

Review

Recent Innovations in Retinal Laser Therapy

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Abstract: The early history of retinal laser therapy began with the observation of solar blindness, leading to the development of various laser technologies for treating retinal diseases. The first retinal photocoagulation machine was developed in 1956, and subsequent advancements introduced ruby and argon lasers. While conventional theories posited that retinal damage was an indispensable prerequisite for therapeutic effects, emergent insights highlight the non-damaging mechanisms, such as photostimulation- and self-repair-related mechanisms. Novel therapies, such as subthreshold micropulse laser (SMPL) and selective retina therapy (SRT), are now being employed alongside innovative delivery systems to improve treatment efficiency and safety. Clinical studies are underway to evaluate the efficacy of these therapies for conditions like diabetic retinopathy and central serous chorioretinopathy. Despite the challenges in standardization and long-term evaluation, these innovations represent significant progress towards safer and more effective laser treatment for retinal diseases.

Keywords: retinal laser; subthreshold micropulse laser; pattern scanning laser; PASCAL; selective retina therapy; endpoint management; navigated laser treatment; targeted retinal photocoagulation; photo-mediated ultrasound therapy



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1. Early History of Photo-Mediated Retinal Laser Therapy

Retinal laser therapy originated from early explorations of photocoagulation, initially using sunlight and later xenon arc technology [1]. The first commercially available retinal photocoagulation machine, the Zeiss photocoagulator with xenon arc, was developed in 1956 [2] and demonstrated promise in the treatment of retinal tears, macular hole, intraocular tumors, and retinal vesicular diseases such as diabetic retinopathy [3,4]. However, early laser systems, such as the ruby laser (694 nm), encountered limitations when employed for vascular closure due to their poor absorption by melanin and blood, resulting in complications such as hemorrhage and scarring [5,6]. The introduction of the argon laser in 1964 marked a significant advancement. Its blue (488 nm) and green (514 nm) laser beams could be strongly absorbed by hemoglobin and melanin, making it more effective for vascular diseases [7]. Concurrently, advancements in delivery systems, such as the integration with slit lamps [8,9] and binocular indirect ophthalmoscopes [10], improved treatment precision. The development of laser technology enabled the delivery of continuous wave (CW) lasers with adjustable wavelength, intensity, spot size, and duration, significantly improving the efficacy and precision of retinal photocoagulation, thereby facilitating its broader clinical application [2,11]. Subsequently, retinal laser therapy has been widely

employed in managing diverse retinal disorders, and its efficacy has been validated by numerous studies, leading to its acceptance as the established treatment for a range of retinal diseases [12–18]. Despite these innovations, laser therapy has been associated with significant adverse effects, including a decline in visual acuity, visual field loss, color and night vision defects, reduction in contrast sensitivity [17,19–22], and more serious complications like choroidal neovascularization (CNV) and subretinal fibrosis [23–25]. In order to minimize these adverse effects, attempts were made to reduce laser-induced retinal damage while maintaining therapeutic efficacy. The intensity of CW laser treatment was decreased to reduce the damage, which was characterized by a barely noticeable lesion on the retina right after the treatment, with limited photocoagulation damage to the RPE and outer retina (threshold treatment) [26]. Such attempts were greatly facilitated by the advent of pulsed lasers in 1990 [27], which allowed for a more precise adjustment of laser parameters.

From sunlight to arc light to lasers, there has been a notable increase in precision and a decrease in unwanted damage in the early history of light-mediated retinal therapy (Figure 1). However, retinal damage has persisted as a necessity in traditional laser treatment, limiting its use in diseases involving the macula. To address these unmet clinical needs, the research focus has shifted toward the development of non-damaging and minimally invasive laser technologies. In addition, the prolonged treatment times and pain associated with conventional laser systems highlight the need for faster, less invasive techniques. In this review, we explore how recent innovations in retinal laser therapy address current clinical needs through three key aspects: mechanisms, laser technologies, and delivery systems. We also discuss emerging techniques still under development, such as photo-mediated ultrasound therapy (PUT). By synthesizing these advancements and challenges, this review aims to bridge the gap between historical knowledge and cutting-edge innovations, offering a valuable resource for researchers and clinicians.

