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OPHTHALMIC LASER THERAPY: MECHANISMS AND APPLICATIONS

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DEFINITION

The term **LASER** is an abbreviation which stands for **L**ight **A**mplification by **S**timulated **E**mission of **R**adiation. The laser is a source of coherent, directional, monochromatic light that can be precisely focused into a small spot. The laser is a very useful tool for a wide variety of clinical diagnostic and therapeutic procedures.

COMMON OPHTHALMIC LASER PROCEDURES

PATTERN SCANNING LASER PHOTOCOAGULATION

The first attempts to make photocoagulation a completely automated procedure involved rather complex equipment, including image recognition software and eye tracking[13]. The complexity of such systems prevented their commercial introduction and acceptance in clinical practice.

A semi-automatic pattern scanning photocoagulator (PASCAL, Topcon Medical Laser Systems Inc.) was introduced by OptiMedica Corp. in 2005[14]. It delivered patterns of laser spots ranging from a single spot to 56 spots applied in a rapid sequence with a single depression of a foot pedal. The control of laser parameters was performed by means of a touch screen graphic user interface, facilitating selection of the different patterns of photocoagulation. The laser was activated by pressing a foot pedal, which was kept depressed until the entire pattern was completed, although it was possible for the physician to release the foot pedal and stop the laser at will, prior to completion of the pattern, if clinically indicated.

Patterns included square arrays with up to 5x5 spots, arcs with the number of concentric rows varying from 1 to 3, circular patterns for photocoagulation of small holes and other lesions in the retinal periphery. Patterns for macular photocoagulation included rings and arcs with adjustable central exclusion zone of up to 2 mm in diameter to allow for laser application reducing the risk of inadvertent damage to the foveal avascular zone.

Note: this chapter contains excerpts from the full chapter by Daniel Palanker, which can be found here.

To deliver the whole pattern within the eye fixation time and avoid beam movement due to the ocular muscles, each exposure was required to be shorter than in conventional photocoagulation: 10-20 ms instead of 100-200 ms, traditionally applied with single spot exposures. Reduced heat diffusion into choroid during shorter exposures also resulted in patients experiencing less pain [15-17]. 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[18].

An automatic laser delivery, guided by diagnostic imaging and stabilized using eye tracking, has been recently introduced in a Navilase™ system (OD-OS GmbH). This system includes retinal image acquisition, annotation of the images to create a detailed treatment plan, and then automated delivery of the laser to the retina according to the treatment plan.

CLINICAL INDICATIONS: TREATMENT OF DIABETIC RETINOPATHY

Photocoagulation has proven safe and effective in the treatment of proliferative diabetic retinopathy. In this disorder the retina becomes ischemic and releases a variety of chemical messengers, most importantly vascular endothelial growth factor (VEGF) that stimulates the growth of new blood vessels and also markedly increase retinal vascular permeability. The abnormal new vessels, and associated fibrous tissue and macular oedema are major causes of the sight-threatening complications in diabetic eye disease. By destroying a portion of the peripheral retina with laser, it has been hypothesized that retinal metabolic demands and available nutrients are better balanced and the stimulus for growth of the new blood vessels is decreased. This treatment has been termed panretinal photocoagulation (PRP) and significantly reduces the risk of vision loss due to neovascularization. The side effects of panretinal photocoagulation – mild nyctalopia and constriction of visual field- are felt to be outweighed by the preservation of the central vision, and have been confirmed in multiple large randomized clinical trials[19]. Similarly, the focal laser photocoagulation to actively leaking microaneurysms, and the grid photocoagulation to areas of diffuse retinal permeability have been shown to reduce clinically significant macular oedema associated with diabetic retinopathy and slow the rate of vision loss. These effects have been confirmed in large randomized multicenter clinical trials[20].

AGE RELATED MACULAR DEGENERATION: EXTRAFOVEAL NEOVASCULAR LESIONS

Another application for laser photocoagulation in the past was for the treatment of extrafoveal CNV membranes that occur in AMD. Intense photocoagulation destroyed the invading vascular membrane usually leaves a chorioretinal scar, and a blind spot or scotoma, but if the lesions treated were outside the center of the macula, the treatment was typically well tolerated by the patients. Currently, many physicians have elected to use PDT as an alternative to intense focal photocoagulation, or to use anti-VEGF therapy, because of later recurrences and eventual spread of lesions into the macula.

