

Novel Retinal Laser Therapies

Xinyi Xie, Qinghuai Liu, Yannis M. Paulus

Xinyi Xie, Yannis M. Paulus, Department of Biomedical Engineering, University of Michigan, Ann Arbor, MI 48105, the United States
Yannis M. Paulus, Department of Ophthalmology and Visual Sciences, University of Michigan, Ann Arbor, MI 48105, the United States

Xinyi Xie, Qinghuai Liu, Department of Ophthalmology, the First Affiliated Hospital of Nanjing Medical University, Nanjing, P.R. China

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Correspondence to: Yannis M. Paulus, M.D., F.A.C.S., Department of Ophthalmology and Visual Sciences, University of Michigan, Ann Arbor, MI 48105, the United States.

Email: ypaulus@med.umich.edu

Telephone: +1-734-232-8105

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ABSTRACT

Retinal laser therapy has been playing a leading role in the care of numerous retinal vascular diseases such as retinal vein occlusions, proliferative diabetic retinopathy, diabetic macular edema, and sickle cell retinopathy since the 1960s. Although conventional retinal laser therapies have several disadvantages, the emergence of novel retinal laser therapies has ensured that lasers will continue to play a critical role in the treatment of retinal diseases. Retinal laser technology has undergone significant innovations to minimize collateral tissue damage while retaining the therapeutic effects. This review summarizes

several novel retinal laser modalities including micropulse laser, selective retinal therapy, nanosecond laser, pattern scanning laser with endpoint management, and navigated laser. The technological basis is described in addition to clinical studies validating their efficacy in patients.

Key words: Retinal laser therapy; PASCAL; Subthreshold micropulse laser; Selective retinal therapy; Photo-mediated ultrasound therapy; Nanosecond laser

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INTRODUCTION

Retinal laser therapy has been a vital therapeutic method in treating numerous retinal disorders including diabetic retinopathy, diabetic macular edema, retinal vein occlusions, and choroidal neovascularization (CNV) since it was first described over 55 years ago^[1]. Even with the development of pharmacologic therapies such as anti-vascular endothelial growth factor (anti-VEGF) treatment in recent years, lasers continue to play a role in the management of several retinal conditions.

Most retinal laser therapeutic approaches are based on the photocoagulation of retinal tissue. The exact biological mechanism of retinal laser photocoagulation remains an area of active investigation. One leading hypothesis of the mechanism is that the destruction of specific retinal cells, such as the most metabolically active photoreceptor cells, could result in a reduced retinal oxygen demand with subsequent down-regulation of angiogenic factors, such as vascular endothelial growth factor (VEGF)^[2,3]. Permanent retinal scarring is considered an unwanted side effect of conventional retinal laser therapy. Recent evidence suggests that reduced intensity and pulse duration retinal lesions might not lead to permanent retinal scarring, and that the outer retina can fill the damaged areas in animal models, including rabbits (Figure 1)^[4]. This remodeling has been demonstrated to result in restoration of retinal function with intact retinal ganglion cells in the lasered region, primarily through

