversible oxidation of essential cell structures - immediate cytotoxic effect. Other effects are: hyperthermia and vascular effects.

### PDT EFFECTS

#### 1. Direct and immediate cytotoxic effect

**2. Vascular effects** - vasoconstriction after application of light; injury of the endothelial cells concomitantly leading to a loss of their tight-junctions, exposure of the underlying basal membrane with consequent platelet activation and formation of the platelet plug. Polymorphonuclear adhesion to the exposed basal membrane with thromboxane and leukotriene release also occurs. First, there is an increased permeability and only after vascular obstruction takes place (not Selective Thermal Photo-thrombolysis).

**3. Hyperthermia** - the rapid vascular destruction prevents heat dissipation, which in time is similar to the described changes originated by photothermal effects.

### TUMOR SELECTIVITY

Although not fully understood, this differential uptake between tumor tissues versus normal tissues is due to different mechanisms which are not only related to the chemical properties of PS, but also to cell and tissue factors:

- **PS properties:** chemical characteristics and affinity for tumor receptors.
- **Cell factors:** high number of receptors for low density lipoproteins (LDL), as seen in cells with a high mitotic ability (neoplastic cells and endothelial cells); as well as enzyme blockages in biosynthetic pathways or degradation of endogenous porphyrins.
- **Tissue factors:** increased vascularization, and permeability, tumor vessels have missing or abnormal lymphatic drainage.

In 1976, Kelly and Snell<sup>6</sup> described the first endoscopic application of PS in bladder carcinoma cases. There are potential applications for superficial and light accessible tumors (skin, mouth or nose cavities, or organs accessible by endoscopy).

### CONCLUSIONS AND CLINICAL APPLICATIONS IN OPHTHALMOLOGY

The photochemical effects are obtained with low irradiance and long exposure times. The most frequently used effect is PDT that involves the presence of a PS, a light that will activate the drug and the presence of oxygen which is behind the generation of cytotoxic radicals and cellular injury. It is used in different specialties in tumors which are small, superficial and accessible by light. PDT was applied in Ophthalmology in the 1980's, by Sery<sup>8</sup>, Gomer *et al.*<sup>9</sup>, and Muphree *et al.*<sup>10</sup>, who were investigating this form of treatment in intraocular tumors. However, selectivity and efficacy as well as the debridement capacity, were not sufficiently high to constitute a successful therapeutic modality. In the late 1980s, studies began to emerge with PDT applications in the treatment of ocular neovascularization<sup>11-14</sup>. Since the introduction of the anti-vascular endothelial growth factor (anti-VEGF), PDT has now a very secondary role in Ophthalmo-

logy, being reserved for the treatment of special forms of age-related macular degeneration (AMD)<sup>15</sup>, polypoidal choroidal vasculopathy (PCV)<sup>16,17,18</sup> and chronic central serous chorioretinopathy (CSCR)<sup>19,20,21</sup>.

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# I. The Essential

## 11 LASER-tissue interaction

### Plasma generation and

### Plasma-Induced Ablation



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#### INTRODUCTION

“In a second there are more femtoseconds than there have been hours since the universe began 14 billion years ago”  
Ella G. Faktorovich

Optical breakdown enables the generation of tissue vaporization designated as plasma, which mediates photoablation. This laser tissue effect is associated with high precision surface effects.

Lasers enabling high energy densities can generate tissue optical breakdown with consequent generation of plasma. This occurs when energy densities exceed  $10^{11}$  W/cm<sup>2</sup>, in solids and fluids, and  $10^{14}$  W/cm<sup>2</sup> in the air. These high energy densities can only be achieved with pulsed lasers, as “Q-switch”, that fire nanoseconds duration pulses and “mode locking” with pulse durations of pico and femtoseconds (Figure 1).

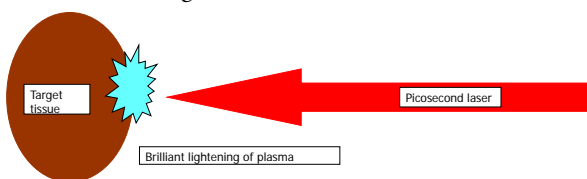


Figure 1. High Energy Pulsed Laser Tissue Interaction.

Optical breakdown is the first step for plasma mediated ablation, enabling:

- Precise tissue removal;
- Absence of thermal effect;
- Absence of mechanical effect.

#### OPTICAL BREAKDOWN

The intensity of the local electric field  $E$  is the most important parameter to determine when optical breakdown can be attained. Optical breakdown will occur if  $E$  supersedes a threshold value, in other words, if the electric field applied determines the ionization of molecules and atoms<sup>2</sup>.

The electrostatics' equation,  $I = \frac{1}{2} \epsilon_0 c E^2$ , unveils how the intensity of the electric field  $E$  relates to the density of potency  $I$ , where  $\epsilon_0$  is the dielectric constant in vacuum and  $c$  the light velocity.

For picosecond lasers, the threshold for  $I$  to generate optical breakdown is around  $10^{11}$  W/cm<sup>2</sup> and corresponds to an electric field  $E$  of  $10^{17}$  V/cm<sup>2</sup>. The latter value is similar to the intra molecular and atomic electric fields of Coulomb, which enable ionization and plasma generation<sup>2</sup>. Within a few hundreds of picoseconds, the striking laser beam is able to generate a high density of free electrons of  $10^{18}$  /cm<sup>3</sup> in the tissue focal volume.

#### PLASMA GENERATION

Q-switched pulses, in the nanosecond range, or Mode locked laser pulses, in the pico or femtosecond range, can generate ionization and the subsequent electron avalanche of plasma-induced ablation or plasma-mediated ablation. According to Puliafito and Steinert<sup>3</sup>, the duration of the laser pulse is fundamental in defining the two possible processes of plasma generation:

- Thermionic emission;
- Multiphoton ionization.

**Q-switched pulses** originate thermionic emission. Thermal ionization triggers the generation of free electrons and optical breakdown is thus generated by nanosecond duration laser pulses and is often accompanied by non-ionizing side effects such as heat. Plasma energies and plasma temperatures are usually higher in Q-switched laser pulses, due to the associated high threshold energy needed for plasma generation<sup>2</sup>.

**Mode locked pulses** originate multiphoton ionization: in pico or femtoseconds, several photons (multiphoton) are simultaneously absorbed originating the energy needed for the ionization required to create an induced high electric field. Multiple photons, rather than just one, will hit electrons more effectively. The extreme brevity of a femtosecond

# 11. Plasma generation and Plasma-Induced Ablation

laser pulse, allows the delivery of a very high number of photons to the tissue per unit time, maintaining the total energy needed and minimizing collateral damage<sup>2</sup> (Figure 2).

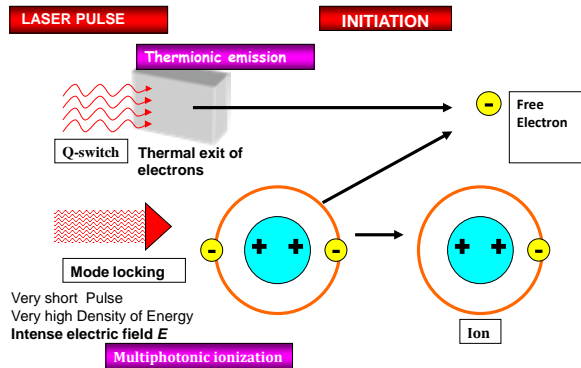


Figure 2. Thermionic emission and multiphotonic ionization – initialization (Adapted from Niemz<sup>2</sup>).

Plasma Generation can therefore be summarized in three steps:

- 1) Absorption of a photon by an atom resulting in its ionization – duet positive ion- free electron.
- 2) Free electrons absorb photons of the beam, gaining velocity or, in other words, increasing its kinetic energy.
- 3) These accelerated electrons collide with another atom, causing the ejection of more electrons, in a continuous process (Figures 3 and 4).

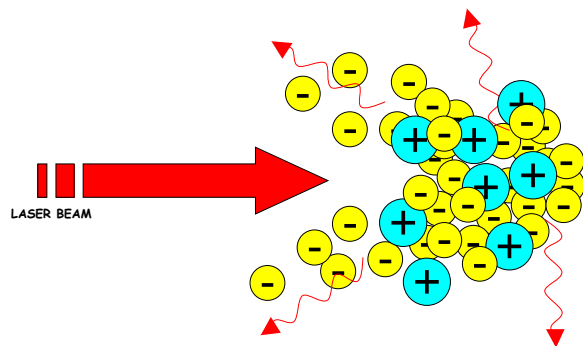


Figure 3. The plasma generation (adapted from Niemz<sup>2</sup>).

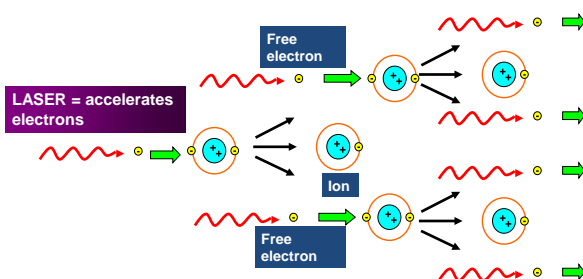


Figure 4. Illustrates the process by which a free electron initiates the characteristic avalanche effect (adapted from Niemz<sup>2</sup>). An electron absorbs a photon and accelerates it. The accelerated electron collides with a nearby atom and creates an ion and two free electrons. Each of the latter two free electrons undergoes the same process, as described above, creating an avalanche of free electrons and ions.

## THE AVALANCHE EFFECT

When a laser pulse (photons) excites unattached electrons, they accelerate and collide with other electrons within the atoms breaking those electrons free and leading to an accumulation of electrons and ions. Free electrons will go on absorbing incoming photons, accelerating and striking other atoms and freeing more electrons, producing an avalanche effect (Figure 4).

Free electrons of the aforementioned avalanche will lose their energy through two possible mechanisms: inelastic collisions or free electron diffusion from the tissue focal volume<sup>2</sup>.

Optical breakdown and plasma generation enable:

1. Energy delivery to both pigmented and non-pigmented tissues, due to the high absorption coefficient of plasma.
2. The absorption of any amount of energy to increase the kinetic energy of electrons. All wavelengths ( $\lambda$ ) are accepted, resulting in an ultra short time (picoseconds) to generate a high level of electron density. There are no restrictions on the photonic energy involved in the process, as it happens in the absorption spectrum of a given chemical element or molecule.
3. Swift and intense ionization, thus avoiding energy dissipation before the electron avalanche, which is created by an ultrashort and intense irradiation (I) leading to optical breakdown.

## PLASMA INDUCED ABLATION TISSUE EFFECTS

The main characteristic of this laser is chopping little portions of the tissue, like a sculptor working on a rock. Optical breakdown is easily started by the interaction of laser beam photons with tissue surface electrons because these are free and accessible. Electrons within solid matter are locked in chemical bonds. Unless a photon, or a number of them, deliver enough energy to the atoms per unit time, electrons will remain attached and light will not be absorbed. In transparent tissues, like the cornea, the laser beam will pass through it without any intended effect<sup>2</sup>.

Multiple photons, rather than just one, will more effectively hit the bound electrons. The extreme brevity of a femtosecond laser pulse, allows the delivery of a very high number of photons to the tissue per unit time, maintaining the needed total energy and minimizing collateral damage<sup>2</sup>.

Plasma induced ablation is primarily caused by plasma ionization as opposed to the more mechanical process associated to photodisruption. Both situations are initiated by a few electrons in a process leading to the accumulation of free electrons and ions associated optical breakdown of tissues<sup>2</sup>.

Femtolasers, ultrashort pulse lasers and ultrafast lasers can generate pulse durations of  $10^{-15}$  seconds requiring effective minimal pulse energy, thus producing a negligible surrounding tissue effect<sup>2</sup>.

These lasers have the unique capacity for photodissection without photodisruption, producing very clean and well-defined tissue removal as long as laser parameters – laser pulse energy, repetition rate, fluence and laser pulse duration – are optimized<sup>2</sup>.



## **APPLICATIONS OF PLASMA INDUCED ABLATION (for Photodisruption see next chapter)**

The electric field strength energy is the major parameter for optical breakdown and the onset of plasma-induced ablation. Irradiance must be intense enough to achieve rapid ionization and enable the appliance of multiple pulses to achieve the intended physical effect, avoiding collateral effects. These lasers are effective not only in pigmented tissue but also in weakly absorbing media due to the increased absorption coefficient of the induced plasma. Potential medical laser applications are thus widened to transparent tissues, such as the cornea and lens<sup>1</sup>.

Cutting explosive devices, manufacturing microchips, cutting biodegradable intra-arterial stents, removing tooth tissue, gene therapy, tissue engineering, corneal and lens surgeries, which are accurate, safer and more predictable, were made possible thanks to this laser-tissue interaction<sup>2</sup>.

## **CONCLUSION**

Optical breakdown is the hallmark of plasma-induced ablation and photo disruption and it occurs if the applied electric field causes the ionization of molecules and atoms<sup>2</sup>. The electric field strength generated on the laser-focused spots, relates to local energy density. Multiphoton ionization is achieved due to the cumulative effect of a number of ultrafast high-energy laser pulses, thus avoiding collateral thermal effects and enabling precision. Effective threshold energy decreases with the square root of pulse duration<sup>2</sup>.

The relevant aspects of this laser-tissue interaction effect are the following: 1) Optical tissue breakdown; 2) Ultrafast duration and high energy density of pulse laser; 3) Minimal or no collateral damage in the surrounding tissue; 4) Wider application to non-pigmented tissues; and 5) Accuracy and precision of application.

Ophthalmology shows the most promising and exceptional clinical applications in corneal and lens surgery.

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# I. The Essential

## 12. LASER-tissue interaction

- Optical breakdown and its mechanical effects
- Photodisruption



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### INTRODUCTION

When using nanosecond Q-switch lasers, the extremely fast increase in temperature and pressure on the tissue spot where the laser is focused, leads to a supersonic expansion of the generated plasma, which becomes an expanding bubble. This will subsequently collapse, creating acoustic waves that propagate radially through the surrounding tissue<sup>1</sup>. The generation of shock waves and jet formation are two other mechanical effects present in this laser tissue interaction<sup>2</sup>.

These phenomena start with the optical disruption and have already been discussed in the previous chapter. This leads to a photodisruption which is the result of the mechanical impacts that determine the overall effect on the tissue.

When the optical disruption and the resulting plasma formation are induced by a Q-switch laser, the amount of energy involved is so high, when compared with the Mode-locking lasers, that the secondary physical phenomena predominate over the ablative effect.

This essentially mechanical effect was given the name “disruption” (from Latin *ruptus* = ruptured) and was studied by Krasnov (1973)<sup>3</sup> and Aron-Rosa (1980)<sup>4</sup>. It has clinical applications in ophthalmology on the lens capsule’s disruption, in the treatment of secondary capsular opacities, in cataract surgery and in urology for lithotripsy.

There are four associated effects on the optical disruption with high energy (photodisruption)<sup>2</sup> (Figure 1):

1. Plasma formation;
2. Shock wave generation;
3. Cavitation;
4. Jet formation.

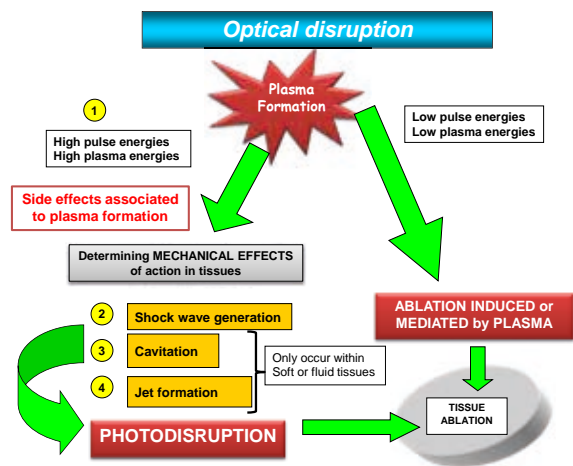


Figure 1. Optical disruption of high energy and the mechanical effects of photodisruption.

The mechanical effects vary linearly with the absorbed energy. Therefore, for the same focus size, the plasma induced by a laser impulse with the duration of 100 ns is approximately 100 times more powerful than if it was induced by a laser impulse of 10 ps. This additional energy is partially converted into the shock wave, cavitation and jet formation.

### THE ROLE OF MECHANICAL EFFECTS IN PHOTODISRUPTION

The propagation of mechanical interactions in photodisruption, similar to a “micro explosion”, separates the tissues, extending its effects to a few millimeters.

# 12. LASER-tissue interaction - Optical breakdown and its mechanical effects - Photodisruption

Photodisruption has a multifactorial effect initiated by the optical disruption and consequent plasma formation. The associated mechanical effects, including shock waves, jet formation and, particularly, cavitation cause the laser action. The two latter effects occur if the process takes place in soft tissues or liquid environments, such as the anterior and posterior chambers of the human eye. The amount of energy in the photodisruption is two or more orders of magnitude higher than the photoablation energy induced by plasma<sup>2</sup>.

## ANALYSIS OF THE PROCESS STEPS SUBSEQUENT TO OPTICAL DISRUPTION IN "Q-SWITCH" LASERS

### 1. PLASMA FORMATION

There are, essentially, three occurrences during plasma formation, two of which are particularly important for clinical and practical reasons:

- Plasma shielding, which has been discussed in chapter 11;
- Brillouin* scattering;
- Multiple plasma generation.

#### 1.a) Plasma shielding

The absorption coefficient of plasma ( $\alpha_{pl}$ ) is higher than the absorption coefficient of tissues ( $\alpha$ ).

This means that plasma, characterized by its high density of free electrons, absorbs the photons produced at the laser source. The recently formed plasma is able to absorb all the photons whatever their wavelength, significantly reducing the amount of laser radiation reaching the tissues. The tissue is therefore shielded against the laser beam photons.

The plasma, by absorbing the light of the incident beam and emitting light radially, achieves a true shielding effect against the beam course<sup>2</sup>. This is one reason why the retina is not affected even if the laser creates a focal area very close to it. The retinal injury can appear due to the mechanical effects and not to the direct laser effects (Figure 2).

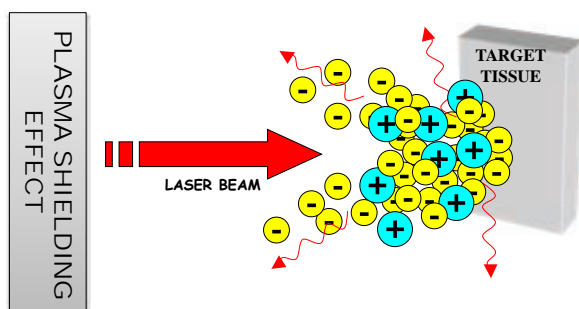


Figure 2. The shielding effect (adapted from Niemz<sup>2</sup>).

The free electrons, by absorbing all the energy from the beam, get more kinetic energy exciting the plasma ions, which emit photons. In addition, the release of radiation from the free electrons constitutes one of the ways to dissipate plasma energy.

#### 1.b) Brillouin scattering

The incident light is scattered by acoustic waves thermally excited and deflected at frequencies corresponding

to the potential frequency of *photons*. During the plasma heating process, acoustic waves are created which result in *Brillouin* scattering<sup>2</sup>.

#### 1.c) Multiple plasma generation

When close to the ablation threshold, one spark is induced on the focal point. However, with a high energy level impulse, a lot of plasma can be ignited. In this case, only the initial part of the laser impulse can induce plasma formation in the focal spot. With a high level of energy, the remainder of the laser beam's impulse induces a cascade of plasma towards the source<sup>2</sup> (Figure 3).

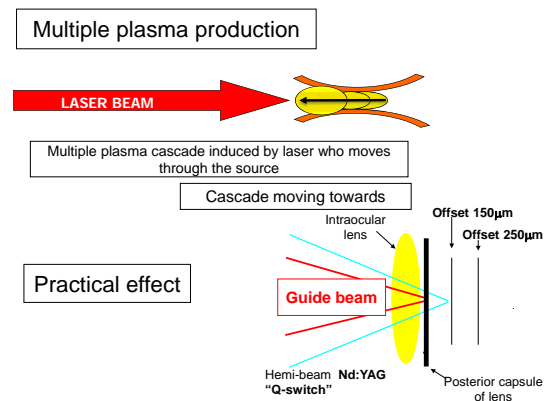


Figure 3. The tissue damage is close to the laser source. It is, therefore, necessary to "offset" the photodisruptor laser delivery system (adapted from Niemz<sup>2</sup>).

The advantage of this phenomenon is the fact that the tissue injury is drawn towards the laser source. It is then necessary for the ophthalmic lasers to have a mismatch (offset) between the focus of the HeNe guide beam and the focus of the Nd: YAG laser (Figure 3). This allows for the photodisruptor effect in the posterior capsule without damaging the optical properties of the neighboring intraocular lens, which is in an anterior position within the capsule (Figure 3).

### 2. SHOCK WAVE GENERATION

Due to its high kinetic energy, the free electrons are not confined to the focal volume but are diffused in the environment. Heavier ions follow them with a certain delay. The delay of the ions' movement creates a shock wave. This shock wave promptly separates from the plasma border. Initially, the wave moves at hypersonic speed (in water at 5000 m/s while sound propagates at 1483 m/s) then, it slows down, stabilizing at the speed of sound for that environment. There is a genuine momentary discontinuity producing a wave similar to the square wave<sup>2</sup> (Figure 4).

The entire duration of the deflection (shock step), for an impulse laser of 30 ps in water, takes 10 ns. The 30 ns attenuation period of the shock wave can cause tissue displacement with a subcellular injury.

Note: If we want to imagine the macroscopic effect of spreading a mechanical wave, we have to imagine that the tissues suffer compression and rarefaction, which correspond to regions of higher and lower density, respectively

**SHOCK WAVE GENERATION OF A PULSE LASER OF 30 ps**

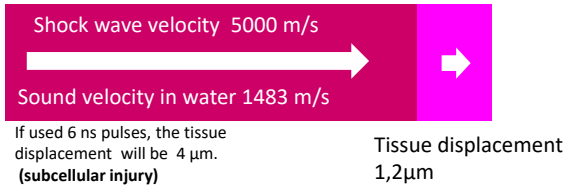


Figure 4. (adapted from Niemz<sup>2</sup>).

Shock wave creation:  
 The electrons are released with a lot of kinetic energy;  
 Matter reorganization after the removal of electrons;  
 Disturbance of matter that spreads to hypersonic speed, then, the speed of sound (e.g. thunder);  
 Space action of 1-4 μm (subcellular injury).

– an exactly analogous process is the sound spread, which is no more than a compression and rarefaction of the air. That is why it only spreads in a material environment and not in vacuum.

Shock wave definition: the shock wave is the propagation of a disturbance at hypersonic speed in material, followed by a dramatic increase in pressure, density and temperature<sup>2</sup>. Such waves are generated by a sudden release of large amounts of energy in a limited space, just as an explosive detonation (chemical energy) or an electric shock (electric power). A non-sustained shock wave loses energy through viscous dissipation and produces the sound wave (e.g. thunder).

**3. CAVITATION**

There has been a lot of interest and studies on cavitation due to its destructive effect on solid surfaces such as ship propellers and other hydraulic equipment. Cavitation occurs when the plasma, induced by laser, takes place within soft tissue or fluids. The formation of a cavitation bubble and its mechanism of action can be seen in the following diagram (Figure 5).

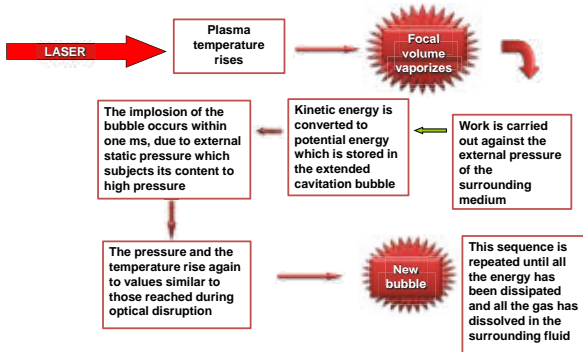


Figure 5. Diagram explaining cavitation formation (adapted from Niemz<sup>2</sup>).

Conversion of the incident energy in the cavitation bubble:

- 19% of energy for picosecond pulses;
- 24% of energy for nanosecond pulses.

The average energy loss of the cavitation bubbles during their first cycle is approximately 84%.

The bubble-induced damage scales with the cubic root

of the contained energy and the tissue damage also scales with the cubic root of pulse energy. Cavitation induces more damage in the tissues than the shock wave<sup>2</sup> (Figure 6).

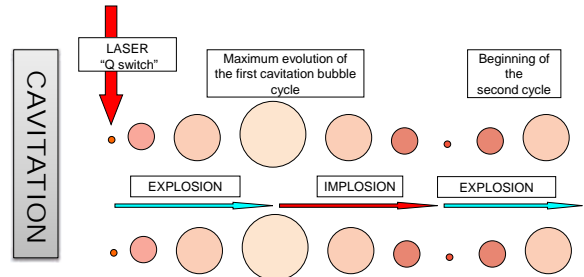


Figure 6. Formation, evolution and dissipation of the cavitation bubble (adapted from Niemz<sup>2</sup>).

The injury, due to the shock wave, is limited to the sub-cellular level as a result of its short extension of displacement, which is 1-4 μm. In turn, given the fact that the diameter of the cavitation bubble may reach a few millimeters, it is believed that the macroscopic photodisruptive effects inside the tissues are mainly originated from the combined action of cavitation and jet formation, which will be shown next.

Cavitation definition: gas formation or steam-filled cavities within a liquid occur when they are subjected to a rapid reduction in pressure below the steam pressure, the liquid saturation pressure (for example: a bottle of sparkling water) or a rise in the temperature to above the boiling-point. Cavitation can be induced by chemical or electrical energy as well as by radiation.

**4. JET FORMATION**

The impact of the high speed liquid jet caused by the collapse of a cavitation bubble can lead to severe injury and erosion of solids.

When cavitation bubbles collapse near to, or in contact with, a solid barrier, a high speed liquid jet is produced against the barrier which has the potential of causing injury.

In water, the jet reaches a speed of 156 m/s, which corresponds to a pressure of approximately 2 Kbar<sup>2</sup> (Figures 7 and 8).

The injury produced by the jet formation is dramatically increased if a gas bubble, of an initial impulse, is reached by the acoustic transient generated by subsequent impulses. The photodisruptor laser equipment, in ophthalmo-

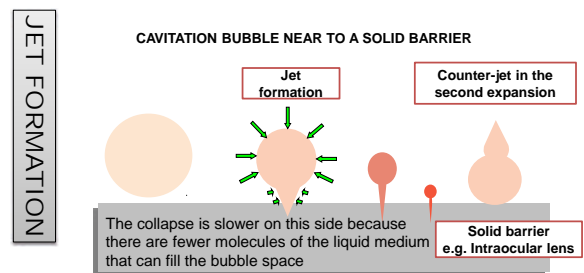


Figure 7. Cavitation bubble near to a solid barrier (adapted from Niemz<sup>2</sup>).

## 12.LASER-tissues interaction - Optical breakdown and its mechanical effects - Photodisruption

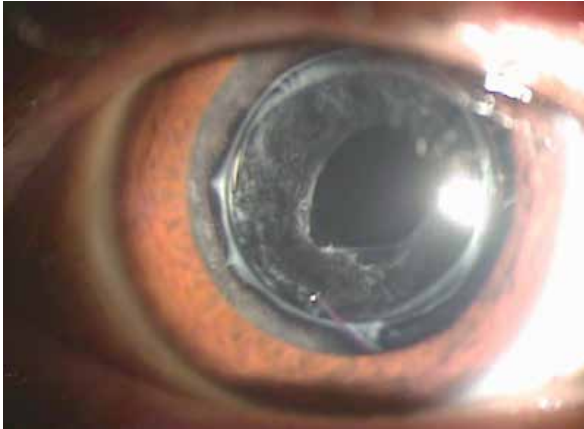


Figure 8. Capsulotomy performed with photodisruptor 1064 nm Nd: YAG laser "Q-switch" coupled with biomicroscope. The intraocular lens acts as a barrier which allows the jet effect to be quite efficient in breaking the capsule lying behind the intraocular lens.

logy, takes advantage of this by increasing efficiency with sequences of shots (1-3 shots) named "burst" action, while the normal action mode is the "single pulse".

### SUMMARY

Physical effects associated with optical breakdown taking place inside soft tissues or fluids occur as a sequential process. This consists of the formation of plasma bubbles, shock waves, generation of bubbles in aqueous medium and their implosion (cavitation) with the consequent disruption of biological tissue (Figure 9).

### GLOSSARY

#### The role of confinement in photodisruptive phenomena

Confinement plays an important role in inducing actions during acoustic processes.

Short impulses, when interacting with a target, induce shock waves due to thermal and mechanical confinement within the optical zone, in other words, in the laser energy deposition zone.

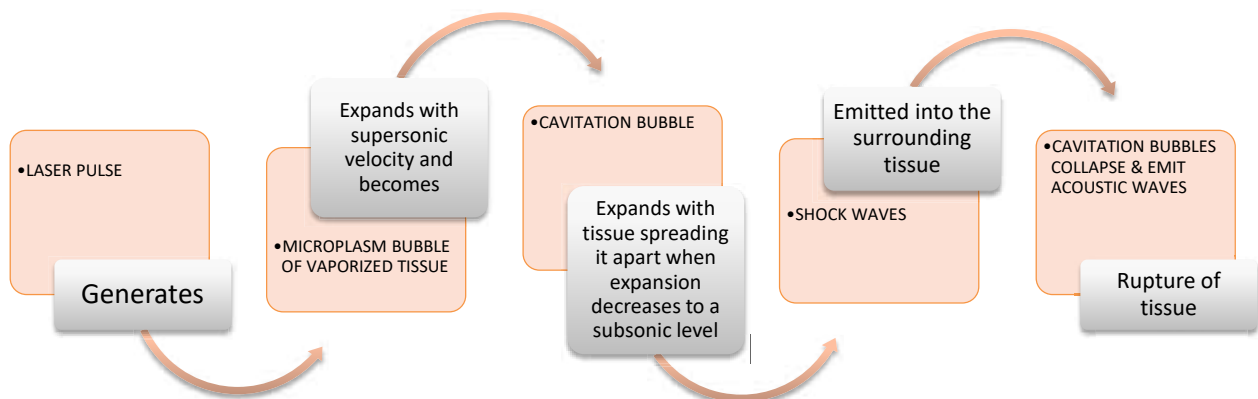


Figure 9. Flow of events associated to plasma photodisruption.

### Photothermal confinement

If  $\tau_p$ , impulse duration time, is short enough (ps), the diffusion is small enough to dissipate the energy during the impulse. All energy is confined within the optical zone and reaches the maximum thermal power density.

### Photomechanical confinement

If  $\tau_p$  impulse duration is short (ps), energy is deposited in the optical zone, which increases mechanical stress before it can propagate outside. Thus, it generates the shock wave that propagates at a supersonic speed in the vicinity.

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# I. The Essential

## 13. Mechanisms of LASER delivery, the Ophthalmology perspective



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### INTRODUCTION

Domestic lamps produce more energy than most lasers with clinical applications. However, the laser light is particularly concentrated, which translates into a high power density (irradiance -  $W/cm^2$ )<sup>1</sup>.

Units: Irradiance ( $W/cm^2$ ); radiant exposure ( $J/cm^2$ ).

Irradiance (power per unit area) is an important factor in determining the laser effect (laser-tissue interaction).

The clinical use of laser requires an understanding of laser tissue interaction mechanisms: Photochemistry (Photodynamic Therapy (PDT); Photothermal; Photoablation; Photoablation induced plasma; and Photodisruption<sup>1</sup>.

The surgeon controls the power, spot size and exposure duration. This doctor must understand the relationship between these parameters and the laser-tissue interaction, as well as have a thorough knowledge of the "beam profile" concept.

Most of the laser beams used in surgeries are Gaussian ( $TEM_{00}$ ) (Figure 1); the power density varies in accordance with the radius of the laser beam, resulting in Gaussian distribution. So much energy is concentrated at the center of the laser spot and there is a progressive decrease whenever passing through in order to reach the spot boundaries. Excessive power density causes vaporization of water at the center of the spot, which can cause a retinal Bruch's membrane rupture, hemorrhages and choroidal neovascular membrane stimuli.

Therefore, in general, the smaller dimension of the laser spot occurs at a plane "behind" the focal plane of the lens.

### ENERGY DISTRIBUTION IN A TYPICAL CLINICAL LASER

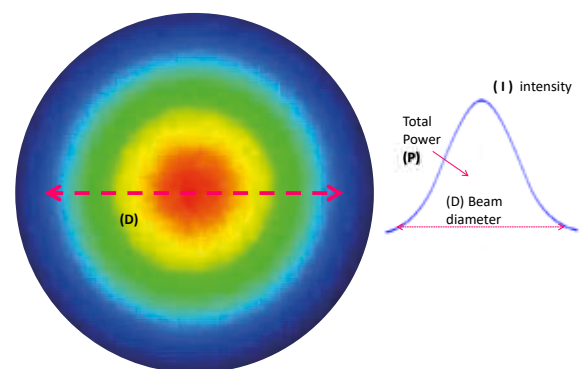


Figure 1. The Gaussian ( $TEM_{00}$ ) laser beam, the most used in surgeries.

This happens because the condenser lens exerts its effect on a beam, which initially is not collimated but slightly divergent.

### THE APPLICATION SYSTEMS / LASER DRIVING RELYING ON OPTICAL ELEMENTS AND THEIR DESIGN

There is a whole set of elements, which is associated with relatively complex optical instruments (e.g. microscopes), including: focalizing lenses (condensation), often



aspheric and achromatic; beam splitters, which make it possible for the laser beam to split into two; prisms that allow redirecting the laser beam; filters that protect against specific wavelengths; mirrors; fixed openings, diaphragms or other variables; laser beam expanders; windows that allow the transition between two optical elements, without changing the laser beam characteristics; and coatings that enhance the transmission of the laser and reduce the reflectivity of the optical elements.

### THE APPLICATIONS OF LASER SYSTEMS IN OPHTHALMOLOGY

The applications of Laser systems in Ophthalmology include<sup>2,3</sup>:

#### a) Slit lamp

Accessory lenses:

- Contact lenses
- Non-contact lenses

#### b) Indirect ophthalmoscope

#### c) Optical fibers

A slit lamp is a microscope with a relatively long focal length, 10 cm.

In a laser output device there is a laser beam expander, followed by a lens that condenses the laser beam at the end of an optical fiber, and then the optical fiber leads the laser beam to the slit lamp adapter.

### A) SLIT LAMP

There are 3 types of adapters for laser slit lamp: parfocal system, defocused system and SureSpot system<sup>2</sup>.

Historically, laser systems used a defocused or parfocal optical delivery system for retinal photocoagulation.

In the past, parfocal systems became the technical industry standard, being used by manufacturers such as Zeiss, Iridex and Quantel. Despite the many advantages that the parfocal technology provides, it still poses some problems, such as its inability to be titrated<sup>2,3</sup>.

#### Parfocal Delivery System

A parfocal system has a low beam divergence, delivering an almost collimated beam. The beam profile on the retina is sharp edged ("top-hat"), providing consistent and uniform energy distribution that results in crisp, well-defined retinal burns<sup>2</sup>. Due to the almost parallel shape of the beam, the beam diameter at the cornea is very close to the retinal diameter for most spot sizes. As a result, the energy density at the cornea is almost equal to the energy density at the retina.

In a parfocal system there is a coincidence between the focal plane of the slit lamp and the focal plane of the laser beam (Figure 2). This feature allows a good definition and laser spot adequately focused to all the dimensions. This laser delivery system can, in some circumstances, lead to large concentrations of energy at the anterior portions of the eye (cornea and lens), especially when it makes use of panfundoscopic accessory lenses and high spot dimensions.

Currently, most of the systems available, using slit lamps are based on the parfocal delivery system. In fact, small fluctuations in the spatial location of the slit lamp do not mean an increase in power density, which makes it a relatively safe system.

### Parfocal System

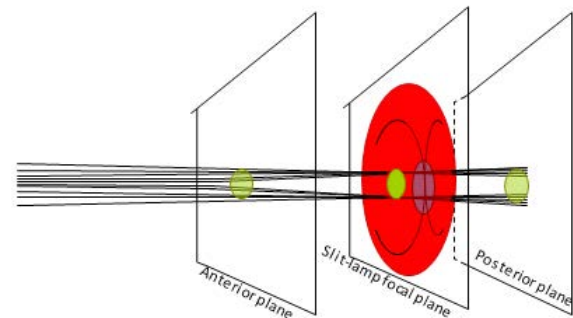


Figure 2. In parfocal system there is a coincidence between the focal plane of the slit lamp and the focal plane of the laser beam and the beam profile on the retina is tendentially sharp edged ("top-hat"), providing consistent and uniform energy distribution that results in crisp, well-defined retinal burns.

Before starting a photocoagulation session, the surgeon should correct the ametropia (adjusting the optical biomicroscope) to get a match between the two focal planes (laser and slit lamp).

### Defocused Beam Delivery Systems

A defocused optical system uses a beam with a very high beam divergence. The beam profile on the retina is Gaussian, with a gradually decreasing energy density towards the periphery<sup>3</sup>. The spot size is changed through a defocusing anteroposterior movement of the entire beam so that the retina is no longer positioned at the beam's waist, which causes the burn to become increasingly blurry.

A key advantage of defocused systems over parfocal technology is that the high beam divergence results in very low corneal radiant exposure, even at larger retinal spot sizes and, thus, minimizes the risk of inadvertent corneal burns. Furthermore, the system permits titration - a fine tweaking of the retinal spot size as well as its energy density - through the slit lamp movement. But, bearing in mind the macular area, this is not an advantage, on the contrary, it causes a non-predictable outcome of the retinal lesion burn, causing intense burns through a low movement forward or backward of the slit lamp's joystick, since there is an extreme increase in the irradiance due to slight movements (Figure 3).

The defocused system modifies the size of the laser spot by varying the distance between the focal planes of the laser beam and the slit lamp. This system is less safe, since minor depth fluctuations lead to significant changes in the size of the spot and, consequently, in its irradiance.

The spot appears with poorly defined edges as they are associated with two effects: the spot blurring which is not coincident with the two focal planes and the attenuation of the limits of the Gaussian distribution of the beam profile.

### SureSpot system

The SureSpot system is a laser delivery system with the features of the defocused system, but without its disadvantages. The variation of the spot size is changed due to

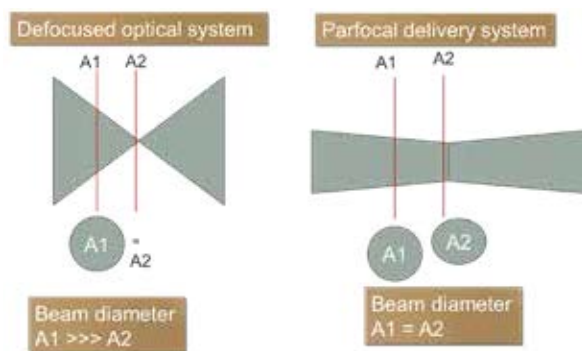


Figure 3. Defocusing the aiming beam creates a big difference between the laser beam diameter (A1 versus A2) in the defocused optical system opposite to the parfocal one.

the distance between the focal plane of the slit lamp and the focal plane of the laser beam<sup>3,4</sup>.

The inherent drawbacks of the defocused system are attenuated in the SureSpot system by changing the beam profile<sup>4</sup>. In the SureSpot system, the beam profile is not Gaussian, in fact it is the opposite. The power density is higher in the periphery of the spot and is reduced toward the center (Figure 4).

This beam profile improves the definition of the spot outside the focal plane of the laser beam and reduces the effect of variation in the power density with depth fluctuations.

The SureSpot optics offer the most advanced technology for laser delivery to the retina. The optics combine the best features of the standard defocused and parfocal optical systems to provide sharp and evenly distributed power on the retina, while maintaining low power density at the cornea and the lens.

### “SureSpot” System

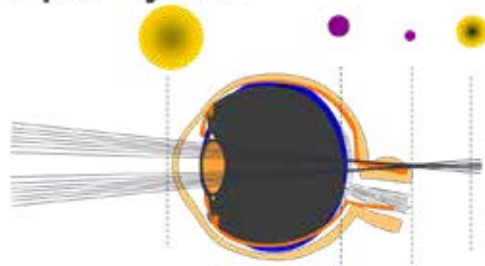


Figure 4. In the SureSpot system, the beam profile is not Gaussian, in fact it is the opposite. The power density is higher in the periphery of the spot and is reduced toward the center.

SureSpot offers several advantages<sup>4</sup>:

- Safety – very low power density on the cornea and lens tissue;
- Precision – Lumenis’ patented optics provide a true 50-micron spot;
- Efficacy – well-defined spot with uniform power density on the retina;
- Focused beam – the laser is always imaged at the slit-lamp focal plane to produce a sharp-edged treatment spot with uniform energy distribution at all spot sizes;
- Power Density – the convergence angle of the spot

remains large so that a lower power density is always maintained at the cornea.

### Accessory lenses for laser application using the slit lamp have two essential functions<sup>5-6</sup>

- a) allowing the laser spot to focus on the structures to be addressed, emphasizing the power density in these structures;
- b) making it possible to create a virtual image of the intraocular structures, which can be viewed through the slit lamp.

There are areas and anatomical structures that cannot be reached by the slit lamp. The accessory lenses are necessary for an optimal visualization and treatment of intraocular structures. The accessory lenses are essentially needed to focus the image of these structures at a point where they can be refocused at the slit lamp.

In addition, the accessory lenses enable the creation of a direct or indirect virtual image of these same anatomical structures (retina, iridocorneal angle) in a spatial location accessible to the focal planes of the slit lamp.

The indirect lens is a positive lens that creates an inverted virtual image of the fundus by refocusing the image upon a virtual space away from the eye<sup>4</sup>. The direct lens is a negative lens that compensates the positive power of the eye, creating a direct image of the eye inside the eye. The direct image for the central lens of the 3-mirror lens (with -60 diopters) creates a direct image of the central retina, in the plane of the posterior capsule of lens (Figure 5).

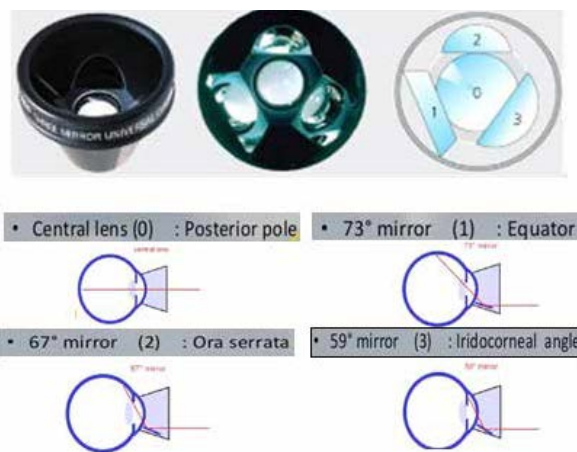


Figure 5. Schematic representation of the ocular structures seen and the mirror angles of the 3 mirror diagnostic and treatment lens.

These types of lenses frequently combine the imaging features necessary for the diagnosis, as well as for the treatment. There are two groups of accessory lenses<sup>6-9</sup>:

- 1) Contact lenses
- 2) Non-contact lenses.

In general, contact lenses are preferred as a means of laser application, providing a greater control over the movement of the eye and the positioning of the lens.

Contact lenses can address the anterior segment or pos-

terior segment. Among the former, there are several therapeutic lenses: Abraham, Peyman, Rich and Goldmann three-mirror lens, Ocular Instruments® and Volk® direct and indirect for the macula, the mid-periphery and the extreme periphery.

Besides fulfilling therapeutic functions, the Rich and Goldmann and other lenses also make the diagnosis possible, allowing the visualization of unreachable anatomical structures under direct observation by the slit lamp.

The next chapter will present the characteristics of the lenses used in laser treatments.

**B) INDIRECT OPHTHALMOSCOPY**

In the early 1980s, Mizuno<sup>10-11</sup> coupled a binocular indirect ophthalmoscope to an Argon laser via a fiber-optic cable, which was presented at the 19th Retina Society Meeting (1986). Although the first binocular indirect delivery system was innovative, it required several modifications before it could be considered a practical alternative to other methods of laser application in the peripheral retina. The indirect ophthalmoscopy laser delivery system provides an effective way to treat the peripheral retinal pathology, while maximizing patients' comfort. Obtaining the best possible view of the retina greatly facilitates the laser delivery. In several cases, the ocular medium can be obscured by vitreous hemorrhage, cataract formation or corneal edema. One of the main advantages of indirect ophthalmoscopy consists of a better visualization of a greater area of the fundus, especially in the cases of poor medium. The ROP laser procedure is highly recommended for pediatric patients, for this reason, this method was adopted by many ophthalmologists as the preferred modality for treating a variety of retinal diseases. In general, the indirect method preferred, but this may depend on the ophthalmologist's experience. The distance between the surgeon's headset and the patient's eye, or the working distance, are important factors for the surgeon to consider. If the working distance is too short, the surgeon will need to bend over a bit more in order to treat the patient, causing back discomfort. In general, physicians who are tall should keep some more working distance. The treatment of the anterior retina, especially in association with scleral depression, is also better achieved with indirect ophthalmoscopy.

The accessory lens creates a reversed virtual retinal image, as you would expect from a positive lens. Thus, the examiner should be familiar with the spatial reorientation of the details in the eye (Figure 6).

For the sake of simplicity, it shall be assumed that the lens is positioned close to the patient's cornea. If this is the case, and if we consider that the average dioptric power of the eye is 60 diopters (cornea = 40 + lens = 20), a lens of 10 diopters is responsible for a retinal 6X magnification (60/10) and a downsizing spot to 1/6 of its original size; a lens of 20 diopters is responsible for a magnification of the retinal image 3X (60/20) and a reduction of the spot size by one third; a lens of 30 diopters is responsible for a magnification of the retinal image 2X (60/30) and a reduction of the spot size to 1/2; a lens of 15 diopters is responsible for a magnification of the retinal image 4X (60/15) and a reduction of the spot size to 1/4 (Figure 7).

**Optical System of the Eye**

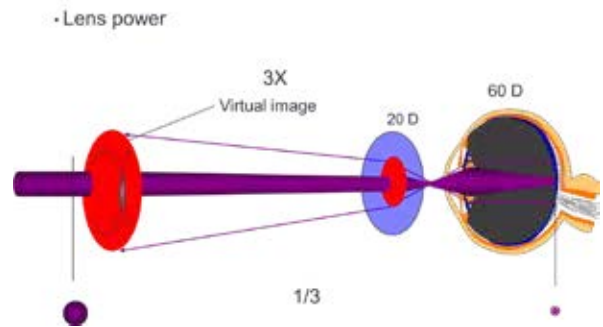


Figure 6. Accessory lens (in this case 20 D) creates a reversed virtual retinal image and the examiner should be familiar with the spatial reorientation of the details in the eye.

**Optical System of the Eye**

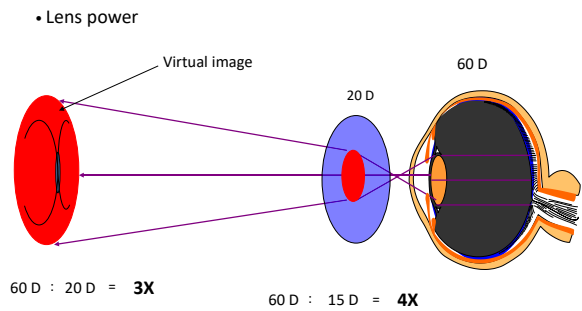


Figure 7. A lens of 20 diopters is responsible for a magnification of the retinal image 3X (60/20) and a reduction of the spot size by one third; a lens of 15 diopters is responsible for a magnification of the retinal image 4X (60/15) and a reduction of the spot size to 1/4.

**C) OPTICAL FIBERS**

Will be discussed in chapter 15.

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# I. The Essential

## 14. Contact lenses

### for LASER treatment



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#### INTRODUCTION

The purpose of auxiliary lenses is optimal visualization and treatment of intraocular structures<sup>1</sup>. Contact lenses are the preferred type of auxiliary lens because they allow both observation and safe treatment of the fundus and the anterior segment of the eye<sup>1</sup>.

Laser lenses have some common features such as a concave posterior surface, to adapt to the corneal curvature, and a concave, flat, or convex anterior surface. Other characteristics may include mirrors to allow the observation of the angle and periphery, a flange to stabilize the lens and prevent blinking, and a knurled edge to facilitate manipulation<sup>2</sup>. The lenses and mirrors are made of glass, bordered by a polymethyl methacrylate or aluminum shell<sup>1</sup>. The anti-reflective coating gives the lenses better definition images, allowing safer laser surgery<sup>2</sup>. Coupling solutions may be necessary for the use of some contact lenses.

For proper clinical lens usage, it is essential to consider its magnification, field of view and spot size<sup>3</sup>. The burn size on the retina compared to the setting at the slit lamp depends on which contact lens is to be used.

There are some contraindications for the use of contact lenses such as cases when patients have been submitted to a recent surgery, suffered a trauma or have abnormal corneal epithelium<sup>1</sup>.

#### CONTACT LENSES FOR ANTERIOR SEGMENT LASER SURGERY

##### LASER SURGERY FOR GLAUCOMA AND IRIS

###### Abraham Iridectomy lens

The Abraham iridectomy lens is a modified Goldmann-type fundus lens with an 8 mm diameter, 66 D, and a 1.6x magnification plano-convex button<sup>4</sup>. The convex lens enlarges the laser beam at the corneal surface, reducing the chances of epithelial corneal changes, and also decreases the laser beam

at the iris surface, increasing the power density. The power density at the cornea is one-fourth as great with the Abraham lens, but it is increased up to four times at the iris surface<sup>5</sup>.

###### Goldmann three-mirror lens

(See below)

###### Single mirror gonio laser lens

The single mirror gonio lens with a 62° mirror, simplifies viewing and treatment of the anterior chamber angle. It has a small diameter, which is easier to manipulate. The NMR-K (Kapetansky) style contact surface design allows gonioscopy and laser trabeculoplasty without methylcellulose<sup>4</sup>.

###### Ritch trabeculoplasty lens

The Ritch trabeculoplasty lens was designed with two 59° and two 64° mirrors and a 1.4x magnifying button placed over each of the 59° and 64° mirrors. The magnifying button reduces the laser spot size by 30% and increases the laser power by 2x<sup>4</sup>. It allows for gonioscopy, Argon Laser Trabeculoplasty (ALT) and Selective Laser Trabeculoplasty (SLT).

#### LASER SURGERY FOR THE PUPILLARY AREA AND SUTURE LYSIS

###### Abraham Capsulotomy YAG laser lens

The Abraham Capsulotomy YAG laser lens, with a diameter of 10.0 mm, has a plano-convex 1.8x magnification button positioned at the center of the lens. It reduces the possibility of pitting the IOL during Nd: YAG laser capsulotomy by stabilizing the patient's eye<sup>4</sup>.

###### Peyman G. Capsulotomy lens

Similar to the Abraham lens, designed for posterior capsulotomy, this lens has a 14 mm diameter anterior surface and central thickness of 12 mm, providing 1.8x magnification and a slightly longer working distance<sup>4</sup>.

### Hoskins nylon suture laser lens

The Hoskins lens (Figure 1) has a 3 mm contact diameter, a 79 mm handle and an image magnification of 1.2x. This lens is used to cut subconjunctival nylon sutures in post-operative situations, such as trabeculectomy flap sutures and cataract wound sutures. The conjunctival blood vessels compressed by the lens allow a clear view of the sutures<sup>4</sup>.



Figure 1. Hoskins lens.

### CONTACT LENSES FOR POSTERIOR SEGMENT LASER SURGERY

Contact Lenses for posterior segment laser surgery consist mainly of two kinds: the negative, or plano-concave lenses, and the positive, convex or high-plus lenses<sup>1,6,7</sup> (Table 1).

#### Plano-concave or negative lenses

The negative or plano-concave lens produces a virtual upright image of the fundus with marked resolution of a small area, which may be useful for the diagnosis and treatment of macular diseases<sup>6</sup>. With negative lenses there is no considerable disparity between the spot size setting of the slit lamp and the burn on the retina. All negative lenses imply shorter working distance for higher myopic patients, therefore, these patients are preferably treated using positive lenses<sup>8</sup>.

#### Goldmann lens

Goldmann fundus lens, the premier contact lens, is a negative lens of -64 D that gives an upright virtual image and is considered standard for macular work<sup>1</sup>.

#### Krieger /Yanuzzi lens

The Krieger lens is a biconcave lens of -92 D that provides an upright virtual image, like the Goldmann lens, but its ophthalmological image is posteriorly displaced at the anterior vitreous. It creates a wider field of view, but shows a decrease in lateral magnification<sup>8</sup>. Therefore, a larger retinal area is irradiated at any particular spot setting and the spot size adjustment is essential<sup>1</sup>.

The Yanuzzi lens is a modification of a prior model designed by Krieger, intended for macular photocoagulation. Theoretically, this lens has better optics than the Goldmann fundus lens, the concave corneal surface is steeper and has a larger diameter, which allows for less distortion to the cornea<sup>1</sup>.

#### Goldmann three-mirror lens

The Goldmann three-mirror lens (Figure 2) is a universal lens, ideal for vitreous visualization and for both observing and treating the posterior pole, retinal periphery and anterior segment<sup>2,6</sup>. It has a central lens (-67 D) with a flat anterior surface and it gives an erect image at the level of the posterior capsule<sup>1</sup>. This lens allows the treatment

in peripheral areas, using the mirrors, within the lens, at different angles (the mirror at 73°, for the equator to the posterior pole, the mirror at 67°, for the ora serrata to the equator and the mirror at 59°, for gonioscopy and trabeculoplasty)<sup>1</sup>. The biggest disadvantage of this lens is its limited field of view. Because of this limitation other lenses with better field of view have been developed<sup>1</sup>.



Figure 2. Goldmann three-mirror lens.

Care should be taken to avoid macula lesions when using the peripheral mirrors. The image of the retina must be seen to be displaced by rotating the lens, if not seen shifting, we are using the central mirror and we will seriously damage the macula.

#### Convex, positive or high-plus lenses

The positive, convex or high-plus lens gives a real but inverted image of the fundus<sup>1,6</sup>. It creates a wide field of view, permitting the simultaneous visualization of the posterior pole and the mid-periphery, reducing the chance of accidental treatment of the fovea which makes these lenses ideal for panretinal photocoagulation (PRP)<sup>3</sup>. In contrast to the plano-concave lens, the panfundoscopic lens produces a different spot size setting of the slit lamp when compared to the resultant retinal burn<sup>3</sup>. The field of view is increased in myopes and decreased in hyperopes<sup>3</sup>. The disadvantages of a positive lens are inverted images, lack of fine resolution and excessive irradiation upon the anterior segment, if a spot size larger than 1000 μm is used. Therefore, a 500 μm spot or less is advisable<sup>1,2,3</sup>.

#### Rodenstock Panfundoscopic lens

The Rodenstock Panfundoscopic lens, introduced in 1969, is the prototype of a panfundoscopic lens. The panfundoscopic lens produces an inverted, real image located in the spherical biconvex anterior lens, consequently requiring the biomicroscope to be pulled away from the patient<sup>1</sup>. It creates a wider field of view, with less lateral magnification and the spot size is 40% larger than the spot size setting of the slit lamp<sup>1,3</sup>. This lens is excellent for PRP from the posterior pole to beyond the equator and it may be helpful for the diagnosis of vitreo-retinal interface pathologies.

#### Mainster lens

The Mainster lens was introduced in 1986 and, like the panfundoscopic lens, it creates an inverted real image. However, the image is anteriorly located with regard to the biconvex anterior lens, which may require moving some patients backwards<sup>3</sup>. The Mainster lens was designed to overcome the small field of view of the Goldmann three-mirror lens and the lesser magnification of the panfundoscopic lens. Hence, it has an intermediate field of view and good lateral and axial magnification, which makes this lens excellent for retinal thickness evaluation, PRP and focal macular laser<sup>1</sup>. The Mainster widefield lens

is aspheric and has a better resolution and less distortion, when compared to Rodenstock lenses.

### Volk TransEquator lens

The primary application of Volk TransEquator lens (Figure 3) is mid-to-far peripheral retinal diagnosis and focal laser treatment<sup>8</sup>.

This double aspheric lens provides a wide field of view for panretinal imaging and treatment, from the posterior pole to the equator. It also allows dynamic movement on the globe with an increased functional field of view. It is a good substitute for the Rodenstock lens<sup>8</sup>.



Figure 3. Volk TransEquator lens.

### Volk QuadrAspheric lens

The Volk QuadrAspheric fundus lens (Figure 4), initially introduced in 1989, has become popular as a wide field fundus laser lens<sup>8</sup>. This lens' characteristic wide field causes a beam spread of approximately 40%, producing burns involving a larger diameter but with a lower energy density<sup>8</sup>. Its 28.6 mm diameter provides a clear advantage concerning peripheral retinal viewing<sup>8</sup>. It produces an inverted real image and its four aspheric surfaces are highly-efficient and have an antireflection coating, reducing peripheral aberrations and facilitating visualization through small pupils<sup>1,8</sup>.



Figure 4. Volk QuadrAspheric lens.

Table 1. Posterior segment laser contact lenses

	Field of view Static/Dynamic	Magnification	Laser spot magnification factor
<b>Macular Contact Lens</b>			
Goldmann three-mirror (central)	36°	0.93x	1.08x
Volk Super Macula 2.2	60°/78°	1.49x	0.67x
Volk Area Centralis	70°/84°	1.06x	0.94x
Volk HR Centralis	74°/88°	1.08x	0.93x
Ocular Mainster High Magnification	75°/88°	1.25x	0.80x
Ocular Mainster Standard Focal/Grid	90°/121°	0.96x	1.05x
Ocular Reichel- Mainster 1x	102°/133°	0.95x	1.05x
Ocular PDT 1.6x	120°/133°	0.63x	1.60xv
<b>PRP Contact Lens</b>			
Panfundoscopic (Rodenstock)	120°	0.71x	1.41x
Volk EquatorPlus	114°/137°	0.44x	2.27x
Volk TransEquator	110°/132°	0.70x	1.44x
Volk QuadrAspheric	120°/144°	0.51x	1.97x
Volk QuadPediatric	100°/120°	0.55x	1.82x
Volk SuperQuad160	160°/165°	0.50x	2.00x
Ocular Mainster Widefield	118°/127°	0.68x	1.50x
Ocular Mainster PRP 165	165°/180°	0.51x	1.96x
Ocular ProRetina 120 PB	120°/136°	0.50x	2.00x
Ocular Reichel- Mainster 2x	117°/142°	0.50x	2.00x

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# I. The Essential

## 15. Optical Fibers

### in LASER Output manipulation



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#### INTRODUCTION

Research and developments in laser technologies created new challenges and opportunities in using light for both medical diagnosis and therapy. Until the deployment of the first laser systems, in the early 1960s, light was used mainly for phototherapy procedures over easy access treatment areas. The development of optical fiber manufacturing processes and technologies made optical fiber endoscopy possible: the optical fiber emerged as the needed tool for safe and practical delivery and collection of laser light, answering to the challenge of using properly configured optical beams in specific light-tissue interactions. This chapter discusses the use of optical fiber technology and materials within laser light applications in the medical field.

In general, a particular medical laser-tissue interaction may be achieved with different laser configurations. Laser light has very unique properties, in particular wavelength definition, brightness, directionality, spatial and time coherence, and a well defined polarization state. These properties have to be carefully matched to the desired laser-biotissue interaction. After choosing the interaction process, tools are needed to deliver and manipulate the light beam, to irradiate the target tissues, and to produce the appropriate optical fluence.

Waveguides are physical devices that allow the transport of radiation through space, minimizing the loss of energy while spatially confining the radiation transport. The name waveguide derives from the electromagnetic nature of light, and is also employed for microwave or radio-frequency radiation. Optical fibers and articulated-arm systems are specific examples of waveguides commonly used in Medical systems.

Waveguides have an input port (for instance the laser system box) and an output port at the beam delivery location, and light propagates between these two points in such a manner the user does not need to worry about beam alignment and energy loss.

Optical fibers are the most appealing light waveguide. Drawn from plastic or silica materials, optical fiber diameters range from a few micrometers to about 1mm. The fibers are normally very light and flexible, allowing easy manipulation, and long distance (>100 km) light guidance, depending on the match between light and optical fiber properties. In fact, the performance of optical fibers was unveiled by Charles Kao just about the time laser systems were being deployed in the early 1960s. Charles Kao understood how glass material properties could be enhanced to tremendously reduce energy losses during light propagation, allowing the development of long-haul fiber communications, but also the development of fiber based endoscopy technologies<sup>1</sup>. Most recently, the deployment of new fiber lasers, where the laser amplifying medium is composed of rare-earth doped fibers, allows the development of compact, high efficiency, and easy integration systems<sup>2</sup>.

#### OPTICAL FIBER STRUCTURE

Optical fibers are produced by drawing structured glass preforms at high temperature, resulting in a cylindrical structure with a core (the central material) and a cladding (layer of material surrounding the core). Additional layers are added, such as buffer materials and an external protective jacket, in order to enhance the chemical and mechanical resistance properties of the fiber. The core material has a high refractive index, and a diameter within the range of 5 to 1000  $\mu\text{m}$ . The cladding layer is characterized by a refractive index with a value lower than that of the core, and its thickness is around 60  $\mu\text{m}$ .

#### HOW DO OPTICAL FIBERS WORK?

Optical fibers light guidance may be understood from the simple physics laws of reflection and refraction of waves at material interfaces. Understanding these laws allows one to fully grasp the behavior of light at the exit fiber tip.

When light crosses the boundary between two distinct optical materials its propagation direction changes – it refracts. Each material is characterized by its “refractive index”, a material constant that relates the speed of light in vacuum to the speed of light in the material. In free air, the refractive index is around 1, while in water it is around 1.33, and in glass around 1.5. This number describes how light slightly slows down when propagating in solid materials.

To describe refraction through a mathematical law, consider an input material of refractive index  $n_{in}$ , in which a light beam propagates, and a second adjacent material of refractive index  $n_{out}$ . The beam of light is incident at the interface of the two materials at an angle  $\theta_{in}$ , relative to the normal interface.

Snell-Descartes law, allows the determination of the output beam direction  $\theta_{out}$ . With some simple maths, Snell-Descartes Law can be rewritten as:

$$\sin \theta_{out} = \frac{n_{in}}{n_{out}} \sin \theta_{in}$$

When the output material has a higher refractive index,  $n_{out} > n_{in}$ , Snell’s law indicates that the output beam direction tends to approach the normal direction of the interface,  $\theta_{out} < \theta_{in}$ . That is depicted by rays r1 and r2 in Figure 1a), where the normal interface is represented by dashed lines. The effect is reversed for light traveling from a higher to lower refractive index material, as illustrated by the transmission of ray r2 to r3. In the absence of absorption, the energy available in the incident beam at each media interface is distributed between the transmitted and reflected beams. The energy distribution into Reflected and Transmitted beams may be calculated from the well-known Fresnel equations. The reflected beam arising from a beam at small angle of incidence will carry a few percent of the initial energy; the energy of the reflected beam increases with increasing incidence angle, and reaches 100% for incidence angles larger than the critical angle, or at grazing incidence.

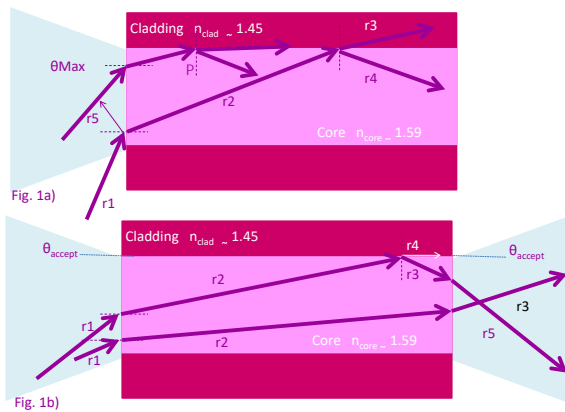


Figure 1. a) Ray tracing of reflection and refraction laws within the core of a waveguide; b) Launching light into waveguides, and the structure of the output beam.

An important and observable consequence of Snell-Descartes law occurs when  $n_{in} > n_{out}$ : light is fully reflected in a certain range of angles of incidence, with no light being

transmitted to the second medium (ray incident at point P in Figure 1a). The smallest angle of incidence for which total internal reflectance occurs is known as the Critical Angle, corresponding to the incidence direction that yields a refracted beam at  $\theta_{out} = 90$  deg. Total Internal Reflectance (TIR) is the basis of light confinement and guidance along optical fibers and other generic waveguides.

The Critical Angle value depends on the fiber core and cladding refractive indexes, through Snell’s law, and will have a corresponding maximum incidence angle at the input fiber facet, marked as  $\theta_{Max}$  in Figure 1a. When light is injected into the fiber core, only the input rays within the cone limited by  $\theta_{Max}$ , the acceptance cone, will be guided along the fiber; any light out of the acceptance cone will propagate within a very short distance in the fiber until it is fully lost through the core-cladding interface. The cone of acceptance also defines how light is transmitted at the fiber tip: the guided light emerges from the output fiber tip, diverging, with a maximum transmission angle  $\theta_{accept}$  (Figure 1b).

In medical applications endoscopic fibers may be immersed in liquids (of refractive index  $n_{ext}$ ). In this case, the acceptance cone may be estimated from the Numerical Aperture NA (derived from Snell-Descartes law):

$$NA = n_{ext} \sin \theta_{accept} = \sqrt{n_{core}^2 - n_{cladding}^2}$$

Optical fibers within flexible endoscopes are used for both light delivery and collection, and can be employed without further optical elements. The NA of standard fibers is typically within 0.1 – 0.5, corresponding to  $\Delta\theta_{accept}$  of 6 – 30 degrees in air. For the same fiber, the light cone exiting the fiber will be less divergent inside bio-tissue, or water solutions, as compared to what can be observed in the free space beam.

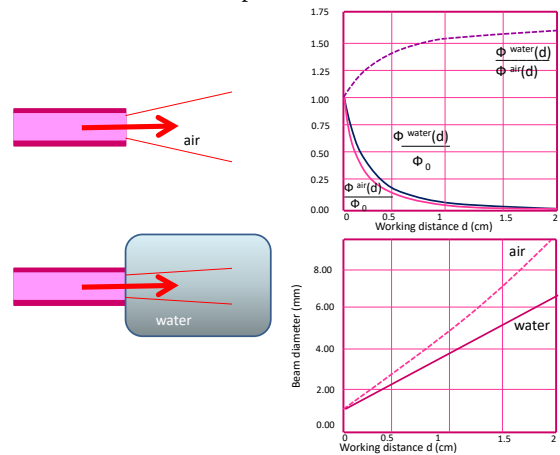


Figure 2. ZrF optical fiber (600 μm diameter, NA=0.2, λ<2400 nm) in free space ( $n_{air}=1.0$ ) and water ( $n_{water}=1.33$ ): (top graph) ratio of fluence  $\Phi(d)$  to the maximum fluence at the fiber tip  $\Phi_0$ ; (bottom graph) beam diameter at different working distances.

Increasing the working distance between the fiber tip and the target tissue will enlarge the illuminated tissue spot. The induced effect upon the illuminated tissue depends on the delivered fluence  $\Phi$  (spatial concentration of laser



energy, in  $J/cm^2$ ) and the irradiance (spatial power density,  $W/cm^2$ ). Both these quantities depend on the spot size. Hence, the maximum available fluence will be higher when delivered in water like tissues, as compared to a free space beam delivery. These quantities are illustrated in Figure 2.

### SPECIAL OPTICAL FIBERS

Standard fibers are typically made of silica glass of high purity, a material with very low light energy absorption within the visible (VIS) and near infrared (NIR) spectral ranges, up to  $2\ \mu m$  wavelengths. This range serves lasers often used in laser clinics, such as Nd:YAG, Nd:YAG+KTP, Argon, Er:YAG, Ho:YAG<sup>3</sup>. Other fiber types are commercially available, such as doped silica or germanium oxide fibers for NIR, or plastic fibers for VIS light. In general, all these materials are performance limited in the UV and IR ranges, where the optical absorption of the fiber material becomes significant. Other devices must be used in these situations. The “articulated arm” is employed for invisible IR or UV radiation. It is assembled from a collection of rigid hollow straight elements interconnected by rotating joints. At the core of each joint, two reflective optical elements (mirrors or prisms) allow the light beam to be redirected along the joined elements up to the final beam delivery location. The rigid articulated structure may limit the degrees of freedom regarding the positioning and manipulation of the terminal hand-piece.

In recent decades, companies and research institutes have been developing new technologies to produce new fibers that can overcome the limitations of articulated arm systems and of standard fibers. One of the most prominent solutions is hollow core fibers for the IR spectral range, used in Er:YAG laser ablation<sup>4</sup>. The tip of these fibers may be closed with a transparent window, preventing dirt from filling the hollow core (Figure 3). Hollow fibers are semi-rigid, with core sizes larger than  $100\ \mu m$ , guiding up to  $20\ W$  average optical power, at Er:YAG and CO<sub>2</sub> laser wavelengths.



Figure 3. Hollow fiber (silica or metal) for infrared radiation (adapted from <sup>5</sup>. Courtesy of Laser Components, GmbH).

### SMALL VS LARGE CORE FIBERS

Optical fibers are available in a wide range of core sizes. Often, large core fibers (up to  $1\ mm$  diameter) with high NA will be preferred for efficient light illumination and high power lasers, increasing the efficiency of launching light into the fiber core, and producing a large illumination spot at the target tissue. Nevertheless, large core fiber rigidity, as compared to smaller core fibers, makes their use much more difficult in guided optical fiber endoscopes. Small core fibers are extremely flexible: they can be entangled along their length, and can be bent down very small curvature radius, down to one centimeter or less, without compromising their wave-guiding properties. Hence, small core fibers are used within small

size endoscopes with some kind of mechanical devices that force the local bending of the fiber tip in such a way that light can be precisely delivered, within a wide field of view. The potential problems of bending optical fibers are not only related to their physical and mechanical integrity, but also to optical power loss! The physical bending of optical fibers changes the wave-guiding conditions in the curved region. Light that is guided in a straight fiber section may leak to the curved region cladding layers, reducing the available power after that point. If the fiber is used to guide a high power laser, the bending loss point may also become a very hot and hazardous point.

### ENERGY DISTRIBUTION AT THE FIBER TIP

The quality of the beam exiting the optical fiber is strongly dependent on the fiber core size. A high quality beam is associated with a smooth and regular energy distribution following a Gaussian or top-hat shaped curve. The beam quality derives from the number of energy modes the fiber is able to guide. The smallest the number, the higher the quality. Single-mode fibers are those that exhibiting single mode propagation at a certain wavelength band. As the fiber core size increases, or if the fiber is used for lower wavelength light, the number of possible propagating modes increases, resulting in a complex energy distribution at the output and vicinity of the fiber tip, with a complex space distribution of hot- and dark-spots<sup>6</sup> (Figure 4).

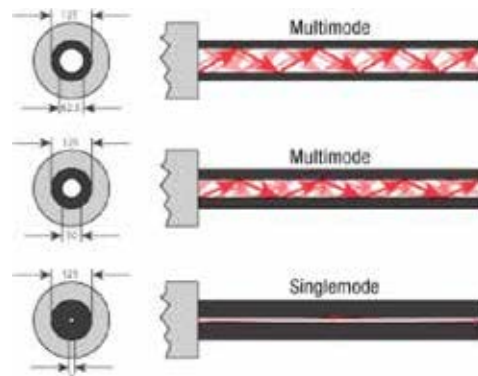


Figure 4. Optical fibre multimodal mode and single-mode. (Adapted from<sup>6</sup>. Courtesy of James Ogden from Extron Electronics Europe).

In this case, the fiber is designated as Multi-mode (MM). Additional consequences of the unexpected energy modal distribution of MM fibers are variability of the energy pattern due to repositioning, bending, or even mechanical pressure on the optical fiber cable<sup>7</sup>(Figure 5). These effects are also present when using the semi rigid hollow-core fibers (Figure 6)<sup>8</sup>, for which the minimum allowed bending radius is of the order of  $30-40\ cm$ . Single-mode fibers have diameters of the order of some micrometers, and require high precision alignments to maximize the guided optical power. High power lasers are difficult to couple into these fibers, so multimode fibers, of the order of  $100-200\ \mu m$  core sizes, are usually preferred. Large-mode-area (LMA) fibers offer the possibility of using a larger core, while preserving single mode operation.

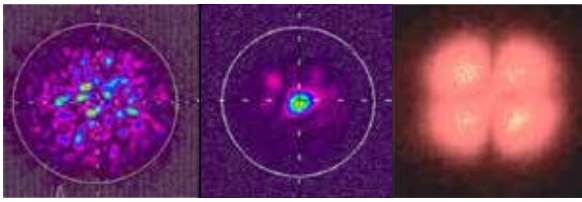


Figure 5. Optical fiber single-mode (SM) vs multi-mode (MM) operation: (left) typical size and mode guiding; (center) MM and SM spot energy distribution; (right) LM<sub>21</sub> multi-mode (adapted from<sup>7</sup>. Courtesy of Rebecca Robinson from the Optical Society).

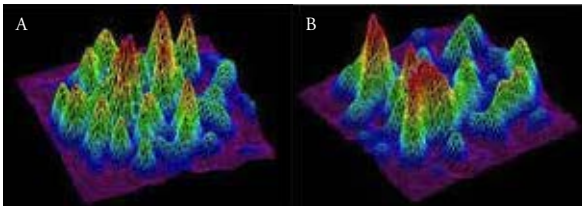


Figure 6. Impact of A) small and B) large hollow fiber curvature on the spot energy spatial distribution. Courtesy of Ophir Photonics Group – Laser Measurement<sup>8</sup>.

### SAFETY HAZARDS AND MEASURES

The use of light tools involving high power lasers and optical fibers demands awareness of the inherent risks and hazards<sup>9</sup>. Modern systems are designed for safety operation and should be equipped with suitable automated interlocks. Nevertheless, the hazards are not confined to laser systems.

**Burn hazards:** optical fiber tips may require a significant amount of time to cool down after the laser has been switched off. As mentioned above, most of the optical fiber delivery systems are characterized as having a low NA: the delivered beam may be concentrated enough to cause damage even in the event of a non-intentional exposure to the output beam. In addition, beam blockers and mirrors which are reached may become extremely hot during light irradiation.

**Fire hazards:** laser treatment areas are rich in oxygen, heat and combustible materials. Endoscope protection layers may be flammable, and should not be exposed to laser radiation. Fire hazard is most critical whenever oxygen gas may be present, even if a small leakage occurs in the vicinity of laser delivery.

**Deviations to planned treatment:** the articulated arm employed for invisible (UV or NIR) radiation delivery uses a visible laser, usually red, to identify the real location of the laser beam. The quality of the alignment and superposition of both visible and invisible lasers is paramount to ensure that the proper laser procedure is applied on the targeted tissue. Misalignments will lead to unpredictable light delivery. As a rule of thumb, during procedures assisted by waveguides, optical fibers and articulated arm light delivery systems, the procedure should be immediately interrupted if the expected light induced effect is not observed. Systems should be checked under controlled conditions. In the case of fibers, the fiber tip should be carefully inspected: a broken optical fiber will generate a severely distorted energy pattern, with possible enlarged irradiation volume and hotspots. In addition, although the fiber material is inert, the presence of small optical fiber debris arising from broken fibers may be deposited in the targeted tissues and trigger inflammation reaction.

### SUMMARY / CONCLUSION

Fiber optics technology and optical fiber manufacturing developments have produced handy and efficient tools for light manipulation in laser assisted medical procedures. Light exits the fiber tip within a cone of light defined by the fiber's numerical aperture, NA. The NA can be small, allowing fibers to be used without the need for further collimating optics, while providing high irradiance spots in front of the fiber tip. Furthermore, additional hand-pieces can be coupled to the fiber to produce different illumination conditions or to optimize light collection in fiber assisted imaging / endoscopy. When using standard optical fibers, the light cone exiting the fiber will be less divergent inside bio-tissue, or water solutions, as compared to that which can be observed in the free space beam. Hence, the maximum available fluence will be higher when delivered in water-like tissues, as compared to free space beam delivery. The light spot energy distribution at the fiber tip depends on the modal energy distribution, fiber bending conditions, and fiber properties. Smaller core diameter is associated with better beam quality. Larger cores are suitable for higher power delivery. Nevertheless, it is important to emphasize the achieved energy transfer, including heat, strongly depends on the optical and thermal properties of the media surrounding the targeted illumination volume. Nowadays, high optical powers can be delivered by optical fibers; special care should be taken to ensure proper conditions of fiber cables and exiting fiber tips, as excessive fiber bending and broken optical fiber tips constitute hazardous points.

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# II. LASER Surgery in Cornea

## 16. Excimer LASER



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### INTRODUCTION

Laser light consists of a coherent (in phase), polarized, monochromatic beam, generated by the stimulated and amplified emission of excited electrons. It requires an excitation and an amplification system. Once laser comes into contact with body tissues, four distinct processes may take action: absorption, transmission, reflection and dispersion. Absorption and transmission have the biggest impact on the human cornea. At wavelengths below 350 nm absorption occurs, while values above this limit are essentially only transmitted. Depending on the wavelength properties, three processes can occur after photoabsorption, namely photothermal, photodisruptive and photochemical effects. Photochemical effects, which occur at short wavelengths, can in turn be divided into photoradiation and photoablation. For refractive surgery, photoablation is of interest, with its action being limited to a few microns on the superficial corneal surface. Excimer lasers (short for excited dimer) work through the excitation of an argon-halogen gas mixture through high pulsed energy, leading to the generation of an unstable, high energy dimer. When returning to a stable state, these dimers emit high-energy photons at wavelengths of 193 nm. The hereby generated energy is amplified by a ceramic resonance chamber responsible for fluence, which must remain constant and generates emissions between 180-200 mJ/cm<sup>2</sup>. As the laser beam comes into contact with the corneal surface, molecular bonds are broken, causing targeted tissue disruption and vaporization called ablative photodecomposition. The energy generated through this process is dispersed through the plume effect, which is a supersonic ejection of molecular fragments, and which thereby avoids collateral thermal damage. Through the use of various mirrors, lenses and prisms it is possible to generate a homogeneous beam. The photoablative energy reaches the corneal surface through a delivery system, which can work through different mechanisms: scanning slit delivery uses a diaphragm to create a rectangular

beam, while an incorporated rotary motion allows one to change the target direction. Through this mechanism, it is possible to correct all forms of ametropia. Scanning slit delivery is better than full-beam delivery systems which cause less discriminate exposure and consequently a more irregular ablation and collateral thermal damage. Another variant is a flying spot delivery system in which small, round beams are generated, creating single small ablations with a Gaussian distribution of ablation intensity. In order to create a regular surface, it is necessary to couple various spots at half their diameter points. Through this minute splitting of laser emission, asymmetric patterns of ablation can be generated in association with topography readings or wavefront analyzers. The more specifically directed the delivery system, the more prone to decentralization it is, therefore demanding an eye tracker system. Since a shorter pulse reduces the risk of thermal damage, flying spot excimer lasers are of benefit, due to their very high pulse frequency. Computerized systems allow for the control of different parameters such as pulse duration, frequency, energy, fluence and rate of ablation whilst also allowing the precise calculation of the ablative profile<sup>1</sup>.

### INDICATIONS

The patient should be 18 years or older, and should have a stable refractive error i.e. within +/- 0.5D in the last 12 months<sup>2</sup>. Recently the American Academy of Ophthalmology (AAO) recommended the cut-off to be 21 years of age<sup>3</sup>. The Food and Drug Administration (FDA) established limits for ametropia correction are indicated below in brackets, although in practice, values above -10.0D and +4D are dreaded because of unpredictability of results outside this range<sup>2</sup>.

### LASIK:

Mild to moderate myopia  $\leq -8D$  sphere ( $\leq -14D$ ); mild to moderate hypermetropia  $\leq +4D$  sphere ( $\leq +6D$ ) and mild to moderate astigmatism  $\leq 5D$  cylinder ( $\leq 6D$ ). A corneal pachymetry  $>500 \mu\text{m}$ , a residual stromal thickness (after

## 16. Excimer LASER

flap removal) of 250  $\mu\text{m}$  (PTA – percentage of tissue altered - under 40%)<sup>2</sup> and a post-operative keratometry of 35/36-48/50D are needed<sup>1,2</sup>. It is especially indicated where rapid visual recovery is required and where there are concerns about post-operative pain<sup>4</sup>.

### PRK:

Mild to moderate myopia  $\leq -6$  sphere ( $\leq -12\text{D}$ ); low hypermetropia  $\leq +4\text{D}$  sphere ( $\leq +5\text{D}$ ), low to moderate astigmatism  $\leq 4\text{D}$  cylinder ( $\leq 4\text{D}$ )<sup>2</sup>. Situations where the creation of a corneal flap is not ideal, like in the case of an epithelial basement membrane disease, are of interest<sup>1,2</sup>. Recently the combined treatment of PRK and corneal collagen cross-linking has been suggested in low-grade keratoconus<sup>5</sup>.

### LASEK:

This technique is especially indicated in patients with a corneal pachymetry of less than 500  $\mu\text{m}$ , deep set eyes or narrow palpebral fissures, post-LASIK correction of the flap, previous intolerance to LASIK in the fellow eye, those who are at an increased risk of trauma and in the case of recurrent epithelial erosions (REE)<sup>1,5,7</sup>. In REE, surface ablation techniques may even have therapeutic properties<sup>4</sup>. They are also a more economical option in comparison to LASIK<sup>5</sup> and additionally may save up to 50-100  $\mu\text{m}$  of corneal stroma in comparison to the former option<sup>4</sup>. Moreover, following intraocular lens implantation procedures, corrections can be performed as soon as 4-6 weeks after surgery<sup>4</sup>.

## CONTRAINDICATIONS<sup>1-4,8</sup>

Absolute contraindications(CI)	Relative contraindications (warning and precaution situations)
<ul style="list-style-type: none"> <li>- Systemic autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, Sjögren's disease, relapsing polichondritis, Wegener's granulomatosis, seronegative spondylarthropathies, among others</li> <li>- Immunodeficiency (HIV is sometimes listed as a relative CI)</li> <li>- Uncontrolled ocular surface disease and other corneal affections like interstitial or neurotrophic keratitis and extensive vascularization</li> <li>- High-grade keratoconus, keratoglobus or pellucid marginal degeneration</li> <li>- Insufficient corneal thickness for the proposed ablation depth</li> <li>- Acute infections of the ocular surface and adnexa</li> <li>- Uncontrolled ocular allergy</li> <li>- Isotretinoin or amiodarone use</li> <li>- Pregnant or nursing women (sometimes listed as relative CI)</li> <li>- Uncontrolled diabetes mellitus</li> <li>- Uncontrolled glaucoma</li> <li>- Significant cataract</li> <li>- LASIK in severe uncontrolled tear production deficiency, epithelial basement membrane dystrophies, Fuchs corneal dystrophy or family history, or significant corneal guttata</li> <li>- PRK in known epithelial healing disorders</li> </ul>	<ul style="list-style-type: none"> <li>- Patients under the age of 18 years (AAO: 21 years). Consider in severe anisometropia or refractive ametropia</li> <li>- Corneal abnormality, excessively steep or flat corneas</li> <li>- Significant irregular astigmatism</li> <li>- Functional monocularity</li> <li>- Controlled glaucoma</li> <li>- Controlled diabetes mellitus</li> <li>- History of uveitis</li> <li>- Incipient cataract</li> <li>- Past history of Herpes simplex or Zoster keratitis</li> <li>- Atopic keratoconjunctivitis</li> <li>- Previous ocular surgery or trauma in the ablation zone</li> <li>- Dermatologic keloid</li> <li>- Sumatriptan use</li> <li>- LASIK in wide pupils, superficial corneal opacities, deep-set eyes and small palpebral fissures and a history of dry eye disease</li> <li>- PRK in predisposition to haze formation and the requirement for a rapid visual recovery</li> </ul>



## PREPARATION

1. Confirm eligibility.
2. Obtain a thorough clinical and ophthalmic history along with current systemic and topical medication use. Important factors that should be taken into account are the patients' age, refractive stability, corneal thickness, occupation and expectations<sup>2</sup>.
3. If there is a history of contact lens use, the examination should be performed after suspending their use for 3 to 5 days, for soft lenses, and 3 weeks for RGP lenses<sup>1</sup>.
4. Perform an extensive refractive evaluation, which should include cycloplegic refraction, dominant eye assessment, pupil diameter measurement, corneal topography, pachymetry, intraocular pressure measurement and complete examination of the anterior and posterior segments and tear film. Address ocular motility issues. A careful examination of the eyelids is also of high importance<sup>1,2</sup>.
5. Explain the procedure and manage patient expectations, referring the possible need for multiple sessions or other procedures.
6. Test the laser for calibration, adequacy of beam profile and alignment. Room environment should be compliant with laser safety guidelines.
7. Apply topical anesthesia and antibiotics.
8. Emphasize importance of eye fixation during the whole procedure.

## LASER TECHNIQUE

### LASIK<sup>7,9</sup>

1. Obtain a superficial corneal flap with the aid of a microkeratome or with femtosecond laser. Newer femtosecond laser platforms have shown a higher predictability in flap thickness and morphology, allowing for safer surgery without the increased risk of inflammation. Define the ring size and progression-stop point according to the corneal keratometry. Consider positioning a Chayet Ring to prevent debris accumulation and to rest the epithelial side of the flap against during surgery.
2. Perform stromal ablation guided by corneal topography or wavefront analysis.
3. Perform interface cleaning – Use non-fragmenting sponge material like MEROCEL<sup>®</sup> to avoid any fragments getting trapped within the interface.
4. Reposition the corneal flap.
5. Instill antibiotic and steroid drops.

### PRK<sup>1,4,7</sup>

1. Apply an optical-zone marker on the corneal surface that is 1mm larger than the treatment zone.
2. Apply a diluted alcohol solution (18-20%) over the epithelium for 20-30 seconds. It is very important to make sure that none of the alcohol contacts with corneal limbal cells. Afterwards remove the alcohol with a balanced salt solution.
3. Remove the epithelium out of the optical-zone mark. Make sure to remove all the epithelium with a microsurgical sponge, and remove epithelium remnants with the help of the excimer lasers' ultraviolet light. Ultimately, perform a scraping

of Bowman's membrane and make sure all the epithelium is removed.

4. Perform stromal ablation one minute after epithelial removal. Interrupt the procedure every time the patient breaks fixation.
5. Instill antibiotic and steroid drops.
6. Apply a bandage contact lens with the help of conjunctival forceps and a microsponge.

### LASEK – Azar flap technique<sup>1,4</sup>

1. Apply multiple circular marks adjacent to the corneal periphery in a flower pattern.
2. A 7-9 mm semi-sharp marker embedded in an 18-20% alcohol solution is applied over the area to treat for 25-30 seconds. Use a dry cellulose sponge to remove the alcohol solution.
3. Separate the epithelium from the underlying cornea with a modified Vannas scissors (one armed), leaving a hinge at the 12 o'clock position comprising about 90 degrees.
4. Displace the separated epithelium, so that it remains attached only by the hinge region.
5. Perform stromal ablation.
6. Hydrate the anterior stroma through intermittent irrigation.
7. Reapply the epithelium, paying special attention to the correct alignment according to previous marks.
8. Let the flap dry for 2-5 minutes.
9. Instill topical steroids and a topical antibiotic.
10. Apply a bandage contact lens without touching it with the help of conjunctival forceps and a microsponge.

Other techniques, such as the Camellin, Vinciguerra butterfly and the McDonald techniques can be used, but a detailed description of these techniques is beyond the scope of this chapter.

### Epi-LASIK<sup>1,4</sup>

1. Mark the epithelial surface with two concentric circles intersected by eight radial lines with the help of an Epi-LASIK maker.
2. Cool the cornea with BSS for 30 seconds.
3. A Barraquer tonometer is used to employ suction on the cornea.
4. Perform epithelial separation with the aid of an *epitome*.
5. Displace the corneal flap nasally with the help of a MEROCEL<sup>®</sup> sponge.
6. Perform stromal photoablation.
7. Repeat the cooling procedure immediately after.
8. Reposition the epithelial flap with the help of a metallic spatula, and restore possible folds through continuous irrigation.
9. Apply a therapeutic contact lens.

## POST-LASER CARE AND FOLLOW UP

After LASIK, apply antibiotic drops four times daily for 1 week and topical corticosteroids four times daily in the first week, followed by a taper over 2 or 3 weeks. In PRK, LASEK and epi-LASIK the therapeutic regimen is to be maintained over a longer period of 3 weeks to several months<sup>1,4</sup>. Consider preservative-free hyaluronic acid

artificial tears for 1–4 months post-operatively according to individual patient need, especially after LASIK procedures<sup>1</sup>. In the case of post-operative pain, topical non-steroidal inflammatory drugs and systemic analgesics can be used in the first 48/72 hours. When a bandage contact lens is applied, its removal is indicated 3 to 5 days after epithelialization has occurred<sup>1,4</sup>. In PRK, a shorter use of topical steroids is acceptable since controversy exists regarding its benefits<sup>10</sup>. Recently the application of mitomycin C has been advocated as a prophylactic method to avoid corneal haze in high risk patients<sup>5,7</sup>. For the monitoring of intraocular pressure (IOP) it is very important to emphasize that Goldman tonometry may significantly underestimate values. Tonopen application at the peripheral cornea has proven to be the less affected method for IOP determination after refractive surgery<sup>11</sup>.

### COMPLICATIONS

In LASIK, microkeratome handling can give rise to flap defects, namely thin, irregular or buttonholed flaps, with steep, flat corneas and deep set orbits being particularly at risk. This complication is reported to occur in 0.3-0.75% of cases, according to major studies. Incomplete or dislodged flaps with folds, epithelial defects, and corneal perforation are other possible complications<sup>1,12</sup>. One has to be particularly aware of the induction of corneal ectasia as it can induce keratoconus-like conditions. Refractive complications include overcorrection and undercorrection issues, induction of corneal islands, flap dislodgement, residual or induced astigmatism, halos and glare and loss of contrast sensitivity<sup>1,12</sup>. Loss of best-corrected visual acuity (BCVA) can be caused by infectious complications, diffuse lamellar keratitis or epithelial ingrowth into the lamellar interface (4.3%)<sup>12</sup> and very importantly, dry eye symptoms which occur in up to 95% of patients<sup>2</sup>. This probably occurs due to corneal denervation, which is essential for tear film homeostasis<sup>13</sup>. Dry eye disease can be effectively managed with preservative-free lubricants, punctal occlusion, topical cyclosporine emulsion, topical steroids, or even autologous serum, amniotic membrane transplantation and scleral lenses if necessary<sup>8</sup>. Recently, the importance of metalloproteinases, especially MMP<sup>9</sup>, has been advocated to treat perioperative ocular surface disease<sup>8</sup>. Also, a novel secretagogue, diquafosol tetrasodium solution, has been advised for post-LASIK dry eye<sup>8</sup>. In PRK, intraoperative complications include insufficient epithelial removal or the occurrence of minimal corneal decentrations, which can give rise to incorrect ablations. Post-operative complications include delayed epithelial regenerations, infectious processes, monocular diplopia, ghost images, decreased contrast sensitivity, halos and glare. Post-operative pain in the first 24 hours is very common. The appearance of corneal haze, peaking 3 months post-operatively, is a very important side effect<sup>14</sup>. Recently the application of ice-chilled irrigation solution has been advocated to reduce the incidence of post-PRK corneal haze<sup>4</sup>. The use of Mitomycin C in established haze and as a preventive treatment in high risk patients has also been described<sup>5,7</sup>. Haze is, however, frequently transitory, generally resolving after 18 months.

In general, LASEK presents less pronounced complications, since it conjugates aspects of the former two techniques. Possible complications include free epithelial flaps, dissolution, fragments, folds and slips but serious complications have not been largely described in literature. Post-operative pain is often less pronounced than with PRK<sup>1</sup>. Despite some controversy in literature, it is described as having advantages over LASIK and PRK, such as less induced ectasia in comparison to LASIK and less induced haze than in PRK<sup>4</sup>. The vitality of the epithelial flap is probably a crucial factor in reducing the wound response and inflammation in the origin of haze<sup>6</sup>. In Epi-LASIK a 3% incidence of stromal penetration was recorded with the use of epikeratomes, although without serious impacts on visual acuity. A mild haze was rarely detected at 3 months' follow-up, with spontaneous resolution thereafter<sup>1</sup>.

### RESULTS

Laser refractive surgery has become an extremely popular technique to correct ametropia. In order to have the expected results, indications have to be followed strictly and expectations must be thoroughly discussed. Many studies compare the advantages of one technique over the other, although there does not seem to be a clear advantage when it comes to the final visual outcome. LASIK permits the treatment of higher myopias<sup>1,2,7</sup> and it allows for a more rapid and pain-free recovery. It is reported by some authors to be safer and more efficacious than other techniques<sup>15</sup>, notwithstanding the possible incidence of total higher order aberrations and fourth order vertical coma<sup>7</sup>. PRK has a lower incidence of corneal ectasia but results in a more difficult post-operative period and can have the important side effect of haze. For LASEK, a lower overall incidence of complications has been described<sup>1,6,7</sup>. In general, retreatment is needed in 0-6.7% along 4 years, in all techniques, according to different authors<sup>1</sup>. Overall, photoablative refractive surgery exhibits excellent results with a great impact on quality of life and patient satisfaction of over 95%<sup>16</sup>.

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# II. LASER Surgery in Cornea

## 17. Femtosecond

## LASER in Refractive

## Surgery



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Femtosecond laser was first introduced in late 2001<sup>1</sup>. It has been crucial for the progression of corneal refractive surgery and its application has increased. It allows precise intrastromal cuts, and it can be applied for the flap formation in laser-assisted *in situ* keratomileusis (LASIK) surgery, small incision lenticule extraction (SMILE), astigmatic keratotomy, channel creation for intracorneal ring segment implantation, and in intrastromal presbyopia correction<sup>2,3</sup>.

### 1. FEMTOSECOND LASERS

Femtosecond lasers use ultrashort pulses (from 6 kHz to 500 kHz)<sup>1</sup>, within a diameter of 1  $\mu\text{m}$  to 3  $\mu\text{m}$  in the infrared wavelength, that is unabsorbed by the tear film and cornea until the beam reaches the corneal stroma<sup>4</sup>. It is a Nd:Glass laser, similar to a Nd:YAG laser<sup>1</sup>, that leads to plasma formation, which in turn induces ablation of the stromal tissue at a specific depth, called plasma induced ablation. It causes minimal collateral tissue damage, producing bubble cavitations that extend and form a resection plane on the interface<sup>3,5</sup>.

The greater the pulse rate, the tighter the cavitations and the softer the corneal stromal beds, resulting in better visual outcomes<sup>5</sup>. The first femtosecond laser to be approved was the IntraLase<sup>®</sup> (Abbott Medical Optics, Inc.), in 2000. Since then, four new systems have been approved, namely the Femtec<sup>®</sup> (20/10, Technolas Perfect Vision GmbH), the Femto LDV (previously Da Vinci, Ziemer Ophthalmic Systems), the Visumax<sup>®</sup> (Carl Zeiss Meditec AG), and the WaveLight<sup>®</sup> FS200 (Alcon Laboratories, Inc.)<sup>1,5</sup>. Nowadays, the surgeon can make the incisions in a horizontal, vertical, or oblique plane<sup>4</sup>.

### 2. CREATION OF THE LASIK FLAP

Laser *in situ* keratomileusis (LASIK) consists of an

anterior corneal flap under which an excimer laser modifies corneal stroma by photoablation. This surgery is an effective surgical treatment for low-to-moderate myopia and hyperopia<sup>6</sup>. Nowadays, there are many alternatives in order to create thinner flaps, such as precise microkeratomes and femtosecond laser, which is a bladeless method of flap creation<sup>7</sup>. Besides allowing lenticule extraction, without requiring microkeratome or excimer laser, femtosecond laser has also the benefit of being the surgeon who controls the type of incision, flap diameter, thickness, hinge position and width<sup>3,8</sup>. Despite being more expensive, it has been proving to be a safe and stable technique, and therefore more predictable, allowing lower risk of complications. In the same way, creation of the LASIK flap with femtosecond laser (femto-LASIK), is less likely to induce changes in the corneal curvature<sup>9</sup> and higher order aberrations. So, at least theoretically, patients will have better contrast sensitivity<sup>2,3</sup>.

Montés-Micó *et al.*<sup>10</sup> studied the effects on contrast sensitivity in 200 eyes and found better results with IntraLase<sup>®</sup> surgery, when compared with the mechanical microkeratomes. Rosa *et al.*<sup>7</sup> compared IntraLase<sup>®</sup> flaps with two mechanical microkeratomes (Hansatome<sup>®</sup> and the Zyoptix<sup>®</sup> XP) and concluded that the thickness of the flaps created by IntraLase<sup>®</sup> was more precise than Hansatome<sup>®</sup> microkeratome, identical to Zyoptix<sup>®</sup> XP and thinner than the flaps created by Hansatome<sup>®</sup>. They also concluded that flap thickness measurement 20 minutes after laser treatment eliminates the effect of variable corneal dehydration, which affects flap measurement by subtraction pachymetry.

It has been reported that 6 months after surgery, patients submitted to femto-LASIK had less total and spherical aberration<sup>5</sup>. Also Krueger *et al.*<sup>11</sup> explored different parameters in patients after femto-LASIK in one eye and a mechanical microkeratome in the fellow eye,

and concluded that aberrations were higher with the mechanical Moria M2 microkeratome. The same results were later confirmed by Buzzonetti *et al.*<sup>6</sup> who studied wavefront corneal aberrations one year after surgery of 24 eyes submitted to LASIK with the Hansatome<sup>®</sup> microkeratome, and 23 eyes from 13 patients submitted to the IntraLase<sup>®</sup> femtosecond. This may be related to the differences in flap thickness.

Whereas mechanical flap is meniscus shaped, the planar femtosecond flap is more predictable and seems to induce less epithelial ingrowth and dry eye<sup>3,5</sup>. Some authors<sup>12,13</sup> compared the flap features created by femtosecond laser and microkeratome and found the femto-LASIK flaps to be more uniform and accurate. Similarly, it seems that femto-LASIK enables faster and better visual recovery, as well as less risk of free and buttonhole caps<sup>7,14</sup>. However, femtosecond laser also has some disadvantages, such as longer suction time, increased treatment time and harder to lift flaps in case of retreatment. It also induces more inflammation and diffuse lamellar keratitis (DLK)<sup>5</sup>, probably by the energy at the interface, more glare and a transient light sensitivity syndrome<sup>7,15</sup>. Nevertheless, these obstacles can be reduced with topical corticosteroids or with newer femtosecond laser platforms<sup>3</sup>.

De Paula *et al.*<sup>16</sup> studied 801 eyes in order to find associations to the development of DLK after femto-LASIK flap creation. They noticed that DLK tended to be insignificant with minor effect on visual acuity, and showed an increased risk of development with higher energy level and larger flap diameter. On the other hand, Choe *et al.*<sup>17</sup> found no difference in the incidence of DLK after femto-LASIK with different energy levels (15 kHz, 30 kHz or 60 kHz). Moshirfar *et al.*<sup>18</sup> showed that intraoperative epithelial defects were most commonly seen with microkeratome, and DLK after femto-LASIK. Femtosecond also does not prevent dry eye syndrome, known to be caused by LASIK, and which is linked to flap creation<sup>8</sup>. Rodriguez *et al.*<sup>19</sup> compared the effect of femto-LASIK and microkeratome in 64 eyes undergoing LASIK, and found a greater reduction in goblet cell density in eyes undergoing femto-LASIK. This is probably due to the time where the suction ring exerts pressure on the conjunctiva. Studies suggest that haze after LASIK is more common in corneas treated with femtosecond laser<sup>20</sup>. Patel *et al.*<sup>20</sup> in a prospective study where fellows eyes were randomized to LASIK flaps created by a femtosecond laser (IntraLase<sup>®</sup>) versus mechanical microkeratome (Hansatome<sup>®</sup>), found no significant statistical differences in contrast sensitivity, refractive error or haze 6 months after surgery, suggesting that either method is plausible.

In conclusion, both femto-LASIK and LASIK with microkeratomes have similar patterns of efficacy and safety, although femto-LASIK seems to be more predictable<sup>5,21</sup>.

### 3. FEMTOSECOND LENTICULE EXTRACTION

Femtosecond lenticule extraction is a new refractive surgery for myopia and myopic astigmatism, that enables manual removal of the intrastromal lenticule bypassing the need of an excimer laser<sup>1</sup>. It seems to be as safe and effective as LASIK, and avoids complications associated with excimer laser ablation, such as stromal hydration

and laser fluence<sup>1,22</sup>. This method is currently performed with the VisuMax<sup>®</sup> femtosecond laser platform (Carl Zeiss Meditec AG, Jena, Germany). An intrastromal lenticule is created between two photo delineated planes and is mechanically removed. In the femtosecond lenticule extraction (FLEX), femtosecond laser creates both the flap and the refractive correction, the refractive lenticule is removed and the hinged flap is repositioned<sup>8</sup>. Small incision lenticule extraction (SMILE) is a flapless laser-correcting surgery, that involves the creation of one or two small incisions and requires an intrastromal lenticule that matches the chosen refractive correction. This lenticule is created with a femtosecond laser and then removed through the incisions<sup>1,8,22</sup>. Since SMILE does not create a flap, there may be biomechanical advantages over LASIK, as it spares complications related to flap-cutting<sup>8,22</sup>. Corneal hypoesthesia is a common side effect after corneal refractive surgeries due to the injury to superficial nerve fibers during the flap creation. It can persist from 3 weeks to 6 months postoperatively<sup>8</sup>. Nevertheless, there is still considerable uncertainty on this topic.

Last year, Meiyang Li *et al.*<sup>23</sup> evaluated corneal sensation through Cochet-Bonnet corneal esthesiometry (Luneau Ophthalmologie Chartres, Cedex, France) after SMILE and femto-LASIK, in 71 patients with myopia. They concluded that there was less impairment of corneal sensation in the SMILE group than in the femto-LASIK group, however, no statistical difference was found after 3 months of follow-up. Similarly, Shengsheng Wei *et al.*<sup>8</sup> found no change on corneal sensitivity after SMILE, and observed a faster recovery when compared with FLEX or femto-LASIK procedures.

Di Wu *et al.*<sup>24</sup> compared corneal biomechanical properties after SMILE (40 eyes) and femto-LASIK (40 eyes). They established that femto-LASIK induces more biomechanical changes.

Klingler *et al.*<sup>25</sup> analyzed corneal endothelial cell density and morphology and found that after 5 years of follow-up both techniques, femtosecond and microkeratome, had not significantly changed the corneal endothelium.

### 4. ASTIGMATIC KERATOTOMY WITH FEMTOSECOND LASER

Astigmatic keratotomy with femtosecond laser is a simple and minimally invasive technique, that shows higher precision and a more accurate planning of the length, depth, and optical zone of the incisions when compared with the mechanical method<sup>1</sup>. It can be performed in cases of natural or residual astigmatism secondary to cataract surgery, penetrating keratoplasty, deep anterior lamellar keratoplasty (DALK) or Descemet's stripping endothelial keratoplasty (DSEK), as long as corneal sutures have been removed<sup>3</sup>. It has higher security and is more predictable, with lesser risk of corneal perforation, comparing with manual keratotomy<sup>3</sup>.

Peter Kim *et al.*<sup>3</sup> reported the use of the anterior segment optical coherence tomography (AS-OCT) as a guide for the incisions planning.

### 5. INTRACORNEAL RING IMPLANTATION

Intrastromal ring implants are alternative treatment

options to post-LASIK ectasia, pellucid marginal degeneration or keratoconus<sup>3</sup>, since they modify the central corneal curvature and regularize the corneal surface<sup>26</sup>. Therefore, they improve visual acuity, mean keratometry and corneal aberrations. This treatment option enables the preservation of central cornea integrity, and it has proved to be more effective as the thickness of the implant increases and the diameter decreases<sup>3</sup>.

Channel creation for intracorneal ring segment implantation can be accomplished with a mechanical device, the PocketMaker (DIOPTEX GmbH)<sup>26</sup>, or alternatively with femtosecond laser, which is faster, safer and more predictable<sup>3</sup>. Mechanical channel creation, depending on the surgeon's skills, may have many complications, such as epithelial defects, corneal perforations, infectious keratitis, asymmetric segment placement, corneal stromal edema, and extension of the incision towards the central visual axis or the limbus<sup>1,27</sup>. Alternatively, the femtosecond laser minimizes procedure time, makes the surgery easier, decreases the risk of inflammation, and improves reproducibility, as it allows the corneal stromal dissection to be planned at a predetermined depth, improving visual acuity results<sup>1,26,27</sup>.

Coskunseven *et al.*<sup>27</sup> reported complications in 850 eyes after implantation of intrastromal corneal ring segments (Keraring®; Mediphacos, Belo Horizonte, Brazil) in keratoconus using a femtosecond laser (IntraLase®; Advanced Medical Optics, Santa Ana, California, USA) for channel creation. The most common intraoperative complication was the incomplete channel creation (2.6%), probably because of the low energy levels of the laser, and the most frequent postoperative problem was segment migration (0.8%).

Ertan *et al.*<sup>28</sup> confirmed the efficacy and safety of femtosecond laser for correction of pellucid marginal corneal degeneration. Some authors<sup>29</sup> found no significant differences in the treatment of mild to moderate cases of keratoconus and post-LASIK ectasia when a femtosecond or mechanical dissection were used.

Alio *et al.*<sup>26</sup> assessed the clinical outcomes after MyoRing® (DIOPTEX GmbH, Linz, Austria) implantation in 12 eyes with corneal ectasia using femtosecond laser technology, and found an improvement of the myopic spherical error. Piñero *et al.*<sup>30</sup> studied 146 eyes with keratoconus and found similar visual outcomes when a mechanical or a femtosecond laser procedure were compared. Nevertheless, more cornea aberrations in eyes with mechanical tunnelization were observed.

Combining collagen crosslinking has shown to be beneficial, with a greater reduction in keratometric values<sup>3</sup>. In conclusion, intrastromal ring implants using femtosecond laser technology proved to be a very good treatment option<sup>31</sup>.

## 6. INTRASTROMAL PRESBYOPIA CORRECTION

For the treatment of presbyopia, the femtosecond laser creates intrastromal compartments for the insertion of biocompatible intracorneal inlays, without the creation of a flap or the use of an excimer laser<sup>1,3,32</sup>. This allows the reorganization of a hyperprolate corneal shape<sup>32</sup>.

Intracorneal inlays include refractive inlays with an annular

refractive zone for near vision, inlays that increase the curvature in the visual axis, and inlays which function as pinholes<sup>1</sup>.

This procedure causes no pain, allows quicker recovery and preserves the strongest anterior corneal fibers<sup>32</sup>. On the other hand, recurrent episodes of corneal inflammation were reported and patients may be dissatisfied with the hyperprolate aberration pattern, which can progress over time secondary to changes in the biomechanical corneal forces<sup>32</sup>.

Ruiz *et al.*<sup>32</sup> performed a minimally invasive intrastromal correction for presbyopia using the Technolas® femtosecond laser system (Technolas Perfect Vision GmbH) in 83 eyes. This procedure showed gains in uncorrected near visual acuity, even though a mild myopic shift in uncorrected distance visual acuity was seen.

Further prospective studies, including a larger number of eyes and longer follow-ups, are required to evaluate the long-term results and support these reported outcomes.

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# II. LASER Surgery in Cornea

## 18. Corneal

# Neovascularization



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### INTRODUCTION

Corneal neovascularization (NV) defines an ingrowth of blood vessels into the corneal tissue, which is normally devoid of vascular and lymphatic structures. Several corneal affections can lead to corneal NV, such as infectious, immunologic, traumatic, anoxic and degenerative causes and the loss of the stem cell barrier<sup>1-3</sup>. The common pathophysiology is a disruption of the natural equilibrium between angiogenic and antiangiogenic factors<sup>1,4</sup>. The appearance of aberrant vessels and lymphatic structures interferes with corneal physiology through the induction of vascular hyperpermeability, exudation, lipid deposition, intrastromal hemorrhage, edema and fibrosis, ultimately interfering with its natural transparency, immunologic privilege and leading to graft rejection in keratoplasty patients<sup>1,3,5</sup>. There are several treatment modalities to achieve antiangiogenesis and/or angioregression. Medical and surgical approaches are available, such as topical corticosteroids, non-steroidal anti-inflammatory agents, anti-VEGF agents, cyclosporine A, laser treatments, fine needle diathermy and keratectomy<sup>1</sup>. Innovative treatments using genetic modulation are under investigation<sup>1</sup>. No gold standard has yet been defined by the scientific community. The medical approach is frequently the first-line treatment option, starting with topical corticosteroids. Anti-VEGF agents, applied through topical, subconjunctival and intrastromal routes or through soaked corneal light shields, have shown promising results, although they seem more useful in combination rather than as an isolated therapy<sup>1</sup>. Less invasive treatments have a more angiorepressive rather than angioregressive effect with other treatment modalities being on demand when it comes to more mature vessels<sup>1</sup>. Photothermal laser (Nd:YAG-KTP 532 nm) and photodynamic therapy with photosensitizers are well established alternatives for the treatment of corneal NV<sup>1</sup>, although without their downsides. Argon laser was first described by Cherry and Garner in 1973<sup>6</sup>.

It operates through the induction of thermal lesions following energy absorption by hemoglobin, ultimately resulting in vascular obliteration<sup>1</sup>. Photodynamic therapy was first described by Fossarelo in 2003<sup>7</sup>. It requires a photosensitizing compound, generally verteporfin although fluorescein and dihematoporphyrin ether (DHE) have also been studied<sup>8,9</sup>, and acts through the induction of free radicals leading to vascular endothelial cell damage, thrombosis and vascular obstruction<sup>1</sup>. This technique has been used with thermal and non-thermal laser sources. The biggest human study on the subject was published by Yoon *et al.* who prospectively studied 18 patients, using a diode laser source and verteporfin as a photosensitizer, showing promising results<sup>2</sup>. In a comparative study dye yellow laser 570 nm and argon laser 514 nm showed similar efficiency<sup>10</sup>.

### INDICATIONS

As an alternative for established corneal NV in eyes that are not suitable for or which do not respond to conventional treatment. To treat corneal NV prior to keratoplasty, in order to reduce the likelihood of rejection.

### CONTRAINDICATIONS

There are no specific contraindications to its use described in literature; however, a prior conventional treatment trial is advised.

### PREPARATION

1. Explain the procedure including that there may be a need for multiple sessions or other procedures.
2. Anesthesia depending on patient sensitivity.
3. Administer pilocarpine 1-2% for pupillary constriction.
4. Apply comfort measures for the patient.
5. Dim down the laser room illumination.
6. Instruct patient to keep very still and maintain steady fixation.

## LASER TECHNIQUE

Argon 514.5 nm laser (AL) (green-blue); Nd:YAG KTP 532 nm laser (KTP laser) (yellow-green); Yellow Diode 577 nm laser (YD laser) (yellow)<sup>11,12</sup>

1. Adjust the spot size to 50-100 µm; exposure to 0.1-0.2 seconds, and power to 0.2-0.8 W; different parameters for yellow light (577 nm), begin with lower parameters in the case of photosensitizer use (see table 1 below)<sup>11,12</sup>.
2. Keep illumination slit as low as possible and the delivery system angled to the cornea so that rays are directed away from the pupil<sup>11</sup>.
3. Preferentially begin treatment behind the limbus, occluding all main feeder vessels<sup>11</sup>.
4. Continue with the main veins (efferents), from paracentral to peripheral regions<sup>11,12</sup>.
5. Proceed to occlude the main arteries (afferents) in the same manner<sup>11,12</sup>.
6. Avoid treatment of central corneal vessels because of possible visual axis interference and since elimination of paracentral and peripheral vessels will lead to their disappearance<sup>12</sup>.
7. Approach any remaining small vessels, preferentially starting at cross-over points and then advance to intermediate sections<sup>11</sup>.
8. In most cases closure can be achieved in one treatment session, but if dense vascularization is present treat three times on the same day<sup>11,13</sup> and re-treat every one<sup>14</sup> or two weeks<sup>11</sup>.

## POST-LASER CARE AND FOLLOW UP

Photothermal laser technique: prednisolone acetate 1-3% administered four times daily<sup>9,13</sup>. Taper steroids over one year<sup>13</sup>. If the initial treatment allowed successful occlusion, re-evaluate after one month and then every 3/6 months<sup>11</sup>. Re-treat if necessary<sup>13</sup>.

## COMPLICATIONS

Several complications of photothermal therapy have been documented, such as temporary intrastromal hemorrhages, corneal lesions, corneal thinning at lipid absorption points leading to descemetocoele, iris damage and iris atrophy (Table 1). Other described complications are necrotizing scleritis<sup>16</sup> and the accidental lysis of keratoplasty sutures<sup>17</sup>. There are rare reports of serious disciform keratitis, possibly associated with non-compliance to post-laser treatment<sup>11</sup>. Fewer complications were reported with yellow light, because of a superior absorption by hemoglobin and reduced total energy need<sup>12</sup> notwithstanding similar vaso-occlusive effects<sup>1</sup>.

## RESULTS

Photothermal laser (Argon 514.5 nm laser (AL), Nd:YAG KTP 532 nm laser (KTP laser), Yellow Diode 577 nm laser (YD laser)). The main downside of this treatment modality is the frequency of adverse reactions, its potentially transitory nature and the possible induction of new vessel formation through the activation of pro-angiogenic factors by thermal tissue damage<sup>17</sup>. Afferent vessel obliteration is less successful because of deeper and narrower dimensions and rapid pulsatile flow<sup>17</sup>. Other possible concerns are the induction of cataracts and retinal damage through accidental direct burns in the macular area<sup>13</sup>. Consequently, photothermal laser has not been widely accepted, and needs further studying for the assessment of its security profile. A possible alternative is the use of a convex lens for a more convergent beam, leading to less surrounding tissue collateral damage<sup>13</sup>. Altogether, studies involving laser treatments for corneal NV have small sample sizes, short overall durations and frequently lack comparative control groups, with further scientific studies being needed for its broader acceptance (Table 1).

Table 1. Summary of studies involving laser treatments for corneal NV, their results and complications

Author	Year	Purpose	Number	Follow-up (months)	Results	Complications
Marsh and Marshall <sup>11</sup>	1982	Argon laser (50 µm; 0.1 s; 0.2-0.8 W) Corneal NV lipid keratopathy	19 cases (N/S)	12	Reduction of lipid deposition (50%). Recurrence (57.8%). Improved visual acuity (VA) (31.5%).	Temporary corneal hemorrhage (63.8%), temporary (31.6%) and permanent (10.5%) pupil peaking, corneal lesions. Iris atrophy in nearly all cases. Serious disciform keratitis (10.5%).
Marsh <sup>13</sup>	1988	Argon laser (N/S) Corneal NV lipid keratopathy	63 cases (N/S)	12-156	Reduction lipid (62%). Improved Snellen VA (48%).	Occasional reactivation of keratitis, responsive to steroids. Descemetocoele (3.2%). Corneal thinning after lipid resorption.

Table 1. Summary of studies involving laser treatments for corneal NV, their results and complications

Author	Year	Purpose	Number	Follow-up (months)	Results	Complications
Nirankari <sup>12</sup>	1992	Argon blue-green laser (514 nm; 50-100 µm; 0.1-0.2 s; 0.2-0.7 W).  Argon yellow laser (577 nm; 50 µm; 0.1-0.05 s; 0.2-0.5 W)  4 groups: graft rejection (11 acute graft rejections of 8 eyes); pre-PK corneal NV treatment (7 eyes); refractory corneal NV (12 eyes); transplant interface corneal NV (3 eyes)	30 eyes (30 patients)	27.1-44.3	Reversal of graft rejection (81.8%).  Reduced graft rejection in pre-PK corneal NV treatment (71.5%) and lack of recurrence of corneal NV (85.8%).  Successful treatment of refractory corneal NV (91.6%).  Regression of transplant interface corneal NV (66.6%).	Temporary corneal hemorrhage (3%).  Iris atrophy in most patients treated with blue laser, none treated with yellow laser.  Possibly fewer adverse effects with yellow light because less total energy is needed.
Baer and Foster <sup>18</sup>	1992	Argon yellow laser (577 nm)  4 groups: refractory graft rejection (5 eyes); pre-PK corneal NV; vascularization affecting visual axis (9 eyes); extensive corneal NV not candidates for PK	25 eyes (23 patients)	5.6-9.3	Resolution of graft rejection (100%).  Stabilization or improvement in visual axis affection (77.7%).  Significant improvements in corneal NV area.  Disappointing results in extensive corneal NV.	
Gerten <sup>14</sup>	2008	Argon laser and bevacizumab co-treatment (50 µm; 1 mJ; 0.1 s and 0.1 mg; subconjunctival bevacizumab)  Pre-PK corneal NV treatment	2 eyes (2 patients)	6 and 18	Marked reduction in NV.	
Lim and Wee <sup>19</sup>	1993	Argon laser (50-200 µm; 0.1 s; 0.4-0.7 W)  Pre-PK corneal NV treatment, in HSV keratitis	2 eyes (2 patients)	2 and 8	Good visual outcome and no graft rejection.  No recurrence.	None.
Gordon <sup>15</sup>	2002	Argon blue-green (488 nm/514 nm) + Fluorescein (150-200 µm; 0.5 s; 200 mW)	15 patients (N/S)	1	Reduced symptoms. Improved quality of life (93%). Stable/improved VA (87%). Cosmetic improvement (46%). Serious recurrence (6%). Frequent re-treatment necessary (3 times mean).	No significant complications.
Sheppard <i>et al.</i> <sup>9</sup>	2006	Argon green laser (514 nm) and intravenous DHE (500 µm; 0.5 s; 0.4-0.8 W)	7 eyes (7 patients)	5.4	Reduction in corneal NV (52.2% ± 19.6%).	No other ocular changes attributable to laser treatment.  Significant short-term photo-toxicity (42.8%).
Fossarello <sup>7</sup>	2003	Photodynamic therapy with verteporfin (non-thermal laser 689 nm)	2 eyes (2 patients)	6	Successful photo-thrombosis immediately after.  Re-treatment necessary (50%).	None.

Table 1. Summary of studies involving laser treatments for corneal NV, their results and complications

Author	Year	Purpose	Number	Follow-up (months)	Results	Complications
Yoon <i>et al.</i> <sup>2</sup>	2007	Photodynamic therapy with verteporfin (non-thermal laser – 689 nm; 3 to 5 mm; 0.6 W/cm)	18 eyes (18 patients)	16.4 ± 4	<p>Notable decrease in corneal NV at 6 month (83.3%) and 14 months (77.8%).</p> <p>Complete occlusion (50%); partial occlusion (27.8%).</p> <p>VA improvement: &gt;1 line (44.4%) and &gt;2 lines (38.9%); none in 50%.</p> <p>Recanalization (22.2%).</p>	<p>Mild corneal edema and superficial hemorrhages (33.3%) after 3 days, but improved in one week.</p> <p>Mild stromal haze (5.6%).</p> <p>No other significant systemic or ocular complications.</p>

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# III. LASER Surgery in Glaucoma

## 19. LASER Iridotomy



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### INTRODUCTION

The first demonstration of the usefulness of light energy to create an iridotomy was just over 60 years ago, using a xenon light source<sup>1</sup>. Since then, with the advent of the slit-lamp laser delivery system, treating the iris and trabecular meshwork became an obvious option, and in the 1970s argon laser became the first to be regularly used for performing a non-invasive iridotomy<sup>2-4</sup>. Although it is well absorbed by iris pigment, argon laser (and Nd:YAG-KTP laser, which is often also referred to as "argon laser") iridotomy alone was associated with some complications, and with relatively high failure and subsequent closure rates<sup>5-10</sup>.

During the 1980s, Q-switched Nd:YAG laser (YAG laser 1064 nm) was introduced. This new device had the advantage of not requiring the presence of melanin, which meant that it was also highly effective in light-coloured irides. Moreover, it required considerably less total energy than pure argon/Nd:YAG-KTP 532 nm laser iridotomy, achieved a higher rate of single treatment success with lower risk of subsequent closure and it was less likely to cause damage to the cornea, lens and retina<sup>9-12</sup>.

### INDICATIONS

Laser peripheral iridotomy (LPI) is indicated to prevent or overcome a suspected relative pupillary block by creating a bypass for aqueous flow. Mainly used for patients in the primary angle closure spectrum, it can also be useful in secondary angle closure glaucomas and in the management of other types of glaucoma with associated pupillary block. The benefit of laser iridotomy is well established for the treatment and prevention of **acute angle closure (AAC) attacks**. It should be performed whenever possible in affected eyes, and also soon after in the fellow eyes<sup>12,13</sup>. The conventional management of **primary angle closure (PAC) and PAC glaucoma (PACG)** also includes LPI.

**Primary angle-closure suspects (PACS)** pose added difficulties to the decision-making process. Not all eyes with such narrow "occludable" angles require iridotomy as most will never develop glaucoma (especially Caucasians), the procedure is not completely devoid of complications and we cannot always predict by gonioscopy alone who will absolutely benefit from it. A consensus has been reached to treat PACS especially if there is more than 2 quadrants of iridotrabecular

contact (ITC) and/or PAC in the fellow eye<sup>12,13</sup>.