Additional applications of retinal photocoagulation include grid and focal treatment of leaking microvascular abnormalities, in branch-vein occlusion and radiation retinopathy; and treatment of retinal breaks and lattice degeneration to prevent retinal detachment.

SELECTION OF OPTIMAL WAVELENGTH FOR COAGULATION

A number of important factors must be considered when choosing the best wavelength for a particular photocoagulation application. The first consideration is to determine what absorbers are present in the site to be photocoagulated. Wavelengths that are highly absorbed by macular yellow (such as 488 nm) are relatively contra-indicated when treating in or near the macula. Absorption of these wavelengths in macular pigments may cause heating and destruction of the nerve fiber layer, resulting in loss of vision. As shown in Figure 3B, in the macular region, wavelengths longer than 500 nm should be chosen, such as the green argon (514 nm) or the frequency doubled YAG (532 nm) or semiconductor yellow (577nm) laser. Melanin provides good absorption at most photocoagulation wavelengths. Wavelength selection is therefore less important when melanin is the primary absorber. To minimize scattering loss in cataract or in vitreous opacities the longer wavelengths (yellow - 577nm or red - 640 to 680 nm) are preferable. If scattering by the ocular tissues is not significant, the argon green (514nm) or doubled YAG (532nm) continue to serve well.

When hemoglobin is the primary absorber (see Figure 17.3B), as in the treatment of vascularized tumors, a wavelength shorter than 600 nm is preferable. Treatment of CNV may be effective using red light through indirect heat transfer from the surrounding melanin. Tunable lasers may provide the flexibility to select a wavelength of choice for required photothermal procedure. However, tunable lasers are more costly, require more maintenance, and are now less commonly employed clinically than previously.

LASER TRABECULOPLASTY

Argon Laser Trabeculoplasty (ALT) is usually applied to patients with open-angle glaucoma whose intraocular pressure (IOP) cannot be controlled by maximum pharmacological therapy. Safety and efficacy of ALT in treatment-naive subjects with newly diagnosed primary open-angle glaucoma has been demonstrated in large multicenter prospective clinical trial (POAG) in 1995 [21]. ALT provided longer control of intraocular pressure (IOP) without the need for additional therapy, and greater stability of visual field and optic nerve status, as compared with timolol monotherapy[22]. ALT lowers IOP by 6-10 mmHg, usually within 4-5 weeks, and lower IOP is usually maintained for several years. ALT is reported to have 70-75% success rate of clinically significant improvement.

With Argon laser (514 nm) or more recently, with the equivalent 532nm Nd:YAG laser, 50 spots of 50 µm in diameter are applied to the 180 degrees on trabecular meshwork (TM) with pulses of 100 ms in duration (Figure 17.1). The mechanisms of action leading to reduction in IOP are not well established. One theory is that the thermal burns created in the trabecular meshwork contract the tissue and open spaces within trabecular meshwork, thus increasing the aqueous outflow and lowering IOP. Another possible theory states that the thermal stress induced by laser therapy causes an increase in metabolic activity of the endothelial cell in the trabecular meshwork, which improves the aqueous outflow.