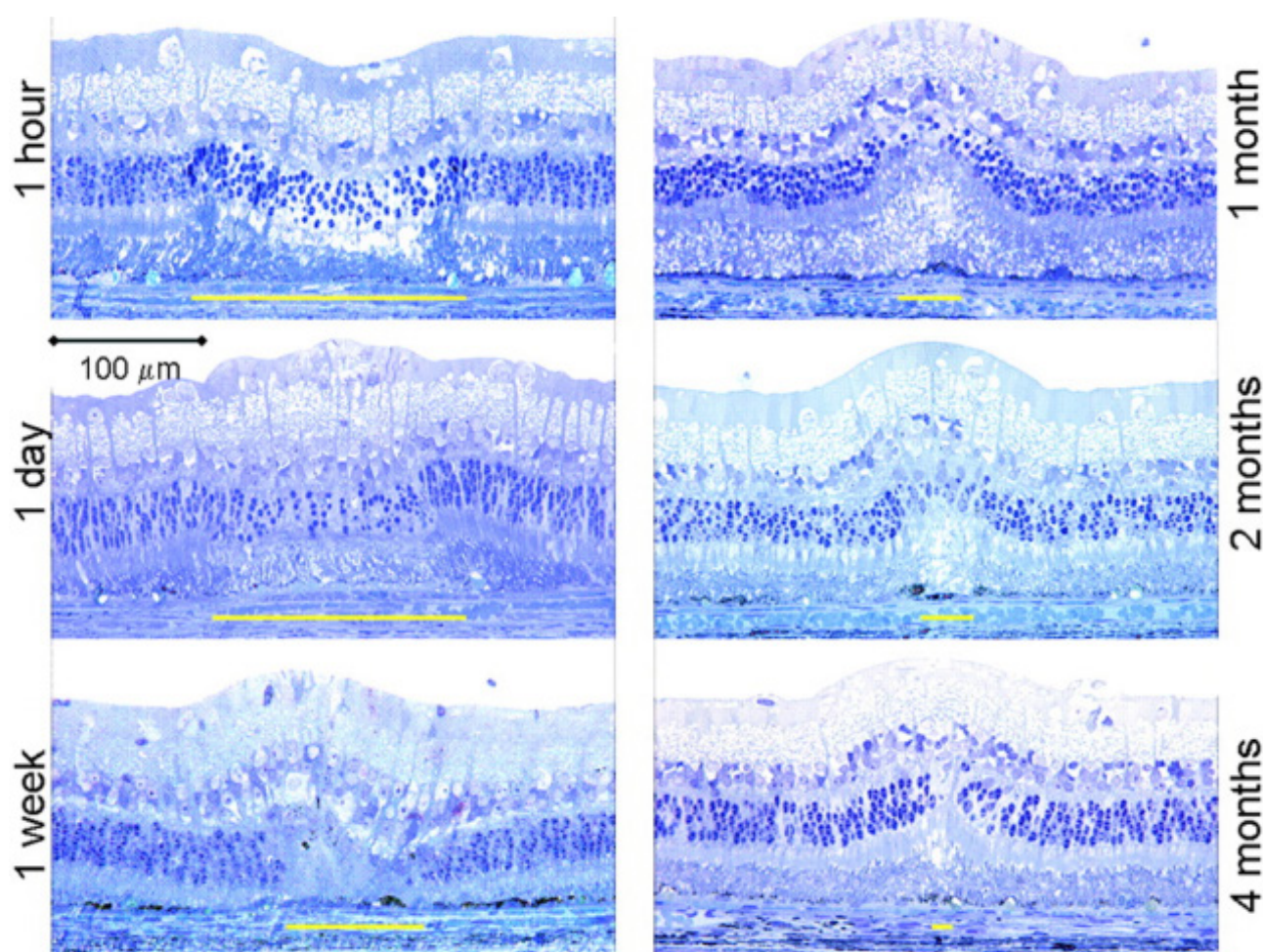


Figure 1 Histology shows retinal filling in of the damaged area in rabbits over four months produced at short (7-ms) pulse duration. The yellow bar indicates the extent of damage at the RPE-photoreceptor junction. Lesions exhibit localization of the damage to photoreceptors. Gliotic replacement of the damaged photoreceptors continues to contract over time, reaching almost continuous appearance of the outer retina with normal morphology at four months. Reprinted from “Healing of Retinal Photocoagulation Lesions.” by Paulus YM, Jain A, Gariano RF, Stanzel BV, Marmor M, Blumenkranz MS, Palanker D. 2008, *Investigative Ophthalmology & Visual Science (IOVS)*, 49(12): 5540-5545.

retinal remodeling rather than proliferation^[5]. Although conventional retinal laser photocoagulation has been proven to be effective and safe for the management of various retinal diseases through large, randomized clinical trials, it carries a risk of side effects such as patient discomfort during treatment, tedious duration of physician application, and decreased peripheral, color, and night vision^[6].

The standard laser treatment is applied using a continuous wave (CW) laser. Light energy from CW photocoagulation is converted into heat in the melanosomes of RPE cells and then diffuses to surrounding tissues. The visible clinical endpoint for conventional retinal photocoagulation is a retinal whitening associated with collateral anatomical and functional damage especially in the overlying photoreceptors. Since photoreceptors are metabolically the most active and numerous cells in the retina, the destruction of a fraction of the photoreceptors is thought to reduce the retinal oxygen demand in panretinal photocoagulation for diabetic retinopathy^[7]. Particularly for macular diseases, the collateral damage can result in an undesirable reduction in vision. To minimize retinal damage without compromising the therapeutic effect, new technologies with refined laser parameters including laser wavelength, pulse duration, laser beam size, and novel laser delivery systems have been developed to modify retinal laser therapy^[8-10]. In this review, we discuss recent innovations in retinal laser therapies including modified pulse duration, laser wavelength, and newly developed laser delivery systems to make retinal laser therapy more selective and precise.

SUBTHRESHOLD MICROPULSE LASER

Principles of Subthreshold Micropulse Laser

A novel laser modality termed subthreshold micropulse laser (SML) was developed to selectively target RPE in order to minimize collateral photoreceptor and neurosensory retinal tissue damage. This theoretically means that such lasers could be applied to the macula with far less likelihood of collateral damage. There is increasing evidence demonstrating that the metabolic activity and gene expression of the RPE can be altered by the application of laser, which results in the release of various cytokines that regulate angiogenesis and vascular leakage. Micropulse pulse duration can localize the laser effects to the RPE^[11,12]. The term “subthreshold” refers to laser energy applied with no visible intraretinal damage or scarring either during or after treatment. Mathematical models of SML have demonstrated that the increase in temperature in the neurosensory retina will not exceed the protein denaturation threshold when the minimum laser irradiance required for activation of the RPE is applied^[13]. This technique can be achieved by delivering micropulse laser as bursts of microsecond laser pulses separated by variable quiet intervals, allowing the tissue return to baseline temperature between pulses. The basic operation mode of SML can be briefly described as adjustment of the duty cycle of the laser. A duty cycle is the portion of a period of time when the laser has been emitted in which the laser is “on”. This “on” time is the duration of each

micropulse (typically 100 μ s to 300 μ s) and the “off” time (1,700 μ s to 1,900 μ s) is the interval between micropulses. When a low duty cycle is used, the “on” time is short which limits the time for thermal dissipation between each pulse thereby reducing collateral damage. So as to achieve the beneficial effects of laser, repeated pulses are added.

Currently, several kinds of commercial micropulse lasers are available for clinical use at wavelengths of 532 nm, 577 nm, 586 nm, 660 nm, and 810 nm^[14]. Among them, 810 nm diode laser, 577 nm yellow laser, and 532 nm green laser are three wavelengths utilized most commonly. A diode laser emitting at a wavelength of 810 nm is in the near infrared portion of the spectrum, which has the feature of deep penetration in the choroid, offering more selective absorption by melanin in the RPE and choroid and reduced absorption by photoreceptors and hemoglobin. This characteristic makes the 810 nm diode laser most suitable for indications requiring a treatment near the foveal zone since it affects mainly the deeper layers of retina while sparing the inner neurosensory retina. For laser with a 577 nm wavelength, the poor absorption of the yellow xanthophyll pigment of the macula may also allow for safer treatment administration closer to the center of the fovea^[15,16].

Clinical studies

SML has been found beneficial in various macular diseases, including central serous chorioretinopathy (CSCR), diabetic macular edema (DME), and cystoid macular edema (CME) secondary to branch retinal vein occlusion (BRVO). The first two macular diseases will be mainly discussed in the following sections.