**Inflammation** is a common cause of secondary pupillary block and laser iridotomy may be required to prevent recurrence of pupillary block. Pupillary block can also develop slowly with a senile cataract or rapidly with **dislocated or subluxated lenses, or with swollen post-trauma lenses**. Iridotomy may not be curative, but helps by relieving pupillary block component, allowing for safer lensectomy. Pupillary block can even occur in pseudophakic eyes, more often with anterior chamber lenses if an iridectomy is absent or occluded. In **plateau iris syndromes** the diagnosis is usually not conclusive until after iridotomy<sup>1,12,13</sup>. Similarly, for diagnostic purposes, it is essential to eliminate the possibility of pupillary block in **ciliary block glaucoma**<sup>1,14</sup>.

Finally, in patients with **pigment dispersion/pigmentary glaucoma** iridotomy can be used to break a reverse pupil block, but its benefit is not clearly established<sup>13</sup>.

### GENERAL RECOMMENDATIONS AND TECHNIQUE (ND:YAG IRIDOTOMY)

The following **recommendations** improve the safety and efficacy of the procedure<sup>1,12,13</sup>:

1. **Miosis** - a drop of pilocarpine (1-2%) to tighten and reduce iris thickness.
2. **IOP-lowering drugs** - To minimize IOP spikes, an alpha-agonist (brimonidine or apraclonidine) is applied before and after the procedure. Very high IOPs (as in AAC) should be addressed first with appropriate medical therapy<sup>15</sup>.
3. **Topical anesthesia**.
4. Use of **iridotomy lens** (Abraham or Wise lens - Figure 1) with coupling fluid. As well as stabilizing the eye, it magnifies and improves visualization, minimizes corneal burns and increases the power density by concentrating the laser energy.
5. **Focus** - Set defocus to zero. Focus on the iris surface and then offset the YAG beam so that it converges slightly posteriorly in the stroma. A bubble of plasma travels towards the surgeon so it is safer to have the focal point within the iris stroma.
6. The iridotomy should be **placed in the periphery of the iris** (Figures 1 and 2):  
A site between the 11 and 1 o'clock meridians (cov-

## 19. Laser Iridotomy

ered by the upper lid) is usually preferred.

Aim for iris crypts or other relatively thin areas, avoiding visible vessels.

7. **Endpoint** - A small (150–200  $\mu\text{m}$ ) but complete peripheral hole is the ideal endpoint. A gush of pigment from the posterior chamber or lens visualization through the iridotomy help in signaling permeability. Transillumination can be misleading, particularly in light coloured irides.
8. **Reassess** in 1–2 hours (IOP spike control) and one week later to confirm opening of the angle.
9. Topical **corticosteroid** (3–4 times a day for 4–7 days).

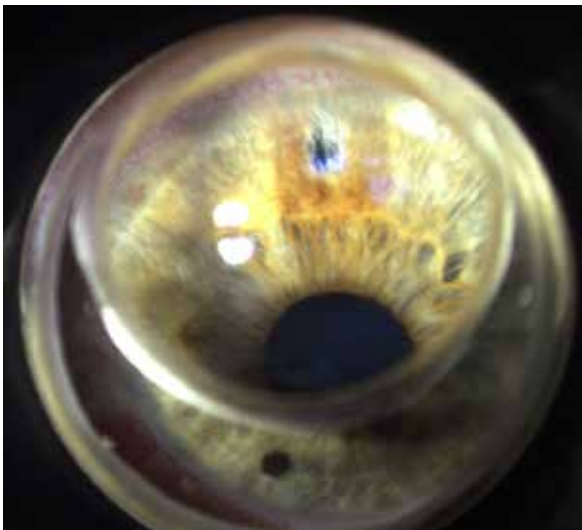


Figure 1. Abrahams iridotomy lens.

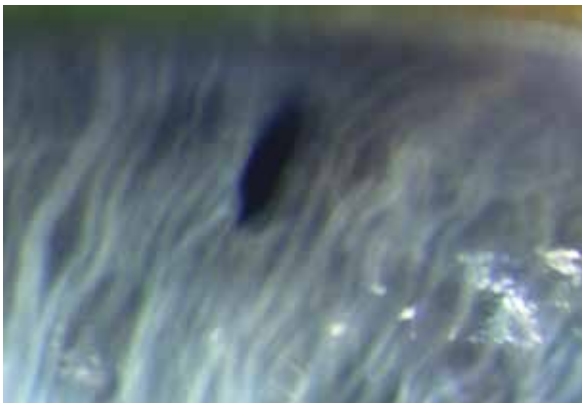


Figure 2. Permeable LPI in light coloured iris after a single 2 mJ burst.

### TYPES AND TISSUE EFFECTS OF LASER

Iridotomy can be accomplished using the photodisruptive Q-switched Nd:YAG laser (Nd:YAG) or the photothermal Nd:YAG-KTP 532 nm (which is still often called Argon Laser) and solid-state lasers.

#### Nd:YAG laser iridotomy (Table 1)

The Q-switched Nd:YAG lasers rely on tissue **photodisruption** to create a rapidly expanding ionic plasma wave. The subsequent shock-wave and mainly

cavitation bubble will in turn cause an explosive disruption of tissue. These mechanical effects are useful in opening transparent tissue as they do not depend on tissue absorption of energy<sup>16,17</sup>. The Nd:YAG laser is preferred by many surgeons because it perforates the iris easily, requiring lower energy than Nd:YAG-KTP 532 nm lasers. It is more difficult to penetrate dark brown irides with photothermal Nd:YAG-KTP 532 nm /solid-state lasers because the former have a tendency to absorb too much energy during treatment. Pale irides do not absorb the laser energy very well. Moreover, Nd: YAG iridotomies may be less likely to close over time<sup>1,8</sup>.

Table 1 - Q-switched Nd:YAG laser parameters<sup>13</sup>

Nd:YAG laser 1064 nm	Power: 1.6 – 6 mJ;	1-3 pulses/ burst	Spot size: 50 – 70 $\mu\text{m}$
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The treatment can be started with relatively low power (1–3 mJ) to thin the iris or with higher power (5–6 mJ and up to 8 mJ) to quickly penetrate the iris, as preferred by some<sup>12,13</sup>.

For lasers capable of multiple bursts, 2–3 shots/burst using approximately 1–3 mJ/burst will be effective in most cases. If a single burst is used, slightly higher power is usually necessary. High-power settings (2–5 mJ) or sequential Nd:YAG-KTP 532 nm/Nd:YAG are needed for some particularly thick, velvety brown irides<sup>1,11,12</sup>.

#### Argon/Nd:YAG-KTP 532 nm or solid-state laser iridotomy (Table 2)

Table 2. Nd:YAG-KTP (still usually referred to as Argon) laser iridotomy parameters<sup>13</sup>

Laser Parameters - Argon		
<b>Medium - Brown irides</b>	Preparatory (stretch) burns	Power: 200–600 mW
		Spot: 200–500 $\mu\text{m}$
		Exposure: 0.2–0.6 sec
<b>Light coloured irides</b>	1st step: Gas bubble	Power: 700–1500 mW
		spot: 50 $\mu\text{m}$
		Exposure: 0.1–0.2 sec
<b>Light coloured irides</b>	2nd step: Perforation	Power: Up to 1500 mW
		Spot: 50 $\mu\text{m}$
		Exposure time: 0.5 sec
<b>Thick dark-brown irides</b>	2nd step: Perforation	Power: 100 mW
		Spot: 50 $\mu\text{m}$
		Exposure time: 0.05 sec
<b>Thick dark-brown irides</b>	2nd step: Perforation	Power: 1500 mW
		Spot: 50 $\mu\text{m}$
		Exposure: 0.02 sec

Nd:YAG-KTP 532 nm and solid-state lasers produce thermal (coagulative) effects with lower energies at lon-

ger exposures or explosive effects (vaporization) if higher energies are used. Unlike Nd:YAG, these lasers act differently in tissues with different amounts of pigmentation, requiring more adjustments and greater variety in techniques according to iris pigment density posterior to the stroma<sup>1,13</sup>. **Sequential Nd:YAG-KTP 532nm/ Nd:YAG LPI** can be useful in patients with thick brown irides, particularly in East Asian and African populations. Nd:YAG-KTP 532 nm laser pre-treatment to thin the iris results in lower energy needed with the Nd:YAG laser, which is then used to penetrate the iris and create an iridotomy. By using only a fraction of the power required for pure YAG laser iridotomy, it is more efficient and carries a lower risk of complications<sup>11-13,18,19</sup>.

## COMPLICATIONS

### 1. Iris hemorrhage

Post-treatment bleeding from the iris is rare with Nd:YAG-KTP 532 nm laser but common after Nd:YAG laser iridotomy (37%-50%)<sup>8,20,21</sup>. The hemorrhage is usually mild and self-limited (Figures 3 and 4). Nevertheless, it may contribute to temporary IOP elevation, inflammation and reduced vision if it involves the visual axis. Applying pressure on the iridotomy lens will usually control the bleeding.



Figure 3. Bleeding immediately after treatment. The presence of large vessels nearby and pigment debris meant that the enlargement was prone to complications.

Bleeding may be limited by pretreating the proposed site with the coagulative energy from a thermal laser. This is rarely performed unless there is a known coagulative disorder or if the patient is on anticoagulants.

### 2. Transient IOP elevation

This is generally due to the release of pigment, blood and other debris clogging up the trabecular meshwork or by an incomplete iridotomy. Unrecognized plateau iris syndrome or other non-pupillary block angle closure mechanisms, inflammation, extensive peripheral anterior synechiae (PAS), and even prolonged corticosteroid therapy are other possible causes for IOP elevation after LPI<sup>1,22-24</sup>. Acute IOP elevation may occur 1–4 hours after laser iri-

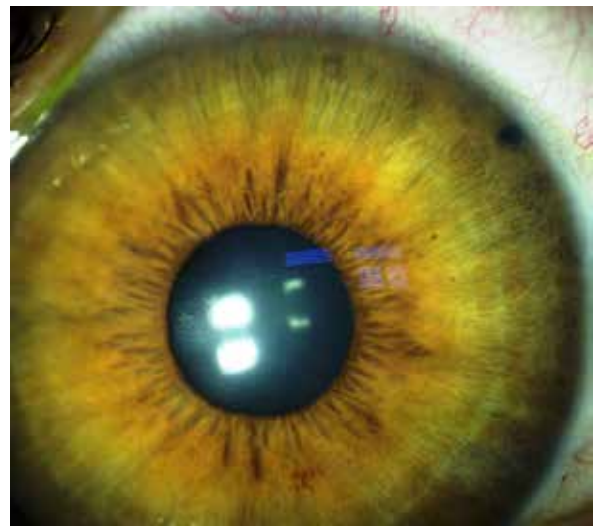


Figure 4. The 2 o'clock meridian was chosen for a 2nd attempt.

idotomy, and is usually mild and short-lasting, particularly if preventive medical measures are taken. In fact, IOP spikes (10 mmHg) were reported in only 2 (0.69%) of 289 eyes 1 hour after LPI in Caucasians<sup>25</sup>. The IOP returns to pretreatment or lower levels within 24 hours<sup>20,25-28</sup>.

However, LPI for primary angle-closure in Asian eyes can result in a significant IOP rise (>8 mmHg) approximately in 10% of cases less than 1h after the procedure. Higher energy and number of laser pulses per treatment, together with shallower central anterior chambers, were found to increase the risk for IOP spikes at 1 hour after laser peripheral iridotomy, as well as its use in the context of acute angle closure closure<sup>29,30</sup>.

In eyes with advanced PACG and extensive synechial closure of the angle, the relative minor trauma from LPI can overwhelm an already compromised trabecular meshwork, precipitating the need for filtration surgery. Such patients should be warned that additional intervention may be required as the IOP elevation can be severe and sustained<sup>1,12,13,31</sup>.

### 3. Post-operative inflammation

Some degree of iritis always follows LPI. Many patients do quite well without treatment, but topical corticosteroid is indicated. Severe inflammation is very rare in non-uveitic eyes following uncomplicated LPI, although posterior synechiae can occur with argon/solid state lasers<sup>1</sup>.

### 4. Corneal injury

Corneal damage can occur either from the pre-existing condition itself (ex: AAC attack) or, to a smaller extent, from the subsequent laser iridotomy treatment. The use of iridotomy lenses minimizes injury, nonetheless if burns do occur they normally disappear shortly after, without long-term effects<sup>1,13</sup>. Thermal lasers cause superficial burns more frequently, particularly with higher energy, if a chromophore (fluorescein) is applied or if the

epithelium is slightly edematous<sup>1</sup>.

A poorly focused Nd:YAG laser treatment can result in localized stromal injury; and severe stromal edema has also been described after iridotomy, attributed to sudden decompression following resolution of AAC attacks<sup>32</sup>. Endothelial damage can happen after iridotomy with argon, solid-state, or rarely with Nd:YAG lasers<sup>33</sup> and, if extensive, can lead to persistent corneal oedema. When the iris is very close or touching the cornea, the laser is more likely to cause injury and if so, power and exposure time should be reduced or a new site should be chosen. With the Nd:YAG laser, focal corneal opacities and reduction in endothelial cell count (ECC) have been found above the treatment site<sup>9,33,34</sup>. However, significant and generalized reductions in ECC after uncomplicated YAG LPI are probably not attributable only to the laser energy by itself<sup>2,33</sup>, particularly if compared with the natural history of the underlying pathological process<sup>35</sup>. Interestingly, in animal models, LPI was shown to cause an extremely fast forward aqueous flow directed against the corneal endothelium, unlike the physiological thermal current<sup>36</sup>.

In summary, clinical evidence and overall common sense support the conclusion that, in marginally healthy corneas, the focal corneal endothelial loss sometimes seen following Nd:YAG-KTP 532 nm LPI (and Nd:YAG to a lesser extent) can predispose to long-term focal or even diffuse corneal decompensation.

### 5. Lens capsular damage and cataract acceleration

**Capsular damage** – Nd:YAG-KTP 532 nm laser iridotomy frequently causes localized injury to the lens at the iridotomy site (up to 50%)<sup>37</sup>. This injury can be seen as a localized whitening of the lens and longer exposures increase the risk of damage<sup>38</sup>. Long-term follow-up has shown that these focal opacities usually do not progress<sup>39,41</sup>. The Nd:YAG laser can also damage the capsule, thus focus is critical. This complication is rarely described<sup>42-45</sup>, but it is also difficult to ascertain for every single patient. As added precaution, the iridotomy should be placed in the periphery, beyond the anterior lens curvature, where the distance between the iris and the anterior lens capsule is greatest. The use of lower power levels and single bursts further reduce the chance of lenticular damage<sup>8</sup>.

**Accelerated cataract formation** – Aside from direct damage to the lens, altered aqueous dynamics and mild iritis may also be responsible for metabolic lens changes that accelerate cataract formation<sup>12,46</sup>. On the other hand, in acute cases of PAC, mild pre-existing cataract may be present in some patients, and worsened by ischaemia during the acute episode<sup>20</sup> rather than by laser damage. Cataract can also be a major contributing factor for acute or chronic angle closure with pupillary block.

Coexistence and progression of lens opacities are frequent problems during follow-up of PAC/PACG patients, irrespective of LPI. They are increasingly being offered lens extraction at an earlier stage<sup>8,31</sup>, probably reflecting some controversy around the role of lensectomy in the management of primary angle closure. In fact, it is believed that the size and position of the lens play a major role in the pathogenesis of PACG and that lens extraction may

be effective as an initial treatment by creating additional space behind the iris, reducing lens-iris contact and the resultant relative pupillary block<sup>46</sup>. Moreover, LPI and chronic topical medication use may also accelerate lens opacification, resulting in progressive vision loss.

Clinical reports of phacoemulsification with posterior chamber IOL implantation in the treatment of acute, chronic and secondary angle-closure are encouraging<sup>13</sup>. However, incisional surgery also carries significant risk, making clear lens extraction controversial in this context<sup>12,13,31</sup>. Also, progression of lens opacities requiring surgery has been reported to occur with similar frequency, whether or not LPI is performed<sup>47</sup>. Thus, the appropriate timing and role for lensectomy regarding LPI for different stages of the PAC spectrum is still unclear<sup>12,13,48</sup>. So far, a consensus exists for the lack of evidence in recommending lens extraction alone (without PI) in eyes with PACG<sup>12,13</sup>. Additionally, in eyes with clear lenses, LPI should be performed first and, if unsuccessful in opening the angle and controlling IOP, lens extraction with IOL implantation should be considered<sup>13</sup>.

### 6. Visual symptoms

Glare, halos, ghost images and linear dysphotopsia are rare (6-12%) but more likely to occur in patients who have partially or fully exposed iridotomies, in contrast to those in whom there is complete coverage by the lid<sup>40,41</sup>. Additionally, temporal placement was found to be less likely to result in linear dysphotopsia as compared with superior placement<sup>49-51</sup>. However, some also place fully uncovered iridotomies in the temporal or nasal periphery without visual complaints<sup>52</sup>.

### 7. Failure to perforate and late closure

The occasional patient may require a second treatment within a few days, but absolute failure is unusual with Nd:YAG lasers. If the initial attempt fails, repeating treatments at the same site are most effective if done immediately because debris clouds the anterior chamber reducing the amount of laser energy reaching the iris. Otherwise, waiting for 1-3 hours will often allow the debris to clear in order to complete the procedure<sup>1</sup>. If one is unsure about the adequacy of the iridotomy, the options are either to choose another site (Figure 3) using higher energy levels/number of pulses or to try enlarging the first opening. Enlarging Nd:YAG iridotomies, although more hazardous, can be accomplished by lowering laser energy parameters or by using an Nd:YAG-KTP 532 nm laser. Nd:YAG-KTP 532 nm laser iridotomies are more prone to closure at a later date, usually by regrowth of iris pigment epithelium<sup>6-8,20</sup>.

### 8. Other complications

**Rare:** retinal burns<sup>10</sup>, cystoid macular edema, and malignant glaucoma<sup>1</sup>.

## OUTCOMES

### 1. IOP control

LPI alone does not prevent patients from requiring additional treatment, even when the iridotomy itself has been successful. In fact, several studies regarding the spectrum of PAC report that 7.1%-28.0% of PACS eyes, 42.4%-



80.0% PAC eyes and 83.3%-100% of PACG eyes required additional medical and/or surgical intervention after LPI<sup>31,53-55</sup>. Therefore, it has become increasingly evident that LPI is probably more useful in the earlier stages of the PAC spectrum.

Higher IOP (> 35 mmHg), extensive PAS (>6 hours) and established glaucomatous optic neuropathy mean LPI is less likely to be effective in lowering IOP and that supplemental medical therapy or surgery are required<sup>12,13</sup>. In AAC, laser iridotomy relieves the attack in most cases. Medium to long-term success rates of laser iridotomy in Caucasians with acute attacks have been reported to be from 65-72%<sup>20,56</sup>. Poorer outcomes were reported in East Asian eyes, with more patients developing raised IOP (>20% in 1 year and almost 60% in 4 years) and chronic angle closure glaucoma after AAC attacks, requiring medical or surgical intervention<sup>57-60</sup>. Some reasons for this marked difference between ethnicities include anatomical variations (angle configuration and anterior lens positioning), severity and duration of attacks or even the increased energy necessary to create iridotomies<sup>61</sup>. In AAC attacks, significant amount of PAS, a higher presenting IOP, longer attack duration, poor initial response to therapy (<30% IOP) and a larger C/D ratio, have been associated with inadequate long-term IOP control after LPI. Again, this is consistent with a more severe disease affecting the angle and the trabecular meshwork<sup>55,59-62</sup>. Close monitoring is therefore strongly advised for all patients, even with successful halting of the attack after iridotomy<sup>1,63</sup>.

## 2. Anatomical improvement

**Angle width** assessment should be performed following LPI, either by gonioscopy alone or combined with angle imaging techniques: anterior segment-OCT (AS-OCT) and ultrasound biomicroscopy (UBM). Recent longitudinal studies after LPI confirm its efficacy in opening the angle, assessed both by gonioscopy and quantitative parameters<sup>64</sup>. Several authors using AS-OCT and UBM in PACS, found that thinner peripheral irides and shallower anterior angle opening at baseline were associated with greater changes in longitudinal assessment, (flattening of the iris convexity and angle widening) after LPI<sup>65-68</sup>. Conversely, eyes with thicker peripheral irides at baseline, particularly in Asian patients, should be followed with caution despite successful LPI<sup>65-70</sup>. The effect of LPI on the **extent of synechial angle closure** is another important outcome, although more subjective and difficult to demonstrate. In cases in which there is residual appositional closure following LPI, there may be progressive synechial closure of the angle, but data supporting this is limited<sup>12</sup>.

## FINAL CONSIDERATIONS

The safety and effectiveness of LPI for PAC/PACG has promoted a gradual shift in the criteria for iridotomy during the past couple of decades. However, more inclusive criteria spurred the debate over treatment algorithms, as we still do not exactly know which eyes will progress to glaucoma, despite early manifestations of narrow angles, and offering iridotomy too soon would expose healthier patients to complications without clear evidence of benefit. Moreover, it could represent an extra burden to

healthcare systems specially in some already deprived and "endemic" areas.

More recently, the role of cataract extraction in the PAC disease spectrum has continued to fuel debate around LPI timing and its indications. In fact, the EAGLE trial recently found clear-lens extraction clinically superior and more cost-effective than laser peripheral iridotomy, recommending it as an option in the first-line treatment for the studied subset of PAC patients. Newer and more objective angle imaging devices are expected to contribute towards predicting the success of laser iridotomy in the future. Hopefully, we will be able to devise a more adequate treatment and follow-up regimen for different patient subsets, according to different anatomical features and the underlying pathogenic mechanism of angle closure.

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# III. LASER Surgery in Glaucoma

## 20. Peripheral iridoplasty/ gonioplasty



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### INTRODUCTION

The first attempts to use laser energy near the iris root to widen the angle were made by Krasnov<sup>1</sup> and Kimbrough<sup>2</sup> in the late seventies, using laser parameters more like penetrating burns rather than the slow contraction burns that ultimately proved to be optimal. The term gonioplasty was first used by Kimbrough, who treated 360° of the peripheral iris through a gonioscopy lens. In peripheral laser iridoplasty (LPI), contraction burns of long duration, low power and large spot size are placed on the peripheral iris to contract the iris stroma between the site of the burn and the angle, physically pulling the iris away from the drainage angle, in order to open it.

### INDICATIONS

LPI is indicated to eliminate the appositional closure of the angle in situations, in which laser iridotomy either cannot be done or does not eliminate appositional angle closure. These scenarios usually occur due to mechanisms other than pupillary block, such as plateau iris and phacomorphic etiology<sup>3</sup>.

LPI helps preventing peripheral anterior synechiae formation in chronic cases of angle closure. It can also be performed prior to Nd:YAG-KTP (still often called Argon) laser trabeculoplasty to allow a better visualization of the trabecular meshwork. Additionally, it may be used to revert an attack of acute angle closure either as an initial approach or when medical therapy fails to abort the attack. Finally, it is a valid option in crowded angles (such as in nanophthalmos), as a tool to widen the angle.

### CONTRAINDICATIONS

Performing LPI depends on a good visualization of the peripheral iris. In that sense, it cannot be done successfully when there is severe and extensive corneal edema or opacification. This problem may be overcome by applying topical glycerin so as to decrease media opacity. In such cases, treating up to 180° may be enough

to break off an acute angle closure.

A very shallow anterior chamber is another contraindication, as the small distance between the peripheral iris and the corneal endothelium increases the chance of causing endothelial burns. In this sense, laser applications must also be timed in order to allow heat dissipation between each application. Finally, LPI should not be attempted in eyes with peripheral anterior synechiae, due to uveitis, neovascular glaucoma or ICE syndrome.

### LASER TECHNIQUE

*Nd:YAG-KTP Laser (blue-green) 488 to 515 nm*

Laser parameters should be adjusted according to iris thickness and colour.

LASER beam variables:

Spot size	300 µm	500 µm
Duration	0.5 sec	0.7 sec
Power	200 mW	500 mW

Procedure:

An Abraham iridotomy lens (Figure 1) is the most convenient since it has a power of +66D thus providing suitable magnification, but one can also use the Wise iridotomy lens or the Goldmann lens.

With the Abraham lens in place, one must carefully direct the beam at the most peripheral portion of the iris and allow a thin crescent of the aiming beam to overlap the sclera at the limbus. The patient must look slightly in the direction of the portion of the iris being treated. The foot pedal should be pressed for the entire duration of the burn, but if bubble formation or release of pigment occurs, one should interrupt the procedure and reduce laser power. On the contrary, if no contraction is seen or no deepening in the peripheral angle either, one must increase the power.

## 20. Peripheral iridoplasty/gonioplasty

This effect of contraction is immediate and accompanied by deepening of the peripheral anterior chamber at the site of the burn.

Lighter irides require more power than darker ones, and sometimes a reduced spot size too, 200  $\mu\text{m}$ .

Treatment consists of 20–24 spots over 360°, leaving a 2-spot diameter between each shot (Figure 2).

It is important to explain to the patient that the procedure may cause discomfort, related to laser burning of the peripheral iris.



Figure 1. Abraham iridotomy lens.



Figure 2. Laser peripheral Iridoplasty. The locations of laser application can be seen as hyperpigmentation spots spread over the 360°.

### POSTLASER CARE AND FOLLOW-UP

Steroid therapy should be administered 3 to 4 times a day for a week. The physician should bear in mind that intraocular pressure (IOP) should be monitored and that gonioscopy should be done as soon as possible to determine the efficacy of the procedure (Figure 3).

### COMPLICATIONS

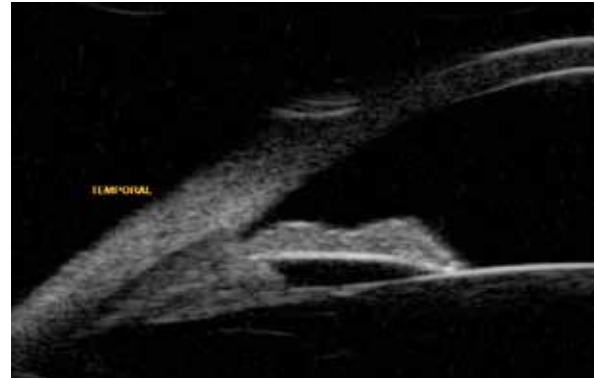
LPI has been associated with the following complications:

- **Mild iritis** (usually responsive to topical steroid treatment);
- **Iris pigment hypertrophy** from the laser burns;
- **Increase in IOP** (rarely);
- **Diffuse corneal endothelial burns** (usually self-limited);
- **Larger pupil diameter** (slow recovery).

### RESULTS

LPI is considered an effective treatment to break an attack of

Pre - Iridoplasty



Post - Iridoplasty

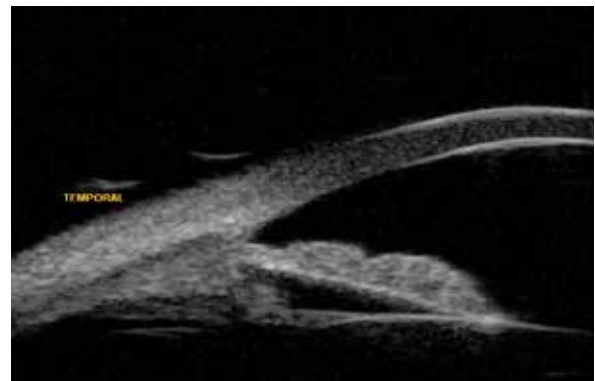


Figure 3. Widening of the angle pre and post peripheral laser Iridoplasty.

acute angle closure, although it does not eliminate pupillary block<sup>4</sup>. It can be used either as an initial approach and/or if medical therapy is ineffective or if local conditions preclude immediate laser iridotomy.

In plateau iris, LPI can be further considered if a prior laser iridotomy was inefficient in opening the angle. By placing laser burns very peripherally, one can eliminate residual apposition closure of the angle for an extensive period of time, although long term efficacy remains to be determined<sup>5</sup>.

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# III. LASER Surgery in Glaucoma

## 21. Trabeculoplasty



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### INTRODUCTION

The application of laser to the trabecular meshwork (TM) was first described by Krasnov in 1972 and also by Worthen and Wickam in 1973, based on the findings that continuous wave argon laser applied to the TM induces significant reduction of intraocular pressure (IOP)<sup>1,2</sup>. The subsequent clinical results of Argon Laser Trabeculoplasty (ALT) as described by Wise and Witter in 1979 became the basis for a new option for the clinical management of open-angle glaucoma (OAG)<sup>3</sup>. ALT was mostly used when an open-angle glaucoma patient was on maximum-tolerated medical therapy and required an additional decrease in IOP. However, with the development of selective laser trabeculoplasty (SLT) by Latina and Park in 1995<sup>4</sup> (approved by the US FDA in 2001), there was renewed interest in trabeculoplasty due to the possibility of repeated treatments and less structural damage to the TM. Since then it has been used either in association with medical therapy or, in selected cases, as primary treatment for glaucoma. Several studies comparing the efficacy of ALT versus SLT showed that they are similar in their complication rates and IOP reduction<sup>5-7</sup>. Multipulse Laser Trabeculoplasty (MLT) is a recent technique that uses low energy applied to the TM, without associated thermal damage. Although MLT still requires clinical validation, small short follow-up studies and reports suggest it is comparable to SLT and ALT<sup>8</sup>.

### MECHANISM OF ACTION

ALT has a photothermal coagulative action. The scarring process that follows the treatment serves to 'tighten' the collagenous ring of the trabecular meshwork, leaving the adjacent non-lasered areas with wide intratrabecular pores that increase the outflow of aqueous humour. Unlike ALT, histologic studies have shown no scarring or coagulative damage of the TM with SLT<sup>9</sup>. SLT uses a laser that selectively targets pigment meshwork cells – selective photothermolysis. This is possible only because it relies on ultra-short duration low fluency pulse

laser (3 ns) (thermal relaxation of melanin is 1  $\mu$ s) which minimizes the thermal dissipation to surrounding tissue, sparing the adjacent TM cells. This allows for less energy application, limiting the destruction of the outflow apparatus in the angle. Injury of pigmented cells may result in the release of chemoattractants that recruit monocytes, which are then transformed into macrophages that clear pigment granules from TM, lowering IOP<sup>10</sup>. The IOP lowering effect of SLT may therefore be explained by biochemical and cellular alterations instead of mechanical effects.

### INDICATIONS

Trabeculoplasty is indicated in primary or secondary OAG, especially in the following situations:

- Uncontrolled OAG on maximal medical therapy;
- OAG with poor compliance;
- OAG in patients not willing to use medical therapy.

### CONTRAINDICATIONS

- Angle-closure glaucoma;
- Glaucoma associated with uveitis, trauma or angle dysgenesis;
- Juvenile glaucoma;
- Relative contraindications are previous failure of trabeculoplasty in the same or in the fellow eye and little or no trabecular pigmentation.

### PREPARATION

- 1 Explain the procedure referring the possible need of multiple sessions or other procedures.
- 2 Room environment should be compliant with laser safety guidelines.
- 3 Apply topical  $\alpha$ -2 agonist (apraclonidine 1% or brimonidine 0.2%) one hour prior to the procedure in order to prevent IOP spikes.
- 4 Pilocarpine 2% one hour prior to the procedure.
- 5 Topical anesthesia (oxybuprocaine hydrochloride 0.4%).
- 6 Comfortable sitting of patient and room with dim lighting conditions.

## 21. Trabeculoplasty

### TRABECULOPLASTY LENSES (Figure 1)



Ritch Lens (ALT)

Magna View (ALT)



Latina Lens (SLT)

Three Mirror Lens (ALT)

Figure 1. Common lenses used in ALT and SLT.

### TECHNIQUE

#### LASER (Table 1, Figure 2):

- **ALT** – Argon or Nd: YAG-KTP 532 nm CW (continuous wave) (green) or Diode 577 nm (yellow);
- **SLT** – Nd: YAG - KTP 532 nm Q-switched (Pulsed Laser).

In ALT the location of the burns should be at the junction of the non-pigmented non-filtering meshwork and the pigmented filtering meshwork. Generally the authors treat 180° at a time. All 360° may be treated if clinically indicated, however this method is more often associated with postoperative IOP spikes. In SLT, the laser beam is focused on the pigmented TM so that the spot size entirely com-

passes the total height of the TM. During the procedure the optimal reaction for ALT is transient whitening and power should be reduced if an air bubble appears. In SLT the power is titrated until the appearance of tiny air bubbles at the site of the laser burn, then the power is reduced until there are no visible bubbles. Avoid Sampaolesi's line and pigmented corneal endothelial cells in both procedures.

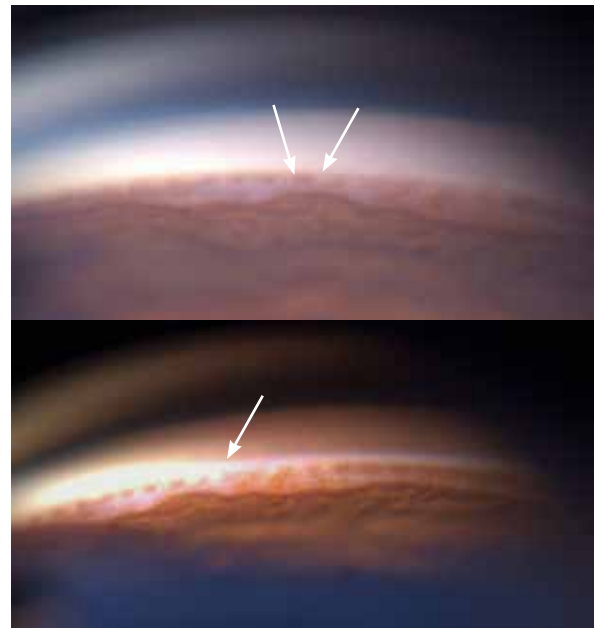


Figure 2. Pseudoexfoliation glaucoma, after ALT. Arrows point towards lasered spots.

### POSTLASER CARE AND FOLLOW-UP

Administration of 1% apraclonidine immediately following the procedure is optional. Patients should be kept in the office for at least 1 hour for IOP revision.

Topical corticosteroid 4 times daily for 4-7 days as well as the previous glaucoma medication. Patients are usually

Table 1. ALT and SLT laser parameters (adapted from European Glaucoma Society Guidelines)

LASER parameters	ALT	SLT
Spot size	50 $\mu$ m	400 $\mu$ m
Duration	0.1 sec	3 nsec
Power	300-1200 mW depending on the reaction	0.4 to 1.2 mJ (per pulse) depending on the reaction
Number of spots	50-100 spots, separated by 3-4 burns width over 180-360°	50-100 non-overlapping spots over 180-360°

seen 1 week after the laser treatment and response to the treatment may take as long as 6 weeks to occur.

### COMPLICATIONS<sup>11</sup>

This is a relatively safe and non-invasive procedure, however the following can occur:

- Transient IOP elevation;
- Mild inflammation;
- Peripheral anterior synechiae<sup>12</sup>;
- Hyphema<sup>13</sup>;
- Damage to the corneal endothelium<sup>14</sup>.

### RESULTS

The success rate of trabeculoplasty varies widely, ranging between 8.1 and 26.1% for ALT and between 6.9% and 35.9% for SLT<sup>15,16</sup>. SLT and ALT seem to provide a similar IOP decrease<sup>16</sup>; the chance of successful ALT retreatment however, is smaller when comparing to the initial procedure. SLT can be repeated but the second treatment

may not be as effective and may not last as long as the first<sup>17</sup>. Trabeculoplasty has a higher IOP lowering effect in pseudoexfoliation and pigmentary glaucomas compared to POAG, but the effect seems to wear off faster<sup>18</sup>.

Most studies focus on the efficacy of trabeculoplasty (Table 2) and findings relating to the comparison of ALT vs SLT (Table 3). Tables 2 and 3 summarize recent or pertinent findings relating to trabeculoplasty (ALT and SLT).

### CONCLUSIONS

Trabeculoplasty is a safe, non-invasive and effective treatment for OAG. In most cases there is a need for retreatment after a variable period of time, so frequent follow-up is often needed.

Trabeculoplasty should always be considered in the treatment of glaucoma, either as primary treatment or as an adjunctive to medical or surgical glaucoma therapy, often increasing the time window until more invasive treatments are required.

Table 2. Studies on the efficacy of trabeculoplasty

Author	Year	Purpose	Number	Follow up	Results
Lee JW <i>et al.</i> <sup>19</sup>	2015	Efficacy of SLT for normal tension glaucoma	41 Eyes	12 Months	A single session of SLT achieved an additional 15% IOP reduction while using 27% less medication.
Hirn C <i>et al.</i> <sup>20</sup>	2014	Efficacy of SLT in OAG patients on prostaglandins	109 Eyes	12 Months	Statistical significant reduction in IOP at 1 year of follow-up. There was no difference between patients on prostaglandins or medication naïve patients.
Mahar PS <i>et al.</i> <sup>21</sup>	2008	ALT as primary treatment in OAG	35 Eyes	12 Months	Pre-laser mean IOP was 27.63 mmHg. The post-laser mean IOP measured at 6 months follow up was 15.5 mmHg with mean decrease of 12.1 mmHg (43.8%).
Silva T <i>et al.</i> <sup>22</sup>	2009	Efficacy of SLT repetition	20 Eyes	12 Months	First treatment achieved 21.8% reduction in IOP. Repetition achieved 20.5% reduction. Repetition of SLT showed similar efficacy.
Gracner T <i>et al.</i> <sup>23</sup>	2006	Long-term follow-up of SLT in POAG	90 Eyes	41 Months	Failure was defined as an IOP reduction of less than 20% or the need for filtering surgery. Success rate as determined by Kaplan-Meier survival analysis was 94% at 12 months; 85% after 24 months; 74 % after 36 months; 68% after after 48 months; and 59% after 72 months.
Shingleton <i>et al.</i> <sup>24</sup>	1993	Long-term efficacy of ALT	93 Eyes	10 Years	Decrease in IOP was 8.9 +/- 5.4 mmHg at 1 year, 10.0 +/- 4.2 mmHg at 5 years, and 8.9 +/- 5.2 mmHg at 10 years. The probability of success at 1 year was 77%, at 5 years 49%, and at 10 years 32%. Failure was most common in the first year after treatment (23%), and thereafter failure occurred at a rate of 5-9% per year. The mean decrease in iop for all 93 eyes at time of maximum follow-up was 6.1 +/- 7.1 mmHg.



Table 3. Comparative studies between ALT and SLT

Author	Year	Purpose	Number	Follow up	Results
Kent S <i>et al.</i> <sup>25</sup>	2013	ALT vs SLT in PXG patients	76 eyes	12 months	IOP reduction 6 months after SLT was 6.8 mmHg and post-ALT was 7.7 mmHg, with no statistically significant difference between procedures.
Rosenfeld <i>et al.</i> <sup>26</sup>	2012	SLT vs ALT in pseudophakic glaucoma	52 eyes	12 months	Mean IOP reduction from baseline was 3.23 mmHg in the ALT group and 4.30 mmHg in the SLT group. SLT and ALT were equally effective in their IOP-lowering capabilities in pseudophakic glaucoma patients during the first 12 months after treatment.
Liu Y <i>et al.</i> <sup>27</sup>	2012	ALT vs SLT in younger patients	42 patients	24 months	There was a statistically significant IOP decrease of 11.1% after ALT and 7.7% after SLT with no statistical difference between the two techniques, both ALT and SLT had a significant ocular hypotensive effect 2 years after treatment.
Russo V <i>et al.</i> <sup>28</sup>	2009	SLT vs ALT in OAG	120 eyes	12 months	There was no statistically significant difference in IOP lowering between SLT (6.01 mmHg) and ALT (6.12 mmHg). In case of retreatment, SLT was better than ALT in IOP lowering.

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# III. LASER Surgery in Glaucoma

## 22. LASER suture lysis



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### INTRODUCTION

Laser suture lysis is a minimally invasive procedure that is used to increase aqueous humour (AH) filtration through the trabeculectomy ostium<sup>1</sup>. It allows one to fashion a subconjunctival lysis of a scleral suture, thus decreasing the tensile strength holding the scleral flap that partially (or completely) occludes the AH outward passage. This increase in outflow can significantly decrease intraocular pressure (IOP), with an enlargement of the subconjunctival reservoir<sup>1,2</sup>. The extent of this bleb enlargement (particularly bleb height) can actually be used to predict the surgical outcome, as demonstrated in a recent anterior-segment optical coherence tomography (OCT) study<sup>3</sup>.

Suture lysis is a valid alternative to releasable sutures. It has the advantage of allowing the surgeon to perform standard, regular scleral sutures (speeding up surgery). Furthermore, knowing the sutures can be easily cut afterwards, the surgeon can place them tightly enough so as to have no flow through the flap at the end of surgery (watertight), thus avoiding the risk of early ocular hypotony<sup>4,5</sup>. The downside is the need for adequate laser equipment in the office in order to be able to perform the procedure. Moreover, suture visualization may be difficult with a thick Tenon's capsule or extensive subconjunctival bleeding<sup>5-7</sup>. Choice between options are at the surgeon's discretion as both techniques seem to provide a similar IOP-lowering effect.

### INDICATIONS

Standard indications for performing laser suture lysis in the majority of studies focusing on this procedure were<sup>7</sup>:

- IOP value near or above target;
- 20% decrease in IOP following a 10 s digital massage.

### IOP-LOWERING EFFICACY

Literature suggests laser suture lysis as a risk factor for filtration surgery failure. The need for an extra procedure to achieve the target IOP implies the surgery itself was

underperforming. In this context, suture lysis can be considered a salvage procedure, one that can apparently have a long-term positive impact after surgeries that are deemed at high risk of failure. As a stand-alone procedure, the surgeon can expect a significant IOP reduction; literature suggests a mean decrease of 7-9 mmHg, but larger drops in IOP are known to occur (including undesirable hypotony)<sup>2,5,7</sup>.

Of note, IOP reduction following laser suture lysis is not related to suture selection (for instance, nasal or temporal suture) nor to the number of remaining scleral flap sutures<sup>6</sup>.

### PROCEDURE / TYPES OF LENSES FOR LASER SUTURE LYSIS

Laser suture lysis is usually performed using a Nd:YAG-KTP 532 nm laser (still often called Argon laser), although a double-frequency YAG laser can also be used. It is an office-based procedure, done under topical anesthesia. The patient is asked to look down, exposing the area for direct slit-lamp observation. A lens is placed on the conjunctiva overlying the scleral flap suture and gentle pressure is then used to blanch the conjunctival vessels to better visualize the scleral suture. The surgeon should then use their preferred settings (Table 1) to perform the lysis.

Table 1. Laser Parameters for Suture Lysis<sup>7</sup>

<b>Spot-Size</b>	50-100 $\mu$ m
<b>Duration</b>	0.1 sec
<b>Power</b>	300-600 mW

A rule of thumb for assessing suture tightness is to check how far apart the two ends of the suture are once it has been cut. An immobile suture implying the locus for outflow resistance was not the flap suture; on the other hand, a large opening of the suture suggests the increased outflow displaced the scleral flap (Figure 1A and 1B). After the suture has been cut, the physician performs a

## 22. Laser suture lysis

digital massage to test for bleb enlargement (Figure 1C and 1D). Of note, one should not perform lysis of both sutures (nasal and temporal) simultaneously.

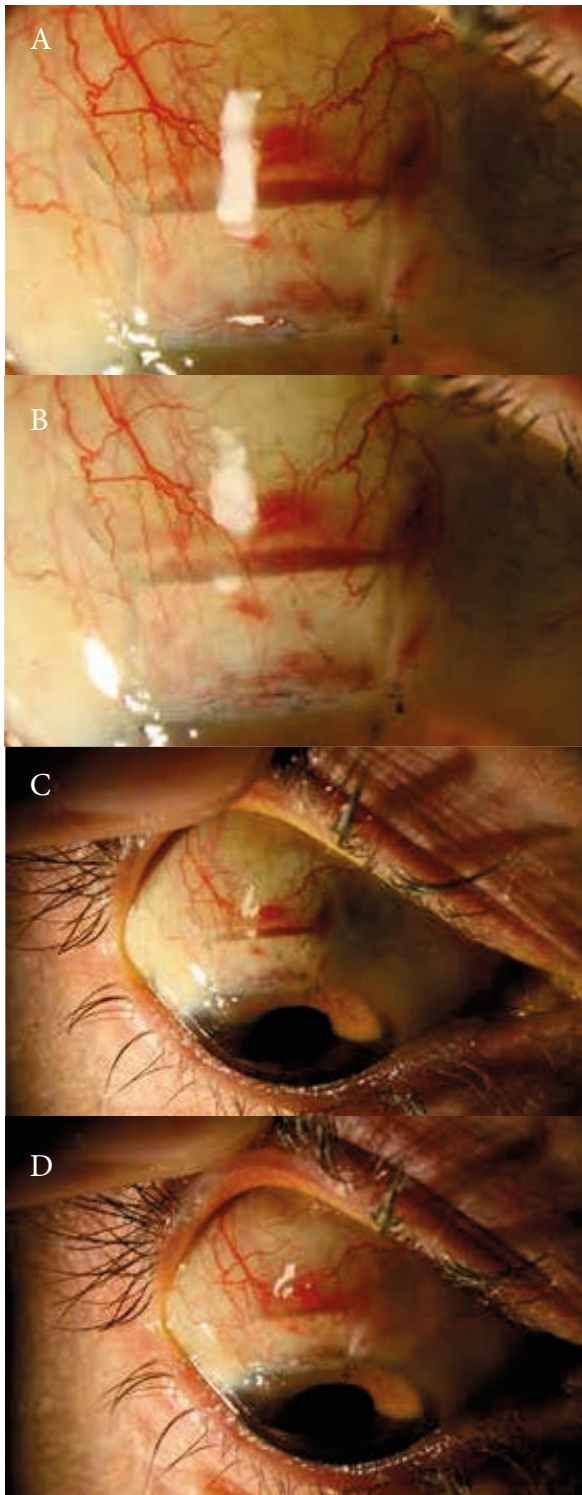


Figure 1. A) before suture lysis; B) after laser suture lysis; C) filtering bleb before lysis; D) filtering bleb after suture lysis.

The choice of the lens for the procedure depends on a variety of factors. Firstly, and foremost, the physician's preference in lens-handling and the degree of conjunctival exposure the lens provides. For instance, while some surgeons would prefer the stability of a Hoskins lens (which has a larger conjunctival contact ring)<sup>7</sup>, others may prefer the better visualization of the suture provided by the Blumenthal lens (Table 2)<sup>4</sup>.

Table 2. Suture Lysis Lens (magnification)

Hoskins	1.2x
Mendelkorn	1.32x
Ritch	1.0x
Blumenthal	2-3x

### TIMING

Before the use of anti-metabolites, the optimal timing for performing suture lysis was within the first two weeks of surgery in one study. However, this concept has been challenged by a number of publications that have successfully attempted this procedure up to 21 weeks after the initial trabeculectomy. While the original theory is that the longer one waits to remove the sutures, the less effective the procedure will be (due to the healing process), it has been suggested that in the long run (>12 months), no difference exists between early and late suture lysis. Moreover, waiting for longer periods before removing these sutures may be safer, as the chances of overfiltration may be significantly lower<sup>6,7</sup>.

### ADVERSE EFFECTS / COMPLICATIONS

One consequence of removing the tensile strength holding the scleral flap in place is excessive AH filtration and eventually hypotony. This finding seems to be directly related to early suture lysis (studies suggest that breaking the suture within the first 10 days could lead to a chance of developing hypotony of up to 4%)<sup>7</sup>.

Mechanically applying a lens over a surface can lead to a number of complications, ranging from conjunctival tearing to subconjunctival bleeding. Moreover, a misdirection in laser application can lead to conjunctival burning although usually to a minimal degree.

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# III. LASER Surgery in Glaucoma

## 23. Anterior Hyaloidotomy

### and transcleral

### cyclophotocoagulation



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#### INTRODUCTION

Aqueous misdirection syndrome (AMS) was first described in 1869 by Albrecht von Graefe<sup>1</sup> and designated malignant glaucoma, as at that time it was refractory to existing treatments. The term was used to define the condition of anterior chamber axial shallowing in the presence of a patent iridotomy, with or without increased intraocular pressure (IOP). Although the pathophysiology behind this condition is not yet fully understood, a fundamental mechanism seems to lie in a change in the anatomic relationship of the lens, ciliary body, and anterior hyaloid face, resulting in aqueous misdirection with increase in vitreous volume due to aberrant flow into the posterior segment<sup>2</sup>.

AMS can occur in aphakic, phakic and pseudophakic patients. Visual acuity is usually reduced due to refractive changes and corneal edema, however, it can be nearly normal<sup>3</sup>.

Risk factors for its development are usually penetrating glaucoma surgery and narrow angle or shallow anterior chamber preoperatively, making this rare occurrence more common among women.

According to the literature, AMS develops in 2% to 4% of patients with a history of angle closure glaucoma who have undergone filtration surgery<sup>4</sup>.

Time of onset varies from pre-surgery to years after surgery. Postoperative manipulation and late changes of the surgical site are risk factors for late onset AMS.

Incidence is small, particularly in open angle glaucoma surgery. The Collaborative Initial Glaucoma Treatment Study (CIGTS) reported an incidence of 0.4% amongst 465 trabeculectomies<sup>5</sup>, and more recently, the Tube Versus Trabeculectomy (TVT) study had a 1% incidence in trabeculectomy patients and a 2.8% incidence after non-valved tube surgeries<sup>6</sup>. Other procedures have also been associated with AMS, namely:

- Iridectomy and iridotomy – higher risk after treatment of pupillary block;
- Cataract surgery – very rare;

- Penetrating keratoplasty;
- Phakic intraocular lens surgery;
- Vitrectomy;
- Intravitreal injection;
- Miotic therapy.

As AMS is a diagnosis of exclusion, treatment should only be addressed after careful slit lamp examination and ultrasonography or optical coherence tomography (OCT). The following conditions should be excluded:

- Wound leak;
- Overfiltration;
- Suprachoroidal hemorrhage;
- Pupillary block;
- Ciliary body edema or rotation;
- Annular choroidal detachment.

Medical treatment should be initiated once the definitive diagnosis is made and involves immediate cycloplegia and aqueous suppression. Osmotic and anti-inflammatory agents are generally used according to need.

The goal of the treatment is to decrease aqueous humor production, to shrink the vitreous body and to move the iris-lens diaphragm backward<sup>3</sup>.

Surgical treatment options aim to restore normal aqueous flow and include laser or incisional surgery. Due to their less invasive profile, Laser procedures when possible are performed first in a step-ladder approach and comprise:

- Argon/Nd:YAG-KTP Laser Photocoagulation (ALP);
- Nd: YAG Q-switch Laser Anterior Hyaloidotomy (YAG QS-LAH);
- Cyclophotocoagulation (CPC).

#### INDICATIONS / CONTRAINDICATIONS

Laser treatment should be performed as early as possible and is recommended even in cases with apparent medical control, due to high risk of relapse after medical treatment is stopped if this is done alone.

Clear visualization is required for Argon/Nd:YAG-KTP



Laser Photocoagulation and Nd:YAG Laser Anterior Hyaloidotomy (YAG-QS-AH).

Ciliary process ALP can be attempted when adequate visualization can be obtained through a wide basal peripheral iridectomy. Relief of ciliolenticular block is thought to occur due to thermal shrinkage of the ciliary processes, but thermal rupture of the anterior hyaloid may also play a role<sup>7</sup>. At least two to five ciliary processes should be accessible for better results.

In aphakic and pseudophakic eyes, laser disruption of the anterior hyaloid allows for communication between the posterior and anterior segments and was shown to re-establish normal dynamics of aqueous humor flow.

When poor visualization contraindicates ALP and YAG-QS-AH, Cyclophotocoagulation is the only Laser treatment option available. Due to the potential complications involved, CPC is usually the final alternative in patients who refuse incisional surgery. Although its mechanism is incompletely understood, CPC is considered to help in the resolution of AMS by inducing the posterior rotation of ciliary processes secondary to coagulative shrinkage<sup>3</sup>. So, besides reducing the production of aqueous, CPC may help by eliminating the abnormal anatomical vitreociliary relationship which seems to predispose to AMS.

### PREPARATION

The procedure should be explained and informed consent from patient or representative person should be obtained (not necessarily written consent, follow local rules).

Medical therapy should be maintained.

When corneal edema is present and clear visualization is needed, topical application of glycerin or hypertonic eye drops can be helpful.

ALP and YLAH are usually performed under topical anesthesia (Oxybuprocaine Hydrochloride 0.4%) but for CPC, peribulbar or retrobulbar anesthesia are the preferred options.

### LASER TECHNIQUE

#### Argon/Nd:YAG-KTP

Laser treatment can be done directly or with a gonioscopy lens (3 mirror Goldmann Lens; Trokel ; Ritch ; Magna View ; Latina...). In order to obtain shrinkage of the ciliary processes, the usual settings are:

Spot size: 50-100  $\mu\text{m}$ ;

Power: 100-300 mW;

Exposure/Duration: 0.1-0.2 sec.

Green 532 nm laser (Figure 1) and 577 nm Yellow laser are the more frequent wavelengths used<sup>7</sup>.

#### Nd: YAG Q-switch Laser Anterior Hyaloidotomy (YAG-QS-LAH)

Hyaloidotomy should be performed peripherally in pseudophakic eyes because, centrally, the capsule and intraocular lens are obstacles to appropriate intersegment communication. The existence of a broad enough iridectomy in these cases is therefore of great help.

Typically, initial laser energy is set between 3-6 mJ per pulse. Pulse number and energy may be increased according to tissue response. Laser treatment can be attempted directly, but is best performed with an iridotomy (Abraham; Peyman; Mandelkorn...) or gonioscopy lens

(Figure 2). If successful, immediate deepening of the anterior chamber is usually observed. Several sessions may be needed to achieve complete permeability<sup>8-10</sup>. We usually use an Ellex Q-switched Nd-YAG Laser with 1064 nm wavelength.



Figure 1. 532 nm Nd:YAG Laser; Three mirror Goldmann lens.



Figure 2. YAG Laser Hyaloidotomy diagram and lens example.

### Cyclophotocoagulation

In transscleral CPC (Figure 3), the most widespread technique, around 18 diode laser burns are performed over 270 degrees, avoiding the 3 and 9 o'clock hours. Sparing of the superior quadrant can be considered if AMS occurs after superior penetrating glaucoma surgery in order to allow for a better preservation of filtration. The probe should be held perpendicularly to the scleral surface, juxtaposed to the limbus with steady indentation, in order for the laser to be delivered at 1.2 to 1.5 mm from the limbus<sup>11,12</sup>. Exposure time is usually set for 2000 ms and energy is titrated between 1500 and 2000 mW maintaining a sub "popcorn effect" value.

In our experience, transcleral CPC is performed with an ARC 810 nm Diode Laser under peribulbar block.

### POSTLASER CARE AND FOLLOW-UP

After laser therapy, medical treatment and close follow-up must be continued.

In ALP and YLAH, maintenance of cycloplegia, aqueous suppression and anti-inflammatory drops is usually enough, however, if CPC is performed, analgesic treatment should be added. Narcotic analgesic combinations such as (paracetamol/phosphate codeine – 500 mg/30 mg) or (paracetamol/ tramadol hydrochloride – 325 mg/37.5



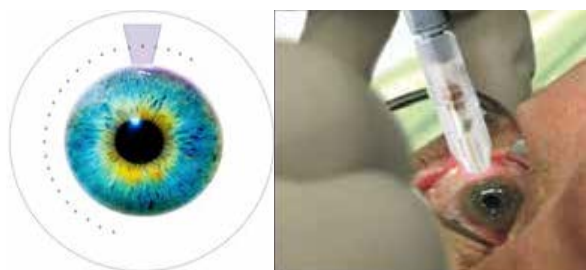


Figure 3. Cyclophotocoagulation treatment diagram and probe. On the left image the grey area marks probe placement and the red dot the laser delivery point. Contiguous probe placement should not overlay the previous grey area.

mg) up to a maximum dosage of q.i.d. usually provide good pain relief. Prescription of a steroid and/or antibiotic ointment t.i.d. and overnight eye patching also brings comfort to the majority of patients. Follow-up visits are usually scheduled in 1-3 days, depending on pre-treatment control and procedure outcome.

### COMPLICATIONS

Inflammation and hyphema are common complications to all the laser procedures described, although usually of no concern. CPC has the increased risk of cystoid macular edema, phthisis, scleromalacia, staphyloma, conjunctival burn and, although rarely, can even be implied in the perpetuation of the pathophysiological mechanism of AMS itself<sup>11-13</sup>.

### RESULTS

Prognosis in AMS was traditionally poor. With swifter diagnosis and prompt medical and surgical management, therapeutic outcomes are nowadays better with appropriate IOP control being achieved in around 90% of cases in most series.

Medical therapy and Laser alone are usually successful in controlling up to 50% of cases, however, lifetime follow-up is needed because recurrence risk is higher in eyes not submitted to incisional surgery.

Despite the usual satisfying efficacy in IOP control, visual acuity reduction is common.

Care should be taken when approaching the fellow eye in patients who have suffered AMS, due to high risk of incidence in the fellow eye. In such cases, miotic therapy should be avoided and if surgery is deemed necessary, cycloplegic and osmotic agents should be used preventively. Some authors consider prophylactic vitrectomy. In any case, close postoperative monitoring is crucial<sup>14</sup>.

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# III. LASER Surgery in Glaucoma

## 24. Cyclophotocoagulation



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### INTRODUCTION

Cyclodestructive procedures result in reduction of aqueous secretion by destruction of the ciliary epithelium and stroma. They are usually reserved for glaucoma refractory to medical therapy and outflow surgeries, painful eyes, and eyes that have little or no vision, because of the associated risk of morbidity. However, as this technique is being continuously refined, a growing number of studies also suggest that its indications should not be limited to eyes with poor visual potential<sup>1</sup>, because the loss of visual acuity seems similar to cases previously reported with trabeculectomy or tube surgery<sup>2,3</sup>.

Cyclodestruction may be achieved by several means, but laser is the main surgical method for reducing aqueous formation<sup>4,6</sup>. Laser delivery is done indirectly through the sclera, or directly by endoscopy.

Transscleral cyclophotocoagulation (TCP) may be performed by either the non-contact or contact technique, the latter being preferred. Initial attempts employed the ruby laser, followed by the neodymium: yttrium-aluminum-garnet (double frequency Nd:YAG) laser, and the diode laser (810 nm), the latter achieving the greatest scleral penetration, as well as improved energy absorption by ciliary epithelium<sup>4,6,7</sup>. Novel techniques, like micropulse cyclophotocoagulation, employ a series of repetitive short pulses of laser energy, separated by rest periods<sup>8</sup>.

Endoscopic cyclophotocoagulation (ECP) is gaining popularity worldwide, and it is becoming an increasingly important alternative for treatment of refractory glaucoma<sup>4,6</sup>. Between 2005 and 2012, the number of ECPs increased by 99% in the Medicare population<sup>9</sup>. The tips of the ciliary processes are visualized directly, and treated precisely, to achieve the desired anatomical effect.

### INDICATIONS

This technique is useful when filtration surgery or tubes are likely to fail, have failed or are not feasible<sup>10</sup>.

Types of glaucoma that are often difficult to treat include neovascular glaucoma, post-traumatic glaucoma, glaucoma associated with aphakia, severe congenital or developmental glaucoma, post-retinal surgery glaucoma, glaucoma associated with penetrating keratoplasties, and glaucoma in eyes with scarred conjunctivae from surgery or disease processes<sup>6</sup>.

It is usually performed after medical therapy and filtration surgeries have been tried and have failed<sup>4,6</sup>. The reason for waiting until such an advanced degree of glaucomatous loss, before considering cyclophotocoagulation, is that it has the potential for significant complications and associated vision loss. However, it should be noted that relatively high rates of vision loss may also be associated with the underlying disease<sup>6</sup>.

### METHODS FOR CYCLOPHOTOCOAGULATION

Normal glaucoma medications, both topical and systemic, are done, including on the day of surgery.

Cyclodestruction is a painful procedure. A retrobulbar anesthetic injection is provided for TCP<sup>4,6,11</sup> with a 50:50 mixture of 2% lidocaine and 0.75% bupivacaine. With the eye in primary gaze, at the infratemporal lower orbital margin, a 25-gauge needle is advanced parallel to the plane of the orbital floor. Once past the equator of the globe, 4-6 mL are injected directly into the posterior intraconal space, and no resistance should be felt. Compression is often applied for 5-10 minutes. General anesthesia is preferred by some practitioners, especially in children, or when infiltration of anesthesia is unsuitable. ECP can be performed with intracameral anesthesia<sup>11</sup>, and preoperative considerations are similar to phacoemulsification.

### A. TRANSSCLERAL CYCLOPHOTOCOAGULATION WITH DIODE LASER (Figure 1)

A lid speculum is placed for optimal exposure. Recognition of the location of the ciliary body is vital.

## 24. Cyclophotocoagulation

Transscleral illumination, with a fiber optic light source directed about 4 mm posterior to the limbus may be used, where the dark demarcation lines indicate the anterior margin of the ciliary body. This poses a unique challenge in the pediatric glaucoma population, and ultrasound biomicroscopy can be used to confirm location prior to cyclophotocoagulation<sup>12</sup>.



Figure 1. IRIDEX Oculight SLx (Iris Medical) for diode contact TCP (left). Transscleral illumination (right).

The tip of the probe is placed parallel with the visual axis, adjacent to the limbus (which positions the fiberoptic laser tip 1.2 mm behind it) and is adjusted accordingly transscleral illumination, to be over the ciliary body. It should be applied firmly against the conjunctiva/sclera to avoid burns.

The initial energy settings are often about 1800 mW with 2 seconds duration (and may be variable, from 1500 mW for dark to 2000 mW for light-colored irises). Lower energy levels can be used with longer durations. Energy is titrated (reductions of 150 mW) to be just below that needed to achieve the “pop” sound indicating tissue disruption. A total of 10-20 shots over 180° and a total treatment per session of up to 270/360 degrees of circumference, avoiding the 3 and 9 o'clock positions to sidestep the long posterior ciliary nerves, is common<sup>4-7,11</sup>. Micro pulse diode laser TCP is a novel method, which delivers a series of repetitive short pulses of energy with rest periods in between, theoretically minimizing collateral tissue damage<sup>7,13</sup>. Technique is comparable as traditional continuous TCP, although through a novel contact probe, applied in a continuous sliding motion also bypassing the 3 and 9 o'clock positions. Described settings are 2000 mW of power, delivered with 0.5 ms on and 1.1 ms off time (duty cycle of 31.3%). Preliminary data suggests it is predictable and effective in lowering intraocular pressure, with minimal ocular complications<sup>8,13,14</sup>.

### B. ENDOSCOPIC CYCLOPHOTOCOAGULATION

Endoscopic cyclophotocoagulation employs an endoscope, which contains the image, light, and the laser guides. It is connected to the console that encloses all of the instrumentation, and a semiconductor diode laser is used as source to deliver energy to the ciliary processes, under direct endoscopic visualization. It can be applied virtually to any patient, despite opacities of the ocular media, a miotic pupil, or previous glaucoma surgery.

The two main approaches to reach the ciliary processes are via a limbal or a pars plana entry. The status of the lens and vitreous are a primary consideration when planning ECP<sup>11</sup>. The limbal approach is generally preferred because anterior vitrectomy and associated risks for choroidal and retinal detachment are avoided. After dilation of the pupil,

a paracentesis is created and the anterior chamber is filled with a viscoelastic agent, also expanding the posterior sulcus. A clear corneal or scleral tunnel is performed to enter the anterior chamber, the 18-gauge diameter probe is inserted through the incision and into the posterior sulcus, the ciliary processes are viewed on the monitor and treatment can begin, in a highly controlled approach, until ciliary process become shrunken and white. In general, 200–360° of this tissue should be treated. Before closure of the wounds, the viscoelastic agent is removed from the anterior chamber<sup>4,6,11</sup>.

It is generally accepted that direct visualization allows the surgeon to have greater control over the procedure, potentially reducing overtreatment and the subsequent risk of late phthisis. Because intraocular pressure (IOP) lowering with ECP seems modest, eyes with highest pressures may be considered more appropriate for TCP, particularly if potential visual function is limited<sup>4-7,11</sup>.

More recently, ECP has been employed as a micro invasive glaucoma surgery adjunct for treatment of patients with coexisting cataract and glaucoma. A number of clinical studies demonstrating the efficacy and safety of combined phacoemulsification and ECP is growing with encouraging results. It should be noted that most of the available data is retrospective in nature, and lacks a control group, to better isolate the IOP lowering effect of ECP from that associated with phacoemulsification alone<sup>15</sup>.

### POST-LASER CARE AND FOLLOW-UP

After the procedure, systemic analgesia may be considered. Topical atropine and dexamethasone are applied, sub-Tenon's injection of triamcinolone may also be administered, and the eye is patched for the day.

Postoperative topical corticosteroids and atropine are applied for 2-3 weeks and tapered according to inflammation. Glaucoma topical medications should be reinstated (prostaglandin analogs may be excluded in the short-term if cystoid macular edema is a concern) and tapered accordingly. The effectiveness of treatment is assessed after 4 weeks<sup>4-7,10,11</sup>.

### COMPLICATIONS

Complication rates after cyclophotocoagulation vary significantly, depending on laser type, glaucoma type and severity, treatment protocol, and other factors.

IOP spikes are common in the immediate period after treatment<sup>16</sup>. Other side effects include pain, vision loss, hyphema, anterior uveitis, and cataract progression. Rarely, hypotony, sympathetic ophthalmia, malignant glaucoma, necrotizing scleritis, subluxation of the crystalline lens and phthisis may occur<sup>5</sup>.

The risk of hypotony, a long-recognized complication, may be mitigated by treating over multiple sessions, and never the entire circumference of the ciliary body<sup>4-7,11</sup>.

Patients with diseases where breakdown of the blood-retinal barrier is present, or with a history of intraocular surgery with or without previous trauma, may be at greater risk of sympathetic ophthalmia<sup>17</sup>. Early recognition and aggressive management with immunosuppressive therapy results in good outcomes for these patients<sup>18</sup>.

In recent studies where TCP has been used as primary surgery, the rates of serious complications seem to be null

or few in number. This may be related to the lower energy settings and the relatively higher proportion of primary open-angle glaucoma and less severe forms of glaucoma, compared to previous studies<sup>4,6</sup>.

## RESULTS

The reported success rates for effective IOP control are quite diverse, as it is the effectiveness of symptomatic relief of pain, in those in whom the procedure is undertaken for discomfort<sup>11</sup>.

A uniform definition of success does not exist. Although an accurate comparison of different studies is difficult, reported IOP reduction varies between 12–65%<sup>5</sup> with IOP < 22 mmHg in 60–84% and re-treatment rate of 28–45%<sup>19</sup>.

A recent meta-analysis on post-keratoplasty glaucoma seems to favor glaucoma drainage device (GDD) surgery to provide the maximum IOP reduction, although there was not a statistically significant difference in IOP reduction between the cyclophotocoagulation and GDD groups, and

a higher rate of graft failure was seen with the GDD group<sup>20</sup>. In pediatric glaucoma, TCP and ECP may become first-line therapy to achieve control of IOP<sup>21,22</sup>.

ECP, used as a stand-alone procedure or as an adjunct to standard external filtration surgery, has demonstrated clinical efficacy and safety in several studies, even for severe refractory and pediatric glaucoma<sup>23</sup>.

Phacoemulsification combined with ECP effectively lowers or maintains intraocular pressure with a reduced medication burden<sup>24,25</sup>, but significant variation of the success rate based on the type of glaucoma still exists<sup>26</sup>.

Over the years, several authors have compared cyclophotocoagulation with other surgical modalities. Outcomes of combined phaco/ECP compared to combined phaco/trabeculectomy show that the first represents a reasonably safe and effective alternative<sup>27</sup>. In refractory glaucoma, there is no difference in success rate between the Ahmed Glaucoma Valve and ECP<sup>28</sup>. However, after failure of an initial drainage implant, a sequential tube had a higher

Table 1. Summary of results in published studies of TCP and ECP over the last 10 years

Authors	Year	Follow-up (months)	Number of eyes	IOP reduction (%)	Success rate (%)	Definition of success	Retreatment (%)
<b>Transscleral cyclophotocoagulation</b>							
Aquino <i>et al.</i> <sup>8</sup>	2015	18	24	45	30	6 ≤ IOP ≤ 21 and 30% reduction	N/A
Schaefer <i>et al.</i> <sup>29</sup>	2015	62.8	32	27.0	65.6	≤18	34
Ghosh <i>et al.</i> <sup>2</sup>	2014	24	46	28.3	84.8	≤21	26
Kraus <i>et al.</i> <sup>21</sup>	2014	65.6	72	28.6	57.7	≤21	45
Panarelli <i>et al.</i> <sup>30</sup>	2014	25.6	20	50.2	80	5 ≤ IOP ≤ 14	N/A
Bloom <i>et al.</i> <sup>31</sup>	2013	12	45	42.8	71	≤21	N/A
Ramli <i>et al.</i> <sup>32</sup>	2012	17.1	90	57.4	54	5 ≤ IOP ≤ 21	13.3
Frezzotti <i>et al.</i> <sup>33</sup>	2010	17.0	124	31.3	63.0	≤21	21.7
Osman <i>et al.</i> <sup>34</sup>	2010	80.2	35	46.4	62.8	≤22	0
Rotchford <i>et al.</i> <sup>3</sup>	2010	60.0	49	45.4	89.8	6 ≤ IOP ≤ 21	36.7
Kaushik <i>et al.</i> <sup>35</sup>	2008	14.3	66	57.1	78.8	5 ≤ IOP ≤ 21	16.7
Iliev <i>et al.</i> <sup>36</sup>	2007	30.1	131	55.0	69.5	6 ≤ IOP ≤ 21	38.9
Ansari <i>et al.</i> <sup>37</sup>	2007	12.5	74	43.0	82.0	30% reduction	1.4
Noureddin <i>et al.</i> <sup>38</sup>	2006	13.7	36	53.0	72.2	≤21	25.0
Grueb <i>et al.</i> <sup>39</sup>	2006	24.0	90	23.8	36.7	4 ≤ IOP ≤ 18 and 20% reduction	30.0
Vernon <i>et al.</i> <sup>40</sup>	2006	65.7	42	50.3	88.1	<22	59.6
Lai <i>et al.</i> <sup>41</sup>	2005	26.5	13	48.6	92.7	≤21	15.4
<b>Endoscopic cyclophotocoagulation</b>							
Kraus <i>et al.</i> <sup>21</sup>	2014	65.5	52	33.2	62	≤21	25
Clement <i>et al.</i> <sup>42</sup>	2013	12	63	24	55.5	4 ≤ IOP ≤ 21 and 20% reduction	N/A
Lindfield <i>et al.</i> <sup>43</sup>	2012	24	56	33.1	76	IOP ≤ 21 and 20% reduction	N/A
Francis <i>et al.</i> <sup>44</sup>	2011	12	25	30.8	88	3 mmHg IOP reduction and discontinuation of non-tolerated medications	N/A
Carter <i>et al.</i> <sup>22</sup>	2007	44.4	34	24.8	53	IOP ≤ 24 and 15% reduction	N/A



initial rate of success than cyclophotocoagulation, but the latter had relatively few late failures<sup>29</sup>.

Table 1 details follow-up times, definition of success, and ocular hypotensive response, of published studies of TCP and ECP, over the last 10 years.

### CONCLUSION

Laser cyclophotocoagulation is an ever-evolving technique. Because of its relative safety and effectiveness, it is overriding traditional indications in patients with end-stage disease and poor vision, and gaining acceptance as first-line therapy of selected individuals.

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# IV. LASER surgery in Iris/Pupil

## 25. Pupilloplasty,

## Photomydriasis and

## Synechiolysis



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### INTRODUCTION

Sustained miosis can cause subjective decrease of visual acuity, worsening of visual field defects and accentuation of visual impairment caused by opacities in the visual axis<sup>1,2</sup>. Conversely, a smaller pupil enhances depth of visual field and minimizes spherical and chromatic aberrations. It is therefore important to reach an equilibrium, with the ideal pupillary diameter calculated to be around 2.4 mm<sup>3</sup>. Laser pupilloplasty is the alteration of pupil size, shape or location using laser technology. Photomydriasis is a variation of pupilloplasty, and consists of using laser to enlarge a miotic pupil<sup>4</sup>. It is usually performed using photothermal laser, like Nd:YAG KTP 532 nm (KTP laser 532) or Yellow Diode laser 577 nm (YD laser 577).

Posterior synechia can also cause decreased visual acuity as well as pupil contour changes associated with glare, decreased focal depth and the release of inflammatory mediators which are a potential cause of cystoid macular edema. Synechiolysis refers to the destruction of posterior synechia in the pupillary area, which can be done with photodisruptive laser, like Nd:YAG 1064 nm Q-switched (YAG laser).

### INDICATIONS

Photomydriasis is usually performed in the following situations: to facilitate visualization or treatment of posterior segment pathology; in the case of a miotic pupil resistant to pharmacological dilation; in pupillary block glaucoma associated with aphakia or pseudophakia as an alternative to laser iridotomy in edematous corneas; to reduce miosis in patients on chronic miotic therapy.

Whenever synechia to the crystalline lens<sup>5</sup>, capsular, intraocular lens<sup>6</sup> or anterior hyaloid are present, Nd:YAG synechiolysis is a possible therapeutic option. Laser synechiolysis is also a feasible alternative to photomydriasis, especially in cases refractory to therapy<sup>7</sup>.

### CONTRAINDICATIONS

- Active uveitis;
- Cloudy cornea precluding adequate visualization of the pupillary area.

### PREPARATION

1. Explain the procedure referring the possible need for multiple sessions or other procedures.
2. Room environment should be compliant with laser safety guidelines.
3. Obtain informed consent from patient or representative person (not necessarily written consent, follow local rules).
4. Mydriasis – tropicamide (1%) and phenylephrine (10%) instilled 3 times with 15 min interval, starting 2 hours before laser.
5. Anti-hypertensive medication – one drop of brimonidine tartrate 0.2% or apraclonidine 1% 1 hour before laser.
6. Anesthesia – topical (oxybuprocaine hydrochloride 0.4%) or, less often, peribulbar anesthesia in nystagmus or uncooperative patients.
7. Comfortable sitting of patient.
8. Darken or semi-darken the laser room.
9. Ask the patient to keep steady fixation.
10. Nd:YAG synechiolysis is greatly facilitated by the use of a contact lens like the Abraham contact lens.

### LASER TECHNIQUE

*Nd:YAG-KTP 532 nm laser pupilloplasty/photomydriasis*

This modality involves 2 stages and laser parameters can be adjusted according to the pigmentation of the iris.

- Stage 1: perform 360° contiguous, concentric laser burns adjacent to the pupillary margin. This will elicit a small contraction of iris tissue.

## 25. Pupilloplasty, Photomydriasis and Synechiolysis

- Stage 2: apply another row of concentric, larger laser shots just outside the previous burns.
- Alternatively, laser shots can be placed radially, on the iris papillae.

Laser beam parameters:

	Stage 1: inner row	Stage 2: outer row
Spot size	200 µm	500 µm
Duration	0.2 sec	0.4 sec
Power	200-400 mW	400-500 mW

### ***Nd:YAG photomydriasis / synechiolysis***

This modality also involves 2 stages and laser settings should be adjusted according to the thickness and color of the iris.

- Stage 1 (radial iridotomy) aims to trace a continuum between a peripheral iridotomy (if present) and the pupillary margin. It is usually done with an energy of 4-5 mJ. For a thin blue iris, the required energy level is lower, 1-4 mJ per shot.
- Stage 2 consists of iridohyaloid, iridolenticular or iridocapsular synechiolysis. It is usually done 2 to 3 days after radial iridotomy. Laser shots are applied all around the pupillary margin, using sufficient energy to destroy the synechia (starting at 1 mJ per shot).

### **POSTLASER CARE AND FOLLOW-UP**

1. A second drop of apraclonidine 1% is instilled.
2. A strong topical steroid is prescribed 4 times a day for 1 week.
3. Tropicamide 1% 1 drop 4 times a day is usually prescribed after Nd:YAG synechiolysis for 1 week.
4. IOP should be checked 1-2 hours after the procedure and the patient reevaluated at 1-2 weeks.

### **COMPLICATIONS**

- Ocular Hypertension;
- Hyphema;
- Pigment dispersion;
- Transient iritis;
- Iris atrophy;
- Glare;
- Cataract.

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# IV. LASER surgery in Iris/Pupil

## 26. Persistent

## Fetal Vasculature



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### INTRODUCTION

Persistent fetal vasculature refers to a group of disorders that are defined by the persistence of various components of the hyaloid vascular system<sup>1</sup>. This definition should be used instead of *persistent hyperplastic primary vitreous* as it emphasizes the fact that the anterior segment of the eye can also be affected. Persistent fetal vasculature can be classified into two types, posterior and anterior<sup>2</sup>. The pupillary membrane is the most anterior portion of the hyaloid vascular system and consists of loops of blood vessels and a diaphanous sheet of mesoderm, and usually regresses during the second trimester.

Congenital fibrovascular pupillary membranes may be considered a variant of persistent fetal vasculature, as there are similar clinical and histopathological findings between the two<sup>3</sup>. These membranes consist of pigmented strands that extend across the pupil, and are associated with prominent iris vessels<sup>4</sup>. Complete membranes are rare. Excision of these membranes can be complicated with significant miosis and it is therefore important to excise as much as possible and to perform iris sphincteromies. The pupil should be enlarged up to 4 or 5 mm.

### INDICATIONS

Treatment of dimness for near vision and dimness in bright conditions.

### EXAMINATION

- Visual acuity should be tested in scotopic and photopic conditions. Near vision must also be checked and recorded.
- Biomicroscopy must also be performed with special emphasis on determining which strands need to be cut in order to obtain a clear visual axis.

### PREPARATION

1. Carefully explain the procedure referring possible complications and possible need for multiple procedures.
2. Obtain informed consent from patient or representative person (not necessarily written consent, follow local rules).
3. Room environment should be compliant with laser safety guidelines.
4. IOP lowering medication (topical apraclonidine 1% or brimonidine 0.2% 1 hour before the procedure) to prevent postlaser pressure spikes.
5. Maximum mydriasis should be achieved (topical tropicamide 1% and phenylephrine 10%).
6. Anesthesia - use topical anesthesia (oxybuprocaine hydrochloride 0.4%).
7. Patient should be sitting comfortably.
8. Facilitate steady fixation using a fixation light and fixating the patient's head.
9. A contact lens should be used as it provides enhanced focusing precision and magnifies pupillary membrane strands. Most frequently used lenses include the Abraham and the Peyman G. capsulotomy lenses.
10. The laser room should have low illumination.

### LASER TECHNIQUE

*Nd:YAG 1064nm Q-switched (YAG laser 1064): 1 - 1.5 mJ/pulse. 2 or 3 sessions (at least 1 day interval)*<sup>5,6</sup>

1. Identify a section of strands near the junction with the iris collarette.

**Important:** the strands in the inferior 90° should be preserved as they prevent the membrane from floating freely in the anterior chamber and reduce the rate of complications (such as endothelial decompensation and secondary glaucoma) (Figure 1).

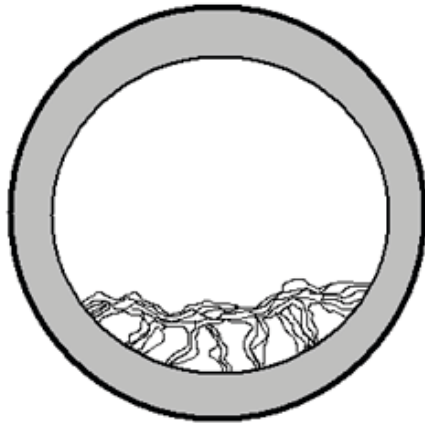


Figure 1. Inferior strands kept after membranectomy.

2. Lysis of the upper strands of the membrane should start at the most inferior strand (nasal or temporal) in order to avoid loss of visualization caused by pigment dispersion and hemorrhages.
3. The procedure should be performed from bottom to top alternating between nasal and temporal segments.

### POSTLASER CARE

1. An increase in intraocular pressure can occur after YAG laser 1064: use topical IOP lowering medication (as described) before the procedure, consider maintaining it for about 1 week post-procedure also. Patients already on glaucoma therapy should be given oral carbonic anhydrase inhibitors both immediately and at 4 hours after the procedure.
2. Anti-inflammatory medication: prednisolone acetate 1% or dexamethasone 0.1% - 1 drop applied immediately after the procedure and then 4 times a day. The treatment should be tapered over one to three weeks.

### COMPLICATIONS

This is a relatively safe procedure. Nevertheless, this procedure can be associated with complications such as **secondary glaucoma, pigment dispersion, microhemorrhages**.

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# IV. LASER surgery in Iris/Pupil

## 27. Corticolytic

## and Membranectomy



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### 1. CORTICOLYSIS

#### INTRODUCTION

Lens cortex can be retained after extracapsular extraction<sup>1</sup> or phacoemulsification cataract surgery, with or without implantation of intraocular lens<sup>2</sup>. Corticolytic refers to the neodymium:yttrium-aluminum-garnet Nd:YAG 1064 nm Q-switched (YAG laser 1064) treatment used to accelerate the absorption of residual cortical matter<sup>1</sup>.

The rate of retained cortex after phacoemulsification cataract surgery has been reported to be 1.8% in a small series of routine surgeries and up to 13% in cases with small pupils. Risk factors for retained cortex after phacoemulsification cataract surgery are: small pupil size, difficulty in removing subincisional cortex, and small capsulorrhexis size. The rate can be higher in complicated cases, such as anterior capsular irregularities or posterior capsular rupture<sup>2</sup>.

Depending on the amount of retained cortex, it may be noticed immediately postoperatively by the surgeon, or it may go unnoticed until it becomes hydrated or moves from a peripheral to a central location<sup>2</sup> (Figures 1 and 2). In the initial postoperative period after cataract surgery, if the patient is symptomatic, there are some possible options: observation, medical management and surgical removal of the cortex. Usually, the first option is preferred, allowing for spontaneous absorption. However if it is not feasible, and if patient symptoms attributable to retained cortex (like impaired vision) overcome the risks of laser lysis, this procedure can be performed<sup>2</sup>. The laser treatment obviates the need to take the patient back to the operating room to remove the lens fragment<sup>3</sup>.

#### PREPARATION

Mydriatics and prophylactic antiglaucoma drugs should be used before beginning the laser procedure<sup>1</sup>.

#### LASER TECHNIQUE

1. Set defocus to zero; laser should be focused posterior

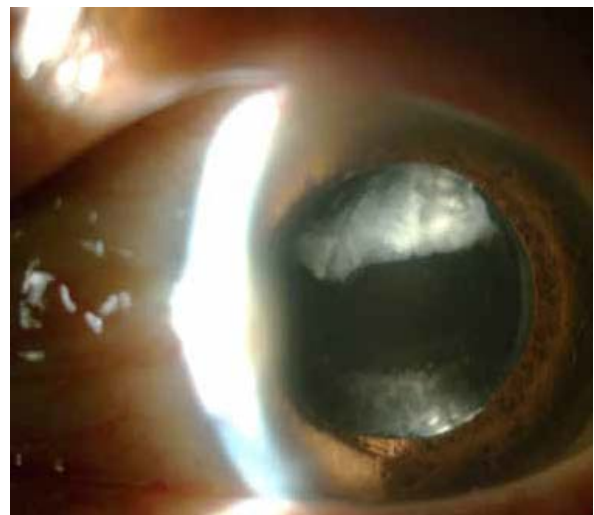


Figure 1. Residual cortical matter detected in a patient twenty years after cataract surgery. This is the appearance after corticolytic in the pupillary area, restoring the visual acuity of the patient.

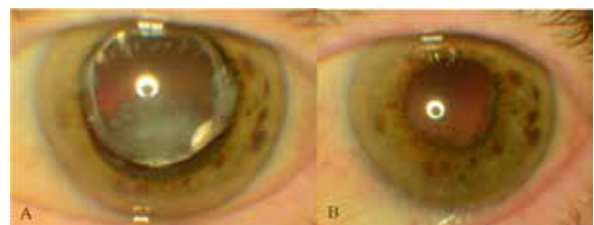


Figure 2. A - Sudden migration of residual cortical matter, causing severe impaired vision in photopic conditions (due to miosis) in a patient with single eye vision, seven years after phacoemulsification. B - Absorption of cortical matter two weeks after corticolytic, restoring the previous visual acuity.



to the intraocular lens and within the substance of retained cortical matter. The aim is not to disrupt the posterior capsule<sup>1</sup>.

2. Pulse mode is preferred over burst mode<sup>1,2</sup>. Energy should be titrated to the lowest amount necessary to induce liquefaction<sup>2</sup> and, in some cases, it can range from 4 to 5 mJ of energy per pulse from a Q-switched Nd: YAG laser 1064.
3. Laser shots are fired several times until the retained cortex becomes emulsified with a milky appearance<sup>1,2</sup>.

An obscured view through the anterior chamber can dictate the end of treatment<sup>2</sup>. The absorption of residual cortical matter is usually completed within one week<sup>1</sup>. Cortex absorption can be particularly slow when the location is posterior to the intraocular lens with an intact capsular bag, as there is little aqueous turnover in this location<sup>2</sup>.

### COMPLICATIONS

A possible complication of this laser treatment is an **intraocular pressure (IOP) rise**. This may happen because of the rapid liberation of lens proteins, as well as secondary inflammation that leads to reduced drainage capacity of the trabecular meshwork. If there is an anterior location of the cortical material and the posterior capsule is intact, more debris should be expected in the anterior chamber and also a higher rate of IOP rise<sup>2</sup>. Anti-glaucoma medications, like apraclonidine or brimonidine eye drops, and topical steroids, like prednisone acetate 1% or dexamethasone 0.1% eye drops, should be used after the procedure<sup>1</sup>.

## 2. MEMBRANECTOMY

### INTRODUCTION

Membranes on the anterior lens surface may be found after the implantation of anterior chamber, iris-fixated or posterior chamber IOLs<sup>1</sup>.

In the literature, the incidence of pupillary membranes after extracapsular cataract extraction and posterior chamber IOL implantation is not uncommon, ranging from 4.4% as reported by Miyake *et al.* (1989)<sup>4</sup> to 11-17% by Walinder *et al.* (1989)<sup>5</sup>. However, these studies were done some time ago, and nowadays, with recent techniques of cataract surgery, incidence rates are probably lower.

It is believed that the mechanism for the postoperative formation of a pupillary membrane is inflammation after intraocular surgery, which disrupts the blood-aqueous barrier, allowing plasma proteins, including fibrin, to enter the anterior chamber<sup>6,7</sup>. The formation of a fibrin membrane may be a kind of immunologic reaction to a soluble antigen derived from dry-sterilized IOLs or residual lens matter, with antibodies passing through the disrupted blood-aqueous barrier<sup>6,8</sup>.

Conditions which course with a disrupted blood aqueous barrier and increased vascular permeability are more likely to be associated with inflammatory membranes. There is a strong association with pseudoexfoliation (PEX) syndrome<sup>6,8</sup>. In one study, the development of pupillary membranes occurred almost 3 times more frequently in PEX eyes compared with non-PEX eyes. Microangiopathy, such as in diabetic retinopathy, and glaucomatous eyes using pilocarpine are other conditions

which are more likely to be associated with these membranes<sup>6</sup>. Pilocarpine changes the permeability of the blood-aqueous barrier and the iris vessels, and promotes the transfer of protein, cells, and fibrin into the aqueous<sup>8</sup>. These membranes can also occur in patients with a history of uveitis and thus, a period with non-active inflammation of at least 3 months (preferably longer) before surgery is desirable<sup>9</sup>.

Histologically, pupillary membranes are composed of fibrin polymorphonuclear leukocytes, and proliferating epithelium from the anterior lens capsule or iris stroma fibroblasts<sup>6</sup>.

The pre and postoperative use of anti-inflammatory drugs (corticosteroids and non-steroidal inflammatory drugs) reduces the probability of membrane formation by reducing the inflammatory reaction and the substratum of the immunologic reaction<sup>3,6</sup>. Mydriatics/cycloplegics help to stabilize the blood-ocular barrier and can provide mechanical breakage of both synechiae and pupillary membranes. When aggressive topical therapy is unsuccessful, oral anti-inflammatory treatment can be used<sup>10</sup>. However, in some cases, visually significant membranes may persist despite medical treatment<sup>8</sup>. In those cases, more invasive procedures may be required to restore functional vision<sup>10</sup>.

### INDICATIONS/ CONTRAINDICATIONS

The membrane should be evaluated by slit-lamp biomicroscopy to determine whether laser treatment is appropriate<sup>1,11</sup>. YAG laser 1064 should be preferred to pars plana surgical membranectomy because it is a non-invasive outpatient procedure and because of patient acceptance<sup>12</sup>. A dense pupillary membrane causes significant reduction of vision often restricted to perception of light<sup>1</sup>, and may require multiple sessions to achieve an adequate opening. The patient should be informed about this possibility. Lengthy sessions with many pulses and liberation of a large amount of debris can lead to post-laser inflammation and elevated intraocular pressure.

Large Elschnig's pearls from old cataracts may liberate protein when opened<sup>11</sup> and result in phacoanaphylactic uveitis<sup>1</sup> and phacoanaphylactic or phacolytic glaucoma. In such patients, Nd:YAG laser 1064 application should be avoided<sup>1,11</sup>, and surgical approach should be considered<sup>11</sup>.

Pars plana membranectomy should be preferred for secondary membranes thicker than 1.20 mm and even for a thinner membrane in the absence of availability of YAG laser 1064. This is also a safe method<sup>12</sup>. Another possible treatment option is an anterior chamber injection of recombinant tissue plasminogen activator (tPA)<sup>7</sup>.

Performing laser membranectomy is different from performing a posterior capsulotomy. Unlike posterior capsules, in which each laser shot results in a large opening because the capsule is thin and under tension, membranes may have little or no elastic properties and are thick<sup>1,11</sup>.

### PREPARATION

Laser membranectomy should be preceded by mydriatics<sup>1</sup> and prophylactic anti-glaucoma drugs<sup>1,11,12</sup>.

### LASER TECHNIQUE

1. High pulse energy may be required and, in some



cases, it can range from 4 to 12 mJ<sup>1,11</sup>.

2. Frequently, more than 100 shots are necessary to achieve a visually significant opening in the pupillary area with a Q-switched Nd:YAG laser 1064<sup>1</sup>. The opening is created by the “chipping away technique” at the edge of the membrane (junction of the pupillary membrane and the iris tissue)<sup>1,10,11</sup> bit by bit, in a manner similar to that of a stonemason chipping away at marble<sup>1,11</sup>.

Residual membrane may remain attached to one side without causing any visual disturbance<sup>1</sup>. Membranes located on the anterior surface of IOLs may present additional difficulties, because they may be firmly attached to the IOL<sup>8</sup>. Early intervention with laser may be particularly important in these pseudophakic patients. The higher energy needed to open membranes compared to capsules can result in severe IOL marking<sup>11</sup>.

Nd:YAG-KTP 532 laser effectiveness in this context is limited because of the low quantity of pigment on the pupillary membrane surface and due to the danger of injuring the retina<sup>6</sup>.

## COMPLICATIONS

In Nd:YAG membranectomy, the parameters which influence endothelial cell loss and damage to the endothelium are generally related to the distance between the pupillary membrane and the endothelium; and to the thickness of the membrane, consequently also to the total laser energy delivered. Further studies into the significance of these parameters are required<sup>6</sup>.

Other possible complications of laser membranectomy, all directly proportional to the energy level and number of pulses applied, can be: elevated intraocular pressure, due to the blockage of the trabecular outflow pathway by cellular debris, phacoanaphylactic uveitis<sup>1</sup>, anterior chamber reaction, corneal edema, and cystoid macular edema<sup>8</sup>.

Thus, the use of Nd:YAG laser is a helpful tool for rapid and painless removal of pupillary membrane developed postoperatively. These membranes may be successfully lysed with laser, restoring media transparency and obviating the need for surgical reintervention<sup>6</sup>.

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# V. Lens Surgery

## 28. Nd:YAG Q-switch

### Anterior capsuloplasty



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#### INTRODUCTION

Cataract surgery is the most commonly performed surgery in ophthalmology, not only to restore vision, but also as a refractive procedure<sup>1</sup>. Since its first description in the fifth century BC and the first report of cataract removal from the eye in 1748, its technique has evolved immensely<sup>2,3</sup>. The two major steps contributing towards this were the development of a technique which allowed for preservation of the lens capsule and the development of phacoemulsification by Kelman<sup>4,5</sup>. Recently, femtosecond laser-assisted cataract surgery (FLACS) has been developed, using femtosecond lasers with 400-800 fs pulse duration, refining some of the crucial steps, namely corneal incisions and anterior capsulotomy (AC)<sup>6</sup>. A number of different variables depend upon the latter, such as AC circularity and posterior lens centration and positioning, all major contributors to the final refractive result<sup>7-9</sup>. Moreover, the automatization of key steps in cataract surgery is expected to increase the safety, consistency and predictability of the procedure<sup>6</sup>. However, despite these technological advances, certain issues such as capsular contraction syndrome (CCS) may still occur and should be considered<sup>10,11</sup>.

#### CAPSULAR CONTRACTION SYNDROME

CCS is a well-recognized entity (Soemmerring's ring<sup>12</sup>), representing an exaggerated fibrotic response induced by metaplastic lens epithelial cells, which resemble fibrocytes with elongated nuclei and react against cytokeratin and smooth muscle actin<sup>13,14</sup>. Phimosis then results from a mechanical shift brought about by the actin filaments and proliferation of the residual lens epithelium cells. CCS can stretch the peripheral zonules leading to rupture and intraocular lens (IOL) displacement<sup>10</sup>. Phimosis can also be so severe that vision becomes affected.

CCS occurs early after surgery (usually within the first 6 weeks) and can be associated with all types of IOL, although it is more likely to occur with silicone lenses<sup>2</sup>.

Patients with conditions such as pseudoexfoliation or uveitis are more prone to developing capsular phimosis<sup>13-16</sup>. Preventive measures include performing a large capsulorhexis (5.5 to 6 mm in diameter), eliminating all lens material and avoiding silicon IOLs<sup>17</sup>. Polishing and thoroughly cleaning the anterior capsule, removing lenticular epithelial cells as much as possible, are other important steps in reducing the likelihood of CCS. Neodymium:yttrium-aluminum-garnet (Nd:YAG) "Q-switch" laser (1064 nm) can be used to treat CCS<sup>16</sup>. This short (ns) high power pulse laser induces the formation of plasma, and shock and acoustic waves leading to cavitation bubbles and tissue photodisruption, working like a laser "scalpel"<sup>18</sup>. Iridocapsular adhesions and membranes might also be present, and may also benefit from laser treatment<sup>19</sup>.

#### INDICATIONS

##### 1. Opacification and phimosis

Opacification and phimosis of the anterior capsule, membranes and anterior capsule remnants<sup>19</sup> are indications for anterior **Nd: YAG Q-switch 1064** capsuloplasty. The idea is to create four to six radial incisions, breaking the capsular ring.

##### 2. Iridocapsular adhesion (ICA)

Iridocapsular adhesion (ICA) usually forms between the anterior capsule and the posterior leaflet of the iris (although both capsules can be involved) and can lead to pupillary distortion and even IOL displacement. Lens retained material, surgical trauma and inflammation can all induce ICA development. **Synechiolysis** intends to break these synechiae and is performed in a similar way as capsuloplasty, but using spots localized to the abnormal area<sup>19</sup>.

##### 3. Vitreolysis

Vitreolysis can also be performed, if needed, using the same technical principles as described above. A miotic pupil may be preferable in this context since it stretches the vitreous band, helping the procedure<sup>19</sup>.

### CONTRAINDICATIONS<sup>6,19,20</sup>

There are some contraindications:

- small, non-dilating pupil.
- uncontrolled elevated intra-ocular pressure.
- opacification precluding a clear view.
- uncooperative patient; patient refusal.
- active uveitis.

### PREPARATION

**Nd:YAG 1064 nm capsuloplasty** (Figure 1) is done under pharmacologic mydriasis<sup>21</sup>. It requires instillation of anesthetic drops (oxybuprocaine hydrochloride 0.4%) and of a glaucoma drug to prevent the development of intraocular pressure peaks. The most commonly used amongst the latter is apraclonidine hydrochloride 0.5%, but brimonidine tartrate 0.1% or a beta-blocking agent such as timolol maleate can also be used<sup>19,22</sup>. If necessary, an oral hyperosmotic agent may also be used<sup>19</sup>.

The patient should be comfortably positioned and the head securely held, if necessary. The room environment should be compliant with laser safety guidelines. The patient is then asked to look straight ahead and not to move.

The procedure can be done using a contact lens, such as a central Abraham or a Peyman YAG planoconvex lens, to stabilize the eye and improve laser beam optics, but one can choose to do it directly. If the latter option is chosen, care must be taken when treating the upper quadrants in order to avoid interference with the upper lid<sup>11,19</sup>.

### LASER TECHNIQUE

This procedure can be performed by a set of laser pulses targeting the anterior capsular border and causing a radial break that enlarges the capsular opening, relaxing the fibrotic ring.

Nd:YAG 1064 nm laser has a constant spot size and duration. The operator can only regulate laser power and laser defocus that should be fixed at 0  $\mu\text{m}$ .

Pulse energy of 2-3 mJ is usually enough. Begin with the lowest energy and increase it if necessary.

One millimeter nicks should be placed radially (at least one in every quadrant) at the border of the AC, and targeting fibrotic areas, in order to prevent the development of tensions which may lead to uncontrollable and undesirable capsular ruptures.

This procedure should be conducted when phimosis is worse than 4 mm to prevent late zonular dehiscence<sup>11</sup>. Damage to the IOL is avoided by anterior defocus of the laser beam (set it at 0  $\mu\text{m}$  and focus the aiming beam just on the anterior surface of the capsular ring or slightly anteriorly for the first spot, then try to go backwards if the capsular rupture effect is not obtained or not completely accomplished).

About 2-4 laser spots are necessary to obtain an adequate nick. At the end of the procedure, a hypotensive agent should be administered again.

### POSTLASER CARE AND FOLLOW-UP

For YAG 1064 nm laser procedures, as previously mentioned, intraocular hypotensive agents should be used immediately after laser treatment (usually one or two drops of apraclonidine hydrochloride 0.5%, five minutes apart).

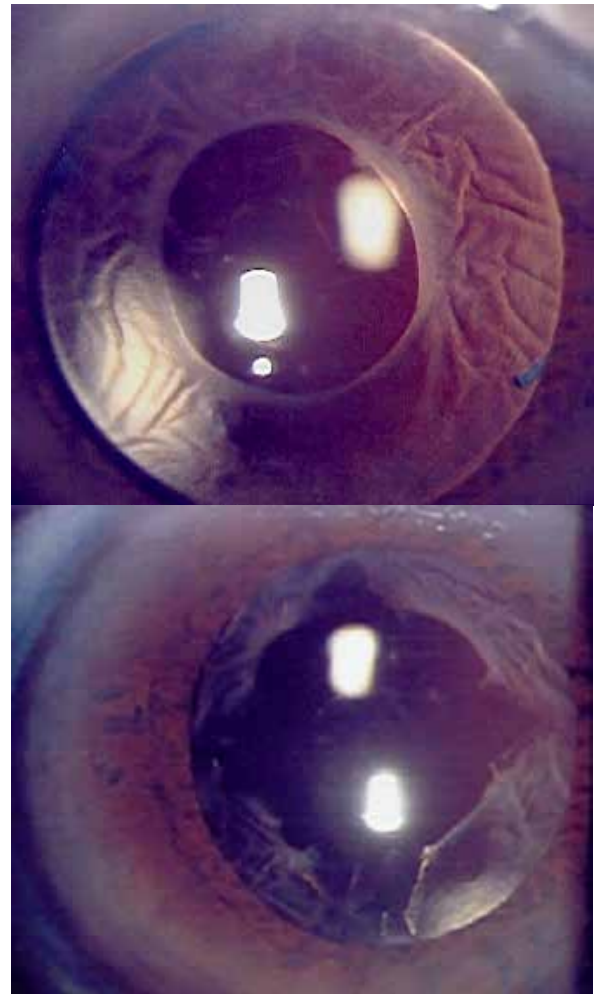


Figure 1. Phimosis of anterior capsule pre and immediately post capsuloplasty with Nd:YAG “Q-switch” laser 1064 nm. Note the four nicks at the border of the anterior capsular opacification ring. One can also see the relaxation of the capsular ring.

The same or a similar drug can be prescribed for ongoing treatment for 3 or 4 days. High risk patients might need a more prolonged period of antihypertensive therapy<sup>20</sup>.

A topical anti-inflammatory drug should be prescribed three times daily for the same period of time (fluorometholone 0.1% or rimexolone 1%). Topical non-steroidal anti-inflammatory agents may be of benefit alone or in association with topical steroids.

### COMPLICATIONS

Nd:YAG 1064 nm Q-switch laser procedures are relatively safe and usually complication-free. Nevertheless, the following complications may occur<sup>19,20</sup>:

- Iatrogenically **high intraocular pressure** – peak or more prolonged;
- **Anterior chamber inflammatory reaction**;
- **Endophthalmitis** – reactivation of otherwise quiescent *Propionibacterium acnes* in the capsule remnants;
- **Hyphema / mild hemorrhages** due to inadvertent iris vessel trauma;

- Incidental **iris trauma** leading to iris distortion or affecting its movement;
- **IOL pitting**;
- **IOL displacement**;
- **IOL luxation** to the vitreous cavity (more common with silicone IOLs);
- **Damage to the corneal endothelium**;
- Unwanted **capsular tear**;
- **Macular edema**;
- **Posterior vitreous detachment / retinal detachment**;
- **Subconjunctival hemorrhages** (when contact lens is misused);
- **Corneal ulcer / traumatic keratitis** (when contact lens is misused);
- Failure to solve the problem, requiring further laser or other treatments.

## RESULTS AND CONCLUSIONS

Outcomes after laser capsuloplasty and synechiolysis are usually good and only one laser session is required most of the time. Using a Nd:YAG Q-switch 1064 nm laser as an office-based procedure with the minimally invasive technique described, one can treat and avoid complications in a very wide range of post-surgical iris/capsule/IOL relationship problems. Standardized technique, experience in the use of the photodisrupting laser, and careful patient selection help in achieving optimum results.

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# V. Lens Surgery

## 29. Posterior

# Capsulotomy



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### INTRODUCTION

Posterior capsule opacification (PCO) or secondary cataract is still the most common delayed complication of cataract surgery. PCO results from the proliferation, growth and migration of cells left on the anterior capsule at the time of cataract surgery<sup>1</sup>. The incidence of PCO has been reported to be about 25 to 50 percent in adults and 50 to 100 percent in children and adolescents 2 to 5 years after surgery<sup>2</sup>.

First presented by Aron-Rosa in 1980, Nd:YAG 1064 nm Q-switch (YAG laser 1064 nm) laser capsulotomy is currently the standard treatment for PCO. This treatment has the following advantages: improvement of visual acuity, improvement of contrast sensitivity, glare reduction and better fundus visualization<sup>3</sup>.

Nd:YAG 1064 nm laser capsulotomy is the most successful and frequent application for Nd:YAG Q-switch laser, and is usually a fairly straightforward and fast process; nonetheless there are certain points to consider to ensure its safe and effective execution<sup>4</sup>.

### INDICATIONS<sup>5,6,7</sup>

- PCO causing reduced visual acuity or excessive glare;
- Capsular block syndrome;
- Re-opacification.

### CONTRAINDICATIONS<sup>8,9</sup>

#### A. Absolute

- Corneal opacity or corneal edema (when the capsule is not visible);
- Corneal surface disorders;
- Inability to steadily fixate the eye;
- Uncooperative or unwilling patients.

#### B. Relative

- Cystoid Macular Edema (CME);
- Eyes with very active inflammation;
- Patients with high risk for rhegmatogenous retinal detachment.

### TIMING OF CAPSULOTOMY<sup>10,11</sup>

YAG laser 1064 nm posterior capsulotomy may be performed three weeks after initial surgery, but it is usually advisable to postpone the procedure if possible.

### PREPARATION<sup>12,13,14</sup>

#### Pupillary Dilation

Sometimes dilation is not required if the procedure is performed by an experienced laser surgeon.

Dilation should be achieved using a weak mydriatic, as identifying the center of the pupil can be more difficult in extremely dilated eyes.

#### Anesthesia

Topical anesthetic drops are commonly used.

Retrobulbar anesthesia should be considered in patients with nystagmus.

#### Contact Lens

A contact lens is used to stabilize the eye, facilitate accurate focus and improve laser optics.

#### Room Illumination

The laser room should be darkened to facilitate capsule visualization.

### LASER TECHNIQUE<sup>1,10,15</sup>

*Nd:YAG 1064 nm Q-switch: 1 - 2 mJ/pulse*

Use the lowest level of energy per pulse that is required to create a window in the posterior capsule. 1.0 to 2.0 mJ per pulse is usually sufficient to create an opening in the posterior capsule. If this amount of energy is not sufficient, it should be gradually increased.

Capsulotomy size must be approximately 3–4 millimeters of diameter. An existing area of separation between the posterior capsule and IOL should be used as a starting point and further areas of separation will appear (Figure 1).



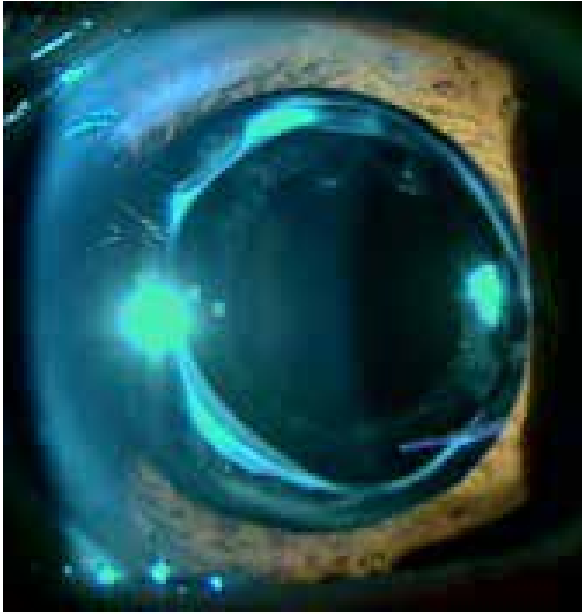


Figure 1. Posterior capsulotomy.

### POSTLASER CARE<sup>16,17</sup>

A – A rise in intraocular pressure is common a few hours after YAG laser 1064 nm laser posterior capsulotomy.

1. One drop of an anti-glaucoma medication applied topically immediately after the laser treatment is usually enough to counter the intraocular pressure spike. The treatment should be continued during at least one week.
2. In pre-existing glaucomatous eyes: chronic anti-glaucoma therapy should be supplemented by oral carbonic anhydrase inhibitors after the procedure and repeated four hours later.

B – Reduction of inflammation

1. Prednisolone acetate 1% or Dexamethasone 0.1% - 1 drop applied immediately after the procedure and then 4 times a day. The treatment should be tapered over one to three weeks.

### COMPLICATIONS<sup>18,19,20</sup>

The most common complications are:

- **Transient elevation of intraocular pressure (IOP)** is the most common complication. IOP starts rising soon after the procedure and reaches its peak after three hours. Baseline IOP levels are typically achieved within one week.
- **Cystoid macular edema (CME)**. Incidence varies from 0.04 to 2.3% in different studies. It is believed that the disruption of the anterior hyaloid during the procedure increases the likelihood of developing this complication.
- **IOL marking/pitting**. This may be avoided by using a lower energy level, single pulse mode and a contact lens. Laser treatment can also be intentionally aimed posteriorly to the posterior capsule (posterior defocusing).
- **Rhegmatogenous retinal detachment**. Incidence varies between 0.1 and 3.6%. The onset of rhegmatogenous

retinal detachment happens usually 4 to 7 months after the laser treatment, even though it can occur earlier.

- **IOL dislocation**, which is more common when the capsulotomy is oversized.
- **Endophthalmitis**, due to release of previously sequestered *Propionibacterium acnes* into the vitreous.
- **Re-opacification of the capsulotomy opening**, caused by proliferation of lens epithelial cells around the capsulotomy opening.

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# V. Lens Surgery

## 30. Pigment

### ND:YAG “Q-switch”

### LASER sweeping



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#### INTRODUCTION

Using a photodisruptor laser like the Nd: YAG 1064 nm Q-switch laser, mechanical effects are produced with plasma formation in the focal spot where the laser is applied. The tissues or the liquid media suffer a micro-explosion with plasma formation. Through the effect of cavitation and aqueous currents, any neighbouring debris or pigment will be swept away and dispersed throughout the aqueous humour<sup>1,2</sup>.

The photonic effect of plasma formation has other features used for therapeutic effect. One such feature is its precision. Plasma acts like a barrier and captures all the surrounding photons hence avoiding any impact outside the focal spot where it is produced. So, if there is pigment on the anterior surface of the intraocular lens (IOL), one applies the focal spot just over the IOL and should thus be able to disperse just the pigment, without affecting the IOL itself<sup>2-4</sup>.

Simultaneously, this absorption of energy by plasma in turn leads to the production of multiple plasma waves, which move towards the laser source, i.e. away from the IOL surface<sup>5</sup>.

This liquid movement effect has an important role as it creates liquid convection currents that spray away the pigment or break down the fibrin bridges which are sometimes associated with them<sup>1,2</sup>.

This ties into another important aspect which is the off setting of the laser beam. This should be set to a zero position, that is, one should not apply any distance between

the aiming beam and the YAG laser beam in order to avoid pitting of the IOL by plasma waves as they travel forward.

(In posterior capsulotomy, a posterior off-set is used in order to allow for sufficient dissipation of plasma waves before the IOL is reached, whilst also allowing for maximum disruptive effect at the capsule - see Chapter 12).

The laser focus of the aiming beam should be positioned just over or slightly before the pigment in order to be effective without pitting the IOL.

#### PREPARATION

Mydriatics and prophylactic antiglaucoma drugs should be used before beginning the procedure<sup>1</sup>.

#### LASER TECHNIQUE

1. First, the laser should be focused near or over the intraocular lens<sup>1,3</sup>. The off set should be set in the zero position.
2. Pulse mode is preferred over single shot mode<sup>1,2</sup>. The energy should be titrated to the lowest amount necessary to induce pigment dispersion<sup>2</sup>, for example, it may range from 1.2 to 2.5 mJ of energy per pulse when using a Q-switched Nd: YAG laser.
3. Laser shots are fired several times until the pigment is dispersed away from the optical axis or thin fibrin membranes are ruptured and dispersed away from the optic axis (Figures 1 and 2).

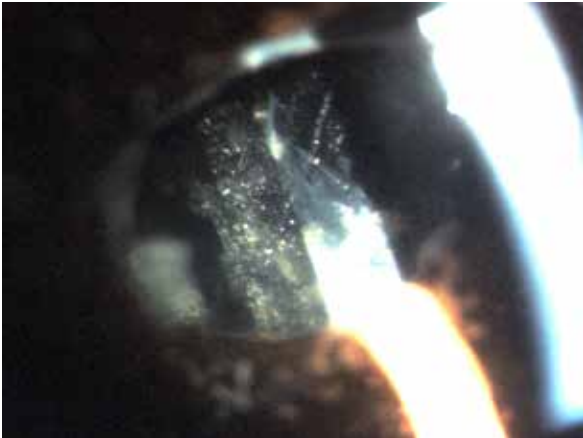


Figure 1. IOL pigment and fibrin bridges - previous to laser.

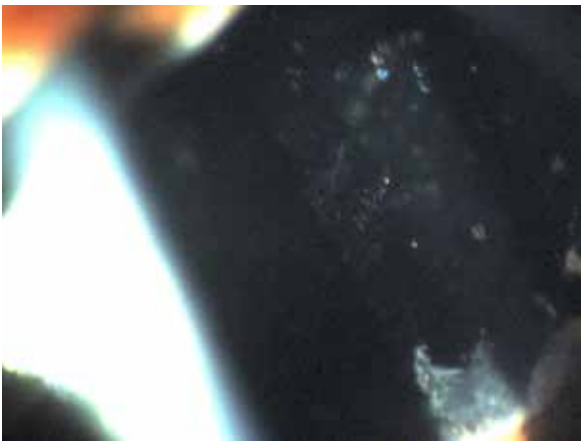


Figure 2. Clear visual axis - after laser.

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### COMPLICATIONS

A possible complication of this laser treatment is an **intraocular pressure (IOP) spike**<sup>3-5</sup>. It can happen because of the rapid liberation of pigment and debris, as well as secondary inflammation that leads to reduced drainage capacity of the trabecular meshwork. This complication is correlated to the number of pulses and the total energy delivered, however further studies on the role of each of these parameters are required<sup>4</sup>.

Anti-glaucoma medication, like apraclonidine or brimonidine eye drops, should be used after the procedure<sup>1,3</sup>. Other possible complications are **phacoanaphylactic uveitis**<sup>3</sup>, **anterior chamber reaction**, **corneal edema**, and **cystoid macular edema**<sup>4</sup>.

### CONCLUSION

The use of Nd:YAG 1064 nm Q-switch laser is a helpful tool for rapid and painless removal of pigment and fibrin membrane/bridges developed postoperatively. These opaque structures may be successfully lysed with laser and patients can reacquire media transparency, thus avoiding surgical intervention<sup>3</sup>.

# V. Lens Surgery

## 31. Repositioning of posterior chamber intra-ocular lens



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### INTRODUCTION

PC-IOL (posterior chamber intraocular lens) dislocation can be secondary to:

- A large capsule;
- Capsular rupture;
- Vitreous pressure;
- Large Nd:YAG 1064 nm Q-switch capsulotomy;
- Intra-capsular synechia;
- Vitreocapsular synechia;
- Vitreous corneal synechia.

If there are no iridocapsular synechia, iridal IOL capture can be solved by pushing the IOL back into its position with the pressure wave generated by YAG laser 1064 nm.

If IOL capture is associated with iridocapsular synechia then repositioning requires previous synechiolysis with YAG laser 1064 nm (5-9 mJ) or vitrectomy. For this issue, some conservative measures which may be beneficial include:

- Supine positioning;
- Reducing vitreous volume using hyperosmotic agents (Manitol 20%, acetazolamide);
- Constricting the pupil using pilocarpine 2%;
- Pressing down on the ciliary sulcus;
- Rotating the IOL manually using a canula (through the side port)<sup>1,2,3,4</sup>.

### LASER TECHNIQUE

*IOL Repositioning with Nd:YAG 1064 nm laser*

1. Explain the procedure referring the possible need for multiple sessions or other procedures;
2. Room environment should be compliant with laser safety guidelines;
3. Apply mydriatic agents (tropicamide 0.5% phenylephrine, 10% [15 min/15 min]);
4. Apply IOP-lowering medication (brimonidine 0.2% and/or acetazolamide 250 mg) 30 minutes before;
5. Focus the laser beam on the lens margin;
6. Power settings of 4-6 mJ are usually adequate;

7. Defocus the beam anteriorly pushing the joystick slightly backwards.

### IMPORTANT TIPS

- If the IOL is a single-piece lens, a pressure wave is usually enough to make it budge;
- If the IOL has haptics manual rotation may be needed;
- If the IOL is in the sulcus laser repositioning may do the trick but surgery may be required;
- If the IOL is multifocal, suturing to the iris (Figure 1) may be required to avoid late decentering;
- If the IOL is toric, sutures are pretty much mandatory;
- If after suturing to the iris, the pupil is asymmetrical or decentered, the following techniques may be beneficial:

#### 1 Pupiloplasty

#### 2 Sectorial Pupiloplasty/ Photomydriasis (Figure 2)

#### 3 Coreoplasty



Figure 1. IOL-iris suture.

## 31. Repositioning of posterior chamber intra-ocular lens

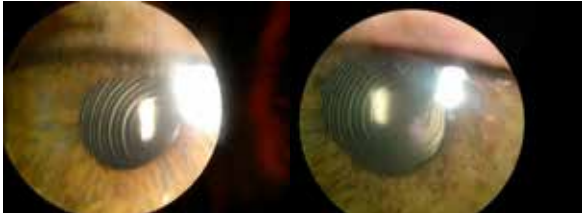


Figure 2. Pre (left) and post (right) sectorial pupilloplasty.

### 1. PUPILLOPLASTY<sup>5,6</sup>

This refers to changing the shape or size of the pupil, using Nd:YAG KTP 532 nm laser and is useful in:

- Aphakia;
- Uveitis;
- Pupil block glaucoma;
- Miotic therapy.

#### LASER TECHNIQUE

*Argon/ Nd:YAG KTP 532 nm laser (KTP laser)*

Please refer to IOL Repositioning with Nd:YAG 1064 nm laser (above), then:

1. Ask the patient to look left and right during the procedure;
2. Use dim illumination;
3. Apply 200 mW burns adjacent to the pupillary margin followed by larger 500 mW outside the initial shot (Figure 3).

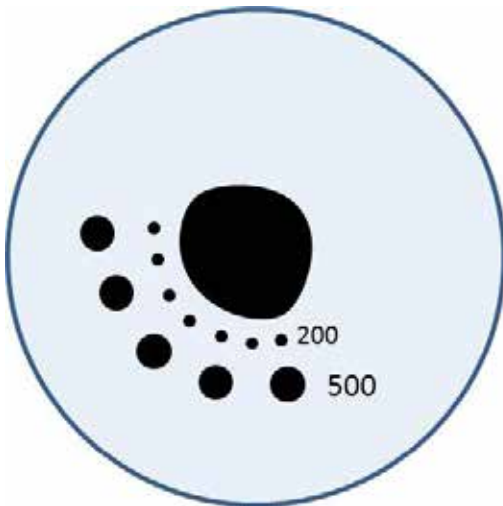


Figure 3. Pupilloplasty.

### 2. SECTORIAL PHOTOMYDRIASIS<sup>6,7</sup>

#### LASER TECHNIQUE

*Argon/ Nd:YAG KTP 532 nm laser (KTP laser) or Yellow Diode 577 nm laser (YD laser)*

Please refer to IOL Repositioning with Nd:YAG 1064 nm laser (above), then:

1. Ask the patient to look left and right during the procedure;
2. Use dim illumination;

3. Apply contiguous 360°, 200 Ø burns (200-400 mW) x 0.1-0.3 sec;
4. Apply a contiguous 360° ring of 500 Ø burns, (200-400 mW) outside the first ring (Figure 4).

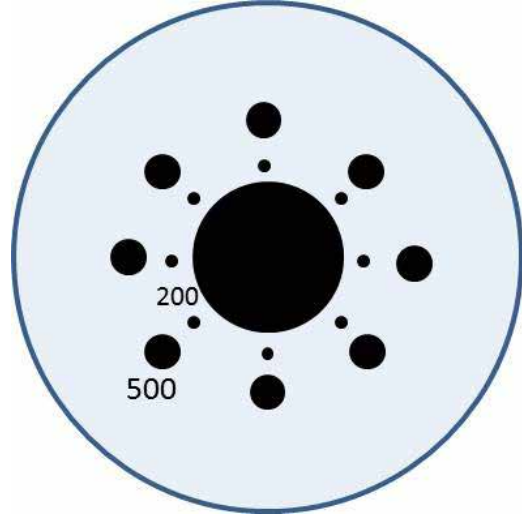


Figure 4. Photomydriasis.

### 3. COREOPLASTY<sup>4,7,8</sup>

Coreoplasty refers to the process of recentering an ectopic pupil by changing its shape or by enlarging it with an Nd:YAG Nd:YAG 1064 nm Q-switch laser (Figure 5) to improve vision in eyes with a decentered IOL.

#### LASER TECHNIQUE

*Nd:YAG 1064 nm laser or Argon/ Nd:YAG KTP 532 nm laser (KTP laser)*

Please refer to IOL Repositioning with Nd:YAG 1064 nm laser (above), then:

1. Use dim illumination;
2. Parameters:
  - Preparatory Argon/Nd:YAG-KTP laser: Apply Ø 50 x 0.05 sec x 800/1000 mW burns in the area to be treated;
  - Then using the photodisruptive YAG laser (with 4-6 mJ power settings) start in the peripheral iris (Figure 5) to avoid hyphema at the outset;
  - Apply successive burns towards the iris collarette and sphincter, and leave the pupillary margin to last since it is more likely to bleed.



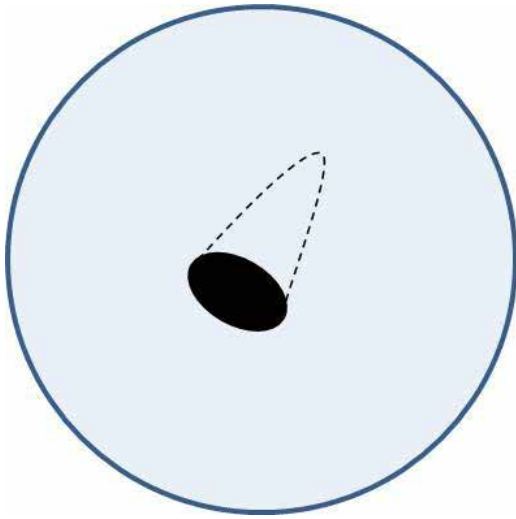


Figure 5. Coreoplasty.

#### POSTLASER CARE AND FOLLOW-UP

Post-op care (1 week): apply steroid drops (prednisolone acetate 1%) and IOP lowering medication (timolol maleate 0.5%).