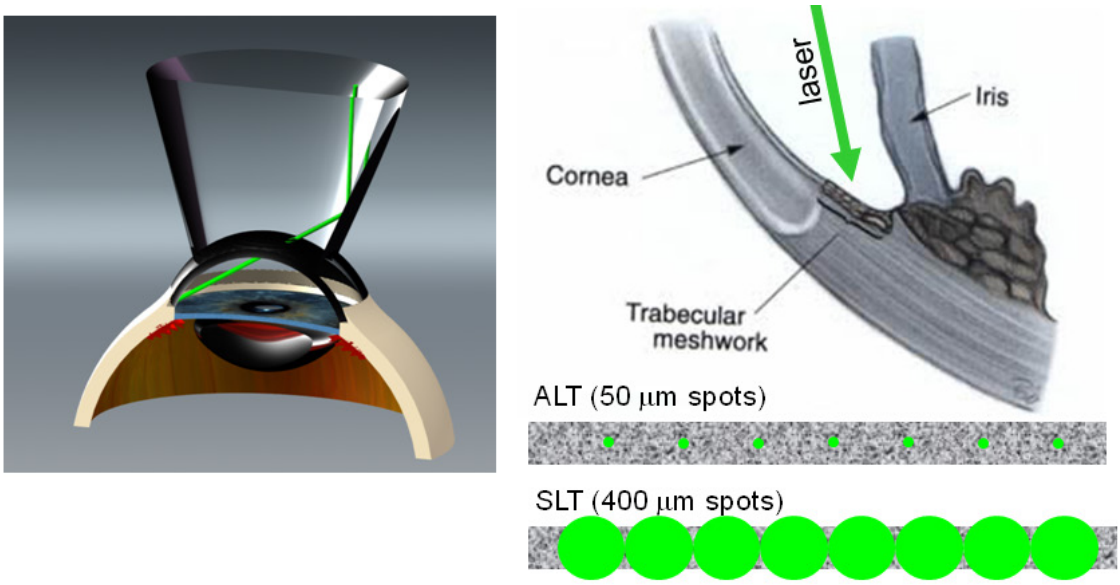

Figure 17.1: *Laser trabeculoplasty: laser beam is directed onto the trabecular meshwork via gonioscopic lens. For ALT, laser is typically focused into 50 µm spots. For SLT, the laser spots are 400 µm in diameter.*

Selective Laser Trabeculoplasty (SLT) was introduced in 1995[23, 24]. The commercially available SLT laser systems (Lumenis Inc., Santa Clara, CA; and Ellex Inc., Adelaide, Australia) include a Q-switched, frequency-doubled, 532-nm Nd:YAG laser, that delivers 3 ns pulses in a 400 µm diameter treatment spot. Typical SLT pulse energy ranges from 0.4 to 1.2 mJ, about hundred times lower than ALT. With 400 µm beam diameter, 100 spots per 360 degrees provide practically complete coverage of the TM (Figure 17.9). SLT has been shown to be an effective alternative to LT [23, 25, 26], in the treatment of patients with Open Angele Glaucoma. SLT leaves the Trabecular Meshwork intact with minimal damage to the endothelial cells lining the meshwork beams[23], in contrast to the ALT, which results in extensive scarring of the meshwork[27]. This observation has led to significant speculation that SLT may be more repeatable than ALT. SLT is easier to perform than ALT due to its larger spot size, and is better tolerated by patients due to reduced pulse energy. Like ALT, the IOP-lowering effect of SLT lasts for several years, but does tend to diminish over time. SLT is effective as primary therapy, can reduce the pharmaceutical burden in medically controlled

eyes, and can prevent or delay the need for surgery in eyes poorly controlled, but on maximally tolerated medical therapy. Both 180 and 360-degree treatments appear to be reasonable as initial therapy, and there seems to be no contraindication to initial 360 degrees treatment. The majority of procedures are performed as 180 degree treatments, with the second 180 degrees done typically 14 days after the first treatment.

Much lower energy requirements in SLT compared to ALT is due to different mechanisms of cellular damage produced by nanosecond and millisecond pulses. Millisecond hyperthermia of pigmented cells leads to cellular damage due to denaturation of proteins and other cellular macromolecules[28]. Nanosecond exposures though are too short to produce thermal denaturation below the vaporization threshold, and cells are damaged by cavitation bubbles forming around melanosomes[28]. With sub-microsecond pulses the heat does not diffuse beyond one micrometer, and thus the damage can be confined within a cell. With 100 ms exposures in ALT the heat diffusion zone can reach 220 µm, covering practically the whole width of TM.

LASER IRIDOTOMY

Laser iridotomy (LI) also called PI (peripheral iridotomy) is performed on the eye to treat angle closure glaucoma, a condition of increased intraocular pressure caused by blockage of the angle of the anterior chamber by the iris. LI is a procedure in which the laser creates a hole in the iris to allow fluid to flow through and relieve pressure in the eye. This typically results in resolution of the forwardly bowed iris and thereby an opening up of the angle of the eye (Figure 17.2). It is also used prophylactically with anatomically narrow angles, in the fellow eye of a patient with primary pupil block angle closure, a patient with primary open angle glaucoma and coincidentally narrow angles, and nanophthalmos. LI is performed ~3mm from iris root under the superior lid to prevent monocular diplopia. Power and pulse duration vary with iris color of the patient. Pulses (100-300 ms) of argon laser (514nm) or 532nm YAG laser focused into 50 µm spot are applied to create a depression. A “smoke signal” or aqueous plume, is seen when the posterior pigment epithelial layer is reached. The process is continued until penetration is complete. A combination of millisecond pulses of Argon laser and nanosecond pulses of Q-switched YAG is often used to perform the procedure. The Argon is used first to initiate tissue removal and photocoagulate vessels to prevent hemorrhages and then the ns YAG is used to complete the iridotomy[29]. The ns YAG laser does not coagulate tissue, and used alone can cause hemorrhages.