Central Serous Chorioretinopathy

Preliminary studies demonstrated subthreshold diode micropulse laser (SDM) can achieve high treatment success with resolution of subretinal fluid for patients suffering from CSCR. In 2008, a prospective, noncomparative case series was performed with 26 eyes with persistent idiopathic central serous chorioretinopathy assigned to SDM laser therapy^[17]. After 6-months follow-up, almost all of the eyes with point source leakage had total resorption of subretinal fluid (SRF). However, patients with diffuse leakage had a less favorable response. Visual acuity improvement was observed in more than eighty percent of the patients. In 2013, a randomized, sham-controlled clinical trial was also conducted to evaluate the efficacy and safety of SDM for patients with CSCR, who were randomized to SDM laser treatment or sham procedure^[18]. At 3 months, the visual acuity was significantly improved in the SDM laser treatment group compared with the sham group. There was also no evidence of retinal damage induced by treatment. In 2009, Ricci demonstrated that ICG dye-enhanced SDM laser represents a viable approach for the management of CSCR with persistent serous neuroepithelial detachment^[19].

In a comparative, controlled, prospective study, 52 eyes from 52 patients with CSCR were treated with either SDM or intravitreal bevacizumab^[20]. The results reported that SDSM laser was superior to intravitreal injections of bevacizumab in the treatment of CSCR, which resulted in enhanced visual acuity and macular perimetry. Additionally, Emin and colleagues have compared the efficacy and safety of subthreshold 577 nm yellow laser and photodynamic therapy (PDT) in the treatment of CSCR^[21]. Although not statistically significant, the rate of complete resolution of SRF and increase in visual acuity were higher in the group that received yellow laser therapy after 12 months. Contrary to the PDT group, no eyes were unresponsive to yellow laser.

Diabetic macular edema

In 2005, a retrospective study reviewed 95 eyes suffering from clinically significant diabetic macular edema (CSME) treated with SDM laser^[22]. The results showed that CSME decreased in 96% and resolved in 79% of eyes treated with SDM laser. The visual acuity was stable or improved in 85% of treated eyes. With minimal chorioretinal damage, SDM was demonstrated to be safe and beneficial in the management of CSME. In 2006, a prospective, 3-month follow-up study evaluated low-intensity, high-density SDM laser for CSME with serial optical coherence tomography (OCT) as the primary endpoint^[23]. OCT central macular thickness demonstrated that 11 of the 18 eyes with persistent or recurrent CSME demonstrated an improvement with a 59% reduction of macular thickness. In 2007, a case series of 25 eyes with a long duration (3 years) of follow-up showed that SDM laser had a beneficial, long-term effect on visual acuity improvement and resolution of diffuse diabetic macular edema^[24]. However, the recurrence of macular edema was noted in 28% of patients in the third year.

There are also several small randomized clinical trials comparing SDM to the Early Treatment Diabetic Retinopathy Study (ETDRS) or modified ETDRS photocoagulation in eyes with diabetic macular edema (DME)^[25,26]. SDM was demonstrated as equal or superior to modified-ETDRS laser photocoagulation with less damage to the RPE and neurosensory retina confirmed by microperimetry and fundus autofluorescence. Although these studies have limitations such as small sample sizes, they have indicated that SDM treatment is likely as effective as conventional focal laser photocoagulation with less retinal damage.

SELECTIVE RETINAL THERAPY

Principles of Selective Retinal Therapy

Many diseases involving the macula, such as age-related macular degeneration (AMD), diabetic macular edema (DME), and geographic atrophy, are thought to be associated with dysfunction of the RPE cells. Thus, selective destruction of RPE cells was desired without causing thermal damage to the neurosensory retina, the photoreceptors, and the choroid. Thermal denaturation of these adjacent layers is possibly not necessary to achieve the desired therapeutic effects. Selective retinal therapy (SRT) was developed to target RPE selectively while sparing the neurosensory retina from thermal damage^[5]. SRT uses repetitive short laser pulses within the microsecond regime, which is shorter than the time needed for produced heat to diffuse to the surrounding layers. Thus, the delivered laser energy is predominately absorbed by melanosomes inside RPE cells causing localized high temperature. This results in explosive vaporization and microbubble formation in the RPE, which triggers mechanical disruption of RPE cells with subsequent proliferation and migration to restore RPE continuity and to improve the physiological functions of the RPE^[27].

Clinical studies

Several experimental studies have confirmed the safety of SRT. The first RPE-selective retinal laser treatment was achieved using 5 microsecond argon laser pulses at 514 nm and a repetition rate of 500 Hz in rabbit eyes^[28]. It verified the clinical potential of microsecond pulses in selectively destroying RPE cells while the surrounding retinal temperature remains at sub-lethal levels. Additionally, the efficacy and safety of SRT have been established through several clinical trials. Clinical applications may include diabetic macular edema (DME), central serous chorioretinopathy (CSCR), and dry

age-related macular degeneration (AMD) treatment of drusen. The first international, multicenter clinical trial involving patients with three pathological conditions, 12 patients with diabetic maculopathy, 10 patients with soft drusen, and 4 with CSCR, was performed with a Nd: YLF laser using a pulse duration of 1.7 μs ^[11]. More than half of the patients underwent a reduction in symptoms due to treatment. The results also demonstrated no visual loss after the treatment, as confirmed by microperimetry.

Diabetic macular edema

In a prospective, two-center, interventional, uncontrolled pilot study, thirty-nine eyes of 39 patients with previously untreated non-ischemic DME were treated with focal laser treatment using a Q-switched frequency-doubled Nd: YLF laser^[29]. The mean best-corrected ETDRS visual acuity (BCVA) was stabilized or improved in 84% of patients 6 months after SRT. More recently, in a prospective clinical study, twenty-three eyes of 21 patients with clinically significant DME were treated with SRT and followed for 6 months^[30]. An improvement visual acuity was noted in around 70% of the patients. In addition, microperimetry demonstrated that the mean macular thickness increased by 3.5 dB after laser treatment.