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# V. Lens Surgery

## 32. Femtosecond

## LASER-Assisted

## Cataract Surgery

## (FLACS)



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Femtosecond (FS) lasers use ultrashort-pulses near infrared wavelengths to induce the formation of plasma, allowing one to cut through tissue while causing minimal damage to surrounding structures. With the use of advanced imaging techniques, they can be focused at a predetermined depth in different optically clear tissues. Femtosecond laser technology was first successfully introduced in ophthalmic surgery as a tool to create lamellar corneal flaps for LASIK surgery. More recently it has been used as a tool to assist in cataract surgery, creating a new era in cataract surgery: FLACS (Femtosecond Laser-Assisted Cataract Surgery).

The use of FS laser in cataract surgery can occur at different stages of the procedure, namely: to create the main and side port corneal incisions, in astigmatic keratotomies, in anterior capsulotomy and in the fragmentation of the cataract nucleus in order to facilitate its removal. These different surgical steps can provide us with a good outline whereupon which to guide the discussion on the innovations, advantages, and pearls relating to FLACS.

### CORNEAL INCISIONS

Clear corneal incisions (CCI) are now used by the overwhelming majority of cataract surgeons to access the anterior chamber. Despite its wide acceptance, it is not a flawless method, as they are proven to be a major risk factor for endophthalmitis<sup>1,2</sup>. CCIs have also been used to correct pre-existing astigmatism and improve refractive outcomes<sup>3,4</sup>. With FLACS, the number, size,

position, depth, and tunnel morphology of CCIs can be adjusted in order to accomplish incisions that are strong, self-sealing and that are either neutral or astigmatism-inducing as needed (Figure 1).

FS laser has been shown to create multiplanar and self-sealing CCIs that are accurately placed, precise, reproducible and Seidel-negative<sup>5-7</sup>. This will potentially improve both the safety and the refractive performance of cataract surgery. Further studies are needed to prove that this potential can be translated into consistent clinical results.

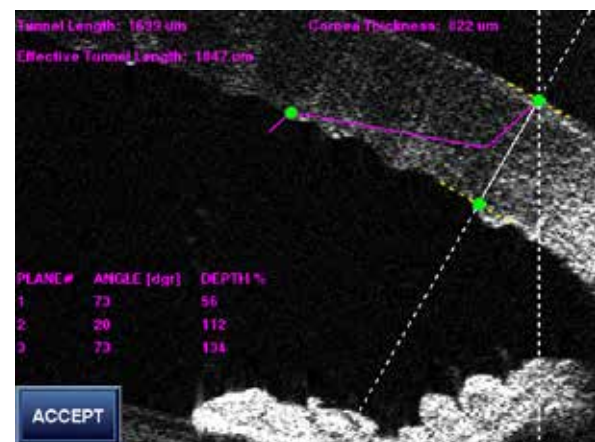


Figure 1. Manual highlighting of a precise and reproducible multiplanar clear corneal incision, accurately placed.

### CAPSULORHEXIS

Constructing an appropriate anterior capsulorhexis can be one of the most difficult surgical steps to master. It is however one of the most important as it influences the space within which the complex movements of phaco will be developed, as well as helping to ensure proper positioning and alignment of the implanted intraocular lens (IOL).

Manual capsulorhexis, even though usually successfully created, is extremely dependent on the skill and experience of the surgeon and on several patient-related variables, such as collaboration, pupil dilation, or anterior chamber depth. Capsulotomy construction is extremely important for estimating effective lens position (ELP), one of the biggest sources of error in IOL power calculation<sup>8</sup>. With the popularization of *premium* toric and multifocal IOLs, the importance of refractive accuracy is now critical. The ability to create precise and predictable anterior capsulotomies should lead to fewer complication rates and to better refractive outcomes (Figure 2). We have observed in the literature that satisfactory results can be achieved with standard manual curvilinear capsulorhexis<sup>9</sup>, however laser assisted capsulotomies appear to be even more precisely sized, shaped and centered than their manual counterpart<sup>10,11</sup>. This has been linked to further improvement in IOL centration and tilt and, ultimately, to more predictable refractive results<sup>12,13</sup>.

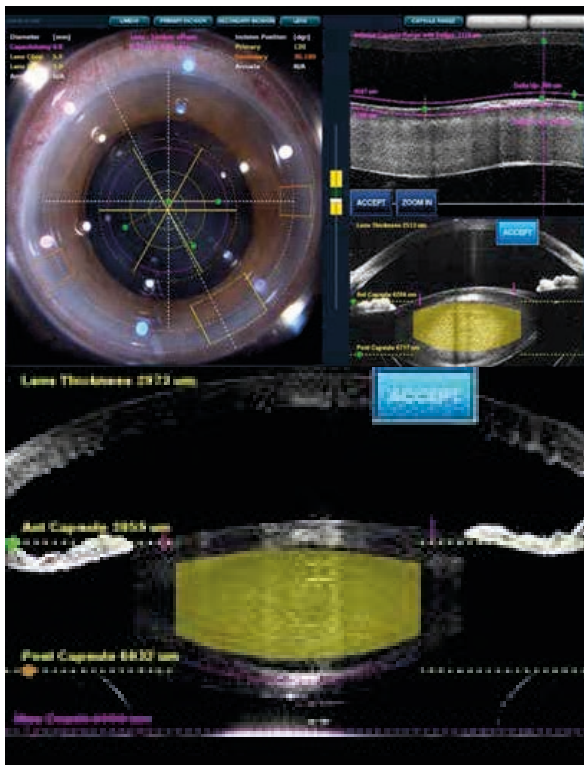


Figure 2. OCT imaging allows for axial and sagittal cross-section viewing of the cornea and lens surfaces, as well as of the iris and posterior capsule safety zones, thus enabling the construction of a precise and predictable anterior capsulotomy, as well as lens fragmentation.

Another important point to consider is whether or not capsulotomies created by FS have equivalent or greater

tensile resistance than manual ones. Early reports on porcine eyes seem to indicate increased strength in FS capsulotomies<sup>14,15</sup>, but results on human eyes are more contradictory<sup>16,17</sup>. Scanning electron microscope (SEM) images of FS capsulotomies show that the edges are micro-serrated. Also, some irregular and misplaced tags were observed, probably due to eye movements during the procedure<sup>16,18</sup>. This makes them theoretically more prone to disruption and capsular tears than smooth-edged manual capsulotomies, although the actually reported rates of tears remain very low<sup>17</sup>. Careful inspection for early detection and proper capsular tag removal technique remain of paramount importance during surgery.

### NUCLEUS PREPARATION

FS laser devices can lay out a pattern of cuts into the lens nucleus that can effectively divide the nucleus into small fragments, thus allowing it to be more easily aspirated (Figure 3). In most hard nuclei some level of ultrasound is likely to be needed, but the goal of this feature is to result in a saving of both energy deployment and time consumption. Initial trials point to a 40% reduction in cumulative dissipated energy during phacoemulsification when preceded by lens fragmentation<sup>19</sup>. Effective phacoemulsification time can also be reduced<sup>20,21</sup>. Both of these features combined are believed to result in significantly less endothelial cell loss, although results are not yet compelling<sup>22,23</sup>.

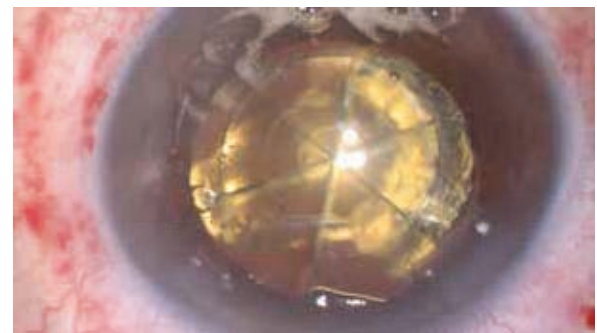


Figure 3. Successful femtosecond laser procedure (clear corneal incisions, anterior capsulotomy and lens fragmentation architecture).

### SPECIAL CASES

Standard phacoemulsification was truly a revolution in cataract surgery and combines high patient satisfaction with a low complication rate. Since most cases have good results with the current gold-standard, any incremental advantage provided by this new technology is hard to prove, in a field already narrow for improvement. However, there is a subset of patients for whom current surgery still brings either suboptimal outcomes or serious safety concerns.

The first of these groups corresponds to patients with high expectations for their refractive outcome. Despite the impressive technical and conceptual advances made in IOL design and selection, the truth is that a very important fraction of patients still presents suboptimal refractive results<sup>24,25</sup>. With current equipment and technique, FLACS performed in standard cases seems

to enhance refractive outcomes, however only minimally when compared with manual cataract removal done by an experienced surgeon<sup>13,26,27</sup>. Anyway, the ability to create precise, reproducible capsulotomies and computer-controlled refractive incisions provides surgeons with a new set of tools to better tailor refractive results that were just not available before.

Patients with diminished endothelial cell density values - like Fuchs' endothelial dystrophy or PKs - are more likely to acutely feel the benefit of the lower phacoemulsification times provided by FLACS. Also, capsulotomy enlargement in capsular phimosis for IOL exchange, cataracts presenting with an overt zonular instability (as in cases of pseudo-exfoliation, Marfan's syndrome or traumatic cataracts), and shallow anterior chambers have a better prognosis if we eliminate the uncertainty associated with a problematic capsulorhexis<sup>28,29</sup>.

### FINANCIAL ASPECTS

One of the main concerns with FLACS technology is whether the substantial investment needed is justified by the added clinical value. Ultimately, this extra cost will be transferred to the patient. However, we learned from the introduction of premium IOLs that patients are willing to pay for new technology if they perceive it as superior. At present, some concerns still remain regarding its cost-effectiveness<sup>30</sup> and it is reasonable to expect that technological evolution and corporate competition will drive down the costs in the near future. It is our responsibility as physicians to provide patients with adequate information to help them understand what this new technology means to their particular case, and ultimately to mobilize the benefits of this new tool from the industry research centers to the individual patient.

### LIMITATIONS, CHALLENGES AND THE FUTURE

FLACS is not without its risks. There are anecdotal reports of capsular block syndrome and dropped nucleus<sup>31</sup>, incomplete capsulorhexis and capsular tears, intra-operative miosis, and endothelial damage<sup>32</sup>. Despite not being sight-threatening, significant conjunctival redness has been reported and can have an important impact on the patient's perception of the surgery's safety. In a recent report from a multi-center case control study, conducted by the European Society of Cataract and Refractive Surgeons (ESCRS), FLACS surgeries actually presented more overall complications than manual surgery. However, if Femtosecond laser specific complications were not considered, standard surgery had more complications<sup>33</sup>.

FLACS is also severely limited by some anatomical constraints: small pupils, corneal opacities, difficult orbital anatomy, and uncooperative or anxious patients, unable to be positioned under the laser.

There is, however, a more exciting debate that goes beyond the discussion on the superiority of FLACS over the current state of cataract surgery. In the future FLACS may provide a tool, not only for further improvement on the existing technique, but also to create new features that are simply impossible with conventional surgery. Real self-sealing incisions with reverse side cuts can drive endophthalmitis rates down even further. Intrastromal

ablations using FS can improve the refractive outcome of the surgery by managing low grade astigmatism. Capsulorhexis can be image-guided to perfectly match the visual axis, improving satisfaction with new multifocal IOLs. The ability to create reproducible, precise posterior capsulotomies can be used to design new premium IOLs. We may now be witnessing a new step in the natural progression that drove us from extracapsular to intracapsular extraction, and then to phacoemulsification. The growing use of FS technology can help bring cataract surgery to the age of image-guided, computer-controlled laser surgery. Despite the limitations and concerns of a newly introduced technique, it has the potential to overcome current limitations, elevate the results we offered to our patients, and establish a pipeline for the development of a new technology and solutions.

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# VI. LASER action in the human retina

## 33. LASER physics



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Laser light is a concentration of photons of the same wavelength that create a high energy beam of monochromatic light. The laser is usually defined by the constitution of the laser medium, its output mode and its wavelength. Its wavelength (laser color) is dependent on the laser medium. The output mode (continuous, pulsed or micropulsed), the power of the beam and its action time are responsible for the type of laser action on tissue. However, the laser-tissue interaction is firstly dependent upon the wavelength that influences its absorption in tissues; and this is, in turn, related to the penetration depth of the laser beam in tissue<sup>1,2</sup>.

Photothermal laser penetrates the optical media: cornea, aqueous humor, lens, vitreous and the various layers of the retina. Its photonic energy is absorbed at the level of the pigmented tissues: melanin and hemoglobin.

The melanin present in the retinal pigment epithelium (RPE) is primarily responsible for laser beam energy absorption at the green, yellow, red or infrared wavelengths. The Nd: YAG-KTP 532 nm laser will mainly be absorbed by the RPE and a little less by melanocytes of the choroid. As we move to longer wavelengths (red and further into infrared) the depth of penetration increases and absorption takes place more and more at the level of the choroid. The melanocytes of the choroid absorb a lot of the energy of diode 810 nm laser, while only 8% of this energy is absorbed by the RPE<sup>1-3</sup>.

Photothermal effects usually occur in three stages: the optical and thermal stages and the denaturation stage; the last depends on the effect of heat on cells and organelles - cellular membranes, proteins (collagen, enzymes), DNA and melanosomes.

### PRIMARY HEAT SOURCE AND HEATED VOLUME

As described in chapter 8 (Laser-tissue interaction: photothermal effect), the heat resulting from the absorption of photonic energy by tissue “endogenous pigments” (melanin and hemoglobin) and the consequent transformation of photonic energy to thermal or vibrational energy at the molecular level, creates a **primary source of heat**<sup>1,2</sup>.

The laser beam impact spot creates a focus of heated tissue. From this primary source of heat, vibrational energy dissipates by thermal diffusion throughout the tissue, building up **the heated final volume**, which has a larger volume than the primary source of heat (Figure 1). This thermal diffusion is dependent on the thermal conductivity of body tissues, which are composed of approximately 60% of water<sup>1,2</sup>.

### TIME IS KEY IN THE DISSIPATION OF ENERGY THROUGHOUT RETINAL TISSUES

The photothermal effect is also dependent on the duration of laser action. If the laser continues to operate (as in the continuous wave (CW) laser), heating is maintained for as long as the laser is on, increasing the temperature at the primary source of heat. Heat then dissipates from this spot, increasing the volume of heated tissue on and around the primary source of heat, originating what is known as the heated final volume. This increase in temperature will reach the choroid and the inner retina. Higher pulse duration implies an increase in the temperature reached at the focus of primary heating, more heat diffusion and a higher heated final volume. On the other hand, if the pulse is very short there will



be no time for heat diffusion and for the build-up of the adjacent heated volume. The time for which depth of optical penetration equals thermal penetration is known as the thermal relaxation time. If pulse duration is less than the thermal relaxation time, an explosive effect will result<sup>1,2</sup> (Figure 1).

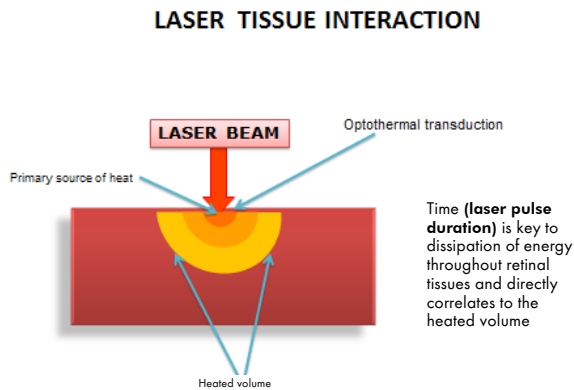


Figure 1. In its interaction with biological tissues, the laser beam undergoes photothermal transduction at the level of the biological pigment (melanin). So, the primary source of heat, which will dissipate energy, is generated and there will be more heat diffusion from the heated tissue as the laser operates, leading to the heated volume at the end of the laser impact.

When using CW, pulse duration is crucial to the effect on adjacent tissues. Short pulse laser effects are limited to the area of impact and there is only absorption of photonic energy. However, we should not forget that in addition to the time of laser exposure (pulse duration), we have to rely on another parameter of the laser beam, namely its power density (beam power per area unit measured in  $W/cm^2$ ). The higher the power density, the higher the thermal effect will be. If the pulse duration time is short enough, a high power density may heat the retinal tissue in such a way that there will be no time for thermal diffusion and the water in the tissue will boil, originating a steam effect and an "explosive" effect at impact site. Higher power density has the capacity to carbonize tissues<sup>1</sup>.

#### THE CAPACITY OF ENDOGENOUS PIGMENTS TO CAPTURE PHOTONS

The capacity of endogenous pigments to capture photons depends on the wavelength involved. Melanin and blood are "endogenous pigments" which absorb the green and yellow part of the spectrum efficiently. The peak of absorption of hemoglobin is precisely in the yellow wavelength. Therefore, when using 532 nm (green) or 577 nm (yellow) laser, or even the diode 810 nm laser, the RPE and/or choroid melanin absorbs the photons and their energy is transmitted to the surrounding molecules, increasing their vibration (Figure 2). This molecular agitation corresponds to the temperature rise<sup>1-3</sup>.

#### LASER INDUCED THERMAL DENATURATION

The heating of tissues leads to denaturation of its constituent proteins, in what is called the thermal denaturation stage. Heat begins by causing dilation of the

local vessels; eventually it causes damage to endothelial cells, and slowing or changing of enzyme activity, particularly in mitochondria; it enhances the production of chemical mediators and heat shock proteins; and leads to intracellular organelle damage. These thermal effects occur in the hyperthermia range ( $42-50^\circ C$ )<sup>1</sup>.

Above  $50^\circ C$  the damage is irreparable. Protein denaturation and collagen retraction occurs, as well as coagulation necrosis (photocoagulation) as the temperature climbs towards  $60^\circ C$ <sup>1</sup>; and at  $62^\circ C$  the result is typically cell death<sup>4</sup>.

As has been shown in previous laboratory studies,  $49^\circ C$  is the tissue temperature needed to stimulate the expression of heat shock protein 70, a naturally occurring ubiquitous cytokine that inhibits inappropriate protein aggregation, inflammation, and apoptosis. At that temperature level, no structural damage is seen in photocoagulated tissues in experimental models<sup>5,6,7</sup>.

Depending on the effect one is after, these thermally induced reactions can be used to cause heavy photocoagulation or only slight injury/stimulation of the RPE cells.

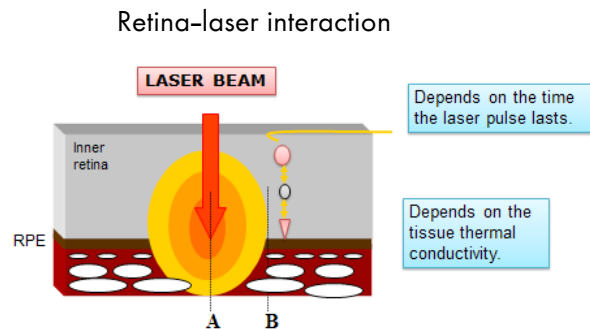


Figure 2. The laser beam is absorbed mainly by the RPE which is rich in melanin. During the laser pulse action time, heat diffuses into adjacent tissues, reaching a heated volume larger than the volume of the primary heat source at the start of the laser impact. The RPE is heated at the site of impact. If the laser beam pulse continues to act, heat will be dissipated and a higher volume of tissue will be heated. Thus, tissue coagulation may occur progressively towards the inner layers of the retina and outwardly towards the choroid, although the latter is cooled by the high-flux choroidal circulation. Later, there will be a repair response to cellular injury; but photoreceptors and the inner layers of the retina will be damaged permanently. This type of injury does not cause significant global functional impairment in the peripheral retina; but the reverse may be true with destruction of macular photoreceptors at the site of laser impact.

#### LASER PARAMETERS AND THE TYPE AND INTENSITY OF THE THERMAL LESION IN THE RETINA

##### Spot area

Laser effect is dependent on the irradiance of the laser beam. This is exponentially (according to the formula for circle area) dependent on the area of the laser spot. So, if we condense the laser beam by means of the optic system linked to the slit lamp, we have an exponential increase in

the beam power. The opposite is also true. An increase in power density, due to the smaller area of the circle where the energy is delivered, has predictable effects on the retina. Indeed, depending in whether the energy of the laser beam is increased or decreased, more or less pronounced effects can be obtained at tissue level<sup>1</sup> (Figure 3).

### Laser-retina interaction

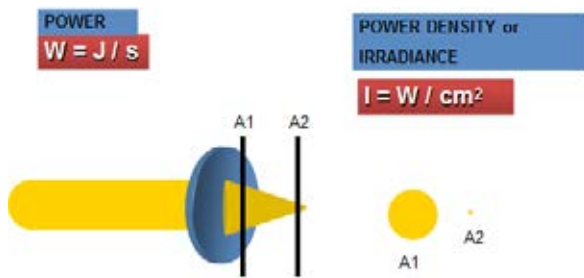


Figure 3. A1 is the area of the circle at target A1 where the laser beam has a large area and consequently low irradiance. On the other hand, at A2 the area of the circle is very small and the irradiance is intense. In this spot area laser effects are very intense, causing retinal lesions. POWER is expressed in Watts. POWER DENSITY or IRRADIANCE is expressed in Watts per unit area ( $\text{cm}^2$ ).

### Laser pulse time

Heating time is crucial in determining the type of laser effect. In fact, as we have seen, when the laser beam is acting, there is continuous photonic to thermal transduction and continuous transfer of heat from the primary heat source to surrounding tissues. For the same wavelength, the same spot area and the same power, the depth of the tissue lesion and the heated volume increase with laser pulse time. They are also dependent on the thermal properties of each tissue however these may be considered roughly similar to those of water since living tissue is composed of almost 60% water.

The higher the laser pulse action time, the greater the energy released, and the larger the heated volume<sup>1</sup>. The diameter of the acute retinal lesion increases logarithmically with increasing pulse duration<sup>8</sup>. The Arrhenius integral  $\Omega$  mathematically describes the changes in temperature in time and space in biological tissue in response to the application of laser energy, and the extent of tissue damage can be quantified<sup>4</sup>.

### Power and pulse length

After the previous considerations, we can easily understand that increasing power causes a regular increase in the effects of the laser beam on the retina, if other parameters are kept constant, like spot size, acting pulse time and wavelength. The diameter of the acute retinal lesion increases linearly with increasing laser power<sup>8</sup>. On the other hand, the power required for the creation of a retinal lesion, like a Bruch membrane rupture and hemorrhage, decreases with decreasing pulse duration<sup>4</sup> (See Chapter 8). If laser is applied at a later date over a previously treated area, heat and damage profiles are altered as a result of the previous

migration of pigment granules into sensory retina and choroid<sup>3</sup> following the initial burn.

### Area and contiguity of burns

According to the formula for sphere area ( $A=4\pi r^2$ ) we can calculate the area of retina as an average of  $1600 \text{ mm}^2$  and the area for pan retinal photocoagulation (PRP) laser as about  $3/5$  of this area (excluding the area anterior to the *pars plana* and between the arcades), corresponding roughly to  $1000 \text{ mm}^2$ . Considering that in PRP spots should be spaced at intervals of one spot-size diameter and that the area of each  $500 \mu\text{m}$  - wide spot ( $\pi r^2$ ) is approximately  $0.196 \text{ mm}^2$ , we need about 2500 spots to cover roughly 50% of retinal surface (and 1000 spots to cover 20% of the retinal area treatable by PRP)<sup>3</sup>. "Mild" PRP coverage consists of about 400-650 burns; whereas full PRP coverage should consist of 1200-1600 plus burns, depending on the patient and the condition. If we use a long action time of the laser beam, the area of each spot increases because of the thermal diffusion, as we have previously seen.

### Laser wavelength and tissue penetration<sup>3</sup>

**Nd: YAG-KTP 532 nm laser (or Argon 514.5 nm):** this wavelength is mainly absorbed by the RPE and a little less by melanocytes of the choroid. Dissipated heat is transferred to the surrounding tissues: the choroid and neuro-sensory retina.

**Yellow KRYPTON 568 nm or diode yellow 577 nm laser:** both have advantages in producing the occlusion of juxtafoveal microaneurysms because the wavelength of yellow coincides with the peak absorption of oxyhemoglobin and is not absorbed by xanthophyll pigment.

**Red 647 nm KRYPTON laser:** this is absorbed by the RPE and choroidal melanocytes. Dissipated heat is also transferred to the surrounding tissues: choroid and neuro-sensory retina.

**Diode 810 nm laser:** most of the energy is absorbed by the melanocytes of the choroid and only 8% by RPE. Dissipated heat is transferred to the surrounding tissues: a lot to the choroid and less to the neuro-sensory retina. Hemoglobin does not absorb light at 810 nm. Microaneurysms may be treated by the thermal effect of heat from the heated adjacent tissue or also indirectly by the release of neovascularization inhibiting factors. The Indocyanine-green intravenous injection powers up heat "uptake" through the vessels with the 810nm diode laser.

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# VI. LASER action in the human retina

## 34. Clinical aspects



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Over the last 30 years, conventional retinal laser photocoagulation for retinal vascular diseases, namely diabetic retinopathy (DR) and retinal vein occlusion (RVO) as well as retinal tears, has been typically performed with a continuous wave laser in the blue, green, yellow or red spectrum. Initially, argon laser at 488 nm and 514 nm was used. Currently, 532 nm solid state diode pumped or diode 577 nm laser are preferred. The pulse duration used has been in the range of 100 to 200 milliseconds (ms), spot size from 100 to 500 micrometers ( $\mu\text{m}$ ) and laser power, to achieve the clinical endpoint, has been between 100 and 750 milliWatts (mW). Laser therapy is empirically titrated to produce a visible clinical effect of greyish whitening of the retina, which corresponds to photoreceptor necrosis and some level of inner retinal damage.

Within the above parameters, laser treatment has proven to be clinically effective<sup>1,2</sup>. However, tissue damage also occurs adjacent to visible retinal burns. Concerns about the destructive power of laser therapy have led to numerous investigations to provide the same therapeutic effect of laser while minimizing the side-effect profile. Techniques including modulation of pulse duration in the millisecond and microsecond domain, lesion intensity, multiple pulses (which allow thermal relaxation and a confined lesion)<sup>3</sup> have been used to reduce tissue damage.

### MODULATION OF PHOTOTHERMAL LASER AND LEVEL OF RETINAL LESIONS

Modulation in the treatment parameters of pulse duration, power, wavelength, and spot size have a predictable impact on the intensity, depth and ultimate size of coagulative lesions, as correctly predicted by the Arrhenius model described below. According to laser parameters we can induce different levels or types of retinal lesions<sup>4-7</sup>.

In conventional laser therapy (photocoagulation) there is a non-treated zone between burns where, logically, no changes in retinal reflectance are observed. The same happens in the outermost ring of a laser burn, corresponding to the hyperthermia zone (Figure 1). Depending on the laser spot power and the Gaussian laser beam profile, there is a core spot area with a more whitish reflectance corresponding to the stronger and more central laser beam. A slightly darker ring just adjacent to the core can also be seen and is caused by the outer profile of the milder laser beam (Figure 1).

If the millipulse lasers (10-30 ms<sup>8</sup> laser burn with mild power) are used, nothing can be seen with funduscopy nor with fundus colour photography. However, these laser lesions can be observed by Autofluorescence (AF), Fluorescein Angiography (FA) or even by infrared retinography<sup>9</sup>. When using micropulse or Endpoint Management (Pascal), the lesions are sub-visible using any method<sup>10</sup>.

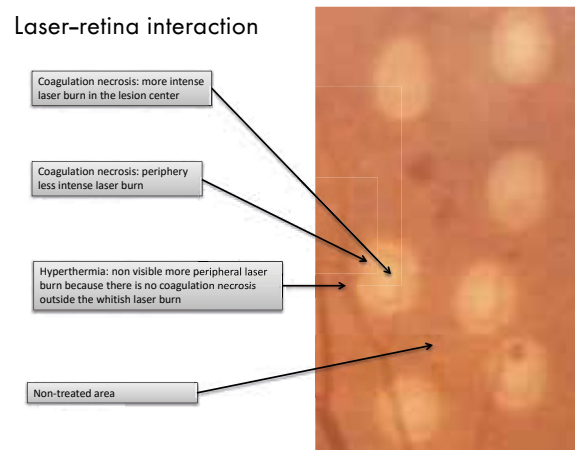


Figure 1. The visible and invisible acute laser lesions in retinal tissue.



**CLINICOPATHOLOGICAL CORRELATION OF PHOTOTHERMAL LASER ACTION ON THE RETINA**

According to the clinical macroscopic aspect observed through the slit lamp, immediately after **conventional laser photocoagulation**, three visible levels<sup>11</sup> of photothermal damage in the retina can be seen (Figures 2, 3 and 4):

Level-I – The lesion is confined to the choriocapillaris (CC), retinal pigment epithelium (RPE) and outer portion of the photoreceptors. Damage is more extensive in the center than the periphery due to the fact that the beam has a Gaussian profile (TEM<sub>00</sub> - TEM = *Transverse Electromagnetic Mode*) (See also Chapter 6). Nevertheless, the damage is not seen in full color retinography.

Level-II – Photothermal effects reach the Outer Nuclear Layer and Plexiform External Layer but does not affect the internal retina. The lesion reaches the level of the CC in the choroid.

Level-III is divided into: mild, moderate and intense. Mild and moderate level III damage correspond to lesions reaching the Outer Nuclear Layer (ONL) and Internal Plexiform layer (IPL), and sometimes the Ganglion Cell Layer (GCL). Intense Level III damage courses with necrosis of the inner retinal layers and reaches the vitreous. Outwardly, the lesion extends beyond the CC; choroidal melanocytes are involved and deep choroidal lesions can be achieved. Bruch's membrane usually remains intact.

**In the millipulse domain** (10-20 ms) and with the laser at 100% continuous wave (CW) power, changes in retinal reflectance are just about visible. Lesions which appear immediately as well as those which appear only 3 seconds after the pulse, can be seen by fundus observation or in full color retinography. The lesions can also be visualized using AF, FA or infrared retinography.

**At subthreshold laser** (micropulse or with Endpoint Management) no macroscopically visible lesions can be observed using OCT-SD, AF, infrared retinography or FA. After a photothermal subthreshold laser lesion the retina begins to repair the injury, as will be discussed in the next chapter. The results are a healing process in which the organelles are repaired and the injured tissue is reorganized.

Level I-III retinal burns as they appear in the acute and chronic stages are depicted in Figures 3 and 4.

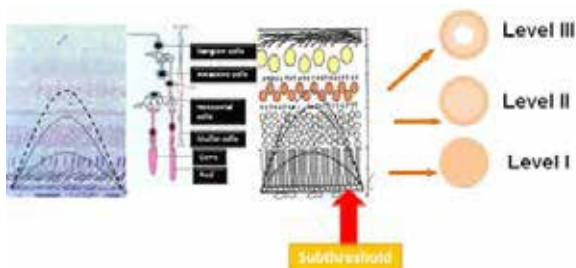


Figure 2. The levels of retinal photothermal damage. Correlation between the intensity effects as observed clinically and the retinal layers affected.

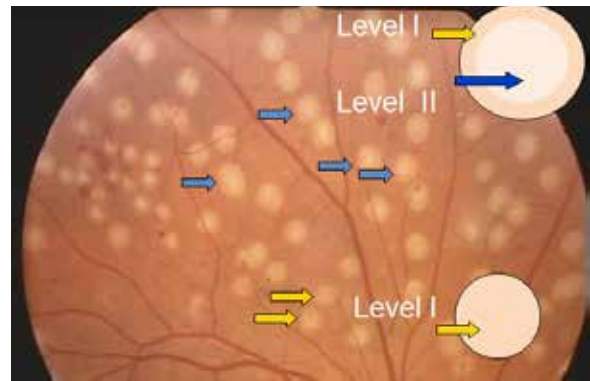


Figure 3. Clinical appearance of **acute Level I and II injury**: acute **level I** injury corresponds to a yellowish gray circle; acute **level II** lesion produces an outer ring area of the same yellowish gray as level I and a central circle with a more whitish area. This is best visualized using a green monochromatic filter.



Figure 4. Clinical appearance of **chronic stage level III burns**: **mild burns** – hyperpigmented continuous or irregular lesion, surrounded by a hypopigmented halo; **moderate burns** – densely hyperpigmented lesions surrounded by a hypopigmented halo. Pigmentation can decrease and become irregular over time; **severe burns** – significant hypopigmented central portion surrounded by a hypopigmented ring.

## AVOIDING BRUCH'S MEMBRANE RUPTURE BY SPATIAL AND TEMPORAL MODULATION OF THE LASER BEAM

Decreasing pulse duration shortens treatment time and minimizes pain during retinal photocoagulation. As it has been seen in the previous chapter, decreasing pulse duration helps to confine retinal damage to the area of photonic absorption. However, the threshold power for thermomechanical rupture of Bruch's membrane decreases with shorter exposure times due to the thermal confinement. At the point of thermal confinement, exposure times are shorter than the time required for heat to dissipate, causing water to vaporize with bubble formation, which in turn may cause Bruch's membrane to rupture and bleed<sup>12</sup>. This is a common phenomenon when using high energy pulses with short pulse duration (10-30 ms), as is used, for example, in pattern multispot lasers. The therapeutic window (TW) for a determined spot size - defined as the ratio of the threshold of power required to produce tissue rupture to that required to produce a mild lesion - represents one means of quantifying the safety of retinal photocoagulation<sup>6</sup>. The larger this ratio or TW, the greater the margin of safety to create a visible lesion without inadvertently inducing retinal rupture. As pulse duration decreases from 100 to 20 ms, the width of the TW decreases from 3.9 to 3.0. When pulse duration is further decreased to 10 ms, the therapeutic window decreases to 2.5, and it approaches 1 at pulse durations of 1 ms. At this point, there is effectively no safe range of retinal photocoagulation: mild lesion and rupture are equally likely to occur independently of power<sup>6,8</sup>.

The research done by Janin *et al.*<sup>6</sup> suggests that 10 to 20 ms represents an optimal range of duration as a compromise between treatment speed and spatial confinement of the lesion on the one hand, and sufficient safety margin to avoid inadvertent ruptures on the other. It would not be possible to efficiently scan patterns of more than a few spots without danger of inadvertent eye movement and spot misplacement with the use of much longer pulse durations. Pulses in the range of 10 to 20 ms, even when delivered as single spots rather than a pattern, may prove advantageous relative to conventional durations<sup>6</sup>.

There are two ways of minimizing the undesirable effect of the rupture in Bruch's membrane by increasing the TW<sup>4</sup>: (a) by modifying the spatial profile of the laser beam - decreasing its central irradiance by coupling the laser into a 200  $\mu\text{m}$  core multimode optical fiber - creating an annular beam with adjustable central irradiance and (b) by pulse temporal modulation, as we have just seen. Pulse shapes can be optimized using a computational model and a waveform generator can be used to produce modulated laser pulses (Figures 5 and 6).

Both the annular beam and modulated pulse provided a 28% increase in TW at 10 ms, affording the same TW as 20 ms pulses with conventional laser parameters<sup>4</sup>.

## DIFFERENCES BETWEEN MILLIPULSE AND MICROPULSE LASER

The **millipulse laser** is a continuous wave laser (CW) with a duty cycle of 100% and pulse duration within 10 to 20 ms (this time ranges between 50 and 200 ms

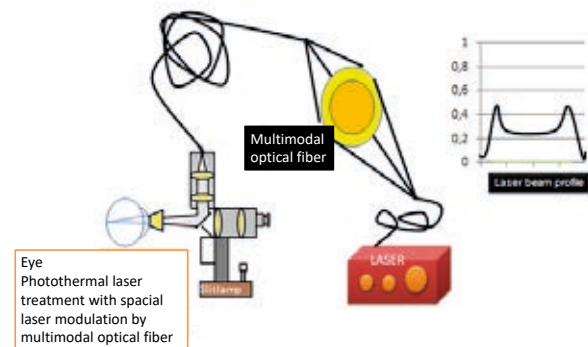


Figure 5. Spatial laser beam modulation by multimodal optical fiber. Laser beam profile with a central area of low energy.



Figure 6. Modifying Beam Profiles with Multimode Fibers<sup>13</sup>. By increasing the launch angle of a Gaussian beam into a multimode fiber, the output beam profile can be modified. As the input angle was increased, the proportion of meridional rays to skew rays increased, firstly, forming a top hat and then a donut beam profile<sup>14</sup>. The top hat profile has a squarer wave appearance and allows for a more continuous and homogenous distribution of the photothermal energy throughout the entire spot area. This avoids Bruch's membrane rupture with short pulses.

with conventional laser). It can be used in the macular area to occlude microaneurysms (focal laser) or in a macular grid pattern, with power densities ranging from 80 to 160 mW and invisible to faintly visible injuries on funduscopy or colour retinography. The thermal injury is produced at the level of the choriocapillaris, RPE cells and outer segments (or even internal segments) of the photoreceptors, depending on the power density used<sup>15,16</sup>. If a higher pulse time is used, as in the case of the conventional ETDRS grid, the lesion has a whitish appearance and is easily identified in the observation of the ocular fundus. The lesion corresponds to thermal injury that reaches the inner layers of the retina. The retina ordinarily has a transmittance of 100% in the visible range but, after denaturation of its proteins (photocoagulation), the light is scattered, generating a whitish tone at the photocoagulated areas<sup>6,12,15</sup>. The number of the laser burns should also be more numerous than that used with conventional laser treatment<sup>17</sup>.

With **micropulse laser** the process of energy delivery is different. This laser is active (laser on) for time intervals of only  $\mu\text{s}$ , delivered within an "envelope" of on and off intervals. A 200 ms "envelope" is filled with 100 pulses of 100  $\mu\text{s}$  (laser on), separated by 1900  $\mu\text{s}$ , time in which there is no laser emission (laser off) and which allows the tissue to



cool. This setting is defined as a duty cycle (DC) of 5%, the most widely used for the retina, but it can be tuned to 10% or 15%, corresponding to greater pulse duration and shorter cooling time and thus more thermal injury. The temperature achieved in the retina with this laser is sufficient to cause hyperthermia but insufficient to cause photocoagulation. Therefore, there is no cell death but only damage to the organelles which will then undergo repair.

The RPE has highly absorbent melanosomes and corresponds to the highest light-absorbing layer of the retina. It is well known that laser-induced retinal damage is caused by thermal denaturation at pulse durations longer than 50  $\mu$ s and by microbubble formation around the melanosomes at pulses shorter than 5  $\mu$ s<sup>18</sup>.

The point of transition at which thermomechanical damage begins to prevail over denaturation occurs just below 50  $\mu$ s pulse duration<sup>18</sup>.

#### ENDPOINT MANAGEMENT PASCAL ALGORITHM - A SPECIAL MILLIPULSE LASER

**Endpoint Management (EpM)** is a feature of PASCAL laser and reflects a sophistication of millipulse laser (Figure 7). First, a test is carried out with a 200  $\mu$ m diameter spot with 15 ms duration in CW mode, and power is increased gradually until a subtle lesion appears 3 seconds after the laser impact. At this point, the power density achieved is considered to be 100%. Next, power density is reduced to 30%, with the same duration of 15 ms and phototherapy may then begin, using these settings. Spots should be closer together in order to have a greater number of spots (approximately 500 spots) than when using more intense laser parameters<sup>7</sup>. The thermal injury in this case, due to the short duration of the pulse, is confined (thermal confinement) to the impact site avoiding thermal dispersion in depth and extension.

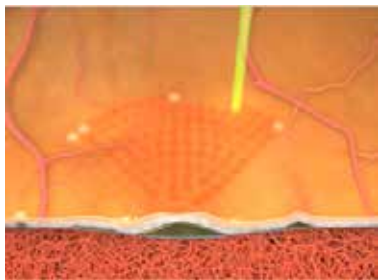


Figure 7. PASCAL Laser with Endpoint Management (EpM). Courtesy of Topcon®.

#### ADVANTAGES OF YELLOW 577 NM LASER

The advantage of 577 nm laser is related to the absorption curve for melanin and oxyhemoglobin which has its peak at or near 577nm. This allows us to use a less powerful laser to obtain the same therapeutic results with less accessory damage and pain.

#### ADVANTAGES OF SCANNING LASER SYSTEMS AND PATTERN LASER

The availability of scanning lasers and laser patterns defined by galvanometers that can be modulated by

the operator allows for quick, precise and uniform treatment<sup>15</sup>, especially when treating the macular area. One of the difficulties of using the micropulse laser is the lack of visible injury making it impossible to visualize the treated area. Scanning laser technology, due to its automated system and the use of the pattern delivery of the beam, overcomes this difficulty.

In order to use a scanning laser, it is necessary to shorten the duration of each individual pulse, from the DRS and ETDRS standard of 100-200 ms to a 10-30 ms pulse duration. This is to ensure that within an array of multiple burns, all are placed precisely where intended and not influenced by ocular movements that typically occur with time durations exceeding 200 ms<sup>15</sup>.

Yellow micropulse laser with the Scan and Multispot features allows for optimal approximation to the therapeutic effect intended. Nowadays, new methods of retinal phototherapy are possible due to access to a more complete range of laser systems with short (tens of millisecond) as well as ultra-short (microsecond) pulse duration.

#### GENERAL CONSIDERATIONS ABOUT ADVANCED RETINAL LASER TECHNOLOGY

Calculations based on the lesion diameter of shorter-pulse-duration laser burns indicate that to maintain the same total treated area as in 1000 standard burns (100 ms, moderate) with a 400  $\mu$ m burn width, a greater number of 20 ms lesions are required, ranging from 1464 to 1979 for moderate and light intensities, respectively<sup>17</sup>. In addition to the reduced lateral dimensions with shorter pulse, lighter burns, there is also a concomitant reduction in the damage to the inner and middle retinal layers<sup>8</sup>, less photoreceptor damage and no formation of "oxygen bridges" between the retina and CC. Consequently, there is poor retinal oxygenation<sup>19</sup> likely to be associated with diminished therapeutic effects.

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# VI. LASER action in the human retina

## 35. The therapeutic

## effect of thermal LASER



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### INTRODUCTION

There has been an interesting debate about what is the *true action* of thermal laser on the retina. The literature in the field of Ophthalmology frequently describes the mechanism of the therapeutic effect of thermal laser as unknown. However, no one denies the existence of a therapeutic effect and also the possibility of adverse consequences when inadequate parameters are used. In practice, laser either works with a more intense heating effect, at around 50-62°C, with a photocoagulating action causing cell death<sup>1</sup>, or with a milder thermal effect in the range of 45-50°C, leading to hyperthermia and photostimulation of the retinal pigment epithelium (RPE) and other retinal cells<sup>2</sup>.

In this chapter we present a review of the literature highlighting the fundamental events, at the cellular level, which are believed to play a role in the therapeutic action of laser (Figure 1).

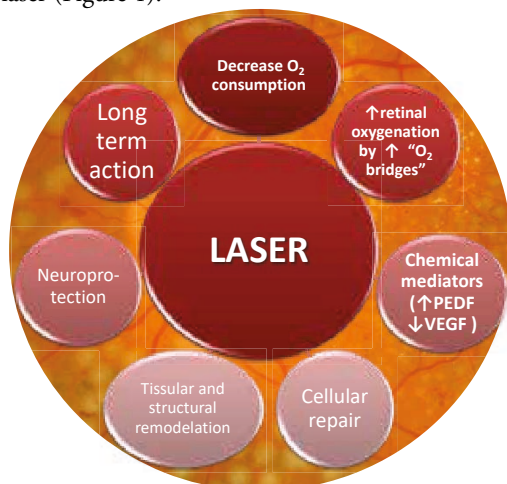


Figure 1. How photothermal laser works in the retina.

### LASER MECHANISMS IN THE RETINA

Multiple studies lead us to consider the following mechanisms (Figures 2 and 3):

#### 1. Decrease in O<sub>2</sub> consumption as a result of photoreceptor (PR) destruction

For a long time this effect was considered the only mechanism of action in laser treatment. The beneficial effects of laser may be explained by PR death, which means improved oxygen availability for the remaining tissues, with reduction of ischemia and VEGF production.

#### 2. Increased retinal oxygenation by choroidal "O<sub>2</sub> bridges"

In tune with the decrease in oxygen requirements after PR cell death is Stéfansson's theory about the opening of genuine "bridges" or "holes" at the external retinal-choroidal level, in that it allows for free diffusion of oxygen from the choroid into the ischemic inner retina, thus inhibiting VEGF production<sup>3</sup>.

This improvement in oxygenation at the inner retinal level has been objectified after panretinal photocoagulation (PRP) by oximetry of the retinal vessels<sup>4</sup> (Figures 2 and 3). This action explains the decrease in VEGF achieved by laser photocoagulation by enhancement of retinal oxygenation<sup>5</sup>.

#### 3. Increased production of RPE-derived chemical mediators - PEDF

Several chemical modulators have been linked to the anti-angiogenic effect of laser and their study has been crucial to the understanding of this process, and seems to be a promising route in the search for new therapies<sup>7,8</sup>. Perhaps the most studied amongst them has been Pigment Epithelium-derived Factor (PEDF), a 50-kDa

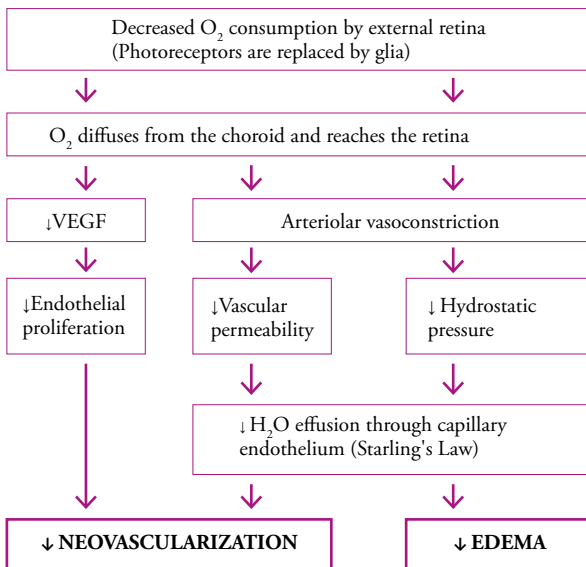


Figure 2. How O<sub>2</sub> leads to improvement of edema and its role in retinal neovascularization<sup>4</sup> (adapted from Stéfansson<sup>6</sup>).

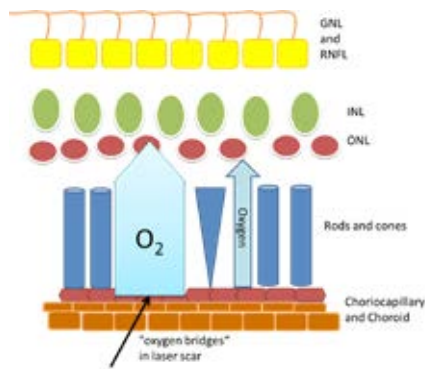


Figure 3. O<sub>2</sub> diffusion from the choroid through the "oxygen bridges" that constitute the laser scars<sup>4</sup> (adapted from Stéfansson<sup>6</sup>).

protein identified previously in conditioned RPE media. It is a member of the serine protein inhibitor, or serpin, family of enzymes produced by RPE cells. These have been strongly implicated in the inhibition of angiogenesis<sup>7,9</sup>, as well as in the inhibition of vascular hyperpermeability in the retina, kidney and brain by counteracting the biological actions of VEGF<sup>10,11</sup>. In short, PEDF counteracts the pro-proliferation, pro-migration and permeability enhancing effect of VEGF over endothelial cells<sup>12</sup>.

The production of antiangiogenic factors including PEDF by RPE cells and infiltrating macrophages after laser photocoagulation was demonstrated by Wilson *et al.*<sup>13,14</sup>. After photocoagulation, PEDF mRNA expression was increased in human RPE cell cultures at 6 hours and remained higher than before photocoagulation for up to 2 weeks<sup>12,15,16,17</sup>.

#### 4. Increase or decrease in the expression of genes involved in the repair process of cell organelles

Microarray-based gene expression analysis demonstrated that laser photocoagulation of mouse eyes has a long-term effect on the expression of genes functionally related to tissue

repair, cell migration, proliferation, protein and nucleic acid metabolism, cell signaling, and angiogenesis, apoptosis and inflammation<sup>14</sup>. Other data revealed that the expression of 256 known genes and their expression sequence tags was changed after laser treatment<sup>14,18</sup> (see Table 1). These genes represent a number of biological processes, including photoreceptor metabolism, synaptic function, structural proteins and adhesion molecules processes<sup>14,18</sup>.

Table 1. Modification of gene expression in the retina after thermal laser (adapted from Wilson *et al.*<sup>14</sup>)

#### Increased expression of twenty-five genes related to several biological processes:

Repair and metabolism of photoreceptors:

Inosine monophosphate dehydrogenase type 1 (IMPDH1)

μ-crystallin

Hex (prh) hexosaminase

Synaptic function: α-transducin

Axonal growth and synaptic function: dynamin

Structural proteins

Adhesion molecules

Angiotensin II receptor type 2, likely angiogenesis inhibitor

VEGF-induced

#### Decreased expression of genes implicated in:

Modulation of endothelial cells

Vascular permeability

Induction of VEGF: FGF-14, FGF-16, IL-1β, calcitonin receptor-like receptor (CRLR), plasminogen activator inhibitor-2 (PAI2)

#### 5. Activation of cell renewal and remodeling of retinal tissues

In photocoagulated areas there is regeneration action, with renewal of intracellular organelles and a reorganization of the local microarchitecture<sup>18-20</sup>. These cell repair and remodeling processes are mediated by genes whose expression is induced after laser, including the already mentioned genes for structural proteins, such as crystallins, among others, that have shown to be increased in specific locations within the retina even 90 days after the procedure<sup>18</sup>. These structural changes are thought to be the basis of the long-term maintenance of laser effects. Also, studies about the plasticity of mammalian retina after injury, have shown that there is not just a restructuring process in a damaged retina, but that in fact neurons can change their connectivity patterns and restore normal retinal anatomy and function<sup>21</sup>. After selective laser photocoagulation of photoreceptors in the rabbit retina, with preservation of retinal inner neurons (bipolar, amacrine, horizontal, ganglion cells), the photoreceptors located outside of the damaged zone migrate to make new functional connections with bipolar cells located inside the lesion<sup>21</sup>. This is an amazing discovery that suggests plasticity in the adult retina and allows new approaches to retinal laser therapy (see also Chapter 36).

#### 6. Increased expression of Matrix Metalloproteinases (MMPs)

The efficacy of laser in the the regression of neovessels



may be in part due to changes in the expression pattern and in the balance between metalloproteinases and their inhibitors<sup>13,22</sup>. One week after laser, an increase in the levels of MMP-3 to twice the control values was detected<sup>21</sup>, as well as an increase in active MMP-2 and MMP-9 of 6.6 and 4.4 fold over baseline, respectively<sup>13,23</sup>. TIMP-1 (tissue inhibitor of metalloproteinases) levels were decreased after the first 4 days only to increase again by day 6<sup>22</sup>. So, these studies suggest that the effects of laser most likely involve more than a change in the relationship between VEGF and other ischemia-related factors, there being also an important part played by the balance between MMP and TIMPs<sup>22</sup>.

### 7. Increased production of heat shock proteins

Heat-shock proteins (HSPs) are a ubiquitous feature of cells, where these proteins help cope with stress-induced protein denaturation, such as that induced by hyperthermia<sup>24</sup>. HSPs act as molecular chaperones and demonstrate crucial protective functions in stressed cells<sup>25</sup>, and induction of their expression correlates with cytoprotection, reduced tissue damage, and accelerated healing in animal models. HSPs are transcriptionally activated in response to stress, so they can act as stress indicators in burn injury or surgical procedures that produce heat-induced change<sup>26,27</sup>. It has been recently hypothesized by several investigators that laser irradiation induces choroidal HSP hyperexpression and that they can have a neuroprotector effect. Indeed, HSP70 may act as a potential endogenous inhibitor of photoreceptor cell death after Retinal Detachment<sup>28</sup> and HSP27 (and also HSP70) appear to be involved in a protective reaction to ganglion cell injury in retina<sup>29</sup>. HSP27 is principally upregulated by astrocytes, while HSP70 is expressed by neurons<sup>30</sup>. As early as 6 hours after laser treatment, HSP27 mRNA level was significantly upregulated as shown by Chidlow *et al.*<sup>29</sup>. Three days after laser treatment, HSP32 immunoreactivity was detected in Müller cells, infiltrating macrophages and proliferating/dividing RPE cells<sup>30</sup>.

Transpupillary thermotherapy<sup>31</sup> is linked to retinal tissue HSP overproduction<sup>32</sup> and the same likely occurs at the outer ring of hyperthermia of a laser spot<sup>14,18</sup>.

### 8. Hyperregulation of the $\alpha\beta$ Crystallins

Binz *et al.*<sup>18</sup> demonstrate that CRY $\alpha$ A and CRY $\alpha$ B, which belong to the family of small heat shock proteins, protecting proteins from heat damage and acting as molecular chaperones ensuring correct protein folding<sup>21,33</sup>, are present in the late stage of retinal laser photocoagulation<sup>18</sup>. Another study in mice showed that, in response to CW photothermal laser, there was a rapid upregulation of  $\alpha$ B-crystallin, the extent of which was related to laser power<sup>30</sup>. Both CRY $\alpha$ A and CRY $\alpha$ B are significantly increased, by 3.7- and 3.1-fold respectively, at 90 days post-photothermal laser<sup>18</sup>(Figure 4). These observations support the hypothesis that these crystallins play a role in maintaining the altered cytoskeletal network within and around the laser lesions, possibly protecting these sites from further damage<sup>18</sup>.

Other structural proteins such as keratin 1-12 (Krt1-12), the retina and brain-specific putative transcription factor tubby-like protein 1 (Tulp1)<sup>18</sup> are also up-regulated; whereas potential

modulators of endothelial cell function, permeability factors, and VEGF inducers, such as FGF-14, FGF-16, IL-1beta, calcitonin receptor-like receptor (CRLR), and plasminogen activator inhibitor-2 (PAI2), are downregulated<sup>18</sup>.

These insights into the effects of laser photocoagulation at the molecular level may provide an important basis for future therapeutic strategies.

In the long term, there are structural proteins that remain changed in time and that are likely responsible for the maintenance of laser action over time, including the stabilization of diabetic retinopathy in the longterm, in contrast to the limited action of drugs<sup>18</sup>.

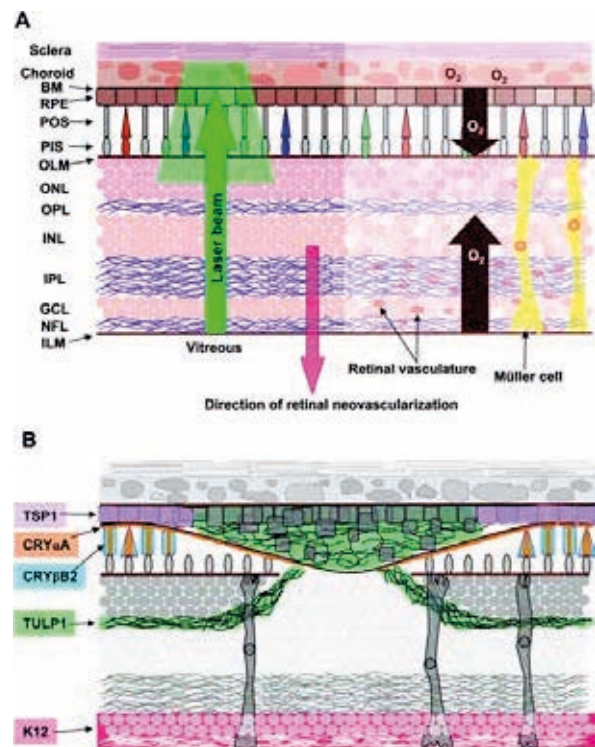


Figure 4. Diagrammatic representation of the photothermal laser effect (photocoagulation) on the retina/RPE tissue complex in the eye, representing genes whose expression is altered in the longterm as a result of this process. A) A 50  $\mu$ m wide laser beam delivering a laser lesion of the same size to the eye. Laser energy is absorbed by the melanin granules in the RPE and choroid. Arrows on the right show the depth and direction of oxygen diffusion from the choroidal and retinal vascular beds into the different layers of the neural retina. Normal retinal vasculature extends from the NFL/GCL to the INL and retinal neovascularization in the majority of cases originates within the INL and IPL, growing toward the NFL/GCL and vitreous. B) Immediately after photothermal laser (photocoagulation), the photoreceptors at the site of laser delivery are lost and the RPE is exposed. Dissipation of the generated heat energy leads to an expansion of the original laser lesion to 2- to 3-fold its original size. In addition, loss of oxygen-demanding photoreceptors within the laser lesion permits oxygenation of the inner retina from the choroidal vasculature, relieving focal hypoxia in the inner retina. The location of TSP1, CRY $\alpha$ , CRY $\beta$ B2, TULP1, and K12 is shown within the lasered retina. Müller cells, which extend from the inner to the outer limiting membrane (ILM, OLM), provide a conduit for signaling within the retina. BM: Bruch's membrane. (Reprinted with permission and courtesy of Binz *et al.*<sup>18</sup>).



### 9. Hematopoietic stem cell migration from bone marrow

Chan-Ling *et al.*<sup>34</sup> have reported that hematopoietic stem cells (HSCs) can differentiate into endothelial cells, participating in retinal and choroidal neovascularization. HSCs can also differentiate into cells expressing markers specific to astrocytes, macrophages/microglia, mural cells or RPE<sup>34</sup>.

There has been growing evidence that hematopoietic stem and progenitor cells are mobilized from the bone marrow into the peripheral circulation in response to RPE damage<sup>35</sup> and that they can migrate to the RPE after physical or chemical injury, proliferate and integrate into injured retinas<sup>36</sup> and regenerate the damaged RPE layer<sup>37</sup>.

### 10. Activation of microglia

Studies by Chidlow *et al.*<sup>30</sup> showed that conventional photocoagulation produces outer retina lesions with photoreceptor cell death and inflammatory response activation. A 3-nanosecond pulse laser produces the same type of lesion but with less intensity<sup>30</sup>.

Rapid activation and migration of microglia and macroglia takes place, together with the expression of proinflammatory cytokines such as IL-1 $\beta$  and TNF $\alpha$ <sup>29</sup>, and the induction of leukocyte adhesion molecules and infiltration by macrophages and neutrophils<sup>30</sup>. This inflammatory reaction is visibly heralded by microglia losing their dendritic shape, acquiring polarization and migrating to the lesion area acquiring phagocytic activity<sup>30</sup>.

### 11. Activation of Müller cells

Injured photoreceptors produce endothelin, which in turn leads to leukocyte infiltration and RPE cell division<sup>38</sup>. Müller cells are also activated<sup>39</sup> by photoreceptor injury through endothelin signalling<sup>40</sup>. It has been documented that photoreceptor cells migrate and repair the lesion caused by photocoagulation, providing the lesions are not too extensive<sup>21,38</sup>. Other cellular responses detected in this context include the upregulation of inducible HSPs observed in Müller cells, astrocytes, and RPE cells<sup>30</sup>.

### 12. Up-regulation of trombospondin-1 (TSP-1), angiotensin II type 2 receptor (Agtr2) and Transforming Growth Factor-beta2 (TGF- $\beta$ 2)

TSP-1 is a cellular matrix protein involved in a range of cellular processes, including response to injury, and is recognized to exhibit system-dependent pro- and anti-angiogenic properties<sup>41</sup>. TSP-1 is one of the most potent anti-angiogenic factors known<sup>42</sup>. Long-term up-regulation of TSP-1 after photothermal laser suggests the latter may induce the anti-angiogenic properties of this gene and its protein product, especially since the overall anti-angiogenic effect of photothermal laser in the retina is well established<sup>18</sup>. There is also an up-regulation of the anti-angiogenic factor angiotensin II type 2 receptor (Agtr2)<sup>18</sup>. Laser photocoagulation of cultured RPE cells increases their production of TGF- $\beta$ 2. It thus seems possible that both these factors play an important role in the processes that occur after laser photocoagulation<sup>43,44</sup>.

### 13. Decreased retinal VEGF production and hyper expression of PEDF and TIM3

VEGF is implicated in neovascularization in ischemic

retinal diseases. It has been known for a long time that VEGF concentrations in vitreous fluid decrease by 70% after successful laser photocoagulation<sup>5,18</sup>. There is a balance between promotion and inhibition of neovascularization and different growth factors and other proteins are involved in each side of the equation. Amongst the inhibiting factors we can highlight PEDF, TIMP3 (Tissue Inhibitor metalloproteinase-3) from Bruch's Membrane or the basal membrane of endothelial cells, and also endostatin and angiostatin. Retinal vascular homeostasis (in the retina as well as in other tissues or tumors) may be interpreted as a balance between factors that promote neovascularization, particularly VEGF and SDF-1 (stromal cell-derived factor-1) and the aforesaid neovascularization inhibitors (Figure 5). It can be argued that regression of neovascularization depends on shifting the balance from pro-angiogenic, anti-apoptotic and cell proliferation-inducing stimuli to anti-angiogenic stimuli with down-regulation of cell proliferation and differentiation-related factors<sup>10</sup>. The expression of the latter is increased after the action of photothermal laser on the retina<sup>14,17,45</sup>. PEDF level is significantly reduced in patients with Diabetic Macular Edema compared with non-diabetic patients or diabetic patients without retinopathy<sup>46</sup>.



Figure 5. Retinal vascular homeostasis may be interpreted as a balance between factors that promote neovascularization, particularly VEGF and SDF-1, and multiple neovascularization inhibitors, particularly PEDF, TIMP3, endostatin and angiostatin.

### CONCLUSION

Photothermal laser used as photocoagulating or photostimulating tool causes RPE cell ablation in the irradiated zone or associated histological damage to photoreceptors and/or inner retinal layers depending on the laser parameters used. At the same time it causes a cellular response that is consistent with an inflammatory response to thermal injury. This cellular response includes rapid activation and migration of microglia together with expression of pro-inflammatory cytokines, infiltration of macrophages and neutrophils, leukocyte adhesion molecules activation, accompanied by the synthesis of trophic factors. At the same time there is upregulation of inducible HSPs in Müller cells, astrocytes and RPE cells, as well as of a number of trophic, anti-edema and anti-neovascularization factors, such as PEDF, that counteract the pro-inflammatory/pro-differentiation factors, thus shifting the balance towards antiangiogenesis and the prevention of edema.

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# VI. LASER action in the human retina

## 36. Structural and functional changes and possible neuroprotective effects induced by photothermal LASER in the retina



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The inherent characteristics of photothermal lasers used for photocoagulation make it impossible to confine the generated thermal energy to retinal pigment epithelium (RPE) cells, mainly due to long exposure times. This necessarily means that the surrounding cells, notably the overlying photoreceptors, will suffer collateral damage when clinically relevant energy settings are used<sup>1,2</sup>.

Over the years, the aim for thermal laser-induced effects on retinal cells has shifted from lethal damage to a regenerative/stimulatory effect, thereby intending to perform a true rejuvenation of some retinal cell types, namely RPE cells, glial cells, Müller cells, endothelial cells, photoreceptors and others<sup>3</sup>. Concurrently with these beneficial effects at the cellular level, and depending on the severity of damage, there is also: a) remodeling of the retinal microstructure associated with fibrosis, scarring and metaplasia of the RPE<sup>4,5</sup>; b) changes in gene expression<sup>6,7</sup> and c) changes in the production of chemical mediators towards those with local anti-inflammatory, anti-edematous and anti-angiogenic properties. Taken together, these data suggest

that photothermal lasers may induce neuroprotective and trophic effects on retinal cells<sup>7</sup>.

We reiterate that the intensity of the lesion, patterned by laser parameters such as spot size, power, and particularly, laser action time and laser output mode, may lead to both stimulatory/regenerative or destructive effects<sup>8-10</sup>. In the macular area, the goal is to attain tissue regeneration with no associated effective or permanent loss of function, either in the impact zone, or in its vicinity<sup>5</sup>. The paradigm has really shifted thanks to the high volume of information gained from studies based on the Arrhenius model, which assesses the effect of temperature on tissues and how the spatio-temporal relationship and amount of energy dispensed can damage retinal cells<sup>1,11,12</sup>.

We will briefly describe the histological effects that result from recent and chronic thermal injury to the retina, namely the restructuring and remodeling effects that occur depending on the laser parameters used (if the retinal lesion is minimal and of small diameter<sup>2,3,8</sup> or larger and heavier), as well as possible retinal neuroprotective effects of photothermal lasers<sup>7</sup>.



### HISTOLOGY OF SHORT-TERM EFFECTS OF CONVENTIONAL PHOTOTHERMAL INJURY - PHOTOCOAGULATION

Considering the conventional continuous wave (CW) level I photothermal lesion, which appears homogeneously white (see Chapter 34), there is, in conjunction with RPE cell destruction in the irradiated zone, also substantial destruction in the outer nuclear layer (ONL) and photoreceptor segments<sup>3</sup>.

Additionally, and within 2 hours of laser injury, the blood-retinal barrier becomes compromised both at the inner (retinal vascular endothelial cells) and at the outer (RPE cells) level, thereby increasing retinal vascular permeability. These effects are consistent with a pro-inflammatory response to thermal injury that develops locally in the retina.

In the following 2 to 4 days there is: a) proliferation of the RPE; b) reversible breakdown of the outer segments of photoreceptors<sup>13</sup> and c) hyperplasia of RPE cells, retinal and choroidal vessels and stromal cells<sup>5,14</sup>. Three days after laser treatment, there are detectable lesions in the retina, and migrating Müller cells, infiltrating leukocytes and dividing RPE cells.<sup>3</sup>

As Binz *et al.*<sup>7</sup> have shown, 90 days after photothermal laser, there is RPE proliferation, loss of photoreceptor inner segments, photoreceptor outer segments, and of ONL, as well as traction of the INL (inner nuclear layer), pulling it into the lesion core. As the outer plexiform layer is situated between the INL and ONL, it stands to reason that this layer is also affected by photothermal laser changes. There appear to be no gross morphological changes in the inner plexiform or ganglion cell layer (GCL)<sup>7</sup>.

If softer laser parameters are used, pro-inflammatory and glial cell responses are substantially attenuated<sup>3</sup>, and the chances of restoring retinal anatomical structure and functionality are higher<sup>15</sup>.

### DAMAGE ASSOCIATED WITH SHORT PULSES AND SMALL DIAMETER BURNS CAN BE ANATOMICALLY AND FUNCTIONALLY REVERSED

Recent work has shown that, after photocoagulation, the resulting denuded regions of the ONL can slowly be repaired by endogenous mechanisms<sup>2</sup> (Figure 1). The width of the retinal damage zone becomes progressively reduced, suggesting that photoreceptors are migrating from unaffected areas to fill in the gap. For this to happen, certain conditions must be met, i.e. laser photocoagulation parameters must avoid a) inner retinal damage and b) permanent disorganization and scarring in the photoreceptor layer<sup>2</sup>.

This process is thought to occur primarily via migration of neighboring photoreceptors, but migration and dedifferentiation of Müller cells may also play a role<sup>16</sup>.

Sher *et al.*<sup>15</sup> demonstrated that in the macular area, if only the outer layers of the retina are acutely damaged with shorter pulse durations (10-20 ms), the retina shows considerable capacity for renewal through regeneration and remodeling. There is RPE migration and proliferation, which restore the continuity of the

RPE monolayer within 1 week. This does not happen when full-thickness damage is produced, using longer-duration pulses of 100 ms.

The injured area (gap) in the photoreceptor layer is initially filled with glia. Over time, photoreceptors from adjacent retinal areas migrate into the damaged zone, thereby reducing its size. With sufficiently small lesions (below 200  $\mu\text{m}$ )<sup>15,17</sup>, and no damage to the inner retinal layers, photoreceptors can completely refill the damaged zone and rewire to local bipolar cells over time<sup>15,18</sup>, thereby restoring retinal structure and function and avoiding the extensive glial scarring and neuronal loss associated with longer-duration retinal burns<sup>8,15</sup>. These effects can be modulated with concomitant administration of pharmacologic agents such as steroids<sup>1</sup>.

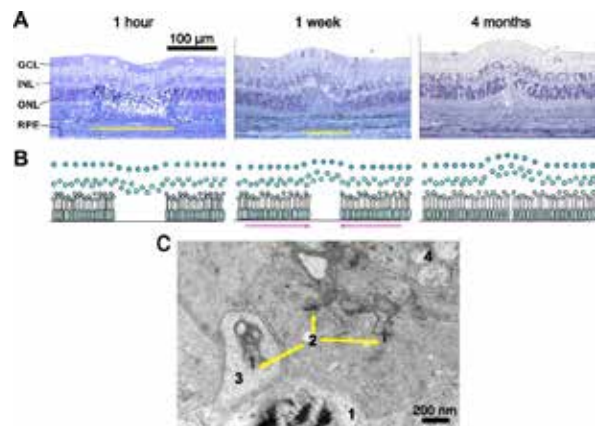


Figure 1. Restoration of retinal anatomy after photocoagulation. A- Toluidine-blue-stained retinal sections at various time points after the “barely visible” grade photocoagulation. Yellow bars show the lateral extent of the photoreceptor layer damage. B- Diagrammatic representation of the restoration of the photoreceptor layer continuity. C- TEM photograph of a central area of a healed 2-month-old lesion showing: (1) the photoreceptor nucleus, (2) photoreceptor ribbon synapses, (3) synaptic vesicles and (4) bipolar cell processes. Reprint with permission and courtesy of Paulus *et al.*<sup>2</sup> and Sher *et al.*<sup>15</sup>.

### RPE PHOTOTHERMAL DAMAGE AND REPAIR

Selective RPE destruction for potential clinical treatment of diabetic macular edema (DME) has a solid evidential basis. With near sub-threshold laser damage, such as that created with retinal regeneration therapy (2RT laser)<sup>16</sup>, and especially when used at the energy levels defined for clinical treatment of DME patients, an almost entirely RPE-specific lesion is produced, leaving an intact basement membrane, which is largely repaired within 7 days<sup>16</sup>.

It is believed that laser-stimulated production of trophic factors by RPE cells, which survive treatment or lie outside of the irradiated zone, underlies the beneficial wound-healing response to retinal laser treatment for DME. The ability to produce this effect with lasers working in the sub-visible spectrum, e.g. micropulse laser<sup>19</sup>, Pascal Endpoint Management at 30%<sup>12</sup> or the developing 2RT laser, along with the almost complete

sparing of adjacent photoreceptors, has been bringing us useful clinical advances<sup>9,20,21</sup>.

If a wound-healing response is required in the retina without the need to confine injury to the RPE, like in retinopexy or in pan retinal photocoagulation (PRP) for proliferative diabetic retinopathy (PDR), conventional CW laser photocoagulation will suffice. However, if photoreceptor sparing is desired, then sub-visible lasers represent an excellent alternative, possibly with similar clinical benefits for DME patients as with conventional full-threshold laser (modified DRCRnet ETDRS grid), but with a more appealing safety profile<sup>1</sup>.

### NEUROPROTECTION AND LASER – CURRENT EVIDENCE

As has previously been discussed, crystallins have a protective effect on enzymes and proteins<sup>22</sup>. Keratin 12(K12) belongs to a family of intermediate filament proteins that form strong cytoskeletal networks giving rise to a rigid epithelial cell layer, which protects its underlying tissue<sup>7</sup>. An up-regulation of K12 in the GCL after thermal damage suggests that this structural protein may have additional heretofore unknown functions contributing to the beneficial effect of photothermal laser on retinal vascular diseases, like diabetic retinopathy (DR)<sup>7</sup>.

TULP1 functions as a transcription factor that regulates a gene network involved in neuronal cell survival. Up-regulation of this gene and protein may protect the remaining photoreceptors across the retina and/or stabilize those photoreceptors bordering laser lesions, by ensuring continuity of cell signaling. The staining pattern (TULP1 expression was found in the core of the laser lesions, in proliferating RPE cells, within the glial scar, and in the GCL) suggests that the up-regulation of TULP1 is induced in response to photothermal laser injury. Interestingly, this was not entirely restricted to laser lesions, but also had a more widespread action, affecting unlasered portions of the retina. This suggests that the up-regulation of this putative transcription factor may have a panretinal effect on photoreceptor survival<sup>7</sup>. On the other hand, TULP1 mutations have been shown to cause early-onset retinal degeneration<sup>23,24</sup>.

After laser treatment there is altered expression of two commonly described trophic factors, namely fibroblast growth factor-2 (FGF-2) and ciliary neurotrophic factor (CNTF)<sup>3</sup>.

Moreover, it has been shown that low energy laser irradiation is able to delay degeneration of retinal ganglion cells (RGC) in adult rodents after optic nerve (ON) transection if administered early after injury<sup>25</sup>. This effect is thought to result from the suppression of microglial activity and proliferation, leading to reduced production of pro-inflammatory molecules. Naveh *et al.*<sup>26</sup> have reported that low energy laser irradiation of eyes with crushed ON exerts an effect on arachidonic acid metabolism similar to that seen with steroidal and nonsteroidal anti-inflammatory drugs, by preventing enhanced production of prostaglandin E2 and leukotriene B4 *in vitro* after trauma<sup>26</sup>.

There is a growing body of evidence suggesting that pigment epithelium derived factor (PEDF) could prevent

neuronal derangements and vascular hyperpermeability in early diabetic retinopathy via inhibition of NADPH oxidase-driven oxidative stress<sup>27,28</sup>. PEDF is critically involved in the antiangiogenic activity provided by Müller cells and microglia, and protects retinal cells from ischemia-induced neuronal cell death<sup>29,30,31</sup>. It has also been shown to promote photoreceptor and RGC survival in more than one type of early-onset retinal degeneration<sup>32</sup>.

Thermal laser-induced RPE and photoreceptor injury induce a repair reaction that increases the expression of PEDF<sup>33,34,35</sup> among other chemical mediators. These mediators have trophic and regenerative actions which may help explain the clinical improvement of diabetic retinopathy after photothermal laser treatment<sup>36</sup>.

Intra-vitreous injection of PEDF may offer a promising strategy for halting the development of DR<sup>31,37</sup>.

### LASER-INDUCED CELL STIMULATION IN THE MACULAR AREA – SUB-LETHAL DAMAGE OF RPE CELLS AND PHOTORECEPTOR OUTER SEGMENTS

For obvious reasons, when the macular area is treated with laser phototherapy, lethal damage to RPE cells and photoreceptors should be avoided<sup>38</sup>. Even if the RPE is lost locally (impact zone), the survival of adjacent RPE cells is important to ensure their regeneration.

It is well known that conventional photocoagulation frequently causes central or paracentral scotomas, with progressive deterioration of the visual function (particularly because these lesions tend to increase over time and approach the fovea<sup>39</sup>). When treating the macula with laser phototherapy, the therapeutic goal is to induce hyperthermia in RPE cells<sup>40</sup>, thus stimulating them to produce chemical mediators that contribute to the resolution of macular edema, namely PEDF<sup>41</sup>, without inducing any lethal damage. Here, the aim of thermal laser treatment is to induce a slight change in RPE cell status<sup>34,42-44</sup> which is hardly seen, if at all, in full color retinography (i.e. barely visible or invisible lesions). The thermal interaction, if occurring above a certain threshold, can damage not only RPE cells rich in melanin, but also photoreceptor outer segments; under these circumstances the lesion then becomes visible looking slightly whitish<sup>12,34,44,45</sup>. However, as we have previously described, RPE cells and photoreceptors can regenerate or be replaced by adjacent photoreceptors, thus decreasing the lesion size and readjusting their function<sup>15</sup>.

### LASER TREATMENT BY PHOTOCOAGULATION IN PROLIFERATIVE RETINOPATHY

After photocoagulation, tissues that were transparent to visible light suffer changes in their optical properties, as they scatter light to the observer and take on a whitish hue<sup>46</sup>. With the photocoagulation effect, we intend to ablate peripheral RPE and photoreceptors, which consume oxygen (especially photoreceptors), and to create "O<sub>2</sub> bridges" (i.e. to facilitate the diffusion of O<sub>2</sub> from the choroid to the inner retina, and to spare oxygen for central retinal neurons), and also to induce a local repair reaction within the damaged tissue that includes the attraction of stem cells<sup>47</sup> to the retina, and changes in gene



expression towards production of mediators involved in cell regeneration and of PEDF (antiangiogenic and neuroprotective)<sup>41</sup> as well as other protective mediators. All these pathways lead to lower VEGF (vascular endothelium growth factor) production and regression of pathological neovascular growth<sup>6</sup>.

Interestingly, not only is there a regression of neovascularization, but retinal areas in the vicinity of the laser impact also acquire a texture that looks healthier than their previous one (i.e. before photocoagulation was performed). Another important point is that, due to tissue remodeling and expression of certain factors, such as crystallins and TULP-1, which have been suggested to act as neuroprotectors<sup>22</sup>, this effect is kept almost indefinitely<sup>7</sup>. Another action of thermal laser is stimulation of heat shock proteins and activation of microglial and Müller cells. These effects are also achieved with lasers that only cause hyperthermia and retinal stress, including 2RT lasers, micropulse and the millipulsed lasers delivered in multispot patterns (like PASCAL)<sup>3,9</sup>.

Regarding prevention or involution of pathological neovascularization, however, it seems that these soft lasers cannot achieve the same anti-neovascularization outcomes as conventional laser, and this may be attributed to their ineffectiveness in producing the aforementioned "O<sub>2</sub> bridges". In order to attain equivalent outcomes with softer laser parameters, the treatment should include a higher number of laser spots (when compared to the numbers used in conventional PRP<sup>48</sup>). Physicians may need to change treatment parameters when using the PASCAL pattern laser therapy for high-risk PDR.

In PRP, in the periphery of each burn there is a ring of hyperthermia and the reparative process occurs in this area and in the center of the burn, as has been described above. There is ongoing debate about which is, in fact, the greatest effect of laser therapy in PDR: the production of chemical mediators, the improved distribution of oxygen, or both<sup>49</sup>.

### CONCLUSION

It has been demonstrated that photothermal laser induces an improvement in oxygen supply to the inner retina coming directly from the choroid, which usually only supplies the outer photoreceptor layer. At the sites of laser lesions, photoreceptors are lost and oxygen can travel through the glial scar of the laser lesion (the so called "oxygen-bridge") to relieve localized retinal hypoxia.

As photoreceptors have extremely high metabolic activity, they are very rich in mitochondria and have a very high oxygen demand, so their destruction decreases retinal oxygen needs, thus improving the balance between oxygen supply and demand in conditions of ischemic retinopathy<sup>50,51</sup>.

Many studies have clearly demonstrated that photothermal laser has a very important effect on the expression of growth factors within the retina and RPE. Indeed, down-regulation of VEGF and up-regulation of a number of cellular or inter-cellular factors, especially PEDF and some structural proteins with sustained neuroprotective properties, have been demonstrated, repeatedly, in patients with diabetic retinopathy after photothermal laser.

The systematic characterization of the retinal response

to differing laser treatments supports the hypothesis that the therapeutic effect is achieved through RPE cell ablation and renewal, either directly or through localized release of mediators (paracrine effects).

Understanding the biological effect of photothermal laser on the retina, i.e. the up or down regulation of factors, and which genes are preferentially affected by laser therapy, provides us with the tools needed to develop biological factors and gene-based therapies that could exert beneficial retinal effects in a non-destructive fashion. Among these tools we can highlight the new generation of friendly lasers that have a preferentially stimulating effect, rather than a destructive one.

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# VI. LASER action in the human retina

## 37. Non-damaging

## Photothermal Therapy

## of the Retina using

## Endpoint Management



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### INTRODUCTION

Retinal photocoagulation, either alone or combined with pharmacological therapy remains the standard of care for various retinal diseases, including proliferative diabetic retinopathy (PDR), diabetic macular edema (DME), vascular occlusions, central serous chorioretinopathy (CSR), and retinal tears. To minimize the side-effects while retaining the therapeutic benefits, and to improve localization of the laser effects to specific retinal layers, various refinements in the treatment parameters have been introduced over the years, including variations in wavelength, pulse duration, and lesion intensity.

During the retinal laser therapy with visible and near-infrared wavelengths, light is absorbed primarily by melanin in the retinal pigment epithelium (RPE) and in pigmented choroid, and to a smaller extent by hemoglobin<sup>1</sup>. Energy deposition by light absorption results in tissue heating, with the maximum temperature in the RPE layer. Generated heat diffuses into the surrounding tissues, including the transparent neural retina, and the depth of the retinal damage is governed by the laser power and pulse duration. Introduction of the pattern scanning approach to retinal photocoagulation (PASCAL)<sup>2</sup> has advanced the use of shorter pulses (10 – 30 ms), which limit heat diffusion, minimizing the inner

retinal damage and pain sensed by the neural endings in the choroid<sup>3,4</sup>. As a result, less-damaging photocoagulation endpoints have been adopted<sup>5</sup>, which helped decrease residual scarring and improved restoration of the retinal structure and function over time<sup>6,7</sup>.

The less damaging approach to retinal laser therapy was initially attempted using near-infrared diode laser (810 nm) with very long exposures (60 seconds) and a millimeter-wide spot on the retina<sup>8</sup>. This approach, termed Transpupillary ThermoTherapy (TTT)<sup>9</sup>, has been tested in treatment of choroidal neovascularization (CNV) in age-related macular degeneration (AMD)<sup>8,9</sup>. Proponents of this approach have hypothesized a selective damaging effect of heating on actively dividing cells in newly formed blood vessels due to their higher susceptibility to thermal injury than non-dividing cells in normal tissue. The estimated retinal temperature rise at clinical settings (810 nm, 800 mW, 60 seconds, 3 mm spot size) is approximately 10°C<sup>10</sup>. The use of TTT encountered difficulties with reliable titration, resulting in frequent occurrences of significant retinal damage<sup>11</sup>. Later, a pulsed version of a similar laser with smaller spot size (125 μm) has been applied to non-damaging retinal therapy. The “micropulsed” laser delivers 100 – 300 ms bursts of pulses of 0.1 – 0.3 ms in duration,

with the average power set below the clinically-detectable tissue damage by adjustment of the pulse duty cycle and peak power. Clinical trials have shown that micropulse treatment of DME delivered with high spot density is equally efficient or superior to the standard mETDRS protocol<sup>12</sup>. A smaller clinical trial demonstrated that the micropulse laser treatment reduced the subretinal fluid and improved visual acuity in patients with CSR, compared to the untreated control group<sup>13</sup>. However, the lack of a well-defined titration procedure is reflected in the variable results of these studies<sup>14-17</sup>. In addition, high density coverage of the macula with relatively small spots and long pulses requires lengthy treatment, which is difficult to perform without a scanner. Moreover, if laser settings are too low, the treatment will be not only sub-visible, but also sub-therapeutic, while if the settings are too high, there is a danger of excessive damage to the retina, especially with the nearly-confluent coverage close to the fovea.

For this purpose, a titration protocol was developed for adjustment of the laser power and duration, based on a retinal thermal model<sup>18,19</sup>. This protocol, called EndPoint Management (EpM), ties sub-visible tissue effects to a visible titration point (Figure 1). For pulse durations exceeding 50  $\mu$ s, thermal denaturation is the primary mechanism of cellular damage<sup>20-22</sup>. In this regime the damage can be described with a first-order reaction kinetics (Arrhenius law) parameterized by an activation energy, corresponding to the denaturation of a single critical component, and assuming an absence of cellular repair during hyperthermia<sup>21</sup>.

Experiments with heat shock protein expression following non-damaging retinal exposures in mouse<sup>22</sup>, as well as a computational analysis of the clinical laser settings indicated that non-destructive thermal therapy corresponds to Arrhenius values within the range of approximately  $0.1 < \Omega < 1$ <sup>23</sup>. In this regime the RPE cells survive the hyperthermia, and respond to the thermal stress by expression of the heat shock proteins. Visible lesions produced at higher laser settings result in lethal damage to RPE and photoreceptors, and have calculated values of  $\Omega \gg 1$ , with the relevant range of  $\Omega$  for retinal thermal therapy spanning several orders of magnitude. The EpM algorithm maps a range of calculated Arrhenius integral values to linear steps in pulse energy, normalized to a titration dose specified at a particular duration<sup>24</sup>. This protocol was calibrated in rabbits using OCT, fluorescein angiography, light microscopy, transmission and scanning electron microscopy<sup>18</sup>.

Significant advantages of the non-damaging retinal phototherapy include the absence of scotomata and scarring, the ability to treat foveal areas, as well as improved preservation of color vision and contrast sensitivity<sup>25</sup>. The lack of chorioretinal damage permits high-density coverage, which greatly improves therapeutic outcomes, compared to conventional sparse laser treatment protocols in the macula<sup>12</sup>. Nearly confluent laser applications could be rapidly delivered over the entire edematous areas, if short pulse treatment and pattern scanning are applied. This approach also allows retreatment of the same areas, even in the fovea.

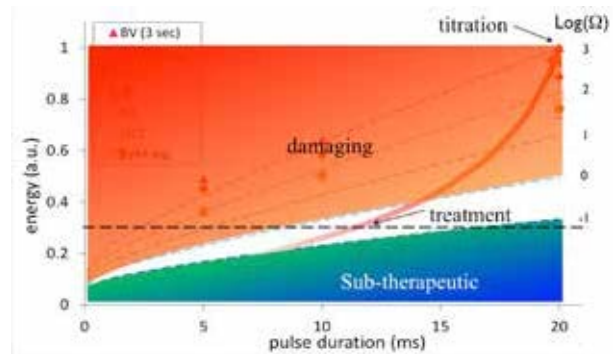


Figure 1. EndPoint Management algorithm relates the titration energy for the barely visible burn (100%) to the treatment energy by adjusting the pulse duration and power. Each iso-Arrhenius line corresponds to retinal lesions of the same clinical grade. RPE response range:  $\Omega > 0.1$ , Damage range:  $\Omega > 1$ . Non-damaging therapeutic window:  $0.1 < \Omega < 1$ .

### INDICATIONS

Macular edema secondary to diabetic retinopathy.  
Chronic central serous chorioretinopathy.  
Macular edema secondary to vein occlusion.

### CONTRAINDICATIONS

Laser should not be applied over areas of hemorrhages or intense pigmentation that could cause photocoagulation of photoreceptors.

### LASER TECHNIQUE (Table 1)

LASER 532 nm (green) or 577 nm (yellow)

#### Titration

Non-damaging retinal laser treatment (NRT) with the EpM algorithm begins with titration of the laser power at 15 ms pulse duration to produce a minimally visible retinal lesion endpoint, which is set as the 100% energy. Since ophthalmoscopic visibility of the lesion increases over time (with lesions initially invisible often becoming visible after several minutes), the lesion appearance should be evaluated at a consistent time-point after laser delivery. For practical usability, an evaluation time-point of 3 seconds was defined for this protocol. For the treatment, laser pulse energy is reduced to a fraction of the titration energy, and the system automatically adjusts the laser power and pulse duration following the EpM line, as shown in Figure 1.

Table 1. Non-damaging photothermal therapy:

	Titration	PTT
Spot size	200 $\mu$ m	200 $\mu$ m
Duration	15 ms	15 ms
Power	Adjusted to barely visible in 3 seconds	Same as titration
Spacing	Single spot	0.25 disc diameter
Energy	100%	30%



### Stage 2 – Treatment (Figure 2)

1. After titration, the pulse energy is set to 30% on EpM scale, and the whole area of retinal thickening, subretinal fluid and RPE changes is treated using patterns with spot spacing of either 0.25 or 0 spot diameters (confluent spots). High density treatment helps maximizing the tissue response.
2. Landmarks (100% energy) could be left on or turned off, depending on physician's preference.
3. For DME, treatment should be performed in the whole posterior pole, including nasal to fovea, except for the foveal exclusion zone of 500 to 250  $\mu\text{m}$  radius.
4. Retreatment can be applied at same area of previous treatments after three months. No need to keep the landmarks in retreatment.

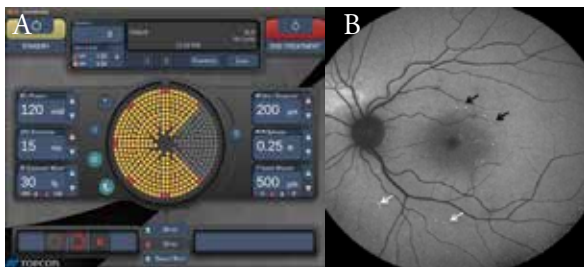


Figure 2. A. Graphic User Interface of the EpM software. Red dots indicate the landmarks (optional). Yellow dots indicate the locations to be treated at 30% energy. B. Fundus autofluorescence (FAF) after photothermal stimulation with landmarks (100% energy) which appear as spots with increased FAF (black arrows). Titration points are also visible in FAF outside the arcades (white arrows). The 30% treatment spots were not visible clinically, by OCT or FAF.

### POST-LASER CARE AND FOLLOW-UP

Patients should be followed closely for evaluation of the potential need of retreatment, which could be performed every three months, in cases of insufficient response or recurrence.

### RESULTS

We conducted an interventional case series to assess safety and initial clinical efficacy of the non-damaging photothermal therapy of the macula for treatment of the CSR. 21 eyes of 20 patients with persistent CSR (longer than 4 months) were treated with the PASCAL Streamline (TMLS, USA) at 577 nm wavelength, using 30% energy and 200  $\mu\text{m}$  retinal spot sizes. On average, 532 spots have been applied per treatment. No visible laser marks could be detected either by clinical observation, OCT, FAF or fluorescein angiography. An average of 12 ETDRS letters gain was achieved by 2 months, and it was sustained during the 12 months follow-up<sup>8</sup>. Central macular thickness decreased from 350  $\mu\text{m}$  to 271  $\mu\text{m}$ , with central maximum thickness reduction of -79  $\mu\text{m}$ . On average, 2.2 treatments per year have been applied to manage recurrent fluid or incomplete resolution. Again, no visible damage to the retina after the retreatments could be seen, but visual acuity and resolution of residual fluid improved. In 81% of the patients fluid was

completely resolved, in 19% resolution was partial, and there were no non-responders to the treatment.

NRT using PASCAL laser with EndPoint Management software at 30% energy was safe, and it improved visual acuity and resolution of subretinal fluid in chronic CSR (Figure 3). Lack of tissue damage allows periodic retreatment without cumulative scarring characteristic to conventional photocoagulation<sup>20</sup>. Endpoint management has also been used to treat diabetic macular edema and yellow 577 nm wavelength Pascal with EpM<sup>®</sup> was found to be safe and effective (Figure 4)<sup>26</sup>.

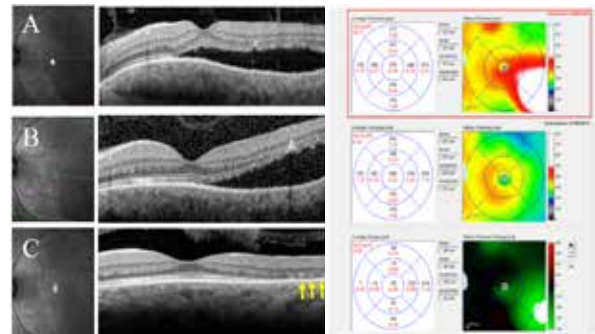


Figure 3. A. Chronic CSR with extensive serous retinal detachment, BCVA 20/25 (B). Re-attachment of the foveal region and improved visual acuity (20/20) one month after treatment. (C) Complete resolution of subretinal fluid with visual acuity of 20/15 two months after treatment. Some discrete irregularities in the RPE and photoreceptors layers are pointed by the yellow arrows. One year after the treatment, patient remains with no fluid and with stable visual acuity of 20/15.

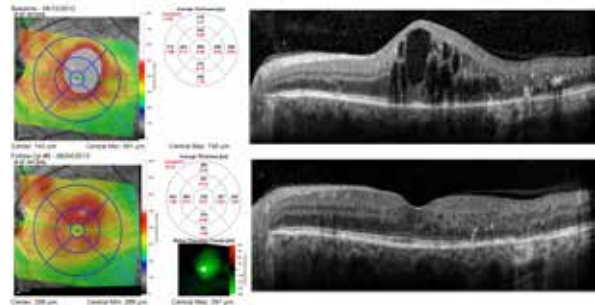


Figure 4. Diabetic macular edema, baseline BCVA 20/80, after four months the NRT treatment BCVA improved to 20/25, with significant decrease of retinal thickness.

### COMPLICATIONS

There are no known complications of non-damaging protocol using Endpoint Management, however, aggressive titration with higher energy could cause photocoagulation of the photoreceptors and therefore induce scotomata, decrease contrast and color vision.

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# VI. LASER action in the human retina

## 38. Micropulse technology

### and concepts



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#### INTRODUCTION

The landmark Early Treatment Diabetic Retinopathy Study (ETDRS) established laser photocoagulation as the conventional treatment for diabetic macular edema (DME). This randomized control trial demonstrated that focal laser photocoagulation reduces the incidence of moderate visual loss from DME by 50% in three years<sup>1</sup>. The laser treatment protocol has been adjusted over the years, and the most commonly used is probably the modified ETDRS focal/grid photocoagulation protocol. However, as our understanding of the workings of laser therapy is advancing, exciting new protocols are now being developed. This chapter will discuss the concept and clinical use of micropulse laser therapy in the context of retinal diseases.

Increasingly, clinical technological development moves from the clinic back to the bench and back to the clinic again. When a technology works, surgeons will use it despite not knowing exactly how it works. Improvement comes when we try to understand the technology and improve on it. There is often resistance to changes as old myths and concepts cloud the judgement. Furthermore, sometimes, clinicians become confused by the technology used for different retinal diseases; the basic mechanism of pathophysiology might be so different, that the same principle might not hold.

#### **DIRECT COAGULATION OF MICROANEURYSMS?**

When laser was first introduced for DME in the ETDRS, we were taught to “shoot at the red dots”. The red dots are microaneurysms, and shooting at them directly suggested that laser worked by direct coagulation. Over the years, physicians noticed that edema would improve even if they missed the microaneurysms.

We now have a better understanding of the absorption

of the laser energy. At the time, with the commonly used argon laser, which has a blue-green wavelength, the majority of the energy is absorbed by the retinal pigment epithelium (RPE). The blood (oxy-hemoglobin) inside the microaneurysms (red dots) is not well absorbed by the laser, and hence the concept of direct coagulation has been brought into doubt.

Furthermore, in clinical studies of treatment trials for DME comparing argon green and krypton red (which are not absorbed by blood). Olk and colleagues<sup>2</sup>, showed no differences in efficacy. Therefore, it is unlikely that direct coagulation is needed for reducing edema, if so the red laser would not have worked, since no direct coagulation of the microaneurysms would be possible.

*So direct coagulation is NOT needed.*

#### **SUBTHRESHOLD CONVENTIONAL LASER SUCH AS ENDPOINT MANAGEMENT**

Bandello and colleagues<sup>3</sup> suggested “light” laser is as effective as “classic” laser treatment. Since we now know that laser scars are not needed, as anti-VEGF does not create any laser scars, yet it is effective in reducing edema in DME, the concept of moving to lighter treatment is not new.

Recently, Endpoint Management<sup>4</sup> proposed that it can reduce collateral damage and can still be effective. The concept is to reduce the energy to just not visible in color photos and mild changes in optical coherent topography (OCT). So far, there is no prospective randomized controlled trial to suggest that it is effective, however, there is a similar study to suggest that it might not be more effective than modified ETDRS laser.

The DRCR.net<sup>5</sup> compared mild macular grid laser (MMG) with modified ETDRS laser treatment, citing the latter as the most commonly used method for performing laser for DME at the time of the study among the network investigators.

MMG burns are located over the entire posterior pole from 500 to 3000  $\mu\text{m}$  from the center of macula, with no burns within 500  $\mu\text{m}$  of the optic disc. The burn intensity of the grid laser is barely visible (light grey); 200 to 300 burns in total are distributed evenly over the treatment area (approx. 2 to 3-burn-widths apart). The MMG burns are lighter and more diffused in nature and are distributed over the whole macula in both areas of thickened and un-thickened retina. Microaneurysms are not directly photocoagulated. In contrast, the modified ETDRS laser comprised of treating only areas of thickened retina (and areas of retinal non-perfusion) and leaking microaneurysms. MMG did not show any superiority over modified ETDRS laser treatment. However, MMG did work in reducing edema.

*So just reducing the power might not be good enough.*

### **SUB-THRESHOLD MICROPULSE LASER**

The concept of micropulse laser is to deliver more energy to the RPE cells without the collateral damage to the neurosensory retina. Laser energy is delivered in pulses of ON and OFF laser period. The OFF period allows the tissue to cool off and hence more energy can be delivered to the targeted tissue (RPE) without heating the surrounding neurosensory retina.

We have published one of the first prospective randomized controlled trials to suggest that micropulse laser is as good as modified ETDRS treatment but with less scarring<sup>6</sup>. Vujosevic and colleagues<sup>7</sup> confirmed our findings but also shown that retinal sensitivity is significantly better in patients treated with micropulse laser. Furthermore, not only the laser scars were not visible on clinical examination, the fundus auto-fluorescence did not change in the micropulse diode laser group even after retreatment. Once we understand that micropulse laser works through activation of the RPE cells and does not cause any visible collateral damage, it seems to make sense to remove the spacing between laser “burns”. This was confirmed in a prospective randomized controlled trial which showed that high density treatment is more effective<sup>8</sup> than low density and modified ETDRS treatment.

*Clinical trial confirmation that micropulse laser works.*

### **RETINAL PIGMENT EPITHELIAL (RPE) CELL DEATH IS NOT NECESSARY FOR EFFICACIOUS LASER THERAPY**

As has been previously mentioned, the mechanism of action of laser therapy in reducing macular edema has long remained unclear. Laser photocoagulation implies the absorption of laser energy by retinal tissue, which is then converted to heat, and produces the characteristic grey burns visible on examination (Figure 1)<sup>9,10</sup>. Most of the laser energy with visible color lasers (green, yellow, red) are absorbed by the RPE cells.

However, several studies have demonstrated that the benefits of laser therapy are due to the healing response triggered in damaged but viable RPE cells at the peripheries of laser burns<sup>9</sup>. RPE cell death may not be necessary for efficacious laser therapy. Sub-lethal thermal injury induces changes in the gene expression of the RPE cell layer, stimulating the expression of molecules and cytokines that

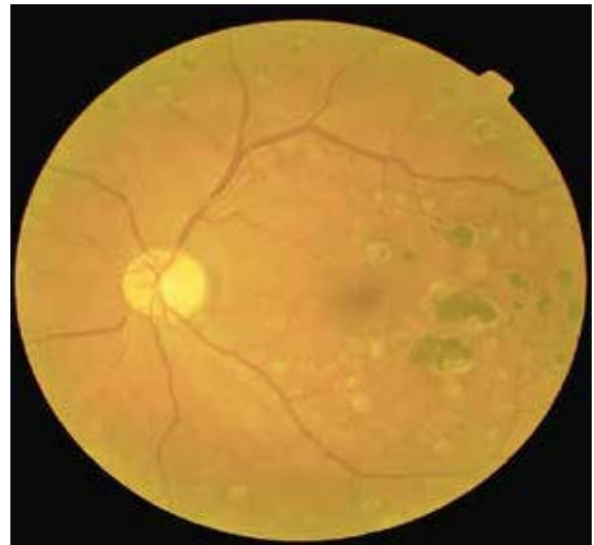


Figure 1. Conventional laser therapy results in characteristic grey scars.

are part of the healing response of the retina<sup>9-19</sup>.

Animal models have revealed that the expression of molecules involved in angiogenesis, is particularly affected by angiogenic factors such as FGF-14, FGF-16, IL-1beta, calcitonin receptor-like regulator (CRLR) and plasminogen activator inhibitor-2 (PAI2) which are down-regulated, whereas the VEGF inhibitor Agr2 (angiotensin II type 2 receptor) is upregulated<sup>20,21</sup>. Similar observations have been made in human cell cultures, with the expression of Pigment Epithelium-Derived Factor (PEDF), a potent anti-angiogenic factor with photoreceptor protective properties, being particularly affected<sup>22</sup>. If cell injury is sufficient in order to activate these pathways, it is therefore not necessary to produce scars with the associated RPE and overlying photoreceptor death, implying changes should be made to the conventional laser treatment protocols.

### **MICROPULSE LASER TECHNOLOGY**

Sub-lethal RPE cell injury with minimal iatrogenic damage to the surrounding tissues can be achieved if laser treatment is delivered in short bursts of energy which are separated by breaks that allow the tissues to cool down (micropulse). This prevents heat dissipation to the surrounding retina as well as to other layers of the retina, thereby reducing collateral iatrogenic damage.

Over the years, the protocol has changed and improved. Typical treatment constitutes 100 pulses of 2 milliseconds (ms), over 200 ms. The total duration of treatment is termed the ‘envelope’, so in this example, it is 200 ms. The ‘duty cycle’ is the total duration of active laser treatment time (ON-time) divided by the total treatment time (envelope time) expressed as a percentage<sup>9</sup>. Hence, if the duty cycle is set to 5%, this implies the laser will be ON for 0.1 ms, then OFF for 1.9 ms.

The duty cycle was reduced from 15% used in earlier studies to the currently recommended 5%. It is believed to be more selective and hence safer, yet it is equally effective. Micropulse technology selectively targets the RPE and leaves

the choriocapillaris and neural retina undamaged. As a result of this lighter treatment, scars are not visible on clinical examination, OCT and fluorescein angiography (Figure 2)<sup>6</sup>.

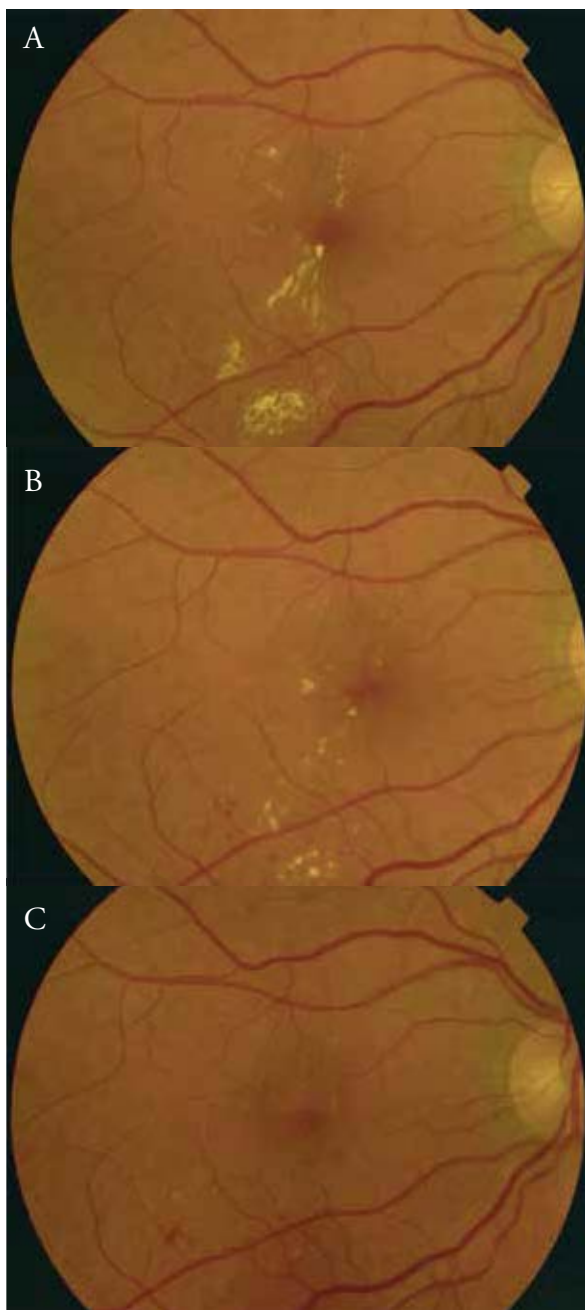


Figure 2. Appearances of the retina before micropulse laser therapy (A), 4 months after treatment (B) and 12 months after treatment (C).

Because no observable burn is produced, it is easy to doubt the efficacy of treatment. However, several studies have now compared micropulse treatment to conventional treatment and demonstrated similar efficacy, with reduced long-term side effects<sup>11</sup>. It is widely known that conventional photocoagulation

induces latent lethal damage and scars expand over time. Spots are therefore spaced out to allow for collateral damage to the area surrounding the initial burn. This is not necessary with the micropulse setting as the purpose of using trains of energy is to allow the cooling of the tissues, thereby avoiding lateral spread of heat. This implies treatment spots can be confluent, generating the idea of high-density treatment.

The therapeutic efficacy of high density treatment has been confirmed in a prospective randomized trial<sup>8</sup>. However, more spots are required to cover the same surface area. Ways to remedy this include using larger spot size, and increasing the speed of the procedure by using a multi-spot laser.

Another difficulty of micropulse treatment of the retina is the lack of visible endpoint and therefore of feedback to help the titration of the power required for the treatment. In the original 810 infrared-laser, there is no visible endpoint even on maximal power on micropulse mode, hence the recently developed yellow micropulse laser has the upper hand.

#### **THE DIODE, GREEN AND YELLOW LASER WAVELENGTHS**

Several laser wavelengths can be used for micropulse laser therapy, including the infrared diode (810 nm), green (532 nm) and yellow (577 nm) laser wavelengths. Whilst micropulse technology was first developed using infrared diode lasers, other wavelengths are now being investigated as each of these has its advantages and disadvantages. This has been discussed in detail in chapter 33.

#### **CLINICAL USE OF MICROPULSE LASER**

In the anti-VEGF era, for most patients with foveal involving DME and visual loss, anti-VEGF is the standard of care. However, for those patients with minimal foveal involving DME with good vision and leakage very close to the fovea, micropulse technology is now a viable option as conventional treatment has unacceptable side effects.

Whilst micropulse laser technology is mostly being used in the context of DME, it has also been investigated in the context of central serous retinopathy<sup>23-26</sup>, macular edema secondary to branch retinal vein occlusion (BRVO)<sup>27</sup>, and even severe non-proliferative diabetic retinopathy (NPDR) and early proliferative diabetic retinopathy (PDR) as well as other macular diseases<sup>28</sup>.

The data on central serous retinopathy is probably the most evidence-based. Multiple studies have shown significant benefit without any visible scarring<sup>23-26</sup>. The role of micropulse laser in patients with macular edema secondary to BRVO<sup>27</sup> in the anti-VEGF era is less certain. It might be able to reduce the treatment burden by reducing the number of injections but the evidence of that is still lacking in any randomized controlled trial. Luttrull and colleagues<sup>28</sup> have suggested micropulse pan-retinal photocoagulation (PRP) can slow progression of diabetic retinopathy but so far no one else has obtained the same result. It might be that we do need to destroy photoreceptors and reduce the oxygen demand in these patients, but the argument for the use of anti-VEGF agents improving retinopathy grade, including reducing diabetic neovascularization, might suggest that



photoreceptor death is not needed. It might be that we need a lot more laser application of micropulse PRP treatment before it would work. One can draw a parallel, when we first moved to short duration multispot laser, such as PASCAL, we had to apply more burns to get the same efficacy. Even if that is the case, the question is whether it would be practical to do, as we might need to perform over 10,000 200 ms micropulse laser applications. A well-designed clinical study might be able to help us to answer that question.

Similarly, Luttrull suggested that micropulse laser can be used to re-vitalize the retina in patients with neovascular age-related macular degeneration (AMD) no longer responding to anti-VEGF therapy<sup>29</sup>, in patients with macular dystrophy and retinal degeneration<sup>30</sup>. There are significant doubts about these claims, but it opens up an exciting research opportunity to further study the technology. For instance, we are now starting a micropulse laser trial to reduce drusen in patients with early AMD, based on the ability of laser to remove drusen with the benefit of the micropulse laser not causing any scarring.

## CONCLUSION

In summary, micropulse laser technology is an evolutionary improvement of the standard photocoagulation protocol aiming at reducing iatrogenic damage to the retina by isolating thermal injury to the RPE. It stems from the observation that retinal cell death (burns) or direct coagulation of microaneurysms is not necessary for efficacy. Indeed, laser treatment achieves efficacy not by destroying the photoreceptor layer as was previously believed, but by stimulating the RPE layer to produce cytokines responsible for the healing response of the retina.

Micropulse technology involves the delivery of short pulses of laser energy, which are interspaced with breaks during which the laser is turned off. This allows the retinal tissues to cool down, therefore isolating the injury to the RPE. Several studies have now demonstrated that micropulse technology has similar efficacy to conventional photocoagulation with reduced side effects. In an era of anti-VEGF treatment, this improvement in laser therapy could be used in different contexts to conventional photocoagulation therapy in DME. Expanding the indications of micropulse laser to other retinal diseases requires more detailed consideration, better understanding of the pathophysiology of diseases, and well-designed clinical trials.

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# VI. LASER action in the human retina

## 39. Retinal LASER

### devices in the market

Multispot laser devices with or without micropulse



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Laser photocoagulation is a proven treatment for retinal pathologies and has been used for more than 60 years to treat a variety of retinopathies. Before the advent of multispot laser systems, surgeons were required to administer a series of single-spot laser burns<sup>1</sup> (Figure 1). When used for grid therapy or panretinal photocoagulation (PRP), which require the delivery of multiple spots, conventional laser treatment is time-consuming and tiring for both patients and surgeons. Furthermore, single-spot treatment is sometimes associated with several side effects (such as irregular spots) and can be painful for patients. The advent of multiple spot lasers, such as the Vitra Multispot (532 nm green Nd:YAG-KTP, Quantel Medical) or the Supra Scan 577 (577 nm yellow multispot or micropulse, Quantel Medical), PASCAL Streamline green or yellow (Topcon Medical Laser Systems), the IRIDEX IQ 577 yellow or green with TXcell scan, the VALON TT/5G, the LUMENIS and the NAVILAS Laser System (OD OS GmbH) (Figures 2 to 6), has changed the face of laser photocoagulation, making it possibly safer, certainly easier and more efficient with respect to the duration of each treatment.



Figure 1. Monospot LASERS on the market - A.R.C. LASER CLASSIC (532 nm); Ellex Integre PROTm (532-670 nm), LIGHTMED LIGHTLas (532 nm).



Figure 2. IRIDEX IQ 577 yellow laser with TXcell scan and pattern delivery system for continuous wave and micropulsed delivery. There is also the same system for green 532 nm and diode 810 nm wavelengths.



Figure 3. Supra Scan 577 (577 nm) yellow laser, Quantel Medical, with pattern and micropulse functionality.



Figure 4. PASCAL Streamline green or yellow laser with pattern and Endpoint Management.



Figure 5. VALON TT/5G laser equipped with multispot scan and pattern delivery system.

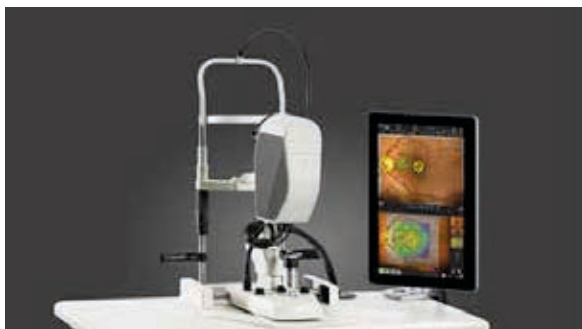


Figure 6. NAVILAS® 577s Laser system equipped with yellow multispot scan and pattern as well as micropulse technology. This system allows one to perform focal laser without a contact lens thanks to its eye-tracking system and the use of infrared light that does not stress the patient's eye. It also captures real-time images of the fundus, including fluorescein angiography, based on which one can program automatic laser delivery. Focal or macular grid laser, as well as panretinal photocoagulation, are possible, as well as registration for future reference<sup>2-5</sup>. There is also available the 532nm green laser.

### WAVELENGTHS CURRENTLY USED IN RETINA TREATMENT

Currently, the photothermal laser most commonly used in Ophthalmology is the Nd: YAG-KTP 532 nm laser (commonly known as KTP laser) which is based on an Nd: YAG 1064 nm laser, near the infrared range. To achieve a beam in the yellow-green range, a nonlinear crystal (Potassium titanyl phosphate -  $\text{KTiOPO}_4$  = KTP or Lithium Triborate frequency upconversion crystal -  $\text{LiB}_3\text{O}_5$  = LBO) is placed at the exit of the beam. This nonlinear crystal halves the wavelength of the laser from 1064 nm to the yellow-green 532 nm wavelength.

Most photothermal lasers currently used in Ophthalmology are pumped by infrared diode laser or laser-diode array and are called DPSS - diode-pumped solid-state laser.

The other wavelength currently used is 577 nm, corresponding to the yellow diode laser, which is increasingly being used in retinal pathology. The diode 810 nm laser is commonly used for PRP and also for macular laser as it can spare the inner retinal layers due to its longer wavelength.

### ADVANTAGES OF MULTISPOT LASERS

Multispot lasers offer a large choice of spot patterns that can be adapted to the type and location of the lesion being treated (i.e. a macular lesion or a peripheral lesion). Personal experience and reports in literature show that multispot treatment is safer and easier to perform than conventional laser treatment<sup>1,6</sup>. A significant advantage of using these lasers is that they reduce the time required for treatment, both by decreasing the number of required sessions and by decreasing the length of each session<sup>6,7</sup>. Furthermore, they cause fewer complications for patients<sup>8</sup>. In terms of duration, multispot treatments take about a third of the time required for conventional laser treatment, produce less scarring, and reduce the occurrence of secondary macular edema, as compared with conventional laser<sup>9</sup>. They are also generally less painful to deliver<sup>10</sup>.

Multispot laser treatment is as effective as conventional laser therapy in treating retinopathy, diabetic neovascularization, and diabetic macular edema (DME)<sup>11</sup>.

The efficacy of multispot lasers can be attributed to several changes that have been made in the treatment parameters for multispot lasers as compared with treatment parameters for conventional lasers. The exposure time to the laser has been reduced and laser power has been increased. The duration of the laser pulse has been reduced from 100 ms to 10 - 20 ms. Once the laser pulse duration is defined, the power of the laser can then be titrated from 200 mW to higher than 600 mW. Decreased duration of exposure and increased laser power result in better localization of the laser to the external retina and a reduction in thermal diffusion, which in turn reduces the amount of associated epithelial scarring, scotoma formation, and inflammation<sup>1,6,9</sup>. Multispot laser is also less painful for the patient, as thermal diffusion in the choroid, where pain receptors reside, is reduced<sup>1</sup>.

Multispot laser allows spots to be delivered almost simultaneously and with greater regularity than conventional treatment. The spots are delivered in a 3x3 or

4x4 matrix, allowing more spots to be delivered in a shorter period of time, thus reducing the total time of treatment. These changes, however, have introduced something new to consider during laser treatment - the determination of threshold power. Because the threshold power depends on the duration of the burns and the location and type of lesion in question, the surgeon must titrate the power during the delivery of the first few spots to achieve the desired effect (see also Chapters 34 and 46).

### MULTISPOT LASER IN PRACTICE

Although the general protocol for multispot treatment is similar for peripheral and macular photocoagulation, treatment parameters are different.

In both peripheral and macular treatment, the first step is to fix the spot diameter. For peripheral treatment, this is usually fixed at 400  $\mu\text{m}$  (200  $\mu\text{m}$  x approximately 2, corresponding to the lens magnification factor). For macular lesions and focal macular edema, this is fixed at 100  $\mu\text{m}$ .

Operators must titrate the threshold power. Threshold power should be a function of the location of treatment and the tissue environment. Focusing the slit lamp is essential for titration; the focus of the slit lamp and the laser should be as similar as possible, in order to precisely administer the laser. The power is then titrated until the desired effect is achieved. This step is arguably the most important.

In PRP, lower power produces smaller laser scars, and slower or less effective regression of neovascularization. The number of spots should be increased and the patient should be followed more closely to retreat if necessary. To achieve regression of neovascularization, 2000 to 6000 spots are generally required.

Too much power can lead to ebullition of water in retinal tissue, originating a disruptive effect. Power should be titrated upwards until tissue blanching is observed; except in the macular area where barely visible spots are preferable. The operator then chooses the pattern, the spacing of the spots (from 0.5  $\mu\text{m}$  to 0.75  $\mu\text{m}$  for peripheral treatment; non-confluent spots for macular edema), and the number of spots.

### THE FUTURE

Multispot laser treatment has had a significant and positive effect on the management of retinal disease. This type of laser delivery is as effective as conventional laser, providing an appropriate treatment intensity, but is better tolerated by patients, produces fewer side effects, and has been shown to be safer<sup>1,2</sup>. It is also more comfortable for the surgeon to perform and reduces the overall duration of treatment.

A number of ongoing clinical studies are investigating the role of tissue-sparing laser treatment for macular pathologies such as DME and central serous chorioretinopathy.

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# VII. Diabetic Retinopathy

## 40. The concept of combined therapy in Diabetic Macular Edema



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### INTRODUCTION

Diabetic macular edema (DME) represents the most important cause of visual loss in diabetic patients<sup>1</sup> and if left untreated > 50% of patients experience a loss of more than two lines of visual acuity (VA) within 2 years<sup>2</sup>.

Laser photocoagulation was considered the standard of care for DME treatment in the past decades, since the ETDRS studies demonstrated that focal/grid laser treatment could reduce the risk of moderate VA loss by about 50%, although only 3% of eyes could achieve vision improvement ( $\geq 3$  lines)<sup>3</sup>. Moreover, laser effects are known to be gradual and a notable number of patients stayed unresponsive to photocoagulation.

The recent advent of a therapeutic approach based on intravitreal injection has completely transformed DME management. In particular, both anti-vascular endothelial growth factor (VEGF) agents and steroid drugs have been shown to be effective in reducing DME and improving VA and in preserving diabetic patients from progression toward more advanced forms of diabetic retinopathy (DR)<sup>4</sup>. When vitreous traction turns out to play a major role in determining DME, surgical approach through pars plana vitrectomy has been as the most useful treatment strategy<sup>5</sup>.

Despite the multitude of different approaches available nowadays for DME, there are still remarkably unmet needs for a universally accepted treatment, which could lead to a sustained functional improvement with a good safety profile, and tolerable burden both for patients and ophthalmologists<sup>6</sup>. Combined treatment may represent an attractive option in order to reduce the global burden of DME both

for patient, and ophthalmologist. Indeed, combined treatments might act synergistically, affecting different pathogenetic pathways at the same time, and resulting in an increase and in a prolonging of their beneficial effects<sup>7</sup>. The aim of this chapter is to review the evidence on the combination of different treatment options for DME, even if a limited number of trials is available offering incomplete and controversial results.

### ANTI-VEGF AND LASER

Ranibizumab, bevacizumab and aflibercept are the most investigated VEGF inhibitors in the most recently published literature. These drugs are usually delivered via intravitreal injection and have a mean duration of action of 4–6 weeks, requiring therefore, frequent monitoring and re-treatment<sup>8</sup>.

Higher frequency of treatments automatically exposes patients to a higher rate of procedure-related side effects (including endophthalmitis, retinal tears, macular holes, and vitreous hemorrhage) and higher systemic exposure to the drug, that may result in decreased retinal perfusion, and higher risk of chorioretinal atrophy and tractional retinal detachment, especially in patients with proliferative DR. Antiangiogenic molecules should be also contraindicated in subjects with high cardiovascular risk and history of thromboembolic events.

To limit both the economical and the medical burden associated with frequent injections, several studies have explored combination regimens featuring macular laser photocoagulation and anti-VEGF drugs in terms of efficacy, safety and number of treatments needed.



### Ranibizumab

The RESTORE<sup>9-11</sup> and the REVEAL<sup>12</sup> multicentre trials have compared 0.5 mg ranibizumab (Lucentis; Genentech USA Inc., San Francisco) monotherapy, laser monotherapy and 0.5 mg ranibizumab + laser combination therapy at 12 months follow-up, demonstrating that combination of ranibizumab with laser is slightly less effective than ranibizumab alone. Moreover, a subgroup analysis from the RESTORE trial indicated that patients with retinal thicknesses >300 µm benefited more from anti-VEGF monotherapy than laser monotherapy or combination treatment, meaning that initial anti-VEGF monotherapy may reduce retinal thickness improving the substrate for subsequent focal laser application<sup>9</sup>.

The READ-2 phase II trial comparing ranibizumab monotherapy, ranibizumab combined with focal/grid laser, and simple focal/grid laser confirmed these results at month 6, showing that patients receiving ranibizumab alone had an average letter gain that was significantly greater (+7.4 letters), when compared to patients receiving either laser therapy alone (-0.5 letter) or combined therapy (+3.8 letters), but not at the 24-months examination (+7.7 for ranibizumab monotherapy, +5.1 for laser, and +6.8 letters for combined therapy) nor at the 36-months examination (+10.3 for ranibizumab monotherapy, +1.4 for laser therapy, and +9.5 letters for combination therapy)<sup>13</sup>. Though there was a substantial decrease of the central retinal thickness (CRT) in the ranibizumab group at 6 months, it increased during further follow-up. In contrast, there was a constant decline in the two other groups during 24 months: this implicates that macular laser photocoagulation helps to reach a sustained decrease in CRT in patients with persistent or recurrent DME. The greater advantage in therapy combining ranibizumab and laser photocoagulation was represented by the reduction of the number of injections when compared to ranibizumab monotherapy.

In a randomized clinical trial conducted by the Diabetic Retinopathy Clinical Research Network (DRCR.net), participants with centre-involving DME were assigned randomly to 0.5 mg ranibizumab combined with prompt or deferred (>24 weeks, if DME persisted or not improved despite injections) focal/grid laser treatment, 4 mg triamcinolone acetonide (IVTA) combined with prompt focal/grid laser treatment, or sham injections with prompt focal/grid laser treatment<sup>14</sup>. Results at 3<sup>15</sup> and 5 years<sup>16</sup> of follow-up suggested that focal/grid laser at the start of the course of intravitreal ranibizumab was not better and possibly worse than deferring laser treatment. A possible explanation for these differences between groups is that potentially destructive effects of the laser treatment are postponed in the deferred laser groups compared to the prompt laser groups.