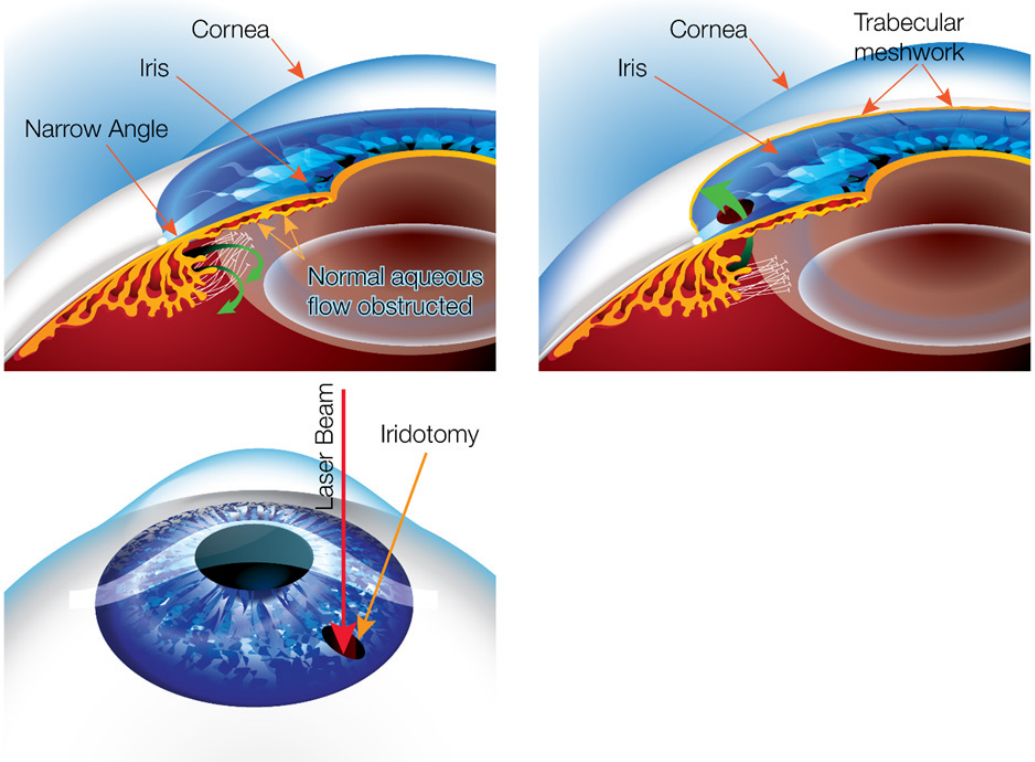

***Figure 17.2**: Laser iridotomy providing an alternative route for the aqueous flow from posterior to anterior chamber of the eye.*

POSTERIOR CAPSULOTOMY

Posterior lens capsule opacification (PCO) is the most common late complication occurring in approximately third of the cataract surgery cases[30]. Laser is used to create an opening in the hazy central part of the posterior capsule situated behind the intraocular lens (IOL) implant. The slit lamp-coupled nanosecond Nd:YAG laser focused into a tight spot can produce extremely high light intensities – in excess of 10^{10} W/cm^2. At these irradiancies photons can ionize even transparent materials via several different mechanisms[6], producing plasma in a focal spot. Plasma energy converting into heat results in rapid vaporization of the focal volume, producing shock waves and cavitation bubbles. Rapidly expanding and collapsing vapor bubbles can rupture (a process called photodisruption) the adjacent opacified posterior lens capsule, providing a clear window for central vision. To avoid damage to the intraocular lens implant, the laser is focused slightly posterior to the capsule in the vitreous (Figure 17.3).