Central Serous Chorioretinopathy

SRT has also been demonstrated to be a therapeutic option for patients with acute or chronic CSCR in several clinical trials. In 2006, a pilot clinical study was conducted to evaluate the therapeutic effects of SRT for five patients with chronic CSCR and SRF resulting from a pigment epithelial detachment (PED)^[31]. The outcomes showed that SRT can be helpful to promote the resolution of SRF. Leakage was no longer detected 4 weeks after SRT in 4 of 5 patients. In addition, no side effects were noted in any of the patients. Another clinical study with more patients suffering from active CSCR demonstrated that all of the patients showed complete resolution of SRF and improvement in mean BCVA 3 months after SRT^[32]. In 2011, 30 eyes of 30 patients with acute CSCR were randomized to receive either SRT treatment or control (no treatment). At 3 months follow-up, the improvement in SRF and mean BCVA in the SRT group was significantly greater than patients in the control group^[33].

Age-related macular degeneration

Roider and colleagues reported in 1999 and 2000 that SRT treatment can contribute to the resolution of soft drusen in patients with dry age-related macular degeneration (AMD)^[11,34]. In 2010, SRT was performed in six eyes of six patients with geographic atrophy (GA) due to age-related macular degeneration^[35]. SRT was not able to stop GA progression as demonstrated by hyperautofluorescent areas of GA.

SRT using a continuous line scanning laser

In recent years, an alternative mode of SRT has been developed, which involves the application of a rapidly scanning CW laser to provide microsecond dwell time exposures to achieve RPE-selective laser irradiation with microsecond dwell times^[36]. This has been validated with experiments in rabbits using a continuous laser beam produced by the scanning mode of the pattern scanning laser (PASCAL, Topcon) to achieve selective targeting of RPE cells.

NANOSECOND LASER

Principles of nanosecond laser

With further investigation in understanding laser-tissue interactions,

there is increasing evidence demonstrating that laser pulse duration plays a critical role in the mechanism of laser-induced tissue injury^[37]. Laser pulse duration longer than 4 microseconds can result in thermal coagulative effects associated with tissue injury. With shorter laser pulses such as nanosecond pulses, the predominant effect will be more localized as micro gas bubble formation around endogenous melanosomes in the RPE leads to subsequent RPE cell damage. The rupture of targeted RPE cells with shorter laser pulses suggests many potential advantages for treating retinal diseases such as AMD, where the dysfunction of the RPE cells is a significant contributing factor to the disease. It has been demonstrated that the proliferation of injured RPE cells are likely to cause stimulation in expression of matrix metalloproteinases (MMPs), which are capable of digesting the main structural elements of the extracellular matrix (ECM) to avoid the drusen-like deposits under the RPE layers^[6]. Moreover, the disordered activity of MMPs plays an important role in early AMD development. The acute effects of nanosecond pulse duration laser have been investigated in animal models as well as on human RPE explants. The results have demonstrated that nanosecond laser has the ability to induce damage to the RPE cells by microbubble formation intracellularly without secondary thermal spread and collateral tissue damage^[38].

Retina regeneration therapy

Studies have also been performed evaluating the use of an innovative, non-thermal, ultra-low energy, short-pulse (3 nanoseconds), 532-nm laser as a novel method to delay the progression of early AMD, called the Retinal Rejuvenation Therapy laser (2RTTM; Ellex Medical Lasers Ltd., Adelaide, Australia). The nanosecond laser is intended to stimulate a biological regeneration of the RPE in patients suffering from relevant retinal diseases such as AMD. Several small clinical trials have demonstrated the potential of 2RTTM to reverse pathologic changes in patients with early AMD, which is characterized by the presence of drusen deposits, pigmentary abnormalities in the macular, and a thickened Bruch's membrane^[39-41]. As reported in 2014, 50 patients with bilateral intermediate AMD underwent a single nanosecond laser treatment in one eye^[39]. The drusen area was graded at baseline, 12- and 24 months post-treatment. The results showed that 44% of the treated eyes had a reduction in drusen area 12 months after treatment, which was maintained out to 24 months post-treatment. There was also a similar effect observed in the 22% of untreated fellow eyes. This single treatment also improved visual function as

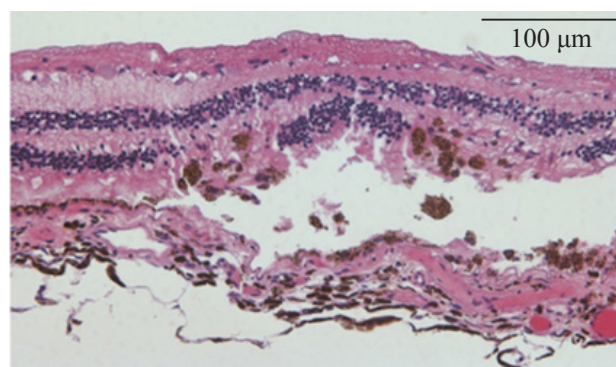


Figure 2 Hematoxylin and eosin (H&E) $\times 10$ magnification section of PASCAL laser shows regions of outer nuclear layer loss filled with an acellular matrix and migrating pigmented cells within the outer retinal layers. There is disorganization of the choriocapillaris layer and areas of retinal pigment epithelial (RPE) atrophy and hyperplasia adjacent to these regions. The inner nuclear layer, ganglion cell layer, and nerve fiber layer appear preserved. Reprinted from "Human Histopathology of PASCAL Laser Burns.", by Paulus YM, Kaur K, Egbert PR, Blumenkranz MS, Moshfeghi DM. 2013, Eye, 27(8): 995-6.