The DRCR.net recently published short-term results (14 weeks) of a phase III, randomized, multicenter, clinical trial which addressed the effect of ranibizumab or IVTA after macular laser for DME in eyes also receiving photocoagulation (PRP) for DR, a treatment which has been frequently associated with exacerbation of DME<sup>17</sup>. The rationale for this randomization was that laser with IVTA or ranibizumab treatment could result in better

visual acuity and reduced CRT in the short term. The study included 340 eyes with DME and severe nonproliferative DR or proliferative DR. Patients were randomized to receive sham injections or 0.5 mg ranibizumab at baseline and at 4 weeks or 4mg IVTA at baseline and sham injection at 4 weeks. Macular laser was performed within 3 to 10 days, and PRP was initiated immediately or within 14 days from the baseline injection. Mean change in VA letter score from baseline was higher in the ranibizumab and IVTA groups. These two groups also had a greater proportion of eyes which improved by ≥10 letters and a lower proportion of eyes with a worsening ≥10 letters at 14 weeks. CRT changes behaved similarly<sup>17</sup>.

### Bevacizumab

Bevacizumab (Avastin; Genentech, Inc.) is a humanized monoclonal antibody FDA approved for colorectal cancer and used off-label for neovascular or vascular-related afflictions of the eye (including age related macular degeneration (AMD), retinal vein occlusions, and DME). A DRCR.net study<sup>18</sup> and the Pan-American Collaborative Retina Study Group (PACORES)<sup>19</sup> have assessed the effects of 1.25 mg bevacizumab alone or with focal photocoagulation, compared to laser only. The best-corrected VA (BCVA) in the groups receiving bevacizumab showed a greater and more prolonged improvement than in the group receiving only focal photocoagulation at baseline. In the DRCR.net trial, a reduction in CRT was present at 3 weeks in 43% of bevacizumab-treated eyes and in 28% of eyes treated with laser alone, and in 37% and 50% of eyes, respectively, at 6 weeks. No differences were found between the bevacizumab monotherapy and combined therapy groups.

In another study, the combination therapy of bevacizumab and computer-guided navigated laser photocoagulation (Navilas laser, GmbH, Teltow, Germany) was retrospectively investigated in 23 eyes. Patients received monthly bevacizumab injections, followed by navigated laser photocoagulation when CRT was <440 µm. Overall, the results demonstrated a significant VA gain and CRT reduction after bevacizumab treatment, stabilized by navigated laser for up to 12 months<sup>20</sup>.

### Aflibercept

VEGF Trap-Eye or Aflibercept (Eylea, Regeneron/Bayer,) is a 115 kDa recombinant fusion protein of portions of VEGF receptors 1 and 2 fused to the constant region of human IgG1, functioning as a soluble decoy receptor for all VEGF-A isoforms, for which it has a higher affinity when compared to all other anti-VEGF drugs. It has a longer half-life in the eye after intraocular injection and it binds other members of the VEGF family as well, including PDGF1 and PDGF2 (platelet-derived growth factor). It has recently been FDA-approved for AMD patients.

Recently, two similarly designed, double-masked, randomized, phase 3 trials, VISTA and VIVID<sup>21</sup>, made a head-to-head comparison between aflibercept and laser for DME. The 872 eyes with DME included were randomly assigned to either intravitreal aflibercept injection 2 mg every 4 weeks (2q4), to 2 mg aflibercept every 8 weeks after 5 initial monthly doses (2q8), or to

macular laser photocoagulation. At week 52, aflibercept demonstrated significant superiority in functional and anatomic endpoints over laser, with similar efficacy in the 2q4 and 2q8 groups despite the extended dosing interval in the 2q8 group. Overall incidences of ocular and non-ocular adverse events and serious adverse events showed no significant differences between groups. No specific data regarding combination therapy of aflibercept with posterior pole laser is currently available.

### CORTICOSTEROIDS AND LASER

Glucocorticoid steroids are able to down-regulate inflammatory cell activity, in particular that of macrophages, which are proven to play an important role in the macular neovascularization and vascular hyperpermeability typical of DME. The recent availability of steroidal sustained-release implants containing dexamethasone, fluocinolone acetonide, and IVTA has made steroids a valuable treatment option, when combined with laser, to achieve a beneficial long-term effect in DME. However, corticosteroid drugs, even if they require less frequent re-treatments compared to anti-VEGF, are associated with cataract progression and intraocular pressure rise in an elevated number of patients.

#### Triamcinolone acetonide

Many clinical trials have investigated the effects of IVTA alone or combined with laser therapy in DME. Most of the studies have shown positive VA outcomes related to the combination approach when compared to intravitreal monotherapy, suggesting a synergic effect between laser and IVTA. In a study of 86 eyes randomized to 4 mg IVTA alone or followed by macular laser photocoagulation, Kang *et al.*<sup>22</sup> found improvement in the VA and CRT in all groups after 3 weeks, but after 6 months, these results were maintained only in the combined group. In a 2-year study recently reported by Gillies *et al.*<sup>23</sup>, eyes with DME treated with IVTA plus laser were twice as likely as eyes treated with laser alone to achieve at least a 10-letter improvement in BCVA from baseline at year 2.

Lam *et al.*<sup>24</sup> performed a randomized controlled trial of 111 patients with DME randomized to grid laser photocoagulation, 4 mg IVTA, or 4 mg IVTA combined with grid laser done approximately 1 month later. They showed that IVTA combined with laser produced a greater reduction in CRT compared to laser alone. However, there was no significant difference in VA after 6 months.

Pseudophakic patients represent a distinct subgroup of patients for the DME management. The DRICR.net trial has generally shown that 4 mg IVTA + laser was less effective than ranibizumab combined with both deferred and prompt laser over a 3-year follow-up<sup>15</sup>. However, specifically focusing on the pseudophakic eyes, the VA improvement in the triamcinolone + prompt laser group appeared comparable to that in the ranibizumab subgroups. Moreover, a recently published analysis suggests that IVTA and laser may be more cost-effective than ranibizumab + laser in pseudophakic patients with DME<sup>25</sup>.

#### Dexamethasone

Favorable results have been reported also with dexamethasone intravitreal implants (Ozurdex, Allergan,

Irvine, CA) in cohorts of patients with persistent DME. The PLACID study<sup>26</sup>, a randomized, double-masked, sham-controlled, 12-month, phase II trial of dexamethasone implant 0.7 mg in combination with laser in patients with diffuse DME found that dexamethasone + laser therapy produced greater improvements in BCVA, CRT, and capillary leakage than laser therapy alone, although this advantage was not sustained for the full 12 months of the study. BCVA gain with dexamethasone plus laser therapy lasted for 9 months (31.7% vs 17.3% at month 9), while CRT was reduced to a significantly greater extent in the dexamethasone implant plus laser group than in the laser-alone group during the first 4 months. Vascular leakage did show a significantly larger reduction in the dexamethasone implant plus laser group than in the laser-alone group over the full 12 months. The combination of dexamethasone intravitreal implant and laser treatment was well tolerated, and no surgeries were required for elevated intraocular pressure over 12 months.

### SURGERY AND LASER

In patients with DME refractory to pharmacological treatment an abnormal vitreomacular interface can be frequently detected, represented by vitreomacular traction (VMT) or by an epiretinal membrane (ERM)<sup>27</sup>. In these cases, vitrectomy can be performed, especially if other ocular conditions requiring surgery are diagnosed, including non-clearing vitreous hemorrhage, tractional retinal detachment, and combined tractional and rhegmatogenous retinal detachment.

Navarro *et al.* were the first to suggest that vitrectomy may prevent the occurrence of DME<sup>28</sup>. The postulated mechanisms of action of vitrectomy include the removal of possible sources of traction, the improvement of transvitreal oxygenation of the retina; and the removal of the posterior hyaloid and of chemical mediators that promote vascular permeability<sup>29,30</sup>. Although vitrectomy is beneficial in DME refractory to conventional non-surgical therapies, clinical outcomes have revealed a significant decrease in macular thickness, but controversial VA improvement. For example, the DRICR.net examined the role of vitrectomy and membrane peeling in the treatment of DME with a tractional component in a small, prospective cohort study<sup>31</sup>, demonstrating at six months postoperatively, VA improvement by more than 2 lines in 38% of eyes and worsening by 2 lines or more in 22% of eyes, and a mean decrease in CRT of 160  $\mu\text{m}$ , with 43% of patients achieving thickness of less than 250  $\mu\text{m}$ .

Kim *et al.* evaluated the efficacy of vitrectomy combined with IVTA and macular laser photocoagulation for the treatment of nontractional refractory DME in 28 patients<sup>32</sup>. The reduction in central subfoveal thickness was the most remarkable finding of this study at six-months follow-up. The major adverse events after triple therapy were development of nuclear sclerotic cataracts (8 among 12 phakic eyes) and elevation of intraocular pressure (8 among 24 eyes).

Saeed *et al.* compared the safety and efficacy of combined vitrectomy, IVTA, and intravitreal bevacizumab with that of IVTA and intravitreal bevacizumab and subsequent macular grid laser photocoagulation for the treatment

of intractable diffuse DME, favoring the safer, cheaper, and more available line of treatment<sup>33</sup>. IVTA and bevacizumab plus grid laser resulted in a more favorable reduction in central macular thickness and improvement in BCVA at 12 months than vitrectomy combined with the same injections. In fact, mean BCVA was better in the vitrectomy group at 3 months, nearly equal at 6 months, and worse at 12 months ( $P < 0.01$ ), while CRT was more improved in vitrectomy than in intravitreal + laser groups at 3 months, but was better in the intravitreal + laser group at subsequent measurement points, meaning that combined medical therapy could have a favorable long-term outcome. The major adverse events were development of cataract (more common in the vitrectomy group) and elevation of intraocular pressure (more common in the medical therapy plus laser group).

### CONCLUSIONS

DME is a complex multifactorial disease with variable clinical manifestations over the life span of each patient. Thus, it is unlikely that a single treatment will be enough for the entire course of the disease. In addition, the experience obtained from both randomized trials and clinical practice has demonstrated that therapy should be tailored for each specific patient's condition.

Combined treatment and a personalized approach are of the utmost importance for the correct management of DME. Economical and practical issues suggest that laser focal/grid laser photocoagulation will still play a pivotal role in future treatment algorithms. The addition of focal/grid laser treatment could help reduce the number of injections, relieving also the global burden of the disease for our patients.

More studies are needed to clarify the long-term results and the safety profile of combined and personalized approaches.

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# VII. Diabetic Retinopathy

## 41. LASER Treatment

### For Proliferative

### Diabetic Retinopathy



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#### INTRODUCTION

Proliferative diabetic retinopathy (PDR) corresponds to an advanced stage of diabetic retinopathy (DR) in which the ischemia-induced release of angiogenic factors is central to the pathogenesis. One of such factors, vascular endothelial growth factor (VEGF), plays a key role in the angiogenesis and neovascularization process, the hallmark of PDR. Studies have shown that VEGF levels are abnormally elevated in the vitreous and they can also be found in much higher concentrations than those occurring in less severe stages of DR<sup>1</sup>.

New vessels initially appear and develop at the interface between the retina and the posterior hyaloid, especially in areas where vitreoretinal adhesion is stronger, such as in the case of the optic disk (NVD), and elsewhere in the vitreous base and in the major vascular arcades (NVE). The preferential new vessel growth in these areas is probably explained by the greater imposed mechanical traction that stimulates the release of pro-inflammatory mediators. The persistence of this adhesion also contributes decisively to bleeding events that cause vitreous or pre-retinal hemorrhage.

Fibrous and glial proliferation is also very frequent and quite often occupies the area of regressed new vessels. Contraction of this tissue contributes to the development of tangential forces in the superficial retina, which may then lead to tractional retinal detachment<sup>2</sup>.

While new vessels can occasionally undergo spontaneous auto-infarction, most cases require treatment to prevent irreversible and severe vision loss<sup>3</sup>.

Treatment goals in PDR include new vessel regression or, if not attainable, new vessel inactivation<sup>3</sup> through the reduction of the neovascularization area, decrease in the distal lumen, induction of gliosis and absorption of retinal hemorrhages<sup>2</sup>.

#### REASONS FOR THE EFFECTIVENESS OF PANRETINAL PHOTOCOAGULATION IN PDR

Panretinal photocoagulation (PRP) emerged in the seventies and still remains the standard of care for PDR. A growing body of evidence supports that there are multiple mechanisms according to which the photothermal laser tissue interaction produces its effectiveness, as will be listed below:

- Induction of a thermal lesion in the ischemic retina, which is responsible for the production of angiogenic factors, changes growth factor dynamics, decreasing levels of VEGF<sup>4-8</sup>, the major angiogenic factor, while increasing levels of anti-angiogenic factors, such as pigment epithelium-derived factor (PEDF)<sup>9,10</sup>.
- Selective retinal pigment epithelium (RPE) and photoreceptor destruction, responsible for most of the oxygen consumption, increases relative oxygen availability in the oxygen-deprived inner retina, therefore reducing the stimuli for further angiogenic factors production<sup>11</sup>;
- RPE and outer retina destruction also contribute to the thinning of the overall retina by creating pathways through the laser scars for oxygen transport between the choroid and the inner retina<sup>12</sup>;
- Laser induced posterior vitreous detachment (PVD), which occurs in 53% of eyes that have undergone PRP versus 7% in a control group, over a one-year follow-up period, promotes new vessels involution and also lowers vitreous hemorrhage incidence, due to traction in the vitreoretinal interface<sup>13,14</sup>.

#### PRP – THE STANDARD OF CARE IN PDR

Based on the Diabetic Retinopathy Study (DRS) results, at the end of the seventies, PRP rapidly became the standard of care for high-risk PDR, a subgroup for which a reduced risk of severe vision loss by 50% following the



PRP was demonstrated, when compared to untreated eyes, over a two and five-year follow-up period<sup>15</sup>. However, the DRS was inconclusive regarding treatment benefits in the absence of high-risk features or in the presence of associated diabetic macular edema (DME). This gap in knowledge was filled by another landmark study, the Early Treatment Diabetic Retinopathy Study (ETDRS), which showed that eyes with severe non-proliferative diabetic retinopathy (NPDR) or with PDR without high-risk features could benefit from early PRP, particularly in the presence of one or more of the following: type 2 diabetes, pregnancy, loss of vision observed at follow-up appointment/s, prior to cataract surgery and in the patient's remaining eye (when the other eye was lost to PDR)<sup>16-18</sup>.

### PRP IN PDR WITH COEXISTING DME

Both the DRS and the ETDRS revealed that PRP can exacerbate preexisting DME, leading to vision loss<sup>18,19</sup>. Nevertheless, the latter study did establish that in the presence of clinically significant macular edema (CSME) either focal or grid laser photocoagulation, should be carried out prior to PRP. In cases of high-risk PDR, owing to the urgency to initiate treatment, both laser for DME and PRP can be performed in the same session<sup>3,18</sup>.

DME exacerbation after PRP might be explained by oncotic fluid accumulation following tissue destruction or cytokine release with subsequent increase in local vascular permeability<sup>20</sup>. This seems a likely pathway considering the photothermal lesion and subsequent inflammation. It is nonetheless intriguing that the magnitude of this inflammatory process is not nearly as marked as one would expect from PRP. Management of DME might also require the association of corticosteroids, namely those administered through an extended release intravitreal implant.

### PRP PROTOCOL BY THE DRS

The original DRS PRP treatment protocol and recommendations are listed in Table 1<sup>21</sup>:

Table 1. DRS PRP treatment protocol and recommendations

	Argon (currently double frequency Nd:YAG laser 532 nm)
Number of burns	800-1600 (500 μm) or 500-1000 (1000 μm)
Exposure time	0.1 seconds
Spot size	500 or 1000 μm
Power	From 400-700 mW, according to spot size
“Optimal” burn	Power titrated to produce a yellow-white burn
Sessions	1 or 2 sessions
Technique	Area to treat included the whole retina, from the equator to the vascular arcades. This included direct focal treatment of both NVE and NVD

### PRP PROTOCOL ACCORDING TO CURRENT GUIDELINES

Various modifications have been implemented in the PRP protocol since the original DRS recommendations. Current guidelines recommend a different laser type, usually frequency doubled Nd:YAG laser (532 nm), with a smaller exposure time (to reduce pain), enough to produce a “dirty white” burn. PRP burns should be located 500 μm away from the nasal margin of the optic disc margin and at least 2 disc diameters (3000 μm) temporal to, above and below the fovea (Figure 1). Directly targeting new vessels or fibrous proliferations should be avoided, due to an increased associated risk of hemorrhage and tractional retinal detachment<sup>22-24</sup>.

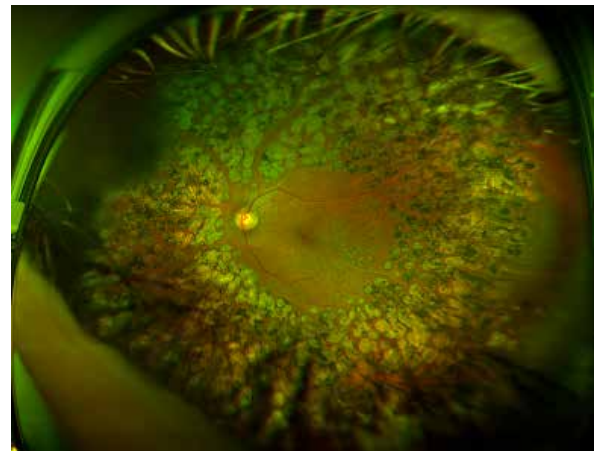


Figure 1. Thirty-eight-year-old female patient who had undergone PRP and vitrectomy four years before due to advanced PDR and pre-retinal hemorrhage in the left eye. Current visual acuity is 80 ETDRS letters.

### MICROPULSED AND MULTISPOT LASER IN PDR

Subthreshold diode micropulse (SDM, 810 nm) laser technology<sup>25</sup> has shown similar effectiveness compared to the conventional argon laser<sup>24</sup>. As previously mentioned, current continuous wave (CW) lasers can operate at a much shorter exposure time (10 ms to 30

ms), significantly reducing pain associated to treatment. Multispot laser delivery systems allow multiple sequential semi-automated burns within a single laser activation, in a previously defined pattern chosen by the operator. This allows faster, more comfortable treatments, not only to the patient but to the laser surgeon as well. Nevertheless, some published results question its effectiveness<sup>26</sup>, reinforcing the need for an optimized protocol, with a larger number of laser spots, to match results in conventional PRP (with exposure times ranging 100 ms)<sup>27</sup>.

### **ENDOPHOTOCOAGULATION AND INDIRECT OPHTHALMOSCOPY**

Laser technological advances have also reached the operation room, by using laser equipped indirect ophthalmoscopes or surgical endo-photocoagulation laser probes which allow intraoperative treatments. Strides have also been made in the development of new PRP lenses, replacing the classical Goldman Three-mirror lens. These new lenses have a bigger field of view and better image quality. Common and currently in use models include the Mainster® 165 PRP, the QuadrAspheric® and Super QuadrAspheric®, as well as many other similarly capable lenses.

### **NUMBER OF SESSIONS REQUIRED FOR COMPLETE PRP**

The “ideal” number of sessions remains a controversial issue. According to the ETDRS, two or more sessions were recommended, though there are ongoing highly disputed debates, nowadays<sup>18,28</sup>. If, on the one hand, fewer sessions allow fewer visits and improved patient compliance, on the other hand, longer sessions lead to decreased patient treatment tolerability. The relation between the number of treatment sessions and the development or exacerbation of DME is another divisive matter<sup>29</sup>. A recent prospective, multicenter, observational and non-randomized study, conducted by the Diabetic Retinopathy Clinical Research Network (DRCR.net), enrolled 155 patients in order to compare the effects of PRP over 1 session versus 4 sessions. While at week 4 of follow-up central macular thickness (CMT) was slightly greater in the 1 session group ( $p = 0.003$ ), at week 34 (primary outcome assessment) this difference had already been reversed, with CMT being slightly greater in the 4 sessions group ( $p = 0.06$ ). A similar trend was found regarding visual acuity<sup>29</sup>.

### **SIDE EFFECTS OF PRP**

Some side effects are associated with PRP, namely pain, impairment of color vision perception and contrast sensitivity, peripheral visual field constriction, DME exacerbation and uveal effusion. Nevertheless, some compromise of the visual function, as a whole, might be a small price to pay in order to avoid impending severe and irreversible visible loss from PDR. Even when adequately performed, PRP does not prevent PDR progression in 4.5% of the cases<sup>18,30–33</sup>. Less intense laser treatments earlier in the disease process and/or supplemented by anti-angiogenic agents might reduce retinal photothermal damage, therefore avoiding, or at least significantly diminishing, the incidence of some of the above mentioned side effects.

### **PERSISTENT OR RECURRENT NEW VESSELS AND IRIS NEOVASCULARIZATION**

While both NVE and NVD usually respond well to PRP, if involution does not follow complete PRP, subsequent “fill in” PRP (placing new laser spots in the untreated retina between previous PRP burns) is warranted<sup>34</sup>. Severe NVE will require retreatment whenever a satisfactory involution has not occurred within one month of treatment. This latter situation might be caused by insufficient previous photocoagulation – over 3000 spots (500  $\mu\text{m}$  in size) might be required in some cases<sup>34</sup>. Directly targeting persistent NVE may be necessary and, in these cases, using a wavelength better absorbed by hemoglobin (yellow 577 nm) with an exposure time equal to, or greater than, 200 ms is recommended<sup>34</sup>. Neovascularization of the iris implies severe retinal ischemia until proven otherwise and demands urgent and complete PRP<sup>34</sup>.

### **PRP IN FIBROSIS, VITREOUS HEMORRHAGE AND TRACTIONAL MACULAR DETACHMENT**

Management of areas of NVE with fibrosis, particularly at the vascular arcades, or NVD with fibrous proliferation, requires taking into account thermal absorption by the fibrovascular tissue and subsequent contraction, which can drag the macula and eventually lead to a macular detachment. Conversely, if the fibrovascular process is not halted, the traction exerted on the new vessels might cause vitreous or pre-retinal hemorrhage. In these cases, current guidelines recommend doing PRP in the more peripheral retina, without directly targeting the fibrovascular proliferations, while also using smaller exposure times (50 ms or less)<sup>34</sup>. By doing so, we can circumvent a complete fibrotic shift in the fibrovascular tissue by the laser and attain a critical balance in order to simultaneously keep tractional forces in check while controlling neovascularization. This will enable a safer vitrectomy and might in some cases even avoid it, fully controlling the fibrovascular process.

While combination therapy with anti-VEGF agents has a growing role in targeting neovascularization, close monitoring is mandated for the worsening of retinal traction. We conducted a study, in which we have shown that the number of laser burns in the peripheral retina was positively correlated to submacular choroidal thickness. Although it was a cross-sectional study design, with its known limitations, we postulated that this increase in the submacular choroidal thickness, after peripheral retina destruction by PRP, might be caused by higher choroidal blood flow in the macular region, contrary to what seems to happen in the more advanced stages of DR<sup>35</sup>.

### **COMBINATION OF PRP AND ANTI-VEGF THERAPY**

New anti-VEGF agents have shown promising results in PDR, demonstrating effectiveness in controlling and inducing involution in new vessels, speeding vitreous hemorrhage absorption, protecting against post-PRP DME, treating neovascular glaucoma and preparing the patient for surgery, if required<sup>36–39</sup>. Despite promising, the above mentioned results stem mostly from small,

single-center studies, lacking the required validation and level of evidence to trigger a paradigm shift in the management of PDR.

As a standalone option anti-VEGF agents will likely be insufficient, due to their short half-life and therefore high recurrence of the neovascular process. Association of PRP might then be indispensable in such strategies, owing to its inherently longer effect.

Our group is coordinating a European multicentric study that aims to compare the safety and effectiveness of combination therapy with PRP and ranibizumab compared to PRP in monotherapy.

## SUMMARY

PRP remains the gold standard for the treatment of PDR. Nevertheless, one must never forget that it has, by design, a destructive and irreversible effect in the mid to far peripheral retina, therefore associated with visual side effects. Fortunately, these are usually minor and do not compromise the patient's quality of life.

Further understanding of disease mechanisms and of the laser tissue interaction, combined with technological advancement, will be of paramount importance in redefining the standard of care in PDR, which will probably shift, in the near future, from isolated PRP to combination therapy in an individualized treatment regimen. Promising strategies include the association of anti-VEGF agents to PRP in order to decrease laser burden, corticosteroids to tackle post-PRP DME (particularly in the single session setting), multispot laser delivery systems with decreased exposure times, photothermal damage, pain and other side effects, and, finally, early (or very early) 25-gauge or 27-gauge vitrectomy.

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# VII. Diabetic Retinopathy

## 42. Photothermal LASER

### in diabetic macular edema treatment



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Diabetic macular edema (DME) is the leading cause of low vision associated with diabetic retinopathy. The Early Treatment Diabetic Retinopathy Study (ETDRS) confirmed, in the 80s, the effectiveness of laser photocoagulation in the treatment of DME (Table 1). This effect was even more significant in the cases of clinically significant DME and when there was involvement or imminent threat to the center of the macula<sup>1</sup>.

Table 1. ETDRS results<sup>1</sup>

ETDRS RESULTS <sup>1</sup>
The ETDRS study reports a 50% reduction in the risk of moderate vision loss (defined as the loss of three or more lines of vision) in patients submitted to (focal or grid) photocoagulation treatment compared to those left untreated (12 % against 24% in three years). However, improvement with respect to VA (gain in 15 or more letters and at least three lines of sight according to the ETDRS scale) was small (<3%).

#### CONVENTIONAL PHOTOCOAGULATION – LASER WITH VISIBLE EFFECT

##### In the past – conventional ETDRS laser in Diabetic Macular Edema

The Early Treatment Diabetic Retinopathy Study<sup>2</sup> (ETDRS) began in December 1979 and encompassed several medical centers. A total of 3711 patients were recruited for a minimum follow-up period of four years. The initial technique (Table 2), required the production of a visible gray-white burn in the macular area, according to the type of treatment carried out<sup>1</sup>.

Table 2. Conventional photocoagulation: initial technique described in the ETDRS study for focal pattern grid macular photocoagulation

The initial technique described in the study ETDRS	
Focal photocoagulation	Grid photocoagulation
The laser should be applied directly to the microaneurysms corresponding to focal points with angiographic leakage; spots from 50 to 100 µm should be used, with an exposure time from 0.05 up to 0.1 seconds and the power adjusted in order to cause the bleaching of the underlying EPR or occasionally making microaneurysms change their color to white or to port-wine, but this process is not mandatory. Start at 100 mW and perform 50 mW increases (the surgeon can power up to 500 mW and 0.2 s pulse duration).	This technique should be carried out in the areas of diffuse leakage and/or non-perfusion in angiography, saving, however, the 500 µm to the central fovea and extending to the temporal side up to 2 papillary diameters. It is recommended to use spots from 50 to 200 µm in diameter, of low intensity, beginning at 100 mW and powering up 50 mW at a time, whenever necessary, to produce a whitish spot in the retina of the treated area, but leaving an equal amount of free space between them.
The treatment of DME diffusion can be combined: focal laser (at the center of the circinate exudates or IRMAs) and pattern grid.	

This conventional technique for macular laser photocoagulation is not risk-free and various side effects associated with this treatment were described over time,



such as foveal burns, central visual field defects, changes in contrast sensitivity, color vision and night vision, retinal fibrosis, choroidal neovascularization and scarring<sup>3-5</sup>. The lack of effectiveness has also often been pointed as an important limitation<sup>5-7</sup>.

### MINIMIZING SIDE EFFECTS AND MACULAR INJURY

In order to mitigate the side effects of conventional laser photocoagulation, described above, significant modifications to the original ETDRS protocol were implemented.

The changes were made in order to apply the laser in such a way that it can act more selectively over the retinal pigment epithelium (RPE), destroying as few photoreceptors as possible, thus obtaining a more tenuous scar, limited to the outer retina (RPE -photoreceptors - outer nuclear layer).

The progressive changes culminated in the **ETDRS modified grid by Lee and Olk (mETDRS)**<sup>5,8</sup> (Table 3).

Table 3. Modified macular grid by Olk and Lee (mETDRS) and Mild Macular Grid (MMG)

- **Macular grid ETDRS modified (mETDRS according to Lee and Olk)**

2 or 3 rows of 100  $\mu\text{m}$  spots applied around the parafoveal region excluding the foveal avascular zone, the spacing should be from 100  $\mu\text{m}$  to 200  $\mu\text{m}$  spots, applying similar treatment to all areas of focal leakage. The spots can be confluent. The objective of the treatment is to get mild to moderate intensity via burn duration of 100ms<sup>5</sup>. Always associate focal laser. Panretinal photocoagulation may or may not be associated<sup>8</sup>.

- **Mild Macular Grid (MMG)**

Spots of 50  $\mu\text{m}$ , applied out of 500  $\mu\text{m}$  from the center of the fovea and also out of 500  $\mu\text{m}$  from the optic disk, 2 to 3 spacing spots apart, applied to all areas of leakage and non-leakage up to a total between 200 and 300 spots. Pulse duration of 50-100 ms. Use the intensity that causes a slightly visible injury (light grey) and do not associate focal laser<sup>9</sup>.

Recently, a new protocol called **Mild Macular Grid**<sup>9</sup> has been proposed, where 50  $\mu\text{m}$  spots, spaced 2 to 3 spots apart, should be applied to all areas of leakage and non-leakage, at a total of 200 to 300 spots with pulse duration between 0.05 s and 0.1 s. Associating focal laser is unwarranted (Table 3).

### DIRECT TREATMENT/MODIFIED ETDRS GRID DRCRNET-2007

After a survey of U.S. ophthalmologists on the type of laser commonly used, the currently designated ETDRS modified grid DRCRnet<sup>9</sup> became adopted (Table 4). This protocol of conventional laser therapy (photocoagulation) in macular area is currently the most used and has been

the treatment arm that serves as a comparison for the clinical trials with anti-VEGF or steroids and the laser used in combination therapy with VEGF (also called "rescue treatment").

Table 4. Modified ETDRS Grid DRCRnet (2007)<sup>9</sup>

#### Direct Treatment/Modified ETDRS grid DRCRNet – 2007

##### Technique

**Direct treatment:** Treat all the microaneurysms in the retinal thickening areas, applying laser spots between 500 and 3000  $\mu\text{m}$  from the center of the macula, directly as in the conventional ETDRS Protocol, not requiring, however, any change in their color. The spots are smaller (50  $\mu\text{m}$ ) and the underlying retinal laser burns, if they exist, should be less intense, being slightly visible and having a slightly greyish tone<sup>9</sup>. The spot duration varies between 0.05 to 0.1 s and laser should not be performed within the 500  $\mu\text{m}$  from the center of the macula.

**Grid:** Applied to all the areas with diffuse leakage or within the areas of non-perfusion, 500 to 3000  $\mu\text{m}$  superiorly, nasally, and inferiorly from the center of the macula, 500 to 3500  $\mu\text{m}$  temporally. Do not apply within 500  $\mu\text{m}$  from the center of the macula. Recommended parameters are a 50  $\mu\text{m}$  spot diameter and 0.05 to 0.1 s spot duration. The power should be titrated to achieve a slightly visible injury (lightly dimmed), with 2 spaces apart between spots; green or yellow wavelengths can be applied.

### LASER PARAMETERS IN THE TREATMENT OF DME AND THE DIFFERENT WAVELENGTHS USED

Retinal laser phototherapy can be performed using radiation of different wavelengths. In the visible spectrum, we have the double frequency YAG laser (532 nm) yellow-green<sup>10</sup>, the krypton yellow (568 nm), the yellow diode (577 nm) and the krypton red (647 nm). In the infrared spectrum, the diode that emits radiation of 810 nm is available and it is more comfortable for the patient due to being invisible. The latter type of laser specifically targets the RPE and the choroid, sparing the neural retina. Approximately 9% of the diode laser energy is absorbed by the RPE and the remainder penetrates into the choroid. Compared to Argon, this amounts to approximately 50% of the energy<sup>11</sup>. The Argon laser (514 nm) and the dye laser (570-630 nm) are currently obsolete. The first one because it proved inefficient and required refrigeration; the latter due to being difficult to operate and having high maintenance costs.

In conventional laser photocoagulation, laser parameters vary between 100 to 200 ms pulse duration, 100 to 500  $\mu\text{m}$  in spot diameter and 100 to 750 mW power. Laser therapy is typically empirical, adjusting the immediate effect on the retina to a greyish-white, or lighter, corresponding to necrosis in the photoreceptors and outer to inner layers of the retina<sup>12</sup>, depending on laser parameters used.

### HOW TO PREVENT INJURY AND ALLOW RETINAL REGENERATION

Current consensus on laser therapy dictates that the smallest energy able to produce a therapeutic effect

should be used. Indeed, it is possible to obtain a therapeutic effect from selective stimulation of the RPE, by using the millipulse and micropulse laser. Several clinical trials have shown the effectiveness of these techniques in various retinal pathologies. In the case of DME, the visual outcomes are equivalent to those obtained by conventional laser, but with less damage to the neural retina, which means better retinal sensitivity measured by visual field tests, contrast sensitivity and microperimetry<sup>13</sup>. The preservation and possible recovery of the photoreceptor layer after this therapy has also been demonstrated in studies with high resolution OCT<sup>14,15,16</sup>.

### THE NEW LASERS - MILLIPULSE LASER AND MICROPULSE LASER

Better understanding of laser in general and of its effect on the retina in particular, culminated in new, more selective, laser techniques (see chapter 35-36).

The new lasers, also called stimulating lasers or the retinal friendly lasers, seem to combine the best of two worlds: efficacy and protection of the retinal tissue.

We will present, in table 5, the possibilities for treatment using the new lasers, invisible or slightly visible lasers. Further details on these techniques are described in other chapters in this manual.

Table 5. Invisible or slightly visible laser in full color retinography – new retinal lasers

Possibilities of treatment using the new lasers, invisible or slightly visible lasers
Light mETDRS <sup>17,18</sup> 50 µm <i>spots</i> , between 50 and 100 ms pulses and low power (from 50 up to 100 mW), causing a barely visible thermal lesion, mainly at the RPE level.
ETDRS 10 ms Grid (10 ms ETDRS) using or not multispot patterns <sup>19,20,21</sup> 100 µm <i>spots</i> , 10ms duration and the power needed, just enough to obtain minimal retinal reflectance modification (120-180 mW) (PASCAL or similar equipment applying or not the multispot functions)
10 ms ETDRS + focal at microaneurysms <sup>20,21</sup> Grid: 10 ms and 100 µm spot diameter and slight increase in power from 50-100 µm spot-size ( focal laser settings)
Micropulsed laser (µPLT) <sup>18,22</sup> High density spot per treated area (HD)
Sandwich µPLT Grid 10 ms ETDRS use up to 500 µm and the HD µPLT within 500 µm <sup>23</sup>
Sandwich µPLT combined with focal laser Parameters of 10 ms to grid 10 ms ETDRS and focal laser <sup>23</sup>
PASCAL with EpM <sup>24</sup> 15 ms, 200 µm, from 100 up to 150 mW to test and 30% EpM

### PHOTOBIOLOGICAL MECHANISMS UNDERLYING THE LASER ACTION ON THE RETINA IN DME

There is growing evidence that there are several photobiological mechanisms underlying the laser action on the retina both in proliferative diabetic retinopathy and DME which explains its effectiveness (see chapter 35). We highlight the following<sup>25,26</sup>(Table 6).

Table 6. Photobiological mechanisms underlying laser action in DME

<b>Photobiological mechanisms underlying laser action in the retina in DME</b>
<p><b>Improvement of internal blood-retinal barrier function</b> Coagulation of diffusion focuses on retinal vascularization achieved by the focal laser.</p>
<p><b>Effect on the external blood-retinal barrier</b> Laser applied to the RPE induces the remodeling or replacement of injured cells with new or neighboring activated cells, leading to improvements in their physiological activity.</p>
<p><b>Better oxygenation</b> When panretinal photocoagulation is associated, the destruction of the peripheral areas of ischemic retina decreases the O<sub>2</sub> consumption by RPE and photoreceptors and reduces the production of mediators responsible for angiogenesis and vascular permeability, such as VEGF. The improvement in oxygenation leads to self-regulatory mechanisms, and as a result of Starling's law, it causes a reduction of vascular caliber in the retinal blood flow, which promotes the reduction in the DME<sup>27</sup>.</p>
<p><b>Other mechanisms most likely responsible for laser action are described in detail in chapters 35 and 36 of the previous section</b> Stimulation of RPE, microglia and astrocytes, endothelial cells renewal by the hematopoietic stem cells (HSC) and the local gene modification leading to a repairing reaction. There is also the acquired knowledge that laser leads to the production of structural and neuroprotective proteins like TULIP-1, crystallins and other heat shock proteins (HSPs), as well as to the production of factors contributing to the balance between VEGF and other pro-edema factors. Laser also upregulates the PEDF (pigment epithelium-derived factor: a neural protector with anti-neovascularization and anti-edema properties) and other anti-edema and anti-neovascularization factors.</p>

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# VII. Diabetic Retinopathy

## 43. Particularities in the Diabetic Macular Edema

### LASER treatment



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For more than three decades, conventional macular laser (ETDRS focal/grid or modified ETDRS Grid) has been the only treatment for diabetic macular edema (DME). During this period ophthalmologists had the opportunity to improve the technique and confirm the initial findings of the Early Treatment Diabetic Retinopathy Study (ETDRS) regarding prevention of vision loss. However, its limitations have also been confirmed, as only 3% of treated subjects report a significant improvement of visual acuity (15 letters)<sup>1</sup>. The treatment protocol has become more or less universal, and the Direct/Grid ETDRS DRCRnet (Diabetic Retinopathy Clinical Research Network) from 2007 has become known as **laser DRCRnet**. Even so, in patients suffering from **diffuse macular edema**, the results are still modest in terms of stabilization or as far as the small gain in vision is concerned. Anti-VEGF monotherapy or combined therapy with focal/grid laser DRCRnet and anti-VEGF or corticosteroids brought further improvements.

**In clinical trials related to the use of anti-VEGF, a significant percentage of patients were treated with combined therapy, including macular laser**

Recent evidence from randomized multicenter studies shows that in diffuse macular edema, intravitreal anti-VEGF agents and slow-release corticosteroids implants lead to a better, faster and more sustained recovery of visual acuity, compared to the laser DRCRnet monotherapy. However, we should not forget that when intravitreal anti-VEGF agents are used as a treatment arm in the literature, laser, either macular and/or panretinal photocoagulation (PRP), is associated, as per protocol, in a significant percentage of cases, ranging from (RIDE/RISE) 21.3% to 40.8% for macular laser and from 0% to 3.2% for PRP<sup>2</sup> (Table 1).

In the DRCRnet Protocol T the percentage of combined therapy with macular laser is 56% with bevacizumab,

Table 1. Long-term outcomes of ranibizumab therapy for DME: the 36-month results from two phase III trials: RISE and RIDE

Percentage of patients that performed combined therapy with laser	Sham/0.5 mg	0.3 mg	0.5 mg	Clinical Trial
Macular laser	72.3	36.8	21.3	RIDE
	74	40.8	37.6	RISE
PRP	13.8	3.2	2.4	RIDE
	12.6	0	2.4	RISE



46% with ranibizumab, and 37% with aflibercept<sup>3</sup>. The percentage of patients who underwent laser combined with VEGF, is high in the group of the low visual acuity, as listed in table 2.

Table 2. Percentage of patients who also underwent macular DRCRnet laser Protocol T<sup>3</sup>

DRCRnet Protocol T <sup>3</sup>	
Center	
≥ 69-78 (20/40)	< 69 (20/50)
Aflibercept - 36%	Aflibercept - 37%
Ranibizumab - 43%	Ranibizumab - 50%
Bevacizumab - 47%	Bevacizumab - 65%

In trials that studied aflibercept (VIVID/VISTA), the percentage of patients who were submitted to combined therapy with laser was lower, ranging from 3.2% in 2q4 of VISTA and 11.1% in 2q8 of VIVID<sup>4</sup>.

The results of the RESTORE study<sup>5,6</sup> and of a recent Canadian study<sup>7</sup> on the use of ranibizumab monotherapy, ranibizumab plus laser or laser monotherapy indicate that the latter has proven to be less efficacious and that the first two options are equivalent in visual outcome. After 3 to 5 years of follow-up, there seems to be a clear reduction of the number of injections required<sup>8,9</sup>. This means that, in the era of intravitreal treatments, macular laser still remains an important weapon in the physicians' armamentarium for the treatment of DME.

### Patients suffering from edema that does not reach the center of the macula were not part of clinical trials with anti-VEGF agents

Cases with edema not reaching the center of the macula were not included in most clinical trials with anti-VEGF agents.

Therefore, it is not possible to draw conclusions about the advantages or disadvantages of the use of anti-VEGF in these situations. However, in the ETDRS study, even the patients suffering from clinically significant diabetic macular edema (CSDME) without involvement of the fovea, benefited from the macular laser treatment. This therapy is therefore recommended for cases of DME which, though not involving the central area, may be a threat to it<sup>10</sup>.

### It is necessary to distinguish between diffuse DME reaching the center of the macula and the other types of macular edema

In focal or multifocal DME, the focal laser photocoagulation is a first-line therapy, provided that:

- the microaneurysms are well identified by angiography;
- the fluorescein leakage points that are detected are not too many and should be more than 500 μm from the center of the macula;
- the eye has not been subjected to previous laser treatment that had an ineffective result.

In diffuse DME, the use of laser photocoagulation in monotherapy, especially if performed with the conventional ETDRS Protocol, is ineffective, because it is associated with worse visual recovery comparing to intravitreal anti-VEGF or corticosteroids monotherapy<sup>6</sup>. Indeed, intravitreal anti-VEGF or corticosteroids should be the first line of therapy. While macular grid laser, per the ETDRS DRCRnet Protocol, is less harmful than the conventional ETDRS laser grid, it should be reserved only in patients resistant to intravitreal agents, as a "sight-saving therapy" in non-responders. Some authors also consider combined use of macular laser with intravitreal therapies right from the start.

### Combined therapy of DME

This topic is further developed in chapter 40. The multifactorial pathophysiology of DME and the multiple cellular and biochemical mechanisms involved confer rationale for combined therapy.

As already mentioned, between 21.3% to 65% of the patients who were enrolled in RIDE/RISE<sup>2</sup> and in the DRCRnet Protocol T underwent combined therapy with laser (ETDRS grid DRCRnet).

Combination therapy with anti-VEGF and macular laser was apparently associated with a reduction in the number of injections required over the long term<sup>8,9</sup>.

In the 3-years extension of the RESTORE trial, a reduction from 6 to 4 injections in patients submitted to ranibizumab plus macular laser was found<sup>6</sup>.

Thus, we can see that laser is still an important adjuvant in DME therapy. However, further studies are needed to clarify the functional benefits of combination therapy<sup>11</sup>.

### The treatment of DME in previously vitrectomized eyes

The treatment of DME in previously vitrectomized eyes should be considered as a special case. The half-life of an anti-VEGF agent in the vitreous of the vitrectomized eyes lasts for only a few hours, so these types of drugs are apparently not indicated for treatment<sup>12</sup>. Postoperative macular laser photocoagulation or possibly slow-release corticosteroids implants will likely be more effective<sup>13</sup>. It is common practice during vitrectomy, in the presence of diffuse macular edema and ischemia of the peripheral retina, to perform PRP therapy, particularly in the extreme periphery.

### SUMMARY

Laser photocoagulation for DME remains an important therapeutic option for the control of the edema and it is expected that new advances in laser technology will allow more effective treatments that are simpler and safer for patients.

Since new intravitreal therapies are invariably more costly for national health systems<sup>14</sup>, in a setting of increasingly

limited resources, one must always bear in mind a careful and individual cost-benefit analysis. It is essential to select the most effective, safest and adequate therapy, while maintaining universal health care coverage affordable - therefore laser will likely keep a very important role in DME.

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# VII. Diabetic Retinopathy

## 44. Diabetic Macular

### Edema treatment –

### new trends



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#### FIGHTING AGAINST A MULTIFACTORIAL DISEASE

Diabetic Macular Edema (DME) is a multifactorial disease where vascular endothelial growth factor (VEGF) is the main factor in increasing vascular permeability since the onset of the disease. However, we have now strong evidence that, at least on the advanced stages and long standing DME, there are a lot of other cytokines involved in the pathologic features of this condition<sup>1</sup>. Inflammation is also a major factor, if not the leading one to maintain a chronic and refractory edema<sup>2,3</sup> (Figure 1). Facing such diverse pathophysiology, a combined regimen of intravitreal agents (anti-VEGF and corticosteroids) and "new lasers" (not the conventional ETDRS protocols) should prove effective by simultaneously targeting multiple points in the disease pathway. Having this into account, we will now present a customized protocol, which comprises the staging of DME and an individually-tailored treatment strategy.

#### CLINICAL STAGING OF DME IS CRUCIAL TO CHOOSE THE CORRECT THERAPEUTIC STRATEGY

DME has a broad clinical presentation, from small exudative microaneurysms associated with focal edema and relatively normal visual acuity until late into the disease to diffuse, chronic and extensive lipid plaques with irreversible microstructural damage and consequent low visual acuity and poor prognosis (Figure 2).

The DRCRnet Protocol T provided some insight by staging DME in two levels based on visual acuity (VA)  $\geq 20/40$  corresponding to ETDRS letter score equal or better 69 letters, and VA  $\leq 20/50$ , ETDRS letter score inferior to 69 letters.

In the latter group, low vision is associated to long lasting

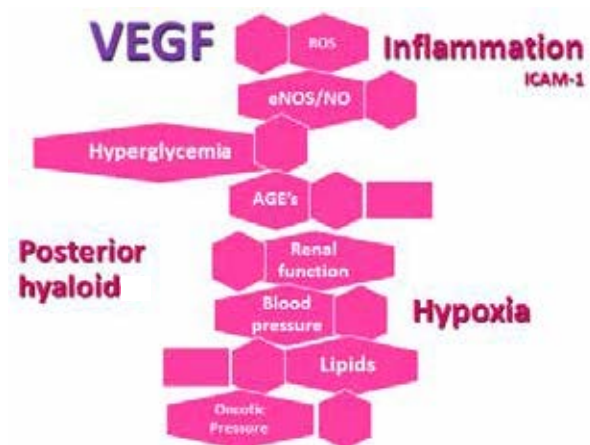


Figure 1. DME is a disease where VEGF is the main factor in increasing vascular permeability, but others, like hypoxia, inflammation and posterior hyaloid traction, also play a role in initiating or maintaining the condition.

edema, permanent structural changes in the retina and an inflammatory component, all contributing to a poor functional outcome. According to these recent findings, it is advisable to split DME patients in two major groups based on visual acuity: better or equal to 20/40 and worse or equal to 20/50. Nonetheless, an ETDRS letter score of 60 letters may be a more realistic split based on real life data.

#### DME LASER TREATMENT: PROMPT VERSUS DEFERRED MACULAR LASER COMBINED WITH ANTI-VEGF – DATA FROM 5 YEARS DRCRnet PROTOCOL I

In Protocol I, DRCRnet assessed the effect of prompt

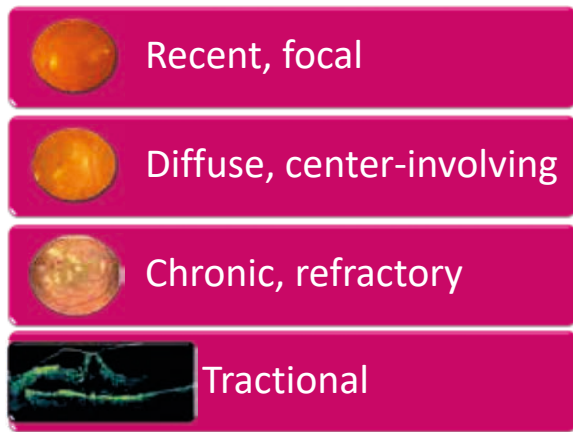


Figure 2. Staging the DME is crucial in planning the therapeutical approach.

macular laser or deferral of macular laser, for at least 6 months, in eyes receiving intravitreal ranibizumab for center-involving DME.

Most eyes treated with ranibizumab and prompt or late laser maintained visual acuity achieved in the first year and obtained a significant reduction of the number of injections in the last 3 years:

- In the subgroup of ranibizumab plus prompt laser treatment, a median of 8, 2, 1, 0 and 0 injections on the 1st, 2nd, 3rd, 4th and 5th year respectively (median of 13 over 5 years) were administered;
- In the subgroup of ranibizumab plus deferred laser treatment, a median of 9, 3, 2, 1 and 0 injections on the 1st, 2nd, 3rd, 4th and 5th year respectively (median of 17 over 5 years) were administered;
- In the deferred group, 44% of patients required macular laser at some point over the 5 year follow-up.

Protocol I also shows that in the group of patients with initial VA ≤ 65 letters that underwent treatment with ranibizumab associated with deferred laser, at 5 years of treatment, a vision gain of 17 letters was obtained<sup>4</sup>.

### Each eye runs on its own lane – analysis of long term results of Protocol I

Recently, Dugel et al<sup>5</sup> presented additional Protocol I results and concluded that the long term (3 years) VA outcome is strongly associated to VA gains, following the initial 3 injections. The visual gain at 3 injections is a strong predictor of response. Therefore, they suggested that alternative therapies should be considered early in the disease course in non-responders after the initial 3 injections.

### TARGETED PERIPHERAL LASER CAN REDUCE NEED FOR ANTI-VEGF INJECTIONS FOR DME

A growing body of evidence supports that identifying peripheral ischemia and treating it with panretinal photocoagulation (PRP) (conventional or milipulse 20-30 ms, with a pattern delivery system like PASCAL) is associated with DME resolution and reduction in the need of anti-VEGF injections over a 3 year period.

Laser therapy can be targeted to these areas rather than to

the entire retinal periphery and less aggressive laser settings can be employed than those used to deliver PRP in the landmark Diabetic Retinopathy Study of the 1980s<sup>6</sup>.

### LASER ADJUNCT TO ANTI-VEGF THERAPY AND CORTICOSTEROIDS – THE LONG-TERM EFFECT

Lasers have a long-term effect on the retina. Binz's studies<sup>7</sup> on the modification of gene expression and protein structure after 90 days of laser, support this notion. In fact, some patients treated with laser photocoagulation, despite poorly controlled diabetes, still maintain a relatively good VA and quiescent diabetic retinopathy for decades. Long-term stabilizing effects of retinal lasers (and possible neuroprotective ones) on visual function, especially in newer, non-destructive, lasers, should be taken into account.

### CLINICAL PRINCIPLES OF LASER USE

A proposed protocol for DME treatment is presented. The photothermal laser has a major role when in the presence of focal DME not involving the center of the macula. Laser in combination therapy also has an important role in the treatment of diffuse DME. Nonetheless, some aspects should be highlighted:

1. Anti-VEGF agents are the first-line therapy in the context of diffuse DME, particularly if VA is poor, as shown by the DRCRnet Protocol T and other clinical trials (RISE, RESOLVE, RESTORE, VIEW/VISTA). In Protocol T, initial results suggested that aflibercept might be superior in the subgroup with initial low VA. However, recent results are not so clear in that regard, since aflibercept and ranibizumab seem to have the same performance at two years in the subgroup with worse baseline VA<sup>8</sup>.
2. Laser photocoagulation as an adjuvant therapy to DME has been applied in clinical trials as a "saving therapy" in non-responders to intravitreal agents<sup>9</sup>. In Protocol T, the association with laser varies between 36 and 65%<sup>10</sup> (Table 1). In other clinical trials, in particular DRCRnet Protocol I and RESTORE laser therapy was also associated. There is evidence that delaying laser at 24 weeks has better results than prompt laser<sup>11</sup>, but if it is deferred to 16 weeks, for example, we do not know if this benefit still exists as clinical practice suggests.

Table 1. Protocol T<sup>11</sup> - percentage of patients who also underwent macular DRCRnet laser

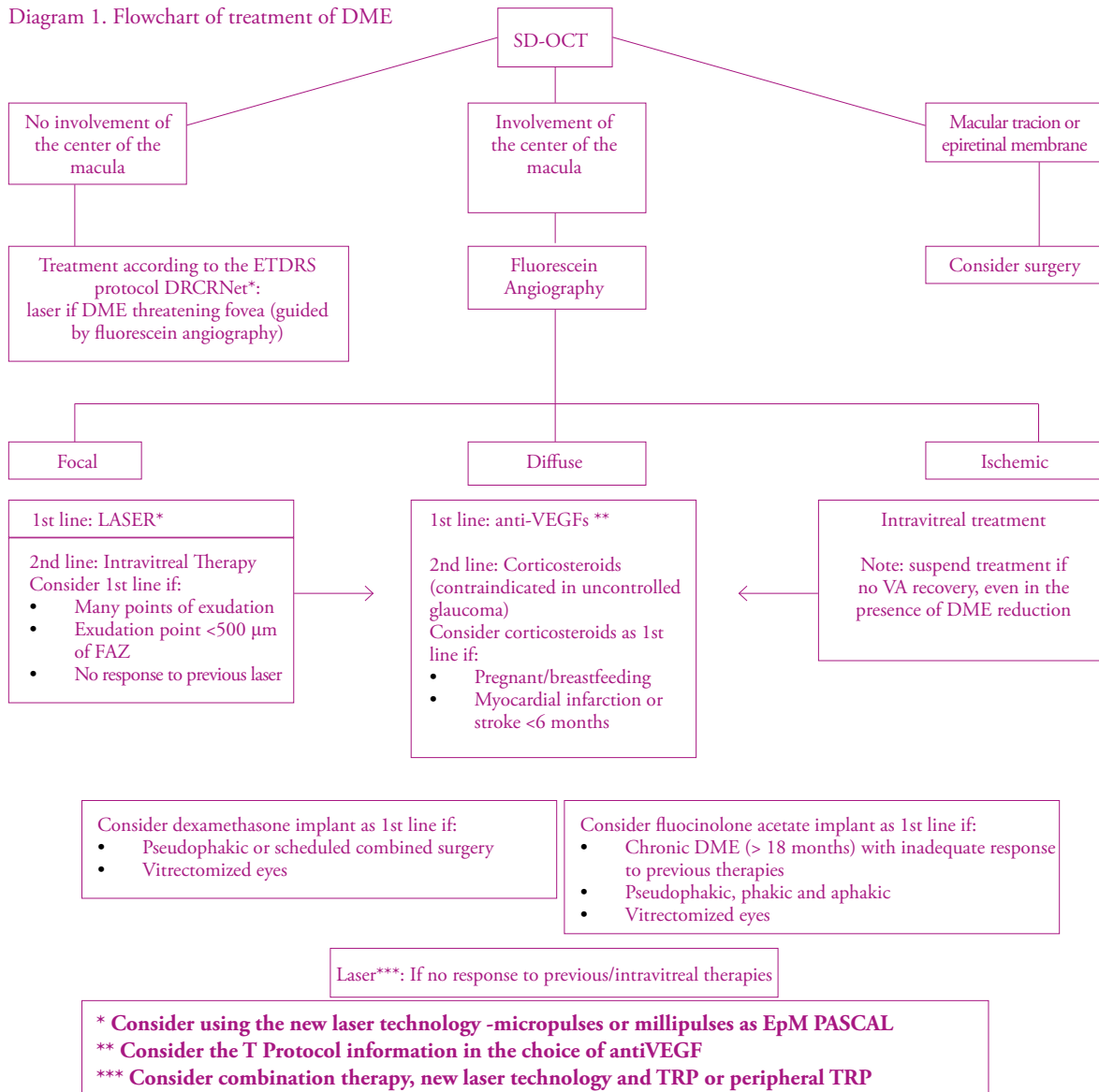
DRCRnet Protocol T <sup>11</sup>	
Cm bined a r	
≥ 69-78(20/40)	< 69 (20/50)
Aflibercept - 36%	Aflibercept - 37%
Ranibizumab - 43%	Ranibizumab - 50%
Bevacizumab - 47%	Bevacizumab - 65%
<b>Injections = 9</b>	<b>Injections = 10</b>

- Results of clinical trials compare anti-VEGF with conventional laser to the retina and not the laser that is proposed today as more retina friendly and indicated for treating macular area in the context of retinal vascular pathology. This way, it can reap the benefits of laser without the injuries that the more aggressive use of laser cause, with good impact on visual function<sup>12,13</sup>.
- Laser is also used in combination to vitrectomy as a therapy of proliferative diabetic retinopathy (PDR) when it is associated with DME. In this case a bigger spot is used (500 μm) and more power is used in performing a PRP<sup>14</sup>.
- Additionally, intravitreal anti-VEGF agents can be used at the time of laser application to reduce the risk of acutely exacerbating DME. The same effect as

- been found by others with intravitreal or sub-tenon corticosteroids<sup>15,16,17</sup>. It may be related to modulation of the repair process and more difficult healing of the retinal injury<sup>18</sup> and decreasing contraction of laser scars.
- Targeted laser photocoagulation of areas of peripheral retinal ischaemia in DME, by reducing vitreous VEGF levels, may lead to a reduction in the number of anti-VEGF intravitreal injections required to stabilise DME.
- Finally, laser (as well as corticosteroids) also has an important role in reducing the number of required anti-VEGF injections<sup>6,19</sup>, thus reducing the burden of treatment and potentially allowing more effective management of DME in a greater proportion of patients<sup>6,15,20</sup>.

### PROTOCOL AND PARAMETERS (DIAGRAM 1)

Diagram 1. Flowchart of treatment of DME





**Insufficient response**

1. Without VA improving.
2. Improvement of VA <5-letters.
3. The same VA with increased DME.
4. Decrease in VA and increase of DME

**Notes:**

- Disperse PanRetinal Photocoagulation (PRP) – perform 2-3 sessions at the periphery and mid periphery, total of 800-1500 spots, 500 µm. Consider in serious and very serious nonproliferative diabetic retinopathy (NPDR).
- Consider as an alternative the full PRP in serious and very serious NPDR<sup>21,22</sup>.
- Full PRP – perform 2-4 sessions to the periphery or mid periphery, about 2000-4000 spots, 500 µm. Consider performing always in presence of proliferative diabetic retinopathy (PDR).
- Consider steroids as first line when: a) pregnancy or breastfeeding; b) high cardio-vascular risk (stroke or acute myocardial infarction <6 meses); c) vitrectomized eyes; d) pseudophakia.
- Consider implant of fluocinolone acetonide: 1. Chronic DME > 18 months; 2. Cases of incomplete response or chronic and persistent DME; 3. Recurrent DME; and 4. Vitrectomized eyes.

We recommend the combined strategy<sup>20</sup>, where the laser has its place. Its great advantage is the reduction of the number of injections required long term<sup>19,23,24</sup>.

In clinical trials when it was considered that anti-VEGF monotherapy was not effective, deferred laser was warranted as per protocol mandatory rescue therapy. Therefore, caution should be taken in the interpretation of clinical trials results, where an apparent treatment arm of anti-VEGF in monotherapy, actually contains a significant proportion of patients performing laser<sup>8,9</sup>, sometimes at the discretion of the investigator.

An insufficient response to anti-VEGF monotherapy treatment after 3 injections, should prompt switch to a combined treatment strategy, namely including laser therapy<sup>5,15</sup>.

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# VII. Diabetic Retinopathy

## 45. Subthreshold

## LASER Therapy:

## Clinical applications



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### INTRODUCTION

Recent advances in laser technology have focused on maximizing the therapeutic benefits of thermal laser while minimizing retinal damage. Conventional laser treatment, as proposed by the Early Treatment Diabetic Retinopathy Study (ETDRS), for the treatment of diabetic macular edema (DME) was associated with a number of significant risks and adverse events, such as severe destruction of retinal photoreceptors, enlargement of laser retinal scars, choroidal neovascularization, subfoveal fibrosis and macular scotomas<sup>1-6</sup>.

Therefore, less aggressive treatment strategies have been proposed. These include the use of barely visible or invisible (subthreshold) laser spots<sup>7-15</sup>. “Light” and “mild” macular laser photocoagulation have shown results comparable to the modified ETDRS protocol in DME<sup>7,8,12</sup>. Although these treatments were aimed to produce ophthalmoscopically barely visible burns at the level of the retinal pigment epithelium (RPE), they were associated with shallow localized visual field losses in the macula, and therefore irreversibly damaged photoreceptors and decreased retinal sensitivity, similarly to the modified ETDRS photocoagulation treatment<sup>7</sup>. In the selective treatment of the RPE, damage is confined to the RPE layer with microsecond-duration pulses and is initially visible in fluorescein angiography (FA)<sup>16</sup>. In this way, there is a theoretical sparing of photoreceptors and of the inner retina. Meanwhile, fundus autofluorescence (FAF) after selective RPE photocoagulation is decreased in the 1st week post treatment, which is followed by increased autofluorescence<sup>17</sup>. In another study, Muqit *et al.* found similar FAF patterns after medium-pulse pattern scanning laser (Pascal) treatment for DME using both ophthalmoscopically invisible or barely visible laser burns<sup>18</sup>. These authors suggested that the evolution of FAF

over time may derive from an increased load of lipofuscin, which results from the coagulated photoreceptors and/or RPE cells<sup>18</sup>. Further evolution of laser treatment has led to the development of subthreshold (invisible) micropulse treatment (MPL)<sup>10,11,13-15,19</sup>. The micropulse mode treatment aims at delivering laser energy in short pulses (“micropulses”) rather than in a continuous way<sup>20</sup>. In this way, in spite of the same laser spot duration, as for example the standard ETDRS (continuous) laser, the micropulse laser using low duty cycle (the frequency of the train of micropulses) and long “off time” between pulses within the exposure envelope (low repetition rate), produces and maintains over time less thermal retinal damage and smaller retinal laser lesions. Moreover, using a longer wavelength (810 nm- infrared wavelength), in the above mentioned micropulse mode, photothermal laser effects can be applied selectively to the RPE (the source of potent extracellular factors), with less or no thermal retinal damage<sup>20,21</sup>. The subthreshold micropulse laser technique is now available also at 577 nm (Y-MPL). Yellow laser is poorly absorbed by the xanthophyll pigment, so it could be used for treatment over the fovea. Being absorbed by both melanin and oxyhemoglobin, 577 nm laser causes less scatter during treatment. Because yellow laser is better absorbed by the RPE and hemoglobin, it can penetrate into the RPE cells adequately to gain a similar effect with less power in comparison to the one used for the 810 nm diode laser (D-MPL), using shorter pulse durations<sup>22</sup>. Thanks to the emerging efficacy and safety of both D-MPL and Y-MPL, the MPL is gaining worldwide adoption, in clinical practice, in different macular diseases<sup>23</sup>.

In this chapter, we will review the most important metabolic effects, clinical safety data and the most frequent clinical applications of MPL.

### METABOLIC EFFECTS AND SAFETY OF SUBTHRESHOLD MICROPULSE LASER

Conventional grid laser causes immediate and permanent damage to the retina and surrounding structures. *In-vivo* studies have demonstrated a loss of the RPE and photoreceptor layers after focal laser treatment, corresponding to the location of visible retinal burns<sup>24</sup>. Damage can be seen in optical coherence tomography (OCT) as ellipsoid disruption and hyper-reflective outer retinal changes consistent with early inflammation and late glial proliferation, and, on FA, as hyper-fluorescent window defects<sup>25</sup>. In contrast, MPL has been shown to treat the RPE selectively without neurosensory or RPE destruction in histopathologic studies<sup>26</sup>. Moreover, *in vivo* no clinically visible retinal damage has been found by means of color fundus photos, FAF, FA, OCT and microperimetry<sup>14</sup>. This laser treatment approach still lacks parameter standardization (especially power and duty-cycle settings), and modality of treatment (confluent or distant spots, foveal treatment versus no treatment). Recently, Luttrull *et al.*, showed that the lowest available duty cycle (5%) in D-MPL is a safe treatment, with a wide therapeutic range as it induces an adequate thermal rise at the level of the RPE cells to stimulate the biological response, while still far below the level expected to produce lethal cell injury, even in dark pigmented eyes<sup>27</sup>. Recently, Y-MPL was compared to D-MPL from both a morphological and functional point of view in patients with DME<sup>28</sup>. **Y-MPL treatment protocol was performed with a 577 nm yellow light (IQ 577 nm Laser System Iridex Corp, California, USA) with the following parameters: 100  $\mu$ m spot size on slit lamp (105  $\mu$ m spot size on the retina), 5% duty cycle of 0.2 sec, 250 mW power, number of spots varying according to the extension of edema. D-MPL treatment was performed with an 810 nm diode laser (Iridex Oculite SLx, Iridex Corp, California, USA) with the following parameters: 125  $\mu$ m spot size on slit lamp (131  $\mu$ m spot size on the retina), 5% duty cycle of 0.2 sec, 750 mW power, and the number of spots varying according to the extension of DME. Spots were delivered in a multiple and continuous fashion (high density treatment), up to the edge of the foveal avascular zone. The results of this study confirmed the safety of both MPL treatments (diode versus yellow laser)<sup>28</sup>. In fact, no laser scars were detected on any retinal imaging modality (color fundus photos, FAF, FFA, spectral domain OCT (SD-OCT)). Additionally, no changes in integrity or reflectivity were detected at the level of the external limiting membrane (ELM), junction of inner and outer photoreceptor segments (IS/OS) or RPE on SD-OCT<sup>28</sup>. Macular laser treatment performed according to the modified ETDRS protocol is able to induce, as early as one day post-treatment, alterations at the level of the outer nuclear layer, photoreceptors and RPE, detectable by SD-OCT<sup>24</sup>. Increased reflectivity of the outer retinal layers was described by SD-OCT after visible and clinically invisible 532 nm macular laser treatment<sup>29</sup>. Luttrull *et al.* showed no visible lesions on time domain OCT after D-MPL<sup>30</sup>. Vujosevic *et al.* showed no visible lesions on both time domain OCT and FAF after D-MPL with 5% duty cycle<sup>14</sup>. In a recent study, no**

detectable retinal lesions were observed after both Y-MPL at 577 nm and D-MPL at 810 nm wavelengths using the lowest duty cycle (5%). In fact, this duty cycle has shown to be the safest one, with a wide therapeutic window and practically no risk in inducing laser burns even in dark pigmented eyes<sup>30</sup>. MPL treatment, in order to be clinically effective, needs to be performed in a contiguous manner, the so called “high density” treatment, thus maximizing the extension of the treated area<sup>15</sup>. This treatment strategy is not associated to an increased risk of retinal laser burns, and can theoretically be performed in the fovea, even though MPL is commonly performed up to the edge of the foveal avascular zone, sparing the center of the fovea.

### SUBTHRESHOLD MICROPULSE LASER IN DIABETIC MACULAR EDEMA

Macular edema is the main cause of visual loss in diabetic patients<sup>31</sup>. Recently, the management of this disease has substantially changed due to advancements in pharmacotherapy<sup>32,33</sup>. However, little has changed in laser treatment since the “gold standard” protocol was proposed by the ETDRS<sup>1</sup>. This treatment consists on visible Endpoint argon laser photocoagulation spots in the macula<sup>1</sup>. The ETDRS demonstrated the efficacy of argon macular laser photocoagulation, in reducing by 50% moderate visual loss in eyes with mild to moderate non-proliferative diabetic retinopathy and clinically significant DME<sup>1</sup>. Traditional theories supported the assumption that laser-induced retinal damage (burning of the retina) was necessary to produce a beneficial therapeutic effect. These include: destruction of diseased retina, increased intraocular oxygen tension and altered production of vasoactive cytokines, including vascular endothelial growth factor (VEGF)<sup>34-37</sup>.

The purpose of the MPL treatment is to avoid any clinically visible damage to the inner or outer retina, thus inducing the stimulation of viable RPE cells<sup>19</sup>. In fact, MPL spares the neurosensory retina and is selectively absorbed by the RPE. However, MPL does not induce the lethal heat build-up within RPE, but rather enhances its therapeutic response<sup>19</sup>. In this way, MPL may induce changes in the expression of multiple cytokines, potent extracellular vasoactive factors produced by the RPE and important mediators of DME<sup>38,39</sup>. In fact, an increased concentration of different cytokines, some of which include: intercellular adhesion molecule (ICAM)-1, interleukin (IL)-1a2, IL-6, IL-8, interferon gamma induced protein (IP)-10, monocyte chemoattractant protein (MCP)-1, VEGF, pigment epithelial-derived factor (PEDF), epidermal growth factor (EGF), human growth factor (HGF), monokine induced by interferon gamma (MIG-1), matrix metalloproteinase 1 (MMP-1), matrix metalloproteinase 9 (MMP-9), plasminogen activator inhibitor 1 (PAI-1), placenta growth factor (PIGF), tissue growth factor beta (TGF), vascular cell adhesion molecule (VCAM), have been found in aqueous humor or in the vitreous of patients with DME<sup>39-41</sup>. Conversely, intravitreal injection of corticosteroids inhibits leukocyte-endothelial cell interactions via downregulation of ICAM-1, IL-6, IP-10, MCP-1, PDGF-AA and VEGF; finally, anti-VEGF agents selectively inhibit only VEGF<sup>39</sup>. Although VEGF



plays an important role in combined angiogenic and inflammatory pathways, selective anti-VEGF treatment will most likely not influence other immunogenic cytokines involved in DME. On the other hand, small physiologic changes in cytokine expression may account for the slower onset and long-lasting benefits observed following all types of laser treatment for DME, as opposed to drug therapy, which usually targets a specific or some few factors for a short period of time<sup>38,39,42,43</sup>. A growing body of evidence has indicated that low-intensity red and near infrared laser promote proliferation of multiple cells, mainly through the activation of mitochondrial respiratory chain and the initiation of cellular signaling<sup>42</sup>. Moreover, D-MPL may cause alteration in the expression of different cytokines produced by the RPE such as VEGF, PEDF, matrix metalloproteinases (MMP)<sup>27</sup>. The advantage of the D-MPL is that, in the absence of laser-induced retinal damage, there is no loss of functional retina which is thus preserved<sup>19</sup>. Finally, high-density MPL treatment, maximizes the therapeutic recruitment of the RPE, as it is contiguously delivered over all the areas of altered retina (“the maximize effective surface area”)<sup>11</sup>. The efficacy of MPL seems to be influenced by the anatomical severity of DME. Recently, in a retrospective pilot study, Mansouri *et al.* detected a significant reduction in central retinal thickness (CRT) and an increased visual acuity in patients with DME and CRT  $\leq 400 \mu\text{m}$  at six months, while no significant changes in CRT or visual acuity were found following treatment with MPL in patients with thicker DME ( $> 400 \mu\text{m}$ )<sup>44</sup>. The exact cause for this lack of response to MPL alone, in patients with severe anatomical disease, is not clear. It is thought that RPE cell stimulation by laser results in the release of cytokines, that decrease the edema and might be responsible for the beneficial effects of MPL<sup>27</sup>.

Severe edema could possibly dilute the concentration of such cytokines or alter the distribution of laser energy throughout the retina and RPE.

Different clinical trials have shown that MPL is an effective treatment option, at least compared with standard macular photocoagulation in DME<sup>1,13,14</sup>. D-MPL has shown to be effective in both DME and macular edema due to retinal vein occlusion<sup>9-15,19,27,45,46</sup>. The 810 nm diode laser is minimally absorbed and scattered by intra-retinal or vitreous hemorrhages, cataracts and even severely edematous retina. Therefore, no significant changes in laser power settings are needed, reducing the risk of error and simplifying the treatment. This has been demonstrated by an increased clinical experience in the use of MPL. Recently, the efficacy of the two different subthreshold micropulse laser wavelengths, the Y-MPL and the infrared MPL - IR-MPL (810 nm), delivered with the same duty cycle, have been evaluated in a prospective, randomized, single institution, comparative 6-month pilot study, for the treatment of mild diabetic macular edema (less than  $400 \mu\text{m}$  in thickness). Both Y-MPL and IR-MPL treatments were performed in a standardized pattern, using in both cases the lowest duty cycle (5%). Even if there was no significant change in best-corrected visual acuity (BCVA), at each follow-up visit, in either the Y-MPL or the D-MPL treatment group at 3 and 6 months, mean central  $4^\circ$  retinal sensitivity, at microperimetry, significantly increased in both treatment groups at 6 months<sup>28</sup>.

Even if its clinical use is still limited, there is evidence that the Y-MPL is as effective and safe as the D-MPL.

In conclusion, subthreshold micropulse laser treatment probably stimulates the metabolic activity of RPE and does not hinder macular sensitivity in patients with center-involving DME (Figure 1).

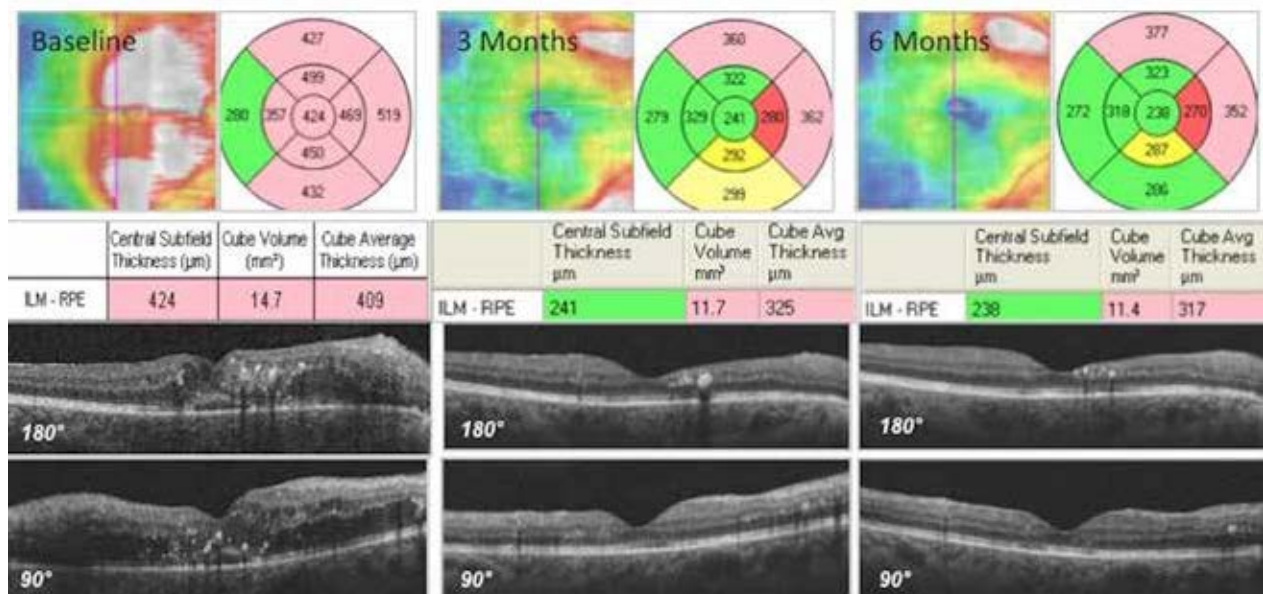


Figure 1. OCT map and linear OCT scans (vertical and horizontal) before (Baseline) and after Yellow MPL in a case of DME. A significant reduction of central macular thickness is detectable at three months after treatment (3 months) and the result is maintained during the follow-up (6 months).



The use of MPL in DME has provided a valuable insight into the mechanism of action of retinal laser therapy, demonstrating that a direct closure of microvascular abnormalities with a relatively heavy burn is not necessary to achieve the desired clinical therapeutic endpoint. **A low energy, micropulse mode, with a low duty-cycle is a novel laser treatment modality that combines clinical efficacy with practically no risk of iatrogenic side-effects. Its use should be introduced into the routine treatment protocols of DME, as primary treatment in mild DME (<400 µm) or combined with intravitreal injections (both anti-VEGF or corticosteroids) in moderate to severe DME<sup>47</sup>.**

### CONCLUSION

The use of subthreshold micropulse laser in some macular diseases, such as DME, has provided a valuable insight into the mechanism of action of the retinal laser therapy, demonstrating that a direct closure of microvascular abnormalities in DME with a relatively heavy burn, is not necessary to achieve the desired clinical therapeutic endpoint. A low energy, micropulse mode, with a 5% duty-cycle is a novel laser treatment modality that combines clinical efficacy with practically no risk of iatrogenic side-effects.

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# VII. Diabetic Retinopathy

## 46. Targeted Retinal

## Photocoagulation.

## PRP with PASCAL



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### INTRODUCTION

Recently, ultra-wide field angiography has gained prominence in the detection of peripheral retinal ischemia, allowing for "Targeted Retinal Photocoagulation" (TRP) i.e. targeted photocoagulation of areas of peripheral ischemia, as an early treatment modality for Proliferative Diabetic Retinopathy (PDR)<sup>1</sup>. Diabetic Macular Edema (DME) with associated peripheral ischemia, an entity that is to be regarded as a variant of DME, as put into evidence by ultra-wide field angiography<sup>2,3</sup>, may potentially also be treated with TRP.

### TARGETED RETINAL PHOTOCOAGULATION (TRP)

The new ultra-wide field systems, including ultra-wide field angiography, have allowed for better identification of peripheral ischemia. On the other hand, new laser systems with defined patterns and with laser action in the order of tens of milliseconds, have allowed us to achieve a mild photocoagulating effect on the retina with decreased inflammatory effects.

Pattern laser<sup>4</sup> action is based on the release of chemical mediators, more than on the ablation of photoreceptors or creating bridges of oxygen.

Targeting ischemic areas with pattern laser may be an option in patients with severe Non-Proliferative Diabetic

Retinopathy (sNPDR) or non-high-risk PDR, and it may prevent progression towards retinal neovascularization<sup>2,5,6</sup>. In this laser strategy, it will be necessary to increase the number of spots and the area of retinal photocoagulation to achieve effects equivalent to conventional laser<sup>7</sup>.

### TRP FOR SEVERE NON-PROLIFERATIVE DIABETIC RETINOPATHY (sNPDR)

More than half of patients (50.2%) with sNPDR will develop PDR in less than one year and about 1/3 of these (14.6%) will present high-risk PDR at the end of this period. Severe NPDR and non-high-risk PDR may be discussed together, because the Early Treatment Diabetic Retinopathy Study (ETDRS) data shows that they have similar clinical courses as well as analogous recommendations for treatment<sup>4</sup>.

So, although the available evidence does not formally support early panretinal photocoagulation (PRP) in these patients<sup>8</sup>, this approach (or TRP with PASCAL or similar pattern lasers or the micropulse non-ablative laser<sup>1,9</sup>) should be an option for these patients especially in the following cases<sup>1</sup>:

- Patients who will not comply with the follow-up scheme (patients should be monitored at least every 4 months);

- Poor metabolic control;
- Previously performed cataract surgery;
- Partial cataract that will prevent future laser therapy;
- Cataract surgery planned for the near future;
- Pregnancy;
- Fellow eye with PDR;
- Severe arterial hypertension;
- Type 1 diabetes (aggressive and fast evolution).

### TRP FOR VERY SEVERE NON-PROLIFERATIVE DIABETIC RETINOPATHY (vsNPDR) AND PDR

In the case of vsNPDR, 75% of the patients will develop PDR in one year and, at the same time, 45% will develop PDR with high-risk criteria<sup>4</sup>. Therefore, we recommend PRP (4 or 5 sessions, with 500  $\mu\text{m}$  spot diameter in the retina and 400-500 burns), with average intervals of 3 weeks between each session. Alternatively, we may consider performing the treatment in one session. The risk of developing or aggravating macular edema can be reduced if 800 impacts of 500  $\mu\text{m}$  are not exceeded or if PRP is performed with a pattern laser. PASCAL laser, or similar pattern lasers, allows treatment with less retinal injury and lower risk of macular edema in "one single PRP session"<sup>3</sup>, (see below).

In the presence of associated macular edema, we should proceed according to the protocol for DME treatment<sup>1</sup>.

The patient should be reassessed approximately 2-4 months after finishing PRP and, if the DR is inactive and stable, reassessment should then be carried out every 6 months.

### GENERAL CONSIDERATIONS ABOUT ADVANCED RETINAL LASER TECHNOLOGY

#### Different effects between millipulsed and conventional laser

Chappelow *et al.* showed that patients undergoing PRP with short-pulse duration pattern scanning appeared to have more incomplete regression of diabetic retinal neovascularization than patients undergoing conventional longer-pulse duration PRP<sup>10,11</sup>. Calculations performed based on the lesion diameter of shorter-pulse duration laser burns, indicate that to maintain the same total treated area as in 1000 standard burns (100 ms, moderate) with a 400  $\mu\text{m}$  beam, a greater number of 20 ms lesions are required, ranging from 1464 to 1979 for moderate and light intensities, respectively<sup>12</sup>.

In addition to reduced lateral dimensions by shorter-pulse, lighter-intensity burns, there is also a concomitant reduction in damage to the inner retinal layers<sup>13</sup>, less photoreceptor damage and no or minimal building of "oxygen bridges". Consequently, there is less improvement of retinal oxygenation<sup>14</sup> that is likely to be associated with diminished therapeutic effects. Therefore, the decreased efficacy should be considered and the patient followed more frequently for recurrence or incomplete regression of neovascularization.

Nevertheless, the amount of heated tissue and injured retina is lower in the millipulsed pattern lasers but has positive results. The tolerance to inflammation and edema caused by thermal injury is better, allowing the use of increased number of spots without the fear of causing

or aggravating the edema. On the other hand, the short duration of the laser pulse and the moderate spot area (spot diameter of 300  $\mu\text{m}$  or less) results in a small scarred area after two or three months<sup>15</sup>. The advantages of this procedure are the decreased peripheral scotoma and less night and contrast disturbance. Therefore, TRP or Pattern laser PRP are more friendly procedures (Figure 1) that can be performed earlier in the evolution of RD disease.

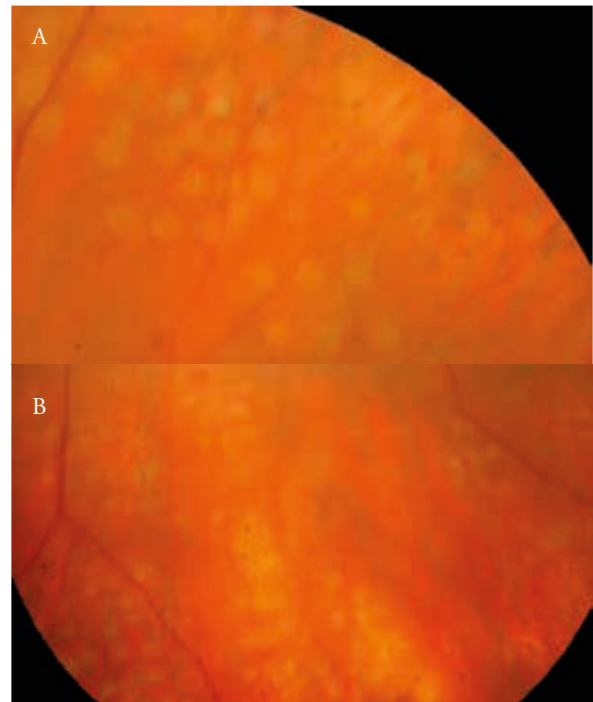


Figure 1. Fresh lesion of Yellow IQ577 Iridex continuous wave, 25 ms, 300 mW, TransEquatorial Volk® lens (x1.44, amplification coefficient) nearly 300  $\mu\text{m}$ . The same parameters were used 2 months before. The healing spot areas are very reduced allowing "normal" retinal tissue between them.

The availability of anti-VEGF agents with the ability to cause temporary involution of residual retinal neovascularization, combined with short-pulse duration therapy, allows for more precise titration of therapy, optimizing the risk-benefit ratio in patients with retinal diseases<sup>13</sup>.

#### Single session PRP

Millipulsed laser cause minor inflammation, edema and pain compared with conventional PRP. Thus, it is advisable to perform pattern PRP in a single session, covering all the periphery and middle periphery with pattern laser spots of about 300 to 400  $\mu\text{m}$ . The number of spots can vary from 1000 to 4000 and, if it is the case of the latter, a nonsteroidal anti-inflammatory drugs (NSAID) and/or sub-Tenon dexamethasone or triamcinolone can be used for preventing macular edema. However, if a treatment dose of say 6000 burns is desired, it is more prudent to perform fewer numbers of burns over more sessions.

#### MULTISPOT PRP - GENERAL RECOMMENDATIONS AND TIPS

For multispot PRP a specific strategy is recommended:



1. Use a widefield laser lens and take into account the amplification factor.
2. Use approximately 300–400  $\mu\text{m}$  spot sizes (200  $\mu\text{m}$  on the slit lamp x 1.44 TransEquator Volk® laser lens or x 1.97 QuadrAspheric Volk® laser lens).
3. Use impulse duration of 20 to 30 ms. (Millipulses of 10 ms duration are more prone to cause Bruch's membrane rupture and bleeding into the vitreous)<sup>5,16</sup>.
4. Choose the pattern; and spacing between spots should be 0.5  $\mu\text{m}$  to 0.75  $\mu\text{m}$  for peripheral treatment. Increasing the spacing of the spots to 0.75  $\mu\text{m}$  allows for better focusing of the beam in the periphery.
5. Titrate the power to achieve the desirable burn intensity. The power is usually titrated upwards until the operator observes tissue bleaching.
6. Treat the retina in 3 concentric zones instead of 5 or 6 radial zones.
7. Consider one single session for sNPDR, vsNPDR or moderate PDR and follow-up closely.
8. In florid PDR in insulin-dependent DM1 patients, do not use multispot and use preferentially a monospot with longer pulse duration (100 ms) to achieve a heavy burn and a scar to enhance the choroid-retinal transmission of oxygen<sup>13</sup>, for a faster effect on neovessels regression.
9. If pain is an issue consider administering NSAID *per os* (ibuprofen or COX2 inhibitors) preferentially 1–2 h before the procedure.
10. Bear in mind: TRP or Pattern PRP, is not as efficacious as conventional PRP. Keep the patient around and follow them up closely.

### LIMITATIONS OF THE PROCEDURE

The management and treatment of patients with retinal disorders with PASCAL or similar pattern laser systems have certain limitations. When a cataract is present a 532 nm laser can suffer significant dispersion. Using a yellow (577 or 568 nm) or an 810 nm diode laser decrease beam diffusion. Using a yellow 577 nm laser and a 2x2 or 3x3 grid can also reduce glare and facilitate patient collaboration. As already mentioned, for PRP, decreasing the power produces smaller scars and causes less regression of neovascularization. A larger number of spots will be necessary to achieve the same efficacy. Somewhere between 2000–6000 burns should be appropriate, and the patient should be monitored more closely to retreat if necessary.

### Vitreous hemorrhage during PRP with multispot laser

Attention to the therapeutic window<sup>16</sup> should be paid, as too much power can lead to a disruptive effect.

If the beam profile is a pronounced Gaussian curve and the spot diameter greater than 200  $\mu\text{m}$ , the use of 10 to 30 ms laser impulse duration can lead to Bruch's membrane rupture and hemorrhage if the window threshold is overridden. This happens because the duration of the laser action does not allow the retinal tissue to cool and the water in the tissue evaporates. Modulation of the laser pulse to a more square profile of the laser beam avoids this problem and makes multispot laser a more secure procedure (see chapter 34).

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# VII. Diabetic Retinopathy

## 47. Endolaser in

# Diabetic Retinopathy



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Diabetic retinopathy (DR) is the most frequent cause of blindness among the active population in developed countries<sup>1,2</sup>. The prevalence of DR increases with the duration of diabetes<sup>3,4</sup>. DR-related complications remain an important problem despite major advances in screening and patient management<sup>5</sup>.

Retinal photocoagulation is one of the main steps to reduce the chances of sight loss, alone or as a co-adjuvant of anti-VEGF<sup>6</sup> or steroid therapy. Panretinal photocoagulation (PRP) is applied to the retina to counteract retinal and iris neovascularization, showing short and long-term efficacy. We know from the barrier theory<sup>7</sup> that removing the vitreous allows for easier diffusion of neovascular factors to the anterior segment, particularly in aphakia. Vitrectomy could be considered a main step in the physiopathology of iris neovascularization. To prevent this, laser acts as an adjuvant treatment in vitreoretinal surgery<sup>8</sup>.

Based on theory, practical experience and clinical trials, we firmly defend the value of PRP in the pre, intra and postoperative phases (Figures 1, 2 and 3)<sup>6</sup>.

### PREOPERATIVE LASER

An important number of eyes with advanced proliferative DR (PDR) can benefit from surgical treatment - *pars plana* vitrectomy (PPV) - and intraoperative photocoagulation<sup>7,9-12</sup>. Endophotocoagulation is done, even in eyes previously treated with panphotocoagulation. The goal is to reduce the neovascular stimulus and minimize or delay recurring hemorrhages<sup>12-15</sup>.

If there is enough eye media transparency, it is important to perform as much laser as possible prior to surgery (Figure 2). It makes surgery safer reducing neovascularization, hemorrhage, hole formation and retinal detachment during surgery<sup>12-14</sup>. Delamination



Figure 1. Right Eye: 36-year-old man. DM1 insulin treated. Vitreous hemorrhage in the previous 6 months having occurred a spontaneous resorption. PDR with fibrovascular membranes over optic disc and temporal superior and inferior arcade where there is a neovascular tuft with a big fibrovascular complex. No previous laser.

of fibrovascular membranes becomes easier, safer and it allows for better visualization and less bleeding when peeling membranes<sup>7,9</sup>. It reduces the length of the total procedure and postoperative bleeding<sup>15</sup>.

Another important adjuvant factor, with a similar effect, is the use of anti-VEGF drugs preoperatively, as they appear to reduce the risk of hemorrhage during PPV

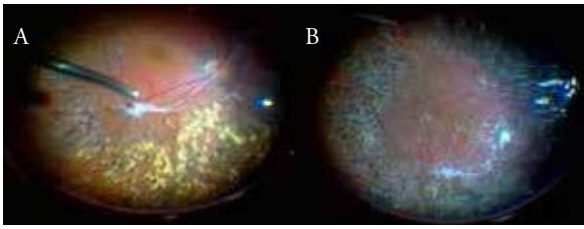


Figure 2. Right Eye: A - Intraoperative image: good preoperative PRP; fibrovascular membranes over the optic disc and the temporal superior (and inferior) arcade, where, before preoperative PRP, there was a neovascular tuft with a big fibrovascular complex; B - View of extensive PRP performed some weeks before surgery (enhanced visualization by triamcinolone).

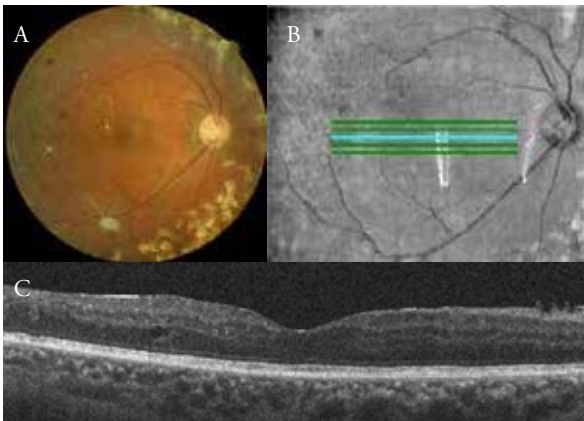


Figure 3. Right Eye: 3 months after vitrectomy using endolaser. Laser complementation in temporal area of the macula: grid pattern displaying very soft laser power. Optical coherence tomography (OCT) two weeks later: no diabetic macular edema and normal morphological structure of the retinal layers. We can see the laser marks on infrared retinography. Visual acuity: 20/32.

(they should be given less than 7 days, ideally 2 days, before PPV to reduce fibrotic shift)<sup>6,13,16</sup>.

Laser treatment, if needed, should be initiated as soon as possible after diagnosis, within a week before surgery. Although preoperative laser can contribute to the fibrotic shift, overall the benefits outweigh this potential hazard in our experience.

### INTRAOPERATIVE LASER

The goal of carrying out endolaser is similar to that of PRP delivered using slit lamp or indirect ophthalmoscopic systems<sup>3</sup>. Endolaser is applied via an optic fiber during PPV, for retinopexy or for retinal ablation in diabetes<sup>17,18</sup>. Endolaser probes are available in several forms: straight or curved, blunt or tapered, simple or aspirating, with or without illumination.

The curved tip is useful for laser on the difficult-to-reach anterior retina. The flexible tip curved laser probe allows even better access to the periphery and pre-equatorial retina, minimizing the need for scleral depression, with less risk of compromising the lens, when treating the opposite side of the eye from the location of the trocar entry. This probe technology is particularly valuable when using wide-field viewing systems. It allows completion of the laser treatment during the surgical procedure.

Care should be taken when applying laser on detached or edematous retina to prevent overtreatment. Obtaining the blanched tissue effect requires higher power in these situations. In the cases of completely regressed neovascularization, endolaser is not required<sup>7</sup>.

Laser-induced thermal tissue necrosis is influenced by three major parameters for each wavelength: power, duration and spot size (the latter controlled by the working distance between the retina surface and the probe tip, and by the angulation of the endolaser tip to the retinal surface).

### Standard settings for Nd:YAG-KTP laser are:

200–300 mW, 100 ms duration, and 100–200 ms interval on repeat mode; continuous burns are used by some surgeons, but there is a risk of an excessive burning while the laser probe changes direction. The power should be adjusted incrementally (30–50 mW steps) until a moderate whitening of retina (light gray-white spot) is achieved<sup>19</sup>. Very intense laser can lead to retinal holes, fibrin syndrome, choroidal effusion or even retinal or choroidal hemorrhage.

Higher power settings, longer duration, decreased distance to the retina surface, less angulation of probe tip, and more pigmentation of tissues result in more intense laser uptake. There is some evidence that short pulse duration high-power laser photocoagulation, during vitrectomy for DR with the power of 340–360 mW and the duration of 20 ms, significantly reduces postoperative inflammation<sup>20</sup>. Laser over blood should be avoided because absorption is higher and can result in inadvertent retinal scarring. It is usually advisable to add a steroid at the end of the intervention to minimize post-laser inflammation, macular edema and the fibrin syndrome (a result of overtreatment)<sup>16</sup>.

### INTRAOPERATIVE SAFETY OF LASER USE

Safety and efficiency must be followed in this order and are not mutually exclusive; on the contrary, they are complementary purposes. There is a risk of serious ocular hazard in this setting not only because we are using class IV lasers, but also because, unlike the laser attached to the slit-lamp, the optic fiber allows laser beams to be focused in all directions, reaching everyone's eyes.

### Laser safety rules should include:

Proper endolaser filter positioning is important to protect the operating surgeon from the laser flash. The assistant surgeon (if the filter is not connected above the observer) and everyone else in the operating room should wear protective goggles with an adequate optical density for the wavelength being used, usually 532 nm<sup>21</sup>.

The laser beam should be activated only when the endolaser probe is located inside the eye and upon the instructions of the operating surgeon; and returned to the stand-by position whenever not in use.

The surgeon is in command of the operation and the nurse staff are co-responsible for the safety of laser use in the operating room.

### POSTOPERATIVE LASER

Follow-up after surgery is essential to determine the need for further laser. This can be done immediately or

delayed in time whenever eye media transparency makes retinal visualization possible (Figure 3). Completing in the posterior areas of the retina having a more accurate visualization and using a slit-lamp is advised.

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# VIII. LASER in Retina/Choroid

## 48. Photocoagulation

### therapy for vascular

### vein occlusion



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Retinal vein occlusion is a common retinal vascular disorder. It can be divided into branch (BRVO)/central retinal vein occlusion (CRVO), and ischemic or non-ischemic types<sup>1,2</sup>. The separation between non-ischemic vs ischemic occlusion is based on the Central Retinal Vein Occlusion Study (CVOS) which defined ischemic CRVO as fluorescein angiographic evidence of more than 10 disc areas of capillary non-perfusion on seven-field fundus fluorescein angiography<sup>1,2</sup>. However, this definition may require updating to be appropriate for the more recently adopted wide-angle imaging and it is also important to note that up to 30% of eyes with initially non-ischemic CRVO may convert to ischemic subtype<sup>3-6</sup>. Treatment focuses on eliminating macular edema (the main cause of visual loss), retinal neovascularization, and anterior segment neovascularization. Treatment also involves management of predisposing risk factors, such as diabetes and hypertension. Pharmacologic treatment with intravitreal anti-vascular endothelial growth factor (VEGF) agents (ranibizumab<sup>7-10</sup>, aflibercept<sup>11-16</sup>, bevacizumab<sup>17,18</sup>) is currently first-line therapy for macular edema. Intravitreal glucocorticoid therapy<sup>19,20</sup> is considered an alternative for patients with refractory edema to anti-VEGF monotherapy. Despite the impressive data from many trials, important questions regarding the treatment of retinal vein occlusion remain: the optimal injection frequency of anti-VEGF drugs during the first year and the possible adjuvant role of more precocious and more intense laser PRP or other laser modalities.

#### BRANCH RETINAL VEIN OCCLUSION

Until recently, the standard care for macular edema was grid laser photocoagulation. The Branch Vein Occlusion Study showed that treated eyes were more likely to gain 2 lines of visual acuity (65%) compared with untreated eyes

(37%)<sup>21</sup>. Then the Standard Care vs Corticosteroids for Retinal Vein Occlusion study (SCORE) results supported grid laser as the continued standard care treatment for macular edema<sup>22</sup>. Newer pharmacologic options (ranibizumab<sup>8,10</sup>, aflibercept<sup>14-16</sup>, bevacizumab<sup>17,18</sup>) have improved the management of macular edema secondary to BRVO, and the visual outcomes of these eyes are better than ever, so these drugs have become the gold standard. The recently completed GENEVA trials showed that sustained-release dexamethasone inserts are superior to sham but drug-related adverse events, namely cataracts and glaucoma, frequently limit their use to the second-line therapy<sup>20</sup>. The association of grid laser photocoagulation could reduce the number of injections, although the percentage of patients who were enrolled in the RETAIN trial and received grid laser photocoagulation with resolved versus unresolved edema was 60% and 63%, respectively, and they did not differ significantly in visual and anatomical outcomes or number of needed injections<sup>9</sup>. On the other hand, Campochiaro *et al.*<sup>9</sup> stated that it would be reasonable to consider adjunctive or alternative treatments, like scatter photocoagulation to the ischemic peripheral retina to decrease VEGF and promote resolution of edema. Furthermore, prospective clinical trials will be necessary before passing final judgment on the effect of scatter photocoagulation. One outcome was the RELATE trial that also failed to identify any evidence of long-term benefit from scatter photocoagulation in patients with chronic or recurrent edema resulting from retinal vein occlusion<sup>23</sup>, however, given earlier in the course of retinal vein occlusion, scatter photocoagulation would provide a different outcome<sup>23</sup>. Sector laser photocoagulation is indicated not only for trying control the edema but also for the treatment of disc or retinal neovascularization,



although available evidence suggests that waiting until vitreous hemorrhage occurs before laser treatment does not adversely affect the visual prognosis<sup>24</sup>.

### CENTRAL RETINAL VEIN OCCLUSION

The CVOS failed to indicate benefit from laser grid treatment, although a trend in favour of treatment was observed in younger patients<sup>25</sup>. There is also no evidence to suggest any benefit from a combination of macular grid laser and intravitreal anti-VEGF<sup>9</sup> or steroids. The same lack of evidence exists for scatter photocoagulation in the reduction of the number of anti-VEGF<sup>7</sup> injections<sup>23,26</sup> for controlling macular edema secondary to CRVO.

These unconvincing outcomes for scatter photocoagulation can result from elevated levels of VEGF. This VEGF production is a consequence of insufficient treatment of all the ischemic areas, mainly the most posterior, and is responsible for paramacular vessel leakage<sup>23</sup>. In addition to this, inflammation contributes to the relapse or the continued existence of macular edema<sup>23</sup>. We can also speculate that a more intense scatter photocoagulation to all areas of retinal non-perfusion, outside the temporal arcade vessels, would produce a better outcome. A similar result can be observed in recurrent neovascularization in proliferative diabetic retinopathy where further photocoagulation (sometimes up to 5000 spots) decreases VEGF enough to involute the neovessels.

Another small study of patients with relatively recent onset of CRVO, with the duration of 8 months or less, concluded that scatter photocoagulation to areas of non-perfusion was beneficial, but the study has some drawbacks<sup>27</sup>.

Panretinal photocoagulation (PRP) is used in the treatment of neovascular complications of CRVO, although the incidence of this complication has decreased with the use of anti-VEGF treatment<sup>11-13</sup>. The CVOS provided guidelines for the treatment and follow-up care of patients with CRVO. However, no definite guidelines exist regarding exact indication and timing of PRP. Intravitreal anti-VEGF injections may also be used as adjuvants in PRP<sup>28</sup>.

Nevertheless, current lack of evidence that the usual scatter photocoagulation can provide a good adjuvant to anti-VEGF therapy for the retinal vein occlusion edema, new technologies and strategies should be researched, including new laser modalities.

### MACULAR GRID LASER

#### Indications

Treatment of macular edema secondary to BRVO of a duration of at least three months with visual acuity of 20/40 or worse and without significant macular hemorrhage and with a fluorescein angiogram showing capillary perfusion in the absence of blood involving the fovea.

#### Preparation

Explain the procedure indicating that this therapy may not improve vision.

#### Laser Technique

1. Comfortable sitting of patient.
2. Under topical anesthesia (oxybuprocaine

hydrochloride 0.4%) insert the lens.

3. Provide laser room with dim illumination.
4. Ask the patient to keep steady fixation.
5. Select Area Centralis lens or equivalent.

### Conventional laser - use the modified grid ETDRS 2007 parameters (see chapter 42, table 4)

Parameters: should be about 100 μm size, 0.05-0.1 s duration, and test burn intensity using low-power burns (60 mW), near the temporal arcade, and increase power sufficiently to give light-grey burns (in areas of edema more power will be needed). Apply burns one width apart, over the area of edema. A fluorescein angiography may help to define the area of leakage.

### Micropulse laser and/or PASCAL EpM (see chapters 37, 38 and 45)

Consider the option of using the laser photo-stimulators, like micropulse yellow 577 nm or PASCAL Endpoint Management yellow 577 nm or green 532 nm.

### Sector Scatter Photocoagulation

Consider performing associated sectorial scatter photocoagulation, depending on the affected branch (see below Panretinal Photocoagulation section).

### Complications

With conventional laser grid some complications may arise, including: premacular fibrosis, accidental treatment of the fovea, visual field defects and decrease in retinal sensibility, pigmented epithelium atrophy or hypertrophy in the macular spots with alterations in the outer retinal layers.

### Results

65% of treated eyes gain 2 lines of visual acuity compared with 37% of untreated eyes. Furthermore, 60% of treated eyes are likely to have 20/40 or better vision at 3 year follow-up, compared to 34% of untreated eyes. Overall, mean visual acuity in the treated group was in the 20/40-20/50 range and in the untreated group it was 20/70.

## PANRETINAL PHOTOCOAGULATION

### Indications

Treatment of ischemic complication: rubeosis and retina neovascularization.

### Preparation

Explain the procedure referring to the fact that this therapy may not improve vision.

### Laser Technique

1. Anesthesia - depends on the patient's sensitivity and is usually necessary. Use topical (oxybuprocaine hydrochloride 0.4%); some patients will require peribulbar anesthesia.
2. Comfortable sitting the patient
3. Provide laser room with dim illumination.
4. Ask the patient to keep steady fixation.
5. Choose a Quadrastrophic lens or equivalent.

**Parameters:** should be about 500  $\mu\text{m}$  size, 0.1-0.2 s duration, and power should be sufficient to give medium white burns. Laser spots are applied around the posterior pole, extending anterior to equator, on the ischemic areas. They should be about 1 burn apart and total 1200-2500 spots, depending on the total area of ischemia.

### Complications

Depending on the intensity of laser parameters and user procedure, some complications may arise after PRP treatment, including: choroidal hemorrhage, premacular membrane, accidental burn of the fovea, macular edema, hemorrhage after Bruch's membrane rupture, choroidal effusion, visual field defects and night vision problems. Some of these are very infrequent and go beyond the benefits of laser treatment.

### Results

The CVOS showed that prophylactic PRP did not prevent iris or angle neovascularization, and recommended this procedure to be performed only when active neovascular disease was demonstrable. However a prophylactic PRP is often done, particularly when a close follow-up is not possible or seems unlikely.

### OTHER LASERS

#### Laser-induced chorioretinal anastomosis

Lasers have been used to purposefully create an anastomosis between a retinal vein and the choroidal circulation. The purpose was to allow the drainage of the obstructed vein and therefore preventing further endothelial damage, reducing venous hydrostatic pressure, and reducing ischemia. The Central Retinal Vein Bypass Study was the first randomized controlled study investigating the efficacy of this treatment. They used a custom-built argon like green laser (or Nd:YAG Q-switch laser if the green continuous wave was unsuccessful) with a spot size of 50  $\mu\text{m}$ , 100 ms duration, and power between 350 to 600 mW to apply spots to rupture Bruch's membrane and a superior and an inferior retinal vein within 2-5 disc diameters of the optic nerve. After 18 months, treated eyes had significantly better visual acuity than controls, but 18.2% developed neovascularization at the anastomosis site and required treatment with additional photocoagulation. Problems with this technique are the lack of reliability in creating an anastomosis (most groups report a 30-50% success rate) and its complications, which include tractional retinal detachment and vitreous hemorrhage<sup>28-32</sup>.

#### Pattern scanning lasers

Automated pattern scanning lasers with shorter pulse durations as low as 20 ms and the ability to deliver multiple spots with regular spacing have been recently developed (PASCAL, Topcon Medical Laser Systems or equivalent systems)<sup>33</sup>.

#### Subthreshold micropulse lasers

There is also investigation into the use of subthreshold micropulse 810 nm laser to treat macular edema secondary to BRVO. Preliminary work has shown that it may be as effective as conventional therapy without visible burns,

although this has yet to be tested in a head-to-head randomized comparison to conventional treatment in this condition. Because there is no visible laser burn, it is difficult to titrate treatment with micropulse. Another possible therapeutic option is the PASCAL grid with Endpoint Management where software programs allow for the creation of visible corners in grid treatments. There is no notice of complications in this kind of laser technique<sup>34-38</sup>.

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# VIII. LASER in Retina/Choroid

## 49. Phototherapy

### for AMD



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#### MACULAR PHOTOCOAGULATION STUDY

The Macular Photocoagulation Study (MPS) was initiated in the 1980s and showed that laser photocoagulation was preferable to observation for choroidal neovascularization (CNV). The same study also showed that only a small proportion of patients' eyes with symptomatic age-related macular degeneration (AMD) met MPS eligibility criteria for laser treatment and that even after a successful closure of the CNV there was a high rate of persistent and recurrent leakage. With the advent of anti-vascular endothelial growth factor (VEGF) agents, which not only treat the existing neovascularization but also reduce the risk of developing CNV, laser photocoagulation has a limited role in the management of CNV secondary to AMD.

#### INDICATIONS

Laser photocoagulation remains indicated for the treatment of well-defined extrafoveal CNV. It can be theoretically considered for classic juxtafoveal membranes if the entire neovascular lesion can be treated without damaging the fovea<sup>1,2</sup>.

#### PREPARATION

1. Explain the procedure mentioning the fact that this therapy may not improve vision and may induce a permanent scotoma.
2. Perform a fluorescein angiography 72 to 96 hours before in order to select treatable cases and to guide treatment.
3. Sign informed consent.

#### LASER TECHNIQUE

1. Anesthesia - use topical (oxybuprocaine hydrochloride 0.4%).
2. Parameters: start by surrounding the neovascular

lesion (200  $\mu\text{m}$  of diameter and 0.2 to 0.5 seconds of duration), then cover the central part (200  $\mu\text{m}$  of diameter and 0.2 to 0.5 seconds of duration) and finally the remaining lesion (200 to 500  $\mu\text{m}$  diameter and 0.5 to 1 seconds of duration)<sup>1</sup>.

#### COMPLICATIONS

There are several possible complications including: choroidal hemorrhage, premacular fibroglisis, accidental treatment of the fovea, rupture and atrophy of the pigmented epithelium<sup>2,3</sup>.

#### RESULTS

Macular photocoagulation study group showed an improvement of best-corrected visual acuity with laser therapy for classic extrafoveal CNV with a mean long-term vision of 20/125 versus 20/200 in non treated eyes. An 8.1% improvement in quality of life was also documented. The benefits were greater during the first year following treatment and persisted for 5 years<sup>4-6</sup>.

#### OTHER LASER STUDIES FOR AMD

##### ATROPHIC AMD

So far there is no approved treatment for geographic atrophy related to AMD. Studies have been conducted to investigate if slowing down or stopping progression of atrophy could be achieved by means of stimulation of the retinal pigment epithelium (RPE). Laser treatment with selective retinal therapy was used, because its energy was mostly confined to the RPE, resulting in less primary damage when comparing to the traditional retinal photocoagulation. However this therapy has not proved successful with enlargement of the atrophic area being greater in treated than in non-treated eyes<sup>7</sup>. Nevertheless, it is possible that a different treatment



strategy (like a non-thermal laser) could play a role in the treatment of atrophic AMD.

#### EARLY AMD

Retinal drusen, especially large drusen, are associated with a higher risk of developing CNV<sup>8-13</sup>. Also, because laser photocoagulation can lead to their disappearance, many studies have been carried out to evaluate the effectiveness and adverse effects of this therapy<sup>14-27</sup>. Although laser could treat drusen, this therapy was not associated with a reduction in the risk of developing CNV, geographic atrophy or visual loss<sup>28</sup>.

Recently there have been important developments in laser technology. Micropulse laser technology uses microsecond pulses of energy (duty cycle) separated by larger periods of tissue cooling (laser off), causing non-thermal damage of the overlying photoreceptor. The nanosecond laser, a non-thermal laser therapy, uses energy that stimulates the RPE and Bruch's membrane without causing collateral damage to the overlying photoreceptor layer. A very promising recent study showed negligible retinal damage and cellular inflammatory response, namely less stimulation of inflammatory cytokines, increase of the heat shock proteins and endogenous trophic factors as well as modification in the matrix metalloproteinases activity. Ongoing trials will study laser intervention in early AMD to determine whether nanosecond laser therapy is able to slow down the progression to advanced AMD<sup>29-31</sup>.

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# VIII. LASER in Retina/Choroid

## 50. Photodynamic

## Therapy



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### INTRODUCTION

Photodynamic therapy (PDT) is not a new technique. However, its interest increased with the appearance of newer photosensitizing agents.

The first description of the use of an exogenous photosensitizer goes back 1500 years, when Psoralen was used to treat vitiligo<sup>1</sup>. Since then, PDT has been used to treat several conditions, including malignancies and skin diseases. In Ophthalmology, PDT was approved in 2000 as an alternative treatment for patients with exudative age macular degeneration (AMD), particularly when laser photocoagulation is not indicated.

With the emergence of antiangiogenic therapies, PDT is used less frequently. However, it remains useful in particular situations, such as in patients with systemic or ocular contraindications regarding intravitreal administration of antiangiogenic drugs or as an adjuvant, in combination with other drugs, and in the treatment of polypoidal choroidal vasculopathy (PCV). PDT is also an important treatment option in central serous chorioretinopathy (CSC) and some chorioretinal tumors<sup>2,3</sup>.

### MECHANISM OF ACTION

PDT requires intravenous administration of photosensitizing agents, which localize the target tissue. Subsequently, light irradiation of the tissue elevates the photosensitizer from the electronic ground state to a higher level. The excited photosensitizer quickly returns to the ground state and transfers energy to other molecules<sup>4,5</sup>. Although the exact mechanisms that induce tissue destruction are not known, cellular, vascular and immune mechanisms have been suggested as possibilities<sup>5,6</sup>.

The cellular mechanism is based on the cytotoxic effects of free radicals on mitochondria, endoplasmic reticulum and lysosomes. This is probably the most relevant mechanism<sup>5,6</sup>. These radicals damage the endothelial cells leading to the

shrinkage of these cells and other cytoskeletal structure modifications. This results in exposure of the vascular basement membrane, which causes platelet adhesion, degranulation, stasis, aggregation of blood cells and vascular occlusion. Activated platelets release eicosanoids, such as histamine, thromboxane and Tumor Necrosis Factor -  $\alpha$  (TNF- $\alpha$ ). These mediators trigger a sequence of events, including amplification of platelet activation, vasoconstriction, thrombosis, vascular hyperpermeability, blood stasis and hypoxia<sup>5,6</sup>.

The immunological mechanism can also play a role in PDT induced tumor destruction. This is based on the high concentrations of cytokines, such as interleukin-1 $\beta$ , interleukin-2 and TNF- $\alpha$ . It is also admitted that PDT may decrease immune response by reducing antigen-presenting cell activity<sup>5,6</sup>.

### INDICATIONS

PDT was approved for the treatment of predominantly classic subfoveal choroidal neovascularization (CNV) due to AMD, as well as for subfoveal CNV due to pathologic myopia and ocular histoplasmosis syndrome<sup>2</sup>. Different studies revealed encouraging treatment outcomes in case studies involving patients with choroidal vascular disorders such as PCV, CSC, choroidal hemangioma, angiod streaks, and inflammatory CNV. Currently, these conditions are considered as non-standard indications<sup>2,3</sup>.

### LASER TECHNIQUE

The greatest linear dimension is determined by measuring the longest fluorescein angiographic diameter of the area of leakage. The size of the area to be treated should include a 500  $\mu\text{m}$  border around the CNV, so a total of 1.000  $\mu\text{m}$  should be added to the greatest diameter of CNV. The treatment area could extend to a maximum of 200  $\mu\text{m}$  away to the optic disk.



Figure 1. Verteporfin and ruler used to calculate verteporfin dosage.

Verteporfin, which is stored as a dry powder, is reconstituted with sterile water and diluted with 5% dextrose solution immediately (Figure 1). This solution is infused intravenously for over 10 minutes, preferably through a large cubital or cephalic vein. Constant monitoring during the entire infusion is recommended to avoid photosensitizer extravasation, which can have serious dermatological consequences. The accurate weight of the patient should be verified before treatment to calculate the dose of verteporfin ( $6.0 \text{ mg/m}^2$  body surface area). The 689-nm diode laser light treatment starts 15 minutes after infusing the verteporfin. The laser treatment is delivered at the slit lamp through a diode-coated contact lens (Figure 2). Laser treatment is applied for 83 seconds, which produces a total energy dose of  $50 \text{ J/cm}^2$  (Figure 3).



Figures 2 and 3. Diode laser and PDT parameters.

These parameters have been studied and appear to be ideal, allowing maximum vascular effect with minimum photoreceptor and pigment epithelial cell damage. In chronic CSC, the area of irradiation is confined to the choroidal abnormalities seen, according to indocyanine green angiography (ICGA)<sup>7</sup> findings. Other investigators studied modifications to standard protocol, changing the fluence, verteporfin dosage and time of laser activation after infusion. Different studies revealed that half fluence PDT can achieve comparable or superior outcomes to standard fluence and decrease the adverse effects for chronic CSC.

**Half fluence** protocol consists of  $6 \text{ mg/m}^2$  verteporfin, total light energy of  $25 \text{ J/cm}^2$  and light dose rate of  $300 \text{ mW/cm}^2$ <sup>8</sup>. Chan *et al.* suggested the use of **half PDT dose** ( $3 \text{ mg/m}^2$ ) and laser delivery at 10 minutes as an effective treatment for chronic CSC<sup>9</sup>.

The increase of activation time to 30 minutes and half dose of verteporfin may be beneficial in chronic CSC patients, but further studies are needed<sup>7,10</sup>.

For PVC, the spot size used is confined to the whole area of choroidal abnormalities, including the dilated aneurysms or polyps, interconnecting vessels and adjacent abnormally dilated choroidal vessels according to ICGA<sup>11</sup>.

#### POST LASER CARE

Post-treatment precautions include avoidance of direct sunlight or bright indoor lights. A wide-brimmed hat, gloves, long pants, long sleeves, eye and face protection from direct sunlight are required for travelling immediately after PDT. Complete avoidance of direct sunlight is strictly prescribed for 2 days, in order to prevent potentially serious skin burns and photosensitivity that may occur from residual circulating photosensitizer after PDT.

#### CONTRAINDICATIONS TO PDT

- Porphyria;
- Severe liver disease;
- Pregnancy;
- Known hypersensitivity to a photosensitizing agent.

#### PDT SAFETY

The TAP and VIP studies published the most complete and extensive data regarding PDT safety. In these studies, a comparison with placebo was performed. PDT is considered to be a safe procedure, with rare side effects (Table 1)<sup>12-14</sup>. Fluorescein and indocyanine green angiography has documented choroidal hypoperfusion associated with PDT in the first days after treatment and, more rarely, in the following months. There are still doubts and controversy regarding the cumulative effect of treatment in the permanent occlusion of the choriocapillaris and the association between this hypoperfusion and possible functional consequences<sup>15</sup>.

Table 1. PDT adverse effects

<b>Ocular effects</b>	Non-specific visual disorders
	Transient loss of visual acuity (18% vs. 0%)
	Severe loss of visual acuity ( $\geq 20$ letters up to 7 days after PDT) (0.7% vs. 0%)
	Scotomatous alterations (6% vs. 3.4%)
<b>Systemic effects</b>	Injection site reactions (13% vs. 5.6%)
	Lower back pain (2.4% vs. 0%)
	Hypersensitivity reactions (3% vs. 0%)
	Alterations to sleep patterns (1.6% vs. 0%)

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# VIII. LASER in Retina/Choroid

## 51. Nondamaging

## retina LASER therapy

## in Central Serous

## Chorioretinopathy



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### INTRODUCTION

Central serous chorioretinopathy (CSC) is characterized by serous detachment of the neurosensory retina and/or the retinal pigment epithelium (RPE), secondary to one or more leakage points at the RPE level<sup>1,2</sup>. The cause of CSC remains unknown, and the diagnosis is based on a clinical history of blurred vision and metamorphopsia with relative central scotoma, non-inflammatory retinal and/or RPE serous detachment on fundus exam, and leakage, pooling and/or window defects on fluorescein angiography<sup>1</sup>. Optical coherence tomography (OCT) aids in diagnosing shallow serous detachments and is especially useful in the follow-up of affected patients<sup>3</sup>. In most cases of acute CSC, retinal detachment resolves spontaneously within 3 months of onset. Treatment should be considered when there is subretinal fluid persistence after 3 months, chronic/recurrent cases. Many therapies, from oral medications to intravitreal injections, were applied with variable and questionable results<sup>4,5</sup>. Alternatively, different laser treatments are available for this pathology with better success<sup>4</sup>. Direct threshold photocoagulation with continuous wave laser can shorten the duration of the serous detachment<sup>6</sup>, but it is not appropriate for juxtafoveal or subfoveal leakage points due to retinal laser burn scars. Photodynamic

therapy is the most studied option and so far is considered as the gold standard approach for this disease. It is possible to treat juxtafoveal and subfoveal leakage<sup>7</sup>, however it can cause adverse effects, including RPE atrophy, choroidal hypoperfusion with choriocapillaris ischemia, and choroidal neovascularization<sup>8,9</sup>. Nondamaging retinal laser therapies appear to be a promising treatment able to help subretinal fluid resolution without secondary damage to the macula. Classic photocoagulation treatment strategy consists of applying laser energy to obtain a confluent coagulation lesion of moderate intensity covering the leakage point<sup>1</sup>. An alternate hypothesis for the photocoagulation mechanism of action suggests that its therapeutic benefits are secondary to biological activation, which does not necessarily occur in laser-necrotized tissue but in still-viable cells stimulated by sublethal thermal stress directly produced with the laser exposure or indirectly caused by the equilibrating thermal wave from the laser burn<sup>10</sup>. Subvisible photocoagulation can potentially localize laser photothermal effects and decrease chorioretinal damage<sup>8</sup>. Nondamaging retinal laser therapy may limit the damage to the neural retina by raising the RPE temperature to just below the protein-denaturation threshold so that the thermal wave that reaches the neural retina is insufficient to cause either damage or a clinically visible endpoint<sup>11</sup>. The micropulsed laser consists of the division of



the laser emission into a “train” of short, repetitive pulses that persist for 0.1 seconds to 0.5 seconds. The “on” time is the duration of each micropulse and the “off” time is the interval between successive micropulses<sup>12</sup>. The “off” time allows heat dissipation, which decreases collateral damage and confines treatment to the RPE. This is a huge difference to conventional continuous wave laser, where the same magnitude of energy is delivered throughout the entire exposure time<sup>13</sup>. The duty cycle is calculated by taking the percentage of the period during which the laser is “on.” For example, with a duty cycle of 10% and a period of 1000  $\mu$ s, the laser would be on for 100  $\mu$ s and off for 900  $\mu$ s ( $0.10=100/1000$ ). The power and duty cycle are both adjustable, permitting the operator to vary the energy delivered<sup>12</sup>. A low duty cycle has to be used, allowing the RPE to return to baseline temperature before the next pulse is initiated. Usually the duty cycle ranges from 5 to 15%. The more it is raised, more cumulative thermal build-up will happen, as it approaches a continuous wave laser. The resting time between successive micropulses reduces the heat in the tissues and regulates the thermal isolation of each pulse contribution, hence greatly reducing the risk of structural and functional retinal damage, while retaining the therapeutic

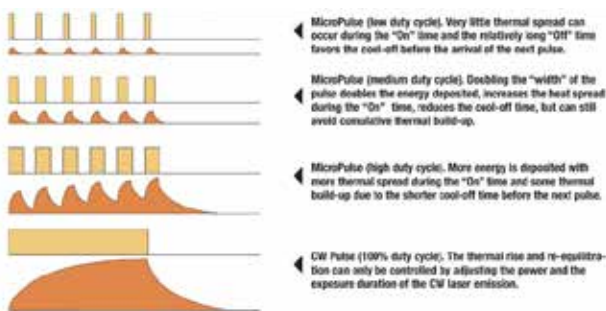


Figure 1. Micropulse tissue heat control.

efficacy of conventional laser treatment by achieving the requisite energy with repetitive low-energy pulses<sup>12</sup>. Significant advantages of the retinal phototherapy with a subvisible endpoint are the absence of scotomata and scarring, the ability to treat foveal areas, and improved preservation of color vision and contrast sensitivity and increase, rather than decrease, retinal sensitivity measured by micropertometry at the locus of laser application<sup>12,14</sup>. Assuming that the efficacy of the treatment would increase if more RPE cells are exposed to thermal stress and considering the lack of chorioretinal damage, a high density therapy is permitted, which greatly improves therapeutic outcomes, compared with conventional sparse laser treatment protocols in the macula<sup>15</sup>. Nearly confluent laser applications and/or retreatment of the same areas, even in proximity to the fovea, could be safely delivered over the entire edematous area. However, the lack of a reliable titration protocol for reproducible subvisible treatment settings inhibited its adoption in clinical practice and was reflected in the variable results of the studies<sup>12</sup>. If laser settings are too low, the treatment will be not only subvisible but also subtherapeutic, whereas if the settings are too high, there is a danger of excessive damage to the retina, especially with the nearly confluent coverage close to the fovea.