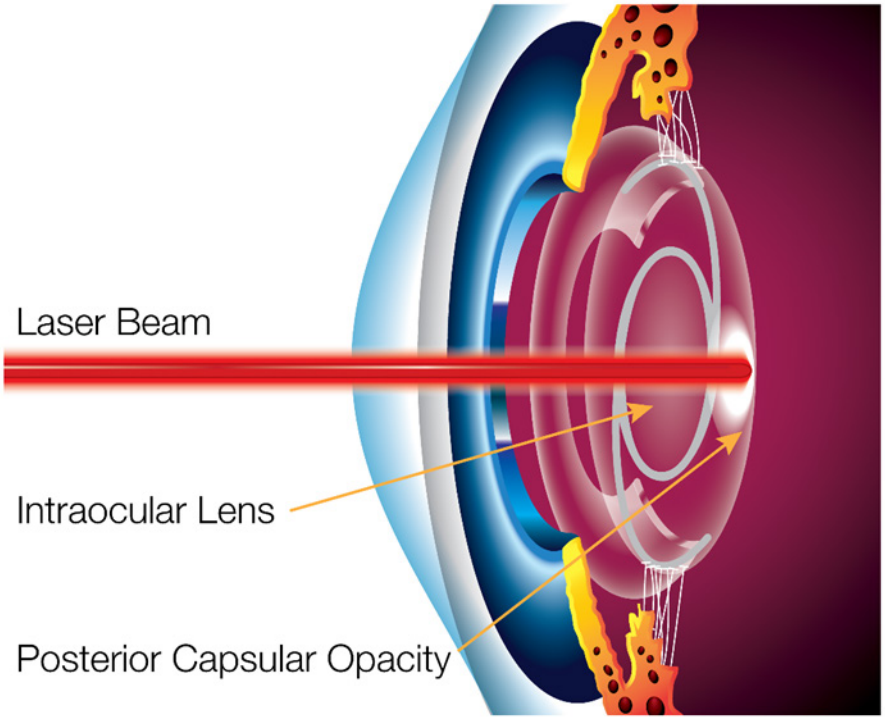

Figure 17.3: *Posterior capsulotomy*

REFRACTIVE SURGERY

Laser-Assisted In Situ Keratomileusis (LASIK) includes 2 steps: 1) cutting of a flap in the cornea (by mechanical microkeratome or a femtosecond laser) to pull it back and expose the corneal stroma for laser ablation; 2) ablation of the corneal stroma with 193nm excimer laser [31]. ArF excimer laser radiation is absorbed in a very shallow layer of the cornea (~200nm), and short pulse duration (10-20 ns) prevents heat diffusion from the light absorption zone during the pulse, by more than a few nanometers. These features enable very precise ablation of the cornea by ArF laser, ejecting the overheated surface material layer by layer, with the steps of about 200nm per pulse. Such precise tissue scalping with very shallow residual tissue damage zone allows precise reshaping of the corneal surface to correct refractive errors. After the laser reshaping of the stroma, the corneal flap is placed back over the treatment area, and its adhesion to the surrounding tissue improves over time due to natural healing.

Development of the femtosecond laser for corneal flap cutting, based on dielectric breakdown of the tissue in the tightly focused laser beam [32], enabled further improvements. Unlike mechanical microkeratome, laser cutting allowed the formation of vertical walls around the planar flap, which enabled better positioning of the corneal flap back into original location after ablation. This improved the consistency of refractive outcomes, and led to wide acceptance of the fs laser in refractive surgery[33, 34]. Ultrafast lasers also enabled refractive surgical procedures based on

intrastromal cutting, without excimer laser ablation: extraction of lenticules[35] and producing pockets for intrastromal rings[36]. The same laser systems have been applied to transplantation of the whole cornea or corneal endothelium[37], so called Endothelial Keratoplasty.

In Laser Thermal Keratoplasty (LTK) long pulses of the mid-infrared laser (Holmium YAG, 2.1mm wavelength) are applied in a ring pattern of 6-7 mm in diameter. Heating of the upper third of the corneal stroma results in collagen shrinkage, thereby steepening it to correct hyperopia[38]. Similar effect can be produced by electric current, the procedure called conductive keratoplasty[39]. This effect may regress somewhat over time.