Figure 3 (A)

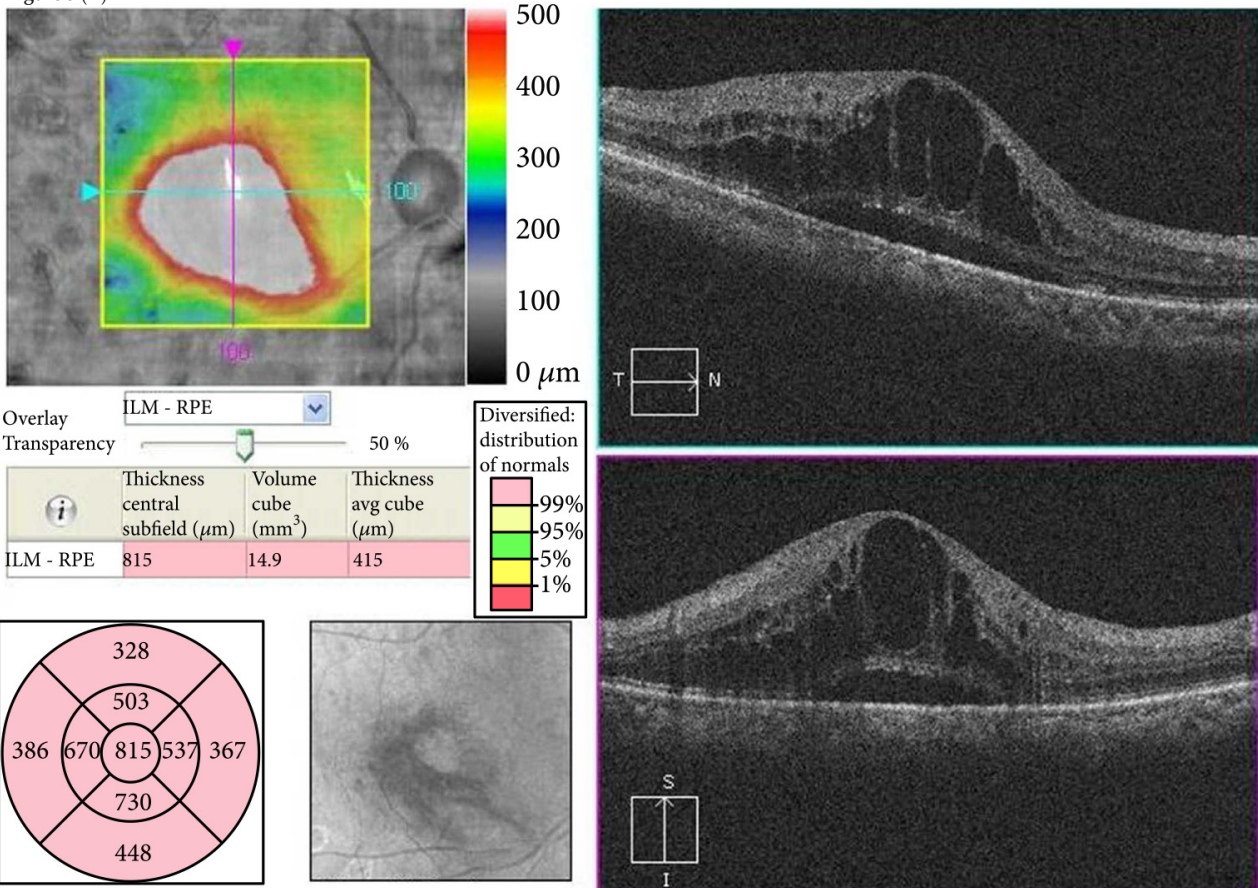


Figure 3 (B)