In addition, high-density coverage of the macula with relatively small spots and long pulses requires lengthy treatment and the difficulty of documentation of treated areas and inadvertent re-treatment of areas during a single session continues to be a problem. Because the modality delivers energy without leaving an observable mark, the surgeon has to keep track of the treated or untreated areas. In 2006, the PASCAL (Topcon Medical Laser Systems, Santa Clara, CA) pattern scan laser photocoagulator with a 532-nm laser was introduced for standard photocoagulation procedures applying a uniform pattern of many laser spots at one time<sup>16</sup>. Due to short pulse duration, the heat is decreased resulting in less thermal damage. The pattern laser technology allows equidistant spacing of individual spots to perform macular grid and panretinal photocoagulation effectively, faster and with less pain than conventional lasers<sup>17,18</sup>. Trying to overcome some of the micropulse issues, the PASCAL Endpoint Management (EpM) was created using a titration protocol for adjustment of the laser power and duration based on a retinal thermal model with 577-nm wavelength<sup>19</sup>. As in micropulse, retinal treatment also begins with titration of the laser power to a minimally visible retinal lesion endpoint. The titration pulse energy is assigned the 100% on EpM settings, and the treatment pulse energy is then defined as a percentage of this titration energy. Each energy level corresponds to a unique pair of laser power and pulse duration. Treatment is usually performed at 30% energy. This level was established as the highest nondamaging setting in animal studies, and should optimize the therapy to work within the range limited from the threshold of HSP (heat shock protein) expression to the thermal damage to RPE cells<sup>20</sup>. It is also a high density therapy, keeping some of the corner spots of the pattern at 100% energy to produce visible landmarks for orientation. Because each spot is irradiated with a pulse shorter than 10 ms, a large number of spots can be quickly placed using pattern scanning, especially with automatic pattern option<sup>19,20</sup>. Achieving similar efficacy as micropulse, the use of Endpoint Management software has some advantages: proper titration protocol provides an appropriate energy level to stimulate RPE in every patient, shorter pulses and the use of patterns make the treatment faster and more reproducible and the landmark allows the recognition of the treated area<sup>21</sup>.

## INDICATIONS

Chronic and/or recurrent CSC. Sub-threshold laser is also valuable in the treatment of macular edema secondary to diabetic retinopathy and vein occlusion<sup>25,26</sup>.

## CONTRAINDICATIONS

Subthreshold laser should not be applied over areas of hemorrhages or intense pigmentation that could eventually cause photocoagulation of photoreceptors.

## MICROPULSE LASER TECHNIQUE

*LASER 577 nm (yellow)*

## TITRATION

Retinal treatment begins with titration of the laser power

to a minimally visible retinal lesion endpoint, outside of the posterior pole (under the inferior vascular arcade or nasally), with many different protocols. The most used are: in continuous wave laser mode achieve a minimal burn, then turn the micropulse mode “on” and increase the power 20%. The duty cycle should be set on 15%. Or in micropulse mode, duty cycle of 5%, achieve a minimal burn and then set the power to 50% of the power that caused the minimal burn (Table 1).

Table 1. Non-damaging photothermal therapy:

	Titration	Micropulse
<b>Spot size</b>	200 µm	200 µm
<b>Duration</b>	200 ms	200 ms
<b>Power</b>	See above	See above
<b>Spacing</b>	Single spot	High density
<b>Energy</b>	100%	Micropulse mode (see above)

## STAGE 2 - TREATMENT

2. After proper titration, the treatment should be applied in the whole detached area. In order to achieve maximum photothermal stimulation of RPE cells, a high density of spots should be applied.
3. The surgeon should not see any marks in micropulse mode, so must be careful to not repeat treatment in the same spot and cause a visible burn. No damage to foveal laser has been described so far, but it is recommended not to aim at the fovea.
4. Retreatment can be applied at same area of previous treatments after three months.

## PASCAL ENDPOINT MANAGEMENT LASER TECHNIQUE

LASER 532 nm (green) or 577 nm (yellow)

See **Non-damaging Photothermal Therapy of the Retina using Endpoint Management** chapter 37.

## POSTLASER CARE AND FOLLOW-UP

Patients should be followed closely for evaluation of need of retreatment that could be done every three months.

## RESULTS

A prospective non-comparative interventional study of 26 eyes used subthreshold micropulse diode laser to treat chronic CSC<sup>22</sup>. In eyes with pinpoint leakage, 57% (n = 15) gained three or more lines of vision. 5 out of 11 eyes with diffuse macular leakage required rescue photodynamic therapy. A pilot randomized controlled trial performed in 2004 assigned 15 patients with acute CSC into a Diode micropulse laser photocoagulation group and an argon green laser group<sup>23</sup>. Diode micropulse laser photocoagulation group had significantly better improvement in BCVA (best-corrected visual acuity) (p < 0.001) at 4 weeks after laser but statistically insignificant at 8 and 12 weeks. In contrast, this same group had significantly better improvement in mean

contrast sensitivity (p < 0.001) at all follow-up visits after treatment. None of these eyes had scotoma, but six patients in the argon green laser group had residual scotoma at 4 weeks after treatment (p < 0.05). In 2013, a randomized, pilot trial involved 15 patients with chronic CSC who were allocated into a subthreshold diode micropulse laser group (10 patients) and a sham procedure group (5 patients)<sup>24</sup>. Subthreshold diode micropulse laser proved to be effective in improving BCVA significantly 3 months later but not in the sham group where all patients needed treatment after 3 months. All treated patients in both groups had an improvement in central macular thickness and leakage on fluorescein angiography. In conclusion, micropulse laser appeared to be effective, safer and non-damaging in treating both acute and chronic CSC and its contribution to the recovery speed was appealing. Recently, Lavinsky *et al.* conducted an interventional case series to assess safety and initial clinical efficacy of the Endpoint Management non-damaging photothermal therapy of the macula for treatment of the chronic CSC. Twenty eyes of 19 patients with persistent CSC (longer than 4 months duration) were treated with the PASCAL Streamline (TMLS, USA) at 577 nm wavelength, using 30% energy and 200 µm retinal spot sizes. No visible laser marks could be detected either by clinical observation, OCT, fundus autofluorescence or fluorescein angiography. An anatomical and functional improvement was achieved by 2 months, and sustained during the 6 months follow-up. This treatment was safe, and it improved visual acuity and resolution of subretinal fluid in chronic CSC<sup>21</sup>.

## COMPLICATIONS

There are no known complications of micropulse or non-damaging protocol using Endpoint Management, however, inadequate titration with higher energy could cause photocoagulation of the photoreceptors and therefore induce scotomata, decrease contrast and color vision.

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# VIII. LASER in Retina/Choroid

## 52. Subthreshold

## micropulse LASER

## central serous

## chorioretinopathy



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Central serous chorioretinopathy (CSC) is characterized by vision loss due to a serous detachment of the neurosensory retina. Choroidal congestion and thickening at the optical coherence tomography (OCT), and choroidal hyper-permeability, detectable using indocyanine green angiography (ICGA), suggest that choroidal dysfunction is an important underlying cause of retinal pigment epithelium (RPE) pump decompensation, leading to subretinal fluid (SRF) accumulation. Two main subtypes of CSC can be distinguished: acute and chronic CSC. In acute CSC, the neuroretinal detachment is caused by a focal leak (called 'hot spot' detectable by means of fluorescein angiography (FA)) in the RPE. The SRF usually resolves spontaneously within a few weeks, and visual acuity recovers to normal in acute CSC. However, visual impairment occurs if fluid persists for more than three months. Chronic CSC can lead to permanent structural damage and often pronounced loss of central vision due to atrophic RPE changes and thinning of the neuroretina. So far, there is no 'gold standard' treatment for CSC. Options for treatment include focal laser of the extrafoveal leak, which carries a risk of scotoma or choroidal neovascularization, and photodynamic treatment (PDT), which is not always effective and has also potential side effects, such as RPE atrophy, choriocapillaris ischemia and transient reduction of macular function<sup>1-3</sup>. Recently, micropulse laser (MPL) treatment without any visible Endpoint seems to be a promising alternative treatment

strategy<sup>4-13</sup>. Several studies with diode MPL (D-MPL) or more recently with yellow MPL (Y-MPL), have shown some efficacy in CSC patients with subfoveal or extrafoveal SRF. However, these studies are difficult to compare, with most of them being retrospective or case series studies, using a different protocol to the MPL treatment or comparing laser with different treatment strategies, such as PDT or intravitreal anti-vascular endothelial growth factor (VEGF) injection<sup>4,9,14</sup>.

In a prospective interventional non-comparative clinical study, Elhamid reported the complete resolution of the SRF in 11 of 15 eyes (73%) treated for non-resolving CSC lasting for more than three months with Y-MPL. Moreover, at six months follow up resolution was obtained in a higher percentage of cases (86.6%)<sup>11</sup>. Their results are partially comparable to those reported by other authors, who reported improvement in 55-75% of the cases<sup>15-17</sup>. A complete resolution of the fluid in only 40% of the cases has been reported by Yadav *et al*<sup>10</sup>. However, the mean follow up period was inferior to two months, not so long enough to evaluate the efficacy of MPL.

An improvement in visual acuity and contrast sensitivity, associated with resolution of SRF, has been reported by some authors<sup>11,13</sup> (Figure 1, 2 and 3).

To date, studies on the treatment of chronic CSC have shown that the subthreshold MPL can provide therapeutic benefits. Scholz *et al.*, in a retrospective study, assessed the efficacy of 577 nm MPL treatment in



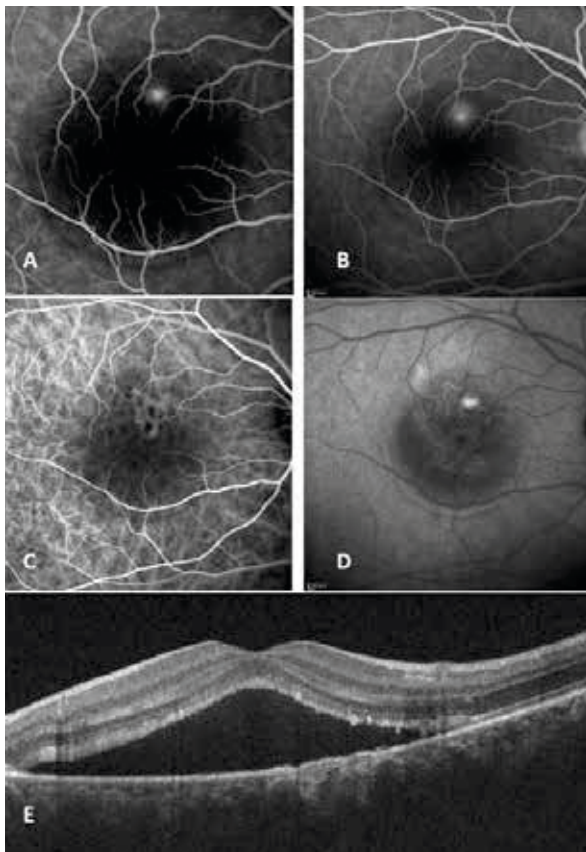


Figure 1. FA and ICGA in a case of acute CSC. A focal leak, called 'hot spot', is detectable by FA (A,B). An area of choroidal hyperpermeability is detectable on ICGA (C,D). OCT shows a serous detachment of the neurosensory retina (E).

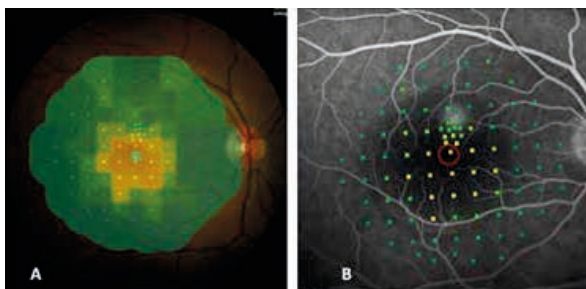


Figure 2. Microperimetry shows reduced sensitivity with relative scotoma in central macula (same case as in Figure 1).

38 patients with chronic CSC<sup>12</sup>, including a subgroup of 18 patients with persistent SRF after PDT. A confluent laser treatment was performed, guided by FA and ICGA. At the last follow up (5.0 ± 3.7 months after subthreshold MPL), the SRF had disappeared completely in 24%, was reduced in 50%, and remained unchanged in 26% of the cases. The best corrected visual acuity (BCVA) showed a small, but significant increase, in 45% of the cases improved by one or more lines; 37% of the eyes remained stable, and 7 eyes (18%) lost one or two lines. In the cases that improved visual acuity there was a significant correlation between the gain in BCVA and the reduction in central retinal thickness (CRT) after MPL treatment.

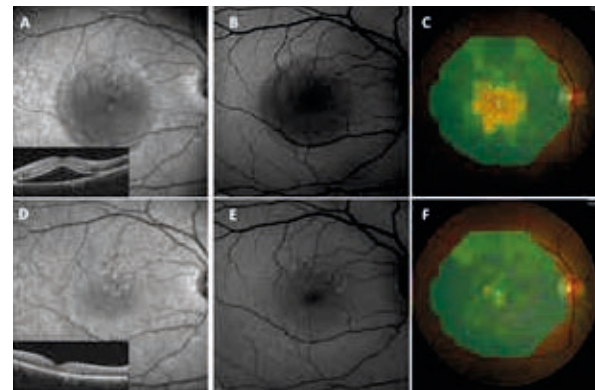


Figure 3. Multimodal images of the case of Figure 1, before and three months after subthreshold Y-MPL performed in the area of the focal leak. The neuroretinal detachment, detectable at infrared image and at OCT vertical linear scan (A), resolved (D). No signs of the performed laser was visible at the fundus autofluorescence (B,E: before and after laser respectively). An increase of retinal sensitivity threshold is detectable in the microperimetry interpolated map (C,F: before and after laser respectively).

The overall small improvement in BCVA was attributed to the long-standing history of CSC of the treated eyes (up to 19 years), which possibly had permanent structural damage that precluded significant visual improvement. However, even severe, long-standing cases could show a reduction in, or resolution of, SRF. Non-responding eyes were associated with a diffuse RPE decompensation and more advanced age, but not with the duration of disease. In the subgroup of patients previously treated with PDT, the results were not as good as in naïve eyes, even if a resolution of, or a reduction in, SRF was still achieved<sup>12</sup>. Better results are reported by Yadav *et al.*, who detected a significant decrease in the SRF at the OCT<sup>10</sup>. They assessed the efficacy of Y-MPL in patients with a history of CSC of more than three months, including both patients with focal leaks (8 eyes) and patients with areas of diffuse leak (7 eyes). Their better results may be due to less severity of the disease. In eight of the 15 studied eyes, Yadav *et al.* performed a microperimetry study too, observing in six eyes (75%) improved thresholds after laser. The two eyes of another patient with bilateral involvement and preexisting disruption of the outer retinal layers as determined by OCT, did not show any improvement in retinal sensitivity threshold<sup>10</sup>.

MPL causes stimulation of a biological response that restores the proper pump function of RPE cells, resulting in enhanced and rapid absorption of the SRF. The 577 nm yellow laser is probably ideal for diseases in which the primary pathology is at the RPE level. It is highly selective for RPE cells and, on the other hand, it is poorly absorbed by the foveal xanthophyll pigments. Therefore, the effects are localized to the RPE and protect the fovea, which can be potentially treated (Figures 4, 5 and 6).

In CSC it is difficult to prove a definitive treatment effect since the natural history of the disease is typically a self-limited process. For this reason, non-randomized uncontrolled studies, using different inclusion criteria, different definition of acute and chronic CSC, and using

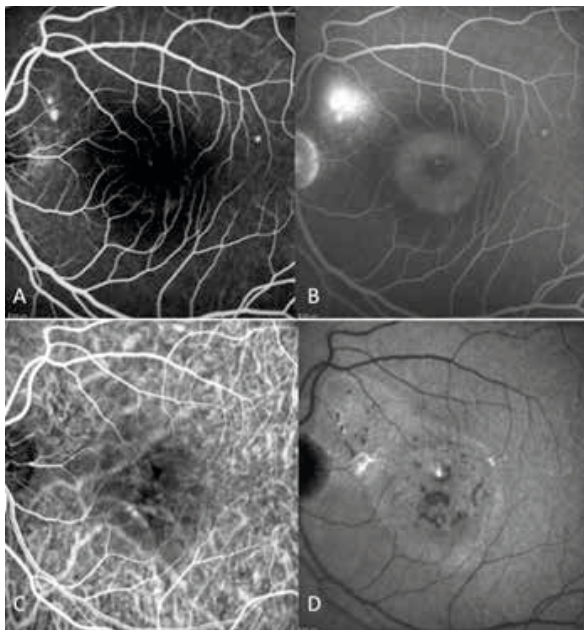


Figure 4. FA and ICGA in a case of chronic CSC. A focal leak, called 'hot spot', is detectable by FA (A,B). Multiple areas of choroidal hyperpermeability are detectable on ICGA (C,D).

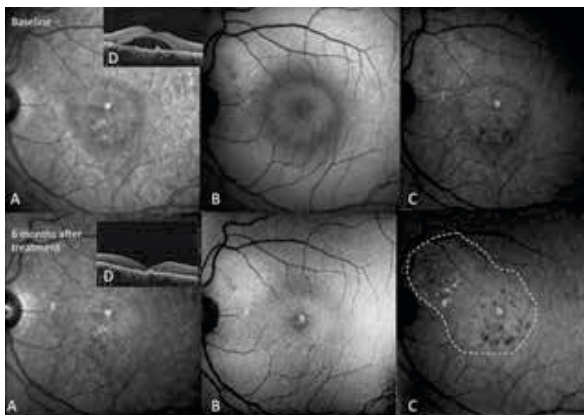


Figure 5. Multimodal imaging of the case of figure 4. Infrared (A), blue-autofluorescence (B), infrared-autofluorescence (C) and linear scan OCT (D) before and six months after D-MPL. The segmented line delineates the treated area.

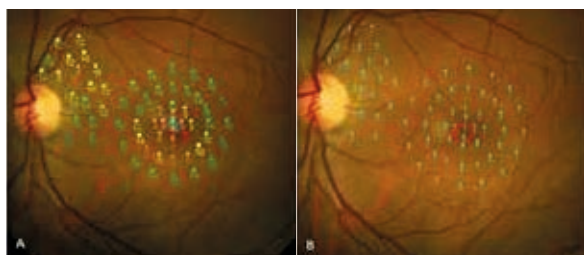


Figure 6. Microperimetry sensitivity map of the case of figure 4 (A). Six months after the D-MPL treatment the microperimetry interpolated map shows an increase in retinal sensitivity in all the treated area (B).

different treatment parameters, are of limited benefit. Large randomized controlled trials are necessary to support efficacy of any treatment over observation alone.

In conclusion, despite these limitations, due to its biological effects, MPL seems to be a promising treatment strategy, particularly in the earlier stages of the disease; it could improve and accelerate SRF reabsorption, preventing the RPE atrophic changes determined by long-lasting SRF.

## CONCLUSION

The use of subthreshold MPL in some macular diseases such as CSC, has provided a valuable insight into the mechanism of action of retinal laser therapy, demonstrating that a direct hypertrophic choroid treatment with a relatively heavy burn in CSC, is not necessary. A low energy, micropulse mode, with a lowest duty-cycle is a novel laser treatment modality that combines clinical efficacy with practically no risk of iatrogenic side-effects.

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# IX. LASER in Retina/choroid other clinical entities

## 53. Idiopathic macular telangiectasia



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### INTRODUCTION

The term retinal telangiectasis, from the Greek *telos* [end] + *aggeion* [vessel] + *ektasis* [dilatation], characterizes a vascular anomaly that can be identified in several ocular disease processes. In the vast majority of cases, these are secondary to local (ocular) or systemic conditions such as retinal vein occlusion, diabetic retinopathy, vasculitis, carotid occlusive disease or radiation therapy. Primary retinal telangiectasis can be found in Coats' disease, Leber's miliary aneurysms, idiopathic macular telangiectasia (MacTel) and in other angiomatous diseases. When retinal capillary ectasia of unknown origin are limited to the perifoveal area, the term MacTel (also known as idiopathic perifoveal/juxtafoveolar retinal telangiectasis) is applied<sup>1</sup>.

MacTel refers to a group of disorders initially categorized by Gass and Oyakawa<sup>1</sup>, based on ophthalmoscopic examination and fluorescein angiography (FA) findings. The classification was later updated by Gass and Blodi<sup>2</sup>, who suggested a distinct pathophysiology for each category (Table 1). In 2006, Yannuzzi et al<sup>3</sup> presented a simplified classification (Table 1) based on new clinical and imaging observations, namely optical coherence tomography (OCT) and high-speed indocyanine green angiography (ICGA). Even though type 3 (occlusive) MacTel is part of Yannuzzi's classification<sup>3</sup>, the author emphasized the rarity of this phenotype (only 7 cases were seen by Gass and Blodi<sup>2</sup> in 28 years). Due to its practicality and simplicity, this new classification is the most widely used in the present day and, therefore, it is the one we will refer to in this chapter.

Although the existence of MacTel was documented over three decades ago, several aspects of this entity remain obscure. Due to insufficient evidence, general recommendations

concerning the treatment of MacTel are not currently available<sup>4</sup>. Most existing data represents anecdotal case reports or retrospective small case series, meaning that a careful interpretation is advised. This chapter will focus on the role of laser therapy in the management of MacTel.

### LASER PHOTOCOAGULATION IN IDIOPATHIC MACULAR TELANGIECTASIA

#### 1. Type 1 MacTel (Aneurysmal) (Figure 1)

Given the rare nature of the condition and the lack of randomized controlled trials conducted to systematically address the natural history and potential long-term treatment effects, general recommendations for the treatment of type 1 MacTel are not available. The decision to initiate treatment must involve the consideration of the associated potential risks and side effects particularly since spontaneous resolution of macular edema has been reported<sup>1,2</sup>. However, when the central vision is at risk due to extension of lipid exudates into the foveola, a therapeutic intervention should be seriously considered. Among the various reported treatments, focal laser photocoagulation of the microaneurysms showed an apparent benefit, resulting in decreased vascular exudation and a potential improvement in the visual acuity<sup>1,2,5-7</sup>. Even though guidelines are lacking, general consensus is that focal laser treatment may be applied as long as the leaking aneurysm is located more than 200-300  $\mu\text{m}$  from the fovea. The functional success is, however, dependent on the extent of pre-existing neurosensory damage caused by longstanding edema or lipid exudates extending into the foveola<sup>4</sup>. Repeated treatment may sometimes be necessary.

Table 1. Classification of MacTel according to Gass and Blodi (blue) and its correspondence with Yannuzzi's simplified classification (orange)

	Clinical Findings	Gender predominance	Mean Age	Subtypes	Yannuzzi's Simplified classification correspondence
<b>Group 1</b>	Unilateral, visible telangiectasis, macular edema, hard exudates	Males	40	A Involved area > 2 clock hours B Involved area ≤ 2 clock hours (focal)	<b>Type 1</b> Aneurysmal Telangiectasia
<b>Group 2</b>	Bilateral, occult telangiectasis, minimal exudation, foveolar atrophy, superficial retinal crystalline deposits	Males = Females	50-60	A Stage 1 Diffuse hyperfluorescence in late phase fluorescein angiography	<b>Type 2</b> Nonproliferative Perifoveal Telangiectasia
				Stage 2 Reduced retinal transparency parafoveally	<b>Type 2</b> Proliferative Perifoveal Telangiectasia
Stage 3 Dilated right-angled venules	10	Stage 4 Intraretinal pigment clumping			
Stage 5 Vascular membranes		B Juvenile familial	-		
<b>Group 3</b>	Bilateral, occult telangiectasis, minimal exudation, capillary occlusion, optic disc pallor	Inconclusive	50	A Occlusive IJRT B Associated CNS vasculopathy	<b>Type 3</b> Occlusive Telangiectasia

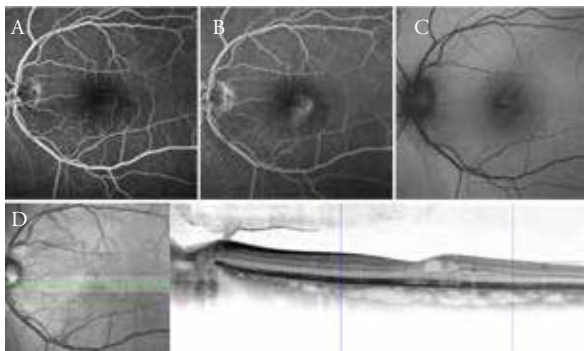


Figure 1. A 45-year-old male with unilateral type 1 MacTel. Note the aneurysms as hyperfluorescent dots in the early phase (A) and diffuse leakage in the late phase (B) of the FA. A cystoid pattern is visible both in the fundus autofluorescence (C) and in the SD-OCT (D) images.

**2. Type 2 MacTel (Perifoveal)**

Various treatment modalities have been investigated in order to treat type 2 MacTel. We will focus on the specific applications of laser treatment, both for nonproliferative and proliferative/neovascular type 2 MacTel.

**2.1. Nonproliferative (figure 2)**

Despite previous individual observations of improvement<sup>6,8</sup>, Nd:YAG KTP 532 nm laser (KTP laser) photocoagulation is no longer the treatment of choice for leaking parafoveal vessels in nonproliferative type 2 MacTel<sup>6</sup>, as more recent evidence suggests no beneficial effect<sup>2,4,7,9</sup>. The use of focal laser photocoagulation neither stops the vascular leakage nor improves visual acuity in the long-term<sup>9-11</sup>. Compared with untreated



Figure 2. A 57-year-old female with type 2 nonproliferative MacTel. Note the bilateral presence of irregularly shaped hyporeflective cavities, atrophy at the level of the external nuclear layer and disruption of the ellipsoid zone in the SD-OCT.

eyes, previous laser photocoagulation has been associated with distortion of retinal vessels, retinal pigment epithelial clumping, new draining venules and retinal hemorrhages<sup>9</sup>. Furthermore, this treatment modality has been reported to further incite the advent of neovascularization<sup>2,11-13</sup>. Because no proven benefit in the visual outcomes has been shown to exist and because there may be an increased risk of neovascularization, the use of focal laser photocoagulation for the treatment of macular edema associated with nonproliferative type 2 MacTel is not currently recommended<sup>4,12,14</sup>.

**2.2. Proliferative/Neovascular**

The resulting scotoma and the potential to trigger further

growth of neovascular membranes do not favor focal KTP laser photocoagulation for proliferative type 2 MacTel<sup>4</sup>. The excellent results associated with intravitreal injection of anti-vascular endothelial growth factor (VEGF) compounds<sup>15,16</sup> have rendered laser photocoagulation obsolete even in extrafoveal neovascular membranes.

### 3. Type 3 MacTel (Occlusive)

Due to the rarity of this condition, there is not enough data to either favor or oppose the use of laser photocoagulation in its management.

### GETTING STARTED

1. Explain the procedure referring to the possible need of multiple sessions and highlighting that the functional success depends on the extent of pre-existing neurosensory damage.
2. Use topical oxybuprocaine hydrochloride 0.4% as anesthesia.
3. Provide the room with dim illumination.
4. Input the desired settings by using the touch screen and selecting from those available in the drop down menu (see Table 2 for the recommended starting parameters for treatment with PASCAL<sup>®</sup>).
5. Apply a coupling agent (e.g. Methocel<sup>®</sup> 2%) in a VOLK<sup>®</sup> Super Macula 2.2, Area Centralis<sup>®</sup> or similar lens.
6. Ask the patient to keep a steady fixation and use your fingers to adjust the lens in order to keep the area of treatment adequately focused.
7. The aiming beam is not visible until the "Standby" button is pressed, which changes the mode to "Treat".
8. Align the aiming beam with the desired area and start treatment.
9. Once treatment has been terminated, place the laser in "Standby" mode.
10. The laser is turned off by selecting "Shut Down" from the screen menu or just turning the key to the "Off" position.

Table 2. Recommended starting parameters for focal laser photocoagulation using PASCAL<sup>®</sup> laser

<b>Power</b>	100 mW
<b>Spot size</b>	100 µm
<b>Duration</b>	10-20 ms
<b>Pattern</b>	Single

### CONCLUSION

Although widely used in the past, the current indications for focal laser photocoagulation in the management of MacTel are scarce. A summary of the recommendations to use this type of treatment is depicted in table 3.

Table 3. Summary of recommendations for focal KTP laser photocoagulation in the management of MacTel

<b>Yannuzzi's Simplified classification of MacTel</b>	<b>Role of Focal LASER Photocoagulation</b>
<b>Type 1</b> Aneurysmal Telangiectasia	Apparently beneficial although functional success depends on the extent of pre-existing neurosensory damage
<b>Type 2</b> Nonproliferative Telangiectasia	No improvement or stabilization. Potentially worsens the disease course and may induce development of neovascular membranes
<b>Type 2</b> Proliferative Perifoveal Telangiectasia	Obsolete due to side effects
<b>Type 3</b> Occlusive Telangiectasia	Not enough evidence to either support or discourage treatment

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# IX. LASER in Retina/choroid other clinical entities

## 54. Coats' Disease



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### INTRODUCTION

Coats' disease is an idiopathic condition characterized by retinal vascular telangiectasia with aneurysmal dilatations present more frequently in the temporal periphery, with associated exudative retinopathy that may involve the macular region. It can be complicated by exudative retinal detachment and neovascular glaucoma with eventual phthisis bulbi<sup>1,2</sup>. Coats' disease is rare, with a reported incidence of 0.09 per 100 000 of the population<sup>3</sup>. Etiology remains unclear. Several candidate gene mutations were suggested, including the Norrie disease protein<sup>4,5</sup>, CRB1<sup>6,7</sup> and PANK2<sup>8</sup>.

Coats' disease is unilateral in at least 90 % of the cases. No racial or ethnic association was described. A clear predilection for gender exists, with more than 75 % of the cases being males<sup>9</sup>. Most cases are diagnosed in the first two decades of life with a mean age of 10 years<sup>1,10</sup>. Coats' disease diagnosed in adulthood is much less common, it seems to be less aggressive and to progress at a slower rate than in children<sup>11</sup>.

The most common complaints at the onset are painless unilateral vision loss often detected during vision screening, strabismus, and leukocoria. Between 60% and 70% of cases are diagnosed during the first decade of life, with the majority of patients presenting vision ranging from hand motion to no light perception. Almost 80% of cases end up with total or subtotal retinal detachment if left untreated. Advanced disease with neovascular glaucoma and eye pain also occurs. Nevertheless, vascular anomalies may be asymptomatic, especially in adults<sup>12,13</sup>. In a recent publication, Blair *et al.*<sup>14</sup> reported that approximately two thirds of patients with Coats' disease had fellow eyes with peripheral areas of avascular retina. Minor areas of nonperfusion in the fellow eye had been reported previously<sup>15</sup> and although they do not seem to progress if untreated, they could be important to the

understanding of the disease.

The most used classification scheme of Coats' disease was proposed by Shields *et al.*<sup>16</sup> (Table 1) and is based on morphology. It is useful to assist in the choice of management and to predict the visual outcome after treatment.

Table 1. Classification of Coats' Disease as described in 2001 by Shields *et al.*<sup>16</sup>

Description	Stage
Retinal telangiectasia	1
Telangiectasia and exudation	2
Telangiectasia and extrafoveal exudation	2A
Telangiectasia and foveal exudation	2B
Exudative retinal detachment	3
Subtotal exudative retinal detachment - extrafoveal	3A1
Subtotal exudative retinal detachment - foveal	3A2
Total exudative retinal detachment	3B
Total retinal detachment and glaucoma	4
End stage disease	5

### INDICATIONS

The aim of the treatment is to destroy the abnormal vessels and ischemic retina, the sources of pathologic leakage and vascular endothelial growth factor (VEGF) secretion, respectively. Multiple modalities have been employed to treat Coats' disease: laser photocoagulation, cryotherapy, subretinal fluid drainage, scleral buckling



surgery, pars plana vitrectomy, and recently intravitreal anti-VEGF therapy<sup>12,17-20</sup>. Treatment is recommended based on patient factors and the severity of disease.

Patients in **stage 1** may be observed only or preferably treated with laser ablation to prevent future exudates, such as those in **stage 2A**<sup>18</sup>.

No consistent standard treatment of advanced Coats' disease is available and major centers of retinal disorders use different therapeutic approaches in the treatment of **stage 2B, 3 and 4**. However, there is evidence that supports the use of anti-VEGF therapy for Coats' disease with retinal edema or exudate involving the macula and with exudative retinal detachment<sup>12,17-20</sup>. As a result, initial treatment frequently consists of a single intravitreal injection of anti-VEGF for any significant macular edema, exudate, or serous retinal detachment, with ablative therapy with laser photocoagulation either concomitantly or following resolution of exudate and edema. Nevertheless, several authors continue to report success with laser ablation as a single modality of treatment even for advanced Coats' disease with high retinal detachment, recommending laser photocoagulation for primary management whenever possible<sup>21-25</sup>. This approach could be especially important in children, as it reduces the number of treatments under general anesthesia and avoids the potential systemic side effects of VEGF-inhibition on developing organ systems. Some reports suggest that laser ablation could have a role even in **stage 5** disease. In combination with subretinal fluid drainage and vitreous infusion, it may be able to preserve the globe and avoid enucleation<sup>2,16,26</sup>.

### CONTRAINDICATIONS

Laser ablation is contraindicated in foveal telangiectasias and ischemia. Treatment is impossible when there is no view of the retina (for example when iris neovascularization and poor midriasis render the pathologic vessels and ischemic retina barely accessible). Laser therapy could also be impossible to perform when total retinal detachment with extensive retina-to-lens touch exists.

### PREPARATION

1. Explain the procedure to the patient or to the parents, referring to the possible need of multiple session and/or association of different treatment modalities.
2. Induce pharmacological mydriasis with tropicamide 0.5%.
3. Patient sitting comfortably.
4. Under topical oxybuprocaine chloride insert the selected lens for ocular laser.
5. Dim lighting should be provided in the laser room.
6. Ask the patient to keep steady fixation and to follow your indications.

This preparation is adequate for adults. Pediatric patients are usually treated with indirect laser ophthalmoscopy under general anesthesia. A lid speculum is used.

### LASER TECHNIQUE

LASER 532 nm (green) or LASER 577 nm (yellow)

Treatment is planned differently in adults and children.

Retinal angiography is performed routinely in adults and treatment is targeted to telangiectatic vessels and to regions of abnormal tissue perfusion (Figure 1). In the pediatric population, treatment has been based on direct visualization of vascular abnormalities. In some centers it is possible to perform retinal angiography under general anesthesia in children and use it as a guide for treatment. Distant and diffuse capillary leakage was described angiographically in Coats' disease<sup>27</sup>. This finding is not secondary to widespread vascular malformations, but it has been interpreted as a remote response to high intravitreal levels of VEGF. Treatment should be limited to telangiectatic vessels, aneurysmal dilatations and unperfused retina. Resolution of diffuse VEGF-induced capillary hyperpermeability will occur, while preserving normal vascular structures.

This treatment modality is based on recent studies and involves two stages. Vascular abnormalities are treated first. Subsequently scatter laser is applied to ischemic retina (Figure 2). Hemoglobin absorbs green and especially yellow light more readily than other wavelengths, such as the infrared spectrum<sup>28,29</sup>. Because of the greater absorption of hemoglobin, yellow 577-nm laser may be the most effective for photocoagulative closure of telangiectasias and aneurysms<sup>21</sup>.

Laser beam variables:

	Telangiectatic vessels	Aneurysmal Dilations	Ischemic retina
Spot size	100-200 μm	100-200 μm	500 μm
Duration	1 s / continuous	0.1-0.3 s	0.1 s
Power	100-750 mW	70-300 mW	100-400 mW

### Vascular abnormalities

To treat telangiectatic vessels, long laser duration with a rapid cycle or a continuous mode should be used. The initial power is set at 100 mW and titrated to achieve a change in color of the vascular lesion from red to white-gray. Some lesions may require power between 300-750 mW<sup>21,23</sup>, especially those in highly elevated detached retina. The aiming beam is focused on the telangiectasia and then it should be moved along the course of the vessel as the desired color change is achieved. After the initial color change, vessels usually reperfuse. Levinson *et al.*<sup>21</sup> treat larger vessels twice in one sitting, and even after a second treatment some return of the red color is described after 5 to 10 minutes. It is important to treat areas of minor telangiectasia, as fluorescein angiography surveillance has demonstrated that tiny lesions can increase in size and cause future exudation<sup>11</sup>. Telangiectasias should be treated both in attached and detached retina and effective treatment could be performed even in high retinal detachments<sup>21</sup>. Aneurysmal dilatations should also be treated. The same color reaction is usually achieved with shorter durations and less power, adjusting the laser parameters to the size of the aneurysms.

### Ischemic retina

Scatter laser is then performed in areas of attached

unperfused peripheral retina in a manner similar to panretinal photocoagulation for diabetic retinopathy. Initial power settings range from 100 mW to 200 mW based on the degree of fundus pigmentation. Power should be titrated to achieve a gray retinal lesion and spots should be placed 1 spot-width apart.

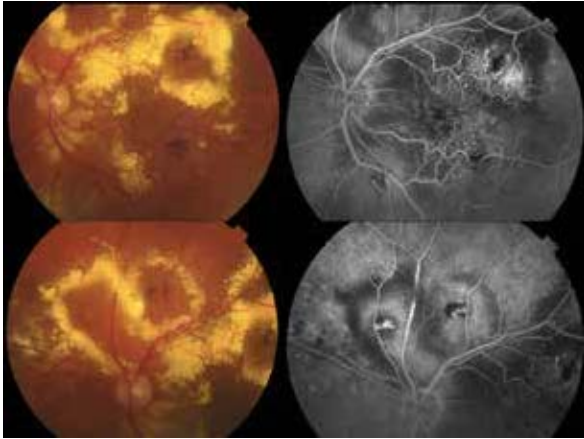


Figure 1. Left: Color fundus photographs of a patient with Coats' disease showing typical telangiectatic blood vessels and retinal exudation; right: fluorescein angiography of the same patient highlights telangiectatic blood vessel, showing typical "light bulb" dilations and areas of capillary nonperfusion.

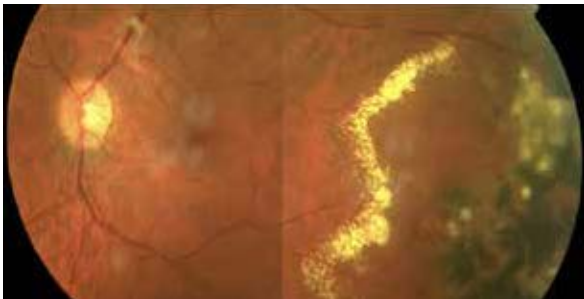


Figure 2. Peripheral telangiectasias and ischemic retina treated with laser in an eye with Coats' disease.

Nowadays, laser treatment is frequently associated with intravitreal anti-VEGF therapy. Some authors argue that intravitreal pharmacological therapy should precede laser, to enhance treatment efficiency by allowing the use of less energy and avoiding the increased risk of inflammation and subsequent fibrosis<sup>20</sup>. Laser and intravitreal injection could also be administered concomitantly, especially in children who need to be treated under general anesthesia.

In cases with highly elevated retinal detachment, it may be impossible to administer intravitreal injections safely without injuring the retina. In these cases, an attempt to flatten the retina with laser treatment must be done first. If exudative detachment fails to respond, anti-VEGF and laser treatment can be considered at the time of subretinal fluid drainage.

#### FOLLOW-UP

Frequently more than one treatment is needed, especially

in more advanced disease. If laser treatment is administered as single therapy modality, the follow-up schedule is at 3 months' intervals, although individual variables should be considered. Persistent perfused telangiectasias need to be retreated, such as any new vascular abnormality. Scatter laser should be performed again if new areas of reattached retina are identified.

Patients that receive combined treatment with anti-VEGF therapy should be examined monthly, to characterize vascular lesions and exudation as the pharmacological effect disappears. In adults, these frequent examinations are easier to perform than in the pediatric population, which usually requires observation under general anesthesia. In children, the benefits of frequent examinations need to be balanced against the risks of repeated anesthesia.

Follow-up intervals increase as complete resolution of the disease is observed, defined by reattachment of the retina and fundoscopic, or preferably angiographic, resolution of exudation.

Occlusion therapy to treat amblyopia should be considered in children under 8 years old, in whom reasonable foveal structure is observed.

#### COMPLICATIONS

**Lens opacification** has been described in 12% of the patients after laser treatment<sup>21,23</sup>. It seems to be secondary to high energy or proximity of the laser application to the lens in cases of marked elevation of the retina. **Mild vitreous hemorrhages** were also reported<sup>21</sup>. Suzani and Moore<sup>30</sup> report a frequent transient deterioration of visual acuity related to **accumulation of macular subretinal fluid** as a response to laser treatment. Other possible complications are those of peripheral retinal photocoagulation for vascular pathologies.

#### RESULTS

Several authors report success treating Coats' disease with laser as a single treatment modality<sup>21-25</sup>. Levinson *et al.*<sup>21</sup> used a 577 nm laser and achieved full treatment in 16 out of 17 eyes (94.1%). Fourteen out of 17 eyes were stage 2B to 3B. The authors needed a mean of 2.5 treatment sessions and reported an average time to full treatment of 11.2 months. Shapiro *et al.*<sup>23</sup> reported the use of a 532 nm laser in 14 eyes, 12 with stage 3A or B. With a mean number of 2.4 laser treatments, a favorable structural response with no exudation in 93% of the eyes was demonstrated. Nucci *et al.*<sup>22</sup> reported complete regressions in 31 out of 32 consecutive cases with yellow laser treatment. All patients had at least one quadrant of exudative retinal detachment with macular involvement. Although results in the resolution of abnormal vascular structures and retinal detachment are good, the visual outcome is poor as advanced disease is usually present at the diagnosis in Coats' disease. Macular subretinal fibrosis is the most frequent cause of low visual acuity at the end of treatment. Persistent macular exudates and retinal detachment preclude good vision. Levinson *et al.*<sup>21</sup> reported a final visual acuity of 20/200 or worse in 70% of cases. Shapiro *et al.*<sup>23</sup> reported that 5 (36%) out of 14 eyes studied had 20/400 visual acuity to light perception

and 2 (14%) had no light perception.

It is still not known if the association of anti-VEGF therapy will improve the visual prognosis in Coats' disease, as few data are available that compare treatment modalities. Ray *et al.*<sup>31</sup> reported structural resolution of disease in the most severe cases treated with bevacizumab and thermal ablation, whereas the matched controls failed therapy with ablative treatment alone.

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# IX. LASER in Retina/choroid: other clinical entities

## 55. Retinal

# Macroaneurysm



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### INTRODUCTION

Retinal arterial macroaneurysms (RAM) are acquired, usually round dilations of the large arterioles of the retina (Figure 1). They can bring about several complications, including subretinal, preretinal or vitreous hemorrhages, macular edema, serous macular detachment, macular deposition of hard exudates, macular holes, and branch retinal artery occlusion. A 10% incidence of bilateral disease exists, and multiple aneurysms in the same eye are occasionally seen<sup>1-3</sup>.

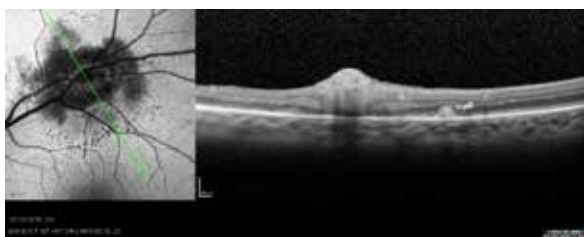


Figure 1. RAM in temporal superior branch of the right eye in a 76-year-old woman, with long standing increased blood pressure.

Formation of RAM is associated with systemic hypertension (in approximately 75% of patients) and atherosclerotic disease, but serum lipid abnormalities have also been reported. About 10% of patients have focal arterial wall atheroma occurring at defects in the wall, which may be sites at risk for aneurysm formation. Over time or after acute hemorrhage, spontaneous thrombosis and closure of the aneurysm may occur; in some cases, the artery may return to normal<sup>4,5</sup>. The female-to-male ratio for macroaneurysms is 3:1. They

occur most commonly in the sixth to seventh decade and are rare before age 60.

### Presentation

Most patients with RAM present sudden onset of painless vision loss in one eye. If the central macula is spared, however, the patient may be asymptomatic. Aneurysms that present without exudation or hemorrhage are asymptomatic.

### Prognosis

The visual prognosis is excellent for many patients with RAM. The natural history of these lesions suggests that most of them close spontaneously, with restoration of near-normal vision.

### Complications

Clinical complications of RAM include vitreous hemorrhage, retinal detachment, macular holes, and choroidal neovascular membrane formation<sup>6</sup>.

Vision loss from macular edema due to chronic exudation is well documented in many patients, and laser treatment may be appropriate. Vision loss resulting from RAM usually results from scarring in the macula due to either chronic edema or hemorrhage<sup>7</sup>.

Additional complications of RAM development include retinal and subretinal hemorrhage, as well as epiretinal membrane formation.

A study suggests that patients with preretinal hemorrhage or vitreous hemorrhage due to RAM have a good visual prognosis. In contrast, visual prognosis is poor in patients with submacular hemorrhage.

The formation of a macular choroidal neovascular membrane and retinal angiomatous proliferation in a consolidating exudate, following treatment of a RAM, has been reported by this author<sup>6</sup>.



### Vascular Signs and Sites of Occurrence

RAM more commonly affects the right eye than the left. Aneurysmal dilation of the retinal arterioles occurs, usually at the site of vessel bifurcation or arteriovenous crossing in the major branch retinal arteries. The superotemporal artery is most commonly involved. However, macroaneurysms have also been reported in cilioretinal arteries and on the optic nerve head. Occasionally, multiple aneurysms are present.

Usually, leakage of protein-rich serum occurs, leading to circinate exudation and macular edema. Serous retinal detachment can occur.

Bleeding is a common complication of aneurysm formation and it can occur beneath the retina, the retinal pigment epithelium (RPE), or the internal limiting membrane (ILM), or into the vitreous. Pulsatile flow is occasionally observed but does not necessarily indicate a higher risk of hemorrhage.

### LASER TREATMENT

No general consensus exists about laser treatment of RAM. The natural history of the disease suggests that spontaneous closure is common. Treatment may not be indicated for most patients.

Moreover, laser treatment may not improve the visual outcome, even when closure is successful, because of chronic edema and macular scarring.

### Laser photocoagulation

The most frequently cited indication for laser photocoagulation of a RAM is persistence or progression of macular exudation. The current recommendation for photocoagulation of macroaneurysms is the use of argon/KTP 532 nm green laser or the 577 nm yellow diode for direct photocoagulation of the lesion.

Some authors have recommended indirect treatment to minimize the risk of arteriolar occlusion and hemorrhage, taking advantage of the stimulation of the vascular stabilizing factors by laser thermal effect. Others recommend low power settings sufficient to create a light to moderate burn intensity, using a large spot size (500  $\mu\text{m}$ ) and long-duration (0.5 s) pulses directly on the lesion. Conventional laser application is currently the most commonly employed treatment for symptomatic RAM. The technique involves delivering visible laser burns to the retina, with light absorption, especially at the RPE and pigmented choroid. Heat conduction extends the temperature increase to the overlying nonpigmented and adjacent cells, until threshold laser lesions become visible owing to a change in the scattering properties of the overlying retina. Conventional Threshold Laser Therapy (TLT) (Table 1) may be burdened by many complications, including enlargement of the laser scar, choroidal neovascularization, and subretinal fibrosis. In addition to these complications, branch retinal artery occlusion, increased retinal exudation and scarring, with possible retinal traction, have also been reported as possible consequences of the laser photocoagulation of RAM. A recent pilot study showed that RAM obliteration with functional improvement can also be achieved using Sub Threshold Laser Therapy (STLT) (Table 1), with no

Table 1. Laser settings for STLT and TLT

	STLT	TLT
Spot diameter	125 $\mu\text{m}$	100 $\mu\text{m}$
Exposure	0.3 seconds (duty cycle 15%)	0.2 seconds
Power	1400 mW	100–300 mW (mean, 233 $\pm$ 55 mW)
Spot number	9–14 (mean, 11 $\pm$ 1.7)	5–10 (mean, 7.4 $\pm$ 1.6)

visible laser scars or complications.

The underlying STLT mechanism is thought to be related to the effects of the retinal hyperthermia below the cell death threshold, although the details of this interaction remain uncertain. STLT works by reducing the duration of laser exposure and using a subvisible clinical endpoint. The selective damage to the RPE cells may lead to an improved balance in angiogenic factors and cytokine release, perhaps including an upregulation of basic fibroblast growth factor, and heat shock proteins<sup>8</sup>.

### Laser hyaloidotomy

In the setting of dense subhyaloid hemorrhage, Nd:YAG 1064 nm Q-switch laser (QS-YAG) hyaloidotomy has been performed to release the sequestered blood into the vitreous cavity.

Release of blood that is sequestered over the macula may reduce the risk of macular scarring and epiretinal fibrosis. This procedure is controversial, however, because of the risk of macular injury and vitreous hemorrhage. Laser treatments are performed under topical anesthesia. Mainster® Focal/ Grid laser lens or Volk® Area Centralis lens is used. Laser is operated at Q-switch mode at energy level between 1.9 – 11.5 mJ from low to high energy level fire at the anterior surface and inferior margin of the hemorrhage away from the fovea and 2 to 3 openings were made until a rapid stream of blood was seen trapped into the vitreous cavity.

### COMPLICATIONS

Complications of laser treatment can include macular infarction from retinal arteriolar occlusion and laser-induced hemorrhage or retinal damage. Increased retinal exudation and scarring with subsequent retinal traction are also possible. However, a recent study of outcomes in patients who have undergone conservative treatment (observation only), laser treatment, or vitrectomy indicate that visual outcomes are good in any of these treatment regimens<sup>9</sup>.

### SURGICAL EVALUATION

In rare settings in which vitreous hemorrhage is present and the etiology of bleeding is unclear, vitrectomy may be indicated. However, removal of dense subretinal hemorrhage is very controversial and has the potential to cause many serious complications<sup>10</sup>.

The goal is to remove the extravasated blood and to assist in the diagnosis and possible treatment. Pneumatic displacement of premacular hemorrhages using SF<sub>6</sub> gas

have also been reported.

More recently, injection of anti-vascular endothelial growth factor (VEGF) agents have also been shown to be associated with good visual outcomes<sup>11,12</sup>.

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# IX. LASER in Retina/choroid other clinical entities

## 56. Drepanocytosis

### Retinopathy



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#### INTRODUCTION

Drepanocytosis or sickle cell disease (SCD) is one of the most common genetic diseases worldwide. It is most endemic in tropical regions, mainly in the Middle East, Mediterranean regions, Southeast Asia and sub-Saharan Africa, especially in Nigeria<sup>1</sup>.

SCD is a chronic hemolytic disorder, inherited in an autosomal recessive way, either in the homozygous or double heterozygous state, that is marked by a tendency of hemoglobin molecules within red cells to polymerize and deform the red cell into a sickle (or crescent) shape, when the partial pressure of oxygen is low, resulting in characteristic vaso-occlusion caused by hemolysis, hemostasis and thrombosis<sup>1,2</sup>.

When inherited in the homozygous state, it is termed sickle cell anemia (Hb SS). Other known types of SCD include hemoglobin SC disease, sickle  $\beta$  plus thalassemia (S $\beta^+$  Thal) and sickle  $\beta$  zero thalassemia (S $\beta^0$  Thal) and other less prevalent double heterozygous conditions<sup>1,2</sup>.

It is a systemic disease that affects almost all the organs and leads to neurological, cardiac, pulmonary, hepatic, renal, ophthalmic, musculoskeletal and dermatological manifestations<sup>3</sup>.

The main pathophysiology associated with ophthalmic manifestations in drepanocytosis is vaso-occlusion that occurs in any vascular bed of ocular structures including conjunctiva, anterior segment, choroid, retina and optic nerve with potential visual impairment<sup>4</sup>.

#### RETINOPATHY IN DREPANOCYTOSIS

The incidence of significant visual loss from sickle cell retinopathy (SCR) is variable but appears to be relatively low in natural history studies. Serious ocular complications are mainly due to proliferative sickle cell retinopathy (PSR) – retinal neovascularization, vitreous hemorrhage, and retinal detachment. The incidence

of PSR increases with age, and it is relatively common between 15 and 29 years of age, but studies were reported in which PSR was detected in children as young as 7 to 13 years of age. PSR is more common in Hb SC disease and sickle cell- $\beta$  thalassemia (approximately 33% and 14%, respectively) than in SS disease (3%), although SS disease results in more systemic complications.

Retinal manifestations of sickle hemoglobinopathies are grouped according to the presence or absence of neovascularization<sup>2,4,5,6</sup>.

#### NONPROLIFERATIVE SICKLE CELL RETINOPATHY

The retinal changes seen in this subgroup follow arteriolar and capillary occlusion.

When an arteriole of intermediate size is occluded by a plug of sickle erythrocytes, hemorrhage may occur, presumably by ischemic necrosis of the vessel wall. Anastomosis and remodeling occur in the periphery, as do the hemorrhagic sequelae (salmon patch hemorrhages, refractile iridescent deposits or spots, and black sunburst lesions)<sup>7</sup>.

#### PROLIFERATIVE SICKLE CELL RETINOPATHY

PSR is secondary to occlusion of peripheral retinal vasculature, which in turn leads to retinal ischemia and proliferation of new vessels, usually at the border between perfused and non perfused retina, with a characteristic sea fan (SF) appearance (Figure 1)<sup>4,7</sup>.

Goldberg and colleagues developed a classification of PSR according to severity of fundus changes (Table 1)<sup>4,8</sup>.

#### LASER TREATMENT

#### INDICATIONS

Treatment is reserved for eyes that have progressed to

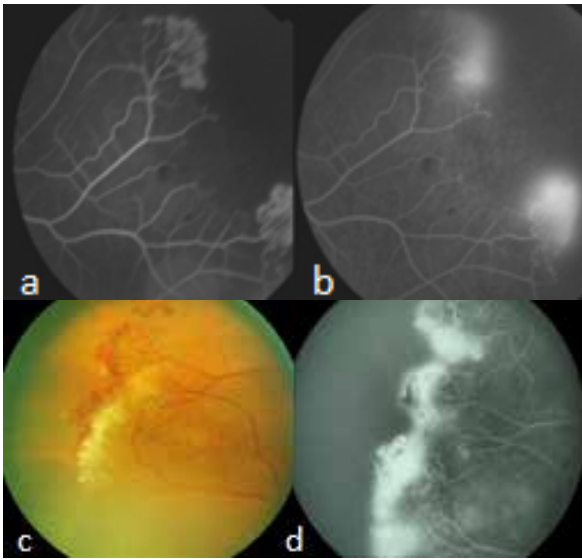


Figure 1. Characteristic angiographic (1a,1b,1d) and retinographic (1c) aspect of a peripheral ischemic capillaropathy resulting in neovascularization and the SF appearance, in SCR. Images: courtesy of Rita Flores, MD (1a, 1b) and Henry J Kaplan, MD (1c, 1d).

Table 1. Staging of PSR

Stage I	Peripheral arteriolar occlusion
Stage II	Vascular remodeling, formation of arteriovenous anastomoses
Stage III	Peripheral retinal neovascularization
Stage IV	Vitreous hemorrhage
Stage V	Retinal detachment

proliferative retinopathy before bleeding and retinal detachment occurrence. The goal of early treatment is to induce regression of neovascular tissue, in stage III PSR, prior to complications, to prevent visual loss.

The treatment is still controversial because many SF regress spontaneously, especially in older SS patients, in whom the incidence of blindness is very small. Therefore, the recommended approach is to treat SF in all SC patients and SS patients below 40 years of age<sup>4,6,7</sup>.

Therapeutic intervention is usually recommended in cases with peripheral neovascularization of more than 60° of circumference. This is particularly the case in eyes with bilateral involvement, spontaneous vitreous hemorrhage, large and elevated sea fans, rapid progression of new blood vessels and cases in which one eye has already been lost to PSR<sup>4,6</sup>.

Patients with recent vitreous hemorrhage and visual acuity impairment are usually followed for at least six months to allow spontaneous clearing<sup>7</sup>.

#### LASER TREATMENT ALTERNATIVES

Historically, SF have been treated in a variety of ways

(diathermy, cryotherapy and transpupillary argon/xenon photocoagulation or transscleral diode laser photocoagulation), always aiming to obliterate the neovessels. Diathermy, which is no longer in use, can cause uveitis and anterior segment ischemia. Cryotherapy is effective in treatment of SF occlusion, although complications (retinal tears and tractional RD) can occur. Even if the SF is not occluded, the decrease in diameter of the neovessels renders the occurrence of vitreous hemorrhage less likely. Transpupillary laser photocoagulation is the safest and the preferred method among the available techniques. Transscleral diode laser coagulation is considered as an alternative only when transpupillary laser coagulation is not applicable due to media opacities<sup>4,7</sup>. Anti-vascular endothelial growth factor (VEGF) therapy as an adjunct to photocoagulation in the management of PSR could obviate the need of pars plana vitrectomy in some patients. However, it is important to emphasize that for many patients there is a risk of worsening the tractional component; this risk is very common in patients with sickle-cell disease due to the use of antiangiogenic drugs<sup>7</sup>.

#### LASER TECHNIQUE

The different types of laser mainly used to achieve these goals are white xenon arc or green Nd:YAG KTP 532 nm laser (KTP laser). The specific laser methods in PSR include feeder vessel coagulation (Figure 2a) and scatter laser coagulation, either sectoral, localized (Figure 2b) or 360°, circumferential, peripheral scatter coagulation (Figure 2c). Scatter laser photocoagulation is considered to be the preferred method for PSR.

In cases of unreliable patients, where compliance with follow-up is suspected, local scatter treatment may be replaced by more extensive, 360°, peripheral treatment (Figure 2c), but there is no clear evidence that the outcome from this technique is any better than either the natural course of untreated disease or local scatter photocoagulation to neovascular fronds. In 360° scatter laser, burns are applied circumferentially to entire peripheral retina - green KTP laser is applied to the retina with a laser setting of 500 μm spot size and 0.1 second duration.

In sectoral ablation, laser is applied only to the localized area around new blood vessels. Laser burns with 500 μm spot size and 0.2 second duration are applied 1-disc diameter anterior and posterior and one hour each side of the SF. Laser therapy is most effective when peripheral lesions are diagnosed early before involving the central retina<sup>4,7,9</sup>.

In the technique involving laser treatment of feeder vessels, heavy laser burns are applied directly to feeding arterioles leading to closure of neovascular fronds. The vessels are treated on a flat area of the retina and posterior to the SF. Initially, all feeder arterioles are treated, followed by treatment of the draining venules with less intensity. Heavy feeder vessel photocoagulation is usually reserved only for difficult cases with repetitive bleeding. Ocular media should be clear enough over the feeder vessels for successful photocoagulation. Xenon arc and green KTP laser photocoagulation are used for feeder vessel coagulation; however, currently Nd YAG:KTP<sup>4</sup> is commonly used by clinicians as xenon had a higher complication rate<sup>10</sup>.

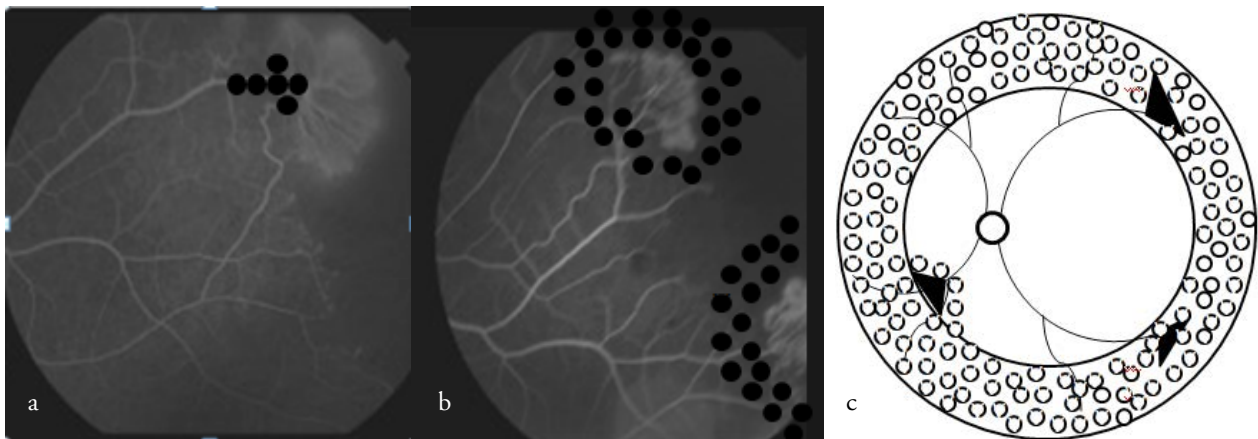


Figure 2. Schematic laser technique in PSR: feeder vessel coagulation (2a); localized or sectoral scatter laser coagulation (2b); 360° or circumferential peripheral laser coagulation (2c). Angiographic images (2a,2b): courtesy of Rita Flores, MD.

### LASER COMPLICATIONS

There are some complications associated with the high power settings used in feeder vessel treatment which have pushed modern clinicians towards local scatter photocoagulation. **Vitreous hemorrhage, rupture of Bruch's membrane, choroidal hemorrhage and ischemia, retinal tears and choroidal neovascularization** are some of those possible complications. Compared with the sectoral technique, 360° scatter photocoagulation is related to a greater incidence of **epiretinal membranes and vitreoretinal traction formation**<sup>7,9</sup>.

### RECOMMENDATIONS AND POSTLASER FOLLOW UP

Beginning in childhood, all patients with SCD should have annual dilated examinations undertaken by an ophthalmologist with expertise in retinal diseases. Any patient with SCD who experiences a change in vision should be referred for ophthalmologic consultation immediately. After the appropriate treatment, 34% of eyes develop new neovascularization; these patients should also be followed yearly<sup>9,10</sup>.

### CONCLUSION

Timely laser photocoagulation, particularly sectoral approach, has been considered safe as well as effective in treatment of PSR in stage III, as it maintains quality of life and preserves vision by preventing vision-threatening complications in the affected population<sup>4,7</sup>.

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# IX. LASER in Retina/choroid other clinical entities

## 57. Ocular Ischemic

## Syndrome



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### INTRODUCTION

Although uncommon, Ocular Ischemic Syndrome (OIS) is a serious blinding condition.

In 1874, Schmidt and Loring reported cases of neovascular glaucoma in patients who suffered cerebrovascular accidents<sup>1,2</sup>. Later, in 1963, Kerns and Hollenhorst described the ocular symptoms and signs occurring secondary to severe carotid artery obstructive disease<sup>3</sup>.

Apart from being a blinding condition, this syndrome is also related to significant cerebrovascular and cardiovascular risk, as it is a potentially fatal condition. Early diagnosis is crucial and management may help to reduce systemic morbidity and to preserve visual function<sup>4</sup>.

### DIAGNOSIS

Ocular signs and symptoms may be the first manifestations of carotid artery disease. Principal ocular symptoms include: sudden loss of vision over a period of seconds to minutes - *amaurosis fugax* or gradual visual loss over days to weeks, prolonged visual recovery after exposure to bright light, and ocular or periorbital pain<sup>5-12</sup>. Symptoms are normally ipsilateral to artery stenosis.

Probably due to the higher incidence of atherosclerosis, men outnumber women by 2:1. It is rare before the age of 50, and more frequent after 65<sup>6,13,14</sup>.

Differential diagnosis is made with retinal vein occlusions, diabetic retinopathy, hypertensive retinopathy, blood dyscrasias or HIV retinopathy. Ocular Ischemic syndrome can occur isolated or in association with these pathologies. An early sign of the anterior segment ischemia is flare in the anterior chamber and/or iris and angle neovascularization, with or without neovascular glaucoma in the absence of retinal ischemic lesion or central vein occlusion. In fact, the major complications of this syndrome are iris neovascularization - *rubeosis*

*iridis* and neovascular glaucoma. It can also present posterior segment signs that can range from unspecific retinal dilated and tortuous veins to neovascularization of the optic disc or retina, variable degrees of retinal hemorrhages, and ghost vessels.

In addition to clinical findings, fluorescein and indocyanine green angiography help to establish the diagnosis revealing delayed arm-to-choroid and arm-to-retina circulation time. Some studies have also reported decreased amplitude of *a* and *b* waves in electroretinography<sup>6,15</sup>. Carotid duplex ultrasonography and color Doppler imaging are two excellent non-invasive tests that provide anatomical imaging and flow velocity information in carotid and in retrobulbar circulation, respectively<sup>16</sup>. Nowadays, magnetic resonance angiography and computed tomographic angiography are replacing conventional intra-arterial digital subtraction angiography<sup>6</sup>.

### MANAGEMENT

Surgical carotid endarterectomy and more recently percutaneous carotid angioplasty and stenting are the gold standard for threatening stenotic lesions, restoring arterial perfusion and preserving visual function. Ophthalmologists have an important role in early diagnosis, coordinating referral to internal medicine specialists, neuroradiologists and neurovascular specialists<sup>17-19</sup>.

Panretinal photocoagulation (PRP) may induce regression of *rubeosis* and minimizes the risk of vitreous hemorrhage and tractional retinal detachment. Unfortunately, regression after laser therapy is not as significant as that seen in patients with iris neovascularization after central retinal vein occlusion<sup>6</sup>. Intravitreal injection of anti-vascular endothelial growth factor (VEGF) agents, such as bevacizumab, has been shown to be effective in



treating iris neovascularization secondary to OIS and should be considered in the management options<sup>10,20,21</sup>. Elevated intraocular pressure (IOP) from neovascular glaucoma may require cyclodestructive therapies and/or filtering procedures associated with intravitreal anti-VEGF treatment<sup>21,22</sup>.

### Nd:YAG-KTP 532 nm (GREEN) LASER TREATMENT PROCEDURE<sup>23-27</sup>

#### GENERAL CONSIDERATIONS

Laser photocoagulation usually comprises a total of burns that should cover the ischemic retinal areas. It may be necessary to extend it from the posterior pole to peripheral retina as in PRP (Figures 1 and 2). Inferior retina is treated first as it might get obscured by vitreous or preretinal hemorrhage developing between sessions. If PRP is completed in two sessions, the second session should be performed after two weeks. If it is completed in 3-4 sessions, an interval of 3-7 days may be sufficient.

#### PREPARATION<sup>23-27</sup>

1. Explain the procedure referring the possible need for multiple sessions.
2. Mydriasis with tropicamide (1%) and phenylephrine (5%) starting 30 min before treatment.
3. Topical anesthesia (oxybuprocaine hydrochloride 0.4%) is applied 5 min before laser
4. Patient sitting comfortably.
5. Steady fixation - apply head strap and adjust fixation target.
6. Insert appropriate laser contact lens - Goldmann 3-mirror/ Volk QuadrAspheric/Mainster standard lens bonded with antireflective coating.
7. Dim light in laser room.
8. Adjust slit-lamp beam and parameters and focus the lesion.

#### LASER TECHNIQUE

Start with 400-500  $\mu\text{m}$  spot size on retina, 0.1 second exposure time and 350-400 mW power. Power is gradually adjusted to achieve the endpoint. Laser treatment should extend slightly anterior to the equator and be applied 500  $\mu\text{m}$  nasally from the optic disc, outside the temporal vascular arcades and two disc diameters temporal to the macula.

More than 700-800 spots are avoided in a single session. Non-confluent laser spots are placed one spot apart and one should avoid major blood vessels, chorioretinal scars, previous laser scars, tractional detachment areas, vortex veins and areas with elevated neovascularization.

Close but non-confluent burns are applied. Peripheral non-elevated neovascularization, persistent or fresh neovascularization areas are treated focally with confluent burns.

All wavelengths are equally effective in inducing regression of OIS. The green wavelengths are generally better tolerated, since the longer diode wavelengths are absorbed more deeply in the retina and potentially cause more pain. The longer red wavelengths are generally used in eyes with media opacities, such as dense cataract or vitreous hemorrhage.

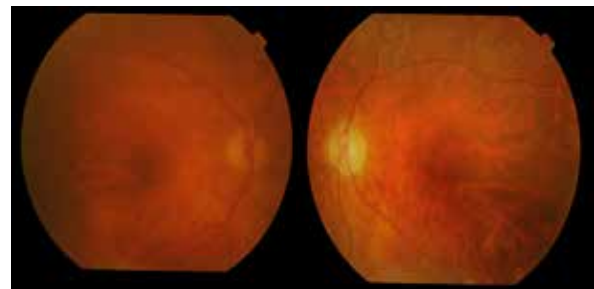


Figure 1. Retinography: Left eye with OIS.

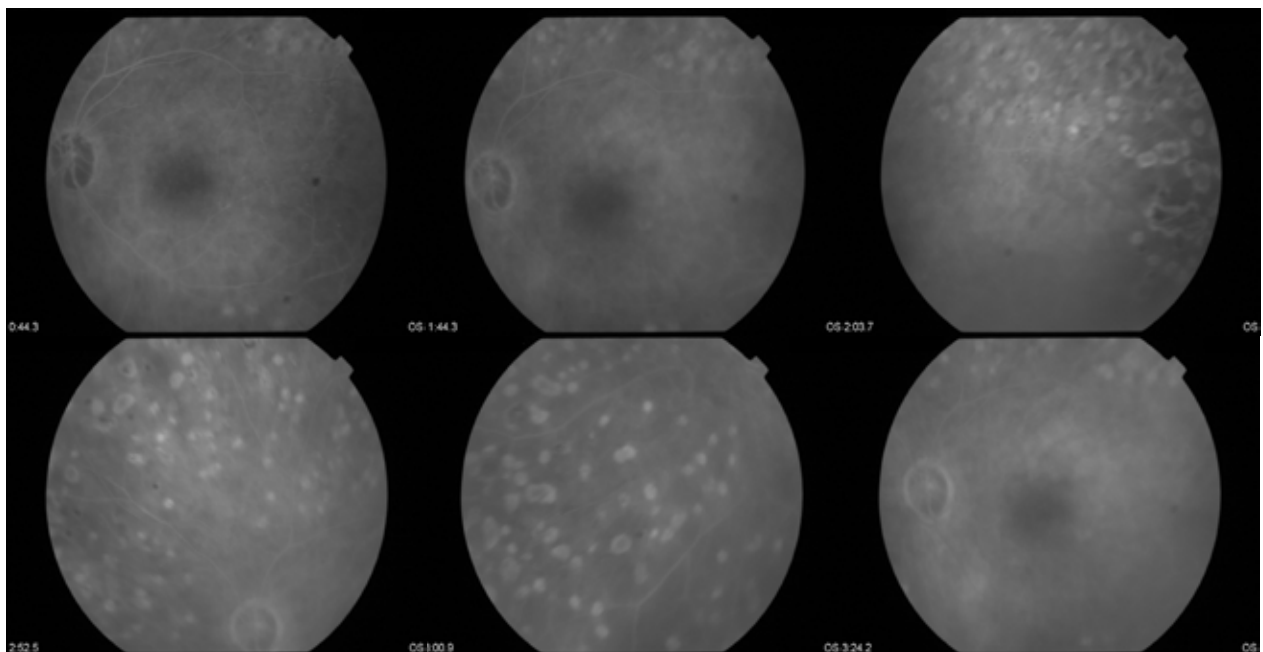


Figure 2. Angiography, left eye: Post laser photocoagulation in a patient with nonproliferative diabetic retinopathy.

## POSTLASER CARE AND FOLLOW-UP

Prescribe topical steroid drops 3-4 times daily during 1 week after treatment.

If new vessels persist despite maximal treatment, patient could be initially observed without treatment.

If vitreous hemorrhage occurs, it is usually mild and tends to clear spontaneously.

In severe cases peripheral cryoablation can be performed and areas with lightly pigmented scars can be retreated.

In addition, anti-VEGF treatment is also an option.

## COMPLICATIONS

Laser photocoagulation is a relatively safe procedure. Complications are those of the PRP procedure for diabetic retinopathy.

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# IX. LASER in Retina/choroid other clinical entities

## 58. Eales' Disease



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### INTRODUCTION

Eales' disease was first described by Henry Eales in 1880 and 1882<sup>1,2</sup>. His original report described recurrent retinal hemorrhages in young males with a history of headaches, constipation, variation in peripheral circulation, dyspepsia and epistaxis. This clinical entity is often bilateral and characterized by retinal phlebitis and vascular occlusion with peripheral ischemia/nonperfusion and, eventually, retinal neovascularization causing recurrent vitreous hemorrhage, a hallmark of the disease.

The disease affects mostly young males (20 to 30 years old) and, although described originally as an idiopathic disease, there has been an increasingly large number of authors over the years suggesting a strong link with tuberculosis (TB). Positive tests for latent tuberculosis, like the tuberculin/Mantoux test and the QuantiFERON-TB Gold, are indeed frequent findings. Some have argued that Eales' disease could be caused by an hypersensitivity reaction<sup>3</sup> to the tuberculous protein, whereas others have proposed an immune-based mechanism<sup>4,5</sup>. The possible connection with TB infection was further reinforced by reports revealing the presence of acid fast bacilli in peripheral retinal lesions and perivascular sheath material in eyes with primary phlebitis<sup>4,6</sup> and *M. tuberculosis* DNA of ocular specimens<sup>7</sup>. Although controversial, it is common practice to rule out a latent TB infection in the presence of a clinical picture suggestive of Eales' disease and most clinicians will recommend a full TB treatment if these tests turn out positive hoping that it may help prevent recurrences.

### CLINICAL PICTURE

Eales' disease causes peripheral phlebitis with vascular occlusion and ischemia leading to retinal neovascularization. The main visual complaints are often related to vitreous

opacities after hemorrhage and, unless treatment is offered at an early stage of the disease, vitreous hemorrhages can be recurrent and visually significant for long periods of time. Nonperfusion areas and neovascularization can be extensive and although most retinal changes are visible at fundoscopy, fluorescein angiography can be useful and is considered a mandatory tool in these cases (Figure 1). Retinal neovascularization can be severe and lead to profound visual loss. It can occur in up to 80% of patients and is usually located at the junction between the vascularized and the non-vascularized retina. When detected, treatment becomes imperative in order to avoid serious and often irreversible complications like tractional retinal detachment and secondary neovascular glaucoma. Active phlebitis will show vascular wall staining and late diffusion in angiography. Active inflammation can eventually lead to venous insufficiency and possible occlusion (Figure 2). After occlusion, neovascular growth will be stimulated and new vessels will grow.

### CLASSIFICATION

Eales' disease can be classified into four stages<sup>8</sup>:

- Stage I: Mild periphlebitis of small peripheral retinal vessels.
- Stage II: Widespread perivasculitis of the venous capillary system with vitreous haze.
- Stage III: Retinal neovascularization with retinal/vitreous hemorrhages.
- Stage IV: End stage disease with recurrent vitreous hemorrhages, retinitis proliferans and tractional retinal detachment.

Other authors have proposed a different classification based on the degree and extent of the microvascular involvement, proliferative retinopathy and vitreous hemorrhage<sup>9</sup>.

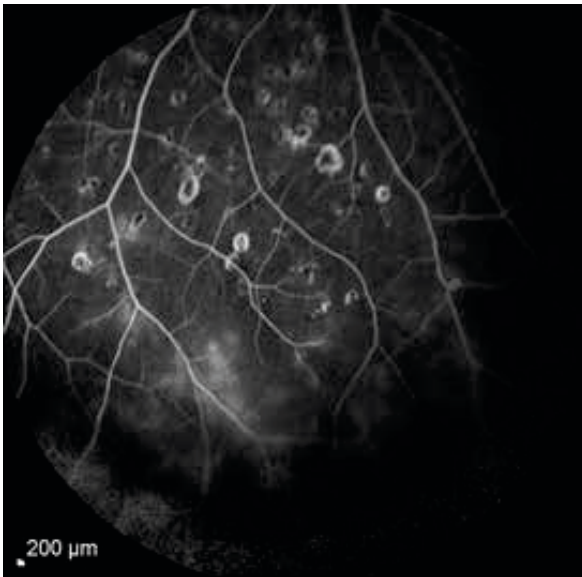


Figure 1. Peripheral venous leakage and nonperfusion in Eales' disease.

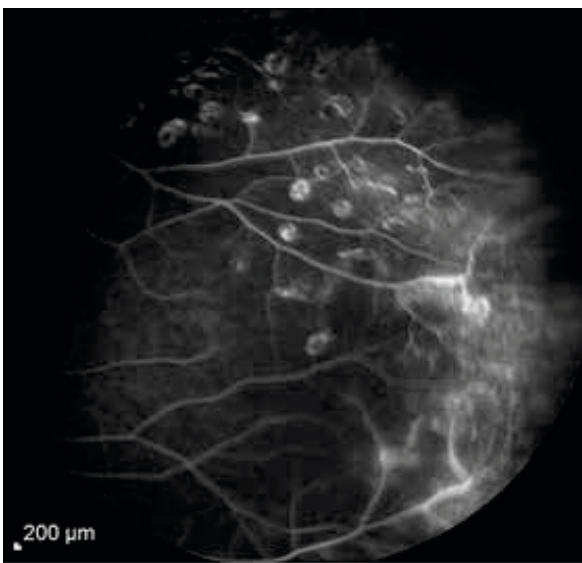


Figure 2. Vascular wall staining and late diffusion in a patient with Eales' disease.

**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis for the inflammatory and proliferative stages of Eales' disease can include several clinical entities, primarily ocular or systemic with secondary ophthalmic involvement (Tables 1 and 2).

**TREATMENT**

**MEDICAL MANAGEMENT**

Corticosteroids are the gold standard of care for the inflammatory stage of the disease with active periphlebitis. Oral therapy with prednisolone (1 mg/Kg/day) is the usual choice for most ophthalmologists. Adjuvant or isolated periocular treatment is also an option and can be effective

Table 1. Retinal vasculitis mimicking Eales' disease

Systemic	Ocular
Behçet's Disease	Birdshot choroidopathy
Leukemia	Coats' Disease
Lyme Borreliosis	Pars Planitis
Multiple Sclerosis	Viral retinitis
Sarcoidosis	Idiopathic retinal vasculitis, aneurysms and neuroretinitis
Systemic Lupus Erythematosus	Idiopathic central serous chorioretinopathy
Toxocariasis	Retinal macroaneurysms
Toxoplasmosis	
Wegener's granulomatosis	

Table 2. Proliferative vascular retinopathy mimicking Eales' disease

Systemic	Ocular
<i>Diabetes mellitus</i>	Branch retinal vein occlusion
Sarcoidosis	Central retinal vein occlusion
Sickle cell disease	Coats' Disease
	Pars Planitis
	Retinopathy of Prematurity

in controlling active vasculitis<sup>10</sup>. Immunosuppressants like cyclosporine or azathioprine can be helpful for patients who do not respond to monotherapy with corticosteroids or who need a steroid sparing agent. As already stated, some authors recommend the use of anti-tubercular treatment (ATT) in Eales' disease patients with positive latent TB test(s). It is also possible to combine the anti-inflammatory treatment with the ATT, if needed.

**LASER PHOTOCOAGULATION**

Photocoagulation is the gold standard of care for the proliferative stage of the disease. The aim is to decrease the release of vasoproliferative factors from the ischemic retina and eventually eliminate the new retinal vessels. Direct treatment with moderately-strong overlapping burns is recommended for patients with retinal neovascularization (Figures 3 and 4). As in other retinal proliferative diseases, panretinal photocoagulation is also recommended in the presence of optic disk neovascularization. In the case of extensive peripheral areas of retinal nonperfusion, scatter photocoagulation is the technique of choice.

The efficacy of laser treatment in Eales' disease has been described in several studies<sup>11-16</sup>. Minor associated complications include retinal hemorrhages and retinal gliosis with eventual formation of epiretinal membrane and retinal tears. It is advisable to start anti-inflammatory treatment, such as corticosteroids, before performing



photocoagulation in the active inflammatory stage of the disease, as laser treatment can worsen retinal neovascularization in the presence of active inflammation.

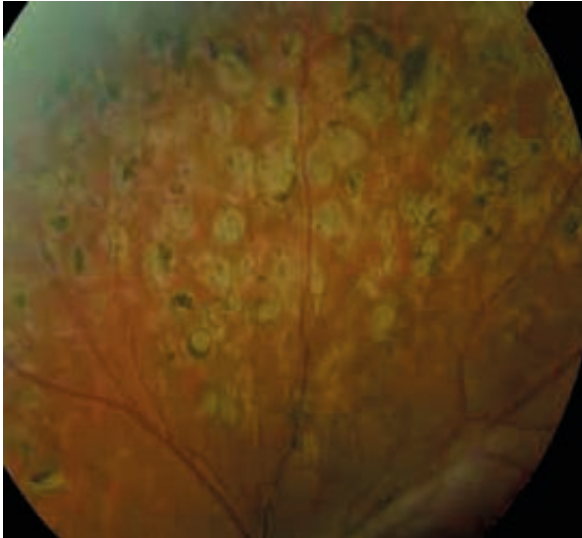


Figure 3. Retinal photocoagulation in a patient with Eales' disease.



Figure 4. Despite previous photocoagulation, there is still leakage from peripheral retinal new vessels in a patient with Eales' disease.

#### OTHER TREATMENT MODALITIES

As in so many other retinal proliferative diseases, anti-vascular endothelial growth factor (VEGF) intravitreal injections can be used as adjuncts to laser photocoagulation with positive results<sup>17-19</sup>.

Vitreectomy may be necessary for chronic vitreous hemorrhage, tractional retinal detachment with posterior pole involvement and combined tractional and rhegmatogenous retinal detachment.

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# IX. LASER in Retina/choroid: other clinical entities

## 59. Idiopathic Choroidal

## Neovascularization



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### INTRODUCTION

The term idiopathic choroidal neovascularization (iCNV) refers to a lesion of choroidal neovascularization (CNV) occurring in a patient under the age of 50, usually unilateral, with a refractive error that does not differ from that of the general population and without any apparent primary ocular or systemic disease usually associated with CNV. The diagnosis of iCNV is made by exclusion of predisposing diseases for CNV such as pathological myopia, angioid streaks, choroidal rupture and other retinochoroidal inflammatory or degenerative disorders. The natural history of iCNV is better than that seen in age-related macular degeneration (AMD) or other degenerative ocular diseases. Many studies indicate that foveal iCNV tends to be small, stable and less likely to cause severe visual loss, if treated<sup>1</sup>. However, severe visual loss will develop in many of the untreated eyes with iCNV<sup>2</sup>. Nevertheless, significant individual variation exists and the natural course of the disease could be unpredictable<sup>1</sup>.

The neovascular membrane is usually located above the retinal pigment epithelium, type 2 CNV, and is frequently extra or juxtafoveal (Figure 1).

### TREATMENT OF iCNV

The treatment options for iCNV are laser therapy, photodynamic therapy (PDT) with verteporfin or intravitreal anti-VEGF injections.

#### Laser treatment

The first treatment option described for iCNV was thermal laser.

The Macula Photocoagulation Study Group (MPS) studied patients with iCNV for 5 years. Treatment was found to be beneficial for juxtafoveal or extrafoveal lesions<sup>3,4</sup>.



Figure 1. Eleven-year-old boy with an iCNV lesion in the left eye.

According to the MPS protocol, either the krypton red 647 nm or argon/Nd:YAG KTP green laser can be used to obliterate areas of CNV. A fluorescein angiography should be carried out 96 hours earlier and used to guide treatment. Intense and confluent photocoagulation burns are required to cover the total area of classic and occult neovascularization. Burns should extend 100  $\mu$ m beyond the perimeter of the lesion. Fluorescein angiography must be repeated 3 and 6 weeks after the treatment.

Laser thermally ablates the neovascular membranes, but collaterally damages the adjacent neurosensory retina and an absolute scotoma will form. The purpose of this destructive treatment is to halt progression of the disease and maintain central vision. Due to the efficacy and safety of anti-VEGF treatments in subfoveal or juxtafoveal CNV lesions, laser is currently advised for the treatment of only certain well-defined and small extrafoveal iCNV lesions.

#### Photodynamic therapy with verteporfin

PDT was conceived as an oncology treatment to occlude neoplastic vessels since retinal vessels are accessible to direct light, it was later applied to ophthalmology. A pharmacological photosensitizer with a specific absorbance profile is administered intravenously. Exposure to an appropriate wavelength of light elevates

the photosensitizer to a higher energy state creating a cascade of photochemical events<sup>5</sup>.

For CNV, verteporfin (6 mg/m<sup>2</sup>) is infused intravenously over a 10-minute period. Five minutes later, the lesion is exposed to a 689 nm light dose of 50 J/cm<sup>2</sup> for 83 seconds. The light is used to induce a photochemical oxidation of vascular endothelium with no thermal damage of the tissue<sup>5,6</sup>. Retinal function is maintained and scotoma does not develop<sup>6</sup>.

However, visual outcomes for patients with subfoveal iCNV are inconsistent and variable and severe damage to the retinal pigment epithelium has been reported after PDT<sup>7,8</sup>.

### Intravitreal anti-VEGF injections

Several retrospective case series and short-term retrospective studies have analyzed the effects of intravitreal anti-VEGF in the treatment of iCNV revealing promising functional and anatomical results<sup>9-12</sup>. Some prospective trials evaluated the efficacy and safety of intravitreal bevacizumab in the treatment of subfoveal iCNV over a period of 12 months. The authors concluded that the treatment was well-tolerated and improved best-corrected visual acuity after the first injection, followed by monthly dosing as needed<sup>13</sup>. However, the results of large, randomized, controlled and long-term clinical trials are expected to establish a real therapeutic effect, safety profile and the optimal administration strategy of anti-VEGF drugs in patients with iCNV.

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# X. Endolaser and Vitrectomy

## 60. LASER delivery in

## operating room



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### INTRODUCTION

The first delivery system, employing portable xenon arc energy, used in vitreoretinal surgery was by Charles in 1979<sup>1,2</sup>. The limitations of this technology encouraged the development of laser endophotocoagulation systems; first with the laser generator unit (argon or krypton) located remotely in an area adjacent to the operating theater (Figure 1a); later with the portable unit (argon, diode or frequency-double Nd:YAG KTP 532 nm) stationed in the operating room (Figure 1b) and nowadays with some of them embedded into the different vitrectomy systems (Figure 1c)<sup>3,4,5,6</sup>.

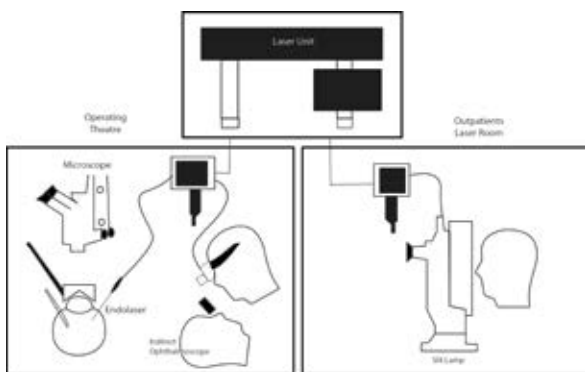


Figure 1a. Laser generator unit — old system of air or water cooled laser unit remotely located in an area adjacent to the operating theater with the fiber optic cable conveying laser light to a control console to which different delivery systems (endolaser probe, slit lamp, etc.) were connected. It was possible to supply a number of operating theaters as well as a slit-lamp delivery system for outpatient use, although not simultaneously.

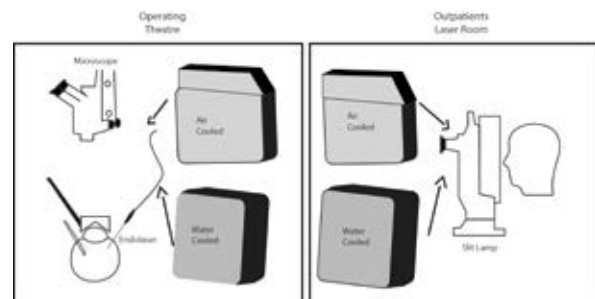


Figure 1b. Portable laser generator unit – portable systems (air or water cooled) stationed in the operating theater or outpatients' laser room in which the endolaser probe is directly coupled by a fiber optic line. The air-cooled units are smaller and lighter than their water-cooled counterparts but emit considerable heat.

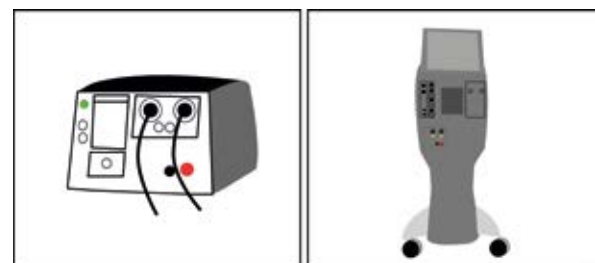


Figure 1c. Portable / embedded laser generator unit – portable air cooled system (left image) and embedded into a vitrectomy platform (right image).

The delivery methodology is as important as the laser system itself. Typically, intra-operative laser has been delivered with endolaser probe application, first developed by Peyman *et al.*<sup>3,7</sup>, although some surgeons have incorporated

indirect ophthalmoscopic transpupillary laser into their armamentarium for intra-operative laser photocoagulation. It is mandatory to provide protection for the operator and observers against exposure to reflected laser light by an appropriate filter, introduced into the viewing system of the operating microscope, or by an electronically controlled shutter, introduced below the objective lens. Lasers are stopped as filter is off or not properly assembled to the operating microscope. However, it is possible that the filter may be connected above the observer scope and that the assistant may not be protected from the laser light. Thus, it is desirable to verify that the filter connection is positioned to protect both the surgeon and the assistant, especially in operating microscopes used by different surgeons (Figure 2). Observation by indirect ophthalmoscopy requires the use of a filter in the plane of the assistant's viewing mirror or the eyepieces of the ophthalmoscope with the assistant and other personnel wearing protective goggles<sup>6,8</sup>.

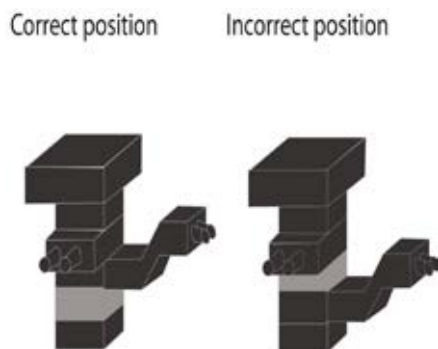


Figure 2. Laser filter (lighter area) connected to the microscope – protecting both observers (left image) and protecting only the surgeon (right image).

Endolaser photocoagulation typically achieves its effect through induction of thermal tissue necrosis at target tissue temperatures of over 60° centigrade. This thermal process for each unique laser wavelength depends upon the power settings and duration of the laser, the degree of underlying pigmentation, the working distance of the endolaser probe tip from the retinal surface and the angulation of the probe tip relative to the retinal surface. Higher power settings, longer duration, more pigmentation of tissues, decreased working distance and less angulation of the endolaser probe tip to the retinal surface result in increased photocoagulation. Any blood on the retinal surface should be avoided due to its intense laser uptake<sup>8</sup>.

#### LASER INTERFACE – PROBE DESIGN

The interface between the laser and the patient depends on the surgeon's choice of endolaser probe or laser indirect ophthalmoscope. Endolaser probes designed to interface with closed microsurgical instrumentation are available in 20-, 23-, 25- and 27-gauge diameters in various styles: straight or curved, blunt or tapered tip, simple or aspirating, or illuminating and flexible or articulated<sup>9,10,11</sup>. Curved laser probe delivery enhances peripheral laser, minimizes potential lens compromise in the phakic eye, and allows far peripheral laser delivery without the need

for scleral depression; this kind of probe technology is particularly valuable in conjunction with wide-field viewing systems and has markedly improved completion of laser treatment during the surgical procedure. Flexible or articulated laser probes are ideal for avoiding inadvertent lens contact, as well as for reducing obliquity resulting in elliptical spots. Illuminated laser probes reduce inadvertent lens contact during phakic retinal detachment repair caused by endoilluminator contact with the lens; additionally, it frees the surgeon's other hand, which can then be used for bimanual surgical techniques within the eye or scleral depression to aid visualization of peripheral retina while applying laser internally. The straight laser probe is better for panretinal laser photocoagulation (PRP) than curved probes<sup>8,12</sup>. Endophotocoagulation lesions are 600-800 µm in diameter, depending on the distance from the tip of the probe to the retinal surface, the beam divergence, and the power setting<sup>12</sup>.

#### SURGICAL TECHNIQUE

The endolaser probe must be held as a writing instrument. The probe tip should be perpendicular to a tangent along the retinal surface to be treated. This will ensure that the aiming beam delivers a round spot onto the retina and a uniform laser spot is achieved; an oblique positioning of the probe results in an irregular and elliptical laser spot and non-uniform laser burns (Figure 3).

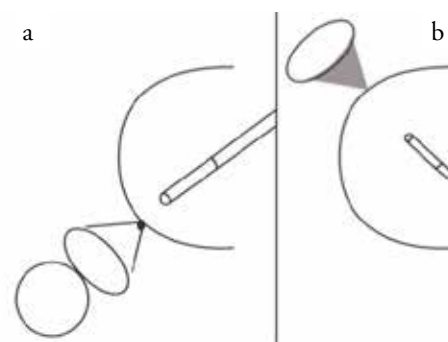


Figure 3. Endolaser probe position-a) perpendicular position results in a round, uniform laser spot; b) oblique position results in an oblique non-uniform laser spot.

The initial settings of the laser depend upon each laser wavelength; for green Nd: YAG KTP 532 nm /argon there should be a duration of 0.1-0.2 seconds and a power of around 200 mW; for diode it should be 0.2-0.3 seconds with 300 mW. The power should be adjusted incrementally (30-50 mW steps) until a light gray-white spot is achieved. It may be advisable to increase the duration to the next level to gain the desired effect at lower energy. The diode laser spot takes a few seconds to become visible. Thus, adjustments of laser power or other parameters should be staged to allow laser spot maturation. A continuous setting can also be used.

To achieve the desired burn spot size and burn intensity, the working distance should be increased or decreased accordingly and the power setting adjusted i.e., increasing the working distance and the laser power results in bigger spots whilst decreasing the working distance and the laser

power results in smaller burn spots (Figure 4). Endolaser can be performed through perfluorocarbon liquids, intraocular gas (air) or silicone oil.

The endophotocoagulator should never be used in air (gas) if there is blood on its tip; thermal damage to the probe, and structural alteration may result.

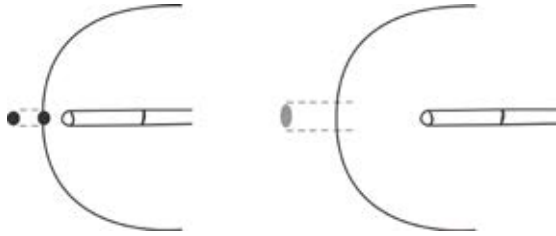


Figure 4. Increasing the working distance with the same laser energy results in less uptake and a bigger burn spot.

### INDICATIONS

Intraoperative laser treatment has revolutionized the surgical management of patients with complex vitreoretinal pathology. In some cases, laser endophotocoagulation can be used for the treatment of bleeding from surface neovascularization. It is an ideal tool for retinopexy and PRP<sup>8,12</sup>. To achieve the chorioretinal adhesions around retinal breaks, giant retinal tear margins and retinectomy edges two or three rows of adjacent multiple laser spots are usually applied. For focal treatment of retinal breaks, the continuous mode can be used to treat in a confluent manner around the breaks. This technique minimizes the possibility of undertreatment or overtreatment, which is intrinsic to the placement of discrete photocoagulation spots in rows. If the retina is detached, fluid-air exchange and internal drainage of subretinal fluid or the use of perfluorocarbon liquids, which bring the retina and retinal pigment endothelium into contact to effectively permit energy absorption, must precede endophotocoagulation. Periodically, during treatment, small amounts of subretinal fluid will shift posteriorly, making repeated internal drainage necessary to permit retinopexy. In certain cases, such as severe proliferative vitreoretinopathy, rows of peripheral laser treatment are applied to “wall-off” the area of prior detachment. The goal for endo-PRP is to achieve a laser pattern similar to that obtained using the slit lamp. The endolaser typically enables easier access to more peripheral retina than the nonoperative systems, particularly if wide-angle intraoperative viewing systems are used. The principal indication for this treatment is diabetic eye disease. Although some surgeons only use laser indirect ophthalmoscope (LIO) during vitrectomy, this method has no known advantages and many disadvantages (iris damage, potential damage of the macula). Small pupils, residual lens cortex and posterior capsular opacification cause problems with LIO delivery during vitrectomy. This delivery system is ideal for performing retinopexy on the contralateral eye in the operating room after vitrectomy repair of retinal detachment<sup>9</sup>.

### COMPLICATIONS

Retinal complications, such as **retinal necrosis**, **choroidal neovascularization**, **tears** or **subretinal hemorrhage** can

result from a too intense laser treatment or from direct impact of the tip onto the retina surface. Any break in Bruch’s membrane (noticed by an audible ‘popping’ sound) may serve as the site of ingrowth of choroidal neovascularization<sup>8</sup>. Other complications such as **fibrin syndrome** can occur if PRP is performed under air to areas of retina that had been detached before surgery because of overtreatment, due to persistent subretinal fluid and the thermal insulation properties of air<sup>12</sup>.

I gratefully acknowledge the help of Alexandra Meireles (Graphic Designer) in preparing the illustrations.

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# X. Endolaser and Vitrectomy

## 61 LASER in retinal detachment with or without vitrectomy



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### INTRODUCTION

Laser treatment in retinal detachment depends on the severity and extent of the retinal damage. When a break occurs with minimal or no retinal detachment, it can usually be treated by creating a laser barrier and retinopexy around the retinal break. Laser for retinal detachment without vitrectomy, or demarcation laser photocoagulation (DLP) refers to the placement of confluent laser photocoagulation burns (usually 3–5 rows) along the margins of a retinal detachment to completely surround it, resulting in a barrier to further extension of subretinal fluid<sup>1,2</sup>. It is less invasive than surgical techniques, time-efficient, inexpensive, requires no trained supporting staff, anesthesiologist or specialized operating room equipment, it is associated with minimal recovery time and unlike pneumatic retinopexy, there are no positioning limitations post-operatively<sup>3</sup>.

When further separation of the sensory retina from the retinal pigment epithelium occurs or when it is predictably impending and unpreventable with DLP (such as when proliferative vitreous retinopathy is present), surgical treatment must be considered. So, the primary goals of the surgery are the closure of the retinal defect, to relieve the tension over the retina, to induce changes in retinal fluidic currents and to create retinopexy<sup>4</sup>. The aim of adjuvant laser retinopexy is to create a permanent closure of the retinal break, as the tamponing effect of the gas used during surgery is only temporary. Laser retinopexy is currently preferred over cryopexy by many surgeons, as it is more precise and has less potential to cause proliferative vitreoretinopathy (PVR).

### INDICATIONS

DLP is used in the treatment of shallow retinal detachments in subclinical or asymptomatic patients (no central acuity or visual field defect)<sup>4,5</sup>, preferably in retinal detachments that are limited (i.e. between 2-5 times diameter of the largest break with a total size less than 2 clock hours and no extension beyond the equator) and anterior to the equator, but neither the extent nor the location of the detachment needs to be an exclusion criterion; however, detachments in the posterior pole should be treated only if at least three confluent rows of laser can be placed in attached retina between the subretinal fluid and the fovea or optic disc without damaging these structures<sup>6</sup>.

For symptomatic detachments it may be an excellent treatment choice for patients who are unable or unwilling to undergo surgery (especially if they have smooth, shallow macular-sparing detachments without proliferative retinopathy), in the understanding that there is a higher likelihood for further surgery than definitive repair. It can also be performed in patients that must wait for a surgery, in an attempt to limit the progression of the detachment.

Where surgery is indicated three techniques can be chosen (depending on the characteristics and seriousness of the rhegmatogenous retinal detachment, the surgeon's experience, and the available resources):

- pneumatic retinopexy (considered when there is a shallow detachment and the break is above the meridian of 4 to 8 hours, with no PVR);
- scleral indentation;
- pars plana vitrectomy (PPV) with or without scleral buckle indentation.

## CONTRAINDICATIONS

### DLP

- PVR;
- Large or bullous retinal detachments;
- Macular or near foveal detachment;
- Detachment near the optic disc.

## PREPARATION

### DLP

- 1 Explain the procedure mentioning the possible need of multiple sessions or other procedures, including surgery. Warn the patient that the bright lights will be intense and that vision will return momentarily after the examination.
- 2 A combination of phenylephrine 2.5% plus tropicamide 1% effectively achieves dilation in most patients. Repeating instillation of dilating drops is sometimes necessary for the pupil to be completely and widely dilated before proceeding.
- 3 Topical anesthetic with 0.5% proparacaine hydrochloride or oxybuprocaine hydrochloride 0.4% should be applied 1 to 5 minutes before the procedure. Retrobulbar block or general anesthesia may be carried out for compliance problems.
- 4 Work under dim light.
- 5 Ask patient to keep steady fixation.
- 6 Perform the DLP (see Table 1 – Laser technique)

### Vitrectomy

- 1 Vitrectomy for retinal detachment may be performed under local anesthesia with sedation or under general anesthesia in the event of a combined indentation technique.
- 2 Place the trocars 4 mm from the limbus in a phakic eye and 3.5 mm in a pseudophakic eye. The infusion probe should be inserted in the inferior temporal quadrant and the surgeon should confirm if the tip is free before opening the infusion.
- 3 Start vitrectomy in the vitreous "core" after inducing or confirming a complete detachment of the posterior hyaloid. In the case of 23 gauge, typical parameters are 5000 cpm and a vacuum set between 300-340 mmHg.
- 4 Perform complete vitrectomy to the vitreous base. The assistant can help in the scleral basis indentation during this stage.
- 5 Heavy liquid can then be injected to ease drainage of the subretinal fluid through the retinal break (we usually start injecting in the posterior pole, and then on the opposite side of the retinal injury, thus directing the fluid to the break and allowing good drainage).
- 6 Perform endolaser (Table 1).
- 7 Fluid-air exchange and drainage of residual subretinal fluid through the retinal break.
- 8 Tamponade: air-gas (SF<sub>6</sub> at 20% or C<sub>3</sub>F<sub>8</sub> at 14%) or air-silicone oil exchange.
- 9 Remove trocars, eventually suturing sclerotomies with a Vycril® 7-0 suture.

Additional surgical steps:

- Additionally, a scleral indentation technique can be performed prior to vitrectomy. After a complete 360° peritomy, we generally use a 2.5 mm large silicone band, sutured 12.5 and 10 mm away from the limbus with a 5/0 polyester suture and tightened to 10 mm after the switch to air<sup>7</sup>.
- In the presence of cataracts, phacoemulsification with intraocular lens placement in the capsular bag can be performed after the indentation technique described above) and the placement of the trocars, and before starting vitrectomy.

## LASER TECHNIQUE

Argon 514.5 nm laser (AL) or ND:YAG-KTP 532nm laser (KTP laser)

Table 1. Laser technique - DLP and Endolaser parameters

	DLP	Endolaser
<b>Power Range</b>	250–400 mW	160–220 mW
<b>Duration</b>	0.1–0.2 s	0.2 s or continuous mode (duration set by the surgeon in each burn)
<b>Spot Size</b>	200-300 μm	determined by the probe distance to the retina

For laser to be effective, the importance of adequate and correctly placed treatment should be emphasized. Laser is applied in three or more rows of confluent gray-white burns that are placed posterior to the entire detachment and which extend to the ora serrata surrounding the entire detachment (Figure 1). Power and duration are adjusted to obtain well visible white burns. Insufficiently confluent or incomplete laser demarcation is likely to predispose to the breakthrough of subretinal fluid. Because the goal of the laser is to create an adhesion scar and not only to perform a photocoagulation, the newer semiautomatic laser delivery systems like the Pascal<sup>7,8</sup> are not indicated for carrying out this laser barrier effect.

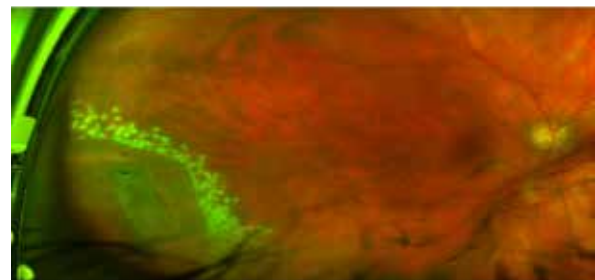


Figure 1. Colour fundus photograph of the temporal retina showing the area of contained residual subretinal fluid after DLT.

Indirect laser delivery system facilitates peripheral treatment in some cases (refer to chapter 63: Retinal Lesions with Difficult Access).

## FOLLOW-UP

Laser photocoagulation rapidly enhances retinal adhesion *in vitro* and *in vivo* to 140% of normal in 24 hours, and twice normal between 3 days and 4 weeks<sup>8</sup>.

Therefore, close follow-up in the first month and regular follow-up after the first month to ensure there is no evidence of progression is advisable. Regimens should be adjusted in a case-by-case basis. A stable retinal detachment with a continuous demarcation line can be followed up at 3 days, 1 week, 2 weeks, 1.5, 3, and 6 months, and then yearly for DLP. Best-corrected visual acuity and stability of rhegmatogenous retinal detachment are assessed at each visit.

When surgery is performed, patients can be followed at day 1, 1 week, 3 weeks, 1.5, 3 and 6 months assessing retinal status, degree of inflammation, intraocular pressure, persistence of the gas bubble, the efficacy of retinopexy, and visual function after complete reabsorption of gas.

## COMPLICATIONS

Insufficiently confluent or incomplete DLP is likely to predispose to the **breakthrough of subretinal fluid** (Figures 2 and 3).

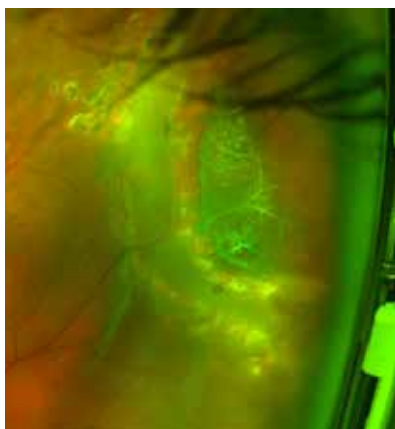


Figure 2. Colour fundus photograph of insufficient laser barrier with breakthrough of subretinal fluid.

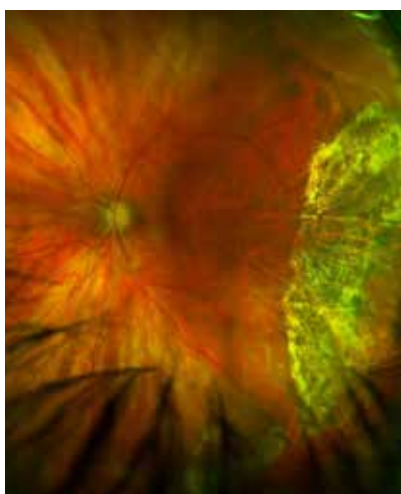


Figure 3. Colour fundus photograph of the same break treated after vitrectomy and endolaser retinopexy.

Other complications of the procedure are rare, but may include **posterior vitreous detachment** with formation of **new retinal breaks, epiretinal membrane formation, hemorrhage and choroidal effusion**.

## RESULTS

DLP is a low-morbidity treatment option for selected macula-sparing retinal detachments. In such cases, barrage photocoagulation is effective in up to 95% of patients within 20 months<sup>9</sup>. A possible indirect benefit of barrage photocoagulation is the early and accurate detection of rhegmatogenous retinal detachment progression, as it begins to cross the laser barrier.

The success rates of the surgery depend on the type of the detachment, the existence of PVR at presentation, and the surgery delay.

The primary rate (retina attached after one surgery) is about 81-92 % in uncomplicated cases<sup>10-16</sup>, and 65-70% in complicated cases, or 75% when no break is found<sup>17-21</sup>. The secondary or final rate (retina attached after multiple operations), is about 95%, related to the existence of PVR or when no break is visible<sup>22,23</sup>.

We expect a visual outcome of 20/40 in the majority of patients, that can be reduced to 44% of chance for this value if the macula is detached<sup>24-25</sup>.

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# X. Endolaser and Vitrectomy

## 62 Peripheral Retinal

## Degenerations

## and Tears



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### INTRODUCTION

Rhegmatogenous retinal detachment (RRD) is a vision threatening condition that affects about 1 in 10000 individuals each year, and it is caused by the accumulation of fluid between the neuroretina and the retinal pigment epithelium in the presence of a retinal break.

It is usually preceded by vitreous syneresis and some degree of posterior vitreous detachment (PVD). Typically, an anomalous PVD occurs, with partial separation allowing dynamic traction between the vitreous and the retina, which can lead to a retinal break. If the break is held open by vitreoretinal traction, it can allow accumulation of liquefied vitreous into the subretinal space, leading to a RRD.

There are no effective methods to prevent the vitreous syneresis and liquefaction that lead to an anomalous PVD, but one can prevent RRD by using laser photocoagulation in order to create a chorioretinal adhesion around the edge of a tear or other predisposing lesions.

### RETINAL BREAKS

Retinal breaks are full-thickness defects in the retina. These can be classified as **tears**, if associated with vitreoretinal traction, or **holes**, if round and unassociated with traction. A tear carries a greater risk of RRD than a hole, as it is associated with dynamic vitreoretinal traction. Between 8% and 26% of patients with acute PVD symptoms have a retinal tear at the time of their initial complaints, therefore a complete fundoscopic exam should always be performed<sup>1-5</sup>. However, a retinal tear does not necessarily lead to retinal detachment.

**Atrophic retinal holes** are full-thickness retinal defects,

unrelated to vitreous traction. They can occur within areas of lattice or degenerative retinoschisis and are an infrequent cause of progressive RRD.

**Horseshoe or flap tears** are caused by vitreous traction, and the characteristic shape is due to a flap of tissue that remains attached to the mobile vitreous, with the apex of the retina virtually always pointing towards the center. Only 5% of eyes with asymptomatic horseshoe tears progress to an RRD<sup>6,7</sup> and treatment of asymptomatic retinal tears should only be considered in eyes with associated risk factors (like previous RRD in fellow eyes and in eyes that have been subjected to cataract surgery)<sup>8</sup>. Besides the conclusions of this recent review<sup>8</sup>, debate on this topic continue and there is not an universal rule. The cost-effectiveness of laser barrier treatment for asymptomatic retinal break may be lower than that of regular examinations, and definitely lower than a RRD. A symptomatic retinal break is defined as a break caused by vitreoretinal traction in patients with a new PVD, or a break associated with new onset flashes or floaters. About half of untreated symptomatic retinal breaks with persistent vitreoretinal traction will lead to RRD if not treated<sup>5,9,10</sup>. As treatment reduces the risk of RRD to less than 5%, prophylactic laser photocoagulation should not be withheld in patients with symptomatic retinal breaks<sup>8-14</sup>.

**Operculated retinal breaks** are defects in the retina caused by vitreoretinal traction pulling a circular piece of retinal tissue (the operculum) free from the retinal surface, thus eliminating the traction (which may or may not remain at the edges of the hole). Operculated breaks usually do



not progress to a clinical detachment unless the vitreous remains adherent to the retina surrounding the break<sup>9,15</sup>.

**Retinal dialysis** is a specific type of crescentic peripheral retinal break at the ora serrata, usually associated with trauma. Traumatic dialysis and tears along the vitreous base are managed similarly to symptomatic tears.

### LATTICE DEGENERATION

Lattice degeneration is present in 6% to 8% of the population and in approximately 30% of the phakic retinal detachments, and is a known, although rather low, risk factor for RRD<sup>16</sup>. It is defined as ovoid spindle shaped areas of retinal thinning, located between the equator and the posterior border of the vitreous base, with overlying vitreous liquefaction and strong vitreoretinal adhesions at the edges. It is usually bilateral and it is frequently located in the temporal and superior fundus. Atrophic round holes may occur within areas of lattice degeneration and are usually innocuous.

The relation between lattice degeneration and RRD is established, however the majority of eyes with lattice are in no danger of RRD, with a lifetime risk of less than 1%. Consequently, lattice degeneration by itself does not justify prophylactic treatment. The small beneficial effect of treating these lesions was insignificant in eyes with myopia of 6 diopters or more and in eyes with both high myopia and more than 6 clock-hours of lattice degeneration<sup>17</sup>. When treatment is applied, some authors recommend photocoagulation over 360° of the peripheral retina, because around 58% of retinal detachments in eyes with lattice arise in areas of previous normal retina<sup>18</sup>. Myopic patients with lattice degeneration and round holes need careful follow-up visits and prophylactic treatment should be considered only when an associated subclinical detachment is documented to enlarge, or when retinal tears develop along the margins of the lesion<sup>16</sup>.

### DEGENERATIVE RETINOSCHISIS

Senile or degenerative retinoschisis is the splitting of the retina into an inner (vitreous) and outer (choroidal) layers, and is present in 3.5% of the general population. It is characterized by a smooth, dome shaped elevation of the inner layer of the schisis cavity, and the separation typically occurs at the outer plexiform layer. Natural history suggests that it is almost always non progressive, with RRD occurring in only 0.05% of patients. Prophylactic treatment is not recommended, unless a significant progression occurs or subretinal fluid posterior to the equator is detected menacing the macula<sup>19</sup>. In some cases, outer and inner layer breaks can develop. Outer layer breaks are usually large, round, located behind the equator and have rolled edges, while inner layer breaks are smaller, round and similar to atrophic holes. Despite the temptation to treat, these breaks usually remain stable. Occasionally, in eyes with degenerative retinoschisis, an asymptomatic retinal detachment develops, confined to the area of the schisis cavity.

### CYSTIC RETINAL TUFTS

Cystic retinal tufts are small congenital lesions of the peripheral retina, slightly elevated and usually whitish in color with variable surrounding pigmentation. They are

firmly attached to the overlying vitreous cortex and are sometimes a cause of retinal tears following PVD. The risk of RRD is however only 0.28%, and these lesions are not worthy of prophylactic treatment. Nonetheless, they deserve regular follow-up<sup>20</sup>.

### OTHER RISK FACTORS FOR RRD

Aside from retinal breaks, other risk factors for RRD must be considered, as they are associated with a considerable higher risk of RRD. These include myopia, lattice degeneration, prior cataract surgery (including refractive lens exchange), prior ocular trauma and history of non-traumatic RRD in the fellow eye. Other reported risk factors for RRD are hereditary vitreoretinopathies (e.g. Stickler Syndrome), prior retinopathy of prematurity, inflammatory conditions (retinitis, acute retinal necrosis), Nd:YAG 1064 nm Q-switch laser capsulotomy and a strong family history of retinal detachment. Despite the absence of appropriate data supporting that therapy lowers the rate of subsequent RRD, the existence of any of these factors may increase enthusiasm for prophylactic therapy.

### PROPHYLACTIC TREATMENT

The prevalence of retinal breaks is much higher than the incidence of retinal detachment, and this may lead to the statement that only those breaks and degenerations more likely to result in RRD should be treated, as extensive prophylactic treatment may cause complications. Several studies have tried to identify those situations where prophylactic treatment is truly indicated, however there are still no randomized controlled trials regarding prophylactic treatment of peripheral retinal degenerations and breaks.

Enough evidence exists for treating the acute, symptomatic flap tears, but there is insufficient evidence for the management of other vitreoretinal anomalies. In these cases the risks of treatment might be unnecessary, hence, they must be weighed against the possible benefit of reducing the rate of subsequent retinal detachment<sup>15</sup> (Table 1). Laser retinopexy is the primary treatment for retinal breaks, and the goal is to create a firm chorioretinal adhesion around the tear in the attached adjacent retina, thus preventing progression to RRD.

Occasionally *pars plana* vitrectomy with cryotherapy or endophotocoagulation is needed in very anterior lesions, as treatment by laser photocoagulation using a slit-lamp may be difficult in these cases.

The primary limitation of prophylactic therapy is related to the fact that most retinal detachments are due to retinal tears that develop in areas of “normal” retina prior to PVD<sup>21</sup>. Also, while the chorioretinal adhesion is created, “closing the door” to fluid entry from the vitreous, the problem of the dynamic vitreoretinal traction is not addressed.

### LASER TECHNIQUE

Laser photocoagulation is performed with a slit lamp delivery system using a fundus contact lens, under topical anesthesia, or using an indirect ophthalmoscopic delivery system.

POWER: 300-500 mW. Media opacity, the presence of shallow subretinal fluid or a relative paucity of retinal pigment epithelium and choroidal melanocytes may necessitate the use of higher powers.

Table 1. Management options (from the American Academy of Ophthalmology Preferred Practice Pattern®; Posterior Vitreous Detachment, Retinal Breaks and Lattice Degeneration)

Type of lesion	Management option
Acute symptomatic horseshoe tears	Treat promptly
Acute symptomatic operculated holes	Treatment may not be necessary
Acute symptomatic dialysis	Treat promptly
Traumatic retinal breaks	Usually treated
Asymptomatic horseshoe tears (without subclinical RD)	Often can be followed without treatment
Asymptomatic operculated tears	Treatment is rarely recommended
Asymptomatic atrophic round holes	Treatment is rarely recommended
Asymptomatic lattice degeneration without holes	Not treated unless PVD causes a horseshoe tear
Asymptomatic lattice degeneration with holes	Usually does not require treatment
Asymptomatic dialysis	No consensus on treatment and insufficient evidence to guide management
Eyes with atrophic holes, lattice degeneration, or asymptomatic horseshoe tears where the fellow eye has RD	No consensus on treatment and insufficient evidence to guide management

Table 2. Follow-up recommendations (from American Academy of Ophthalmology Preferred Practice Pattern®; Posterior Vitreous Detachment, Retinal Breaks and Lattice Degeneration)

Type of lesion	Follow-up interval
Symptomatic PVD with no retinal break	Depending on symptoms, risk factors and clinical findings, patients may be followed in 1-8 weeks, then 6-12 weeks
Acute symptomatic horseshoe tears	1-2 weeks after treatment, then 4-6 weeks, then 3-6 months, then annually
Acute symptomatic dialysis	1-2 weeks after treatment, then 1-3 months, then 6-12 months, then annually
Acute symptomatic operculated holes	2-4 weeks, then 4-6 weeks, then 3-6 months, then annually
Traumatic retinal breaks	1-2 weeks after treatment, then 4-6 weeks, then 3-6 months, then annually
Asymptomatic horseshoe tears	1-4 weeks, then 2-4 months, then 6-12 months, then annually
Asymptomatic operculated tears	1-4 months, then 6-12 months, then annually
Asymptomatic atrophic round holes	1-2 years
Asymptomatic lattice degeneration without holes	Annually
Asymptomatic lattice degeneration with holes	Annually
Asymptomatic dialysis	If untreated, 1 month, then 3 months, then 6 months, then every 6 months If treated, 1-2 weeks after treatment, then 4-6 weeks, then 3-6 months, then annually
Eyes with atrophic holes, lattice degeneration, or asymptomatic horseshoe tears where the fellow eye has RD	Every 6-12 months

**DURATION of PULSE LASER:** 0.1 to 0.2 sec.

**SPOT SIZE:** 300 to 500  $\mu\text{m}$  in the retina.

Treating lens: use TransEquator® or QuadrAsferic® or equivalent, bearing in mind the amplification factor of each lens.

Three to four rows of creamy white contiguous laser burns are placed, in flat retina, adjacent to any subretinal fluid, fully encircling the lesion. The anterior border is the most difficult to treat however its treatment is the most important.

Several features can make retinal breaks difficult to treat, for example a very anterior lesion or the presence of significant subretinal fluid or vitreous hemorrhage.

When an extensive treatment is performed, a systemic analgesic can be administered. Activity restriction is advised for a few days, especially if substantial subretinal fluid is present.