CATARACT SURGERY

Conventional cataract surgery involves manual formation of an opening in the anterior lens capsule, fragmentation and evacuation of the lens tissue using ultrasound probe, and implantation of a plastic intraocular lens into the remaining capsular bag. The size, shape and position of the anterior capsular opening (one of the most critical steps in the procedure) is controlled by a freehand pulling and tearing the capsular tissue. Recently developed new laser-based technique greatly improves the precision and reproducibility of cataract surgery by performing anterior capsulotomy, lens segmentation and corneal incisions with a femtosecond laser[11]. Exact placement of the cutting patterns in tissue is determined by imaging the anterior segment of the eye using integrated Optical Coherence Tomography[12], as illustrated in Figure 17.4. Femtosecond laser produces 3-dimentional patterns of cutting to soften the crystalline lens and to cut a round opening in the anterior capsule. Three-dimensional cutting of the cornea based on diagnostic imaging can improve safety by creating multi-planar self-sealing cataract incisions, and can reduce residual astigmatism by exact placement of the limbal relaxing incisions.

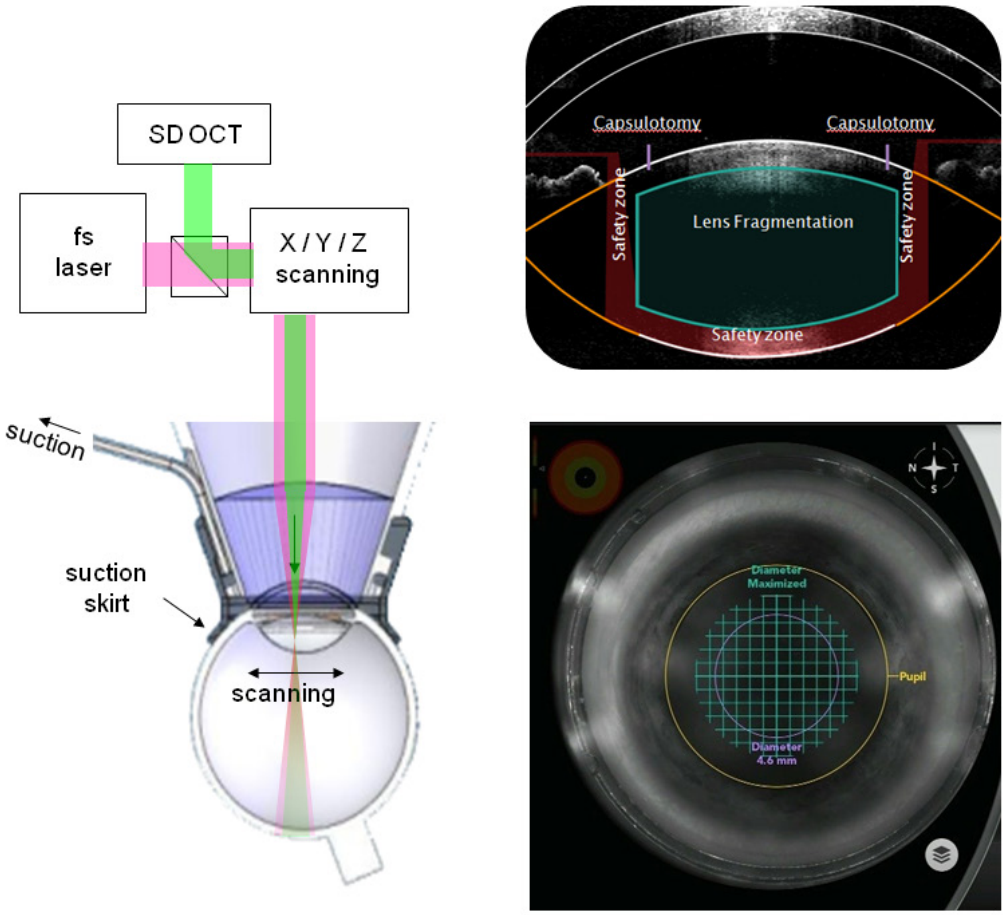

Figure 17.4: *Left: system diagram, including the OCT and femtosecond laser combined by a common scanner. Right: Side and top views of the eye, with overlay of the planned laser patterns.*

OTHER PROCEDURES (LESS COMMON OR UNDER INVESTIGATION)

- **Anterior Stromal Puncture** for traumatic recurrent corneal erosion.
- **Laser Suture Lysis** for post-filtration or cataract surgery.
- **Oculoplastic Surgery** (CO2 or Argon laser): port-wine stain, capillary hemangioma, basal cell carcinoma, trichiasis, xanthelasma, phthiriasis palpebrarum.
- **Photomydriasis** (to enlarge pupil)
- **Anterior Synechiolysis** for iris incarceration, adhesions involving anterior and posterior capsule, and vitreous body strands.

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