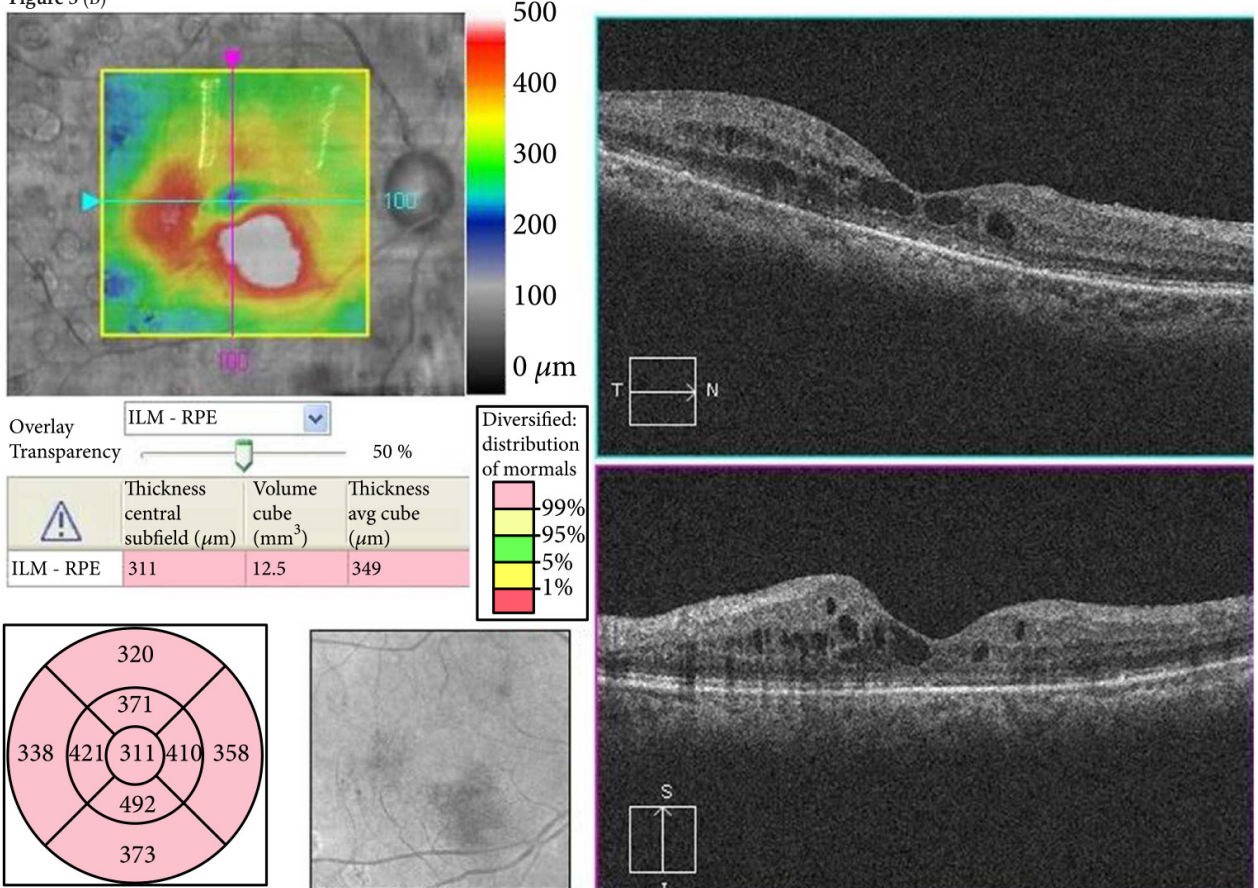
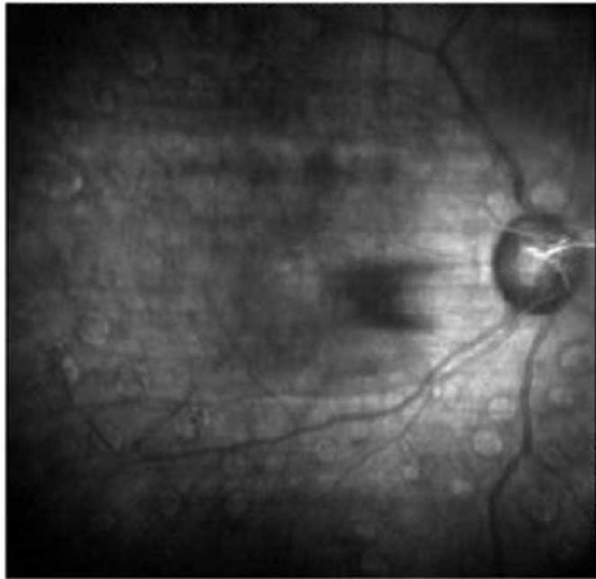
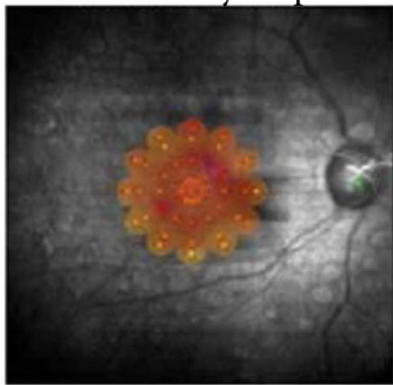
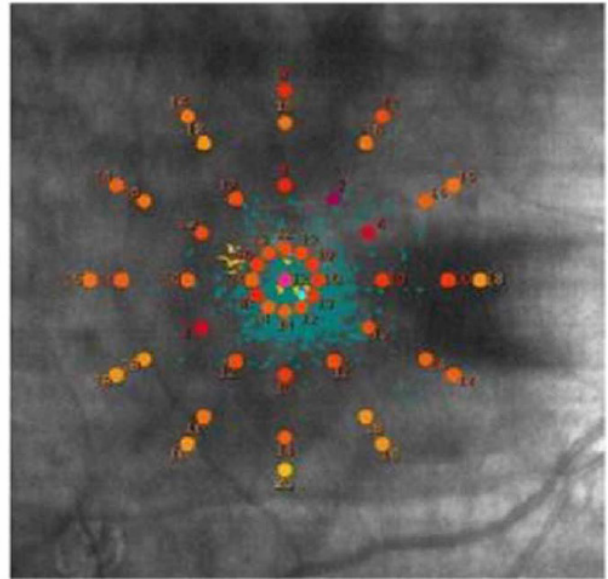


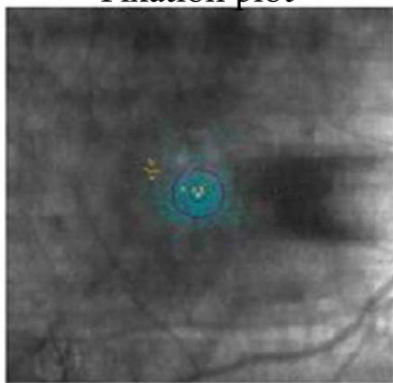
Figure 3 (C)