### COMPLICATIONS OF LASER PROPHYLAXIS

While being generally a safe procedure, complications of laser retinopexy may occur. These include: **inadvertent laser to the macula**, **choroidal effusion** (particularly in cases where laser is excessively used), **angle closure glaucoma**, **epiretinal membrane formation**, **anterior segment laser burns**, **hemorrhage** (of the retina, vitreous or choroid), **choroidal neovascular membrane formation**, and the formation of **new retinal breaks**.

### FOLLOW-UP

Between 5% and 14% of patients with an initial retinal break will develop additional breaks during long-term follow-up<sup>5,22,23</sup>. Retinal detachment may also occur despite appropriate treatment, especially in the setting of persistent vitreoretinal traction, and one must remember that the laser-induced chorioretinal scar may not be completed for up to one month. It is therefore crucial to make a good follow up of patients after prophylactic laser treatment, to ensure that new retinal breaks are timely detected (Table 2).

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# X. Endolaser and Vitrectomy

## 63. Retinal lesions with difficult access

Photocoagulation via indirect ophthalmoscopy and transscleral diode laser photocoagulation



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### INTRODUCTION

Conventional transpupillary laser delivery systems incorporate a slit-lamp biomicroscope for viewing the ocular structures. Unfortunately, these accessories lack versatility and often cause discomfort for the patient<sup>1</sup>. Treatment of the far retinal periphery is often difficult, particularly in the presence of intraocular lens, retinopathy of prematurity, media opacities and corneal edema, amongst others<sup>2</sup>. Moreover, some debilitated patients cannot sit or require an assistant to hold their head forward in proper position against the headband. In eyes harboring a small gas bubble, multiple light reflexes reflecting off the bubble make laser photocoagulation at the slit lamp often difficult to achieve.

For these difficult settings, indirect ophthalmoscopy with photocoagulation or transscleral diode laser photocoagulation can be an alternative (Figure 1). Because the field of view with the indirect ophthalmoscope is large, skip areas are easily avoided, foveal landmarks are easily identified, and patient set-up time is minimal. A great benefit of both techniques is the ease with which one can perform retinal ablation while performing scleral depression, particularly in very peripheral lesions and poor transparency media.

### INDICATIONS

This treatment is indicated for eyes with small pupils, with focal opacities, gas-filled or having gas bubbles, eyes harboring peripheral retinal pathology such as retinal breaks, lattice degeneration or peripheral



Figure 1. Indirect ophthalmoscopy with laser photocoagulation.

neovascularization, or any eye requiring laser out to the *ora serrata*.

It is also indicated for patients with limitations to seat behind a slit lamp (ex. anesthetized patients; physical limitations; babies and infants).

### 1. INDIRECT LASER OPHTHALMOSCOPY

The indirect laser ophthalmoscope consists of a standard argon/ Nd:YAG KTP 532 nm laser (KTP laser)(green) console joined to a binocular indirect ophthalmoscope via a quartz fiber and a fixed safety filter fitted over the binocular ophthalmoscope eye-pieces. As with most laser

systems, it allows for the adjustment of the laser power output and duration of the pulse, however the laser spot size on the retina will depend on the lens used for photocoagulation, the refractive status of the eye and the working distance between the surgeon's eye, the lens and the patient's retina<sup>3</sup>. For instance, a 30D lens will reduce the spot size to ½ and a 20D lens will reduce it further to 1/3. The spot will be smaller in a myopic eye than in an emmetropic eye and bigger in a hyperopic eye.

Knowledge of how the spot size can be altered in the indirect laser delivery system allows the beginner laser surgeon to gain proficiency rapidly. If the laser focus is initially above the image plane, then movement of the surgeon's head toward the patient will make the spot size smaller, until it is at the image plane. If the surgeon continues to move toward the patient, then the spot will gradually become larger. Accuracy is enhanced when the laser surgeon is sitting rather than standing, although this posture makes access to all retinal areas more difficult. Whether the surgeon is standing or sitting, depression of the foot pedal without moving the head becomes difficult when panretinal laser photocoagulation is being administered. For this reason, systems allowing multiple laser shots to be fired when the pedal remains depressed are greatly preferred.

### CONTRAINDICATIONS

Macular photocoagulation is a contraindication to this procedure. Because of system instabilities, laser lesions cannot be placed more accurately than  $\pm 200 \mu\text{m}$  from the desired target, even under ideal conditions. This virtually precludes its use in macular photocoagulation.

### PREPARATION FOR INDIRECT LASER OPHTHALMOSCOPY

1. Explain the procedure mentioning the possible need of multiple sessions or other procedures. Warn the patient that the bright lights will be intense, that scleral depression may be uncomfortable and that vision will return momentarily after the examination.
2. A combination of phenylephrine 2.5% plus tropicamide 1% effectively achieves dilation in most patients. Repeating instillation of dilating drops is sometimes necessary for the pupil to be completely and widely dilated before proceeding.
3. Topical anesthetic with 0.5% proparacaine hydrochloride or oxybuprocaine hydrochloride 0.4% applied 1 to 5 minutes before the procedure will relieve pain, discomfort and blinking reflex. If many burns are being placed in a sensitive eye, a retrobulbar block of 2 ml 2% lidocaine hydrochloride will allow for more comfortable photocoagulation. However, it has the disadvantage of limiting the patient's extreme gaze positions.
4. Work under dim light.
5. Have the patient lie down on a stretcher or let them sit up with the head against a backrest to minimize head movement. Ask them to keep looking at a steady point in accordance with the retina zone you are treating.
6. Stand or sit opposite the area of the fundus to be examined.

### LASER TECHNIQUE

*Nd:YAG KTP 532 nm laser (KTP laser) / Argon 514.5 nm laser (AL)*

Laser beam variables:

Duration: 0.05 s to 2 s

Power: 200 mW – 400 mW continuous pulse

It is recommended that lower-power settings should be used initially, such as 200 mW power with an effective retinal spot size of 330  $\mu\text{m}$  and 0.2-second pulse duration. The power is increased gradually until a reproducible burn is achieved. The power density required to produce a laser spot on the retina depends on the pigmentation of the retina and the clarity of the optical media. Higher powers per square millimeter are needed for more lightly colored fundi. To obtain sufficient power densities at the fundus in eyes with media opacities, higher laser powers must be dialed in at the console. If the laser spot becomes elliptical rather than round, such as during treatment of the far retinal periphery, the area of the laser spot is reduced and the spot becomes hotter. To avoid choroidal burns, the hand-held lens should be tilted as necessary to keep the laser aiming spot on the fundus as round as possible.

During scleral depression, less power is needed to obtain a lesion compared to treating a "nondepressed" retina. This is probably due to the stretching of the vascular choroid over the scleral depressor, which reduces the choroid's ability to cool the retina and pigment epithelium during the laser pulse.

Spot Size:

The size of the laser spot on the retina can be gauged by placing the aiming spot near an anatomical landmark of known diameter, such as the optic disc or the major retinal vessels. To change the size of the laser beam, the laser surgeon can move the point of focus either toward or away from the image plan by moving their head. Some manufacturers allow the spot size to be altered by simply moving a lever located on the headset. This will, in reality, move a set of zoom lenses that will change the point of focus.

Extremes of gaze:

The extremes of gaze allow the surgeon better access to the peripheral retina if the patient is cooperative. With a non-cooperative patient or when a retrobulbar block is performed, scleral depression can be performed mechanically with a cotton-tipped swab or a thimble-type depressor<sup>4</sup>.

### Tips:

- The same laser energy given over a longer pulse duration is less likely to cause choroidal hemorrhage than repeated shorter pulses.
- The cornea must be kept moist by occasionally closing the patient's eyelids or instilling saline drops or artificial tears.
- Gas-filled eyes:  
Gas dramatically changes the optical power of the eye, as the posterior surface of the lens in the air-filled vitreous cavity forms a powerful plus lens resulting in a highly myopic (approximately 60D) eye. With air-filled phakic eyes, the 20D lens should be moved away from the patient's eye to obtain a reasonably small spot size.

The optical situation of a gas-filled aphakic eye is one of



the most difficult in which to produce a laser lesion on the retina because the laser spots tend to be very large (the refractive power of the cornea is neutralized because of the gas present at the posterior surface of the cornea). In air-filled aphakic eyes, the lens should be moved closer to the patient's eye.

## COMPLICATIONS

**Choroidal hemorrhage** resulting from a burn that is too hot is the most common complication. This occurs most commonly in the retinal periphery or in eyes with focal lenses or media opacities. Hemorrhages can be largely prevented by avoiding short-duration burns, carefully monitoring the brightness of the laser aiming beam on the retina and reducing the power when it appears too bright, and also keeping the aiming beam spot as round as possible. If a choroidal hemorrhage occurs, the intraocular pressure should be raised by gently pressing on the globe with a finger to stop the bleeding. Surrounding the hemorrhage site with two or three rows of laser photocoagulation burns may be prudent and may prevent retinal detachment.

**Macular or foveal burns** are virtually always preventable due to the wide view provided by the indirect laser system. However, if a patient seems very anxious, complains of pain repeatedly during photocoagulation, or cannot control his fixation, a retrobulbar block should be strongly considered.

## 2. TRANSSCLERAL DIODE LASER PHOTOCOAGULATION

Diode laser photocoagulation largely replaced cryotherapy in the transscleral treatment of very peripheral retinal lesions or in eyes with media opacities. The near infrared wavelength of the diode laser combines high transmission through the sclera with high uptake in melanin cells, therefore having the ability to induce a focal tissue effect that is limited to the outer retina and inner choroid, with minimal damage to the inner retina, outer choroid, or sclera<sup>5</sup>. As a result, there is less extensive tissue effect and also less marked inflammatory side effects in comparison with transscleral cryotherapy, including breakdown of the blood-ocular barrier associated with cystoid macular edema, and release of retinal pigment epithelium cells with epiretinal membrane formation and proliferative vitreoretinopathy<sup>6,7</sup>. Furthermore, it can be accomplished through silicone scleral explants or glaucoma drainage devices.

In transscleral laser coagulation, a hand-held laser probe delivers laser energy at its distal tip. This technique allows coagulation of the periphery even in the presence of a poorly dilated pupil while sparing the lens. The aiming beam of the transscleral diode laser also provides precise localization during an indirect ophthalmoscopic view of injuries. This is an advantage over cryotherapy, during which the surgeon may mistake the indentation of the probe shaft for the cryoprobe tip and thus unintentionally administer posterior (even macular) freezes<sup>8</sup>. Retinal blanching can usually be seen even in cases where the fundus view is obscured by subretinal fluid, cataract, or blood.

Transscleral laser application has also been used as an alternative treatment method for transpupillary retinal

photocoagulation, particularly in patients with retinopathy of prematurity<sup>9</sup>. Spot size in transscleral coagulation is approximately 1000  $\mu\text{m}$ , allowing significantly fewer laser spots to be administered during transscleral coagulation as compared with the transpupillary approach for the coagulation of the same area of the avascular retina<sup>10</sup>. Also, in contrast to the transpupillary approach, the laser beam is perpendicular to the ocular wall and retina, thus making photocoagulation of the peripheral retina easier. However, for less peripheral lesions to be treated, conjunctival incisions are necessary.

## CONTRAINDICATIONS

Macular or very posterior lesions.

## PREPARATION FOR TRANSSCLERAL DIODE LASER PHOTOCOAGULATION

The same as for indirect laser ophthalmoscopy (see above). However, as it is generally a more painful procedure, it should be performed under subconjunctival, peribulbar or retrobulbar block with 2 ml 2% lidocaine hydrochloride, or under general anesthesia.

## LASER TECHNIQUE

*Diode laser 810 nm (DL) infrared*

Laser beam variables:

Duration: 100 ms to 3 s (or more)

Power: 100 mW – 1000 mW continuous pulse

The target area is visualized with an indirect ophthalmoscope while a transilluminating aiming beam from a red emitting diode laser facilitates precise placement of the probe over the target area. A foot switch activates the laser and in all cases the desired visible end point is the grayish-white appearance typical of a threshold diode laser lesion. The target area is irradiated until a reaction is observed. The power is increased in 100 mW increments if a lesion is not observed after an exposure of up to 2-3 seconds. The power is decreased following an intense blanching reaction, an audible 'popcorn' effect, or a hemorrhagic lesion. Higher powers are required in the presence of lower retinal pigment epithelium pigmentation, subretinal fluid or hemorrhage.

### Tips:

- More efficient tissue effect, with far lower incidence complications, is achieved by increasing energy delivery through lengthening the duration of laser delivery rather than increasing the power.
- Other tricks in using the probe include indenting the sclera, keeping the probe at 90° to the sclera so that the aiming beam is small and round on the retina, making adjustments for pigment variations in the treated areas of the fundus, and stopping laser treatment with an endpoint of light graying, which then evolves to a whiter lesion with time.

## COMPLICATIONS

**Scleral thermal effects** defined as color changes at the treatment sites observed on the sclera are typically noted in eyes where the sclera was thin or blue.

**Apparent ruptures of Bruch's membrane:** tiny visible



tissue disruptions deep to the retina, often accompanied by a small audible pop are more likely to occur in eyes that received higher mean total energy.

**Intraocular hemorrhage** can occur and is generally pinpoint and confined to the retina or choroid and seldom affects the surgical outcome.

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# XI. Pediatric and hereditary conditions

## 64. Retinopathy of prematurity



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### INTRODUCTION

Retinopathy of prematurity (ROP) is a vasoproliferative disease, secondary to an inadequate vascularization of the immature retina in pre-term infants. Despite advances in neonatal medicine, ROP remains a significant cause of blindness and visual impairment.

In the 1980s, after the publication of CRYO-ROP study<sup>1,2,3</sup>, transscleral cryotherapy became the first effective treatment for avascular retinal ablation in ROP. During the 1990s, the development of laser systems coupled with an indirect ophthalmoscope allowed for retinal laser "ablation", by photocoagulation of the avascular retina, to gain acceptance as an alternative to cryotherapy with equivalent or superior outcomes. Although laser photocoagulation involves a steep learning curve, many studies have reported functional and structural results superior to those of cryotherapy. It was found to be more controlled, less traumatic and with fewer intraoperative and postoperative complications, such as myopia<sup>2-7</sup>. Thus, laser photocoagulation is nowadays the treatment

of choice for ROP.

Meanwhile, new therapies are currently being investigated, including anti-VEGF drugs.

Intravitreal injections of anti-VEGF drugs seem promising for the treatment of ROP, and encouraging results have been presented, such as those in the BEAT-ROP study<sup>7,8</sup>.

It seems to be a relatively quick and easy treatment, associated with a lower rate of myopia when compared with laser therapy<sup>9</sup>. However, more controlled studies are necessary to evaluate its long-term safety.

### INDICATIONS

Previous guidelines of CRYO-ROP study recommended treatment for threshold ROP within 72 hours.

However, a recently ETROP study showed benefits with early treatment, which should be considered in high-risk or type 1 pre-threshold ROP within 48 hours<sup>10,11</sup>.

Treatment is also indicated in cases of aggressive posterior ROP, despite its relative ineffectiveness (Table 1).

Table 1. Definition of threshold ROP, pre-threshold type 1 ROP and aggressive posterior ROP

<b>Threshold ROP</b> Classic indication for treatment after the CRYO-ROP study in 1988.	Stage 3, in zones I or II, with at least 5 contiguous clock hours or 8 noncontiguous clock hours, with plus disease.
<b>Pre-Threshold Type 1 ROP</b> Treatment has been indicated since the ETROP study in 2004.	Any stage of ROP in zone I with plus disease. Stage 3, zone I, without plus disease. Stage 2 or 3, zone II, with plus disease.
<b>Aggressive Posterior ROP</b> Definition introduced in international classifications of ROP in 2005.	Uncommon, severe, and rapidly progressing. Zone I or II, with plus disease, which does not follow a stage-based evolution pattern.

**PREPARATION**

1. The purpose of treatment, risks and possible complications should be explained to the parents.
2. Treatment can be performed in the neonatal intensive care unit or in the operating room, depending on the convenience or resources available.
3. Pharmacological mydriasis (traditionally performed with tropicamide 0.5% and phenylephrine 2.5% drops, 30–40 minutes before the surgical procedure).
4. Anesthesia - the type of anesthesia should be decided case-by-case by a team that includes an ophthalmologist, a neonatologist and an anesthesiologist. However, it is recommended general anesthesia or analgesia with sedation.
5. Always apply topical drops of oxybuprocaine.

**LASER TECHNIQUE** <sup>2,3,6,8,12</sup>

The surgical material necessary for this procedure is: pediatric lid speculum; scleral depressor; laser system combined with an indirect ophthalmoscope; 28D, 20D or Volk Pan Retinal<sup>®</sup> 2.2D lens; and a syringe with an irrigation solution (Figure 1).



Figure 1. Surgical materials required for laser treatment of ROP.

The two main wavelengths of light currently used in retinal photocoagulation are 810 nm and 532 nm. The diode laser 810 nm (DL) has a theoretical advantage because it is not so extensively absorbed by the vascular tunic of the lens or by persistent fetal vasculature, causing less risk of cataract formation, synechiae and vitreous contraction.

*Nd:YAG KTP 532 nm laser (KTP laser) or Diode laser 810 nm (DL)*

The most common approach is transpupillar.

The goal of the treatment is the "ablation" of the entire avascular retina by photocoagulation. It generally starts from the anterior edge of the vascularized retina and is applied out to the *ora serrata*.

The ridge should not be included due to the risk of hemorrhage, and because its benefit has yet not been proven. In a first treatment, the benefit of photocoagulation

posterior to the ridge has also not been demonstrated.

The expected result from each laser pulse is a moderate white burn on the retina, however, with diode laser 810 nm these changes are more subtle.

The power and pulse duration depend on many factors, including media opacity and pigmentation of the retinal pigment epithelium. Initial power settings normally vary from 200 mW to 400 mW and pulse duration varies from 0.1 second to 0.3 second, with repeat mode set at 0.4 second.

Spot size is not pre-established with indirect laser. It depends on the type of the indirect lens used, the patient's refractive state and the surgeon's experience and skills. Hence, it is difficult to make spots that are consistently of the same size.

The distance between the spots should be approximately half the diameter of the spot, keeping in mind that a more confluent photocoagulation pattern has shown evidence of being more effective in reducing the number of re-treatments and the rate of progression to more severe stages. The total number of spots per treatment varies, depending on the area of avascular retina to be treated and the size and distance between the spots.

Laser is performed during a single session and the treatment should be concluded with a close examination of the retina to search for non-photocoagulated areas (skip areas), which is a cause of an unsuccessful therapy (Figure 2).

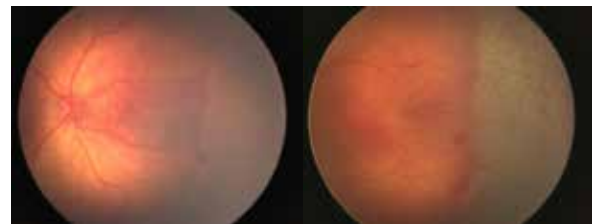


Figure 2. Laser photocoagulation of avascular retina.

**POSTLASER CARE AND FOLLOW-UP**

After treatment, topical antibiotic, corticosteroid and cycloplegic should be applied to reduce infection risk and inflammation (for example 3 times a day during 1 week). The newborn must be evaluated one day after treatment to check for early-onset complications and 1 week later to monitor the results. The frequency of serial re-observations should be determined by the patient's response to treatment. Regression is considered to happen when there is a lack of active neovascular tissue and if plus disease is in remission. When the first ablation treatment fails, there are no protocols regarding complementary photocoagulation nor regarding the opportune time to retreat. Options include ablation of non-photocoagulated areas and photocoagulation posterior to the ridge after a period of observation of at least 2 weeks.

**COMPLICATIONS** (Table 2) <sup>2,6,8</sup>

The most frequent ocular and systemic complications are outlined in table 2:

Table 2. Complications of laser treatment

<b>Ocular</b>
Pain
Cornea, iris or lens burns
Hyphema, vitreous or retinal hemorrhage
Rupture of Bruch's membrane, choroidal hemorrhage
Inadvertent foveal photocoagulation
Epiretinal membrane
Myopia
Inflammation
<b>Systemic (more frequently associated with anesthesia)</b>
Apnea
Bradycardia
Need for re-intubation

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# XI. Pediatric and hereditary conditions

## 65 Familial exudative vitreoretinopathy



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### INTRODUCTION

Familial exudative vitreoretinopathy (FEVR) was described in 1969 as a disease with ocular findings similar to those of ROP, but occurring in full-term newborns<sup>1</sup>.

FEVR is a rare inherited disorder of retinal angiogenesis, seen in non-premature children, with asymmetrical bilateral expression. Its inheritance pattern can be autosomal dominant, autosomal recessive, X-linked or sporadic<sup>2</sup>.

FEVR manifests by peripheral avascular retina, particularly in the temporal area, which leads to neovascularization, exudation, fibrovascular proliferation, vitreoretinal traction with the formation of folds, ectopia of the disk and macula and retinal detachment<sup>2</sup> (Figure 1).

The main differential diagnosis includes retinopathy of

prematurity and Coats' disease<sup>2</sup>.

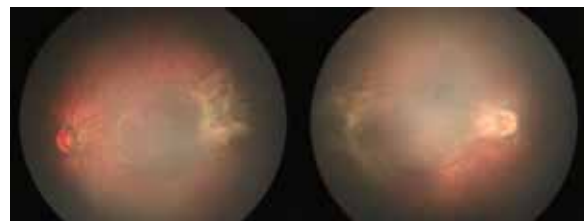


Figure 1. Fundoscopic findings of FEVR.

The most common classifications used in FEVR staging are<sup>1,2</sup> (Table 1):

Table 1. FEVR classification

Gow and Oliver's Classification <sup>3</sup>	Pendergast <i>et al.</i> 's Classification <sup>4</sup>
<b>Stage I</b> - Asymptomatic, changes in the vitreoretinal interface and peripheral avascular areas	<b>Stage 1</b> - Avascular retinal periphery
<b>Stage II</b> - Proliferative and exudative stage in which neovascularization can be observed, as well as fibrovascular proliferation and subretinal and intraretinal exudation	<b>Stage 2</b> - Preretinal neovascularization a) without exudate b) with exudate
<b>Stage III</b> - Scarring lesion that causes tractional or rhegmatogenous retinal detachment and retinal folds	<b>Stage 3</b> - Retinal detachment not involving macula a) without exudate b) with exudate
	<b>Stage 4</b> - Retinal detachment involving macula a) without exudate b) with exudate
	<b>Stage 5</b> - Total retinal detachment



The available therapeutic options are cryotherapy, laser photocoagulation and vitreoretinal surgery. The choice depends on the stage of the disease and resources available<sup>1,4,5</sup>. Laser treatment should be used to ablate peripheral avascular areas in case of neovascularization with leakage in fluorescein angiography, exam which should be performed whenever possible. Cryotherapy can be used for treatment of neovascularization in patients with non-dilating pupils or with hazy media, however, nowadays this is rarely considered an option. In patients with retinal detachment, surgical intervention should be considered<sup>4,6</sup>.

### INDICATIONS

Prophylaxis in the avascular areas using laser photocoagulation is controversial and there is no consensus in the literature.

The main indication for laser is neovascularization and retinal exudation.

In cases of retinal detachment, laser photocoagulation can be used in combination with vitreoretinal surgery.

### PREPARATION

1. The purpose of treatment, risks and possible complications should be explained to parents.
2. Pharmacological mydriasis (traditionally performed with tropicamide 0.5% and phenylephrine 2.5% drops, 30–40 minutes before the surgical procedure).
3. Anesthesia – in most cases, due to patients' age, it is recommended general anesthesia or analgesia with sedation.
4. Always apply topical drops of oxybuprocaine.

### LASER TECHNIQUE, POSTLASER CARE AND FOLLOW-UP

1. There are no established protocols for FEVR treatment, partially due to the low prevalence of the disease.
2. Surgical technique consists on the ablation of the entire avascular retina, a process extremely similar to the one described in the previous chapter - Retinopathy of Prematurity (chapter 64).
3. It is crucial for patients to be monitored throughout their lives to check for ocular and systemic changes that may be associated with the disease.

### COMPLICATIONS

Immediate postoperative care and ocular complications of laser treatment are also similar to those described in the previous chapter 64.

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# XII. LASER In retina/ choroid: tumors

## 66. Malignant

## melanoma



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### INTRODUCTION

Uveal melanoma is the most common primary intraocular tumor in adults, and approximately 80% arises from the choroid<sup>1,2</sup>. Choroidal melanomas usually appear clinically as a pigmented or amelanotic elevated lesion. Diagnosis includes direct visualization through indirect ophthalmoscopy, ultrasonography showing an acoustic hollowing of the tumor, choroidal excavation, orbital shadowing, a "collar-button" configuration, and a double circulation pattern in fluorescein angiography. Histopathologically, melanomas present three cell types: spindle A, spindle B and epithelioid cells<sup>2</sup>.

For many years, enucleation was the standard therapy for primary choroidal melanomas. Since the 1990s, its treatment perspective has changed and shifted toward the combination of different modalities<sup>1</sup>. The factors influencing treatment choices are tumor size, localization, growth pattern, status of the opposite eye and patient age and health. In 1961, Meyer-Schwickerath, a German ophthalmologist, was the first to treat a malignant choroidal melanoma with laser<sup>3</sup>, opening a new paradigm in the ocular tumors management<sup>4</sup>. Transpupillary thermotherapy (TTT) was introduced later, in 1994, and was found to have fewer complications, greater penetration, and a better tumor destruction effect compared to laser photocoagulation. Other conservative treatments such as plaque radiotherapy, radiotherapy with charged particles and even conservative local resection can also be used, however they are not in the scope of this chapter.

In thermotherapy a near-infrared diode laser (810nm), is used to induce temperatures between 45–65°C (at a sub-photocoagulation level) producing local hyperthermia and thus generating an irreversible cytotoxic effect. TTT may be an option in intra-ocular tumors such as melanomas, retinoblastomas and hemangiomas, with the laser directed transpupillary into the tumor center<sup>1</sup>.

Histopathologic results of experimental TTT performed in human choroidal melanomas prior to enucleation did not show any damage in the remaining intra-ocular structures. In the tumor, TTT produces necrosis and vascular occlusion up to 3.9 mm of depth<sup>5</sup>, which is significantly higher than the 0.2 to 1.0 mm of depth achieved with photocoagulation<sup>6</sup>.

### INDICATIONS

In small tumors as primary therapy:

- 12 mm or less in basal diameter;
- 4 mm or less in thickness;
- Located posterior to the equator of the eye;

Risk factors for tumor growth are: tumor thickness >2 mm, subretinal fluid, symptoms, orange pigment, tumor margin touching the optic disc, and ultrasonographic hollowness<sup>7</sup>.

### CONTRAINDICATIONS

TTT is not indicated if<sup>2</sup>:

- The pupil cannot be dilated sufficiently;
- There is difficulty positioning the patient;
- The tumor is located in the far periphery so that its full extension is not visible with a wide field contact lens;
- Anterior or posterior segment opacities preclude a clear view;
- Tumor abutting or overhanging optic disc;
- The pre-treatment amount of subretinal fluid measures more than 3mm in elevation. In these cases TTT may cause a hole in the atrophic retina, resulting in retinal detachment<sup>1,8</sup>.

### PREPARATION

- 1 Explain the procedure mentioning the possible need of multiple sessions or other procedures.

2. Dilate the pupil with tropicamide 1% and phenylephrine 10%.
3. Anesthesia – use peribulbar or retrobulbar anesthesia.

### LASER TECHNIQUE

#### *Laser Near-Infrared Diode 810 nm*

Direct laser application is made over the entire surface of the tumor with overlapping spots, and also in the adjacent retina including 1.5 mm beyond tumor margin. The laser beam can be delivered onto the eye by indirect ophthalmoscopy using a 20D lens, or by slit lamp using contact lens.

Table 1. Laser beam variables

<b>Spot size</b>	2-3 mm
<b>Exposure time</b>	Approximately 60 seconds
<b>Power</b>	300-600 mW - less power for darker pigmentation, more power for amelanotic tumors.  Goal: Grayish discoloration of tumor

Due to pigment variation of lesions, treatment starts with a central application on the tumor surface at a relatively low power (for example, 450 mW for normal pigmentation, 600 mW for amelanotic tumors and 300 mW for dark pigmentation), so that little or no visible effect is seen after a 1 minute exposure<sup>2</sup>. Depending on the degree of pigmentation the laser power setting is increased in 50 mW after each minute of exposure until a grayish or slightly white color develops 40-45 seconds later. This subtle discoloration is a useful indication of the power that is needed to obtain a temperature just in the sub-photocoagulation level<sup>1</sup>. The response of TTT in amelanotic melanomas can be enhanced by intravenous injection of indocyanine green prior to TTT, as the green dye increases the absorption of infrared light in the tumor. This is called “dye-enhanced TTT”<sup>1</sup>.

### POSTLASER CARE AND FOLLOW-UP

After the first session, a complete ophthalmic exam should be performed at intervals of 2 months. The decision to perform a new treatment session is based on both the ophthalmic and angiographic evaluations, as well as on tumor dimensions on ultrasonography.

### COMPLICATIONS

Potential complications of TTT include retinal and choroidal vascular occlusion, retinal hemorrhage, tractional retinal detachment, epiretinal membranes, cystoid macular edema, optic nerve edema, retinal neovascularization, serous retinal detachments, retinal breaks, iris atrophy, anterior synechiae and postoperative pain.

### RESULTS

In the next table we present the results of some significant studies (Table 2).

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Table 2. Results of some studies in the treatment of choroidal melanomas

Author	Laser	Number	Results
Shields JA, 1990 <sup>4</sup>	Xenon-arc lamp versus argon laser photocoagulation	38 patients xenon arc photocoagulation (n=22) argon laser (n=16)	Tumor regression rates 71–86%. Re-growth within 3–6 years in 14% of tumors treated with xenon-arc and 64% of those treated with argon laser.
Shields CL, 1996 <sup>9</sup>	Primary transpupillary thermotherapy (Diode 810 nm)	17 patients	All patients responded at a minimum of 6 months of follow-up. Final visual acuity was the same or improved in ten eyes (59%) due to resolution of subfoveal fluid, and decreased in seven (41%) as the result of treatment in the fovea.
Shields CL, 1998 <sup>10</sup>	Primary transpupillary thermotherapy (Diode 810 nm)	100 cases	Successful treatment in 94 eyes (94%). Final visual acuity was the same or better than the pretreatment visual acuity in 58% of cases and worse in 42%. Poorer vision was caused by treatment through the foveola for subfoveal tumor, retinal traction, retinal vascular obstruction, optic disc edema, and unrelated ocular ischemia.
Godfrey DG, 1999 <sup>11</sup>	Primary transpupillary thermotherapy (Diode 810 nm)	14 patients	Mean preoperative tumor height of 1.79 mm decreasing six months later to a mean of 0.54 mm (follow up range from 7 to 28 months). Three patients required retreatment for lack of regression or recurrent growth. One treatment failure in a juxtapapillary tumor.
Shields CL, 2002 <sup>12</sup>	Primary transpupillary thermotherapy (Diode 810 nm)	256 patients	Complete tumor control in 91% of cases after a mean of three treatment sessions. Risk factors for tumor recurrence included increasing number of thermotherapy sessions (reflecting a less responsive tumor) and optic disc overhung by tumor. The visual acuity after treatment was 20/20 to 20/40 in 50%, 20/50 to 20/100 in 18%, and 20/200 or worse in 32%. Patients with tumors abutting or overhanging the optic disc or those requiring more than three sessions for tumor control are more likely to develop ultimate tumor recurrence.
Shields CL 2002 <sup>13</sup>	Combined plaque radiotherapy and transpupillary thermotherapy	270 patients	Transpupillary thermotherapy was applied in 3 sessions at 4-month intervals. The tumor decreased in thickness from a median of 4mm to 2.1 mm by 2 years' follow-up. Recurrence was 2% at 2 years and 3% at 5 years. Risk factors for tumor recurrence included macular location of the tumor epicenter, diffuse tumor configuration and tumor margin extending underneath the foveola.
Mashayekhi A, 2015 <sup>7</sup>	Primary transpupillary thermotherapy (Diode 810 nm)	391 patients (review included a 1995 to 2000 group and a 2001 to 2012 group)	Tumor recurrence in the 1995 to 2000 group was 29% at 5 years and 42% at 10 years; in the 2001-2012 group there were 11% at 5 years and 15% of recurrences at 10 years. Features predictive of tumor recurrence were the presence of symptoms, shorter distance between the tumor and the optic disc, subretinal fluid, and elevation of residual tumor scar. Presence of orange pigment before TTT, tumor recurrence and extraocular tumor extension were predictive of distant metastasis.



# XII. LASER In retina/ choroid: tumors

## 67. Retinoblastoma



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### INTRODUCTION

Retinoblastoma is a malignant tumor arising from immature retinoblasts of neurosensitive retina. It is the most frequent intraocular malignancy in children with an estimated incidence of 1 in 15.000 births<sup>1</sup>. Retinoblastoma occurs in cells that have cancer-predisposing variants of both copies of *RB1* gene<sup>2</sup>. There are two phenotypical forms of the disease: the unilateral unifocal disease, generally associated with somatic mutations in the retina, and the bilateral multifocal disease associated with germ line mutations. The most important differential diagnosis are persistent fetal vasculature, Coats' disease, ocular toxocariasis and retinopathy of prematurity.

The most commonly used classification for intraocular retinoblastoma staging, the International Classification of Retinoblastoma<sup>3</sup>, is presented in table 1.

The first strategy used for the management of this pediatric tumor was systematic enucleation. External beam radiotherapy followed, not only allowing to save lives but also some useful vision. Research for other therapeutic options was prompted by the resistance of certain tumors to irradiation, onset of non-ocular tumors secondary to radiation and cosmetic consequences<sup>4</sup>. Today, conservative treatment can include any of the following: systemic chemotherapy, local chemotherapy (intra-arterial, sub-tenon and intravitreal), cryotherapy, laser therapy and radiotherapy (external or brachytherapy). These modalities are oftentimes used in association, and their choice is based on several factors, mainly tumor size, location and available modalities. As new strategies are introduced, more eyes and visual functions are preserved. Two wavelengths of laser are currently used to treat retinoblastomas: 532 nm KTP laser, which photocoagulates tissue inducing a temperature over 65°C; and the 810 nm diode laser, which induces a sub-photocoagulation temperature (between 45 and 65°C), achieving

hyperthermia. The first to be used was 532 nm KTP laser and it was traditionally applied to treat the retinal edge surrounding the tumor in an attempt to destroy blood supply, so inducing tumor regression of the tumor. Generally performed using an indirect ophthalmoscope, a double row of white burns was applied surrounding the tumor, using powers of 250-350 mW and burn durations of 0.3-0.5 s. The use of photocoagulation wavelengths directly over the tumor has been subjected to debate due to the fear of liberating tumor cells into the vitreous cavity. Newer generations of 532 nm laser allow continuous delivery similar to that of the diode laser<sup>5,6</sup>. This is the technique we currently use. Diode laser (810 nm) is applied directly over the tumor surface using an indirect ophthalmoscope or an ophthalmic microscope adapter. Hyperthermia has a direct cytotoxic effect which can be augmented by both chemotherapy and radiation. The combined use of heat in the hyperthermia range and chemotherapy has become popular and is referred to as thermo chemotherapy<sup>7</sup>. Cryotherapy is usually preferred over transpupillary laser for small anterior tumors which are easily accessed, while the latter is applied to small posterior tumors.

### INDICATIONS<sup>8,9</sup>

- Primary treatment of small tumors up to 3 mm thickness and 3 to 4.5 mm in diameter with no evidence of seeding and located posterior to the equator (Group A tumors).
- Adjunctive treatment after systemic or intra-arterial chemotherapy.
- Small tumor recurrences.

### RELATIVE CONTRAINDICATIONS<sup>6</sup>

- Tumor >4.5 mm in diameter or >2.5 mm in thickness (unsatisfactory tumor control rate).



## 67. Retinoblastoma

- Vitreous seeding (not affected by laser therapy).
- Tumor located anteriorly to the equator (more appropriately treated with cryotherapy due to less risk of damage to the iris or lens).
- Tumor margin within 4.0 mm of the foveola.
- Tumor touching the optic disc.

Table 1. International Classification of Retinoblastoma, Philadelphia version<sup>3</sup>

Group	Quick reference	Specific features
A	Small tumor	Retinoblastoma $\leq 3$ mm in size (basal dimensions or thickness)
B	Larger tumor	Retinoblastoma $> 3$ mm in size or macular location ( $\leq 3$ mm to foveola) or juxtapapillary ( $\leq 1.5$ mm to disc) or clear subretinal fluid $\leq 3$ mm from margin
C	Focal seeds	Retinoblastoma with subretinal seeds and/or vitreous seeds $\leq 3$ mm from retinoblastoma
D	Diffuse seeds	Retinoblastoma with subretinal seeds and/or vitreous seeds $> 3$ mm from retinoblastoma
E	Extensive retinoblastoma	Extensive retinoblastoma occupying $> 50\%$ globe or neovascular glaucoma; opaque media from hemorrhage in anterior chamber, vitreous or subretinal space; invasion of post-laminar optic nerve, choroid, sclera, orbit, anterior chamber

### PREPARATION

1. The nature of the disease as well as the purpose of treatment, risks and possible complications should be explained to the parents.
2. General anesthesia due to patients' age.
3. Mydriasis.
4. After thorough examination of ocular fundus.

### LASER TECHNIQUE

*Nd:YAG KTP 532 nm laser (KTP laser) or Diode laser 810 nm (DL)*

This technique is based on our experience with Nd: YAG-KTP and published reports on both Nd: YAG-KTP and infrared diode<sup>4</sup>.

Laser beam variables:

Laser type	532 nm	810 nm
Duration	Continuous	0,5-9 s
Power	80-100 mW	500-700 mW

\*spot size is not pre-established with indirect laser.

### Important

Laser beam is applied directly over the tumor. With 532 nm laser, treatment endpoint is observed as a subtle whitening of tumor surface. With 810 nm diode laser, a visible change in the tumor may not be seen until a follow-up examination.

### POSTLASER CARE AND FOLLOW-UP

Control under general anesthesia 3 to 4 weeks after treatment. Several treatment sessions may be necessary.

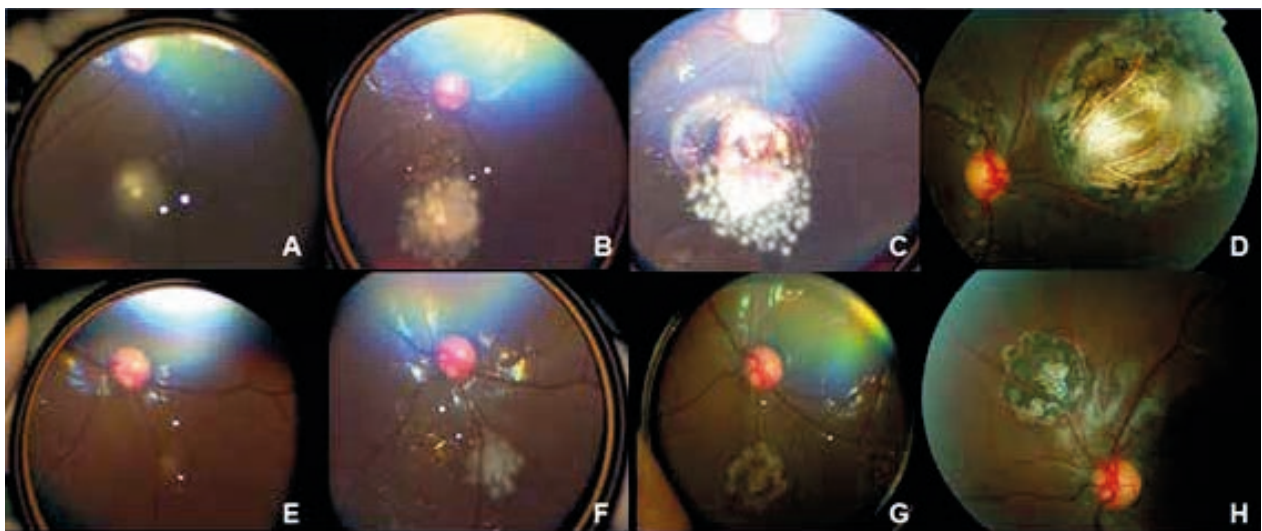


Figure 1: Indirect ophthalmoscopic fundus photographs of the right (row above) and left (row below) eyes of a child with bilateral retinoblastoma treated exclusively with laser. **A** and **E** show small tumors nasal to the optic disc, at diagnosis. **B** and **F** is the result after initial laser treatment. **C** shows the relapse at six months immediately after re-treatment. **G** discloses a flat scar six months after treatment. **D** and **H** show the aspect 4 years after treatment, with flat scars in both eyes. Images reproduced with permission<sup>10</sup>.

## COMPLICATIONS<sup>8</sup>

Complications are more frequent when treating more peripheral lesions or when visualization is poor (due to the presence of limited pupillary dilation or vitreous haze). The following are possible complications:

- Tumor seeding into vitreous;
- Retinal fibrosis and traction;
- Retinal vascular occlusion;
- Vitreous hemorrhage;
- Retinal hole;
- Transient retinal detachment;
- Iris atrophy and focal cataracts (exclusive of thermotherapy).

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# XII. LASER In retina/ choroid: tumors

## 68. Retinal capillary hemangioma

# hemangioma



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### INTRODUCTION

Retinal Capillary Hemangioma (RCH) is composed of a proliferation of capillaries and pericytes amongst a matrix of interstitial cells<sup>1</sup>. It stems from a loss of function mutation in the VHL gene, which in its wild form is responsible for the degradation of hypoxia induced factor<sup>2,3</sup>. The latter in turn downregulates vascular endothelial growth factor (VEGF) amongst other proteins<sup>4-6</sup>.

In its isolated form, RCH has a prevalence of about 1 in 110.000 cases<sup>7</sup>; however in up to 58% of cases it may be associated with the dominantly inherited cancer syndrome von Hippel-Lindau disease (VHL), which tends to be the earliest and most common presenting feature, usually being diagnosed at about 25 years of age.<sup>8</sup> The likelihood of co-existing VHL disease can be estimated based on age, results of DNA testing, associated parental history and results of systemic screening, as described in detail by Webster *et al*<sup>9</sup>. Currently VHL germline mutation screening is widely available, with a detection rate as high as 80-100%<sup>10,11</sup>, and a negative result allows for the exclusion of VHL disease with a high level of certainty.

The progression of RCH may be summarized in 4 stages, as per the grading system developed by Vail and Duke-Elder and later modified by Lane *et al*<sup>12-14</sup>. It can expand and develop prominent feeder vessels and associated exudation. Complications such as proliferative vitreoretinopathy and exudative and/or tractional retinal detachment characterize the terminal phase.

### LASER PHOTOCOAGULATION FOR RCH

Treatment of RCH depends essentially on its size and location in the retina.

Numerous existing case series point out that small RCH (<4mm) tend to respond well to laser photocoagulation with sustained regression<sup>14-19</sup>. The authors favor a

stepwise approach where laser is applied around and over the hemangioma (Figures 1 and 2), over several sessions each about 1 week apart, until the lesion is obliterated. It is important to avoid an excessively high density of power in order to decrease the risk of iatrogenic hemorrhage. Settings within the range of 300-500  $\mu$ m for size and 0.15 – 0.40 s for exposure should allow for effective photocoagulation without explosion or rupture of the lesion. Feeder vessels are best left untouched, unlike what was traditionally thought, since they will regress in parallel with the tumor lesion. Applying laser directly over these structures would likely carry an unnecessarily augmented risk of hemorrhage.

In our experience, sectoral panretinal photocoagulation laser covering the same quadrant as the RCH (Figure 2) is also helpful in promoting tumor regression; it

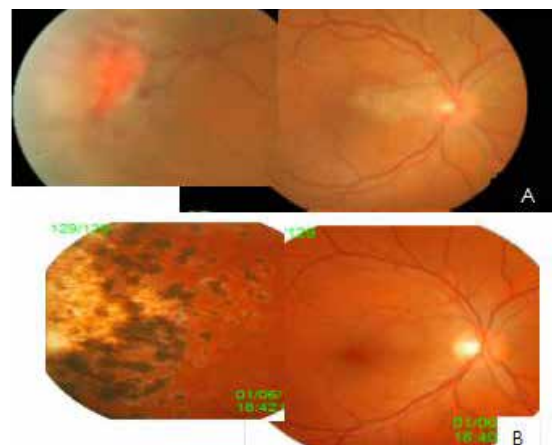


Figure 1. Color fundus photographs of the right eye of a 41 year-old patient with RCH. Pre-treatment (A) and at 3 years follow-up after treatment (B). Vision remained stable at 20/40.

would make sense for this to be through laser induced downregulation of VEGF levels<sup>20</sup> and upregulation of pigment epithelium-derived factor (PEDF)<sup>21,22</sup>.

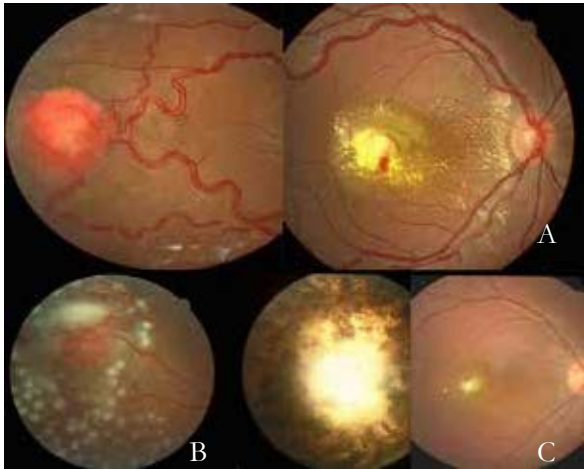


Figure 2. Color fundus photographs of the right eye of a 26 year-old patient with RCH. Pre (A), during (B) and post-treatment (C) at 2 years' follow-up. Pre- and post-treatment vision was 20/600 and 20/400 respectively.

### OTHER THERAPIES FOR RCH

Large and/or or juxtapapillary tumors warrant other therapeutic methods such as photodynamic therapy (PDT). Tumor recurrences have led to repeating treatments and modifying PDT protocols<sup>23-25</sup>, as well as combining treatment with anti-VEGF and anti-inflammatory injectables, altogether with favorable results<sup>25-28</sup>.

Tumor related complications such as retinal detachment may require more invasive measures such as vitreoretinal surgery. Local<sup>29-32</sup> or systemic<sup>33-35</sup> VEGF inhibition has resulted in the reduction of tumor exudation, but has been notably inefficient in achieving actual tumor regression.

### CONCLUSION

Management of a patient with RCH starts with screening for other features of VHL disease; testing for a sequence variant in the VHL gene may allow for confident exclusion of the diagnosis. Local management depends on the dimensions and location of the tumor. Those less than 4mm in size respond well to laser photocoagulation; this is performed over and around the RCH, in several sessions if necessary, with no need to target the feeder vessels directly. Larger or juxtapapillary tumors, and those that are complicated with retinal detachment, require other therapeutic measures, the success of which will depend mostly on the stage of the RCH. Early diagnosis is therefore crucial for a good outcome.

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# XII. LASER In retina/ choroid: tumors

## 69. Pigmented lesions

### of the retina and choroid

#### accessible to OCT



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Although rare, eye tumors raise some important diagnostic issues, particularly small pigmented lesions of the choroid, with a thickness exceeding 1 mm but less than 3 mm, denominated indeterminate melanocytic lesions (IML). They essentially correspond to large nevus or small choroidal melanomas (SCM).

The documented growth of these lesions has been considered the most important signal of evolution to melanomas<sup>1-3</sup>. However, the presence of some risk factors, such as orange pigment on the surface of the lesion, subretinal fluid, symptoms (photopsias, floaters or blurred vision), proximity to the optic disc within 3 mm, absence of drusen and halo, thickness greater than 2 mm and ultrasound hollowness, may herald suspicious lesions that require close monitoring or earlier treatment. The coexistence of 3 or more risk factors is correlated with a 50% increase in the risk of tumor growth, being highly suggestive of malignancy<sup>4,5</sup>. Thus, the differential diagnosis between choroidal melanoma and pseudomelanomas<sup>6</sup> takes on great importance and is critical to patient survival. The smaller the melanoma is when detected and treated, the better is the life prognosis<sup>7</sup>. Shields *et al.*<sup>8</sup> identified 1739 pseudomelanomas in an analysis of 12000 patients referred for uveal melanoma over a 25-year period. The most frequent diagnosis included choroidal nevus (49%), peripheral exudative hemorrhagic chorioretinopathy (8%), congenital hypertrophy of pigment epithelium (6%), hemorrhagic detachment of retina or pigment epithelium (5%), circumscribed choroidal hemangioma (5%), age-related macular degeneration (4%), hyperplasia of retinal pigment epithelium (RPE) (2%), optic disc melanocytoma (2%), choroidal metastasis (2%) and hemorrhagic choroidal detachment (2%).

Lesions with a thickness of 3 mm or less can be

particularly challenging to distinguish clinically. This group comprises several small tumors of the retina and choroid, as well as other non-neoplastic lesions. Most of them appear clinically as a small dome shaped solid mass with variable pigmentation, from orange to dark brown, localized at the posterior pole or mid periphery.

Currently, spectral domain OCT (SD-OCT), more sensitive and with a higher resolution, has become a vital tool to study vitreous-retinal pathology regarding diagnosis, staging, therapy and response to treatment.

Applied to posterior choroidal tumors, OCT made possible, in a first phase, to identify retinal changes induced by the presence of a choroidal injury, as well as to evaluate qualitatively and quantitatively the risk factors for malignant transformation.

However, conventional SD-OCT presents some limitations with regard to the evaluation of the structures beyond the retinal pigment epithelium (RPE), in particular the Bruch's membrane and the choroid. That limitation can be overcome with the use of equipment that use laser sources with higher wavelengths such as swept-source OCT (SS-OCT) or with the use of a new image modality, enhanced depth imaging OCT (EDI-OCT). This designation was introduced by Spaide<sup>9</sup> to describe a method of image associated with the SD-OCT that enables high-resolution OCT imaging of deep located structures, such as external retinal layers, the choroid and lamina cribrosa.

In recent years, there have been several studies<sup>10-19</sup> reporting isolated cases or series of melanocytic and amelanocytic choroidal tumors (mainly melanoma, nevus, hemangioma, osteoma, melanocytoma and metastasis), as well as retinal tumors (vascular and hamartomas), with a detailed description of their tomographic features, allowing the diagnosis and determination of their location on the retina or choroid.

Therefore, with this technique it is possible to locate lesions and study their intrinsic characteristics with respect to homogeneity, pigmentation, choroidal shadow, choriocapillaris (CC) compression and dimensions. It is also possible to identify the anterior limits (Bruch's membrane) and lateral boundaries between the injured and healthy choroid. Determining the posterior limits (choroido-scleral junction), however, depends on pigmentation and thickness. Tumors with a thickness less than 1 mm are perfectly identified with OCT, and may be evaluated quantitatively (including thickness and lateral limits). In tumors with heavier pigmentation, greater thickness or with a basal diameter greater than 9 mm, the EDI-OCT is not able to determine their dimensions<sup>12</sup>.

In spite of these limitations, EDI-OCT is a new technology for imaging small retinal and choroidal tumors, allowing visualization of details previously not detected with other imaging modalities.

### CHOROIDAL NEVUS

Choroidal nevus is defined by the Collaborative Ocular Melanoma Study (COMS) as a choroidal melanocytic lesion that is 5 mm or less in the largest basal diameter and no more than 1 mm in height<sup>20,21</sup>. Most choroidal nevus are asymptomatic. However, when located in the macular region (Figure 3) they may cause visual loss due to photoreceptor disruption, edema, serous retinal detachment or secondary choroidal neovascularization<sup>22</sup>. The typical choroidal nevus appears as a small gray to brown choroidal tumor with bland surface features, often associated with drusen and retinal pigment epithelial clumping<sup>20</sup>.

Tomographic features<sup>23-25</sup> include (Figures 1, 2 and 3): dome shaped hyperreflective choroidal mass with choroidal shadowing deep to the nevus depending on its pigmentation; choriocapillaris compression; RPE irregularity, nodularity (drusen) or atrophy; pigment epithelium detachment (PED) and chronic retinal degenerative signs – intraretinal cystoid edema, photoreceptor loss, and irregularity or disruption of ellipsoid, external limiting membrane, outer nuclear and outer plexiform layers.

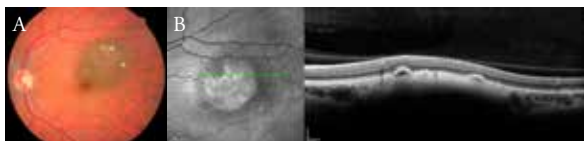


Figure 1. Melanocytic Nevus. (A) Color fundus photograph shows a subretinal melanocytic lesion, with drusen on the surface, at the macular area of the left eye. (B) SD-OCT: The lesion is well distinguished from surrounding normal choroid, appearing as a slightly elevated highly reflective band at the Bruch/RPE/CC layer, with posterior shadowing and irregularity/nodularity of RPE (drusen).



Figure 2. EDI-OCT: flat nevus with PED; the margins of the tumor are well demarcated making possible the correct measurement of its basal diameter.



Figure 3. SD-OCT: slightly elevated juxta foveal nevus associated with RPE and outer retinal abnormalities, as well as cystoid edema, causing metamorphopsia.

### IML AND SMALL CHOROIDAL MELANOMA

Uveal melanoma<sup>20,26-28</sup> is the most common primary intraocular malignant tumor, and 80 to 90% arise in the posterior uvea. IML (between 1-3 mm) and small choroidal melanoma can present a diagnostic challenge. One of the barriers to early detection of small choroidal melanoma relates to its clinical similarity to benign choroidal nevus: subretinal dome shaped gray to brown mass. The diagnosis of suspicious lesions depends on documented growth and detection of some risk factors. SD-OCT has shown superiority in the detection of these features, when compared to fundus observation<sup>25,29</sup>.

Tomographic features<sup>11,25,30</sup> of IML and small choroidal melanomas can be quite similar to a nevus (Figures 4 and 5). Most prominent and characteristic features are subretinal fluid, subretinal material compatible with lipofuscin and shaggy photoreceptors, which may represent swollen photoreceptor tips or macrophages with lipofuscin on the detached posterior retinal surface. Large melanomas are not accessible to OCT study and the resultant image is of poor quality due to the lesion thickness.

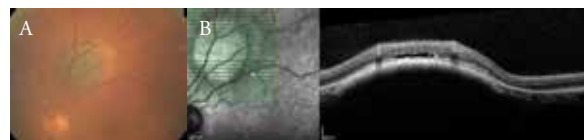


Figure 4. IML/ Small Choroidal Melanoma. (A) Fundus color photograph shows melanocytic lesion with halo; (B) SD-OCT: elevated lesion with deep posterior shadowing, outer retinal and RPE abnormalities, shallow subretinal fluid/retinal cleft and presumed dispersed lipofuscin in the subretinal space.

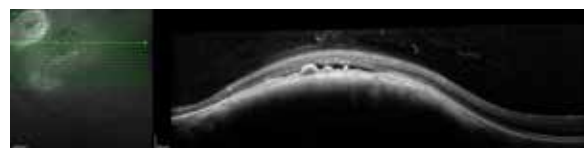


Figure 5. IML/SCM SD-OCT: elevated lesion with deep posterior shadowing, outer retinal abnormalities and drusen of the RPE; shallow subretinal fluid/retinal cleft.

### CHOROIDAL HEMANGIOMA

Circumscribed choroidal hemangioma<sup>20,31-33</sup> is a benign vascular tumor of the choroid, usually present as an isolated orange solid mass, typically located in the paramacular area. These lesions are often diagnosed when they impair vision due to hyperopic shift, subretinal fluid or degenerative changes in the macular retina and RPE.

Tomographic features<sup>14,31</sup> include (Figure 6): medium hiperreflective tumor with a smooth anterior contour, without choriocapillaris compression; partial optical shadowing; cystoid retinal edema; retinoschisis; outer retinal abnormalities (irregularity or disruption of the external limiting membrane, ellipsoid, outer nuclear and outer plexiform layers); and subretinal fluid. Characteristically expanded vascular interfaces are found in the choroidal vascular layers (choriocapillaris, Haller's layer and Sattler's layer).



Figure 6. Circumscribed Choroidal Hemangioma. (A) Color fundus photograph shows an elevated macular orange tumor; (B) SD-OCT: elevated choroidal lesion, without choriocapillaris compression; partial optic shadowing; outer retinal abnormalities; cystic edema and retinoschisis.

### CHOROIDAL METASTASIS

Choroidal metastasis<sup>20,34</sup> represent the most common intraocular tumors. In males, the most common primary cancer sites are lungs, gastrointestinal and kidneys, whereas in females breast cancer is the most common cancer to metastasize to the choroid. Choroidal metastases are usually of small-to-medium size with a mean thickness of 3 mm and a tumor epicenter in the macular or paramacular region. They may affect both eyes and often present as isolated or multiple yellow masses, with a plateau configuration and associated subretinal fluid.

Tomographic features<sup>15,35-37</sup> include figure 7: hiperreflective tumor with irregular (lumpy-bumpy) anterior contour, choriocapillaris compression and posterior shadowing; overlying RPE and outer retinal abnormalities (loss or disruption of ellipsoid layer, external limiting membrane, outer nuclear layer, and outer plexiform layer); shaggy photoreceptors; and subretinal fluid. The inner retinal layers are commonly preserved.

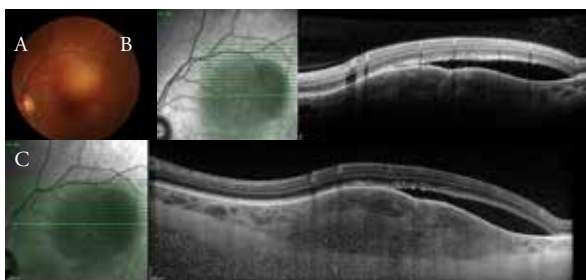


Figure 7. Choroidal Metastasis. (A) Color fundus photograph shows a macular elevated amelanotic tumor. (B) SD-OCT: elevation of the retina due to choroidal mass with slightly "lumpy-bumpy" surface; subretinal fluid with "shaggy" photoreceptors. (C) EDI-OCT: tumor with medium reflective signal, without optical shadow; the inner limit of the sclera is visible permitting measurement of tumor thickness.

### OPTIC DISC MELANOCYTOMA

Optic disc melanocytoma<sup>20,38,39</sup>, which develops from uveal melanocytes, is a hamartoma often difficult to

distinguish from a malignant melanoma. Clinically, it appears as a dark brown or black, flat or slightly elevated mass overlying the optic disc, usually located inferotemporally. Other visual impairments besides enlarged blind spot are rare. However, associated optic disc edema, retinal edema, subretinal fluid, retinal hemorrhage or exudation and retinal vein occlusion have been described.

Tomographic features<sup>40-42</sup> include (Figure 8): hiperreflective nodular tumor with dense posterior shadowing; disorganization of the retina overlying the tumor; and compressive or infiltrative changes in the optic nerve, peripapillary choroid, and retina.

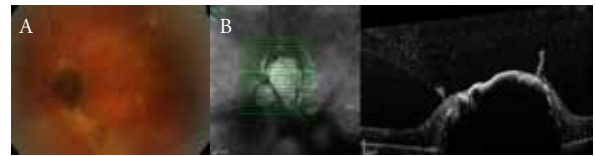


Figure 8. Optic Disc Melanocytoma. (A) Color fundus photograph shows a very dark tumor overlying the optic disc inferotemporally. (B) SD-OCT: hiperreflective nodular tumor with dense posterior shadowing; disorganization of the retina overlying the tumor.

### MELANOCYTOSIS

Ocular melanocytosis<sup>20,43</sup> is a unilateral, congenital condition characterized by hyperpigmentation of the episclera and uvea. When the periocular skin is involved, the condition is known as oculodermal melanocytosis (Nevus of Ota). Patients with ocular melanocytosis are at increased risk of developing glaucoma or melanoma of the affected eye.

Tomographic features<sup>18,44</sup> include (Figure 9): lesion with a smooth anterior contour; thinned or compressed choriocapillaris; an intact overlying retina. When compared with the uninvolved eye, the most important and distinctive abnormality is an increased subfoveal choroidal thickness with apparent increase in the choroidal perivascular stromal tissue.

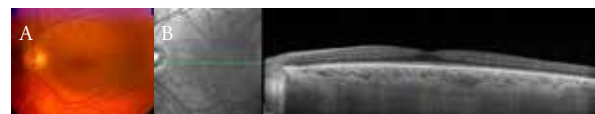


Figure 9. Melanocytosis. (A) Color fundus photograph shows hyperpigmentation of macular area. (B) EDI-OCT: increased choroidal thickness with increased stromal tissue.

### CONGENITAL HYPERTROPHY OF RETINAL PIGMENT EPITHELIUM (CHRPE)

CHRPE<sup>6,20</sup> is a common fundus condition usually detected as an incidental finding. It usually presents as a unilateral, deeply pigmented, flat lesion with a sharp demarcated margin. It may display a depigmented lacuna within the lesion.

Tomographic features<sup>16,45</sup> include (Figure 10): flat tumor well individualized from contiguous healthy retina; abnormalities of overlying retina with retinal thinning and photoreceptor loss; irregular and thickened RPE; normal structure of underlying choroid with decreased reflectivity, except in the areas of intralacunar lacunae where RPE is absent.

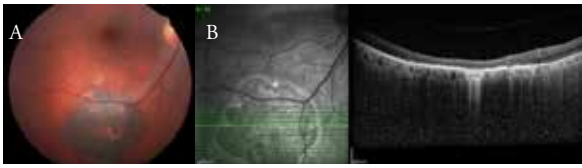


Figure 10. CHRPE (A) Color fundus photograph shows a peripheral flat dark brown lesion with irregular well defined limits and with hypopigmented lacunae. (B) EDI-OCT: flat RPE lesion with lacunar optical transmission, outer retinal thinning with photoreceptor atrophy.

### REACTIVE HYPERPLASIA OF THE RPE

RPE is known to be capable of reactive hyperplasia in response to ocular insults such as inflammation or trauma. RPE hyperplasia<sup>46</sup> results in a proliferation of RPE cells, usually forming a small pigmented retinal lesion that is very irregular in shape. These lesions can present as a flat sheet of pigment or a distinct mass that clinically may simulate a choroidal melanoma.

Tomographic features of RPE reactive hyperplasia can be quite similar to CHRPE (Figure 11): flat lesion well individualized from contiguous healthy retina; abnormalities of overlying retina with retinal thinning and photoreceptor loss; and irregular and thickened RPE. The structure of the underlying choroid depends on the previous insult responsible for the hyperplastic response.

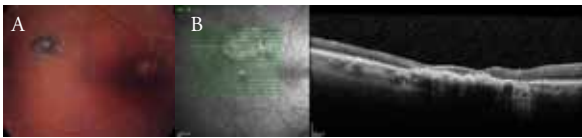


Figure 11. RPE Reactive Hyperplasia. (A) Color fundus photograph shows a flat dark brown irregular macular lesion. (B) SD-OCT: retinal thinning and photoreceptor loss; irregular and thickened RPE with optical shadowing.

### SIMPLE HAMARTOMA OF RPE

Simple hamartoma of the RPE<sup>47-49</sup> is an uncommon lesion that appears as a small localized, elevated black lesion, usually located in the foveal region. It generally remains stable with minimal effect on visual acuity.

Tomographic features<sup>48</sup> include (Figure 12): nodular hyperreflective tumor above the retinal surface; abrupt and rectified margins, clearly defining its limits; and complete optical shadowing of the deeper retina, RPE and choroid.

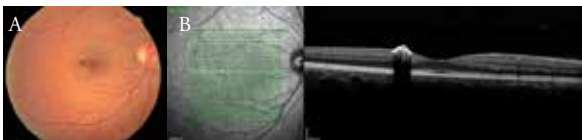


Figure 12. Simple Hamartoma of RPE. (A) Color fundus photograph shows a small black lesion located temporal to the fovea in the right eye. (B) SD-OCT: nodular hyperreflective lesion above the retinal surface, surrounded by healthy retina; rectified margins; complete optical shadowing of the deeper retina, RPE and choroid.

### TORPEDO MACULOPATHY

Torpedo maculopathy<sup>50</sup>, also called solitary hypopigmented nevus, is a recently described solitary congenital RPE nevus. Clinically, it is characterized as an asymptomatic, flat, ovoid lesion with well-defined margins and variable pigmentation. These lesions are generally longer in the horizontal axis than in the vertical axis and they are typically located temporally to the center of the macula with a tip that points towards the central macula.

Tomographic features<sup>51,52</sup> include (Figure 13): flat lesion with overlying RPE and outer retinal structural abnormalities such as thinning of the retina and RPE, photoreceptor loss, outer retinal clefts; and increased reflectivity of the choroid.

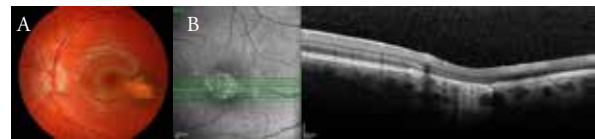


Figure 13. Torpedo Maculopathy. (A) Color fundus photograph shows a slightly pigmented ovoid lesion with well-defined margins located temporally to the fovea in the left eye. (B) EDI-OCT: RPE and retinal thinning with photoreceptor atrophy, and increased reflectivity of the choroid.

### RETINAL CAPILLARY HEMANGIOMA (Retina hemangioblastoma)

Retinal capillary hemangioma<sup>53,54</sup> is a benign vascular tumor that arises from the retina or optic disc. It may be unilateral or bilateral and usually enlarges progressively, leading to exudative or tractional retinal detachment. It generally appears as a red spherical lesion, fed and drained by dilated tortuous retinal blood vessels. When hemangiomas develop from the optic disc, they may appear less well defined and without obvious feeding vessels. This tumor may occur isolated and in a syndromic setting as a manifestation of the von Hippel-Lindau syndrome. Commonly, there is intraretinal and subretinal exudation, particularly when the tumor is greater than 2-3 mm in diameter.

Tomographic features<sup>55</sup> include (Figure 14): hyperreflective full-thickness retinal mass with domed shaped surface and deep optical shadowing; vitreoretinal traction; retinal disorganization; intraretinal edema; and surrounding subretinal fluid.



Figure 14. Retinal Capillary Hemangioma. SD-OCT: hyperreflective dome-shaped retinal mass with optical shadowing and retinal disorganization.

In conclusion, most small pigmented lesions can be safely monitored by serial observation and ancillary testing. SD-OCT is a useful diagnostic modality for imaging



the retina and the choroid. It allows the detection of specific tomographic features as well as some subclinical abnormalities frequently present in these tumors.

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# XIII. LASER in vitreous

## 70. Anterior segment vitreolysis



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### INTRODUCTION

The presence of vitreous in the anterior chamber is an ominous complication for eye surgery (mainly cataract surgery), occurring less frequently in degenerative conditions such as zonular dehiscence. Glaucoma, endothelial dysfunction with corneal edema, pupillary distortion, chronic anterior chamber inflammation with macular edema and posterior traction with retinal breaks and detachment are late complications. Vitreous may also bridge the anterior and posterior segment and increase the risk of endophthalmitis. Management options include surgical removal of vitreous strands, but also less invasive measures such as laser vitreolysis. The treatment decision is made upon identification of vitreous in the anterior chamber.

In 1983, Katzen *et al.* described the use of Nd:YAG 1064 nm Q-switch laser (QS-YAG) for cutting vitreous strands adherent to corneal incisions with effective restoration of pupillary shape and relief of posterior segment traction and associated cystoid macular edema<sup>1,2</sup>. It has since become the standard of care.

### INDICATIONS

Vitreous strands in the anterior chamber adherent to corneal wounds, causing pupillary distortion or originating posterior vitreous traction with cystoid macular edema<sup>3</sup>. Vitreous strands should be stable for at least 2-3 months, while medical treatment (e.g., for macular edema) should be attempted.

### CONTRAINDICATIONS

Symptoms of photopsias or untreated retinal pathology such as breaks or tears<sup>4</sup>.

Active intraocular inflammation or uncontrolled ocular hypertension are relative contraindications - laser treatment should be deferred until inflammation and

hypertension are pharmacologically controlled<sup>5</sup>.

### PREPARATION

1. Explain the procedure mentioning the possible need of more than one session or even surgical approach.
2. Induction of myosis - pilocarpine 1%, one drop every 20 minutes for one hour prior to the procedure.
3. Topical anesthesia - oxybuprocaine hydrochloride 0.4% one to two drops applied just before the procedure.
4. Patient sitting comfortably and with steady fixation.
5. Apply a contact anterior chamber lens with appropriate lubricant gel coating.
6. Do not forget the posterior shift setting that should be at zero (See also chapter 12).

### LASER TECHNIQUE

*Nd:YAG 1064 nm Q-switch laser (QS-YAG)*

*Laser beam variables:*

Single pulse (advisable, although multipulse may also be used);  
Spot size 8  $\mu\text{m}$  (fixed by default);  
Duration 4 ns (fixed by default);  
Power 1.4 to 2.5 mJ.

*Treatment sequence:*

Explain the patient about the normal shutter sound during treatment.

Align the red aiming beam on the vitreous strand next to the pupillary margin or on a narrower portion of the strand. Start with low power settings and allow for small increments (0.1 mJ) until a photo-disrupting effect is observed<sup>6</sup>.

Several pulses are usually necessary to cut the strand. Always wait for the strand to settle into position before continuing with treatment. A complete cut occurs when

traction is relieved on the pupillary margin and the pupil reassumes its normal circular shape.

In the presence of multiple vitreous strands, start treatment anteriorly and proceed inwards. This will enable you to first remove those vitreous strands that may impede your vision of the posterior structures. Likewise, treat from the top down as gas bubbles may impede vision of higher vitreous strands if the lower ones are treated first<sup>7</sup>.

**Important:** if the red aiming beams are not clearly in focus, nor coincidental or superimposed, do not fire. If in doubt, focus on the vitreous strand and pull back the joystick slightly. This will enable you to clearly visualize the two aiming beams before refocusing them to one spot<sup>8</sup>.

#### POST-LASER CARE AND FOLLOW-UP

The patient should be warned about possible symptoms of photophobia, blurred vision and floaters, which should clear in 2 to 3 days. There are no restraints on patients' everyday activities.

We advocate the use of topical steroid drops (e.g., prednisolone acetate, dexamethasone phosphate) four times daily tapered to once daily after seven days, along with a non-steroidal anti-inflammatory drug (NSAID) (e.g., ketorolac, bromfenac, nepafenac) once daily to three times daily for two weeks. Induction of mydriasis with topical cyclopentolate may be necessary for one to two weeks if active anterior chamber inflammation is present. Duration and intensity of anti-inflammatory therapy should be tailored to each patient, as response to treatment is entirely variable. Ocular hypertension should be treated pharmacologically if present, avoiding the use of prostaglandin analogs because of the risk of increased inflammation.

Follow-up visits should be scheduled 3 to 5 days after treatment and thereafter as needed.

#### COMPLICATIONS

This is a relatively safe procedure and the overall risk is low. Complications may follow due to poorly controlled anterior chamber inflammation or vitreous strand traction with consequent retinal breaks and detachment. Accidental delivery of laser pulses to the cornea, the trabecular meshwork or the iris may result in iatrogenic corneal edema and leukoma, ocular hypertension, hyphema, iris atrophy and increased anterior chamber inflammation with spillover of cells to the anterior vitreous and macular edema.

In phakic patients with zonular dehiscence and anterior vitreous movement, one should consider the risk of traumatic cataract with laser treatment<sup>9,10</sup>.

#### CONCLUSIONS

Anterior segment vitreolysis by means of QS-YAG laser is currently the most effective technique for cutting vitreous strands thus preventing or treating their complications. Appropriate patient selection, accurate management of laser technique and timely follow-up care will deliver the best results while avoiding major adverse effects.

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# XIII. LASER in vitreous

## 71. Posterior

## vitreolysis



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### INTRODUCTION

Clinical use of Nd:YAG 1064 nm Q-switch laser (QS-YAG) in the posterior segment of the eye is restricted to very specific indications. Fear of damaging ocular tissues further limits its applications<sup>1</sup>. Laser vitreolysis by means of QS-YAG pulses was first described by Fankhauser in 1985<sup>2</sup>. Since then several studies have elicited a number of benefits from such a technique.

Posterior vitreolysis is usually an option in patients for whom pars plana vitrectomy is contraindicated or has to be postponed, as well as in any patient wishing to avoid or refusing more invasive procedures<sup>3,4</sup>.

QS-YAG has been described in a wide array of vitreous and retinal pathology, such as vitreoretinal traction associated with retinal breaks, tractional retinal detachments including macular detachments, proliferative retinopathy associated with sickle cell disease, posterior partial vitreous detachment and recurrent vitreous hemorrhage associated with mechanical vitreous traction<sup>3,5</sup>. Nevertheless, the use of QS-YAG in symptomatic vitreous opacities remains its commonest and probably least controversial application. As such, in this chapter we shall give particular attention to this indication.

### VITREOUS OPACITIES AND VITREOLYSIS

Floater are a common visual complaint. They usually originate in vitreous opacities related to normal vitreous senescence (degeneration) and posterior detachment<sup>1</sup>. In patients younger than 50 years, floaters are usually associated with the presence of vitreous opacities in the posterior aspect of Cloquet's canal<sup>6</sup>, while in patients older than 50 years this usually relates to posterior vitreous detachment<sup>7</sup>. Floaters can also arise in the context of vitreoretinal pathology such as retinal breaks, high myopia, trauma and uveitis, among others<sup>7</sup>.

Vitreous floaters affect 1% of the general population and

tend to resolve spontaneously. They are usually small and located outside the visual axis, moving peripherally with time, thus becoming asymptomatic. In some patients, however, floaters may impair vision and become particularly stressful<sup>1</sup>. Such intolerance may arise after cataract surgery, which renders preexisting opacities more noticeable, or in patients with visually demanding occupations or activities<sup>4</sup>.

In such cases, QS-YAG vitreolysis may be an interesting alternative to either a wait-and-watch attitude or a pars plana vitrectomy with the associated risks of intraocular surgery. Several authors argue that for a specific array of patients, laser may be the most suitable therapeutic strategy<sup>3</sup>.

### INDICATIONS

According to Fankhauser<sup>5</sup>, laser vitreolysis follows three main therapeutic indications:

- Removal of symptomatic vitreous opacities in the optic axis or preventing a proper fundus observation by the ophthalmologist;
- Removal of vitreous traction over retina;
- Facilitation of vitreous hemorrhage clearing (e.g. pre-macular hemorrhage)<sup>5,8,9</sup>.

In any patient with the above inclusion criteria a full ophthalmic examination should be performed with particular attention to vitreoretinal anatomy and pathology. The number, location and type of vitreous opacities or strands should be noted, as well as the presence of retinal traction, underlying vessels and retinal proximity<sup>3</sup>.

As previously stated, we shall focus on the treatment of vitreous floaters. Proposed treatment criteria include:

- Floater originating in localized vitreous opacities;
- Persistence of symptoms over three months without signs of improvement;
- Floater located in the visual axis with visual

impairment;

4. Anxiety or other psychologic conditions originated or aggravated by the presence of floaters<sup>1</sup>.

### CLASSIFICATION OF VITREOUS OPACITIES

Several classification systems have attempted to characterize and thus predict the outcome of QS-YAG laser treatment of vitreous floaters.

Tsai WF *et al.*<sup>1</sup> proposed a classification of floaters as pre-papillary opacities, usually related to a circular vitreous opacity (Weiss's ring) and center-vitreous opacities. On the other hand, Vandorselaer *et al.*<sup>10</sup> divided vitreous opacities into "well suspended" and "ill suspended" by means of Scanning Laser Ophthalmoscope examination. Well suspended vitreous opacities would respond better to laser treatment. Another classification system<sup>7</sup> proposes three types of floaters with different treatment outcomes:

1. posterior vitreous detachment with veil formation, with very good treatment outcomes;
2. dense vitreous opacities (clumps) with good treatment outcomes;
3. fine vitreous opacities (threads) with poorer treatment outcomes.

### CONTRAINDICATIONS

Laser treatment of vitreous opacities should be deferred in patients with active inflammatory vitreous or retinal pathology, patients complaining of photopsia and found to have vitreoretinal traction, patients with high lenticular astigmatism (impairing proper focusing of laser beams), and young patients with multiple small opacities close to the retina. Laser is contraindicated in retinal breaks or retinal detachment<sup>1,7</sup>.

Vitreous strands without associated retinal traction or barely visible are not amenable to laser treatment. The presence of active retinal neovascularization is also a relative contraindication<sup>3</sup>.

### PREPARATION

- 1 Explain the procedure referring the possible need of multiple session or other procedures.
- 2 Balance patient expectations with procedure risks.
- 3 Induction of mydriasis - tropicamide 1% and phenylephrine 2.5-10% applied 30 min to 1 hour before the procedure, several times until full mydriasis.
- 4 Under topical anesthesia (oxybuprocaine hydrochloride 0.4%) insert the contact lens.
- 5 Adjust laser spot size to 8  $\mu\text{m}$  and pulse duration to 4 ns<sup>11</sup>.
- 6 Place illumination source and aiming beam at an angle with 15° between them.
- 7 Adjust laser settings to single pulse burst. Multipulse should be used exceptionally (many authors advocate it should be formally avoided)<sup>3</sup>.
- 8 Dim the lights in the laser room.

### LASER TECHNIQUE

*Nd:YAG 1064 nm Q-switch laser (QS-YAG)*

In the posterior pole the Q-switch laser has a larger range of indications and fewer sessions are needed; however, complications are more frequent than with the mode-locked Nd: YAG laser, that is not usually accessible in the

clinical practice. This difference is due to the higher energy needed with the QS-YAG laser<sup>8</sup>, its photodisruptive effects and the cavitation and shock-wave formation and consequent vitreous traction. With "mode-locking" laser the energy (femtosecond lasers) does not simply break the floater into smaller pieces. The high power density of this laser energy converts the collagen and hyaluronic molecules to a gas, which is then resorbed into the eye<sup>11</sup>. It is important to make sure that the laser light source and aiming beam are aligned within the same vertical axis before proceeding with vitreolysis<sup>11</sup>.

An indirect ophthalmoscopy lens or a three mirror Goldmann fundus lens can be chosen for this procedure.<sup>3</sup> Other types of lenses are now available to treat vitreous opacities in specific locations<sup>11</sup>.

One should start with low, sub-threshold, energy settings (about 2.5 to 6 mJ/ pulse), increasing power progressively as needed up to 20 mJ. The further posteriorly located or the larger the vitreous density, the higher the amount of energy needed. Most of the times energy settings between 6 and 12 mJ will be enough<sup>5</sup>.

One method consists on focusing the aiming beam directly on the retina and then moving it anteriorly towards the center of the globe until reaching the desired vitreous opacity. A clear view of the opacity is mandatory for a precise focusing in order to avoid hitting the retina or the lens. Laser treatment of vitreous opacities located less than 3-4 mm away from the retina or 2-3 mm away from the lens should be avoided, and this safety margin should be increased when performing the first cases, in which only opacities located in the mid third of the vitreous and away from the macula should be selected<sup>11</sup>. Patient's direction of gaze may be important to place the vitreous opacity away from the macula, optic disc or major retinal vessels.

When treating several vitreous opacities, one should start with those located more anteriorly in order to allow better visualization of the posterior ones. It is also advisable to start with vitreous opacities located superiorly due to the gas bubbles that tend to form and obstruct their view when starting with the lower ones.

When treating a vitreous opacity located in the posterior vitreous, chromatic aberrations may lead to the laser beam being focused posteriorly to the desired area. In such cases, it is advisable to select "anterior offset mode" when available<sup>11</sup>.

The mean duration of a treatment session should be around 15 minutes, and normally two or more sessions are necessary<sup>7</sup>.

A particular technique that has been suggested when performing laser vitreolysis is T-shaped membranotomy, as described by Cees<sup>4</sup>. An incision is created in the detached posterior hyaloid allowing vitreous opacities to move either to the nasal or temporal aspects, so rendering them less visible to the patient<sup>4</sup>.

### POSTLASER CARE AND FOLLOW-UP

Instillation of a steroid drop 3-4 times daily for one week is advised<sup>7</sup>. Ocular hypertension was seldom observed and hypotensive drugs are usually not recommended. The patient should be observed during the first days after treatment.



## COMPLICATIONS

Nd:YAG laser results in two different physical actions: thermal, leading to tissue vaporization; and mechanical, through shock waves. Complications usually arise due to the photodisruptive effects of the QS-YAG laser (see also chapter 12). In this regard, one should pay particular attention to the energy levels selected for laser treatment in order to prevent such complications<sup>10</sup>. It has been shown in animal models that the risk of **retinal injury** is correlated with the laser power and distance to the retina. Damage occurs with power settings of 9 mJ or more within 2 mm of the retinal surface<sup>12</sup>. Therefore, there should be a distance of 2 to 5 mm to the neighboring tissues for safe laser delivery<sup>8,10</sup>. A sharp focus is essential in order to prevent these complications<sup>1</sup>. In the presence of vitreous haze (due to cells, pigment or hemorrhage) dispersion from the focal area is likely to occur increasing the risk of retinal injury. The smaller the angle of the intraocular laser optical cone, the greater the risk. Shock waves irradiating from the focal area are the primary mechanism of tissue damage<sup>12</sup>.

The main complications of laser vitreolysis include **lens damage (cataract formation)**, **retinal and retinal pigment epithelium damage (retinal break, hemorrhage, scarring)** and **bleeding from blood vessel damage**<sup>1</sup>.

## CONCLUSIONS

QS-YAG vitreolysis is currently the most harmless and least invasive technique for the treatment of symptomatic vitreous opacities<sup>10</sup>.

In agreement with available literature, this procedure may be regarded as a safe, first line treatment of specific vitreous opacities in selected patients.

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# XIV. LASER in Oculoplastic Surgery

## 72. CO<sub>2</sub> LASER:

### blepharoplasty

### and resurfacing



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#### INTRODUCTION

Skin resurfacing with the CO<sub>2</sub> 10600 nm laser systems remains the gold standard technology for the most dramatic clinical and histologic improvement in severely photodamaged and scarred facial skin<sup>1</sup>. In the early 1990s, the development of high energy pulsed CO<sub>2</sub> systems revolutionized aesthetic laser surgery and ushered in a new decade of rapidly evolving laser technology.

As life progresses, skin experiences degrading influences of sun, age and environmental pollutants such as smoke. Even though the body's extensive reparative processes attempt to restore normal architecture, the pattern of the collagen bundles breaks into disjoined and fragmented bundles. This loss of regularity is reflected on the epidermal surface with the appearance of lines and wrinkles, also known as rhytids<sup>2</sup>.

The benefits of using the CO<sub>2</sub> laser rather than the cold-steel scalpel in blepharoplasty are reduced operative time, less bleeding, superior intraoperative visibility, less bruising and swelling, no pain or discomfort, and a shorter recovery period. The surgery can be combined with resurfacing which induces significant improvement in the surface appearance of the skin. Alteration of the collagen in the papillary and upper reticular dermis is the method used to achieve this goal. Before the advent of lasers (Figure 1), those changes were produced by a variety of topically applied chemical agents or by mechanical appliances such as dermabraiders.

#### PREOPERATIVE EVALUATION AND PATIENT SELECTION

Facial resurfacing is an elective cosmetic procedure. Counseling patients about realistic expectations and postoperative care is critical before undertaking any such

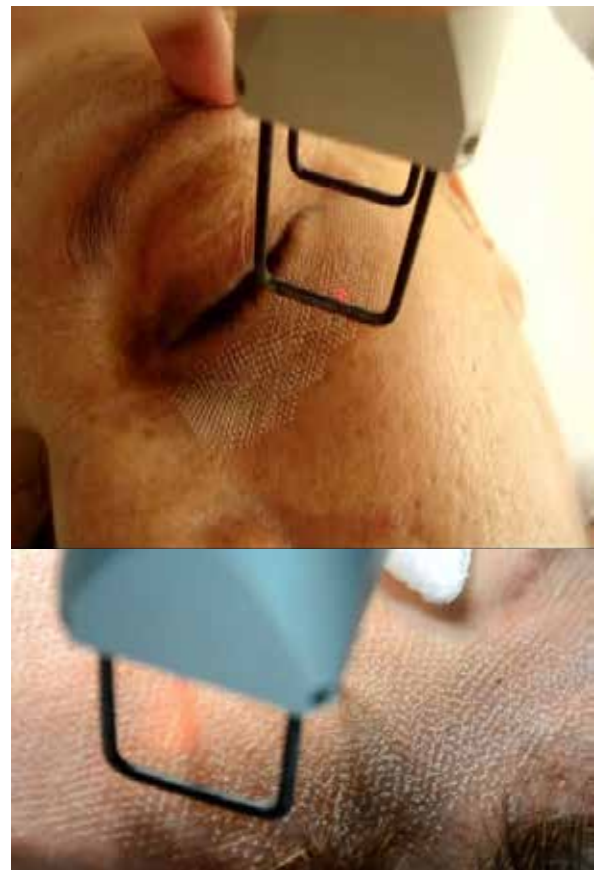


Figure 1. Ablative resurfacing treatment. The surface epithelium is completely removed.

procedure<sup>3</sup>. Special care should be taken to understand which areas of the face are of concern to the patient. Indications for facial laser resurfacing include the Fitzpatrick skin type classification scale and the presence of facial rhytids, skin laxity (Figure 2), dyschromia, atrophic acne scarring, rhinophyma and scar revision.



Figure 2. 71-year-old man with bilateral eyelid dermatochalasis who underwent bilateral upper blepharoplasty, lower transconjunctival blepharoplasty and lower eyelids CO<sub>2</sub> laser resurfacing: (A) preoperative and (B) 6 months postoperative.

Explaining the procedure beforehand to the patient is crucial. Show the prospective patient a photo album of pictures taken daily of actual patients who have undergone laser skin resurfacing during their first two postoperative weeks. This review can be most helpful in postoperative recuperation (Figure 3).

### REJUVENATION PROCESS

Using the CO<sub>2</sub> laser for skin resurfacing yields an additional benefit of collagen tightening through the heating of dermal collagen. The triple helical structure of collagen is altered, resulting in the shortening of the fibers by one third<sup>4</sup>. Persistence of this collagen contraction results, in part, from these shortened fibers serving as a scaffold for neocollagenesis. Apart from this, time, wound healing and fibroblast up-regulation of immune modulating factors leading to persistent collagen remodeling may explain continued clinical improvement seen up to 1 year after the procedure (Figure 4)<sup>5</sup>.

### ANESTHESIA

For a deep and full face resurfacing, laryngeal mask anesthesia is commonly used. Other options include nerve blocks, regional infiltration, IV sedation or topical agents. A drop of topical anesthesia should be placed in the conjunctival cul-de-sac<sup>6</sup>.



Figure 3. 68-year-old woman with bilateral eyelid dermatochalasis who underwent bilateral upper and lower blepharoplasty using CO<sub>2</sub> laser: (A) preoperative, (B) 7 days and (C) 3 months postoperative.



Figure 4. 74-year-old woman with bilateral eyelid dermatochalasis who underwent bilateral upper and lower blepharoplasty using CO<sub>2</sub> laser: (A) preoperative and (B) 6 months postoperative.

### PATIENT PREPARATION

Most practitioners recommend preparing the skin with a non-flammable cleanser such as a 10 percent povidone solution.

### SAFETY REMINDERS

All surgical personnel must wear protective eyewear<sup>7</sup>. Surgical instruments must be laser impermeable and non-reflective to avoid possible ricochets. Free flowing oxygen should be avoided to prevent risk of a flash fire. Laser safe metal shields are placed over the corneas<sup>8</sup>.

### APPLICATION OF LASER

Most machines have a pattern generator for cutting and resurfacing. Proceed with the upper and lower blepharoplasty using a 0.2 mm handpiece, in a continuous wave mode, 5 W power, for incision and tissue dissection<sup>9,10</sup>. This mode produces a continuous laser beam with no variation over time. Alternatively, some surgeons use the ultrapulse mode, which produces short pulses of laser at very high energy levels that are sustained over the entire duration of the pulse. When skin resurfacing is desired, a computer pattern generator handpiece should be attached.



Figure 5. 75-year-old woman who underwent full face resurfacing combined with four-lid blepharoplasty: (A) preoperative and (B) 1 month postoperative.

### OPERATIVE TECHNIQUES FOR ABLATIVE RESURFACING LASER SELECTION

Ablative resurfacing lasers are limited to two wavelengths. The erbium-YAG (Erb) laser emits at 29400 nm and the CO<sub>2</sub> emits at 10600 nm. A reasonable choice for applied fluence with both the long pulsed erbium and CO<sub>2</sub> lasers is 15-20 J/cm<sup>2</sup>. At this level about 80 µm of tissue will be ablated per pass<sup>11</sup>. The number of passes over specific areas must be individualized for each patient. General, conservative guidelines are: forehead = 2-3 passes; intraorbital eyelids = 1 pass; cheeks = 2-3 passes; perioral lips = 2-3 passes with only 1 pass crossing the vermillion border; angle of the mandible = 2 passes; and the upper neck 1 pass. The areas adjacent to these treatment zones should be treated with reduced fluence and density to avoid demarcation lines by blending or feathering. After the last pass, do not hydrate or remove the desiccated skin. Place occlusive dressings at the end of the case. One possibility is a biosynthetic dressing (e.g. Flexzan). As an alternative, petrolatum ointment may be applied.

### IMPORTANT RECOMMENDATIONS

- Topical antibiotics should be avoided. Healing balms have been advocated including Crisco and Vaseline. The most important objective is keeping the wound moist which promotes rapid re-epithelialization. The treated skin should not be allowed to 'dry out'.
- A yellowish serous transudate will be prominent on the treated dermal surface for 3 to 5 days. Expect moderate erythema and some edema, especially in

periorbital and perioral zones<sup>12</sup>.

- Pain is usually minimal. Prescribe anti-herpetic and oral antibiotics for prophylaxis.
- Since this early recovery period is a vulnerable one for the patient, emotional support and encouragement are important during this time<sup>13</sup>.
- Complete re-epithelialization should occur around day 7 to 10 and will be manifested by smooth pink skin. It will take a month for the epithelium to regain its full thickness (Figure 5 and 6).
- Make-up and other cosmetics can be slowly introduced, usually one at a time to facilitate identification of potential irritants. Sun block of at least SPF 30 should be used.



Figure 6. 65-year-old woman who underwent bilateral upper blepharoplasty using CO<sub>2</sub> laser and full face resurfacing 7 days postoperative.

### COMPLICATIONS

Postoperative care and complication recognition are perhaps the most difficult parts of laser facial resurfacing. Avoiding complications is the goal of appropriate postoperative care as outlined above. However, complications do occur and most can be overcome with patience and treatment such as bacterial cellulitis<sup>14</sup>, herpetic and fungal, pruritis, milia, post-inflammatory hyperpigmentation and hypopigmentation<sup>15</sup>, scarring and persistent erythema.

### CONCLUSION

Facial laser resurfacing is an effective tool in skin rejuvenation. It can be a very satisfying and valuable procedure for the practice of oculoplastic surgery. High-energy pulsed CO<sub>2</sub> laser irradiation of periorcular skin can safely and effectively improve dermatochalasis,



thereby offering a less invasive alternative to surgical blepharoplasty. In addition, the skin-tightening effect of the CO<sub>2</sub> laser can be used to the surgeon's advantage, making it unnecessary to pull skin as tightly during concomitant blepharoplasty or facelifting procedures. Because periorbital rhytides can be treated simultaneously, periocular rejuvenation can be further optimized.

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# XIV. LASER in Oculoplastic Surgery

## 73. Trichiasis



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### INTRODUCTION

Trichiasis is a disorder in which eyelashes or cilia are abnormally directed posteriorly towards the surface of the eye. Management options include mechanical epilation and more definitive measures such as electrolysis, radiofrequency ablation, cryotherapy, laser ablation and eyelid surgery<sup>1,2</sup>. Treatment decision is made according to the number, distribution and severity of the abnormal eyelashes but even though many techniques have been developed, they often are initially successful but have poor long-term results with frequent recurrences.

In 1979, Berry described Argon 514.5 nm laser (AL) treatment for trichiasis<sup>3</sup>, and since then it has been used for the treatment of cases involving a few scattered eyelashes and/or when the induction of larger areas of inflammation is undesirable<sup>4-12</sup>. Other lasers have also demonstrated efficacy and safety in these situations, like diode<sup>13-14</sup> or ruby laser<sup>15</sup>, all of them being suitable alternatives to electrolysis, radiofrequency or cryotherapy<sup>16</sup> in selected cases of trichiasis.

### INDICATIONS

Treatment of small numbers of eyelashes (up to six).

### CONTRAINDICATIONS

As lasers are absorbed by melanin or pigmented hair this technique is sensitive to hair color. Hypopigmented lashes (like in recurrent cases after undergoing repeated treatments with other methods) may not absorb laser energy quite well, making treatment difficult or even impossible.

### PREPARATION

1. Explain the procedure referring to the possible need of multiple sessions or other procedures.
2. Anesthesia - depending on the patient's sensitivity anesthesia is rarely necessary. A topical (oxybuprocaine chloride) or most often a local infiltration of lidocaine 2% can be used.

Alternatively, topical cream of lidocaine 2.5% and prilocaine 2.5% (EMLA® AstraZeneca AB) can be applied 30 minutes to 2 hours before the procedure, preferentially with an occlusive patch.

3. Patient should sit comfortably.
4. Under topical oxybuprocaine chloride insert a metallic contact lens for ocular laser protection. Laser room should have dim light.
5. Ask the patient to keep steady looking up (if you are treating lower eyelid) or down (when treating upper eyelid) and preferentially use your fingers to adjust the eyelid and maintain the eyelash aligned with the laser beam.

### LASER TECHNIQUE

*Nd:YAG KTP 532 nm laser (KTP laser) or Yellow Diode 577 nm laser (YD laser)*

This modality is based on our experience and recent studies and involves 2 stages. Laser parameters can be adjusted to the thickness of the eyelash.

Laser beam variables:

	Stage 1: initial spots	Stage 2: tissue vaporization
Spot size	100 µm	150 µm
Duration	0.1s	0.2s
Power	300 mW	400-500 mW

#### *Stage 1 - The first burns*

Direct the beam coaxially to the eyelash follicle to create a crater (this orientation of the eyelid is crucial), you should see vaporization during this stage. Continue until 2-3 mm of depth is reached.

#### *Stage 2 - Coagulation of the bed of follicle*

Change the laser parameters and continue directing the beam coaxially to the lash root to destroy residual follicular tissue (adding both stages you may need up to 30-40 bursts).



**Important:** avoid tissue retraction using short pulses near the surface and longer pulses only deeply to vaporization. Avoid making coalescent craters for a bottom to top healing instead of lateral and retractile healing of the eyelid (Figure 1).

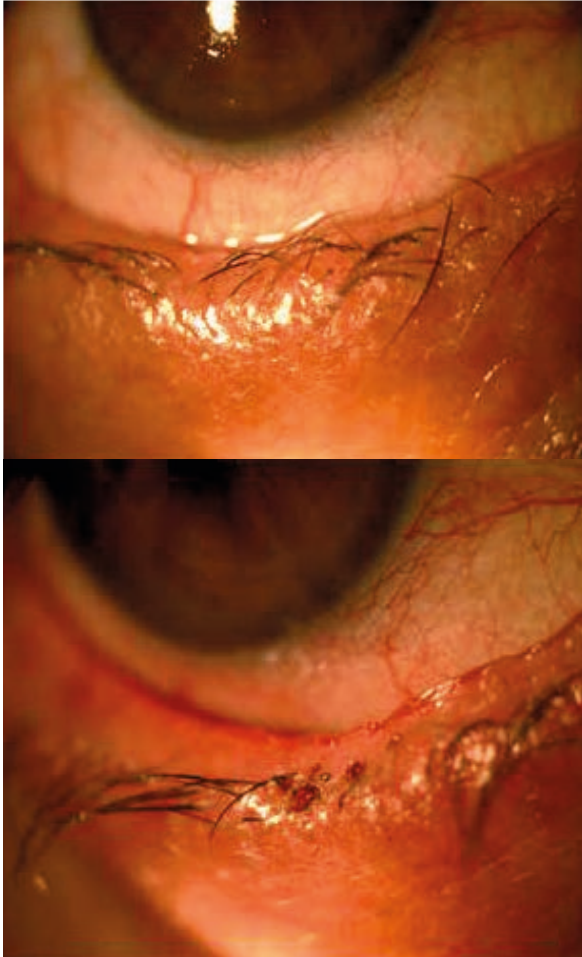


Figure 1. Trichiasis pre (upper) and post (bottom) laser

Some authors use energy bursts with higher duration (1 to 3 seconds) or even continuous, depending on the eyelash features, using only a few shots to effectively destroy the subcutaneous lash and its follicle<sup>6</sup>. This is usually more painful and local infiltration with anesthesia is advisable. To improve the absorption of laser energy a blue skin marker pen can also be used to mark the base of the eyelash<sup>7</sup> or even transfer a drop of the patient's own blood (for example at the site of local anesthetic infiltration) to the lash base<sup>6</sup>. This is a simple, safe, and effective method in cases of pale lashes. Attention should be paid to the retractile effect of long pulses that can lead to additional trichiasis and lacrimal film instability.

#### POSTLASER CARE AND FOLLOW-UP

Antibiotic ointment t.i.d. for a week.

#### COMPLICATIONS (see table 1)

This is a relatively safe procedure and the complication

rate is usually higher among patients treated previously with cryotherapy or lid surgery.

- **Recurrence** rate is variable and can be high with only one session (up to 50-60%) decreasing considerably with additional treatments.
- **Mild hypopigmentation.**
- **Notching, lid margin retraction and mild contour abnormalities.**

#### RESULTS

Several studies evaluate the success rate and safety of argon laser photocoagulation as a tool in the treatment of trichiasis (Table 1). Even though it is not as effective as cryotherapy or radiofrequency, it has less destructive effects than the first<sup>1,16,17</sup> and is more accessible to an ophthalmologist. When you start using it you should bear in mind that the recurrence rate with only one session is high but with one or two more sessions the final success rate can reach more than 90%, according to the literature and our experience. However, one limitation of these studies is the short follow-up time, as in our experience that recurrence can occur several weeks later. Nevertheless, the precision, ease of performance, and lack of complications make it a very interesting technique.

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Table 1. Efficacy and complication rates of argon and diode laser photocoagulation in trichiasis treatment

Author	Year	Purpose	Number	Follow up (months)	Results	Complications
Al-Bdour <sup>4</sup>	2007	Argon laser (50-100 $\mu\text{m}$ spot size, 0.3 s, 500 mW)	68 eyelids (54 patients)	8	Success rate 61.1% (1 treatment session) and 85.2% with up to 3 sessions	Mild skin hypopigmentation (12%) and notching (8.8%)
Başar E <sup>5</sup>	2000	Argon laser (100-200 $\mu\text{m}$ spot size, 1W, 0.2 s)	60 eyelids (45 patients)	4-12	Successful treatment of 45 eyelids (75%) with 1 session, retreatment success of 53%	Mild hypopigmentation (5%) and mild lid notching (5%)
Unlü K <sup>8</sup>	2000	Argon laser (50- 200 $\mu\text{m}$ spot size, 0.2 s, 1 to 1.2 W)	36 eyelids (22 patients)	10.6 (mean)	Successful treatment in 55.5% with 1 laser session and up to 88.9% with 2 or 3 sessions	None
Ladas ID <sup>9</sup>	1993	Argon laser in recurrent trichiasis (50-100 $\mu\text{m}$ spot size, 0.2 s, 1 to 1.2 W)	92 eyes		Recurrence rate of 64.1%, with a new session final success rate of 91.3%. The number of misdirected eyelashes per eyelid affects the rate of recurrences	None
Huneke JW <sup>10</sup>	1992	Argon laser (50 $\mu\text{m}$ spot size, 300 mW, 0.5 s)	91 eyelids (77 patients)		62% initial success rate. 37% required repeated treatment to the same area	None
Sharif KW <sup>11</sup>	1991	Argon laser in recurrent trichiasis (50-200 $\mu\text{m}$ spot size, 0.2 s, 1 to 1.2 W)	28 eyelids (21 patients)	6.57 (mean)	Successful treatment in 67.9% of the eyelids after 1 or 2 laser sessions. Remaining 32.1% required 3 to 4 sessions. Significant correlation between the number of aberrant lashes per eyelid and the number of required laser sessions	
Campbell DC <sup>12</sup>	1990	Argon laser in recurrent trichiasis (50-100 $\mu\text{m}$ spot size, 0.05 to 0.10 s, 1.2 to 2 W)	15 eyelids (12 patients)	3-6	Success rate 80%, with the need for up to 3 treatments	
Pham RT <sup>13</sup>	2006	810 nm diode laser	153 eyelids (87 patients)	6	Average number of eyelashes per patient was reduced from 3.58 to 0.73	None
Strempel I <sup>14</sup>	2000	806 nm diode laser	301 lashes (19 eyes)	4	Destruction of two-thirds of the eyelashes	None

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# XIV. LASER in Oculoplastic Surgery

## 74. Periocular skin

### conditions – benign lesions



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#### INTRODUCTION

Currently a large number of laser modalities are available for periocular treatments. Although this skin treatment technology belongs predominantly to the dermatology domain, as ophthalmologists we should know the options and indications in order to better inform and refer our patients (Table 1). This anatomic area, prone to the development of photoaging changes, benign and malign tumors and degenerations, should always be subjected to our scrutiny.

Selective photothermolysis is a fundamental concept, which states that precise tissue damage can be achieved by applying laser energy of an appropriate wavelength

and pulse duration<sup>1</sup>. This principle guides the selection of which laser is best suited for a particular cutaneous lesion. The three important parameters to be taken under consideration are:

1. The laser wavelength, which should be preferentially absorbed by a target chromophore (water, hemoglobin or melanin);
2. The pulse duration, which should affect the target before causing thermal lesion to the surrounding tissue;
3. The fluence (energy delivered per unit area) which should not go beyond a level that causes diffuse thermal damage.

Table 1. Lasers used for treatment of periocular conditions

Laser	Wavelength (nm)	Main chromophore	Periocular applications
KTP	532	Hemoglobin, Melanin	Endonasal lacrimal surgery, trichiasis, benign eyelid tumors, hemangiomas, telangiectasias <sup>2,3</sup> , pigmented lesions (Q-switched-KTP) <sup>4</sup>
PDL	595	Hemoglobin	Superficial vascular abnormalities (port-wine stains, telangiectasias, infantile hemangiomas) <sup>2</sup>
Ruby	694	Melanin	Pigmented lesions (Q-switched-ruby), epilation
Alexandrite	755	Melanin	Deep vascular lesions, epilation, pigmented lesions (Q-switched-Alex) <sup>5</sup>
Diode	810	Melanin	Epilation <sup>6</sup>
Nd:YAG	1064	Melanin	Angiomas <sup>6</sup> , venous malformations <sup>7,8</sup> , epilation, pigmented lesions (Q-switched-Nd:YAG) <sup>9</sup>
Er:Glass	1440, 1550	Water	Non-ablative fractional resurfacing
Er:YAG	2940, 2960	Water	Cutaneous resurfacing <sup>10,11</sup>
CO2	10600	Water	Orbital lymphangiomas <sup>10</sup> , blepharoplasty <sup>11</sup> , cutaneous resurfacing <sup>11-14</sup> , eyebrow lift <sup>14</sup> , pigmented lesions <sup>4</sup> , periocular benign lesions

KTP: potassium-titanyl-phosphate; PDL, pulsed dye laser; Nd:YAG: neodymium-doped yttrium aluminum garnet; Er:Glass: erbium-doped glass fiber; Er:YAG, erbium-doped yttrium aluminum garnet; CO2: carbon dioxide.

Taking these principles into account several new technologies have emerged: for example, the fractional photothermolysis, which induces microscopic gridded columns of thermal injury and stimulates dermal collagen and elastic tissue formation minimizing diffuse damage<sup>15</sup>.

### INDICATIONS

1. Periocular benign lesions. Although controversial, laser can also be used in selected cases of periocular malignant tumors<sup>16,17</sup>.
2. Vascular lesions (angiomas, telangiectasias, lymphangiomas).
3. Pigmented lesions.
4. Facial rejuvenation.
5. Epilation of eyebrows.

### PATIENT PREPARATION

1. Explain the procedure mentioning the possible need of multiple sessions.
2. Proper eye protection is crucial - the patient should wear metal goggles or opaque metal corneal shields (Figure 1) and the staff should wear wavelength-specific goggles throughout the whole procedure.
3. Anesthesia - when using corneal shields use topical anesthesia (oxybuprocaine hydrochloride 0.4%) and an ophthalmic ointment to protect the cornea.

Topical skin anesthesia is usually not necessary when treating small lesions, but it can be useful when treating larger areas. In those circumstances you can use topical anesthesia (topical cream of lidocaine 2.5% and prilocaine 2.5%, EMLA® AstraZeneca AB, applied 30 minutes to 2 hours before the procedure), nerve blocks, local infiltration of lidocaine 2%, systemic opiates or intramuscular non-steroidal anti-inflammatory drugs. Sometimes, especially in children, general anesthesia is needed to complete the treatment.



Figure 1. Metal corneal shields.

### A. ABLATIVE LASER TREATMENT FOR PERIOCCULAR TUMORS

Photoablation is based on the principle of selective photothermolysis, it works by targeting water, the major constituent of skin, causing a sudden rise in temperature and producing vaporization. The most used lasers for ablation therapy are the **CO<sub>2</sub> laser** (10 600 nm), which produces a good tissue contraction and hemostasis<sup>18</sup>, and the **Er:YAG laser** (2940 nm), the wavelength of

which is near the peak absorption of water, allowing an optimal ablation effect with minimum thermal damage. Although not as effective for haemostasis as the CO<sub>2</sub> laser, the **Er:YAG laser** allows faster healing with less pain and fewer complications<sup>19</sup>, which has made it an ideal tool for the treatment of the delicate periocular region.

In this chapter we will consider four distinct and very common benign skin lesions, which you certainly observe recurrently: xanthelasma, milia, syringomas and seborrheic keratoses.

### Xanthelasma

It appears as a yellowish, flat and soft plaque located most commonly on the medial portion of the eyelid (Figure 2). Histologically it is characterized by well-defined deposits of cholesterol and other lipids in macrophages, which develop into foam cells. These changes occur initially in the connective tissue around the perivascular spaces in the upper dermis of the eyelids<sup>20</sup>. Hyperlipidemia, thyroid dysfunction, and diabetes mellitus have been described as possible pathogenic triggers<sup>21</sup>.

Several methods can be used to treat xanthelasma, including simple surgical excision, cryotherapy and chemical peeling with trichloroacetic acid. However its superficial location makes it an excellent target for laser therapy: CO<sub>2</sub> laser, Er:YAG, PDL, Q-switch 1064 nm-Nd:YAG, diode laser, all of which have been used with success (Table 2). Either Argon or Nd:YAG-KTP 532 nm laser have also been an option, causing a superficial photocoagulation with dermal appendages preservation<sup>22</sup> and less scarring, but with a significant recurrence rate<sup>29-31</sup>.



Figure 2. 48-year-old woman with bilateral xanthelasma.

### Syringoma

Syringoma is a common benign tumor of eccrine sweat duct origin<sup>32</sup> that typically affects young women and mainly involves the periorbital area. It presents as asymptomatic discrete soft 2-4 mm flesh yellowish colored papules (Figure 3).

Although benign, syringomas can pose significant cosmetic concerns, given the exposed periorbital location and the tendency to have multiple lesions. Conventional treatment options include surgical excision, electrodesiccation, chemical peelings, topical atropine or tretinoin, cryotherapy, and laser therapy, but it is very difficult to perform a complete excision<sup>32-34</sup>. Both CO<sub>2</sub> and Er:YAG laser treatments have become the treatments

Table 2. Lasers used for treatment of xanthelasma

Author	Year	Laser Used	Number	Results	Complications
Karsai S <sup>23</sup>	2010	PDL (585 nm; up to 5 sessions at 2- to 3-week intervals)	20 patients (38 xanthelasmas)	Good clinical response (51% cleared) in two-thirds; excellent clinical response (75% cleared) in one quarter at 4 weeks	None
Saif M <sup>24</sup>	2007	CO2 laser (10600 nm)	25 patients	Most patients with satisfactory cosmetic appearance	5 eyelids (5.7%) with pigmentary changes and recurrence in 8 lids (9.1%)
Raulin C <sup>25</sup>	1999	Ultrapulsed CO2 laser (10600 nm; 1 session)	23 patients (52 xanthelasmas)	Complete removal	Transient pigmentary changes (4% hyperpigmentation and 13% hypopigmentation). No visible scarring. 3 patients (13%) with recurrence after 10 months
Alster TS <sup>26</sup>	1996	High energy pulsed CO2 laser (10600 nm)	2 patients with bilateral xanthelasmas	Complete eradication with no recurrence within an 8 to 12 month follow-up	None
Berger C <sup>21</sup>	2005	KTP laser (532 nm)	60 eyelids (45 patients)	85.7% with respectable reduction after 1-3 sessions	None
Abdelkader M <sup>27</sup>	2015	Erbium:YAG laser (2960nm) versus argon laser (514 nm)	20 patients (30 xanthelasma) treated with erbium:YAG laser. 20 patients (40 xanthelasma) treated with argon laser	Erbium:YAG: Complete removal in 1 session Argon: 71.4% with excellent results, 20% very good, 5.7% good, 2.8% with satisfactory results. Large lesions needed more than one session	Erbium:YAG laser: 2 patients developed hypopigmentation
Mannino G <sup>28</sup>	2001	Erbium:YAG laser (2960 nm)	30 patients (70 xanthelasmas)	All lesions removed	None
Basar E <sup>29</sup>	2004	Argon green (514 nm)	40 eyes with xanthelasma	85% good, 10% fair and 5% poor cosmetic results	6 out of 40 recurred after one year
Hintschich C <sup>31</sup>	1995	Green argon (514 nm)	32 xanthelasmas	Good and very good results in 80% of cases	Recurrence in 14 out of 25 lids after 12-16 month

Fl: Fluence; dt: duration; ss: spot size; dm: diameter; en: energy; fq: frequency.



Figure 3. 41-year-old woman with bilateral periocular xanthelasma who underwent CO2 laser resurfacing: preoperative (left) and final result (right).

of choice with good results (Table 3), and combination methods have also been described. Periorbital xanthelasma are treated with two passes of a CO2 laser at the settings of 0.2 second pulse duration, 5 watts and 3 mm spot size.

### Milia

Milia are small white or yellowish nodules produced in the

skin due to the retention of sebaceous secretion (Figure 4). They can occur at any age and have different presentations, from the benign primary form on the cheeks and eyelids to more severe variants like milia en plaque, multiple eruptive milia, milia post-photodermatitis and milia post-trauma, which are very difficult to treat<sup>39</sup>. Treatment involves topical retinoids, electrodesiccation, dermabrasion and cryotherapy, and more recently ablative laser with CO2 and Er:YAG lasers, but literature is still scarce<sup>40-42</sup> (Table 4).

### Seborrheic keratosis

Seborrheic keratosis is a benign and very common skin lesion that occurs in middle-aged and older individuals. It has a variable presentation but it usually forms an exophytic, sharply demarcated, “stuck on the skin” lesion with a verrucous, rough surface<sup>43</sup> and it can mimic malignant lesions, especially squamous cell carcinoma, both clinically and pathologically (Figure 5). Dermatosis papulosa nigra (DPN) is a common variant in darkly pigmented individuals.



Table 3. Lasers used for treatment of syringoma

Author	Year	Laser Used	Number	Results	Complications
Lee SJ <sup>35</sup>	2015	CO2 laser (10600 nm, 2 sessions with 2 months interval)	29 patients	Marked clinical improvement (51-75%) in 10 of the 29 patients (34.5%), moderate clinical improvement (26-50%) in eight (27.6%), near-total improvement ( $\geq 75\%$ ) in seven (24.1%) and minimal improvement (0-25%) in four patients (13.8%) within a 2-month follow-up	None
Cho SB <sup>36</sup>	2011	CO2 fractional laser system (10600 nm, 2 sessions with 1 month-interval)	35 patients	15 of the 35 patients (42.9%) with marked improvement (51-75%), 12 (34.3%) with moderate (26-50%), five (14.3%) with minimal (0-25%) improvement and three (8.6%) with nearly total ( $\geq 75\%$ ) clinical improvement at a 2-month follow-up	5 lids (5.7%) with pigmentary changes and 8 (9.1%) lids showed recurrence
Park HJ <sup>37</sup>	2007	Multiple-drilling using CO2 laser (10600 nm)	11 patients	Excellent clinical response in 7 patients, good response in the remaining	None
Wang JI <sup>38</sup>	1999	CO2 laser (10600 nm)	10 patients	Successful elimination of the syringomas in all patients within one or two sessions at a median follow-up of 16 months	Prolonged erythema was the most common side effect (lasting from 6-12 weeks)

Fl: Fluence; dt: duration; ss: spot size; dm: diameter; en energy; fq: frequency

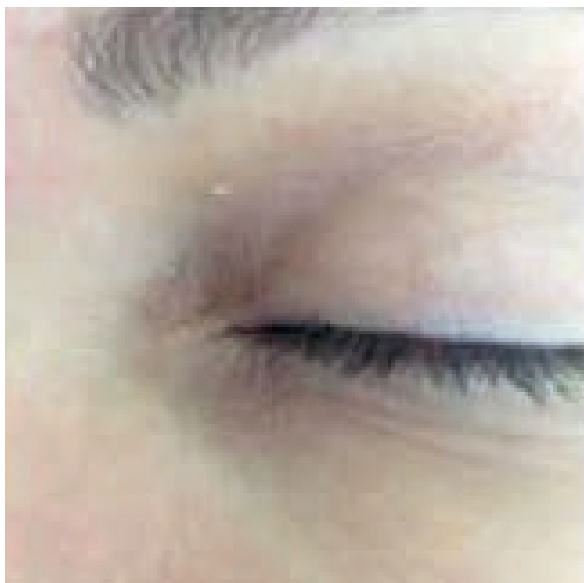


Figure 4. 26-year-old woman with milia.

The etiology is unknown, although heredity, sunlight, human papilloma virus (HPV) and somatic mutations have been suggested as risk factors. Treatment options include cryosurgery, curettage, electrosurgery, and shave removal. Several lasers (Er:YAG laser, CO2, pigment-specific lasers like alexandrite and diode, KTP and PDL) have proved to be effective in its eradication<sup>44-48</sup> (Table 5).

## B. ABLATIVE LASER TREATMENT FOR RHYTIDES AND TEXTURAL IRREGULARITIES

### Ablative fractional resurfacing

Currently, ablative fractional lasers are approved by the



Figure 5. 71-year-old man with a right periocular seborrheic keratosis who underwent CO2 laser treatment: (left) preoperative and (right) postoperative.

U. S. Food and Drug Administration (FDA) for the treatment of rhytides, furrows, fine lines and textural irregularities<sup>49</sup>. A number of recent studies have shown clinical improvements in periorbital photo-aged skin including rhytides, laxity and dyschromia when treated with ablative fractional CO2 lasers (Figure 6). Er:YAG fractionated laser systems have also showed promising results in the treatment of photo-aged skin.

### Non-ablative fractional resurfacing

The concept of non-ablative fractional photothermolysis is relatively recent, introduced in 2003. It is currently FDA approved for the treatment of pigmented lesions, periorbital rhytides, skin resurfacing<sup>50</sup>, melasma, acne, surgical scars, and actinic keratoses. Fractional non-ablative laser treatments typically result in quicker healing and less downtime than ablative lasers but require more treatments to achieve similar results.

Table 4. Lasers used for treatment of milia

Author	Year	Laser Used	Number	Results	Complications
Tenna S. <sup>40</sup>	2014	CO2 fractional laser (10600 nm) in milia en plaque	1 patient	Good results after only two treatments	Within 1 year few recurrent milia present
Pozo Jd <sup>41</sup>	2010	CO2 laser vaporization in different variants of milia (10600 nm, 2 passes in each session)	4 patients	All patients with marked improvement after a few sessions and after a 12-36 month follow-up	None
Voth H <sup>42</sup>	2011	Erbium:YAG laser in refractory milia (2960 nm)	1 patient	Nearly complete resolution and excellent clinical results lasting for a 12 month follow-up	None

Table 5. Lasers used for treatment of seborrheic keratosis

Author	Year	Laser Used	Number	Results	Complications
Gurel MS <sup>44</sup>	2014	Er:YAG lasers (2960 nm) versus cryotherapy	42 patients	Er:YAG lasers: complete healing of all lesions following the first treatment Cryotherapy group: healing rate of 68% (p < 0.01)	Er:YAG laser-treated group with significantly lower hyperpigmentation and more erythema
Khatri KA <sup>45</sup>	2003	Erbium:YAG laser (2960nm)	79 lesions	All lesions completely removed after a single session	None
Kim YK <sup>46</sup>	2014	Long-pulsed alexandrite laser (755 nm, 1-3 sessions at 1 month intervals)	13 patients	Mean 1.1 ± 0.4 sessions needed. Most of the lesions became crusted within a few days and spontaneously peeled off within 7 days	None
Garcia MS <sup>47</sup>	2010	Pulsed dye laser (PDL) 585 nm versus curettage and electrodesiccation	10 patients	No significant difference between the three treatment modalities. Mean lesion clearance of 96% through curettage, 92.5% through electrodesiccation and 88% for laser.	Laser was considered the most painful method. The most common adverse outcome was hyperpigmentation (for all the modalities)
Culbertson GR <sup>48</sup>	2008	532 nm diode laser and color enhancement	326 patients	Complete resolution of 93% of lesions. 7% of SKs required a second session of treatment	Hypopigmentation in 6% of patients, associated with old, chronic, or recalcitrant lesions.

Fl: Fluence; dt: duration; ss: spot size; dm: diameter; en: energy; fq: frequency.

## COMPLICATIONS

Nowadays, helped by the technical refinement of this technology, laser exerts a tremendous fascination on patients and has a huge marketing power that sometimes makes it seem an easy and innocuous technique. We know that this is not true, our own experience with laser use in retina, glaucoma and refractive surgery for decades has made us aware that it can have serious effects, especially when performed by inexperienced hands.

1. CO2 laser - **Prolonged erythema, hyper- and hypopigmentation, and hypertrophic or keloid-like scarring** are among the most common complications

of CO2 laser. Excessive lateral thermal damage (LTD) caused by the conduction of heat to surrounding tissues during laser induces **excessive inflammation, persistent vasodilatation, profuse transfer of melanin from the hair follicle melanocytes to the regenerated epithelial cells and deposition of collagen**<sup>51,52</sup>.

2. Erbium: YAG laser - even though it can cause the same adverse effects as the CO2 laser, due to both its wavelength of 2940 nm (near the peak absorption of water) and its extremely short pulse duration, it is very efficiently absorbed, allowing athermic ablation of very thin skin layers, with minimal lateral thermal injury<sup>53</sup>.



Figure 6. 36-year-old man with bilateral periocular syringomas who underwent CO2 laser treatment: preoperative (upper image) and laser application (bottom image).

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# XIV. LASER in Oculoplastic Surgery

## 75. Ablative Laser

### Treatment For

# Pigmented Lesions



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#### INTRODUCTION

Laser treatment of pigmented lesions is based on the principle of selective photothermolysis<sup>1</sup>, which states that a laser light must emit a wavelength that is specific and well absorbed by the particular chromophore being treated. The ability to treat pigmented lesions with greater safety and efficacy is a result of these advances in laser technology. Melanin is the target chromophore for pigmented lesions. Melanin absorption decreases as the wavelength increases, although a longer wavelength allows deeper tissue penetration.

Argon laser 514.5 nm (AL 514.5 nm)/Nd:YAG KTP 532 nm (KTP laser 532) or Yellow Diode laser 577 nm (YD laser 577 nm) target the melanin chromophore, but side effects such as dyspigmentation and scarring have limited its widespread use<sup>2</sup>. Also, continuous wave carbon dioxide (CO<sub>2</sub>) lasers (10600 nm) were used mainly for epidermal lesions, in which denuding of epidermis occurred, raising the risk for post-procedure erythema, infection, pigmentary changes and scarring. Q-switched (QS) lasers produce rapid pulsed bursts of energy that match the thermal relaxation time of the small particles of melanin. QS lasers used in pigmented lesions include the **QS ruby** (QSRL, 694 nm), the **QS Nd:YAG** (532 and 1064 nm), and the **QS Alexandrite** (QSAL, 755 nm) lasers.

Since 2004, with the introduction of fractional photothermolysis (FP) by Manstein and Anderson<sup>3</sup>, several short studies and case reports have demonstrated efficacy in treating pigmented lesions such as melasma, solar lentigines, dermatosis papulosa nigra, post-inflammatory hyperpigmentation (PIH), Becker's nevus and nevus of Ota. FP is the fractional emission of light into microscopic treatment zones (MTZs), creating small columns of injury to the skin in a pixilated fashion.

Epidermal and dermal disruption occurs in these focal zones of thermal injury, stimulating dermal collagen production and elastic tissue formation. Histology after FP has demonstrated that there is a localized, well controlled melanin release and transport mechanism for epidermal and dermal pigment evacuation<sup>4</sup>.