Sensitivity map



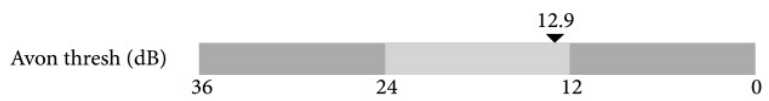
Fixation plot



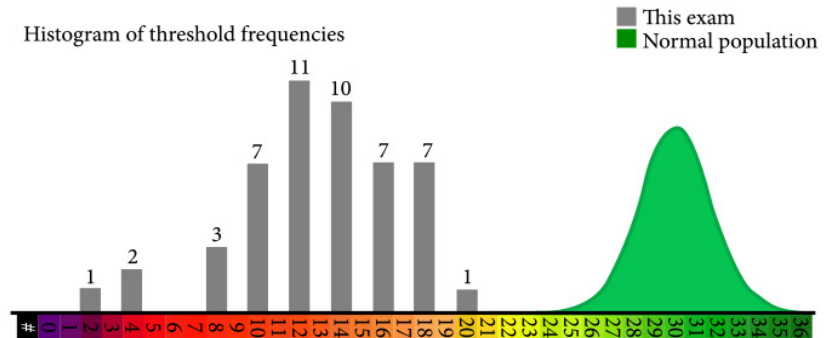
Bivariate contour ellipse area:
 63% BCEA: $0.8^\circ \times 0.8^\circ$ Area = 1.9°^2 , angle = -19.3°
 95% BCEA: $2.4^\circ \times 2.3^\circ$ Area = 17.4°^2 , angle = -19.3°

Macular intergrity:

- Custom grid -

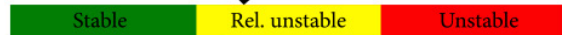


Histogram of threshold frequencies



P1 = 68%, P2 = 94%

Fixation stability



Fixation graph

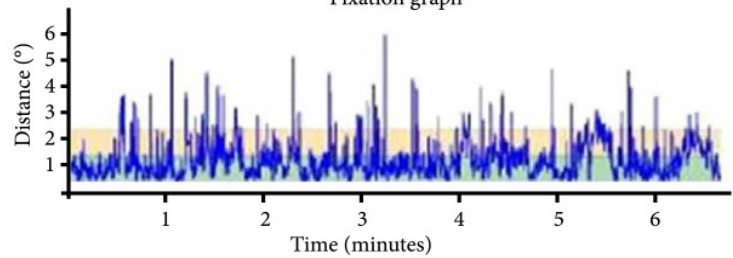
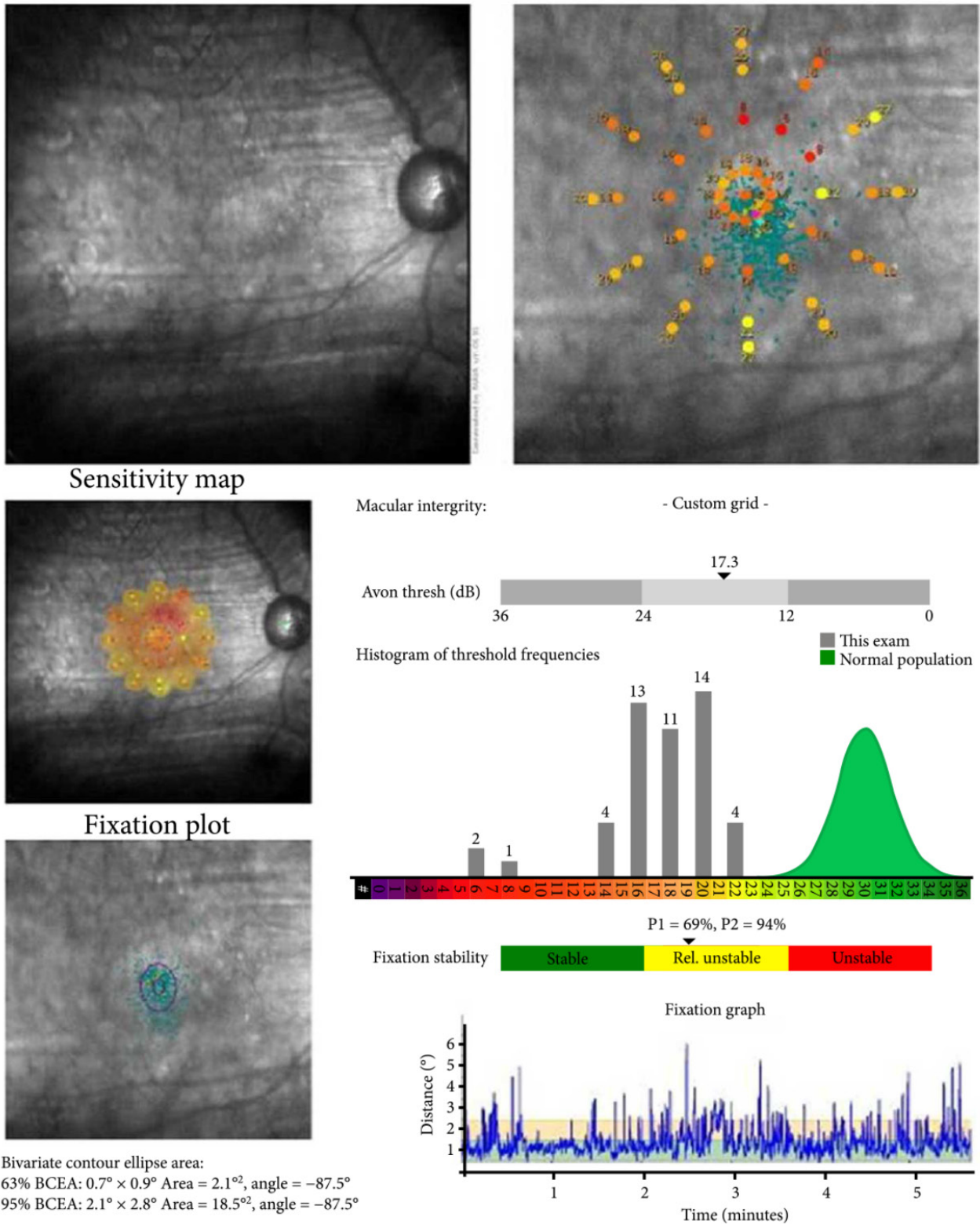


Figure 3 (D)



Bivariate contour ellipse area:
 63% BCEA: 0.7° × 0.9° Area = 2.1°², angle = -87.5°
 95% BCEA: 2.1° × 2.8° Area = 18.5°², angle = -87.5°