In general, lesions where the pigment is very superficial in the epidermis (such as lentigines) are treated with lasers of shorter wavelengths, such as QS-ruby (694 nm), QS-KTP (532 nm), or pulsed dye (510 nm). Deeper lesions, such as tattoo pigment or nevus of Ota, may be treated with QS-Nd:YAG at 1064 nm or an intermediate laser, such as QS-Alexandrite (755 nm). Recent developments during the past decade have also proved to be effective in treating pigmented lesions, with FP being at the leading edge of laser treatment.

#### EPIDERMAL LESIONS

Pigment is situated at the dermoepidermal junction or in the epidermis for epidermal lesions.

Any treatment that damages the epidermis will result in improving the epidermal pigment.

#### 1. LENTIGO SIMPLEX, SOLAR LENTIGO

Lentigo simplex are benign, oval, brown macules in children and are not associated with sun exposure<sup>5</sup>.

Solar lentigines are benign, small, brown macules that often develop in adults after years of sun exposure<sup>5</sup>. They are considered to be one of the earliest signs of photoaging, and removal of these lesions is one of the most frequent procedures performed in laser centers. These lesions must be distinguished from their non-malignant and malignant counterparts by expert physicians, however clinical differentiation between an early malignant melanoma in situ (MMIS) and a benign lesion can be challenging.



## 75. Ablative Laser Treatment For Pigmented Lesions

Lasers that have been used to treat lentigines include the CO<sub>2</sub>, argon 514.5 nm, QS Nd:YAG, QSRL, QSAL and long-pulsed Alexandrite laser (Table 1).

### 2.EPHELIDES

Ephelides (freckles) are small brown macules that appear on sun-exposed areas usually during the summer months. Unlike solar lentigines, they are generally present in early childhood, and the only histologic abnormality is the increased production of melanin pigment<sup>5</sup>. Lasers used in the treatment of ephelides include QSAL and Nd:YAG

lasers (Table 2).

### 3.CALM (*café-au-lait macules*) and Nevus Spilus

CALMs vary in color from light to dark brown.

Histologically, basilar hyperpigmentation is present<sup>5</sup>. When dark macules or papules are found within a CALM, the lesion is defined as a nevus spilus.

Lasers that have been used to treat CALMs and nevus spilus are pulsed dye laser (PDL), Er:YAG (erbium-doped yttrium aluminum garnet), QS Nd:YAG, QSRL and QSAL (Table 3).

Table 1. Lasers used for treatment of lentigo simplex, solar lentigo

Author	Year	Laser used	Number	Results
Fitzpatrick <i>et al</i> <sup>6</sup>	1994	CO <sub>2</sub>	26 patients (83 lentigines)	100% of lentigines had 100% clearance
Stern <i>et al</i> <sup>7</sup>	1994	Argon CO <sub>2</sub>	13 patients (99 lentigines)	Argon: 25% excellent results; 62% good results CO <sub>2</sub> : 23% excellent results; 61% good results
Kilmer <i>et al</i> <sup>8</sup>	1994	QS Nd:YAG	37 patients	75% of pigment cleared in 60% of the lesions at higher fluences
Kagami <i>et al</i> <sup>9</sup>	2007	QSAL	49 patients	2% of patients had 96-100% clearance 24.5% of patients had 76-95% clearance 26.5% of patients had 51-75% clearance 20.4% of patients had 26-50% clearance 8.2% of patients had 0-25% clearance
Sadighha <i>et al</i> <sup>10</sup>	2008	QSRL	89 patients	Complete resolution of 100% of lesions
Wanner <i>et al</i> <sup>11</sup>	2007	Non-ablative fractional	50 patients	73% of facial skin had at least 51% improvement 55% of non-facial skin had at least 51% improvement

CO<sub>2</sub>= Carbon Dioxide; QS Nd:YAG= Q-switched neodymium-doped yttrium aluminum garnet; QSAL=Q-switched Alexandrite laser; QSRL=Q-switched ruby laser

Table 2. Lasers used for treatment of Ephelides

Author	Year	Laser used	Number	Results
Jang <i>et al</i> <sup>12</sup>	2000	QSAL	197 patients	64% of patients had at least 76% clearance with 1 treatment 100% patients had at least 76% clearance with an average 1.5 treatments
Rashid <i>et al</i> <sup>13</sup>	2002	Long pulsed Nd:YAG	14 patients	71% of patients had > 50% improvement

Table 3. Lasers used for treatment of CALM and nevus spilus

Author	Year	Laser used	Number	Results
Alster <sup>14</sup>	1995	PDL pulsed dye laser	30 patients (34 CALMs)	100% of CALMs had 100% clearance
Greveling <i>et al</i> <sup>15</sup>	1997	QSRL QS Nd:YAG	6 patients	100% patients had 90-100% improvement of nevus spilus
Kagami <i>et al</i> <sup>9</sup>	2007	QSAL	49 patients	7.1% of patients had 96-100% clearance 25% of patients had 51-75% clearance 14.3% of patients had 26-50% clearance 46.4% of patients had 0-25% clearance 8.2% of patients had 0-25% clearance

**DERMOEPIDERMAL LESIONS**

Pigment is situated at the dermis and epidermis. These lesions include Becker’s nevus, PIH, melasma and nevocellular nevi.

**1. BECKER’S NEVUS**

Becker’s nevus presents clinically as a brown irregular patch accompanied by dark, coarse hair. The lesion usually appears in adolescence and in male patients.

Histologically, smooth muscle fibers are often present in the dermis, along with a basal layer hyperpigmentation and a large number of melanocytes in the epidermis<sup>5</sup>.

The pigmented portion of Becker’s nevus has demonstrated to improve with QS lasers, the Er:YAG laser and the 1550 nm fractional Erbium-doped fiber laser. In 2005, Trelles and colleagues concluded that a single pass with the Er:YAG was more efficacious in pigment removal in Becker’s nevus than three treatment sessions with the Nd:YAG (Table 4).

Terminal hair reduction is improved by using long-pulsed ruby and alexandrite lasers.

**2. POSTINFLAMMATORY HYPERPIGMENTATION**

PIH can result from hemosiderin or melanin deposition. Hydroquinone 4% cream and a sunscreen with broadspectrum UVA and UVB protection are typically

first-line agents to improve PIH. Topical retinoids, steroids, vitamin C, and chemical peels have also been used with varying success for PIH.

PIH has been reported to improve with the 1064 QS Nd:YAG laser with low fluence<sup>18</sup> and as well as with FP<sup>19</sup>. Since PIH has been previously reported as a side effect of FP<sup>20</sup>, care must be taken when using these lasers to improve PIH.

**3. MELASMA**

Melasma is a common pigmentary condition characterized by brown patches on the sun-exposed areas of the face, and most commonly occurs in women.

Although many treatment modalities have been studied, there is no cure, and recurrences are common.

Laser therapy has been used to improve melasma, but care must be taken when treating this condition, because worsening of the disease or PIH may occur after treatment. QSRL (694 nm)<sup>21</sup>, QS Nd:YAG (1064 nm)<sup>22-24</sup>, QSAL (755 nm)<sup>25,26</sup>, CO2 (10600 nm)<sup>25-27</sup>, Er:YAG (2940 nm)<sup>28,29</sup> lasers and 1550 nm fractionated erbium doped fiber laser (Fraxel re:store)<sup>30-32</sup> have all been studied in the treatment of melasma (Table 5). Recently, a fractional CO2 laser (Ultrapulse Active FX, Lumenis, Yokneam, Israel) was shown to result in improvement when the patient was pretreated with a topical bleaching regimen<sup>27</sup> (Table 5).

Table 4. Lasers used for treatment of Becker’s Nevus

Author	Year	Laser used	Number	Results
Trelles <i>et al</i> <sup>6</sup>	2005	Er:YAG QS Nd:YAG	22 patients	Er:YAG 54% patients had complete clearance QS Nd:YAG 9% patients had 51-99% clearance 45.5% of patients had 26-50% clearance
Glaich <i>et al</i> <sup>7</sup>	2007	Non-ablative fractional	2 patients	100% of patients had > 75% improvement

Table 5. Lasers used for treatment of Melasma

Author	Year	Laser used	Number	Results
Cho <i>et al</i> <sup>23</sup>	2009	QS Nd:YAG	25 patients	28% of patients had > 75% improvement 44% of patients had 51-75% improvement 20% of patients had 26-50% improvement 8% of patients had < 25% improvement
Lee <i>et al</i> <sup>24</sup>	2009	Nonablative fractional	25 patients	60% of patients improved at 4 weeks and 52% at 24 weeks
Wanitphakdeedecha <i>et al</i> <sup>29</sup>	2009	Er:YAG	20 patients	15% of patients had > 50% improvement 32.5% of patients had 26-50% improvement
Trelles <i>et al</i> <sup>27</sup>	2010	Fractional Carbon Dioxide	30 patients	Laser + bleaching creams: 80% of patients had very good results at 10 months Only laser: 0% of patients had improvement at 10 months

#### 4. NEVOCELLULAR NEVI

It is currently not known whether removal or treatment with laser technology will affect the risk of malignant transformation of these lesions. Although laser technology has been successfully used to remove and lighten nevi nevocellular, these lesions should be removed using biopsy or excision.

#### 5. CONGENITAL NEVI

Lasers used for congenital melanocytic nevi (CMN) are the pigment-specific lasers such as the QSRL, QSAL, QS Nd:YAG, long-pulsed ruby and diode lasers<sup>33-39</sup>; resurfacing lasers such as the Er:YAG and the CO<sub>2</sub><sup>40-42</sup>; and more recently, a combination of both<sup>43</sup>.

#### 6. JUNCTIONAL AND COMPOUND MELANOCYTIC NEVI

Lasers used to improve junctional nevi include QSRL, QSAL, and frequency-doubled QS Nd:YAG (532 nm) lasers, whereas the longer-pulsed ruby, diode and alexandrite lasers have shown greater improvement with CMN<sup>33,36,44-47</sup>.

#### DERMAL LESIONS

Dermal lesions such as nevus of Ota, nevus of Ito, Hori's nevus, and blue nevi contain a pigment that is deeper in the dermis. As a result, lasers with longer wavelengths that are able to penetrate into the appropriate depth provide greater clearance.

#### 1. NEVUS OF OTA AND NEVUS OF ITO

Nevus fuscoceruleus ophthalmo-maxillaris of Ota, or a nevus of Ota, was first described in 1939 as a pigmented nevi affecting the skin and eye<sup>48</sup>. This usually presents in childhood/adolescence as brown or blue-grey pigmented macules in areas innervated by the first and/or second branches of the trigeminal nerve, particularly the forehead, temple and periorbital skin, with variable involvement of the conjunctiva, sclera and/or tympanic membrane<sup>49</sup>.

There is higher incidence in Asian populations and women<sup>50</sup>. The pathogenesis involves incomplete migration of melanocytes between the neural crest and epidermis during embryonic development<sup>51</sup> resulting in irregular groups of elongated dendritic melanocytes scattered among dermal collagen bundles<sup>52</sup>. Variations in depth and density of dermal melanocytes account for differences in lesional color<sup>53</sup> due to the Tyndall effect, in which longer wavelengths of light are absorbed by dermal melanin whilst shorter wavelengths are reflected. Nevus of Ito is a similar lesion but it develops in the shoulder.

The QS lasers including QSRL, QS Nd:YAG and QSAL have been used to treat these lesions. However, not all lesions respond, and the destruction of dermal melanocytosis using Q-switched laser systems carries a high risk of post-inflammatory hyperpigmentation and hypopigmentation. Recently, a fractionated Nd:YAG laser has been reported to clear nevus of Ota<sup>54</sup>, and lasers with shorter wavelength such as QS Alexandrite-755 nm and QS Nd:YAG-532 nm have demonstrated to be safe and effective treatments for some nevus of Ota<sup>55,56</sup> (Table 6). Although noticeable improvements may take longer to appear, side effects are limited, and patient downtime is shorter. Moreover, post-inflammatory hyperpigmentation, the most concerning side effect in the treatment of Asian patients, can be effectively avoided with this method.

In order to achieve optimal improvement, it is advisable to perform multiple and repeated test patches as depth/density of dermal melanocytosis and facial skin thickness change from patient to patient. Therefore, an individualization of therapy, with combination of wavelengths, may be necessary.

#### 2. HORI'S NEVUS

Hori's nevus (also called acquired bilateral nevus of Ota-like macules or acquired dermal melanocytosis) develops

Table 6. Lasers used for treatment of Nevus of Ota and Nevus of Ito

Author	Year	Laser used	Number	Results
Kono <i>et al</i> <sup>57</sup>	2003	QSRL	153 patients	Mean number of treatments to achieve 75% clearance of nevus of Ota = 3.5 for children and 5.9 for adults
Chan <i>et al</i> <sup>58</sup>	2000	QSAL QS Nd:YAG	171 patients (211 sites)	QSAL: 7% of sites had 75-99% improvement of nevus of Ota 19% of sites had 50-74% improvement 17% of sites had 25-49% improvement 26% of sites had 25% improvement, and 31% of sites had no change QS Nd:YAG: 2% of sites had 100% clearance 18% of sites had 75-99% improvement 20% of sites had 50-74% improvement 24% of sites had 25-49% improvement 17% of sites had 25% improvement 19% of sites had no change Both: 8% of sites had 100% clearance 52% of sites had 75-99% improvement 21% of sites had 50-74% improvement 19% of sites had 25-49% improvement
Kagami <i>et al</i> <sup>9</sup>	2007	QSAL	38 nevus of Ota; 2 nevus of Ito	5% of patients had 96-100% clearance 22.5% of patients had 76-95% clearance 55% of patients had 51-75% clearance 10% of patients had 26-50% clearance 2.5% of patients had 0-25% clearance
Kouba <i>et al</i> <sup>4</sup>	2008	Fractionated Nd:YAG	1 patient	Complete clearance of nevus of Ota
Felton <i>et al</i> <sup>55</sup>	2014	QS Nd:YAG 1,064 nm QSAL 755 nm QS Nd:YAG 532 nm	21 patients	QS Nd:YAG 1,064 nm: 97% mean improvement QSAL 755 nm: 80% mean improvement QS Nd:YAG 532 nm: 90% mean improvement
Choi <i>et al</i> <sup>66</sup>	2014	QS Nd:YAG 1,064 nm	19 patients	18 patients reached near total improvement

on the face as bilateral blue-gray macules. QS lasers, which have been reported to treat Hori's nevus, include the QS Nd:YAG laser, QSRL, and QSAL (Table 7).

### 3. BLUE NEVI

Blue nevi are blue papules or nodules with well-defined borders<sup>5</sup>.

Histologically, they are a wedge-shaped proliferation of deeply pigmented spindled and dendritic melanocytes with scattered melanophages in the dermis<sup>5</sup>.

QSRL has been used to treat blue nevi. In 1995, Milgraum and colleagues reported the use of QSRL in two patients, achieving complete clearance of both lesions<sup>62</sup>.

Table 7. Lasers used for treatment of Hori's Nevus

Author	Year	Laser used	Number	Results
Polnikorn <i>et al</i> <sup>59</sup>	2000	QS Nd:YAG	66 patients	26% of patients with 1-2 treatments had > 50% improvement 50% of patients with 42 treatments had >50% improvement
Lam <i>et al</i> <sup>60</sup>	2001	QSAL	32 patients	>80% of patients had > 50% clearance >28% of patients had 100% clearance
Manuskiatti <i>et al</i> <sup>61</sup>	2003	QSRL Scanned CO2	13 patients	QSRL: 40% of patients had 25-50% clearance 60% of patients had < 25% clearance CO2 + QSRL: 70% of patients had 50-75% clearance 20% of patients had 25-50% clearance 10% of patients had < 25% clearance

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# XIV. LASER in Oculoplastic Surgery

## 76. Periocular lesions

### associated to HPV



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The human papillomavirus (HPV) is a member of the Papovavirus family, which has a circular double-stranded DNA. It is considered the most common sexually transmitted disease and can infect the ocular surface as well<sup>1-3</sup>. The transmission mode in adults is by direct contact<sup>1</sup>. This virus has been implicated in many periocular lesions<sup>4</sup> such as conjunctival<sup>5-8</sup>, lacrimal system<sup>9,10</sup> and eyelid papillomas<sup>4</sup>. The role of HPV infection in pterigium<sup>11,12</sup>, conjunctival intraepithelial neoplasia and squamous cell carcinoma<sup>13,14</sup> remains unclear. Although HPV is a tumorigenic virus it commonly produces benign tumors with low potential for malignancy.

#### CONJUNCTIVAL PAPILOMAS

Conjunctival papillomas are benign squamous epithelial tumors. A strong association exists between them and type 6 and 11 HPV<sup>15,18</sup>, with low-risk oncogenic potential. Usually they appear in the palpebral or bulbar conjunctiva but can also spread out through all the conjunctival tissue. When the lesion involves the caruncle it can extend to and/or invade the lacrimal canaliculum<sup>5-8</sup>. On the tarsal conjunctiva they tend to be sessile due to the compression of the lesion against the ocular globe. The same lesions can be found on the lacrimal punctum, canaliculus or sac, and may compromise their functions leading to epiphora and increasing the risk of secondary infection. The eyelid papillomas secondary to HPV infection are usually multiple and most frequently found in young adults. The type 6 HPV has been found in these lesions.

#### INDICATIONS

Treatment of small conjunctival, eyelid or lacrimal system papillomas.

#### CONTRAINDICATIONS

There are no absolute contraindications to laser treatment, however, if a malignant lesion is suspected, excision or a previous biopsy should be done.

#### PREPARATION

1. Explain the procedure mentioning the possible need for multiple sessions or other procedures.
2. The room environment should be compliant with laser safety guidelines.
3. Anesthesia - depends on the patient's sensitivity and it is usually necessary. Topical oxybuprocaine hydrochloride 0.4% or most often a local infiltration of lidocaine 2% can be used.
4. The patient should sit comfortably.
5. Use viral mask both for the doctor and patient in order to avoid dissemination of viral particles or virus towards the respiratory tract.
6. Under topical anesthesia (oxybuprocaine hydrochloride 0.4%) insert a metallic contact lens for ocular laser protection.
7. Laser room dimly lit. Use an efficient fume-cleaner and goggles for protection.
8. Ask the patient to keep looking ahead at one fixed point and use your fingers to adjust the eyelid and maintain the lesion aligned with the laser beam.

#### LASER TECHNIQUE

For little lesions, particularly when well circumscribed and in tarsal conjunctiva, we perform the procedure at the office using a *Nd:YAG-KTP 532 nm (green)* ophthalmic laser, using the amplification and precision of the slit lamp visualization<sup>19-25</sup>.

## 76. Peri-ocular lesion associated to HPV

Laser beam variables (more details in chapter 78) should be adjusted to the type of lesion to treat as follows:

<b>Spot size</b>	a- In a pediculated lesion, create a laser demarcation incision acting as a scalpel: 50 to 100 $\mu\text{m}$ b- In a more sessile lesion keep using the laser with 200 to 500 $\mu\text{m}$ spots
<b>Duration</b>	100 to 200 ms or shorter depending on the desirable effect; shorter time can increase the vaporization action and favor the cut; the longer the time the more coagulated the tissue becomes
<b>Power</b>	Cause an ignition or scalpel laser effect increasing the power from 200 mW up to 600-700 mW For photoevaporation consider 200 to 700 mW

### CASE 1 - HPV CONJUNCTIVAL PAPILOMA (Figure 1)

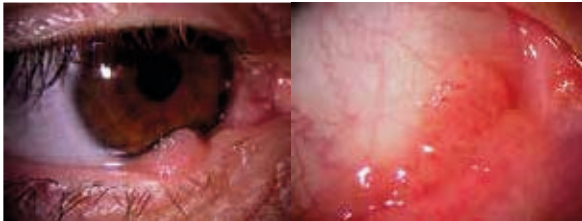


Figure 1. Patient with multiple periocular papillomas. Conjunctival papilloma is seen in the lower eyelid margin (left) and inferior conjunctival fornix (right).

The laser parameters used were:

- Spot size - the standard spot of the equipment;
- CO<sub>2</sub> laser (10600 nm) - set in an ultra-pulsed mode delivery and equipped with an automatic scan;
- Power: 750 mW.

A high power fume-cleaner and goggles for eye protection are always necessary, as well as a wet field and tissues to avoid fire ignition.

The patient underwent a treatment using the CO<sub>2</sub> laser and the lesion was evaporated without thermal lesion of the surrounding tissues, and healed without scar or retraction.

### CASE 2 - HPV SUPERIOR PALPEBRAL PAPILOMA (Figures 2 to 4)



Figure 2. Patient with an eyelid papilloma, pre-laser treatment.



Figure 3. Same patient as in figure 2 (above), after Nd:YAG-KTP laser treatment.

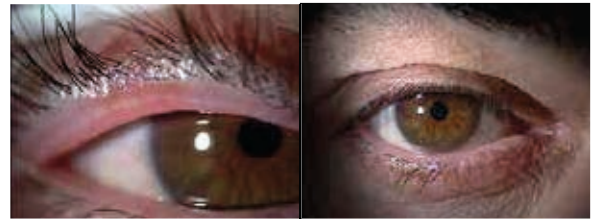


Figure 4. Same patient (Figures 2 and 3) 5 weeks (left) and 3 months (right) after treatment.

### CASE 3 - PAPILOMA OF THE LACRIMAL PUNCTUM (Figures 5 and 6)



Figure 5. Patient with a punctum-canalculus papilloma.



Figure 6. Same patient (Figure 5) immediately after treatment.

Laser parameters:

*Laser Nd: YAG-KTP (532 nm) set at a slit lamp.*

- Spot size:
  - a) In a pediculated lesion, begin creating a demarcation incision acting as a scalpel laser (ignition of the laser photothermal effect) with 50 to 100  $\mu\text{m}$  of spot size;
  - b) In a more sessile lesion continue with 200 to 500  $\mu\text{m}$ .
- Time of impulse duration: 100 to 200 ms or shorter depending on the desirable effect; shorter time can increase the vaporization action and “explosion” of the tissue and favor the cut; longer time has a coagulation effect.
- Power:
  - a) For ignition or to act as a scalpel laser increase

- the power from 200 mW to 600-700 mW;
- b) To cause photoevaporation consider 200 to 700 mW.

### POSTLASER CARE AND FOLLOW-UP

Antibiotic ointment t.i.d. for a week. Alternatively, use cotton swabs to apply povidone iodine 10% to the scar t.i.d for 4-5 days.

### COMPLICATIONS

This is a relatively safe procedure and complications are rare. It may cause **hypopigmentation of the skin**, more significant among black or oriental patients.

### RESULTS

Results are esthetically good with preservation of the anatomy. The healing takes about 2 weeks, leaving almost no scars. Recurrence is more frequent in conjunctival papillomas, specially in bigger lesions.

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# XIV. LASER in Oculoplastic Surgery

## 77. Periocular

## vascular skin lesion



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### INTRODUCTION AND LASERS

The main lasers used to treat vascular lesions are pulsed dye laser (PDL) and Nd:YAG KTP 532 nm (KTP laser). Recent works show the efficacy of the long pulse Alexandrite and Nd:YAG 1064 nm continuous wave (CW-YAG) lasers in leg vascular anomalies and vein telangiectasias, however they are not in the focus of this chapter.

The most important chromophore for vascular lasers is oxyhemoglobin, which has peaks of absorption at 418, 542 and 577 nm. PDL focuses on the 577nm peak, the most distant from melanin absorption peak and the one that allows more beam penetration through the tissue<sup>1,2</sup>. PDL is available with hand pieces producing 2, 3, 5, 7 and 10 mm diameter beams of laser light (table 1). Fluence (the total energy per unit area) ranges therapeutically from 3 to 20

J/cm<sup>2</sup>. Smaller spot sizes result in less energy delivered to tissues due to photons scattering<sup>3</sup>. Desirable laser settings should result in some purpura without excessive edema, crusting, blistering or other epidermal changes<sup>4</sup>.

The KTP laser uses a Nd:YAG crystal (1064 nm) to produce light, which is then passed through a potassium titanyl phosphate crystal in order to yield a frequency-doubled wavelength of 532 nm. The 532 nm light delivered by the KTP laser is close to the 542 nm absorption peak of oxyhemoglobin. Although this wavelength penetrates only 0.75 mm into the dermis, vascular damage is relatively specific. Some patients prefer KTP because it has fewer side effects, however the new PDL lasers have proved to be more effective even with large caliber facial vessels.

Table 1. Types of PDL lasers

Manufacturer	Name	Wavelength(nm)	Pulse duration (ms)	Spot Size - Fluence
Candela	Vbeam	595	0.45-40	3 mm - 40 J/cm <sup>2</sup>
				5 mm - 30 J/cm <sup>2</sup>
				7 mm - 20 J/cm <sup>2</sup>
				10 mm - 10 J/cm <sup>2</sup>
				12 mm - 7 J/cm <sup>2</sup>
				3x10 mm - 25 J/cm <sup>2</sup>
				7 mm PL - 15 J/cm <sup>2</sup>
				10 mm PL - 10 J/cm <sup>2</sup>
Cynosure	Vascular Workstation	585-597	0.5-40	5 mm - 40 J/cm <sup>2</sup>
				7 mm - 20 J/cm <sup>2</sup>
				10 mm - 10 J/cm <sup>2</sup>
				12 mm - 7 J/cm <sup>2</sup>



## INDICATIONS

### 1. PORT-WINE STAINS

Port-wine stains (PWS) are vascular malformations, usually present at birth. They increase in size as the child grows and become darker, thicker and can cause an important psychological distress. PWS should be differentiated from infantile hemangiomas (which are classified as vascular tumors and regress within months or years) and can be associated with severe syndromes (e.g. Sturge-Weber and Klippel-Trenaunay syndromes) that should be excluded.

### LASER TECHNIQUE

*PDL* therapy remains the treatment of choice for pediatric and adult PWS.

1. Topical anesthetics can be used, however in pediatric patients, particularly those with extensive lesions, general anesthesia is often required. A disadvantage of topical anesthetics is the vasoconstriction that occurs, which may hamper the visualization of the vessels.
2. Usually used fluences, with a 7 mm spot, are in the range of 4.5 to 8 J/cm<sup>2</sup>, with the lower range applied to pediatric patients and sensitive anatomic sites like the periorbital area. Pulse durations for ideal laser treatment are in the 1-10 ms range for PWS and depend on the vessel diameter.
3. Treatment of PWS with the 585 nm, 0.45 ms laser, is usually performed with the largest beam spot size available. Typical treatment fluences are 5.0-7.0 J/cm<sup>2</sup> with a 7 mm spot and 5.0-6.0 J/cm<sup>2</sup> with a 10 mm spot size, depending on the age of the patient and thickness of the lesion<sup>5</sup>.
4. Overlapping 10-15 % of the individual circular pulses is recommended to avoid a honeycomb pattern of clearing. Surpass these values can cause scarring in sensible areas. The size of the treatment area is mainly determined by the patients' tolerance to the procedure<sup>6</sup>. Skin cooling methods attached to PDL allow the use of higher fluences, with less risk of epidermal damage and less pain<sup>7</sup>.

Treatments are repeated at 4-6 week intervals, until vessel clearance. Normally two to four treatments are needed. The combination of concurrent epidermal cooling and longer pulse durations have reduced the PDL induced purpura. Periorbital, neck and chest are the areas with better responses to PDL, in contrast to central cheeks and upper lip<sup>8,9</sup>.

### 2. HEMANGIOMAS

Infantile hemangiomas are classified as vascular tumors, affect 10% of all infants, and 16% of the facial hemangiomas involve the periorbital area. Most of them will spontaneously involute and do not require treatment. Indications for treatment are potential functional impairment (periorbital - amblyopia, strabismus), risk of ulceration (secondary to a rapid growth, recurrent trauma) and cosmetic disfigurement (tip of the nose, vermilion of the lip, nipple)<sup>10,11</sup>.

### LASER TECHNIQUE

*PDL* is the laser of choice, although the discovery of propranolol for the treatment of infantile hemangiomas

has revolutionized this field. Superficial hemangiomas, before or immediately after the beginning of the proliferative stage, are the most successful responders to PDL, while the raised (>3mm) and deep cavernous type are poorly affected.

The best results are achieved using PDL at 595 nm, 9-10 mm spot size, 1.5 ms pulse duration, and fluence of 6.0-6.5 J/cm<sup>2</sup> when cryogen cooling is used.

After complete treatment, some areas may develop atrophy and hypopigmentation<sup>12,13</sup>.

### 3. TELANGIECTASIAS

Telangiectasias are arborizing vessels and can be caused by actinic damage, rosacea, connective tissue disease, telangiectasia macularis eruptiva perstans, hepatic dysfunction, or post-trauma.

### LASER TECHNIQUE

Telangiectasias usually respond faster and better to *PDL* than PWS.

1. A 3 mm spot is usually used to minimize the risk of post-treatment purpura and pain.
2. Treatment parameters used for telangiectasia are pulse durations of 15-40 ms with fluences of 10-16 J/cm<sup>2</sup><sup>14</sup>.

Two studies have compared the KTP laser and PDL for the treatment of facial telangiectasias. In both studies, patients preferred the KTP laser due to a reduced incidence of post-treatment purpura, pain, and swelling<sup>15,16</sup>.

### 4. VASCULAR MALFORMATIONS

Venous malformations are compressible, blue-purple vascular nodules or plaques present at birth. Venous malformations and deep hemangiomas are located deeper into the dermis or subcutaneous tissue and require a continuous wave laser with longer wavelengths like Alexandrite (755 nm) or CW-YAG (1064 nm). The CW-YAG is the most efficacious, however has a higher incidence of scarring and depigmentation<sup>17,18</sup>.

### 5. OTHER BENIGN VASCULAR DISORDERS

PDL can also treat benign cutaneous disorders such as areas of permanent cutaneous erythema due to rosacea, radiotherapy, trauma or scars. The therapeutic approach is similar to PWS, with a spot size of 5 mm or greater and covering a wide surface area. The use of a 10 mm spot size with low energies and longer pulses, which are immediately below the purpura threshold, allows the treatment of telangiectasias and permanent erythema without inducing significant purpura<sup>19</sup>.

## COMPLICATIONS AND THEIR MANAGEMENT

### PULSED DYE LASER (PDL)

1. There is a high risk of eye damage with PDL due to the absorption of the PDL wavelength by the pigmented and vascular portions of the retina. Goggles made of didymium, which have a narrow band of absorption in the 500 nm visible spectrum, are ideal for eye protection. Patients should wear metallic eye-shields<sup>20</sup>.

2. An already reported complication that occurs with the use of PDL in periorbital skin is the development of **vitreous floaters**. Although the exact mechanism is not known, it is proposed that both patients and laser operators should be protected by proper eyewear<sup>21</sup>.
3. **Hyperpigmentation** is the most frequent adverse event. It generally resolves after 6-12 months and it is more common in darker skin types.
4. **Hypopigmentation** appears following the development of crusting or scabbing. It indicates the use of overly aggressive laser fluences or improper skin-cooling techniques. It can last over 3 months.
5. **Blistering, crusting, atrophic scarring and hypertrophic scarring** can also occur, although very rarely with the new long pulse and epidermal-cooling techniques<sup>22</sup>.
6. **Tissue whitening** immediately afterwards indicates epidermal damage caused by overly aggressive laser parameters or poor skin cooling techniques. To avoid epidermal necrosis the area should be immediately cooled with ice.
7. **Post-operative purpura** is associated with short pulsed PDL and can last for 7-10 days. Employing longer pulse durations can allow purpura-free treatments at the expense of the loss of some efficacy and an increase of the number of treatments needed. For smaller lesions, in which similar sized laser spots are not available, laser light may be delivered through a small hole cut out on a cardboard in order to reduce unwanted purpura in perilesional skin.
8. **Reticulation erythema** after PWS treatment may be seen if small spots are performed without any overlapping. New sessions are needed to clear the remaining lesion.
9. PDL wavelength cannot reach the deep hair follicle and cause hair removal. However, the eyelashes are horizontally located below a thin skin, making them vulnerable to PDL effects and **potential permanent hair loss**<sup>23</sup>.

Sun exposure and tanning prior to treatment should be avoided due to an increase in melanin content. Melanin absorbs the laser light decreasing its effectiveness and resulting in an increased risk of **hypopigmentation**. After treatment several weeks should pass before any UV exposure. Patients should avoid applying make-up until the fourth day after treatment.

#### **POTASSIUM TITANYL PHOSPHATE LASER (CONTINUOUS WAVE KTP LASER)**

1. The advantage of the KTP laser is that target vessels are not ruptured, causing less purpura.
2. Following treatment, there may be some **erythema and urticarial edema** in the treated skin, lasting up to 24 hours. Cool dressings, ice and the application of a mid-potency topical corticosteroid immediately after treatment will reduce the redness and swelling.
3. **Crusting** develops infrequently, but it may occur with overly aggressive therapy, improper cooling techniques or after treatment of tanned skin.
4. Patients with darker skin types will often have **long-lasting depigmentation, blistering, or significant**

**crusting**, as there is a significant melanin absorption at this wavelength.

5. **Bacterial infection** may occur in the case of epidermal disruption, and prompt treatment should be prescribed.
6. **Scarring** rarely occurs, but it may result from excessive fluence, overlapping of laser pulses or inadequate skin cooling.

Like with PDL, sun exposure and tanning prior to treatment should be avoided and sunscreen should be used for 4-6 weeks after laser treatment<sup>24</sup>.

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# XIV. LASER in Oculoplastic Surgery

## 78. Periocular skin

### lesions - use Nd:YAG

### KTP at office



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#### INTRODUCTION

The frequently called “KTP laser” is a double frequency Nd:YAG that emits green light at 532 nm. This wavelength is well absorbed by oxyhemoglobin, melanin or other dark pigments and has a relatively shallow depth of penetration that makes it a good option for the treatment of superficial vascular and pigmented benign lesions<sup>1-6</sup>. Additional advantages, if the correct laser parameters are used, are a good hemostasis, bloodless field, quick healing, no scarring, and a small risk of secondary infection<sup>7</sup>.

#### THE FUNDAMENTS OF KTP LASER USE ON PERI-OCULAR LESIONS

In ophthalmic surgery “KTP laser” has the enormous advantage of being adapted to a slit lamp, making the procedure very accurate for the treatment of vascular and pigmented benign peri-ocular lesions<sup>8-11</sup> such as small aging skin lesions, seborrheic keratosis<sup>12-13</sup>, xanthelasma<sup>14-22</sup>, eyelid hemangiomas<sup>23-25</sup>, cutaneous horn, milia<sup>26-29</sup> and others<sup>30</sup>.

For the treatment of peri-ocular lesions both evaporation and coagulation can be used. This is dependent on the lesion to be treated and obtained by changing the laser parameters<sup>4,5,8-11</sup>.

If the lesion is benign and sessile it can be vaporized. Sometimes, the first laser burn can be difficult to perform, especially in very light skin, as the laser will not be well absorbed<sup>1</sup>. The problem can be overcome by using a small spot diameter of 100  $\mu\text{m}$  and a high power density (400-500 mW) in order to cause a small burn with some carbonized particles, which will absorb laser light efficiently. Another alternative is to induce a local punctiform hemorrhage to allow the absorption of the laser, or mark the area of treatment with a surgical dermatographic pen<sup>1-11</sup>.

For benign and pedunculated lesions the laser can be used as a scalpel. The power should be increased and the spot diameter decreased by 50-100  $\mu\text{m}$  in order to use the laser beam to cut around the peduncle of the lesion. To allow smooth scarring formation, the skin should be smoothed by vaporizing the treated area and boundaries, leaving the sides slightly rounded<sup>1-11</sup> (Figure 1).

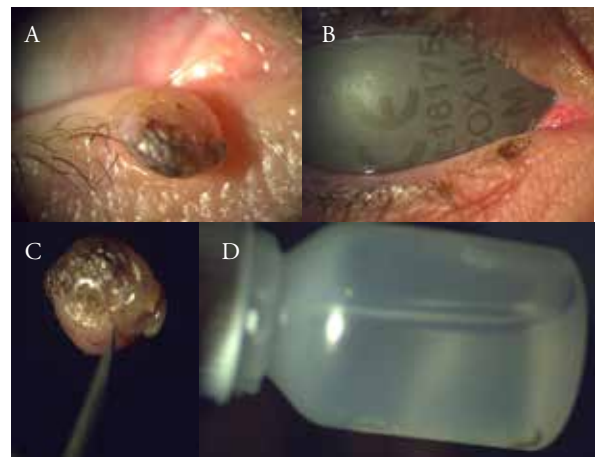


Figure 1. For benign and pedunculated lesions (A) the laser can be used as a scalpel. Using a metallic shield contact lens protector, delimitation of the base of the lesion is made using thin spot laser (B). The specimen is collected (C), immersed into formalin (D) and send to histological exam.

The “KTP laser” can also be used to treat vascular lesions<sup>23-25</sup>. Since it only penetrates about 1 mm into the skin, it is more effective when these are small and flat. The aim of laser therapy is to induce the regression and/



or shrinkage of the vessels. By pointing the laser beam at the vascular lesion or vessel, it may become thrombotic or spastic due to collagen heat shrinkage. When treating vascular lesions, the patient must be advised that multiple laser treatments may be necessary and that there is a relatively high risk of temporary hyperpigmentation/hypopigmentation, especially in dark skins. There is also the risk of skin disruption, but this is usually caused by inadequate treatment parameters: very short duration combined with too high fluency.

Like in other laser treatments the safety rules should be respected, and a corneal eye metallic shield is always required when treating peri-ocular areas (Figure 2).

There is very few information in the literature describing the use of "KTP laser" set on the slit lamp for peri-ocular lesions. We present some cases treated over the last years using this technique (Figures 3 to 14).

**INDICATIONS**

1. Small benign lesions.
2. Small vascularized lesions.
3. Small pigmented benign lesions.

**PREPARATION**

1. Explain the procedure mentioning the possible need for more laser sessions (vascular cases) or other procedures.
2. Anesthesia - depends on the patient's sensitivity and it is usually necessary. Topical (oxybuprocaine hydrochloride 0.4%) or most often a local infiltration of lidocaine 2% can be used. Topical cream of lidocaine 2.5% and prilocaine 2.5% (EMLA® AstraZeneca AB) applied 30 minutes to 2 hours before the procedure is also an alternative.
3. The patient should be sitting comfortably.
4. Under topical anesthesia (oxybuprocaine hydrochloride 0.4%) insert a metallic contact lens for ocular laser protection.
5. Laser room should be dimly lit.
6. Ask the patient to keep looking up at a fixed point (if you are treating lower eyelid) or down (when treating upper eyelid) and preferentially use your fingers to adjust the eyelid and maintain the lesion being treated aligned with the laser beam.



Figure 2. Metallic eye contact lens protector.

**LASER TECHNIQUE**

*Nd:YAG KTP 532 nm laser (KTP laser) set to a slit lamp*

The parameters are adjusted to the type of lesion to be treated. We present some cases and the parameters used.

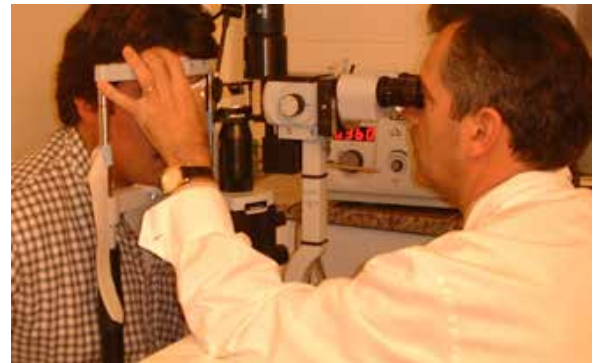


Figure 3. "KTP Laser" at office.

**EYELID PAPILLOMA**

**CASE 1**

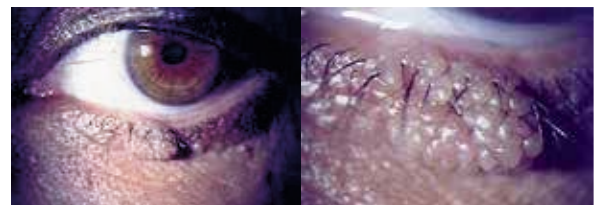


Figure 4. Human papilloma virus (HPV) on the left inferior eyelid. 40-year-old woman with a long standing lesion with recent and accentuated growth.

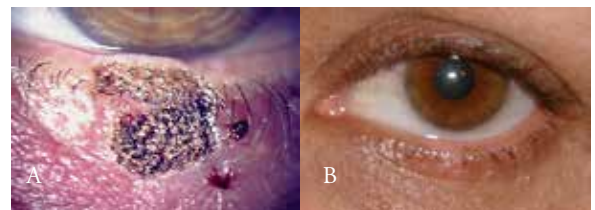


Figure 5: HPV immediately (A) and 20 days after treatment (B).

Laser beam variables:

	Stage 1: initial spots	Stage 2: tissue vaporization
<b>Spot size</b>	100 µm	300-400 µm
<b>Duration</b>	100 ms	50-100 ms
<b>Power</b>	500 mW	300-600 mW

**CASE 2**



Figure 6. Fibroepithelial papilloma in a 36-year-old woman with a pedunculated tumor in the left inferior eyelid and small similar lesions on the left superior eyelid.

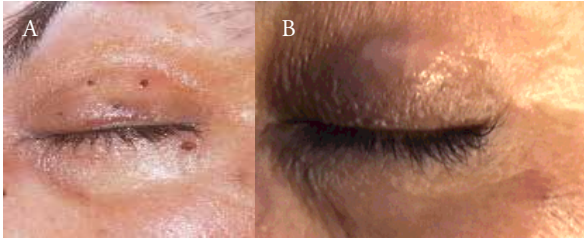


Figure 7. Fibroepithelial papilloma immediately (A) and 11 days after treatment (B).

Laser beam variables:

	Stage 1: initial spots	Stage 2: tissue vaporization
<b>Spot size</b>	100 $\mu\text{m}$	300-400 $\mu\text{m}$
<b>Duration</b>	100 ms	50-100 ms
<b>Power</b>	500 mW	300-600 mW

### CASE 3



Figure 8. (A) 56-year-old man with multiple benign wart-like tumours on both superior eyelids, suggestive of Trichilemmomas (viral wart with trichilemmal differentiation). (B) immediately after laser treatment.

Laser beam variables:

	Stage 1: initial spots	Stage 2: tissue vaporization
<b>Spot size</b>	100 $\mu\text{m}$	300-400 $\mu\text{m}$
<b>Duration</b>	100 ms	50-100 ms
<b>Power</b>	500 mW	300-600 mW

### MOLL'S GLAND CYST

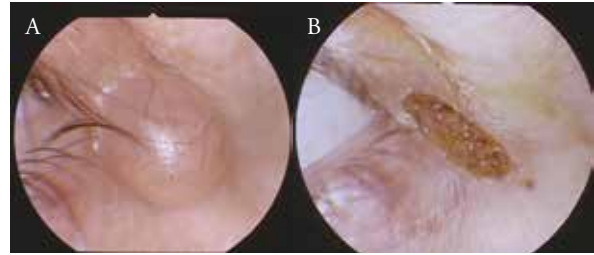


Figure 9. Moll's gland cyst before (A) and immediately after laser treatment (B).

Laser beam variables:

	Stage 1: initial spots	Stage 2: tissue vaporization
<b>Spot size</b>	100 $\mu\text{m}$	300-400 $\mu\text{m}$
<b>Duration</b>	100-200 ms	100 ms
<b>Power</b>	500 mW	400-500 mW
<b>Particularities</b>	Focus the spot laser over the blood vessel for better laser absorption or paint the skin with a dermographic pen.	Evaporate the capsule tissue to avoid relapse of the cyst.

### CUTANEOUS HORN

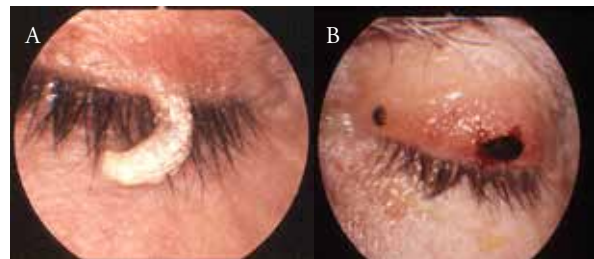


Figure 10. Cutaneous horn before (A) and immediately after laser treatment (b)

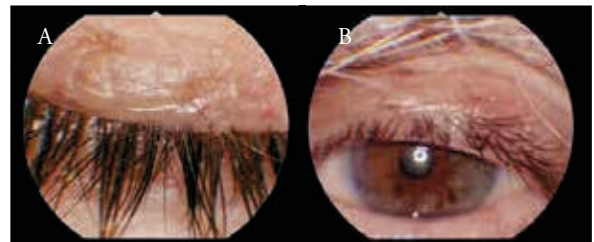


Figure 11. Cutaneous horn 1 month after laser treatment.



Laser beam variables:

	Stage 1: initial spots	Stage 2: tissue vaporization as a laser scalpel
Spot size	100 µm	100 µm
Duration	100-200 ms	100-200 ms
Power	500 mW	400-500 mW
Particularities	Focus the spot laser over a skin ink mark to "ignite" the laser action.	Make a groove around the base of the lesion and finally separate the lesion from the eyelid and send it to histologic exam. Smooth the wound with larger (400 µm) spot and shorter (50 ms) impulses.

**PYOGENIC GRANULOMA**



Figure 12. Pyogenic granuloma before (A) and after (B) treatment.



Figure 13. Temporal sequence of the treatment shown in figure 12. Multiple sessions were needed with progressive transformation of the lesion. Initially, without skin disruption, only photocoagulation of the underlying blood vessels was performed. Weekly treatments allowed to reduce its volume and bloody appearance. The remaining lesion was finally photo vaporated.

Laser beam variables:

	Stage 1: initial spots	Stage 2: tissue vaporization
Spot size	300 µm	100 µm
Duration	200 ms	100-200 ms
Power	150-200 mW	400-500 mW
Particularities	Focus the spot laser over the skin allowing a whitish color change and retraction without having skin rupture. Wait one week and repeat.	

**TRICHIASIS**

(see chapter 73)

**EYELID HEMANGIOMA**

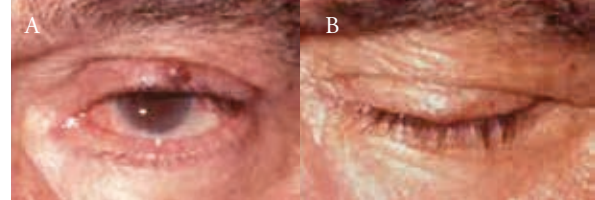


Figure 14. Hemangioma before (A) and immediately after treatment (B).

Laser beam variables:

	Stage 1: initial spots	Stage 2: photocoagulation
Spot size	300 µm	Shrink the lesion and allow for a whitish color change without skin rupture.
Duration	100-200 ms	
Power	100-300 mW	

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# XIV. LASER in Oculoplastic Surgery

## 79. Conjunctival

### lesions



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#### INTRODUCTION

Conjunctival papilloma is a human papillomavirus (HPV) associated benign tumour of the conjunctival mucosa<sup>1</sup>. HPV-6 and HPV-11 are the major HPV types responsible for the benign conjunctival lesions. In childhood, papilloma represents 7-10% of all conjunctival tumours. These lesions are frequently multiple, with high recurrence rates<sup>2,3</sup>. Techniques such as surgical excision and cryotherapy are available, however their effectiveness is limited by the possible spreading of the virus, haemorrhage and high relapse rates<sup>3</sup>. These complications may be largely reduced with CO<sub>2</sub> laser treatment<sup>2</sup>.

As our experience refers mainly to conjunctival papillomas, this chapter will largely focus on these lesions. However, reports of conjunctival nevus excision are available in the literature. These lesions may be associated with a developmental disorder characterized by unilateral ocular and/or periocular pigmentation - oculodermal melanocytosis ("Nevus of Ota"). This condition is particularly common amongst Asian populations and female gender<sup>4,5</sup>. Recent prospective analysis underline the efficacy of the Q-switched Nd:YAG- KTP 532 nm (QS-KTP laser) in humans with conjunctival nevus<sup>6-8</sup>.

#### INDICATIONS

Treatment of conjunctival nevus and warts.

#### RELATIVE CONTRAINDICATIONS

##### Conjunctival nevus:

Lasers cannot be applied to the sclera in oculodermal pigmentation due to potential damage to the choroid or retina<sup>6</sup>.

This technique does not allow for the subsequent histopathological exam of the lesion. To decrease the risk of overlooking malignant lesions, only patients whose

nevi have not changed in size or colour over a 5 year period should be selected for this procedure<sup>7</sup>.

#### PREPARATION

##### Conjunctival warts and nevus:

1. Explain the procedure mentioning the possible need for more than one session or other procedures.
2. The room environment should comply with laser safety guidelines.
3. Anaesthesia: proparacaine hydrochloride 0.5% applied into the conjunctival sac.
4. Comfortable sitting of the patient.
5. Place a metallic contact lens in patient's cornea.
6. Set the room with dim lighting.
7. Ask the patient to keep looking ahead at one fixed point.

#### LASER TECHNIQUE

##### Conjunctival nevus:

532 nm (green) QS-KTP laser;

Spot size 200 µm;

Duration 0.1 sec;

Power 300-340 mW;

Laser ablation is focused on the pigmented conjunctiva, and laser spots should be targeted without interstitial gaps.

##### Conjunctival wart:

CO<sub>2</sub> laser in continuous mode, starting power at 6.0 W.

#### POSTLASER CARE AND FOLLOW-UP

##### Conjunctival nevus and warts;

Topical corticosteroid t.i.d. for 3 days.

Follow-up examinations should take place at 1 day, 3 days, 1 week, 1 month, 3 months, 6 months, and 12 months after treatment.



Figure 1. Patient with relapsing conjunctival warts after surgical excision complemented with cryotherapy.

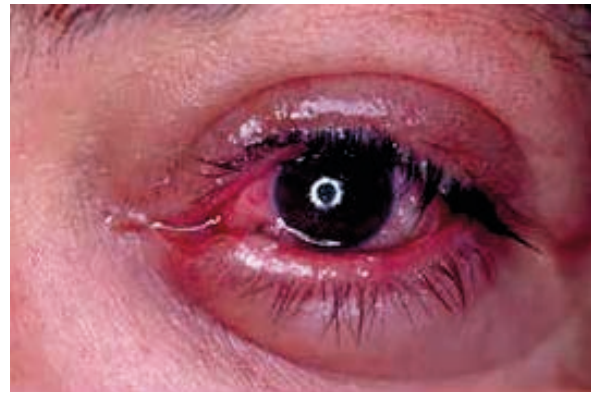


Figure 2. Same patient, first day after CO2 laser treatment.



Figure 3. Same patient, one week after CO2 laser treatment: conjunctival burns still present.

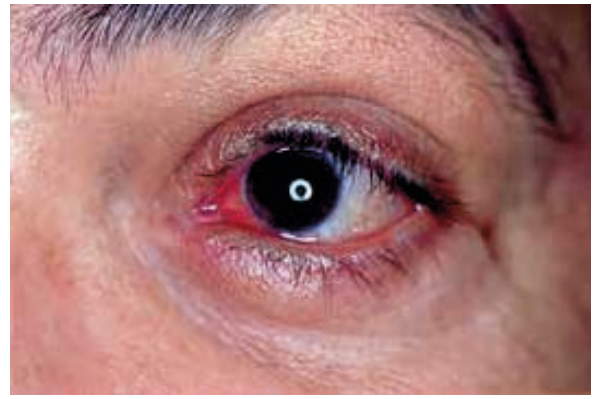


Figure 4. Same patient, two weeks after treatment: non-visible papillomatous lesions, along with partial conjunctival healing.

**COMPLICATIONS**

Table 1. Summary of results and complications

Author	Year	Technique	Number	Follow-up (months)	Results	Complications
Kwon JW <i>et al</i> <sup>8</sup>	2006	Argon laser (200 μm spot size; 0.1 s, 300-340 mW)	30 eyes (28 patients)	12	Complete lesion disappearance within 2 days	No recurrences No conjunctival scars or injections
Park JH <i>et al</i> <sup>6</sup>	2014	Combination treatment (scleral surgery + argon laser 1 mm, 10 ns, 120 mJ/cm <sup>2</sup> )	50 eyes (47 patients)	≥3	94% strongly satisfied	4 conjunctival neovascularization 4 conjunctival cysts 1 with both conj. cyst and neovascularization
Shin KH <i>et al</i> <sup>7</sup>	2013	Argon laser (200 μm spot size; 0.1 s; 321.50±9.23 mW)	230 eyes (230 patients)	36-100	Complete removal of the conjunctival nevus in all cases	185 conjunctival injection 6 subconjunctival haemorrhage

**RESULTS**

The literature supports QS-KTP laser for the treatment of conjunctival nevus. There is less evidence on CO2 laser for conjunctival warts, as there are only a few cases reported. The accessibility and familiarity of the ophthalmologist to these devices make them a potential therapy for this type of lesions. Moreover, laser beam treatment can be performed in an

outpatient setting, often requires less than 5 minutes to complete, the nevus can be removed immediately after the first procedure, and this technique can be used for nevi of any dimension<sup>7</sup>. When using laser therapy, the ophthalmologist should inform the patient about the possible need for further treatments, as one session may not be enough for the complete removal of the lesion.

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# XIV. LASER in Oculoplastic Surgery

## 80. Transcanalicular

## diode laser-assisted

## dacryocystorhinostomy

## (TCLA DCR)



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### INTRODUCTION

The acquired impermeability of the nasolacrimal duct or lacrimal sac distal to the common canaliculus is treated by creating a new route of drainage between the lacrimal sac and the nasal cavity: that is called a nasal osteotomy or rhinostomy. The surgical technique, dacryocystorhinostomy (DCR), can be performed through the skin, conjunctiva, endonasal, transcanalicular or a combination of them.

### ANATOMICAL BASIS

**Drainage system:** The tear drainage starts at puncta. The tear ducts continue vertically for 2 mm along the ampulla, and then at a medial 90 degrees angle to the canaliculi. In more than 90% of cases, the two canaliculi merge at the medial end forming the common canaliculus<sup>1</sup>. The lacrimal sac rests on the lacrimal fossa. Further down, the lacrimal sac extends into the nasolacrimal duct. The nasolacrimal duct runs through the bone and ends at the inferior meatus of the nasal cavity.

**Nasal Anatomy:** The middle meatus is located between the middle turbinate and the lateral nasal wall. The turbinate insertion site on the sidewall of the nose is called axilla. The three important references in this meatus are the uncinat process, the ethmoid bulla and the maxillary line (lacrimo-maxillary suture). For endoscopic and transcanalicular DCR the most important reference

point is the maxillary line<sup>2</sup>. Behind the maxillary line is the lacrimal bone, with a thickness of about 106  $\mu\text{m}$  which allows the use of laser to perform the osteotomy.

### INDICATIONS AND CONTRAINDICATIONS

The differential diagnosis between epiphora and tearing is obtained through clinical history, anatomic or functional permeability testing of the drainage system, and secretory function tests. Patients with a history of acute or chronic dacryocystitis, sac mucocele, lacrimal or nose surgery, or bone fractures involving the area of the lacrimal drainage system, are not good candidates for transcanalicular diode laser-assisted (TCLA) DCR<sup>3</sup> and even contraindicated for this surgical technique. The presence of dacryolithiasis, lacrimal fistula, lacrimal sac or nose tumors, extensive polyposis, allergic or atrophic rhinitis, sarcoidosis, and Wegener's granulomatosis are also contraindications<sup>3</sup>.

### TREATMENT OF NASOLACRIMAL DUCT OR LACRIMAL SAC OBSTRUCTION, DISTAL TO THE COMMON CANALICULUS:

DCR is the treatment of choice and TCLA DCR is the most recent surgical technique.

### PREPARATION

**Materials:** The basic material needed to perform TCLA DCR includes a punctum dilator, a Bowman lacrimal

probe, number 1, 0 or 00, a lacrimal cannula for irrigation, the laser console, an optical fiber between 400 to 600  $\mu\text{m}$  in diameter, for single or multiple use, and silicone tubes or other materials<sup>4</sup> for canalicular intubation.

For nasal endoscopies and intraoperative correction of some anatomical variations a turbinate retractor is needed, as well as an 1 or 2 mm caliper suction cannula, a 14 cm bayonet forceps, a 12 cm ethmoid Blakesley forceps with 45° angle and a 0° nasal video endoscope connected to a television monitor, for example the Storz® device (Figure 1).

**Laser characteristics for TCLA DCR:** To be used in TCLA DCR, the laser should allow the use of the optic fiber (Figure 2), have an effective ablation, induce a good hemostasis, have a narrow range of penetration not destroying or damaging surrounding tissues<sup>5</sup> and cut accurately<sup>6,7</sup>. Several types of laser devices have already been used, some of them meanwhile substituted by others with higher efficiency, cheaper and less damaging to the surrounding tissues.

The laser diode has a wavelength between 810-980 nm and can be driven by an optical fiber. It has increased its popularity in recent years due to the portability of the console (Figure 3), the possibility of multi-purpose, efficacy of cut, good hemostasis and good absorption by melanin and hemoglobin. The diode collateral damages are less than with other laser<sup>3,8</sup> due to its wavelengths properties and the shape of the optic fiber tip, which allows the laser to act only in a short space.

#### LASER TECHNIQUE

**Anesthesia, vasoconstriction and observation of the nasal cavity:** The TCLA DCR can be performed under general anesthesia<sup>8,9</sup> or loco-regional blocking of the nasociliary nerve using 2% lidocaine with epinephrine 1: 200,000 (one injection between the medial canthus and caruncle, 12.5 mm in depth, using 8 to 10 cc of a mixture of 0.5% lidocaine and 2% bupivacaine with 5 IU/ml hyaluronidase)<sup>10</sup>. The vasoconstriction of the nasal cavity is achieved after nasal packing with gauze soaked in 2% lidocaine with epinephrine 1: 200,000 and oxymetazoline

hydrochloride 0.5 mg/ml<sup>3</sup> or phenylephrine hydrochloride 5 mg/ml 10 minutes before surgery. After removal of the nasal gauze, the endoscope is introduced until it reaches the middle meatus. Once there (Figure 4, left) it should be taken into consideration the local anatomy: the axilla, maxillary line, uncinat process, the relations between the different structures and the possible presence of inflammatory, infectious or tumoral disease.

**Probing and introduction of the optic fiber:** After dilation of the lacrimal puncta, probing of the upper and lower lacrimal canaliculi should be made with a Bowman lacrimal probe to assess the presence of adhesions along the canaliculi. With the endoscope inserted into the middle meatus, remove the probe and introduce the optic fiber through the upper punctum down to the lacrimal sac (Figure 4, center/right).

When the position is correct, between the maxillary line and the uncinat process, the tip of the optic fiber is visible by transillumination through the lacrimal bone. Anatomical variations or a canalicular obstruction might be present, preventing the progression of the optic fiber, or the fiber may have followed a false path.

**Osteotomy:** The osteotomy should be done between the maxillary line and the uncinat process. Laser console must be set to pulse mode. The parameters vary from author to author; we use 90 ms pulses with 50 ms intervals, and power must be initially set to values between 8-10 watts<sup>8,11</sup>. The intervals allow the tissues' temperature to recover. Supporters of the continuous mode claim that it is more accurate and causes less damage to the surrounding tissues<sup>12</sup>.

The osteotomy is done by contact laser, and it should always be performed under endoscopic visualization. After the initial opening, called puncture, the tip of the fiber can be seen, as well as the coagulation and necrosis of the surrounding nasal mucosa (Figure 5). The osteotomy should be extended laterally, also by contact, by at least 5 mm, and the aspiration cannula can be used as a guide for the final dimensions. Some surgeons combine the transcanalicular route with the endonasal surgery. In this



Figure 1. Storz®.



Figure 2. Optic fiber.



Figure 3. Laser diode console.



Figure 4. Left: Middle meatus structures. Center: Introduction of the fiber into the lacrimal punctum. Right: transillumination of the aiming light through the nasal lateral wall.

case the surgery is initiated via transcanalicular and the extension of the osteotomy (up to 10 mm in diameter) is performed by the endonasal approach. The risk of canalicular burn<sup>6</sup> decreases, however, the risk of orbital damage induced by laser is higher.

**Irrigation and adjuvant treatments:** After reaching the desired osteotomy diameter, the fiber is removed. At this stage, the irrigation of the canaliculi can optionally be carried out with sterile solution and the application of adjuvant treatments such as mitomycin C (MMC).

**Bicanalicular silicone intubation:** The silicon stent's metallic guides are inserted sequentially, caught in the middle meatus under endoscopic visualization (Figure 6), and withdrawn from the nasal cavity with an endonasal forceps. The stent is then adjusted and the guides are removed. The two ends of the stent are joined by knots and allowed to stay freely in the nasal cavity. The stent used depends on the surgeon's preference.

#### COMPLICATIONS

The TCLA DCR is a minimally invasive surgical technique. However, canalicular stenosis<sup>3</sup>, necrosis of the medial canthus<sup>13</sup> and temporary changes of olfaction<sup>14</sup>, among other complications<sup>9</sup> may occur, some of which are common to other DCR techniques.

#### POSTLASER CARE AND FOLLOW-UP

Postoperatively the patient should apply a topic (eye drops) antibiotic such as tobramycin and an anti-inflammatory such as dexamethasone, five times a day for 10 days. Oxymetazoline hydrochloride spray 0.5 mg/ml every twelve hours for 3 days should be prescribed for the nose. The silicone stent is removed within 8 to 12 weeks after surgery.

#### RESULTS

Among all DCR techniques, the TCLA DCR is the fastest technique, taking between 8 to 25 minutes, while external DCR ranges from 78 to 118.6 minutes<sup>8,9,6,15</sup>. The risk of morbidity is lower than in external DCR. The success criteria most often used are the absence of epiphora and permeability for probing, which are, respectively, a functional and an anatomical criterion. The success rate varies between 34 and 95.2%<sup>8,16-19</sup>. In a study, the success rate was 52% in the group with less than thirty years old and 88% in those over sixty years old<sup>11</sup>. There are very few studies in the pediatric age<sup>18</sup>.

#### CONCLUSIONS

External DCR is still the gold standard treatment for the obstruction of the nasolacrimal duct or any other obstruction distal to the canaliculus. However, in selected patients, TCLA DCR is a good option<sup>20</sup>. TCLA DCR is a minimally



Figure 5. Left: Laser transillumination; Middle: osteotomy; Right: mucous discharge from the lacrimal sac.

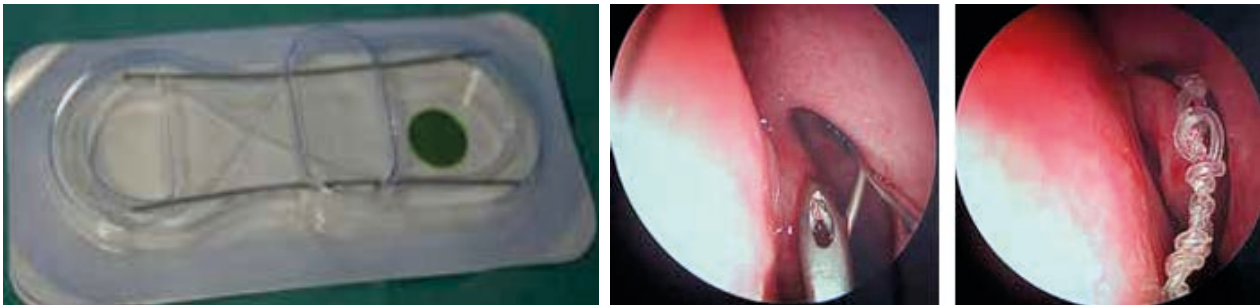


Figure 6. Left: silicone stent (FCI®). Center: pulling the silicone stent metallic guides with an endonasal forceps. Right: silicone stent ends are tied together and released in the nasal cavity.

invasive surgery, with less morbidity than external DCR, it is faster, does not damage the lacrimal pump and does not leave any skin scar. However, there is no consensus regarding the use of MMC, the most adequate energy that should be used or the postoperative treatments.

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**Commercial interests:** The authors do not have any commercial interest in any of the brands mentioned or shown in photographs.

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# XV. Diagnostic LASER

## 81. Optical Coherence

### Tomography (OCT)



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#### PRINCIPLES OF OCT

Optical coherence tomography (OCT) produces real-time, non-contact, high resolution, cross-sectional images of the retina, optic nerve and anterior chamber structures, enabling the identification of alterations in their morphology<sup>1,2</sup>. The images are composed with a low coherence interferometer using a near-infrared light (830 nm) system that measures wave-phase differences between a measuring beam and a reference beam. Small changes in the sample arm path length can be evaluated with great precision<sup>3,7</sup>.

Although OCT technology started with “time domain”, the newer generation of commercial OCT, described as “spectral domain”, is capable of acquiring sizable image sets over short time periods<sup>6</sup>. Besides interferometry, “spectral domain” OCT systems use a laser beam in the near infra-red range, depending on the manufacturer. In some equipments a tracker laser beam system continuously monitors the position of the eye. It is a mathematical function to assess interference patterns as a function of frequency. Thus, light scattered from different depths within the tissue can be measured simultaneously and images can be acquired 50-100 times more quickly than in the “time domain” systems<sup>6</sup>. In addition, it provides a depth of resolution of 7  $\mu\text{m}$  (27000–40000 scans per second), representing a greater detail than “time domain” does<sup>8</sup>.

There is also equipment associated to OCT for assessing the retinal pigment epithelium (RPE) autofluorescence that uses laser. A low beam energy blue laser stimulates the autofluorescence of the RPE. It takes advantage of the natural fluorescent properties of lipofuscin; the very faint blue laser beam enhances the autofluorescence of the RPE and captures fundus autofluorescence (FAF) images, providing both structural and metabolic information about the retina, namely RPE condition. Abnormal accumulation of lipofuscin is associated with a number of retinal diseases. Characteristic autofluorescence patterns seen in FAF images can reveal the extent of geographic atrophy. It can also assist clinicians in determining the diagnosis and management of hereditary conditions such as Best’s disease and Stargardt’s

disease and is becoming an essential tool in the management of degenerative diseases of the retina.

#### INTERPRETATION OF THE OCT IMAGE

A reliable exam should have a signal strength  $\geq 7/10$ . The strength of the OCT signal from a particular tissue structure at a given depth is defined by the amount of incident light that is transmitted without absorption or scattering to that depth layer, and the proportion of light that is directly backscattered<sup>1</sup>. The reflectivity of a structure depends not only on its composition but also on the direction of the reflected rays. If the structure is perpendicular to the incident light, the reflectivity will increase.

The interpretation of the OCT image (Figure 1) involves the **architecture** and the **thickness** of the specific structure.

For the **architectural** analysis, OCT produces a colored map according to the reflectivity of each structure: Red indicates hyperreflective; yellow/green, moderately reflective and black hyporefective. A black and white code can be also used where white represents hyperreflective, gray moderate and black hyporefective. Finally, a negative pattern is also an alternative (Figures 1a, 1b and 1c).

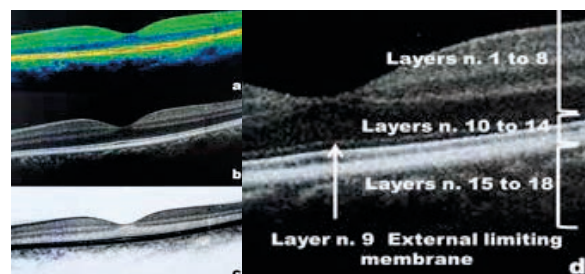


Figure 1. The macula architecture of the same patient represented in different map codes. a- colored, b- black and white and c- negative. d- the macular retinal layers: layers n. 1 to 8 represent the internal retina, n. 10 to 14 the external retina both separated by an external limiting membrane (layer n. 9). Layers n. 15 to 18 represent choroid.

# 81. Optical Coherence Tomography (OCT)

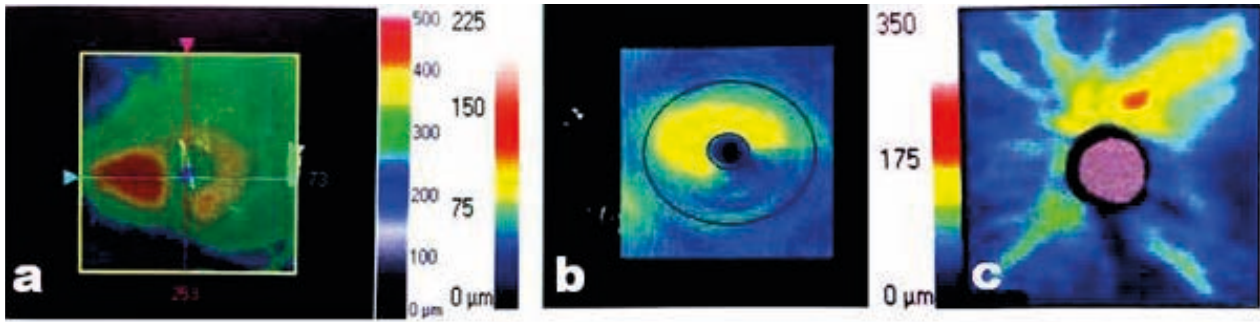


Figure 2. The thickness maps. a- on the macula map, there is an increased thickness in the temporal quadrant; b- on the GCIPL map, a thickness defect in the inferior nasal sector; and c- in the pRNFL, a decreased thickness in the inferior nasal quadrant.

For the **thickness** analysis, there are several representations:

- Thickness map: a colored map where black represents the lowest thickness, and white the highest, varying from blue, green, yellow and red. Used for the macula, the complex of the macular ganglion cell and internal plexiform layer (GCIPL) and peripapillary retinal nerve fiber layer (pRNFL) (Figure 2).
- Deviation map: a black and white photograph in which a deviation signal is introduced: yellow “as borderline” (within the lower 1%-5% of normal distribution), or red “outside normal limits” (within the lower 0%-1% of normal distribution). Used for pRNFL and GCIPL (Figure 3).
- Thickness graphs: rounded or linear and colored green, yellow, or red representing: “within normal limits” (within 95% normal distribution), “borderline” (within the lower 1%-5% of normal distribution), or “outside normal limits” (within the lower 0%-1% of normal distribution), respectively, for a specific area (quadrant or sector). Used for macula, GCIPL and pRNFL<sup>9-11</sup> (Figure 4).

- Tables: with a colored background, using the same code as the thickness graphs, appearing gray when there is no normative database (e.g. children < 18). Used for GCIPL and optic nerve head (ONH) parameters (Figure 5).
- Guided progression analysis: comparison of macula, RPE and pRNFL thickness over time.
- En face (Figure 6)<sup>12</sup>: coronal scan of inner limiting membrane (ILM), RPE, ellipsoid zone or inner/outer segment junction of photoreceptors that provides meaningful images of the topography of abnormalities observed in B-scans.

## ANTERIOR SEGMENT OCT (AS-OCT)

AS-OCT clearly identifies structures including the cornea, sclera, iris and lens anterior capsule<sup>1</sup>. By narrowing the field of view, higher transverse magnification images of the anterior eye can be obtained<sup>1</sup>. A close-up view of the angle region shows the iris contour and epithelium, the corneoscleral limbus and the anterior chamber angle<sup>1,13</sup>. AS-OCT also provides several parameters for the angle assessment: anterior chamber, angle opening distance, and trabecular-iris space area (TISA)<sup>13</sup>.

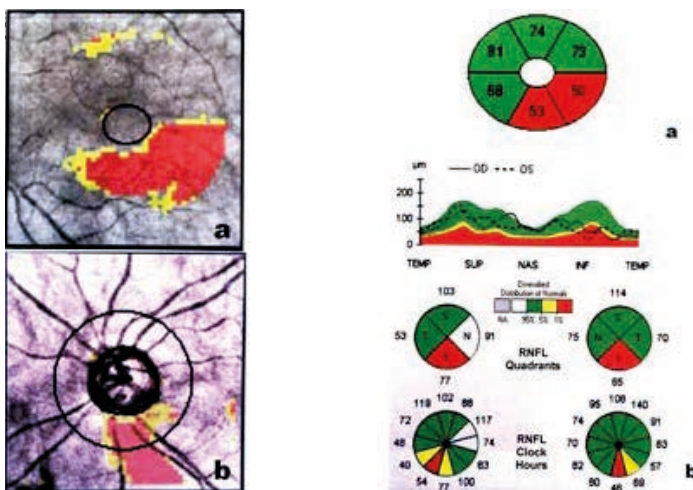


Figure 3- Deviation maps. a- for GCIPL, a decreased thickness in the inferior nasal sector; b- in the pRNFL a decreased thickness in the inferior nasal quadrant.

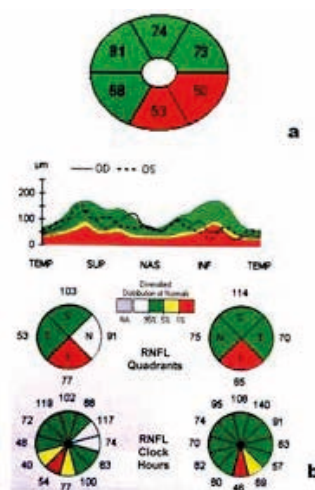


Figure 4- Thickness graphs. a- the GCIPL graph shows a decreased thickness in the inferior nasal sector; b- the pRNFL, an increased thickness in the nasal quadrant of the right eye and a decrease in the inferior quadrant of both eyes.

	OD $\mu\text{m}$	OS $\mu\text{m}$
Average GCL + IPL Thickness	68	63
Minimum GCL + IPL Thickness	56	58

	OD	OS
Average RNFL Thickness	81 $\mu\text{m}$	81 $\mu\text{m}$
RNFL Symmetry	60%	
Rim Area	0.84 $\text{mm}^2$	0.88 $\text{mm}^2$
Disc Area	2.04 $\text{mm}^2$	2.30 $\text{mm}^2$
Average CD Ratio	0.77	0.79
Vertical CD Ratio	0.77	0.80
Cup Volume	0.468 $\text{mm}^3$	0.529 $\text{mm}^3$

Figure 5- Tables. a- in GCIPL analysis a decreased thickness; b- for ONH parameters, the gray squares represent no possible comparison with a normative base.

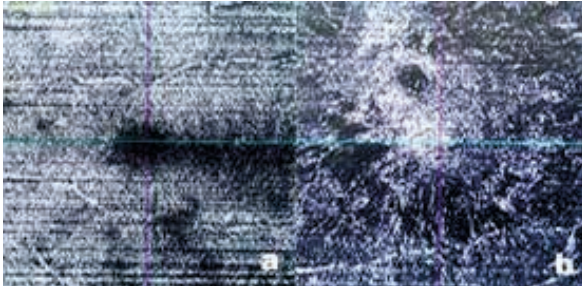


Figure 6. En face OCT of ILM. a- normal scan; b- an epiretinal membrane and its typical wrinkling of the ILM surface.

It is useful to measure tear meniscus and diagnose pterygia, pinguecula, and scleromalacia after surgery; architectural analysis of cataract surgery (cornea, lens, and biometry), refractive surgery and ectatic disorders, Descemet's membrane detachment and keratoplasty, corneal dystrophies and corneal verticillata (en face OCT), tumors<sup>13</sup>. Although OCT was not developed to evaluate filtering blebs, AS-OCT can visualize filtering blebs and can reveal the details of their morphology<sup>13</sup>.

### MACULA-OCT

The macula-OCT images correspond to the histological appearance of the retina<sup>14</sup>. The vitreous is typically black or not reflective, although sometimes posterior hyaloid can be seen. The superior reflection on an OCT scan corresponds to the nerve fiber layer and has high reflectivity. The external line, on the bottom of the OCT scan, represents RPE, Bruch's membrane and the choriocapillaris. Between those two layers, fifteen alternating reflectivity layers have been distinguished by Staurenghi and define the complex anatomical details of the macular retina (Figure 1d)<sup>15</sup>. The retina can be divided into two major regions that are separated by an external limiting membrane (layer numbered 9; Figure 1d): the external retina, that includes layers 10 to 14, and the internal retina between layers 1 and 8. Disorganization, thinning and discontinuity in external retina suggests RPE and photoreceptor diseases as well as thick, continuous, homogenous, hyperreflective material between Bruch's membrane and the RPE. The macula-OCT is exceptionally useful for demonstrating and quantifying external retina changes in vascular diseases and vitreoretinal disorders such as macular hole, macular edema and vitreomacular traction syndromes<sup>14</sup>.

For an appropriate OCT image analysis every single layer should be carefully examined. Blood vessels, for example, are most readily identified by their shadowing effects upon deeper structures<sup>1</sup>. Retinal abnormalities with hyperreflectivity are: fibrosis, hard exudates, melanin and hemorrhage. Hard exudates and hemorrhage produce shadowing of deeper retinal structures. Serous fluid, which contains few cells, is optically transparent, so it is clearly recognizable in OCT as a region devoid of reflectivity. Retinal edema, and hypopigmentation of the RPE may also result in reduced backscattering. On the contrary, retinal atrophy (as whole or some layers) increases backscattering

and creates a mask effect on deeper layers<sup>14</sup>. The ability of OCT to provide direct visualization as well as quantitative information makes it useful to longitudinally track small alterations in tissue structure associated with the progression or resolution of disease<sup>1</sup>.

### OPTIC NERVE HEAD OCT (ONH-OCT)

The ONH-OCT analysis involves 3 parts:

- The ONH parameters: width and area of neuroretinal rim at different meridians, the size of the disc and cup and cup/disc ratio that are represented in a table<sup>9-11</sup> (Figure 5b).
- The pRNFL thickness: measured in the shape of a circle with a 3.46mm diameter around it, which is represented in several graphics, relating to quadrants (temporal, superior, nasal, inferior) or hours (1-12h)<sup>9-11</sup> (Figures 2c, 3b and 4b).
- The GCIPL thickness: measured from the outer boundary of the pRNFL to the outer boundary of the inner plexiform layer (IPL); thus, a combination of the retinal ganglion cells layer (GC) and the IPL. The graphic representation is in sectors (superotemporal, superior, superonasal, inferonasal, inferior, inferotemporal)<sup>9-11</sup> (Figures 2b, 3a, 4a and 5a).

In general, it is easier to detect preperimetric glaucoma in the pRNFL, although in rare cases optic nerve analysis may be preferable. In some patients, analysis of macular ganglion fibers is as effective as pRNFL measurements<sup>2</sup>. ONH-OCT is also useful in distinguishing papilledema from pseudopapilledema like optic drusen<sup>16</sup>.

### CHOROID-OCT

The choroid is composed of 3 layers that include choriocapillaris (layer 15 by Staurenghi), Sattler's layer (layer 16), Haller's layer (layer 17) and terminates at the choroid sclera junction (layer 18) (Figure 1d)<sup>15</sup>. Average thickness of the subfoveal choroid is 287  $\mu\text{m}$ <sup>3</sup>. The method of imaging choroid is called enhanced depth imaging (EDI) OCT (Figure 7).

Choroidal thickness has a diurnal variation that should be taken into account in clinical practice. Decreased thickness is found in age-related choroidal atrophy and high myopia, and increases in central serous chorioretinopathy<sup>3</sup>.

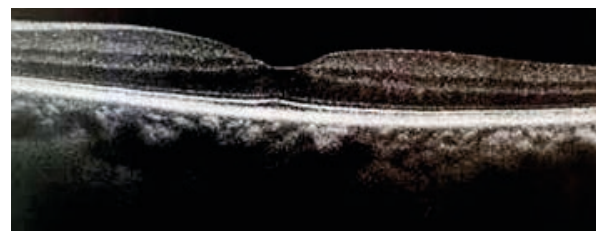


Figure 7. The normal choroid image obtained by EDI OCT.

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# XV. Diagnostic LASER

## 82. LASER Swept

### Source Optical Coherence

### Tomography (SS-OCT)



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#### INTRODUCTION

Optical coherence tomography (OCT) has revolutionized the way ophthalmologists approach an increasing number of ocular pathologies. The advent of Fourier domain techniques used in spectral-domain OCT (SD-OCT) made it finally possible to overcome the slow scan speed limitations of time-domain OCT (TD-OCT), operating 100 times faster, with higher scan densities and higher axial resolution (1 to 3  $\mu\text{m}$  with SD-OCT versus 10  $\mu\text{m}$  with TD-OCT). SD devices, in spite of also using a broadband and continuous wave light source, do not depend on the reference arm delay, as they use a reference arm fixed at a length approximately similar to the one of the sample. The interference fringe created by the light reflected by the reference arm and the light reflected by all the depths in the sample, after being dispersed by a spectrometer, is then simultaneously collected in a charge-coupled device (CCD), allowing a significant reduction in the acquisition time.

Unfortunately, to visualize deeper structures, higher frequencies are needed and this is where the SD-OCT technology becomes less sensitive, due to increasing subsequent reflection and lower signal-to-noise ratio. In fact, SD-OCT technology takes the posterior vitreous, due to its usual transparency and consequent lower signal, as the highest sensitivity area, allowing a good imaging of the neurosensory retina as far as the retinal pigment epithelium (RPE). By placing the choroid near the zero-delay line, namely using the enhance-depth imaging (EDI) method, choroidal visualization is possible<sup>1</sup>. However, due

to scattering and low penetration through the RPE, the choroidoscleral boundary is not always perfectly perceived. In short, with SD-OCT we can obtain high sensitivity and good resolution images, from both superficial and deeper plans, but not at the same time.

#### PRINCIPLES OF THE SWEEP SOURCE OCT (AND OCT ANGIOGRAPHY)

Swept source OCT (SS-OCT) technology, although also based on the “Fourier transform”, uses a totally different principle. A short cavity-swept tunable laser, instead of a superluminescent laser, able to emit different frequencies of light, is used. Swept laser sources achieve very small instantaneous bandwidths (=linewidth) at very high frequencies (20–200 kHz). A narrowband 1050 nm laser light source is used, which has a longer wavelength than SD-OCT, which is usually around 840 nm (Table 1), allowing a deeper tissue penetration with less scattering. This not only allows a better view of deeper structures, but also permits imaging through media opacities, such as a cataract<sup>2</sup>.

Photodetectors are used, as in TD-OCT, instead of charge-coupled device (CCD) cameras, allowing a further increase in axial resolution (1  $\mu\text{m}$ ).

Since imaging occurs twice as fast as with SD-OCT devices (100000 A-scans/sec versus 50000 A-scans/sec) (Table 1), it minimizes the effect of the patient’s eye movements on scan quality. The use of an invisible light source, unlike SD-OCT, is also less distracting for patients, allowing for a faster examination workflow. SS-OCT also ena-



# 82. Laser Swept Source Optical Coherence Tomography (SS-OCT)

Table 1. Characteristics of SD-OCT versus SS-OCT

	Spectral-domain OCT	Swept-source OCT
Light Source wavelength	840 nm	1050 nm
Scan speed	50000 A-scans/s	100000 A-scans/s
B-scan acquisition time (line resol: 1024)	± 0.04 s	± 0.01 s
3D acquisition time (resol:512x128)	± 2.6 s	± 0.65
Max. overlapping scan count (line 1024, 3D 512x64)	Max. 50 line (3D n/a)	Max 96 line (3D max.4)

bles higher density raster scan protocols, acquiring wide (12mm x 9mm) field scans (versus conventional 6 mm x 9 mm in SD-OCT), with a simultaneous high quality visualization of both macula and disc, and a similar resolution from both the vitreous, retinal and choroidal plans in the same scan (Figure 1).

SS-OCT technology has also enabled the *in vivo* non-invasive visualization of retinal and choroidal vessels without the use of a contrast dye<sup>3</sup>. Using sequential repeated cross-sectional OCT scans in a fixed retinal tissue area, and by analyzing the phase shift or variance, it is possible to image the motion of scattering moving particles such as erythrocytes, distinguishing perfused blood vessels from static tissue by allowing isolation of motion - OCT angiography<sup>3</sup>. A split-spectrum amplitude decorrelation (SSAD) strategy is used, since static tissue presents a high correlation between sequential frames and blood flow induces a reflectance variation over time. By splitting the spectrum of the light source, decorrelating each of its components and then averaging them, a minimization of motion artefacts and consequent improvement of signal-to noise ratio is obtained. A selective vascular optical dissection is therefore achieved.



Figure 1. SS-OCT scan in a healthy eye, enabling differentiation between the choriocapilaris and choroidal middle (S - Sattler) and outer (H - Haller) layers. The black arrows highlight ciliary artery vessels crossing the sclera. Photo courtesy of Zofia Michalewska, MD, PhD.

### CHOROIDAL IMAGING

The growing interest in the choroidal profile has lifted the veil and provided a deeper understanding of certain ocular pathologies. The higher resolution of choroidal imaging with SS-OCT allows the discernment of its individual layers, distinguishing the choriocapillaris, the Sattler and the Haller layer (Figure 1). Michalewska *et al*<sup>4</sup> also demonstrated the ability of this technology not only to visualize the lamina suprachoroidea but also to delineate, in some cases, a

presumed suprachoroidal space. With this technique a proper identification of the layer (or layers) involved in a specific chorio-retinal condition is achievable, therefore providing a deeper understanding of its pathophysiology. Choroidal automatic segmentation and the creation of choroidal thickness profiles and maps is now feasible.

### Pachychoroid diseases

Recently Freund described an entity named pachychoroid as a spectrum of diseases related to permanently increased choroidal thickness as central serous chorioretinopathy (CSC), polypoidal choroidal vasculopathy (PCV), pachychoroid pigment epitheliopathy or neovascularopathy. Choroidal hyperpermeability and vascular congestion, as well as RPE related abnormalities have been consistently documented in this entity, in a multimodal approach. SS-OCT has demonstrated that focal or diffuse choroidal thickening is present in CSC, especially in its outermost Haller layer (Figure 2). Furthermore, *en-face* SS-OCT may help to distinguish these RPE and choroidal CSC related abnormalities from secondary choroidal neovascularization (CNV)<sup>5</sup>. Similar focal and diffuse choroidal vessel dilation has been described in PCV patients, in both affected and fellow eye, as well as an abnormal choroidal branching vascular network<sup>6</sup>. SS-OCT is useful in distinguishing the polyps from adjacent RPE detachments or vascular abnormalities.



Figure 2. A horizontal scan crossing the fovea in a patient with chronic CSC. The most remarkable feature is the thickened choroid, especially in its outermost Haller layer, where enlarged vascular lacunae can be seen. However, a more precise identification of the choroidoscleral boundary is achievable. Pigment epithelium atrophic areas (between arrows) and clumping are characteristic.

### Choroidal neovascularization

A choroidal thinning has been repeatedly proved to occur

with normal aging. *En-face* SS-OCT has permitted a quantitative and qualitative differential assessment of vascular choroidal changes with age<sup>7</sup>. A more pronounced relative choriocapillaris thinning in aging eyes has been described<sup>7</sup>, which may be potentially relevant for the understanding of the underlying mechanisms in age-related posterior segment conditions, such as macular degeneration and glaucoma. Improvements in SS-OCT technology have recently enabled not only detailed CNV visualization, but its location relative to the outer retina and RPE or Bruch's membrane as well. Furthermore, by using *en-face* OCT angiography both the structure and also the flow index of the CNV area have been registered in pilot studies<sup>8</sup>. Using the decorrelation SSAD strategy has allowed the distinction of different vascular network patterns related to CNV. A decreased flow was found in both inner and outer choroidal vessels in CNV eyes and a higher flow index was also found in larger CNV and in type II CNV, compared to both type I or mixed patterns<sup>8</sup>.

### Choroidal nevi and tumors

Due to their heavily pigmented nature, choroidal nevi are difficult to access with OCT. With the advent of EDI technology, a significant increase in signal penetration was achieved, overcoming their shadowing and backscattering properties. However, the visualization beyond the anterior tumor has remained compromised. SS-OCT penetrates melanin better and offers a clearer view of the choroid, and it has proved to be better at depicting some intralesional findings, with a certain potential predictive value. Although EDI-OCT has been shown to identify secondary retinal changes, distended bordering vessels and the nevus-scleral interface in a similar way to SS-OCT, the visualization of intralesional details as vessels, seen in 100% of the patients, cavities in 20%, granularity in 47% and abnormal choriocapillaris in 58% was significantly better with SS-OCT<sup>9</sup>. Furthermore, although the morphology of amelanotic lesions was identically defined by both devices, melanotic lesions presented a better delineation with SS-OCT (100 versus 50%)<sup>9</sup>.

### VITREOUS-RETINA INTERFACE

The advent of OCT has led to a growing interest in vitreous anatomy. A better understanding of its structure and relation to the inner retina and disc, as well as its age-related degeneration<sup>10</sup> has resulted in a series of studies, including those reporting the use of the newest vitreolytic agents. Using SS-OCT, Itakura *et al*<sup>10</sup> first reported the finding of a posterior precortical vitreous pocket and the connecting channel to Cloquet's canal, opening the door to other related publications<sup>10,11</sup>.

Some authors have found some interesting changes in choroidoscleral contour in eyes with some vitreo-retinal disorders such as full-thickness macular hole and epiretinal membranes (ERM)<sup>12,13</sup> (Figure 3). In fact, the choroid has been implicated as having a role in the etiopathogenesis of macular holes, as changes in the choroidoscleral boundary have also been detected in their fellow eyes. On the other hand, the suprachoroidal lamina was also visible in the affected eyes, suggesting that traction may be transmitted through the retina to the choroid and expand the theore-

tical suprachoroidal space, making suprachoroidal lamina visible. These same authors also found that eyes with ERM presented a distortion in their choroidal profile, and this finding tended to normalize 3 months after surgery, which led them to hypothesize that generalized vascular changes and increased choroidal thickness in the fovea could contribute to the pathophysiology of ERM<sup>12,13</sup>.

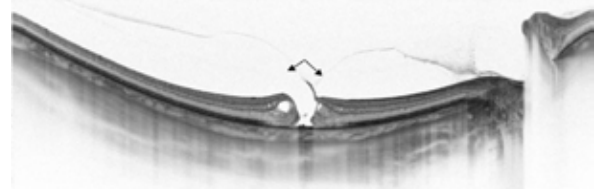


Figure 3. SS-OCT in a patient with a macular hole and vitreous traction. The choroid is slightly thinned and irregular. A simultaneous high resolution imaging both from the vitreous and the choroid is achievable with this technology. Photo courtesy of Zofia Michalewska, MD. PhD.

### GLAUCOMA ASSESSMENT

The wide-field technology enables the simultaneous visualization of both disc and macula, overcoming the need for two different scans and the resulting problems caused by differences in head position and alignment between scans. This also allows the tracking of a retinal nerve fiber layer (RNFL) wedge-like defect, correlating them with a macular ganglion cell defect. A quantitative assessment of multiple layers such as the RNFL, the ganglion cell layer plus the inner plexiform layer, the inner and outer retinal layers and the choroid is achievable (Figure 4). To assess glaucoma progression, delineation of the ganglion cell complex, formed by the RNFL (axons of retinal ganglion cells), ganglion cell layer (ganglion cell bodies) and inner plexiform layer (dendrites of retinal ganglion cells) is crucial<sup>14</sup>. As dendritic shrinkage may be the first morphological change in glaucomatous eyes, inner plexiform thinning should be an early biomarker of the disease, even before RNFL is affected.

On the other hand, an *en-face* SS-OCT view of the lamina cribrosa, implicated as the principal site of glaucoma damage, enables its morphological assessment, including the thickness of its walls or the size of its pores<sup>15</sup> (Figure 5). The choroid has also been shown to have a potential role in glaucoma patients, since it supplies the blood to the prelaminar optic nerve head, and its thinning could also be related to glaucomatous damage (Figure 4).

### CONCLUSION

Major advances in laser imaging in the last decade are providing us with a new level of knowledge for the understanding of retinal diseases, improving our diagnostic skills and follow-up assessments. Developing OCT laser technology is encouraging us to try to look beyond what we can see as a sharper image will always enable a clearer perception.

*(A special thanks for the imaging support kindly provided by Prof. Zofia Michalewska, Chair of Ophthalmology Unit at K. Jonscher Hospital, Poland; Ophthalmic Clinic "Jasne Blonia" in Łódź, Poland, who has vast experience and knowledge in SS-OCT).*

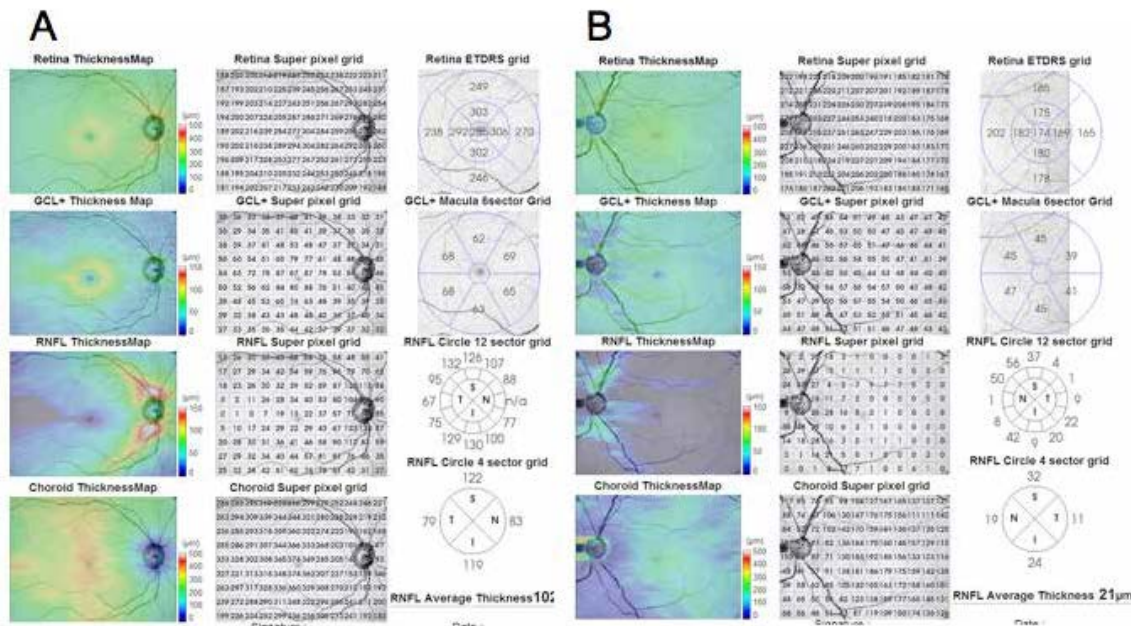


Figure 4. Simultaneous mapping measuring retinal, ganglion cell plus inner plexiform (GCL+), RNFL and choroidal layer thickness in normal (A) and glaucomatous (B) eyes. Notice the correlation between the GCL+ and RNFL loss in glaucoma (B), where a choroidal thinning is also evident.

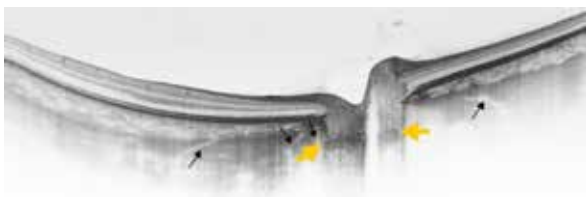


Figure 5. Scanning through the optic disc allows a deeper visualization of the lamina cribrosa profile (yellow arrows). Delineating its anterior and posterior boundaries, as well as its thickness and 3D profile, is now feasible. Photo courtesy of Zofia Michalewska, MD, PhD.

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# XV. Diagnostic LASER

## 83. Confocal

## Scanning LASER

## Ophthalmoscope - cSLO



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### INTRODUCTION

In the 1980s, Pomeranzeff and Webb<sup>1</sup> proposed a way of imaging the retina using much less light than conventional indirect ophthalmoscopy or photography. The system, the scanning laser ophthalmoscope (SLO), consists of scanning the fundus with a very narrow laser beam and detecting the reflected light with a high sensitivity detector (one pixel detector). The device was further improved by the use of pinholes<sup>2</sup> that blocked the returning scattered light. In fact, the system operates under the same principles as confocal microscopy and it is known as the confocal scanning laser ophthalmoscope (cSLO).

The cSLO has the ability to produce rapid images at low light levels using specific wavelengths. The system produces a high-quality image of the retina using less than 1/1000th of the light needed for conventional indirect ophthalmoscopy<sup>3</sup>. The facility to image with several different wavelengths, simultaneously or not, offers the potential for spectral imaging of retinal tissue. Retinal cameras image all points of the retinal region simultaneously or in parallel, but, in contrast, the SLO images the region of the retina point by point<sup>4</sup>. This allows observation of the fundus with lower light illumination intensity, permits video rating image in reflected light or fluorescence and shows increased contrast due to the reduction in stray light and scatter from out of the focal plane. The laser used for illumination can employ monochromatic light from visible to the near infrared spectrum (Figure 1).

### METHOD

A focused laser beam is swept across the fundus to form a rectangular pattern (or raster) on the retina. Light is collected by a photomultiplier from each retinal point as the laser beam sweeps across it. The sweep of the laser beam that forms the retinal pattern is synchronized

with the acquisition and storage of the corresponding data. Thus, each point on the acquired image (pixel) corresponds to a particular point in the retinal pattern, so the image of the fundus is constructed point-by-point<sup>5</sup>.

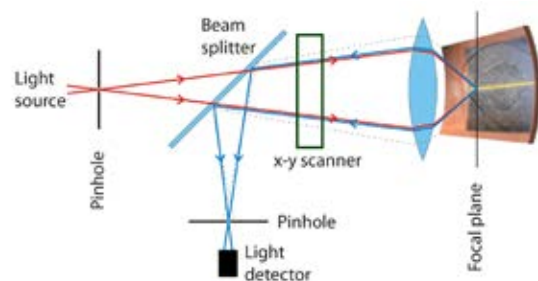


Figure 1. Schematic diagram of cSLO.

In conventional ophthalmoscopy, a complete optical image of a retinal region is either viewed directly, recorded on photographic film, or monitored by a camera. Since the SLO illuminates only a single retinal point at a time, only 0.9 mm of the patient's pupil, corresponding to the diameter of the laser beam, is used for illumination, and the rest is available for light collection. Therefore, the SLO is a highly light efficient instrument with a large range of depth of field.

The size of the laser raster on the retina is controlled electronically allowing it to "zoom" in on features of interest by reducing the size of the retinal raster.

cSLO raster scans a focused illumination spot in two dimensions across the sample, causes apertures in the back-scattered light through a confocal pinhole, and detects these on a single pixel detector such as an avalanche photodiode (APD) or photomultiplier tube (PMT)<sup>6</sup>.



A confocal image differs from a conventional monochromatic image because the contrast in a confocal image arises mainly from differences in reflection and refraction rather than differences in absorption of the incident light. This means that the confocal image does not show the same variation with wavelength that is found with monochromatic fundus camera images<sup>7</sup>.

### CLINICAL APPLICATIONS

The method provides continuous retinal observation at light levels that are safe and comfortable for the patient and permits a variety of applications that are difficult or impossible with conventional ophthalmoscopic methods<sup>3</sup>. Depending on the wavelength used to scan the retina, the images acquired represent the structures where the reflection predominantly takes place.

Images of different wavelength (Figure 2) can be combined in several ways, either to enhance and facilitate the detection of particular features or to produce pseudo-color images simulating fundus photography. Several cSLO systems producing true-color wide-angle fundus images have been proposed<sup>8-10</sup>. True-color was achieved either using white light or RGB laser beams and three independent detectors.

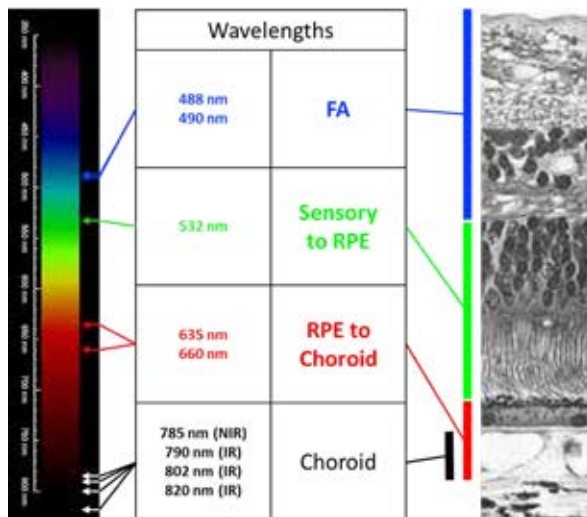


Figure 2. Commonly used light wavelengths and related main visualized structures.

The confocality, besides contrast improvement, also allows tomographic acquisition<sup>11-13</sup>. Therefore, a set of images of equally spaced planes of the retina can be acquired. Each image corresponds to a location of the confocal plane. Subsequent processing enables the extraction of 3D information about the structures of interest, for instance, the morphology of the optical disc.

Several cSLO systems have been proposed that are able to resolve individual cones on the fovea or even rods<sup>14-16</sup>. Many of those systems apply Adaptive Optics to correct eye optic aberrations. However, similar resolutions have also been reported using systems without such corrections<sup>17</sup>.

Multiple applications of cSLO in fundus imaging and function include infrared, fundus autofluorescence (FAF), red-free, fluorescein and indocyanine green (ICG) angiographies, ultra-width field fundus images,

electroretinography and microperimetry.

Finally, these systems may be combined with other optical diagnostic tools such as optical coherence tomography (OCT) to create multimodal imaging techniques that combine the benefits of high-resolution, high-speed *en face* imaging of SLO with the depth-resolution inherent in OCT<sup>6</sup>.

Some examples are presented in figures 3, 4 and 5.

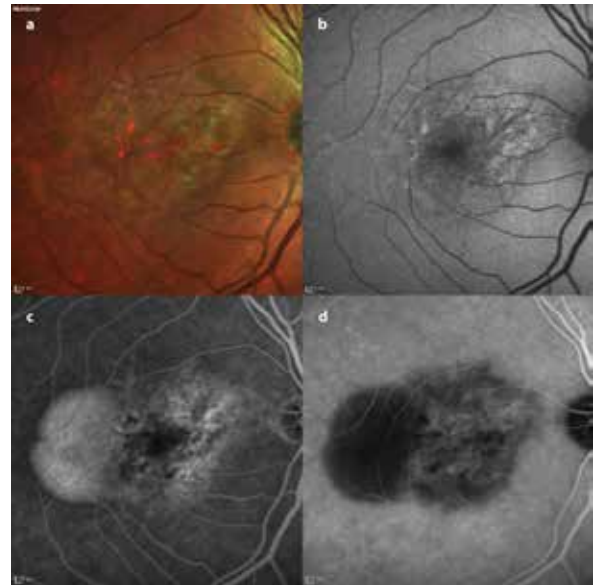


Figure 3. Multicolor image (a), FAF (b), fluorescein angiography (c) and ICG (d) acquired with cSLO.

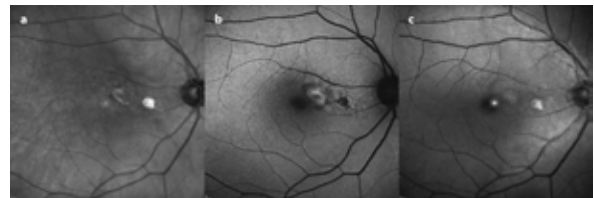


Figure 4. Infrared (a), FAF (b) and red-free (c) images obtained with cSLO.

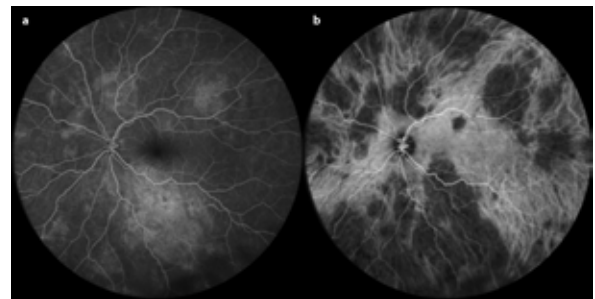


Figure 5. Ultra-widefield simultaneous images of fluorescein angiography (a) and ICG (b) obtained with cSLO.

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# XV. Diagnostic LASER

## 84. Optical Coherence

### Tomography Angiography



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#### BACKGROUND

Over the last decades, substantial developments in retinal imaging revolutionized our understanding of retinal and choroidal diseases. A myriad of imaging devices is now available at our discretion, representing a unique opportunity to offer our patients better clinical care. A remarkable example is the optical coherence tomography (OCT). Since its debut more than two decades ago, the technology behind OCT evolved drastically, with profound improvements in speed, resolution and image depth. Time-domain (e.g. Stratus OCT) systems were rapidly outshone after the emergence of spectral-domain (SD) OCT platforms. These systems convey fast scanning speeds and eye tracking, leading to the acquisition of noninvasive, *in vivo*, high-resolution cross-sectional images that approach histological sections of the retina<sup>1-3</sup>. Refinements included in enhanced depth imaging (EDI) and swept-source (SS) OCT systems brought deeper penetration and improved signal strength in the choroid, thus facilitating a qualitative and quantitative assessment of this structure<sup>4</sup>. OCT angiography (OCTA) represents a new era of OCT development and a true extension of capabilities from SD-OCT, with even faster scanning and sampling techniques<sup>5</sup>. This chapter will focus on the characteristics of this new imaging device, along with some clinical examples of its application and its currently known limitations.

#### OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY

By conveying noninvasive, three-dimensional scans of both the superficial and deep retinal capillary plexuses and the choriocapillaris, OCTA offered new insights into the retinal and choroidal microvasculature both in healthy<sup>6-8</sup> and disease<sup>9-13</sup> states. OCTA detects endoluminal flow by mapping erythrocyte movement over time and comparing sequential OCT B-scans at a given cross-section, thus allowing simultaneous visualization of structure and blood flow<sup>14</sup>. The split-spectrum amplitude-decorrelation angiography (SSADA) algorithm and the motion

correction tool are two patented primary technologies developed to improve the signal-to-noise ratio of flow detection and to remove unavoidable saccadic artifacts, respectively<sup>15,16</sup>. These technologies have significantly improved the quality of OCT angiograms. The first and most widely available OCTA device is the RTVue XR Avanti (Optovue Inc., Fremont, California, USA). This instrument has an A-scan rate of 70,000 scans per second, using a light source centered on 840 nm and a bandwidth of 50 nm. The tissue resolution is 5 mm axially and there is a 15 mm beam width. Two image sets are performed, each set comprising two raster volumetric patterns (one vertical and one horizontal), covering options of 2x2 mm, 3x3 mm, 6x6 mm, and 8x8 mm. Other platforms are now beginning to emerge, namely the Zeiss AngioPlex OCT Angiography (Carl Zeiss Meditec AG, Jena, Germany) and the Spectralis OCT Angiography (Heidelberg Engineering, Dossenheim, Germany).

The inherent advantages of OCTA are its ability to optically dissect and visualize flow in different layers of the retina, the high resolution obtainable and the freedom and safety of frequent examinations due to its noninvasive nature<sup>17</sup>. Layer segmentation is automatically generated to identify areas of interest, such as the superficial and deep retinal vascular plexuses or the choriocapillaris. The superficial vascular plexus, located in the ganglion cell layer (GCL) and the nerve fiber layer (NFL) is exposed at a thickness of 60  $\mu\text{m}$  from the internal limiting membrane (ILM). Although anatomically distinct, the two deep plexuses, located in the inner nuclear layer (INL) and outer plexiform layer (OPL), cannot be individualized and are thus seen as one single vascular plexus. The parameters for the deep plexuses are defined with reference to the inner plexiform layer (IPL) in a 30  $\mu\text{m}$  thick scan<sup>18</sup>. To evaluate the choriocapillaris, segmentation is automatically performed at the level of Bruch's membrane. An example of a healthy subject's superficial and deep plexuses and choriocapillaris imaged with OCTA is depicted in Figure 1.

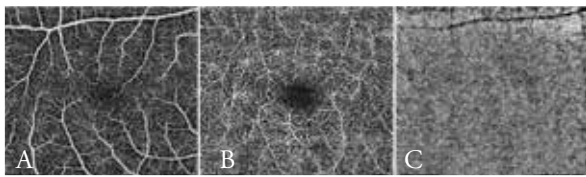


Figure 1. OCTA of a healthy subject showing the superficial vascular plexus (A), the deep vascular plexus (B) and the choriocapillaris (C). A clear individualization of the superficial and deep vascular plexuses is a remarkable novelty in retinal imaging brought about by OCTA that could not be observed with conventional angiography systems. These images are used with permission from Marques *et al.*<sup>1</sup>.

## CLINICAL APPLICATIONS

### 1. AGE-RELATED MACULAR DEGENERATION

In addition to providing enhanced anatomic detail, OCTA allows quantitative metrics of the choroidal neovascularization (CNV) area and generates data on vascular flow<sup>19</sup>. Several studies have demonstrated that OCTA can accurately identify type 1, type 2 and type 3 neovascularization<sup>11,12,14,20-23</sup>, offering an unrivaled morphological characterization of the CNV net (e.g. tree-like, glomerular, fragmented) that far exceeds fluorescein angiography (FA), indocyanine green angiography (ICGA) and OCT. In addition, the presence of a fibrovascular capsule, afferent feeder trunk and peripheral anastomosis within the CNV can be clearly assessed<sup>12</sup>. OCTA may also be useful in the screening of eyes at risk for CNV. A pilot study by Palejwala *et al.*<sup>24</sup>, showed that OCTA was able to identify foci of CNV that were not identifiable in FA and structural OCT. Whether nonexudative CNV is a predecessor of wet age-related macular degeneration (AMD) or a distinct clinical entity is yet to be determined, as well as whether we should start anti-VEGF treatment in these cases<sup>13</sup>.

### 2. DIABETIC RETINOPATHY

In patients with diabetic retinopathy (DR), OCTA shows a foveal avascular zone (FAZ) larger than in healthy subjects (normal FAZ ~500  $\mu$ m). According to Lumbroso *et al.*<sup>18</sup> this is an early sign of DR that may be present before the development of microaneurysms. A loose microvascular network with large and sparse meshes can also be shown, even in patients with mild nonproliferative DR<sup>10,25,26</sup>. Microaneurysms appear as focally dilated saccular or fusiform capillaries in OCT angiograms of the superficial and/or deep capillary plexus. Retinal non-perfused areas are seen as lesions with no or sparse capillaries. Neovascularization at the optic disc or at the posterior pole can also be imaged and are clearly discernible with OCTA<sup>18,27</sup>.

### 3. RETINAL VASCULAR OCCLUSIONS

Kashani *et al.*<sup>28</sup> showed that OCTA findings in retinal vein occlusions were consistent with clinical, anatomic and FA findings. Capillary dropout and focal non-perfusion appearing as dark areas (similar to FA), disruption of the foveal ring, an increased FAZ and collateral vessels can be

expected, both in the superficial and in the deep vascular plexuses of patients with branch retinal vein occlusions<sup>1</sup>.

### 4. GLAUCOMA

The optic nerve head can be imaged with OCTA. In healthy subjects it shows a very dense vascular network around the disc that cannot be detected in FA. Jia *et al.*<sup>29</sup> have found that this network is greatly attenuated in glaucomatous discs. Further studies are needed to determine its correlation with the rate of progression and whether disc perfusion can be used as a prognostic indicator<sup>1</sup>.

### 5. MISCELLANEOUS

Reports on OCTA characteristics of miscellaneous causes of CNV (angioid streaks, central serous chorioretinopathy<sup>30</sup>, macular telangiectasia type 2<sup>31</sup>, inflammatory diseases<sup>14</sup>, etc.) have already been published but a thorough description of such findings is outside the scope of this chapter.

### LIMITATIONS

Despite the potential benefits of OCTA, our expectations must be tempered, given our limited experience with the device.

Even the best imaging methods have flaws and current OCTA devices sometimes produce extra or missing pieces of information or translation, called artifacts. Spaide *et al.*<sup>32</sup> described various artifacts seen in OCTA images, occurring due to image acquisition, intrinsic characteristics of the eye, motion, image processing and/or display strategies. Several authors have recommended excluding images from analysis/interpretation when they have: a) poor quality (signal strength index  $\leq 40$ ) or b) residual motion artifacts (discontinuous vessel pattern or hazy images).

Another important limitation of current OCTA platforms is that they are limited to the macula, thus invalidating an assessment of the retina outside the vascular arcades. This would be especially useful in the evaluation of peripheral ischemia in diabetic retinopathy, vein occlusions, sickle cell retinopathy, among others.

### CONCLUSION

We embark on this new era of retinal imaging with great expectations in mind, hoping that OCTA can point out new clinical coordinates to improve the everyday management of our patients. Although still far from perfect, the new functionalities and technical enhancements that continue to ripen, will most likely bring further improvements.

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# XV. Diagnostic LASER

## 85. Wavefront

# Aberrometry



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### INTRODUCTION

The eye works as an optical system with the purpose of focusing an image onto the retina. The most common refractive errors are defocus and astigmatism, but there can also be optical imperfections, such as high order aberrations (HOA) that contribute to visual quality deterioration. HOA are not routinely screened in clinical practice and are not corrected by conventional methods. These aberrations are mainly caused by errors in the cornea and lens and vary with pupillary size, accommodation, tear film and age<sup>1,2</sup>. Wavefront aberrometry in ophthalmology grew as a response to the demand from refractive surgery to deliver “supervision”.

### PRINCIPLES

Wavefront aberrometry is based on the physical optics expression of light as a wave. According to this definition, light spreads in every direction as a spherical wave, similar to the wave effect after a rock is thrown into a lake. A wavefront is composed of light waves that are all in-phase. Light from a source at infinity is expressed as a plane wavefront, and in an emmetropic eye is focused onto the retina (Figure 1). An imperfect optical system generates distortion of the wavefront and, therefore, aberrations<sup>3,4</sup>.



Figure 1. Light propagation according to aberrometry principles.

Aberrometry studies the light wavefront transmission to the eye's refractive media. Aberrations can be measured as a test light beam enters the eye (ingoing aberrometry) or from the wavefront that emerges from the eye (outgoing aberrometry)<sup>1</sup>. Devices used to measure aberrations are usually classified into three types:

1. outgoing aberrometer that measures the wavefront that is reflected from a light directed at the fovea, as in the Hartmann-Shack sensor;
2. ingoing aberrometer that analyses the distortion of an image projected onto the retina, as in the Tscherning aberrometer or the sequential retinal ray tracing method;
3. ingoing aberrometer based on retinoscopic principles, as in the optical path difference method<sup>5</sup>.

Wavefront shape analysis relies on the decomposition of data into a series of components. Although numerous methods were developed for this purpose, Zernike polynomials are the most popular equations in clinical practice. They consist of independent trigonometric functions that are representative of waveform shapes, deconstructing the waveform aberration into several standard-shapes. By simplifying the error into known patterns it becomes easier to read the optical system that represents each eye. The Zernike coefficient represents the weight of each polynomial on the waveform aberration; the zero order has one term and represents a constant; 1<sup>st</sup> order has two terms that represent prisms (tilt in both the X and Y axis), 2<sup>nd</sup> order has 3 terms that represent defocus (myopia/hyperopia) and regular astigmatism on the horizontal and vertical axis; higher orders represent monochromatic aberrations such as coma and trefoil (Figure 2)<sup>1,5</sup>.

Second order terms represent the majority of aberrations in the normal individual and are corrected by optical correction aids. HOA can represent up to 20% of the aberrations of an eye with mild refractive error and therefore have a small impact on visual quality<sup>4</sup>. They have a higher impact on diseases such as keratoconus or after refractive surgery<sup>3,4</sup>.



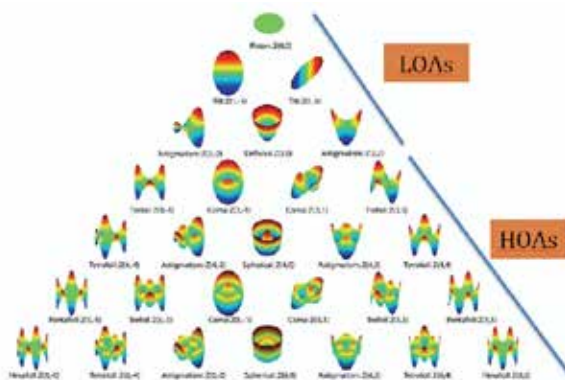


Figure 2. Zernike polynomials (HOA: high order aberrations; LOA: lower order aberrations).

**CLINICAL APPLICATIONS**

Wavefront technology has been important for the understanding of the relationship between anatomical structures, optics and subjective visual quality. Wavefront analyses have shown a strong correlation between the visual symptoms and ocular aberrations, for example monocular diplopia in eyes with coma and starburst and glare in eyes with spherical aberration<sup>6</sup>. In eyes with mild nuclear cataracts, the spherical aberration tends to become negative, and is dominant over coma-like aberration. In contrast, positive spherical aberration and coma, like dominant aberrations, are characteristic of mild cortical cataracts<sup>5</sup>.

**Refractive Surgery**

Wavefront analysis confirmed the increase in HOA following conventional corneal based refractive surgery, such as ASA or LASIK, which is mainly spherical aberration (positive after myopic treatments and negative after hyperopic) and coma (decentered ablation). The increase in HOA is correlated with the amount of refractive correction<sup>7</sup>. The use of wavefront aberrometry to guide an excimer laser ablation is based on the theoretical advantage of correcting, not only spherocylindrical errors but also HOA, while minimizing the induction of new aberrations by the laser ablation - wavefront guided ablations. Although a few studies show better HOA induction profile, better contrast sensitivity, reduced glare and halos of wavefront-guided vs conventional treatments, there are important obstacles to a perfect result that should be addressed: reproducibility of the wavefront map; HOA fluctuation induced by the tear film (dry eye) and lens; treatment precision; individual healing response to the laser ablation<sup>8</sup>. The main goal of a recent profile - Wavefront-optimized ablation - development is to reduce the induction of spherical aberration, producing an aspheric ablation by applying a pre-calculated spherical aberration. Most of the population has a low magnitude of HOA and would probably not benefit from a wavefront-guided treatment profile. Several studies have supported that idea when they fail to show a clear superiority of a wavefront-guided over an optimized profile.

**Corneal diseases: keratoconus - Diagnostic and treatment**

Wavefront analysis of keratoconic eyes shows a characteristic increase in coma aberration, particularly vertical coma. This finding is helpful in detecting the disease and keratoconic suspicious corneas, when evaluating patients for refractive surgery. Coma and its magnitude are also used for grading the severity of keratoconus (Amsler-Krumeich-Alio) (Table 1)<sup>2</sup>. Recently Alfonso et al. demonstrated the importance of coma and its orientation to distinguish different types of keratoconus, and when implanting intrastromal rings<sup>9</sup>. Despite being classified as non-inflammatory corneal ectatic disorders, keratoconus and pellucid marginal degeneration (PMD) differ in their patterns from the HOA. The magnitude of coma is significantly higher in keratoconic eyes and spherical aberration is negative, in contrast to the increased positive spherical aberration of PMD.

Table 1. Amsler-Krumeich-Alio Keratoconus Classification

<p><b>Stage I</b></p> <ul style="list-style-type: none"> <li>• Mean central K readings <math>\leq 48.00</math> D.</li> <li>• RMS of coma-like aberration from 1.5 to 2.50 <math>\mu\text{m}</math>.</li> <li>• Absence of scarring.</li> </ul>
<p><b>Stage II</b></p> <ul style="list-style-type: none"> <li>• Mean central K readings <math>&gt; 48.00</math> to <math>\leq 53.00</math> D.</li> <li>• RMS of coma-like aberration from <math>&gt; 2.50</math> to <math>\leq 3.50</math> <math>\mu\text{m}</math>.</li> <li>• Absence of scarring.</li> <li>• Minimum corneal thickness <math>&gt; 400</math> <math>\mu\text{m}</math>.</li> </ul>
<p><b>Stage III</b></p> <ul style="list-style-type: none"> <li>• Mean central K readings <math>&gt; 53.00</math> to <math>\leq 55.00</math> D.</li> <li>• RMS of coma-like aberration from <math>&gt; 3.50</math> to <math>\leq 4.50</math> <math>\mu\text{m}</math>.</li> <li>• Absence of scarring.</li> <li>• Minimum corneal thickness 300 to 400 <math>\mu\text{m}</math>.</li> </ul>

**Cataract Surgery**

In order to improve ocular optical quality in pseudophakic patients, intraocular lens (IOL) should be able to compensate average positive spherical aberration of the cornea. Clinical studies confirm that reduction in spherical aberration increases contrast sensitivity and mesopic visual quality. IOL customization is a new concept that goes further than achieving emmetropia after cataract surgery. The goal is to estimate the ideal magnitude of spherical aberration within the eye and IOL to optimize optical quality. Therefore, modified IOL with different amounts of negative or even neutral spherical aberration were designed to fulfill this objective (Table 2)<sup>10</sup>.

Table 2. Induced spherical aberration of different IOLs

Intraocular Lens	Induced Spherical Aberration ( $\mu\text{m}$ )
Alcon IQ (SN60WF)	-0.20
AMO Tecnis	-0.27
B&L Akreos	0
Spherical IOL	+0.18

Although HOA degrade quality vision in most circumstances, in some cases they may have a beneficial effect. The induction of specific HOA, like spherical aberration, may expand depth of focus, ameliorating presbyopia symptoms without significantly compromising vision quality. The increase in depth of focus can reach up to 2 D with 0.6  $\mu\text{m}$  of spherical aberration and is reduced over 0.9  $\mu\text{m}$ . A trade-off between sharper image and an increase in depth of focus should be considered individually while selecting the IOL.

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# XVI. LASER In Research

## 86. LASER Doppler

### Flowmetry



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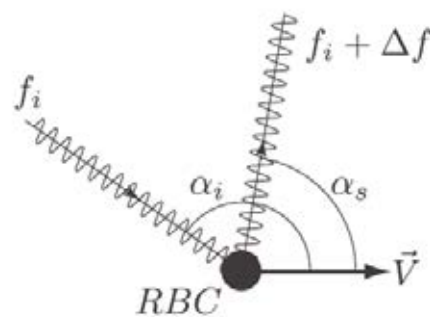
#### INTRODUCTION

The Doppler principle has led - over the last 40 years - to the measurement of blood flow in a number of tissues in the body<sup>1</sup>. In 1972, we witnessed the first measurement of blood velocity in human retinal vessels<sup>2</sup>. The measurement of blood flow in the ocular fundus is of scientific and clinical interest, since it provides the possibility of acquiring knowledge about the physiology of deep vascular beds and the early assessment of blood flow changes. The Laser Doppler Flowmeter (LDF) continuously records the blood flow in the tissue of (i) the optic nerve head, (ii) the sub-foveal choroid, and (iii) the iris<sup>3</sup>.

#### BASIC PRINCIPLES

The Doppler effect was first described in 1842 by the Austrian physicist Christian Doppler in an article entitled "on the colored light of double stars and some other heavenly bodies"<sup>4</sup>. Consider a single particle such as a red blood cell (RBC) moving at velocity  $V$  in the direction shown in figure 1. A laser beam of single frequency  $f_i$  is incident on this RBC at an angle  $\alpha_i$  with  $V$  and scattered by the RBC in various directions. In the direction of the detector, the frequency of this light differs from  $f_i$  by an amount,  $\Delta f$ , which corresponds to the so-called Doppler shift. Its magnitude depends upon  $V$ ,  $\alpha_s$ ,  $\alpha_i$ , the index of refraction  $n$  of the medium containing the particle and the wavelength  $\lambda$  of the laser light in vacuo<sup>3,5</sup>.

When a laser beam illuminates a tissue containing a network of microvessels having RBCs moving at various directions at different velocities, the light scattered by the RBCs consists of a summation of waves at different frequencies due to the numerous Doppler shifts undergone by the incident light<sup>6</sup>. This concept has since been used for a number of medical devices focusing on ocular blood flow. One such device is the confocal LDF, which provides noninvasive measurements of retinal capillary blood flow<sup>7</sup>. This instrument detects the light scattered by the RBCs within an annulus corresponding to 180  $\mu\text{m}$  at the fundus.



$$\Delta f = n |\vec{V}| (\cos \alpha_s - \cos \alpha_i) / \lambda,$$

Figure 1. The Doppler effect. The frequency of the light scattered by the particle with velocity  $V$  in the direction defined by  $\alpha_s$  is shifted in frequency by an amount  $\Delta f$  compared to that of the light of frequency  $f_i$ , which is incident on the RBC at an angle  $\alpha_i$ . Figure and formula adapted from Riva et al<sup>3</sup>.

The pupil of the optic system is large enough (4 mm) to allow measurement without pupil dilation<sup>8</sup>.

#### CLINICAL PROTOCOL AND PARAMETERS

Before starting the procedure, a resting period is necessary to attain stable cardiovascular conditions, namely blood pressure and heart rate. Other relevant study requirements are: abstinence from alcohol, coffee, smoking, exercise and heavy meals<sup>3</sup>. Table 1 describes some strategies on how to prepare to perform the doppler flowmetry.

The measured parameters are:  $V_{el}$ , the mean speed of the RBCs in the sampling volume (proportional to the mean

Table 1. Laser doppler flowmetry - anatomic area, technique and laser power<sup>3</sup>

<b>Optic nerve head</b>	Aim at disc sites free of large vessels	100 $\mu\text{m}$
<b>Subfoveal choroid</b>	Ask the patient to look directly at the probing beam	100 $\mu\text{m}$
<b>Iris</b>	Aim at a small area while asking the patient to fixate a point	150 $\mu\text{m}$

$\Delta f$ ); and Vol, the number of moving RBCs in this volume (proportional to the area under the curve). These LDF parameters are determined using the following equations:

$$Vel = \frac{\int_{30\text{Hz}}^{\Delta f_{\text{high}}} \Delta f P(\Delta f) d\Delta f}{\int_{30\text{Hz}}^{\Delta f_{\text{high}}} P(\Delta f) d\Delta f},$$

$$Vol = \frac{1}{A_{\text{dc}}^2} \int_{30\text{Hz}}^{\Delta f_{\text{high}}} P(\Delta f) d\Delta f,$$

Adapted from Riva *et al*<sup>8</sup>.

$A_{\text{dc}}$  is the amplitude of the direct photocurrent (DC, non-Doppler-shifted light). Doppler shifts below 30 Hz are filtered out to avoid artifacts caused by slow motion of the tissue and eye motion. For optic nerve head ( $F_{\text{onh}}$ ) and iris ( $F_{\text{iris}}$ ) measurements,  $\Delta f_{\text{high}}$  is set at 3000 Hz because the Doppler shifts from this tissue are below this value. For subfoveal choroidal measurement ( $F_{\text{ch}}$ ), a value of 20000 Hz is most often appropriate. The RBC flux in the optic nerve head ( $F_{\text{onh}}$ ) is calculated as  $F_{\text{onh}} = k \cdot Vel_{\text{onh}} \cdot Vol_{\text{onh}}$ . A similar definition applies for  $F_{\text{ch}}$  and  $F_{\text{iris}}$ .  $Vel_{\text{onh}}$  is expressed in Hz and  $Vol_{\text{onh}}$  and  $F_{\text{onh}}$  are in arbitrary units;  $k$  is a proportionality constant. The same applies for the LDF parameters measured from the choroid and iris<sup>3,9</sup>.

It is important to understand the reasons why LDF provides only relative measurements<sup>9</sup>. Laser radiation upon a tissue undergoes scattering and absorption. Both processes influence the penetration pattern of the laser light. Penetration may differ from one region of a tissue to another, depending on the optical properties of the tissue. Thus, spatial or temporal variations in tissue structure and vascularization – as is the case, for example, in the optic nerve head in glaucoma – will affect the LDF measurements. Furthermore, direct comparison between the LDF values from different tissues may not be valid because of variations in optical properties, resulting from differences in tissue structure and composition. In particular, comparing  $F_{\text{onh}}$  data from healthy individuals and patients with glaucoma or  $F_{\text{ch}}$  data from healthy individuals and patients with age-related macular degeneration may be problematic under certain conditions. Furthermore, measurements obtained with different lasers may not be comparable if the optical characteristics of the lasers (wavelength, beam divergence, penetration into the tissue) are different. The measured flow is usually referred to as ‘blood flow’. However, what is actually measured is the flux of the RBCs<sup>10</sup>.

## ANALYSIS

Like any clinically relevant measure, blood flow measurement should be accurate, reproducible and sensitive. Studies have demonstrated a coefficient of reproducibility between 0.7 and 0.95 for flow measurements and an interobserver coefficient of variation of less than 6%<sup>11,12</sup>. Figure 2 shows an example of an LDF graph obtained with confocal technology.

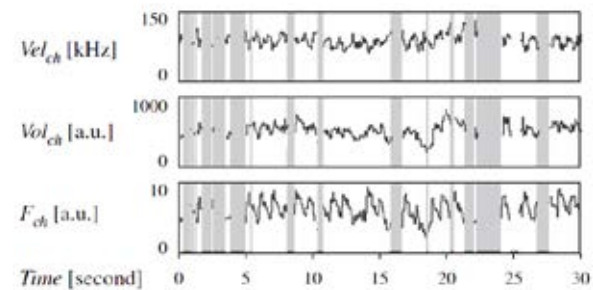


Figure 2. Confocal LDF. The grey bars in the recordings represent the portions of signal during eye or head motion and blinks. The software for determining these LDF parameters allows for rejection of the blinks or other spurious signals caused by eye motion, which cause gaps in the continuous display of the data. Adapted from Riva *et al*<sup>8</sup>.

## CLINICAL UTILITY

The use of LDF represents an important advance in hemodynamic analysis by providing sub-capillary resolutions. Numerous studies have found that retinal capillary blood flow is reduced in glaucoma patients compared to healthy individuals<sup>13,14</sup>. Reduced retinal capillary blood flow has also been found to correspond to visual field defects<sup>15</sup>. Additionally, it has been linked to pathological structural parameters in glaucoma<sup>16</sup>.

## LIMITATIONS AND FUTURE CHALLENGES

A central question in the application of LDF to the optic nerve head is the depth of the sampling volume. This depth determines the relative contribution to the Doppler sign of the superficial layers, those supplied by the central retinal artery, and the deeper layers supplied by the short posterior ciliary arteries. These two vascular beds may have different blood flow regulation properties. In addition, high-quality images are required for data to be reliable, which are not often obtained in all patients, as clear optical media and good fixation are required. Some questions are yet to be addressed: (i) the exact sampled volume, (ii) the optimal probing beam wavelength, (iii) the effect of beam focus, ocular fundus pigmentation and ocular refraction, (iv) the effect of media opacities, (v) the influence of pupil dilation in hemodynamic pa-

rameters, (vi) the best physiological stimuli to use and (vii) how some pathologies affect scattering properties of the tissue.

An extensive coverage of the possible applications and future updates on LDF technology are beyond the scope of this chapter, which aims at providing an introduction to the basic principles, clinical procedures, advantages and limitations of LDF.

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# XVI. LASER In Research

## 87. *In Vivo* Confocal Microscopy of the Cornea



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The cornea is a highly differentiated tissue to allow light refraction and transmission. Waring *et al.*<sup>1</sup> subdivided the cornea into six layers: *epithelium*, *basal membrane*, *Bowman's layer*, *stroma*, *Descemet's membrane* and *endothelium*. Corneal confocal microscopy (CCM) extended the evaluation capacity of the normal and diseased cornea, since it enhances spatial resolution beyond biomicroscopic limits. CCM enables the visualization of corneal cells. Except for Descemet's membrane, all the corneal layers are visualized *in vivo* under CCM<sup>2</sup>.

### NORMAL CORNEA

**Corneal epithelium:** Under CCM, superficial cells (Figure 1A) are about 30-50  $\mu\text{m}$  in length and 5  $\mu\text{m}$  thick<sup>3</sup>. These cells are polygonal, with well-defined borders and different sizes<sup>4</sup>. The nucleus of these cells is quite visible, small, round and dark, surrounded by a perinuclear<sup>3</sup> hypo-reflective dark ring and highly shining cytoplasm<sup>5</sup>. The wing cells are located in the intermediate portion of the corneal epithelium and have variable shapes and sizes up to 20  $\mu\text{m}^2$ . Their reflectivity is the lowest of all the corneal cells<sup>6</sup>. These cells are characterized by the presence of well-defined and shining borders. The nucleus of these cells is hard to distinguish and does not have the dark ring which can be seen in the superficial epithelial cells<sup>6</sup>.

The epithelial basal cells (Figure 1B) are about 10-15  $\mu\text{m}$  in diameter<sup>4</sup> and form a regular mosaic pattern, with dark cellular bodies and shining borders<sup>4,7,8</sup>. The nucleus of these cells is not visualized under CCM.

**Corneal nerves:** Nerves of the sub-basal nerve plexus (Figure 2A) are easily identifiable under CCM<sup>9</sup>. They are threadlike, devious and highly reflective, with branches Y- or T- shaped (Figure 2B) and thinner connection fibers H- shaped (Figure 2C). The varicosities<sup>10</sup> are the

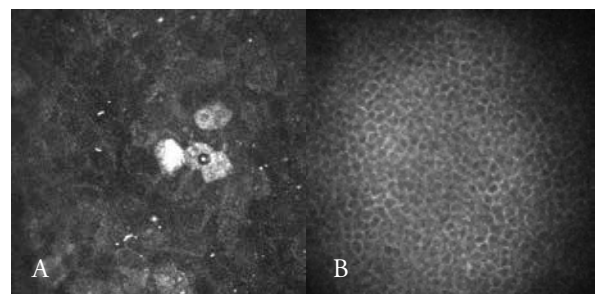


Figure 1. Corneal epithelium: (A) superficial epithelial cells; (B) basal epithelial cells. Images obtained by a confocal scanning laser microscope (HRT II + RCM), CRIO – CHUC.

accumulation of mitochondria and glycogen<sup>11</sup>. Stromal nerves are wider under CCM (Figure 2B), looking rectilinear, highly reflective and with bifurcations<sup>9,10</sup>. Stromal nerves appear in the anterior stroma, and are thus more difficult to find in the medium stroma and being absent in posterior stroma<sup>12</sup>.

**Bowman's layer:** When using *in vivo* CCM, the location of Bowman's layer is defined by the presence of the sub-basal plexus<sup>2</sup>. In spite of being an acellular layer, the presence of Langerhans cells in this membrane has been described, associated with the sub-epithelial plexus. Under CCM<sup>13,14</sup> they appear like shining corpuscles 15  $\mu\text{m}$  in diameter.

**Corneal stroma:** In anterior stroma (Figure 3A), the keratocyte nuclei present smaller dimensions than in the other layers, are more shining and have a characteristic multi angle morphology. In medium stroma, the keratocytes present a smaller density and their nucleus is more regular, generally more oval-shaped<sup>8</sup> and with occasional indenta-

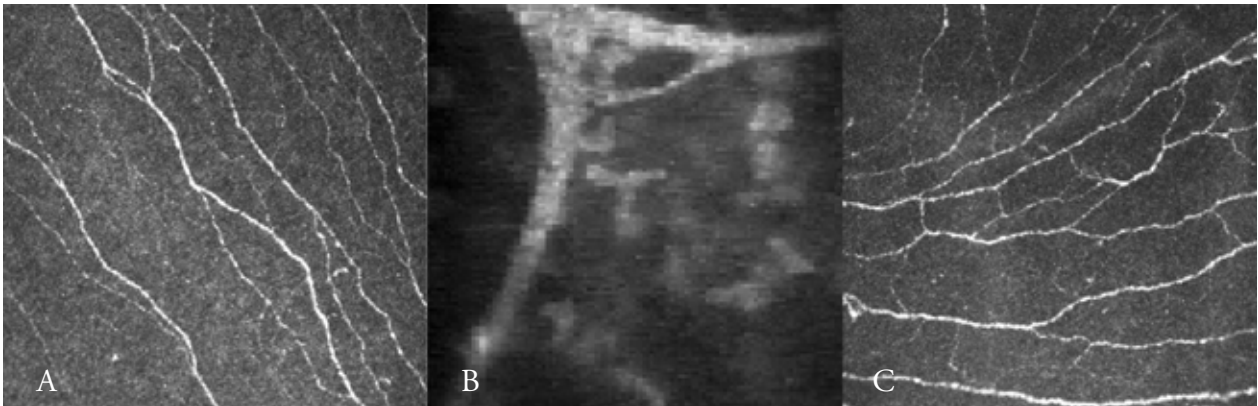


Figure 2. Corneal nerves: (A) sub-basal nerve plexus; (B) corneal nerve with Y-shaped branch in medium stroma; (C) bifurcations H-shaped in nerves of the sub-basal plexus. CRIO – CHUC.

tions<sup>15</sup>. In posterior stroma (Figure 3B), the keratocytes are more elongated and needle-shaped<sup>7,16,17</sup>.

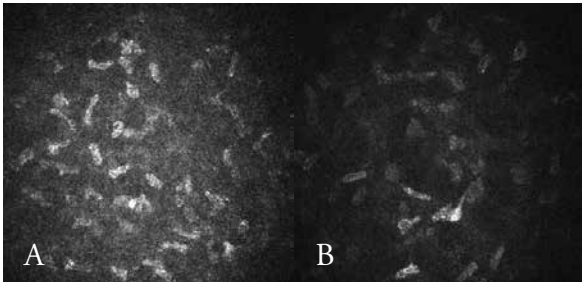


Figure 3 - Corneal stroma and keratocytes: (A) anterior stroma; (B) posterior stroma. CRIO – CHUC.

Nuclei in keratocytes present a different aspect, according to proliferation<sup>16,18,19</sup>. The keratocytes that are quiescent or inactive, present white, oval-shaped or bean-shaped nuclei on a dark fundus, and cellular extensions are not visualized<sup>18,20,21</sup>. Activated or proliferating fibroblasts, which imply proteic synthesis, take a wider and more shining shape, with it being possible, in most situations, to observe their cellular extensions<sup>22-24</sup>.

**Descemet Membrane:** The descemet membrane is not visualized under CCM, corresponding to an acellular layer between the posterior stroma and the endothelium<sup>25</sup>.

**Corneal endothelium:** The endothelium appears at CCM with the hexagonal pattern of the endothelial cells disposition (Figure 4) with a shining cytoplasm, dark cellular walls and invisible nuclei.

### CLINICAL APPLICATIONS

CCM had a very significant impact on the diagnosis and therapeutical evaluation of different corneal pathologies. CCM evaluates the endothelium (Figure 5) even in the presence of corneal edema or moderate opacities, which are extremely difficult to evaluate when using specular biomicroscopy.

In the dry eye syndrome (Figure 6) CCM detects and quantifies epithelial alterations, inflammatory and immune cells, corneal nerves, keratocytes and Meibomian

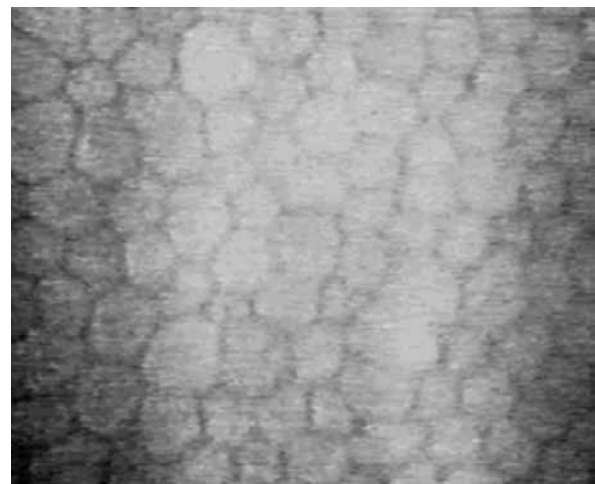


Figure 4. Corneal endothelium. CRIO – CHUC.

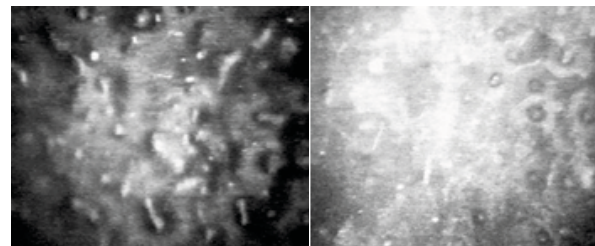


Figure 5. *Guttatas* in Fuchs dystrophy. CRIO – CHUC.

gland evaluation. Through the ability to evaluate subclinical findings, we can stratify the patients at an early stage, which seems an asset for the planning and performance of clinical trials.

CCM may be used in the evaluation of pathologies which induce corneal deposits such as amiodarone-induced keratopathy<sup>26</sup> (Figure 7), cystinosis<sup>27,28</sup>, quinolones<sup>29</sup> or amyloidosis<sup>30-33</sup> and also in rarer conditions such as silver<sup>34</sup> or chloroquine<sup>35</sup> deposits.

In LASIK – *laser in situ keratomileusis*, CCM has been useful in the evaluation of flap thickness<sup>36</sup>, nervous regeneration, interface particles (Figure 8), diffuse lamellar keratitis<sup>37,38</sup> (Figure 9) and in the evaluation of keratocyte density.

After penetrating keratoplasty (Figure 10), at the immediate post-surgery period, activated keratocytes may be observed, with a honeycomb distribution pattern and high haze. In the third month, this keratocyte activation is frequently observed and they remain organized in the aforementioned pattern. We can also observe a significant decrease in the keratocyte density in all the stromal layers, as well as the presence of thinner, curvilinear nervous fibers with abnormal branching (Figure 11).

These studies enabled us to conclude that the normal architecture of corneal nerves is absent even after corneal sensitivity recovery<sup>39</sup>. After the cross-linking of corneal collagen induced by riboflavin stimulation through ultraviolet-A radiation, CCM reveals a honeycomb pattern in the anterior stroma but no endothelial alteration. Total stromal recovery within six months after surgery can be observed<sup>40,41</sup> (Figure 12).

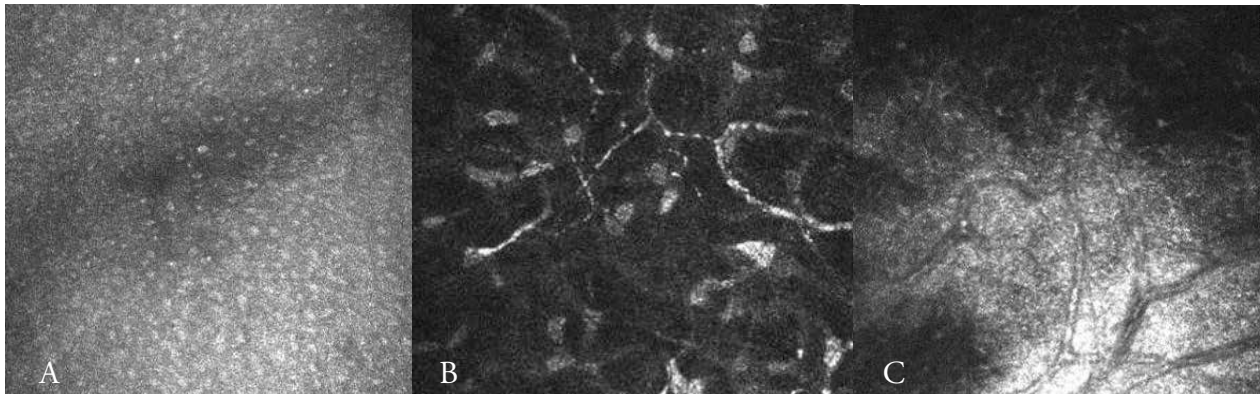


Figure 6. Dry eye syndrome: (A) corneal metaplasia, with increase in cellular size, nuclear activation and decrease in nucleus/cytoplasm relation; (B) abnormal deviation of corneal nerves; (C) neovessels. CRIO – CHUC.

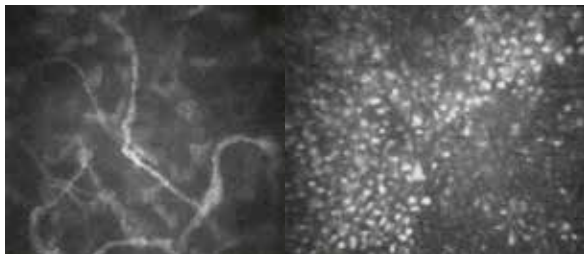


Figure 7. Amiodarone-induced keratopathy stage 3: left – stromal nerves with irregular morphology; right – basal epithelium with shining hyper-reflective intracellular deposits. CRIO – CHUC.

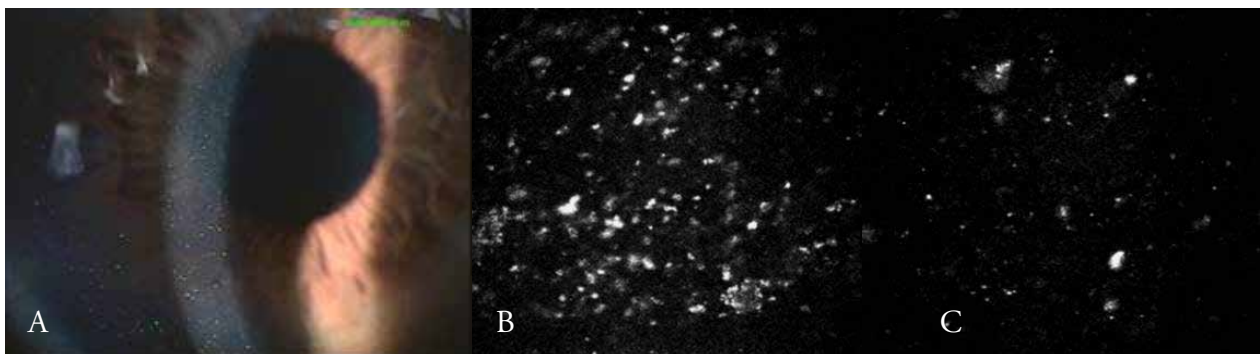


Figure 8. LASIK: (A) interface particles with biomicroscopy examination; (B) CCM examination after 8 days; and (C) after 3 months. CRIO – CHUC.



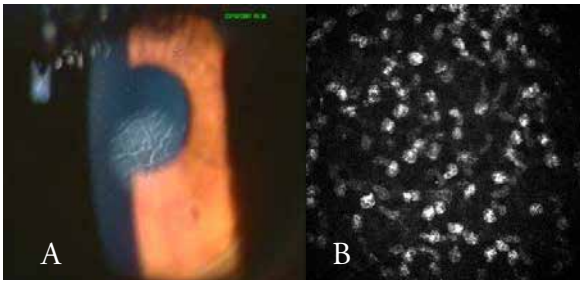


Figure 9. Diffuse lamellar keratitis stage 3: (A) biomicroscopy examination; (B) CCM examination with round/oval cells and eccentric hyper-reflective nuclei. CRIO – CHUC.

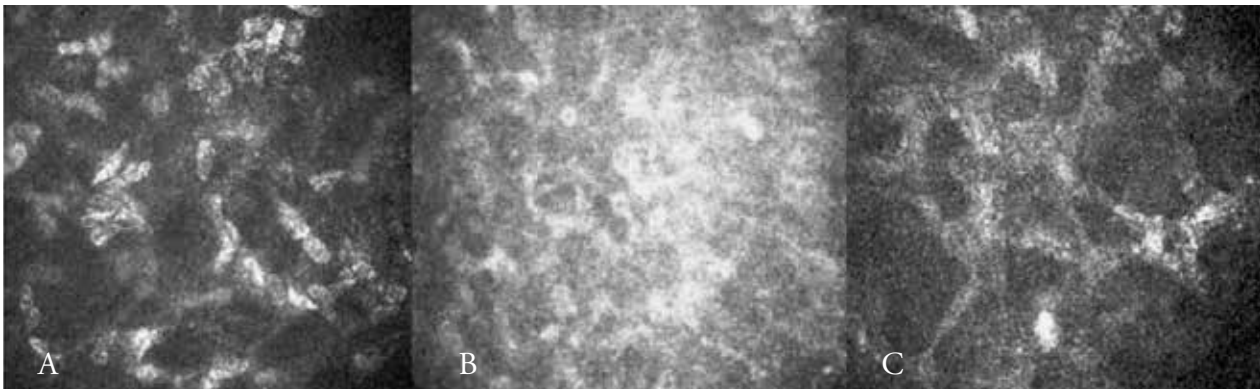


Figure 10. Penetrating keratoplasty: on the 3rd day after surgery we can observe activated keratocytes (A) and high haze (B). In 3 months we can still observe a honeycomb pattern (C). CRIO – CHUC.

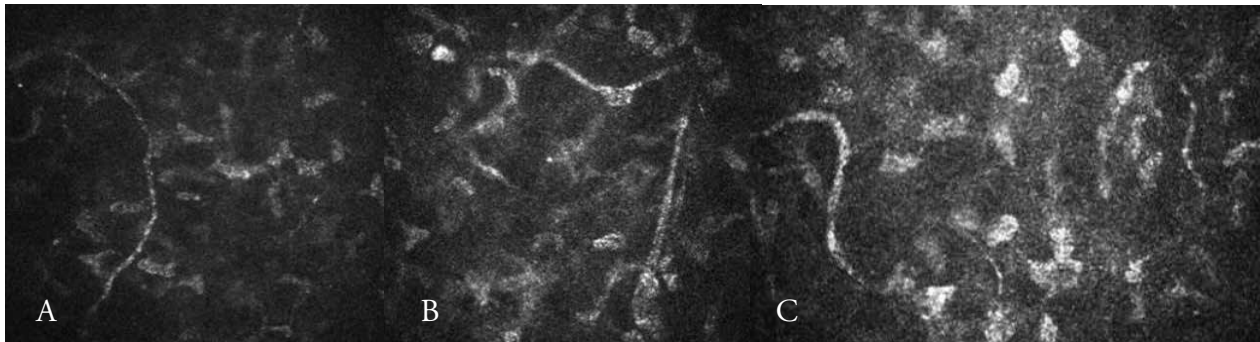


Figure 11. Corneal nerve regeneration seven years after penetrating keratoplasty: (A) thin nerve fiber; (B) and (C) fibers with increased tortuosity. CRIO – CHUC.

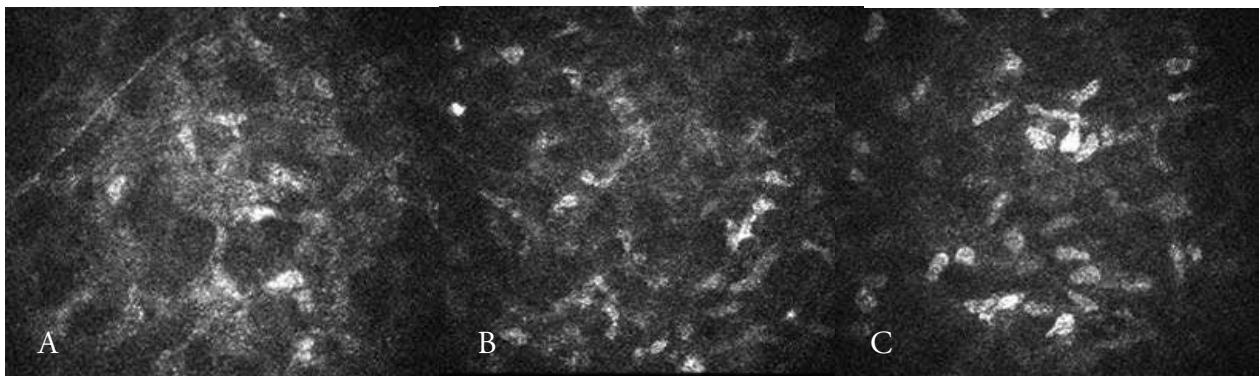


Figure 12. Corneal crosslinking: (A) in the 1st month we observe keratocyte density decrease and also edema; (B) after 3 months we see the beginning of the stromal repopulation by keratocytes and sub-clinical haze; (C) after 6 months the keratocyte density is normal, though we can still see some activated keratocytes. CRIO – CHUC.

CCM *in vivo* is used for the post-surgical evaluation of intrastromal rings<sup>42</sup> (Figure 13). The deposits located in the ring implantation channel and in adjacent stroma are particularly evaluated<sup>43</sup>.

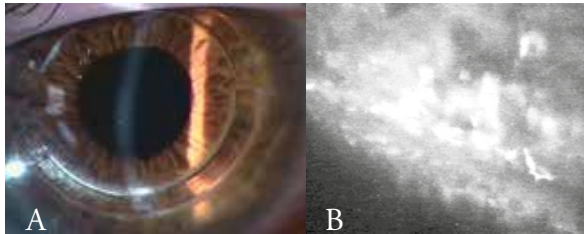


Figure 13. (A) Intrastromal rings 8 months after surgery; (B) CCM shows the presence of deposits in the ring channel and surrounding stroma. CRIO – CHUC.

Several studies use CCM in the evaluation of infectious and non-infectious keratitis such as Thygeson's punctate keratitis<sup>44</sup>, central toxic keratitis<sup>45</sup> and Mooren's ulcer<sup>46</sup>. In herpetic keratitis, CCM detects the alteration of corneal nerves<sup>47</sup> and the inflammatory component<sup>48</sup> of the disease. Epithelial infiltration by inflammatory dendritic cells, stromal involvement with focal and diffuse infiltrates, density decrease of sub-basal plexus nerves and loss of endothelial cells can be observed.

CCM is extremely useful in the diagnosis of atypical herpetic keratitis, since it enables us to infer the diagnosis through the presence of imaging signs, a much faster process than conventional fungal and acanthamoeba cultures. The differential clinical diagnosis in acanthamoeba keratitis is particularly difficult, mostly in herpetic keratitis. CCM contributes towards an early diagnosis allowing the imaging of trophozoites and the double cysts wall (Figure 14), as we have also demonstrated<sup>49-55</sup>. As this pathology implies long treatments, CCM has a paramount role in therapy monitoring, since it is a quick, non-invasive examination that can be repeated whenever needed. CCM has shown high sensitivity and specificity in fungal keratitis diagnosis<sup>49,56,57</sup>. Under CCM, fungi are characterized by hyper-reflectivity and filamentary structure as is the case with *Fusarium*<sup>58</sup>, or intra-epithelial opacities, as in microsporidium infection<sup>59,60</sup> (Figure 15). The evaluation of antifungal therapeutic efficacy may be performed using CCM<sup>59</sup>.

In the literature there are several other studies concerning the evaluation of therapeutic efficacy when using CCM. In our study, we found that the use of topical mitomycin C 0.02% in PRK, for a maximum period of 15 seconds, does not affect endothelial cell density<sup>61</sup> and does not induce keratocyte alterations when compared to standard PRK<sup>62</sup>.

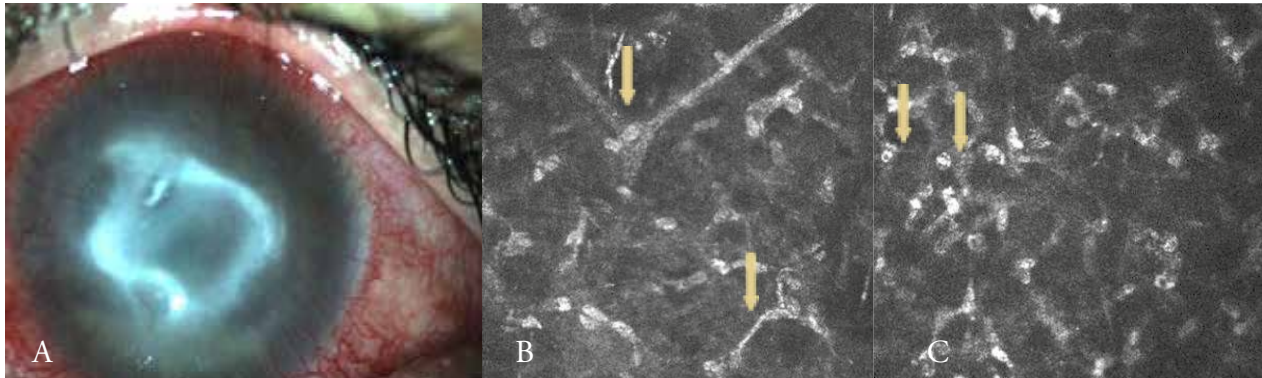


Figure 14. Acanthamoeba keratitis: (A) biomicroscopy image showing the ring-shaped stromal infiltrate; (B) radial keratoneuritis and dendritic cells; (C) cysts in anterior stroma. CRIO – CHUC.

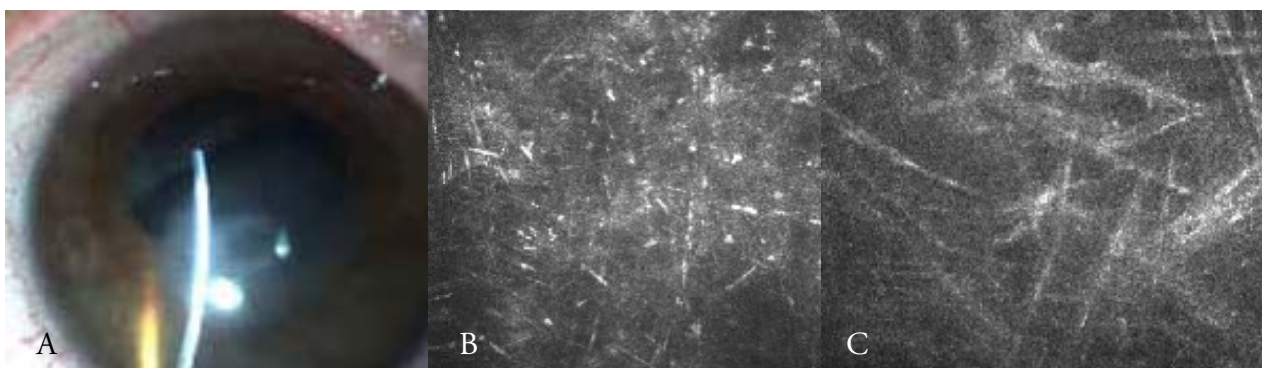


Figure 15. Fungal keratitis: (A) biomicroscopy; (B) hyphae, hyper-reflective filaments with 4-8  $\mu\text{m}$  thickness; (C) hyphae. CRIO – CHUC.



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# XVI. LASER In Research

## 88. Pupillometry



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### INTRODUCTION

Pupils control the amount of light entering the eye. Their motility is dependent on the contraction of the iris sphincter, under parasympathetic enervation, and the iris dilator, controlled by sympathetic nerves.

The pupillary light reflex (PLR) is a four-neuron arc (Figure 1) and its assessment reflects the integrity of the retina, optic nerve, brainstem and autonomic nervous system.

Besides retinal luminance, other factors, such as accommodative state, age and emotional condition<sup>1</sup>, as well as drugs and medications, may influence the pupillary diameter.

Pupillometry, studying the pupil response to light and its redilation, as well its diameter in different light conditions, is a non-invasive, objective method of assessing pupil dynamics, including relative afferent pupillary defect.

First established in the 1960s, in Psychology and Psychiatric studies<sup>2</sup>, pupillometry is used in research and clinical practice in Ophthalmology.

Several pupillometers (such as the Espion V6, see Fig. 2), testing one or both eyes simultaneously, use infrared light and video eye-tracking system, allowing pupil visualization and measurement in the dark, without causing unwanted pupillary constriction by ambient light. Evaluated parameters, after a period of dark adaptation, may include baseline pupil diameter; latency of contraction and dilation; initial, minimum, maximum and mean pupil diameter; amplitude of contraction and dilation speed.

### RETINAL AND OPTIC NERVE PATHOLOGY

Many studies have been performed in different retinal and optic nerve pathologies, since this is an objective measurement of neural dysfunction, serving as a complement to other techniques such as electroretinography: these include retinitis pigmentosa<sup>3</sup>, multiple sclerosis and optic neuritis<sup>4</sup>, dominant optic atrophy<sup>5</sup>, glaucoma<sup>6,7</sup>, anterior ischemic optic neuropathy<sup>8</sup>, Leber hereditary optic neuropathy, among

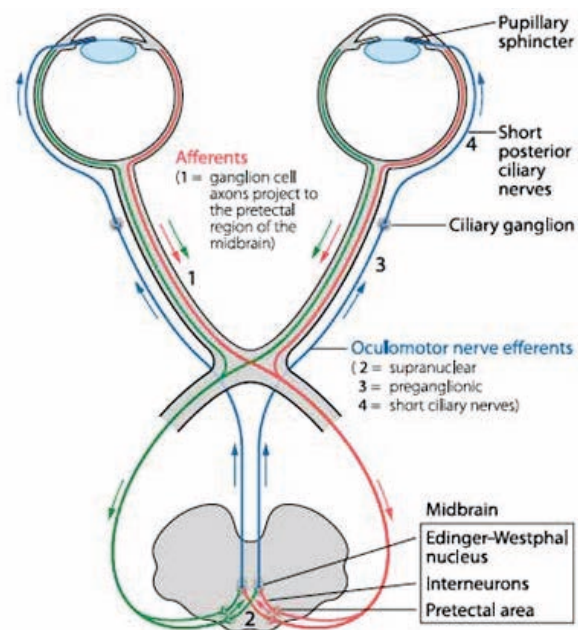


Figure 1. Anatomy of the pupillary light reflex. Retinal ganglion cells (1) carry information through the optic nerve to one of the pretectal nucleus (2) in the dorsal midbrain, after decussation of half the fibers at the level of the optic chiasm. Interneurons project from the pretectal area to the Edinger-Westphal subnucleus (EWN) of the oculomotor cranial nerve, on both sides of the midbrain, giving rise to bilateral pupillary constriction with unilateral light presentation (consensual reflex). Neurons from the EWN (3) innervate the ciliary ganglion, from which the short posterior ciliary nerves arise and innervate the iris sphincter. Not shown here, cortical afferents are responsible for the near reflex, whose center is probably more ventrally located than the pretectal nucleus. Adapted from Clinical Neuro-Ophthalmology. A Practical Guide. Schiefer U, Wilhelm H, Hart W. Springer. 2007. (Published with permission and courtesy of H.Wilhelm and B.Wilhelm and Springer Science and Bus Media B V provided by Copyright Clearance Center)



Figure 2. Espion V6 pupillometer.

others. Also, pupillometry has been used in monitoring response to gene therapy in diseases like choroideremia<sup>10</sup> and Leber congenital amaurosis<sup>11</sup>.

Several works using chromatic pupillometry<sup>3,8,9</sup> have helped studying different cell populations involved in the PLR. Intrinsically photosensitive retinal ganglion cells (ipRGCs, also called melanopsin-expressing retinal ganglion cells), containing the photopigment called melanopsin, serve the majority of the PLR and are also involved in the circadian rhythm and melatonin production. These cells are able to produce a sustained post-illumination pupillary contraction after being stimulated by a high-intensity blue light (480 nm), lasting up to 30 seconds.

Cones and rods also contribute to the PLR; rods respond to low-intensity blue light and cones to red light (660 nm), causing a fast pupillary response, as opposed to ipRGC.

By controlling the different wavelengths of the exposing light, one is capable of understanding which cell subpopulation/s is/are mostly affected in different conditions.

### REFRACTIVE SURGERY

Measurement of the pupil diameter in mesopic and scotopic conditions is part of the pre-operative assessment for corneal and intra-ocular refractive surgery; larger pupil diameters increase the risk of halos and glare, especially if smaller ablation zones are used.

Monocular and binocular devices have been manufactured, with the former leading to, theoretically, increased pupil

diameter due to less amount of light entering the eye<sup>12,13</sup>. Also, devices that do not allow for patients to fixate a distant target may induce artificially smaller pupils.

Monocular, handheld devices include the NeurOptics (Figure 3), Pupilscan and the Colvard pupillometer, the latter using light amplification technology.

Procyon has developed a binocular pupillometer (Figure 4), using an infrared video system, allowing correction for accommodation and ametropias. Corneal topographers and wavefront analyzers may also measure pupil diameter binocularly but often induce pupillary constriction because of near targets for fixation; newer aberrometers and autorrefractors, such as WAM 5500 Binocular Accommodation Instrument, may give a truer pupil size by avoiding accommodating targets.



Figure 3. NeurOptics monocular pupillometer.





Figure 4. Procyon binocular pupillometer.

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# XVI. LASER In Research

## 89. Adaptive Optics



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### INTRODUCTION

Adaptive optics (AO) is a relatively new technology, the main purpose of which is to improve the performance of optical systems by reducing the effects of optical aberrations. It was first envisioned in 1953 by Horace W. Babcock<sup>1</sup> to minimize the effects of atmospheric distortion in ground-based astronomical telescopes and laser communication systems. Its working principle is based on the deformation of a mirror that compensates for wavefront distortions. More recently, this technology has been extended to ophthalmology.

In 1994, Dr. Josef Bille and his team<sup>2</sup> at Heidelberg were the first to apply this type of wavefront technology to the eye by creating the first Shack-Hartman wavefront sensor. The first working AO technology applied to optical imaging systems was presented by Liang, Williams & Miller<sup>3</sup> in 1997 and since then, development and interest continues to increase. AO applications in ophthalmology can be divided broadly into two fields, retinal imaging and testing visual function, which will be reviewed in this chapter.

### PRINCIPLES OF ADAPTIVE OPTICS

The human eye functions as a complex optical system, the purpose of which is to converge image-forming rays onto the retina, allowing us to see. In a perfect optical system, image-forming rays are planar and converge onto a single point. However, we know the eye is not a perfect optical system and that distortions in the wavefront passing through the pupil, known as optical aberrations, occur.

Aberrations impair both the quality of the image formed in the retina and the images taken of the retina by ophthalmic imaging cameras. Correction of low-order aberrations such as myopia, hyperopia and astigmatism, which account for most of the overall wavefront aberration of the eye, has long been achieved in the majority of the population with spectacles, contact lenses and refractive surgery. In contrast, high-order aberrations such as coma, spherical aberration and trefoil account for less than 10%

of the total variance of the wavefront aberration of the eye, but their correction is needed to achieve cellular-resolution imaging. With the advent of AO, monochromatic aberrations beyond defocus and astigmatism were finally able to be corrected<sup>4,5</sup>.

Ophthalmological AO technology works by measuring and correcting ocular aberrations in real time using three components: a wavefront sensor, a corrective element and a control system. The Shack-Hartmann wavefront sensor is the most commonly used to measure ocular aberrations. It uses a two-dimensional array of small lenses that samples the local portion of the incident wavefront at different pupil locations and focuses it onto a charge-couple device. The position of these convergence spots is then calculated with an algorithm and any displacement from its reference position is directly related to the slope and amplitude of the wavefront. A phase modulator such as a deformable mirror corrects the measured aberrations. Some systems have multiple corrective elements, one for low order aberrations and a second one for higher order aberrations. Finally, a software system programmed with a computer controls the interaction between the wavefront sensor and the corrective element (Figure 1).

### ADAPTIVE OPTICS IN RETINAL IMAGING SYSTEMS

The retina is an anatomically layered structure that is frequently affected by both primarily ocular and systemic diseases. Thus, the ability to properly image the retina, and the development of new optical technology for analyzing its images has been an area with exponential growth.

AO technology, by compensating for aberrations in the optical path and providing a nearly diffraction-limited imaging, has changed the way we view the retina by allowing us to image the living retina with a microscopic resolution<sup>6</sup>. Until now, AO has been successfully integrated with three ophthalmic imaging technologies – conventional fundus cameras, scanning laser ophthalmo-

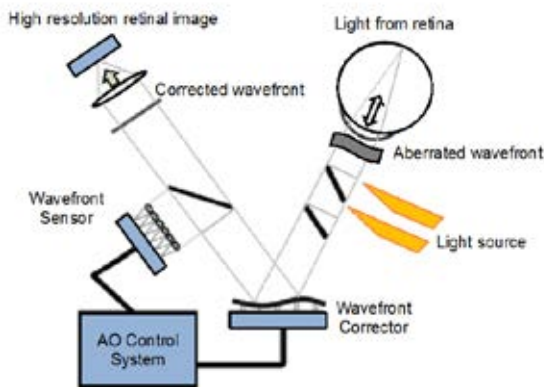


Figure 1. Basic layout of an AO retinal imaging system.

scopy (SLO) and optical coherence tomography (OCT).

### 1. FUNDUS CAMERA

The first AO fundus camera was developed in 1997 and it provided retinal images previously only accessible by histology. By using a deformable mirror it was possible to view *en face* images of the retinal layer with unprecedented transverse resolution showing photoreceptors, retinal vessels and nerve fiber bundles. Current AO cameras use a superluminescent diode to illuminate the retina and a high speed CCD for faster modulation and efficiency<sup>7</sup>.

### 2. SCANNING LASER OPHTHALMOSCOPE

SLO is a technique that acquires images by raster scanning an imaging beam on the retina and measuring the backscattered light intensity. By applying AO technology to SLO (AOSLO) it operates similarly to confocal microscopy<sup>8</sup>. A pinhole is used in front of the light detector to exclude light not originating from the retinal focal plane to avoid ocular aberrations. This provides an *in vivo* imaging of the human retina allowing visualization of the different layers and even quantitative measures of cone physiology<sup>9</sup>, imaging of the retinal vasculature and nerve fiber bundles<sup>10</sup>. Although AOSLO provides less axial resolution than OCT, it provides a greater accuracy for eye tracking<sup>11</sup> so a combination of both methods has recently been attempted.

### 3. OPTICAL COHERENCE TOMOGRAPHY

The combination of AO and OCT has arguably been one of the most beneficial in terms of imaging of the posterior segment of the eye<sup>12</sup>. AO technology has been applied to all major OCT designs, increasing lateral resolution, reducing speckle size and increasing the sensitivity to weak reflections resulting in the capability of three-dimensional cellular imaging of the retina with a resolution of  $3 \times 3 \times 3 \mu\text{m}$ <sup>13</sup>. The main focus has been on imaging the cone photoreceptor mosaic<sup>14,15</sup>, the retinal pigment epithelium, retinal vasculature and also the retinal nerve fiber layer and lamina crivosa<sup>16</sup>. This has allowed the study of a number of clinical conditions such as inherited retinal degenerations<sup>17</sup>, age-related macular degeneration, diabetic retinopathy<sup>18</sup>, retinopathy of prematurity

and optic neuropathies<sup>19,20</sup>.

### ADAPTIVE OPTICS IN THE TESTING OF VISUAL FUNCTION

Compared to AO imaging technology, the development of new AO systems for vision testing applications has been slower. However, AO vision testing has been used as a valuable research tool. By using technology to compensate for aberrations in the optical path, AO allows a never before seen imaging and microscopic control of the visual retinal stimuli, creating the potential to explore the neural limits on vision much like electrophysiologists have done with electrodes. Early experiments have shown that correction of monochromatic aberrations results in improved contrast sensitivity and visual acuity<sup>21,22</sup>. These experiments have been used to try to improve corneal ablation laser patterns for refractive surgery but the visual benefits of correcting aberrations have been difficult to prove.

### APPLICATIONS AND FUTURE DIRECTIONS

AO has already been established as an important research tool worldwide which is evident by the growing number of publications and experiments using this technology. Nevertheless, it has not achieved widespread clinical use mainly because of the high cost of commercial prototypes but also due to the complexity of the systems used and the time required to obtain, process and analyze the retinal images.

It is expected that AO technology will soon translate into clinical applications. By providing high-resolution retinal imaging, one can expect new information on microstructural retinal pathologic changes previously only visible with histology. This may be the key to detect early signs of retinal diseases as well as tracking disease progression and monitoring *in vivo* the effects of therapies at a cellular level<sup>23</sup>.

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# XVI. LASER In Research

## go.Clinical

## Applications of

## Intraoperative OCT



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The widespread adoption of optical coherence tomography (OCT) has transformed the clinical care of ophthalmic diseases. The outstanding cross-sectional anatomical information acquired with OCT has optimized the diagnosis, surveillance and treatment paradigms for both anterior and posterior segment diseases. The translation of this technology to the operating room may have profound implications for the optimal surgical management of ophthalmic diseases<sup>1</sup>.

Over the last few years, there have been significant advances in integrative technology for intraoperative OCT (iOCT). This has resulted in the development of multiple microscope-integrated systems and a rapidly expanding field of image-guided surgical care<sup>2</sup>.

The ZEISS RESCAN 700 OCT engine SD OCT (spectral domain) is a wavelength 840 nm Class 1 laser device, according to IEC 60825-1:2001, with a scanning speed of 27,000 A-scans per second, scan parameters A-scan depth: 2.0 mm in tissue, axial resolution: 5.5  $\mu\text{m}$  in tissue. This device allows real-time reassurance during retinal surgery, when coupled with ZEISS OPMI LUMERA 700 and the non-contact fundus viewing system ZEISS RESIGHT Family<sup>3</sup>.

Indeed, the prototype microscope-integrated iOCT system includes a heads-up display system, external video display panel and foot pedal control of the OCT scanner<sup>4</sup>. Intraoperative OCT is an emerging technology and its use has been described for a wide variety of conditions and procedures, including vitreomacular interface diseases, retinal detachments, lamellar keratoplasty, glaucoma surgery, cataract surgery and retinopathy of prematurity, providing the surgeon with information that would otherwise be unavailable through the *en face* view of the microscope with rapid feedback and minimal disruption to the surgical flow<sup>1,4</sup>.

Nowadays, prospective clinical studies have already been published reporting the role of iOCT toward better understanding the pathophysiology of diseases and tissue alterations that occur during surgical manipulations. The use of an iOCT can expand upon visual cues during surgery, helping in the decision-making process and allowing additional deliberate surgical maneuvers aimed at improving surgical outcomes<sup>1,2,4-6</sup>. In fact, the PIONEER and DISCOVER studies both demonstrated a potentially significant percentage of cases in which iOCT altered surgical decision-making in both anterior and posterior segment surgery<sup>2</sup>.

According to the PIONEER study, which involved 531 eyes (275 anterior segment cases and 256 posterior segment cases), the surgeons' feedback indicated that iOCT informed surgical decision making and altered surgeon understanding of underlying tissue configurations in 48% of lamellar keratoplasty cases and 43% of membrane peeling procedures. The iOCT demonstrated a finding disparity in the surgeon's assessment and definitively changed surgical management in 9% and 8% of lamellar keratoplasty and epiretinal membrane peeling cases, respectively<sup>1</sup>.

The DISCOVER study, which included 227 eyes (91 anterior segment cases and 136 posterior segment cases), concluded that the iOCT data provided information that altered the surgeon's decision-making in 38% of cases of lamellar keratoplasty and in 19% of cases of membrane peeling procedures.

Current areas of exploration and development include OCT-compatible instrumentation, automated tracking, iOCT software platforms, and surgeon feedback/visualization platforms<sup>2</sup>.

The intraoperative imaging presented in this chapter was obtained using the RESCAN 700. The system is based



on the LUMERA 700 (Carl Zeiss Meditec) platform. Anterior segment imaging was achieved with the standard microscope viewing system. For posterior segment imaging, the RESIGHT 700 lens system or a contact lens was used for surgical and iOCT visualization.

### I- CLINICAL APPLICATIONS OF iOCT IN ANTERIOR SEGMENT SURGERY

#### Deep Anterior Lamellar Keratoplasty (DALK)

Intraoperative OCT enables real-time visualization of all the surgical steps of the DALK procedure, such as trephination depth and proximity of the cannula tract to Descemet's membrane, assessment of the Descemet's membrane position and its integrity after the attempted big-bubble delivery and assessment of graft-host apposition<sup>7,8</sup> (Figure 1).

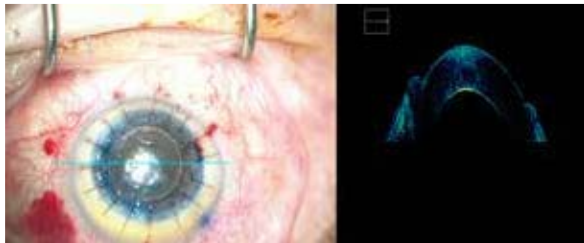


Figure 1. Anterior segment iOCT: surgical view of final graft-host apposition. Courtesy of Madhavan Rajan, MD.

#### Cataract surgery

Intraoperative OCT was found to be beneficial during all critical steps of cataract surgery, enabling assessment of wound morphology in clear corneal incisions (Figure 2), wound gaping at the end of surgery, adequacy of stromal hydration, subclinical Descemet's detachments, adequate groove depth and evaluation of the final position of the intraocular lens in the capsular bag<sup>9</sup>.

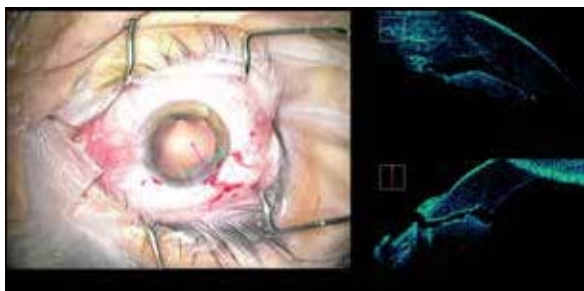


Figure 2. Anterior segment iOCT: surgical view of triplanar clear corneal incision.

### II – APPLICATION OF iOCT IN GLAUCOMA SURGERY

Intraoperative OCT is useful in glaucoma surgery, especially involving non-penetrating surgical techniques: it helps the surgeon to find the right plane to create the trabeculodescemet membrane, it allows for non-contact evaluation of Schlemm's canal localization and non-contact evaluation of suture tension.

In penetrating glaucoma surgery, iOCT is useful in determining the depth of the scleral dissection (Figure 3), the intrastromal bed, the release of peripheral anterior synechia and the efficacy of needling with respect to breakage of loculations<sup>10</sup>.

When the surgery involves long tube devices implantation iOCT permits the surgeon to visualize the path of the valve tube<sup>10</sup>.

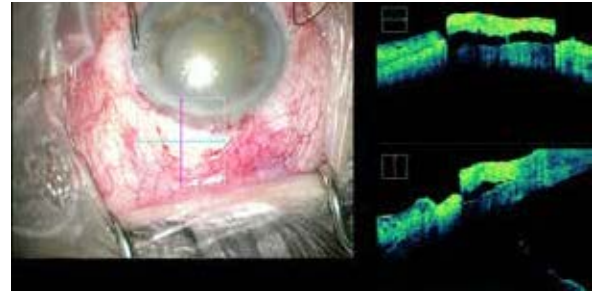


Figure 3. Anterior segment iOCT: surgical view of the scleral flap, depth of the scleral dissection and the intrastromal bed. (Courtesy of Cláudia Gonçalves, MD)

### III – APPLICATION OF iOCT IN POSTERIOR SEGMENT SURGERY

#### Epiretinal Membrane (ERM), Vitreomacular Traction (VMT) and Macular Hole (MH) surgery

The most commonly reported impact of the iOCT in ERM surgery is related to the completeness of the membrane peel, as it helps reveal residual membranes<sup>1</sup> (Figure 4).

Additionally, alterations in the outer retinal architecture were noted with observation of the expansion between the ellipsoid zone and the retinal pigment epithelium after peeling<sup>11</sup>.

According to the PIONEER study in 10 of 81 cases (13%) in which the surgeon believed that the membrane peeling was complete, iOCT revealed residual membranes that resulted in additional peeling. In 94% of the cases, when the surgeon was unsure if membrane peeling was complete, iOCT provided the definitive answer. Overall, the iOCT gave an answer that definitively reversed surgical decision-making in 13% of the cases. The iOCT information following membrane peeling gave information that impacted the surgeon's understanding of the completion of surgical objectives and potentially impacted surgical decision-making in 41% of the cases<sup>1</sup>. In a study by Falkner-Radler and colleagues that included 51 patients with ERM, 8 of those having additional lamellar macular holes, 11 having VMT and 8 patients with full-thickness macular holes (FTMH), iOCT enabled membrane peeling to be performed without using retinal dyes in 40% of cases<sup>12</sup>.

In cases of VMT surgery, iOCT confirms the release of traction and may identify subclinical changes (e.g. occult FTMH) that may impact surgical decision-making<sup>1,13</sup>.

Using iOCT imaging in FTMH enables identification of changes in hole architecture, residual internal limiting membrane as well as expansion of the ellipsoid zone to RPE height that is noted after membrane peeling<sup>1,14</sup>.

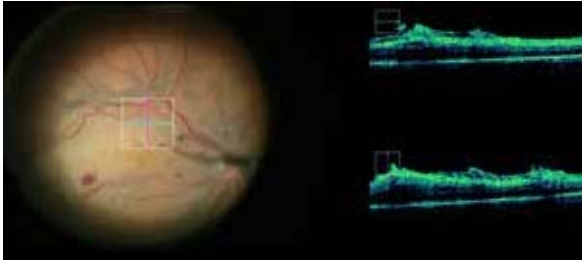


Figure 4. Posterior segment iOCT: surgical view following membrane peeling, revealing a residual membrane. (Courtesy of Lurdana Gomes, MD)

### Retinal Detachment (RD) surgery

The iOCT is helpful in RD surgery, providing extra information, such as the detection of otherwise invisible membranes, the location of small tears, identification of the retinal plane under suboptimal conditions and identification of variable amounts of residual subretinal fluid following perfluorocarbon liquid placement<sup>1,15</sup>.

In a consecutive case series study that included nine eyes of nine patients with macula-off RD operated by a single surgeon, iOCT clearly demonstrated the presence of submacular fluid (SMF) at the beginning of the surgery, macular flattening under perfluoro-n-octane (PFO) in all eyes, small residual SMF under PFO in six of the nine eyes and increased occult SMF following air-fluid exchange in all the eyes (Figure 5). The confirmation of persistent occult SMF demonstrates a pathophysiological rationale for initial face-down positioning after retinal detachment repair<sup>16</sup>.

In another study that evaluated microarchitectural changes that occur during intraoperative repair of RD, the iOCT demonstrated significant alterations in foveal configuration, including the formation of macular holes and persistent subretinal fluid. These features may help to prognosticate outcomes<sup>17</sup>.

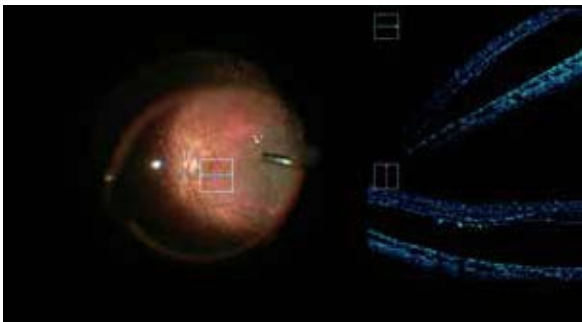


Figure 5. Posterior segment iOCT: surgical view of persistent occult SMF after macula-off RD repair.

*Note: Our special thanks to all who provided images.*

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# XVII. Good Practices in Medical LASER

## 91. LASER safety and risk management



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The ISO 31000 standard<sup>1</sup> addresses the organizations risk management in a global perspective, noting that there may be positive risks (opportunities) and negative risks (threats). Either one or the other should be analyzed and "treated" conveniently assuring the organization's sustainability. The positive risks allow us to lead the processes for favorable activities and avoiding risks. This allows avoiding damages, losses, accidents which will have a negative impact on the organization. If ophthalmologists and organizations do not use medical lasers in accordance with good practice, they may be responsible for an accident that will cause harm to the patient, medical personal, give the organization a bad name and it could have huge financial impact by the responsibility for the accident. Therefore, it is important to (Figure 1):

1. Identify the risk and declare it as such (positive or negative);
2. Evaluate the risk and prioritize it;
3. To plan and schedule risk minimization actions;
4. Track and report their results;
5. Take control measures (actions deemed appropriate to improve);
6. Learn from this action: to acquire concepts and improve processes).

### 1. SIGNALING AND EVALUATION OF HAZARDS AND RISKS

It is imperative to assess all potential hazards and risk of exposure related to high levels of laser emission. In addition, it is necessary for both users and operators to understand all the complexity regarding the laser rationale. Many clinicians who choose to work with lasers, without a consistent knowledge are unable to perform risk assessment on a daily operational basis, and are therefore, jeopardizing the safety of everyone involved. In fact, safety is only



Figure 1. The 6 steps of the risk management concept as referred by ISO 31000 standard.

ensured when everyone has adequate understanding and experience of laser dynamics and complexity<sup>2-8</sup>.

### Laser knowledge

Knowledge of lasers includes:

1. Features of laser light;
2. Properties of each laser wavelength;
3. Absorbing chromophores of each wavelength (selective photothermolysis);
4. Dosimetry (power, power density, pulse parameters, fluence, energy density, etc);
5. Spot size, delivery systems and instrumentation;
6. Application (medical and surgical) techniques.

Once these attributes are well understood, the clinician can anticipate potential hazards. Hazards are all of those potentially dangerous conditions that are associated with an unanticipated interaction or exposure of tissues or

materials to laser energy.

All persons who are in the laser treatment room have the risk of eye exposure when working with a Class 3b or Class 4 healthcare laser system. If not protected, people may suffer damage to several ocular anatomic structures or skin, depending on the laser wavelength beam. There are several risks for all technicians involved (physician, assistant, nurse practitioner, patient, patient support person, technician office manager, laser safety officer (LSO), scrub nurse and biomedical engineer). Relevant risk approach and its management according ISO 31000 in a sensible and proper manner, often at lower cost to the user, provides the level of safety and protection for all concerned.

## 2. IMPLEMENTATION OF THE CONTROL ACTIONS

Control actions consist in all measures taken by healthcare team to prevent exposure to identified hazards. Once hazard based risks are identified, and the potential of exposure to those risks assessed, the user can develop and implement control measures.

These measures translate into policies and procedures, that have clear statements of scope (who is affected by the policy), rationale (why it is necessary), who is responsible for implementation and enforcement, and methods for on-going monitoring<sup>2-8</sup>.

**There are three categories of control measures:**

- A. Engineering controls** are the inbuilt safety features supplied by the manufacturer in compliance with International Electrotechnical Commission (IEC) and Food and Drug Administration (FDA) guidelines;
- B. Procedural controls** are the policies and measures in healthcare facilities;
- C. Administrative controls** are the infrastructures of the laser safety program.

### A. Engineering controls

These include but are not limited to: guarded footswitch, audible and visible emission indicators, stand-by control, emergency off control, housing interlocks and beam attenuators.

### B. Procedural control measures

These are operational activities, specific to equipment and practice, and include but are not limited to: ocular protection, flammability hazard prevention, controlled access, management of plume, control of electrical hazards and control of the delivery system and beam emissions.

Controlling hazards in the laser treatment room depends on: controlled access to the room and equipment, proper use of personal protective devices, monitoring testing and operations of the laser and vigilance by each laser team member.

### Controlled Access

Controlled access is based on the identification of the nominal ocular hazard area (NOHA), or in American Standards, called the Nominal Hazard Zone (NHZ). The NOHA is a mathematical calculation, resulting in an area around the laser, within which laser hazards may exist

and protective measures are required.

The maximum permissible exposure (MPE) value is a mathematical calculation based at variables including wavelength, power, distance and time of exposure, which results in the amount of time (usually milliseconds) an unprotected eye can be exposed to laser radiation without causing injuries.

All these values should be explicit in the documentation made available by the laser manufacturer, they can be calculated by the LSO, or the LSO can designate the entire room as the controlled area.

A controlled access area is, for example, a treating room where the ophthalmologist can have access to a photothermal laser assembled to a slit lamp for treating their diabetic patients or an operating room where endophotocoagulation with optic fiber delivery laser system or a CO2 laser device could be used. The first room, because the type of laser system coupled to the slit lamp and oriented to a rough wall, has fewer safety concerns comparing with the operating room. In this particular room, the delivery laser system allows the laser beam take every direction in the space. The LSO should evaluate and determine the right safety procedures in each situation.

Standards indicate procedures for maintaining a controlled access area. Several key points are listed below (Table 1):

Table 1. Procedures for maintaining a controlled access area. Several key points

1. Regulation warning signs (must comply with specific countries' standards), posted visibly, at eye level, on each entryway into the NOHA and removed or not when use of the laser is completed.
2. Appropriate protective eyewear for laser in use is placed with the warning signs at each entryway. These are posted for staff to use in case of emergency entry into the laser room and are removed from the entryways only at the conclusion of the procedure.
3. Windows are covered with blinds, shades or other non-flammable barriers that reduce transmission of the beam to acceptable levels below the MPE for laser wavelengths that can penetrate glass.
4. Everyone within the NOHA is authorized by the LSO.
5. Doors are kept closed, but never locked during laser use.

Control of access to all devices is accomplished by key storage away from the console. Protective eyewear, corresponding to the laser in use, should be available at the NOHA entryway, to be used by anyone who must enter the laser room in an emergency. Signs should only be posted when the laser is in actual use, and could be removed or covered when the laser is turned off and key removed.

Clinicians should insist on comprehensive staff training in order to respect protocols. Regardless of what equipment is being used, who owns the equipment and the professional staff is responsible for patient advocacy and safety.

### C. Administrative controls

These must be in place before the laser can be used and include: appointment of a LSO, organization of a laser safety committee (LSC), development of documentation



tools, education and training of all personnel, compliance with Occupational Health and Safety rules, development of a formal audit and technical management plan.

### *The Laser Safety Officer (LSO)*

**The LSO is the technician in charge for the management of risk, and the authority to ensure compliance with all applicable standards and rules.** This technician must be competent to assess all systems and certify the skills of all personnel involved in the laser practice.

The LSO is often responsible for technology assessment and advising users on potential laser purchases, as well as on compliance with standards and regulations.

In some situations, especially in a private practice, the physician who owns and runs the practice or clinic seems to be the likely candidate for LSO. Careful analysis of the duties of the LSO must be made before making this decision, keeping in mind that if the laser is to be used by several clinicians, the LSO must be available during use. However, every clinician must be responsible for safety when operating the system.

### *Education and Training*

Education (didactic knowledge) and training (operational skills) provide clinicians with the basic information needed to establish a laser safe environment.

This is an individual responsibility without universal criteria, and with several levels of resources in different regions of the world. It is the responsibility of the individual facility or practitioner to establish acceptable criteria for certification and accreditation, and to approve the candidates.

### *Documentation*

Out of all the "security" procedures, the documentation should become a priority. Without proper documentation, there is no objective or factual sustainable support for that claim. The documentation should be included in the formal audit process.

Laser users are constantly challenged to redefine who they are, what they do, and their scope of practice for each new laser system or application. It must be remembered that each new system requires a new risk assessment and an analysis and review of facility security policies and procedures.

### *Preventive actions/steps*

The implementation of preventive actions in laser medical devices is of vital importance to ensure its correct operation. The lack of these safety procedures in a systematic way can cause serious damage to the equipment as well as for the patient. Below follows a list of several procedures we should take into account (Table 2; also see chapter 92).

## **3. OCULAR HAZARDS AND ADEQUATE PROTECTIVE EYEWEAR**

Class 3b and Class 4 lasers have the potential to damage the eye through both direct and reflected beam, and should **never** be operated without first assessing the need for proper protective eyewear<sup>9,10</sup>.

The classification of the laser is based on whether or not the MPE is longer or shorter than the human aversion

Table 2. Equipment security features

1. Casing of protection	6. Emission Indicators
2. Beam attenuator	7. Conector remote control
3. Output Disconnect	8. Interruptor w / protection
4. Power Meters	9. Optics (protection filters)
5. General control button	10. Labels and Stickers

response. As already referred, MPE is a calculation that determines how long an unprotected eye can be exposed to a laser beam before injury occurs. The aversion response is that autonomic response (within 0.25 seconds) of the eye blinking and moving away from an intense light. The lower classifications (class 1, 2) have extended MPE measurements, and do not require protective eyewear, since the human eye will avert from the bright light long before the beam can injure the unprotected eye. In the case of a higher classification (class 3b-4) the MPE is shorter than the aversion response, and therefore, protective eyewear must be worn at all times during laser activation (Figure 2).



Figure 2. A broken optic-fiber. Note the output of the laser beam from the broken point of the optic-fiber.

Safety procedures, including eye protection, flammability, reflection and administrative control measures, are determined by the classification of the laser. Current classifications have been adopted by the IEC as follows:

**Class 1:** safe under every conceivable condition of use; 1M: safe for viewing without optical aids, but potentially hazardous with magnification aids (microscopes, loupes, binoculars, etc); **Class 2:** Visible wavelengths (400-700 nm) safe if viewed for less than 0.25 seconds; 2M: visible wavelengths (400-700 nm) not safe with optical viewing aids;

**Class 3R:** Marginally unsafe for intrabeam viewing of beams with diameters >7 mm;

**Class 3B:** Unsafe for intrabeam viewing, causing skin and eye injury from direct but not necessarily for diffuse energy;

**Class 4:** High power causing skin and eye injury from direct and reflected energy.



## a. Ocular Hazards

Levels of ocular injury are determined by the interaction with the tissue and absorption chromophores which are present in the structures that are exposed. Delivery systems, power and energy density, and clinical application techniques also contribute to the type and severity of the damage that can occur<sup>9,10</sup>.

Long wavelengths (CO<sub>2</sub> and Er:YAG) are absorbed by water in the tissues, and therefore, can absorb at the tear layer covering the cornea. As the water is vaporized, the beam interacts with the tissues of the cornea to cause burns. Short wavelengths (near infrared through visible range) penetrate through water and can spread through all anterior structures of the eye, absorbing melanin and hemoglobin in the retina, causing permanent damage to central vision. Accordingly, everyone in a laser treatment room, inside the designated controlled area, must wear appropriate protective eyewear at all times when a laser is being applied. An exception to the rule is when the physician is working through a properly filtered microscope, like the slit lamp or the operating microscope (Figure 3). Several criteria listed below should be used to select eyewear with emphasis on the fact that all eyewear must be approved by the LSO (Table 3).

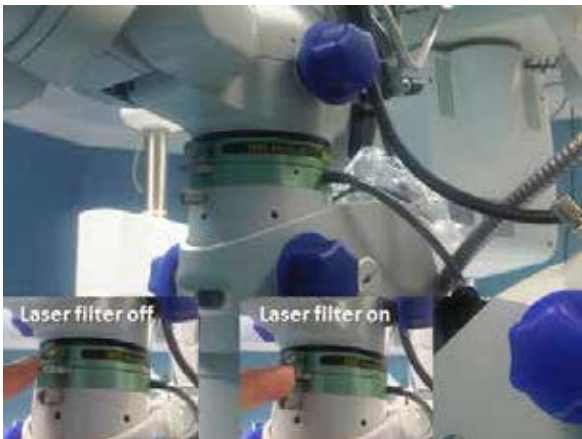


Figure 3. Before performing endolaser the nurse staff and the surgeon should certify that the operating microscope laser filter is on. If the laser filter is before the beam splitter, both surgeon and assistant must have ocular protection. On the other hand if the laser filter is after the beam splitter (as in this figure) only the surgeon uses ocular protection and the assistant must use appropriated protection goggles.

Table 3. Criteria to select eyewear

1. Observable labels stating wavelength in nanometers
2. Visible label stating the optical density
3. Shield protection in both sides
4. Appropriate visible light transmission
5. Resist shock, scratching, and front surface reflection
6. Have proper size and be comfortable

## b. Wearing goggles inside the NOHA

When LSO classifies the entire treatment room as the NOHA, consequently, everyone in the same physical space must wear eye protection adopting the same optical density and obviating the use of observer goggles (low optical density or marked “for observation only”). In line, it is important that users wear goggles that will allow enough adequate visible light transmission.

Each individual should be responsible for examining their goggles before wearing them, to check the correct tags and to evaluate and confirm their safety (Figure 4).



Figure 4. The goggles have a label on its lens or frame indicating the optical density for each wavelength range. Each person is responsible for confirming that the goggles are appropriated for the laser wavelength in use and has correct optical density that allows adequate ocular protection. The colors of the glasses do not confer any secure indication, only the label on the goggles can do it.

Despite the routine safety inspections made by the LSO or by the laser company personnel, each physician must ensure that the goggles are in safety conditions, in each treatment session.

Due to treatment in the periorbital area, metal corneal eye shields or tightly fitting peri-orbital goggles, should be used to avoid eye injuries. One should take into account that ocular damage may be preventable if all persons are properly trained and protected.

## Flammability and Reflection

The hazard potential for laser flammability is a concern in oculo-plastic procedures. The body of the patients and staff present in the laser room must be protected from deleterious and harmful laser beam exposure, particularly when using CO<sub>2</sub> or Er:YAG laser.

Flammability is a potential laser hazard associated with most high power systems, like CO<sub>2</sub> or diode laser systems for oculoplastic or lacrimal procedures. Many flammable products are used routinely in clinical procedures, and the LSO, as well as the laser team, must continually assess devices in use in the laser target site, for compatibility with the beam. Furthermore, a standard equipment fire extinguisher should be conveniently installed near this laser room. On the other hand, regarding all patients who undergoing hairline procedures, the area must be cleaned

removing any cosmetic product (hair spray, gels, nail polish, etc.) that may contain flammable components. Reflection is a hazard whenever a laser beam comes into contact with specular materials or instruments. In addition, the LSO should evaluate the potential for hazards from any metal cabinets, wall coverings or furniture in the laser treatment space, before recommending the equipment replacement.

### Testing and calibration

In refractive surgery it is imperative to check fire and/or calibrate a laser prior to use, and it is advisable to register this in the operative records. Infrared lasers with coaxial visible aiming beams must be tested for alignment and for the presence of an appropriate beam mode, while fiber-optic lasers must be calibrated for adequate transmission across the fiber, in order to ensure accurate and consistent power density delivery to tissue. Beam mode must be TEM<sub>00</sub> (fundamental mode) indicated for a clean circle without distortion. The mode is critical to maintain power density in tissue, and therefore have clinical effects. Testing should be done before the first patient of the day and then repeated if the laser is moved or if the delivery system is changed. The testing and calibration should be performed at a scheduled time by the preventive/corrective maintenance team of the equipment (see next chapter).

### Electrical Hazards

Lasers are electrical devices and should be treated with the same caution as any other electrical equipment. This may be overlooked by technicians, especially those using hand held or small mobile devices. It must be emphasized that all electrical safety procedures should be followed, and an occupational health and safety plan for response to fire should be in place and included in staff education programs.

## 4. CONTROL AND MONITORING SAFETY PROGRAMS

Included in the administrative controls, safety audits monitor the compliance with facility policies and procedures (Table 4). The LSO will determine the frequency of the audit, which is based on the number of lasers, number of users, case numbers and number of people involved. The greater the numbers and heavier the use, the more frequent the audit should be. Audits should be done at least once per year. Moreover, audits help identify areas requiring further education and training, the purchase of new equipment or the need for additional control measures.

## 5. INTERNATIONAL REGULATIONS AND PRACTICE GUIDELINES CURRENTLY AVAILABLE

International regulations are available through the IEC, documents 60601, 60825, and 60825-Part 8. Despite its non-regulatory role, these standards are the global benchmarks for laser safety, and include normative and informative guidance for manufacturers, professional clinicians and managers of laser use facilities<sup>11</sup>. In some countries (USA, Australia, Canada), these standards are harmonized with the national standards and serve as

Table 4. Audit requires completing each of the following steps:

1. Inventory all equipment and develop a checklist
2. Inspect every item on the checklist, assessing its condition, placement, and handling
3. Interview staff working with the laser systems
4. Observe laser procedures (set up, testing, and intraoperative management)
5. Document results
6. Remedy deficiencies identified
7. Monitor outcomes and follow-up

consensual documents for best practice.

In the United States, several states have regulations requiring the registration of laser systems, and proof of administrative controls as defined by the American National Standard (ANSI Z136.3). ANSI standards are the basis for laser safety requirements as determined by the Occupational Safety and Health Administration (OSHA) which is a governmental branch of the Department of Labor<sup>12</sup>.

In what regards Europe, the guideline is the IEC-60825 document which offers non-regulatory guidance for identification and control of major hazards associated with medical lasers. The companion document 60825-Part 8, includes additional informative sections with expanded descriptive procedures focused on laser users, and is a helpful outline for policy development and safety management. In cases of accident investigation, or establishment of a research project, clinicians can use the guidance and the advices of a medical physicist, a laser protection advisor (LPA), a LSO, or a company specialized in laser safety.

## 6. LASER SURGERY SHOULD BE PERFORMED ONLY BY LICENCED DOCTORS

The American Academy of Ophthalmology stated in 2015 that laser surgery should be performed only by licensed doctors of medicine or osteopathy. Ophthalmologists have been among the principal pioneers and innovators in the field of laser surgery and they have learned and gained mastery of laser surgery techniques through residency and fellowship training. Therefore, they are the best prepared in diagnosing, dispensing laser care and postoperative follow-up to the patients. At the same time, optimization of the outcome depends on timely recognition and management of both the anticipated and unforeseen complications and only ophthalmologist can do this accurately<sup>13</sup>.

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# XVII. Good Practices in Medical LASER

## 92. Maintenance and

## management of

## LASER technology



Luis Mendes, Ricardo Bastos  
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### INTRODUCTION

Preventive/corrective maintenance in medical devices that use laser technology is of vital importance to ensure its correct operation. The lack of this maintenance entails several risks for the equipment, and, more often, to the patient. This must be done in accordance with the manufacturer's instructions and with the regularity designated by him<sup>1-5</sup>.

Even if an equipment is rarely used or if apparently it does not show any anomalies, its maintenance should not be postponed nor ignored. This incorrect procedure may result in very expensive damage to the equipment as well as reduce its reliability. It is common to find equipment that users deem to be in perfect condition and operational, however, after technical inspection, it turns out, for example, that the energy selected does not match the energy delivered by the laser. Other times, the shape or profile of the laser spot is not ideal, due to damage not visible in an optical fiber or simply to the existence of dirt in the optics, whether internal or external.

This kind of undervaluation of maintenance leads to wrong parameterization of the equipment by the user resulting in lack of effectiveness in the treatment administered to the patient or compromising the integrity of structures affected by the laser beam.

User safety is also obviously undermined if there are anomalies in the protection devices. These are typically electrical risks (risk of electro shock) and risks inherent to the use of laser light (optical filters of protection, goggles and others, which may present anomalies or be incorrectly scaled for the device in use).

All systems and laser light delivery interfaces, as well as all

peripherals that attach to the equipment, such as a pedal, are obviously covered by this obligation of periodic maintenance. In conclusion, only in accordance with the manufacturer's standards, one can ensure the integrity of laser equipment or peripherals and accessories, reducing the risk for both the user and the patient. As the risk of equipment breakdown decreases, the operating costs also decrease, improving its accuracy and reliability.

### MAINTENANCE MANAGEMENT FOR LASER EQUIPMENT AND ACCESSORIES

Management should always be centered in articulating those involved in technical assistance to equipment. This must contemplate the timing and recording of the preventive and fixing assistance. The equipment itself should be labeled with the date, identity and number of the document that recounts the intervention carried out, as well as the date of the next intervention (Figure 1).

Although user information about the condition of equipment is privileged, without the record of all occurrences, it is more difficult for a technician to diagnose a problem in multiuser scenarios, such as, a hospital unit. Therefore, a record of occurrences should also be kept and made available to the service technician.

### PLANNING AND BUDGETING OF PERIODIC MAINTENANCE

It is not mandatory to be the same entity to buy the equipment and manage the equipment maintenance. However, the entity responsible for the acquisition of the equipment must include in their operating costs

Equipment: Brand and model  LASER Class	Series number	Date of the intervention	Periodic/ routine reparative intervention	Entity/person who carried out the intervention	Number of registration document from the intervention	File location	DATE OF NEXT INTERVENTION

Figure 1. Label scheme which should be attached to the equipment.

funds devoted to periodic maintenance to ensure that the equipment does not go through maintenance due to lack of budget. As a general rule, it is estimated that the initial cost of the equipment represents approximately a quarter of the total amount spent during its whole life. Approximately 6% of the purchase price will be spent annually for maintenance and repairs as well as for the replacement of consumables.

### MAINTENANCE LEVELS

Besides the manufacturer or its representative, it is desirable for users and intermediate technical teams (if any) to work together to ensure the good condition of the equipment contributing to its longevity and reliability.

#### User

Unlike what is usually thought, maintenance is not, in any way, limited to the manufacturer of the equipment. Users have a fundamental role in first line maintenance as well as in the verification of its correct operation. Aspects like cleaning (Figure 2), dust removal and verification of safety tests, must be carried out regularly by users of the equipment in order to minimize a deeper intervention to be carried out by the manufacturer. It is not uncommon to find equipment connected to the mainstream unnecessarily or equipment with no protective cover when they are inactive and disconnected from AC power. Small gestures as covering the equipment during periods of inactiveness can safeguard the equipment from dust accumulation and proliferation of fungi or other environmental hazards where the equipment is installed.

#### Local technical teams

If there are local technical teams, as in some hospital units, with the proper training, these may carry out deeper interventions to the equipment. Small mechanical adjustments, cleaning, removal of dust in areas inaccessible to the user, replacing fuses and bulbs, lubrication and such things can be performed (Figure 3). To carry out these interventions specific training is required by the manufacturer or its representative to these local technical teams, so that they are an asset and not an obstacle to the proper functioning of the equipment.

### OTHER CONSIDERATIONS

In addition to the periodic maintenance specified for



Figure 2. Example of external optical cleaning.

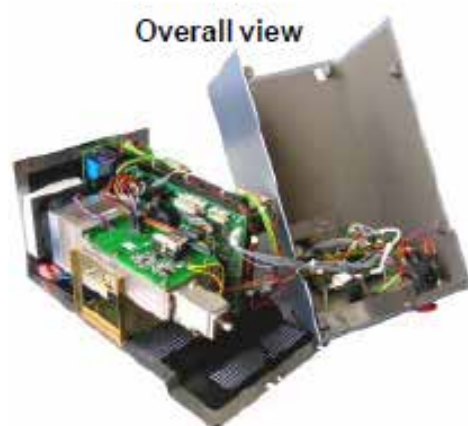


Figure 3. Inside view of a laser unit.

each equipment, it is necessary to ensure, at the outset, the necessary conditions for its proper operation since its installation. Floating supply voltages or voltage spikes must be prevented using stabilizers or voltage regulators. If the environment is too moist or too hot or too cold,



actions must be taken in order to prevent their harmful influence on laser equipment.

All the specifications of the equipment can be found in the user manual, so it is good practice that all users read and be familiar with its contents.

The adoption of a quality management system requires that all these procedures regarding the proper functioning of the equipment are known to all those concerned. We are referring in particular to the role of the user as responsible for the good operation of the equipment and the communication of any anomaly. User training should therefore be carried out by the laser safety officer or local installation responsible (Clinical Director) and this should be demonstrated by registration and signing of the document attesting that such training was held.

It is imperative that all accessories purchased later are under the jurisdiction of the maintenance team and that they are validated, in order not to compromise either the safety of the user and patient or the integrity of the equipment.

### MOBILIZATION NEEDS EQUIPMENT

One last word for equipment with mobilization needs: working conditions (power supply, cooling, etc.) may not be the same in all places where the equipment operates. Accordingly, all those involved in the maintenance of equipment whether they are management leaders, technical teams or even users should know this. As such, the best packaging and transport solution should be planned, its working conditions should be verified at the time of departure and arrival by a competent technical team.

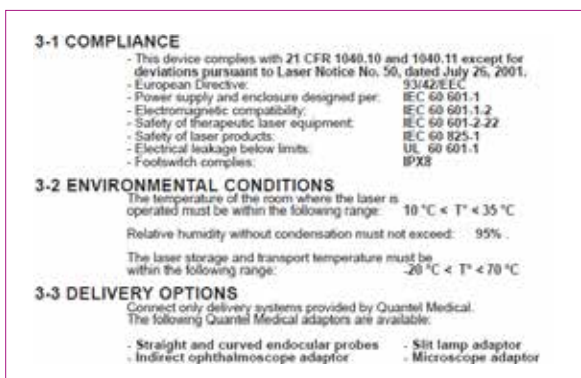


Figure 4. Example of certifications and environmental working conditions of Quantel Medical laser equipment.

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# XVII. Good Practices in Medical LASER

## 93. LASER risk

### management in

### Ophthalmology and

### accreditation

#### LASER ophthalmic systems, installation and processes



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**It is highly recommended that only those facilities, which are licensed under the regulatory authorities, may have operating laser systems class 3b or 4 installed.**

This means that patients may have the assurance that there is a Clinical Director, a doctor responsible for the facilities, the equipment, the processes and treatment. At the same time, this doctor may also perform the duties of Laser Safety Officer (LSO)<sup>1-5</sup>.

#### **ACCREDITATION - LASER OPHTHALMIC SYSTEMS, INSTALLATION AND PROCESSES**

In the process of certification of the laser installation and processes, as mentioned before (see chapter 91), it **is the duty of the LSO to set the rules for safe use and procedures as well as the risk management measures**. Bearing in mind the guidelines of good practice in using lasers, already described (chapter 91), and the local specificities of the equipment concerned, as defined in the terms of the ISO 31000 standard, the LSO should devise the adequate place and all the necessary rules and regulations that must be followed for a safe use of each laser and respective installation and also provide the risk management plan for each piece of

equipment or laser facility<sup>5,6</sup>.

The LSO should take the characteristics of the laser system into account (as previously described), facility plans (a single equipment or several pieces of equipment but to be used by a sole ophthalmologist at a time), the conditions for use (a single-user or multi-users), the usage frequency, carefully pondering the characteristics of the laser room and the nominal ocular hazard area (NOHA). This plan in general should follow step by step the items of the ISO 31000 standard:

1. Identify the risk and declare it as such (positive or negative);
2. Analyze risk and prioritize it;
3. Plan and schedule risk minimization actions;
4. Track and report their results;
5. Take control measures (actions deemed appropriate to improve);
6. Learn from this action: to acquire concepts and improve processes<sup>1</sup>.

The plan should include: the laser safety standards of each equipment, make them known to all ophthalmologists and staff, document the records of training of all elements

with access to equipment and NOHA, including the administrative personal, and ensure that they are put in place at the time when the laser operates.

The medical personnel is encouraged to participate in training meetings and register the participation on their curriculum:

- Conduct training with equipment on biological models;
- Control the complications inherent to procedures;
- Participate in training courses;
- Participate in wet labs;
- Participate in seminars.

Even though it may seem that the cost of laser safety training is high, it is always far less than the cost of one incident.

### **PARTICULARITIES OF OPHTHALMIC LASER SYSTEMS<sup>2-6</sup>**

In Ophthalmology some lasers are built accopolated with a slit lamp or a laser refractive unit and the direction of the laser beam is well defined and always the same. Besides, it should be oriented to a nonflammable roughened or matt wall.

Moreover, the equipment has a built in protective filter in order to protect the eyes of the surgeon.

#### ***The Nd:YAG-“Q-switch” laser for ophthalmology***

The Nd:YAG-“Q-switch” laser for ophthalmology has a convergent and polarizing beam that act together on the beam focus and creates the conditions to induce the plasm formation by optic disruption. This only happens on the focusing beams, at the slit lamp focus, aproximately 8-10 cm away from the slit lamp laser beam exit, where the patient, properly positioned for treatment, has his eyes. The ophthalmologist should be aware that the laser spot is properly designed on the target, all staff should wear apropriated goggles and there should be no caregivers or family members in the room.

#### ***The photothermal laser systems for photocoagulation or laser photothermal laser treatment***

The photothermal laser systems (Nd:YAG KTP 532 nm laser (KTP laser), Yellow Diode 577 nm laser (YD laser), Diode laser 810 nm (DL) or other photothermal lasers) are usually accopolated to a slit lamp and have an integrated filter built in from the manufacturer with adequated protective properties.

The ophthalmologist should be aware that the filter is on for his own protection. All assistants (nurses or others) must wear adequated protective goggles and not be within the beam scope and avoid reflection from the contact lens surface. The laser beam should be directioned at a nonflammable matt or rought wall that avoids reflection of the beam.

#### ***Photodynamic Therapy (PDT) lasers – a low risk laser***

PDT lasers are also of low risk. They usually use 810 nm diode laser with a low fluence and the laser effect only occurs in the tissue where the photosensitizer is accumulated. They are used in ophthalmology without significant risk concerns and the risk management has no special features.

#### ***Excimer or femtosecond lasers***

These lasers are accopolated to the microscope of the systems and have a built in laser beam oriented towards the operating field. The laser beam is foccused on the plane of the eye in a lying position during the procedure and the laser energy is absorbed by the eye tissue (cornea and lens) and there is no special risk for the surgeon or the staff. On the other hand, there is some particular risk in the Excimer laser plumage and an aspirator device should be held in place when operating the laser.

At the beginning of the procedure, laser operator personnel should titrate and calibrate the laser, assuring a perfect level of fluence.

#### ***Operating room lasers with optic fiber and CO2 laser with articulated arm***

In the operating room, using handpieced optic fibers that can give to the laser beam every possible direction in the space, carries great concerns regarding laser risk. The same concerns exist for the CO2 laser with articulated arm and handpiece scanner delivery system.

In that situation the laser risk management should take into account these modalities and risks. The LSO should design a plan of risk management more rigorous with all the rules for the laser risk management in a real risk environment as in the NOHA of a laser of the 3b or 4 class laser.

### **PERFORMANCE STANDARDS IN OPHTHALMOLOGY**

1. Place the laser so that the beam is directed at a nonflammable roughened or matt wall.
2. There should be a screen behind the laser to avoid reflections.
3. Only office assistants or observers equipped with goggles beside or behind the surgeon or laser are allowed.
4. It is forbidden to look into the laser beam, even with protective goggles.
5. At least one pair of goggles according to wavelength used and an optical density of at least 3 must be available in the room.
6. Always check if the glasses wavelength is in accordance with the used laser.
7. Remove the safety key when the laser is not in use and save it so the laser is not used by unauthorized persons.
8. When using the laser, keep the danger sign on the door and keep the door closed.
9. If a system is used without slit lamp, the door must be locked and all in addition to the patient should wear appropriate goggles.
10. Exclusively use therapeutic contact lenses adopted for the wavelength in use.
11. Maintain the laser in the standby position before and immediately after treatment.
12. Test the guide beam alignment and energy necessary for optical disruption in the air, before using the Nd:YAG laser-fotodisruptor.
13. Test the fluency of the excimer laser at the beginning of the procedure and perform the aspiration of fumes produced during the laser procedure.

## SAFETY LASER

### Each laser must have information about:

- 1 Its classification and information regarding the timely maintenance;
- 2 The rules and safety procedures (described above), laminated and attached to the equipment console and validated annually by the ophthalmologist.

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# XVII. Good Practices in Medical LASER

## 94. Equipment available

## in Ophthalmology



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### INTRODUCTION

Laser devices used in ophthalmology are very useful tools. They allow precise treatment of a range of eye disorders and are safe, accurate and at relatively low cost. Different lasers emit specific wavelengths of light and they are generally grouped into three main types: photocoagulating lasers, photodisrupting lasers and photoablating lasers<sup>1</sup>.

Usually, they are named according to the active material used as a laser medium. The effects on eye tissues result from the combination of the function of the molecular composition of the target tissue and the wavelength and power of the laser light<sup>1,2</sup>.

- The “old” *argon* laser 498 and 514.5 nm emits blue-green wavelengths;
- The *Nd:YAG 1064 nm Q-switch laser (QS-YAG)* generates short-pulsed, high-energy light beams to disrupt (cut, perforate, or fragment) the tissue;
- The *diode* laser 810 nm has similar applications to both the argon and the Nd:YAG KTP 532 nm laser (KTP laser). The advantage of diode lasers is that they are more portable, produce less heat and require much less maintenance than other types of lasers;
- The *excimer* 193 nm laser emits ultraviolet light, vaporizing tissue by breaking down molecular tissue bonds in a minuscule area;
- The *Femtosecond* laser in general causes plasma formation and ablation plasma induced with its near-infrared scanning pulse focused to 3  $\mu\text{m}$  with an accuracy of 1  $\mu\text{m}$ . This makes Femtosecond laser-assisted surgery amenable to anterior chamber targeting at various depths and it is being used in refractive, cornea and cataract surgery.

Most ophthalmic laser systems consist in a laser module (laser medium, laser pump, laser cavity and cooling system) that is typically coupled with a slit-lamp biomicroscope. Other laser-energy delivery systems

include indirect ophthalmoscopes, intraocular probes and interfaces for operating microscopes<sup>1</sup>.

In this chapter, some examples of the laser devices used by ophthalmologists nowadays are mentioned. It is very important to follow protective measures in order to reduce the exposure of the eye and skin to hazardous levels of the laser radiation. One of them is to wear the proper laser safety goggles designed to filter the specific wavelengths of the laser being used<sup>1,2</sup>.

*\* the author has no financial interest in the equipment mentioned in this chapter. The information about the laser devices and the respective images have been authorized by the manufacturer/distributors companies.*

### CATARACT AND REFRACTIVE LASER DEVICES

#### ALCON/WAVELIGHT®

##### Excimer Laser EX500®

The WaveLight® EX500 Excimer Laser operates at 500 Hz, with an average treatment time of approximately 1.4 seconds per diopter.



Figure 1. Excimer Laser EX500® 3. Courtesy of ALCON®.



### Femtosecond laser FS200<sup>®</sup> for refractive surgery

This device allows a fast flap creation (6 seconds), the 200 KHz Femtosecond laser delivers precise, predictable outcomes. It has an automated vacuum control of the patient interface for consistent suction and minimized intraocular pressure and ocular distortion.



Figure 2. Femtosecond laser FS200<sup>®</sup> 4. *Courtesy of ALCON<sup>®</sup>.*

### Femtosecond laser LENSX<sup>®</sup> for cataract surgery

Approved in the EU and in the USA for cataract surgery. It allows an enhanced procedure automation, precise and customizable incision architecture, capsulotomies and lens fragmentation patterns.



Figure 3. Femtosecond laser LENSX<sup>®</sup> 4. *Courtesy of ALCON<sup>®</sup>.*

### BAUSCH & LOMB<sup>®</sup>

#### Femtosecond Laser VICTUS<sup>®</sup>

A single laser platform that enables surgeons to perform capsulotomies, fragmentation, arcuate incisions, corneal incisions, and LASIK flaps.

### NIDEK<sup>®</sup>

#### Topo-Assisted Excimer Laser

**EC-5000 Quest<sup>®</sup>** has 200 Hz active eye tracker with no minimum pupil diameter and innovative algorithms for optimized treatments and excellent surgical outcome.

### ZEISS<sup>®</sup>

#### MEL 80<sup>®</sup> Excimer Laser

It has a wide field of application, including Femto-

LASIK, LASIK, customized treatments and topography guided treatment, surface ablation treatments as PRK and LASEK and Therapeutic treatment as Phototherapeutic Keratectomy (PTK).



Figure 4. MEL 80<sup>®</sup> Excimer Laser. *Courtesy of Zeiss<sup>®</sup>.*

### Mel 90<sup>®</sup> Excimer Laser

It has the FLEXIQUENCE switch function (250 Hz / 500 Hz), the ablation profile Triple-A (in addition to energy correction, it comprises an aspherically optimized design that also focuses on minimal tissue removal) and intra-operative ablation speed of up to 1.3 seconds per diopter that create entirely new treatment prospects.

### ZIEMER<sup>®</sup>

#### FEMTO LDV Z8<sup>®</sup>

It is a femtosecond laser for refractive and cataract surgery.

### PHOTOTHERMAL LASER (PTL) AND PHOTODISRUPTOR LASER (PDL) DEVICES

### ALCON<sup>®</sup>

#### Laser Purepoint<sup>®</sup> (PTL)

KTP 532 nm laser photocoagulator with integrated voice confirmation technology, with a multifunctional foot pedal that allows surgeon control of standby to ready and power settings.



Figure 5. Laser Purepoint<sup>®</sup> 5. *Courtesy of ALCON<sup>®</sup>.*

### ELLEX<sup>®</sup>

#### Ultra Q reflex (PDL)

A multi-modality YAG laser, Ultra Q Reflex<sup>™</sup> offers an innovative solution for the treatment of vitreous strands and opacities (and also performs capsulotomy procedures).

#### Solitaire<sup>™</sup> (PTL)

Solitaire<sup>™</sup> is a full-featured, portable green laser.

### Integre Pro Scan™ (PTL)

It combines multi-color photocoagulation and pattern scanning.



Figure 6. Integre Pro Scan laser<sup>6</sup>. Courtesy of ELLEX.

### Rapide™ (PTL)

Fast pattern scanning laser, delivering quick, precise and consistently better performance in the treatment of retinal disease.

### IRIDEX®

#### Green Laser (PTL)



Figure 7. OcuLight® Green Laser (IQ 532™), GL, GLx and Tx<sup>7</sup>. Courtesy of José Cotta, medical equipments SA and IRIDEX®.

#### Yellow 577 nm Laser with MicroPulse® IQ 577™ (PTL)



Figure 8. MicroPulse technology for fovea-friendly laser therapy for retinal disorders, and repeatable micropulse laser trabeculoplasty for glaucoma therapy<sup>7</sup>. Courtesy of José Cotta, medical equipments SA and IRIDEX®.

### OcuLight® SL/SLx (PTL)

#### 810 nm infrared laser

A laser source for multiple delivery devices and applications, require no regular maintenance or special electrical/cooling, and allow easy transport with their compact design.

### LUMENIS®

#### Green Laser - Novus® Spectra™ 532 nm (PTL)

#### Multicolor Photocoagulation Laser system - Novus® Varia

(532 nm green, 561 nm yellow, 659 nm red)

Compact multiwave photothermal laser.



Figure 9. Novus® Varia<sup>8</sup>. Courtesy of José Cotta, medical equipments SA and LUMENIS®.

#### YAG Laser (PDL) - Aura® PT (PDL)

(1064 nm QS-Nd:YAG laser)



Figure 10. Aura® PT. Courtesy of José Cotta, medical equipments SA.

#### Other laser devices (PTL, Q-Switch laser for SLT and PDL)

#### Selecta®

(1064 nm YAG mode, 532 nm SLT mode and 532 nm photocoagulator mode)

The Lumenis Selecta® Trio™ represents the next generation of multi-modality products, offering retinal, cataract and advanced glaucoma therapies in a single platform.



Figure 11. Lumenis Selecta® Trio™. *Courtesy of José Cotta, medical equipments SA.*

### **NIDEK®**

#### **KTP laser (PTL)**

Compact green laser **GYC-1000®**.

#### **YAG Laser (PDL)**

**YC-1800®** ophthalmic photodisruptor.

#### **Multicolor Pattern Scan Laser (Multiwave PTLD)**

Customizable in one, two, or three of the most popular colors: Green (532 nm), Yellow (577 nm), Red (647 nm).

### **TOPCON®**

#### **Pascal Streamline Photocoagulator® (PTL)**

The main features include short pulse duration, less heat diffusion to the retina with less collateral damage to surrounding tissues, uniform, predictable pulses and precise pattern. It can be used for patterned laser trabeculoplasty (PLT).

#### **Pascal Streamline 577™ (PTL)**

The longer wavelength of the 577 better targets the RPE with less scatter than 532 or 561 nm lasers. The combined absorption by both melanin and the oxyhemoglobin makes the 577 more efficient. Energy is concentrated into smaller volumes allowing use of a lower power and shorter pulse durations.



Figure 12. Pascal laser (Streamline®)⁹. *Courtesy of group TAPER and TOPCON®.*

#### **PASCAL Synthesis Pattern Scanning Laser® (PTL)**

The PASCAL® Synthesis™ is Topcon's premiere dual-port pattern scanning retinal laser, available in both 532 nm and 577 nm wavelengths.



Figure 13. Pascal Synthesis Pattern Scanning Laser®. *Courtesy of group TAPER and TOPCON®.*

### **QUANTEL MEDICAL®**

#### **Supra Scan 577™ (PTL)**

Supra Scan is a 577 nm photocoagulation laser that offers a large choice of laser treatment options improving the photocoagulation experience for both patient and retinal specialists. These include the following: **Pattern Scan** (short pulse durations: 10-20 ms); **Yellow** (more efficient by the use of a lower power level (vs 532 nm / 561 nm or 586 nm, with combined absorption by both melanin and good penetration through cataracts and hazy media) and **Micropulse™** mode (tissue sparing treatment that avoids scarring, this subthreshold treatment option is increasingly generating interest among retinal physicians).



Figure 14. Supra scan 577™ 10. *Courtesy of José Cotta, medical equipments SA and QUANTEL®.*

#### **Vitra Multispot® (PTL)**

##### **532 nm Multispot Laser**

It allows short pulse durations (10-20 ms).

##### **Monospot**

Possible application: titrate and finishing touches in classic treatments.

#### **Supra Complete photocoagulation range (PTL)**

##### **SUPRA 532 nm (green)**

Standard photocoagulation

Wavelength benefits:

- Highly absorbed by the melanin in the RPE;
- Well absorbed by hemoglobin.

#### **SUPRA 577 nm (yellow)**

Gold standard to treat near the macula.

Wavelength benefits:

- Peak absorption by oxyhemoglobin;
- Negligible absorption by xanthophyll pigment;
- Low light scattering.

#### **SUPRA 660 nm (red)**

The ideal choice in case of hazy media.

Wavelength benefits:

- Minimally absorbed by hemoglobin;
- Well absorbed by melanin.

#### **SUPRA 810 nm (Infrared)**

Alternatively, when deep penetration is required.

Wavelength benefits:

- No absorption by hemoglobin;
- No absorption by xanthophyll pigment;
- Low absorption by melanin.

#### **SoLuTis® (SLT)**

##### **Glaucoma Laser Therapy**

SoLuTis is a Q-switched 532 nm SLT laser. In contrast to classic laser procedures (ALT, MLT, PLT), the SLT procedure is characterized by the absence of thermal effects. The laser energy is selectively absorbed by pigmented cells. The main features are the extremely short duration (4 ns  $\Leftrightarrow$  0.00000004 sec), the large spot size (400  $\mu$ m) and the ideal 532 nm wavelength to target melanin cells.



Figure 15. SoLuTis® SLT laser<sup>11</sup>. Courtesy of José Cotta, medical equipments SA.

#### **Optimis Fusion™ (PDL)**

Integrated SLT / YAG Platform that combines traditional YAG photodisruption treatments and advanced SLT photoregeneration therapy in one integrated platform.



Figure 16. Optimis Fusion Laser<sup>12</sup>. Courtesy of José Cotta, medical equipments SA and QUANTEL®.

#### **Optimis II® (PDL)**



Figure 17. Optimis II®. 1064 nm Nd:YAG photodisruptor laser<sup>13</sup>. Courtesy of José Cotta, medical equipments SA.

#### **ZEISS®**

##### **Visulas® YAG III (PDL)**

The Visulas YAG III photodisruptor laser is used for applications like posterior capsulotomy and iridotomy as well as IOL polishing.



Figure 18. Visulas® YAG III. Courtesy of Zeiss®.

##### **Visulas® 532s (PTL)**

It is designed in particular for retinal photocoagulation, trabeculoplasty and iridotomy for the treatment of glaucoma. The VISULAS 532s with the VITE option is mainly used for multi-spot panretinal and grid photocoagulation.

##### **Visulas® Trion (PTL)**

Intelligent multi-wavelength laser for highly selective treatment choices, it is designed for photocoagulation of the retina, trabeculoplasty and iridotomy for the treatment of glaucoma. The VISULAS Trion with the VITE option is mainly used for multi-spot panretinal and grid photocoagulation.



Figure 19. Visulas® Trion. *Courtesy of Zeiss®.*

### OD-OS

NAVILAS® Laser system NAVILAS® Laser system equipped with yellow or green 532nm multispot scan and pattern as well as micropulse technology (model 577s).

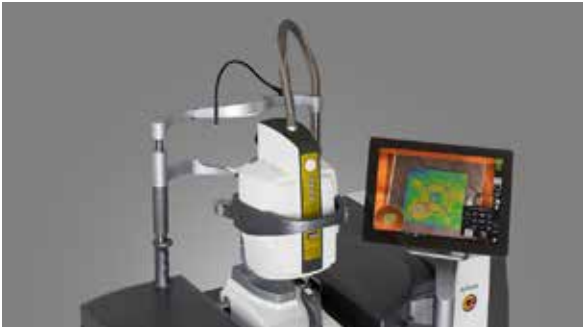


Figure 20. NAVILAS® Laser system equipped with yellow or green 532nm multispot scan and pattern as well as micropulse technology. This system allows one to perform focal laser without a contact lens thanks to its eye-tracking system and the use of infrared light that does not stress the patient's eye. It also captures real-time images of the fundus, including fluorescein angiography, based on which one can program automatic laser delivery. Focal or macular grid laser, as well as panretinal photocoagulation, are possible, as well as registration for future reference<sup>2-5</sup>.

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# XVIII. The Future and The Present

## 95. What's new in laser technology in Ophthalmology



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### INTRODUCTION

Laser (light amplification by stimulated emission of radiation) is an equipment capable of emitting a powerful, highly monochromatic and coherent beam of electromagnetic radiation. Different lasers emit electromagnetic waves with characteristic properties and energies, and these individual specific features are largely used for a variety of purposes in modern Ophthalmology<sup>1,2</sup>. Current therapeutic applications of these lasers will be reviewed in this chapter, with special focus on the most recent innovations. Other recent developments as eye-tracking laser technologies and new diagnostic laser-based technologies such as sweep source optical coherence tomography (SS-OCT) and optical coherence tomography angiography (OCTA) will also be addressed.

### LASER IN REFRACTIVE AND CATARACT SURGERY

#### EXCIMER LASER

Modern refractive surgery dates back to the discovery of the 193 nm argon fluoride excimer laser photoablation in 1980. In photoablation the shorter ultraviolet (UV) wavelengths do not cause temperature rises, and tissue simply disappears at the site of impact. This way, the targeted surface can be precisely removed with brief laser pulses. This laser is widely used in refractive procedures such as the *laser-assisted in situ keratomileusis* (LASIK), a term coined in 1991 by Pallikaris *et al*<sup>3</sup>. In LASIK a flap is cut in the cornea with a microkeratome (or more recently with a femtosecond laser), and pulled back to

expose the corneal bed for precise laser ablation with the excimer laser<sup>2</sup>. Other corneal refractive techniques that use the excimer laser are *photorefractive keratectomy* (PRK) and *laser-assisted sub-epithelial keratectomy* (LASEK). One other application of excimer laser is *phototherapeutic keratectomy* (PTK), in the treatment of corneal pathologies such as corneal dystrophies, recurrent erosions, scarring and irregular astigmatism<sup>4,5</sup>.

#### FEMTOSECOND LASER

The development of the femtosecond laser was another revolutionary step in refractive surgery. It was pioneered by Kurtz *et al* in 1998 and later commercialized by IntraLase Corporation<sup>6</sup>. The high-power, low-exposition time (femtosecond) laser causes plasma-induced-ablation via “optic breakdown”, by increasing electric fields with plasma ionization, which is accompanied by a very precise excision, with no mechanical ruptures. Femtosecond lasers have a low threshold energy of dielectric breakdown with an accordingly reduced cavitation bubble size. The associated tissue damage is reduced, allowing for more precise surgical procedures<sup>2</sup>. There are two general categories of commercially available femtosecond lasers: higher energy–lower frequency and lower energy–higher frequency<sup>7</sup>.

Femtosecond lasers that are used for LASIK procedures (FS-LASIK) are solid-state focusable plasma photoablative lasers that operate in the infrared spectrum at wavelength value of at approximately 1000 to 1053 nm. Unlike mechanical microkeratomes, with femtosecond laser flap-cutting in LASIK it is possible to precisely cut different geometries, allowing a variation in flap width,



flap depth, hinge width, and side-cut angles that may lead to a better positioning of the corneal flap after excimer ablation<sup>7</sup>. Safety is also enhanced, as the corneal tissue does not need to be dissected if an aberrant flap is created, allowing the corneal tissue to revert to its previous shape and clarity on dissolution of the gas bubbles. These advantages, together with improved consistency of refractive outcomes, led to a wide acceptance of the femtosecond laser in refractive surgery<sup>7,8</sup>.

Recently, femtosecond lasers also enabled refractive surgical procedures for myopia based only on intrastromal cutting by laser, with subsequent lenticule extraction, and with no need for excimer laser ablation (*small incision lenticule extraction* - SMILE)<sup>9</sup>. Other corneal procedures that are possible with femtosecond include: crafting a precise, interlocking graft–host junction for penetrating keratoplasty, creating donor lamellar buttons for both anterior and posterior lamellar keratoplasty, dissecting tunnels for intracorneal ring insertion, creating flaps or pockets for corneal inlays, and cutting astigmatic keratotomy incisions<sup>7,10,11</sup>.

In cataract surgery the femtosecond laser is also being increasingly investigated (femtosecond laser-assisted cataract surgery - FLACS). The scanning femtosecond laser can produce fine cutting patterns in tissues with their placement defined by integrated OCT or Scheimpflug imaging<sup>12,13</sup>. Femtosecond laser incisions in the anterior capsule are much more precise in size and shape than manual capsulorrhexis, and segmentation and softening of the lens may simplify the subsequent ultrasonic phacoemulsification<sup>13</sup>. Femtosecond lasers have also been used in the construction of multiplanar self-sealing cataract incisions for the improvement of the safety of the procedure and for exact placement of limbal relaxing incisions in order to reduce residual astigmatism<sup>13,14</sup>.

## LASER RETINAL THERAPY

### LASER RETINAL PHOTOCOAGULATION AND MULTI-SPOT LASER

Photocoagulation is caused by an increase of temperature in tissues via absorption of laser energy, which causes denaturation of tissue proteins and coagulation at the absorbent site. The discovery of the argon laser in 1964 by Bridges provided a new laser tool with emission in the blue (488 nm) and green (514 nm) range of the spectrum. This new laser had the advantage of being strongly absorbed by hemoglobin and melanin, enabling effective retinal photocoagulation. This was a very important step in the treatment of several retinal conditions including macular edema and proliferative retinopathy, which can be caused by a wide spectrum of diseases, namely diabetic retinopathy and retinal vein occlusion<sup>2</sup>. Argon laser remained the basis of modern clinical photocoagulation for the next 35 years. Recently, however, water-cooled argon lasers have been replaced and the most common lasers used today in photocoagulation are frequency-doubled Nd:yttrium aluminium garnet (YAG) (532 nm) and yellow semiconductor laser (577 nm)<sup>2,15</sup>.

Recently a new method of photocoagulation has been introduced by Blumentkrantz *et al* at Stanford University,

in which patterns of multiple laser pulses are applied using a computer-guided scanning laser. The PAttern-SCAnning Laser – PASCAL – photocoagulator (Topcon Medical Laser Systems, Santa Clara, California, USA) is a 532 nm double-frequency Nd:YAG multi-spot laser for retinal photocoagulation<sup>16,17</sup>. The multispot laser delivers patterns of multiple uniform laser burns simultaneously, from a single spot to 56 spots, in a rapid sequence with a single depression of a foot pedal. The control of laser parameters is performed by means of a touch-screen interface, facilitating selection of the different patterns of photocoagulation. The laser is applied by pressing a foot pedal until the entire pattern is completed. However, it is possible to release the foot pedal and stop the laser at will, prior to completion of the pattern, if necessary. Available patterns include square arrays, arcs and circular patterns, making it useful not only for panretinal photocoagulation but also in performing grid patterns and in the treatment of retinal breaks, for example<sup>17</sup>. To deliver the whole pattern within the eye fixation time and avoid beam movement, exposure must be shorter than in conventional photocoagulation (about 10–20 ms instead of the traditional 100–200 ms). Short pulse lesions appear smaller and lighter than conventional burns produced with the same beam size, and therefore a larger number of them are required to treat the same total area<sup>15,18</sup>. These devices save time, streamline patient flow for the retina practice and reduce discomfort from long laser sessions<sup>15,16,19</sup>. Owing to reduced pulse duration, the heat diffusion into the inner retina and choroid is decreased, resulting in less pain and reduced inner retinal damage and scarring<sup>18,20,22</sup>. Rapid scanning of the laser beam in this system also allows for microsecond exposures, sufficiently short for selective treatment of the retinal pigment epithelium (RPE)<sup>2</sup>. While most published clinical studies relate to investigations undertaken with the PASCAL system, there is currently a range of new options: Valon TT (frequency doubled Nd:YAG 532 nm), Valon 5G (frequency doubled Nd:YVO 532 nm), Vitra Multispot (532 nm green Nd:YAG, Quantel Medical), Supra Scan 577 (577 nm yellow multispot or micropulse, Quantel Medical), Array LaserLink (532 nm, 577 nm, 659 nm, Lumenis), and the TxCell™ Scanning Slit Lamp Adapter coupled to the IRIDEX IQ 532™ or IQ 577™ laser (532 nm, 577 nm).

### SUBTHRESHOLD MICROPULSED LASER

Advances in laser delivery systems have led to a new approach called subthreshold micropulse mode. The subthreshold laser is above the threshold of biochemical effect but below the threshold of a visible, destructive lesion, thereby potentially preventing or limiting the progressive enlargement of laser scars<sup>23</sup>. Subthreshold laser denotes the use of lower energy levels aiming to cause sub-lethal injury to targeted RPE rather than destroying it and is based on the hypothesis that benefits are derived from RPE cell stimulation.

In micropulse mode, the laser energy is delivered with a train of repetitive pulses that are shorter than the thermal relaxation time of the target tissue. Each micropulse is part of an “ON-OFF envelope” the width of which is typically in the range of 0.1–0.5 s, and this envelope

duration constitutes the exposure duration. The “ON” time is the duration of each micropulse. The “OFF” time between successive micropulses reduces heat in tissues and regulates the thermal isolation of each pulse contribution<sup>23</sup>. The pulse train of micropulses is characterized by a *frequency* (repetition rate in hertz) and a *duty cycle* (percentage of time the laser is ON during the pulse envelope). Repetitive bursts of micropulses summate to produce the desirable therapeutic effect<sup>23</sup>. Given that a temperature rise is insufficient to cause damage to the surrounding retinal tissue, subthreshold micropulsed laser minimizes scarring and laser spots are generally undetectable during an ophthalmic and angiographic examination<sup>15,24</sup>.

Some studies have reported that subthreshold micropulsed 810 nm diode laser is as efficacious as conventional laser in diabetic macular edema (DME)<sup>15,25</sup>. The main drawback however is the absence of a visible end-point and the constant worry of undertreatment<sup>24</sup>. Also, most studies evaluating this approach have been non-randomized, uncontrolled, retrospective and of insufficient power to provide good knowledge of how to routinely apply this therapy in clinical practice.

#### **NANOSECOND LASER (2RT ELLEX)**

A new frequency-doubled nanosecond-pulsed Nd:YAG laser (532 nm) with discontinuous beam energy distribution (2RT Laser; Ellex, Adelaide, SA, Australia) was recently developed, and is being investigated as a retina rejuvenation therapy for the treatment of DME and intermediate age related macular degeneration (AMD)<sup>26,27</sup>. This low-energy, subthreshold, nanosecond laser has been designed to induce targeted RPE injury (through the formation of microbubbles around the melanosomes, which expand and coalesce, causing intracellular damage), but without associated retinal neuronal damage or significant retinal gliosis. A process of extracellular signaling occurs in response to the death of the targeted RPE cells, which causes the neighboring RPE cells to migrate and proliferate, and this process appears to stimulate cellular rejuvenation by reversing impaired transport mechanisms across the RPE-Bruch's membrane complex. In AMD, for example, the nanosecond laser treatment was shown to reduce Bruch's membrane thickness, a key pathologic change in AMD, and to resolve drusen, while preserving retinal structure<sup>28</sup>.

#### **LASER DELIVERY WITH EYE-TRACKING**

Combining laser delivery systems with eye-tracking technology may further advance the planning and application of laser with high precision by using stabilized retinal image. An automatic laser application, guided by diagnostic imaging and stabilized using eye-tracking, has been recently introduced – the navigated laser photocoagulator Navilas® (OD-OS GmbH, Teltow, Germany). This system is an advanced focal/panretinal photocoagulation device which includes multimodal retinal image acquisition (color, red-free, infrared, fluorescein angiography), annotation of the acquired images to create a detailed treatment plan, and automated delivery of the laser to the retina according

to the treatment plan<sup>15</sup>. The system also allows for the importation of images captured externally. The treatment plan based on either fundus photography or fluorescein angiography is overlaid on to a real-time retinal image of the patient's fundus while treatment is in progress. The eye-tracking mechanisms compensate for the eye's excursions during treatment and use registration of retinal vessel positions and multiple retinal landmarks to limit the possibility of inadvertent placement of laser burns<sup>29</sup>. The laser is a 532 nm frequency-doubled diode-pumped solid-state. The Navilas® Laser System 577+ features the yellow 577 nm wavelength.

Initial studies of clinical efficacy in diabetic retinopathy are promising. In focal treatment this system seems to increase the accuracy in targeting microaneurysms, with a reported high accuracy rate<sup>29</sup>. Navilas® also has several navigation functions for panretinal laser treatment, including imaging and delivery of single and multispot laser patterns into the far periphery by continuous repositioning of the laser beam relative to eye movements. Owing to stable fixation, multispot treatment patterns may be applied with longer pulse durations (100 ms or longer)<sup>30</sup>.

#### **LASER-BASED IMAGING TECHNIQUES: SS-OCT AND OCTA**

OCT uses low coherence light. A low coherence light source consists of a finite bandwidth of frequencies rather than just a single frequency. OCT typically employs near-infrared light. One of the most recent developments is the use of narrowband swept lasers. Swept lasers enable operation at long wavelengths such as 1000 and 1300 nm, provides high-definition image of the retina and, in contrast to OCT at 800-nm, simultaneously increases choroidal penetration significantly improving choroidal visualization. These characteristics make SS-OCT useful for choroidal evaluation in several pathologies secondary to or correlated with choroidal dysfunction<sup>31</sup>. Longer wavelengths also overcome lens opacities, thus allowing visualization of the macula in eyes with poor fundus view. The scan speed in SS-OCT instruments is twice that of spectral domain OCT (SD-OCT) devices (100 000 A-scans/sec), enabling faster acquisition of B-scans, widefield B-scans (12 mm) and more accurate 3D imaging of the vitreous, retina, choroid and optic nerve, at the same time. Automatic segmentation of different retinal layers and choroid is also possible with SS-OCT<sup>31</sup>. Another breakthrough innovation is the OCTA. Recently, several theoretically based OCT angiography methods were developed for 3-dimensional noninvasive vascular mapping at the microcirculation level. This relatively new imaging technique maps erythrocyte movement over time (this is, vascular flow) by comparing sequential OCT B-scans at a given cross-section. In particular, the use of the split-spectrum amplitude-decorrelation angiography algorithm improves the signal-to-noise ratio of flow detection. By applying this algorithm, OCTA can clearly visualize chorioretinal vascular lesions. Co-registration with OCT B-scans from the same area allows for simultaneous visualization of structure and blood flow. The OCTA RTVue XR Avanti (Optovue Inc, Fremont,

California, USA) is now available. It has an A-scan rate of 70 000 scans per second, and uses a light source centered on 840 nm and a bandwidth of 50 nm. Recent OCTA-based studies reported detailed macular images of choroidal neovascularization; dense and decreased microvascular networks in normal and glaucomatous optic discs, respectively; the abnormality of the inner/outer retinal vascular plexus and invasion into the outer and subretinal space in eyes with macular telangiectasia type 2; and characterization of vascular lesions in different stages of diabetic retinopathy. Importantly, this new technology provides us with the possibility of non-invasive imaging of vascular changes in the macula, at different levels, from the inner plexus to the subretinal space and choriocapillaris, without the risks of more invasive techniques such as fluorescein angiography<sup>32,33</sup>.

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