Figure 3 The right eye of a 70-year-old woman with diabetic macular edema treated with EPM and the PASCAL Streamline yellow laser: (A) Optical coherence tomography (OCT) before treatment. Macular edema containing cystoid macular edema and serous retinal detachment were observed in the fovea; (B) OCT at 6 months post treatment. Cystoid macular edema was significantly reduced, the serous retinal detachment resolved, and the foveal contour returned; (C) Macular sensitivity before treatment; (D) Macular sensitivity at 6 months after treatment. Sensitivity improved from 12.9 dB to 17.3 dB after treatment. Reprinted from “Subthreshold Photocoagulation Using Endpoint Management in the PASCAL® System for Diffuse Diabetic Macular Edema” by Hamada, M., Ohkoshi, K., Inagaki, K., Ebihara, N., Murakami, A., Journal of Ophthalmology, 2018; 2018: 7465794

measured by flicker sensitivity, using macular flicker perimetry, in both the treated and untreated eye for at least 12 months. Compared to spontaneous reduction in drusen load in the control, natural history AMD cohort, the regression of drusen deposits from 3-nanosecond laser treatment was significantly greater. This study also demonstrated the safety of nanosecond laser treatment. No retinal damage was observed after treatment on OCT images. Additionally, the nanosecond laser-induced molecular wound healing changes in the RPE that has been investigated in both enucleated human eye and mouse eyes. It has been found that the repaired RPE monolayer showed reduced AMD-associated pathology, with an associated increase in the expression of several ECM genes, including MMP-2, MMP-3^[38,42]. Recently, small clinical studies have also shown 3-nanosecond laser treatment to be safe and effective in reducing DME^[43].

Pattern scan laser

A semi-automated pattern-scanning retinal photocoagulation system, known as PASCAL (Topcon, Santa Clara, CA), was first introduced by Blumenkranz *et al.* in 2006^[44]. PASCAL allows for patterns of 4 to 56 burns to be rapidly applied in less than one second using a scanning laser with a pulse duration of 10–30 ms, which makes the laser treatment more comfortable and efficient than conventional single-spot delivery systems. With short laser pulse durations, PASCAL also takes advantage of improved lesion localization, increased safety, and reduced collateral injury while achieving similar clinical efficacy compared to conventional laser therapy. Human histological analysis of PASCAL laser burns have demonstrated that damage is limited to the outer retina (Figure 2)^[45].

PASCAL has also been shown to be an excellent laser method to treat patients with macular edema. Patterns for macular photocoagulation, including rings and arcs with a central foveal exclusion zone, allow for improved safety by ensuring that no laser burn can be placed closer than a preset distance from the center of the foveal avascular zone^[46]. While some studies have found it to be less effective than conventional laser, these studies have not accounted for the significant increase in the number of laser spots that are required to achieve an equivalent treatment area with shorter pulse duration laser burns^[47-49].

Endpoint Management

Endpoint Management (EPM) is a commercially available, model-based titration algorithm developed for both the 532-nm and 577-nm PASCAL laser which allows for quantifying laser dosimetry predictably ranging from non-damaging to intense coagulative tissue effects^[50]. PASCAL with endpoint management software enables grid pattern laser photocoagulation to precisely control low-level laser energy at short durations relative to a visible titration level. The titration algorithm begins with titrating laser power to a barely visible burn. After defining this energy as the 100% nominal energy level, other pulse energies can be selected as a percentage of that threshold by clinicians to be delivered to the treatment locations. This provides an approach to provide reproducible subvisible retinal laser therapy. As illustrated in several small clinical trials, subthreshold photocoagulation using PASCAL treatment with endpoint management software have provided significant beneficial effects to patients who suffer from CSCR and DME (Figure 3)^[51,52].

Current Clinical Challenges and Future Directions

While these retinal laser therapies can provide unprecedented treatment speed and targeted therapy, clinical challenges persist in the field. The largest clinical challenge is the lack of prospective, randomized controlled trials evaluating the efficacy of these

treatments with long-term clinical follow-up. In conditions that can wax and wane (CSCR and DME) and can take years to progress (early dry AMD), the small size of most studies and the limited duration of follow-up makes the clinical conclusions that can be drawn limited. Large randomized controlled, prospective clinical trials are needed to help us develop stronger evidence-based clinical guidelines. There has also been limited adoption of these novel laser systems by clinicians, possibly due to a lack of new payment to offset the cost of purchasing these new laser systems. Pharmacologic therapies are increasingly being demonstrated in large clinical trials funded by pharmaceutical companies, including anti-VEGF therapies, whereas laser therapies do not receive similar funding.

Scientifically rigorous studies have shown promising results with regard to the efficacy of intravitreal steroids and anti-VEGF therapies, but the repeated and long-term injections can be a considerable burden on the patients, physicians, family members, and the healthcare system while carrying infrequent but devastating ocular and systemic risks. In the future, we will increasingly consider the combination of laser and pharmacologic therapies. Clinical trials are needed evaluating possible synergistic effect from concurrently applied treatments, such as studies that have demonstrated that triamcinolone can affect the healing of retinal photocoagulation lesions^[53]. Lasers could also be envisioned in the future in theranostic applications using laser to activate nanoparticles to deliver targeted therapy.

CONCLUSION

Although large, randomized trials are still needed for validation, pre-clinical studies and small clinical trials have demonstrated the efficacy and safety of these novel retinal laser technologies for the management of retinal pathology. Furthermore, the development of nanosecond laser therapy has further expanded applications for retinal laser therapy beyond the conventional indications. We expect that continuous innovations in laser therapy and improvements in the understanding of the mechanisms of retinal laser therapy will ensure that lasers continue to play a critical role in our care of patients for many years to come.

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