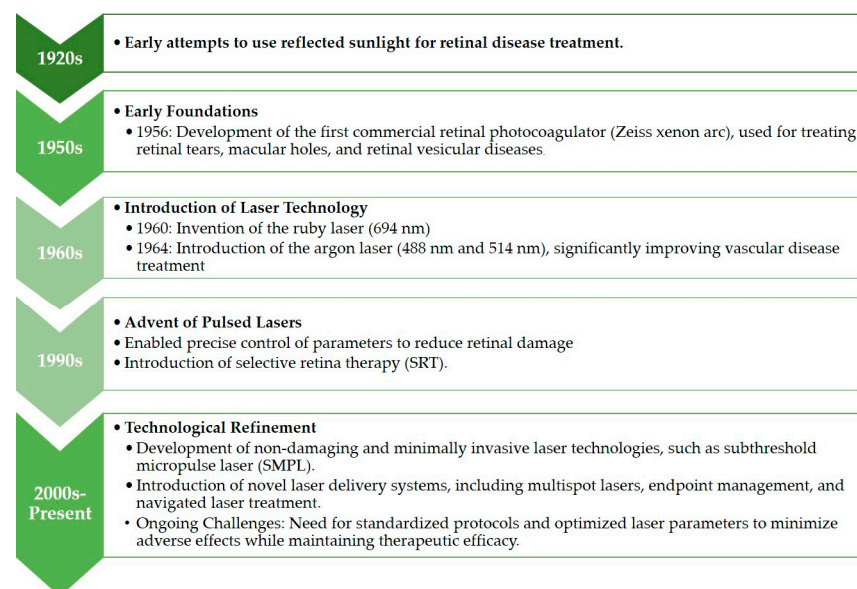


Figure 1. Timeline of the development of photo-mediated retinal laser therapy.

2. Mechanisms of Retinal Laser Therapy

2.1. Laser Photocoagulation

Conventional retinal laser therapy was believed to act primarily through the effect of photocoagulation. When light irradiates the retina, chromophores in the retina and choroid absorb light energy and transfer it into heat, causing protein denaturation known

as photocoagulation [11]. Depending on the duration and intensity of the laser, the heat may spread laterally and vertically, resulting in secondary damage to adjacent tissues.

The primary chromophores in the posterior segment of the eye include melanosomes in the retinal pigment epithelium (RPE), melanocytes in the choroid, xanthophyll primarily in Muller cells and neurosensory retina, and hemoglobin in the blood vessels of the neurosensory retina and choroid [28]. Among them, RPE melanin is the strongest absorber, particularly when the light wavelength is above 500 nm [29]. For laser wavelengths between 514 and 810 nm, the temperature consistently reaches its peak at the RPE and then rapidly declines towards the retina, with a somewhat slower decrease towards the choroid [30]. In the early practice of retinal photocoagulation, high-intensity lasers were employed to obtain an immediately visible and distinct white retinal laser spot (suprathreshold) [31]. The high power of the laser results in the diffusion of heat, which causes damage to the surrounding tissue. Typically, the laser spot continues to expand after treatment.

2.2. Traditional Theories for the Therapeutic Mechanisms of Retinal Laser Therapy

For years, the assumption was that retinal damage was inevitable or even the purpose of the treatment. The therapeutic effects of this “destructive” treatment were believed to be based on photocoagulation. However, the veracity of this assumption is questionable. In the case of diseases such as retinal tears and peripheral degeneration, this assumption appears to be justified, given the necessity for scar formation to facilitate re-adhesion of the retina to the choroid. However, in the context of diseases such as diabetic retinopathy (DR) and macular edema, this damage may not be a prerequisite. The mechanism underlying the laser treatment for retinal diseases like DR remains incompletely understood, even after more than six decades of its application. The following hypothesis has been proposed to explain the mechanism [32]: The thinning of the retina due to laser photocoagulation reduces the oxygen demand, and the thinner retina and retinal scar also allow oxygen to travel more easily from the choroid to the inner retina, thus relieving hypoxia. Additionally, these alterations result in vasoconstriction within the retina, which can help to reduce edema. Furthermore, the reduction in hypoxia can also reduce growth factors like vascular endothelial growth factor (VEGF), impeding neovascularization.

2.3. New Insights into Therapeutic Mechanisms of Retinal Laser Therapy

As laser technology has advanced, novel insights have emerged regarding the mechanisms of retinal laser treatment. If the traditional understanding of laser treatment is based on the destruction of retinal tissue, a new understanding has emerged that the therapeutic effect could be derived from the self-protective and self-repairing of the retinal tissue. One theory is that the expression of biological factors such as heat shock proteins (HSPs) are upregulated under thermal stress, which does not result in cell death [33,34]. The activation of HSPs in retinal pigment epithelium (RPE) cells upregulates the endoplasmic reticulum unfolded protein response, thereby improving cell function and metabolism, inhibiting apoptosis, and promoting local and subsequent systemic therapeutic immunomodulation [35]. The enhancement of cellular function leads to the restoration of normal expression and responsiveness of RPE-derived cytokines, interleukins, and other chemical mediators of retinal function and autoregulation [29]. These processes, known as photostimulation, ultimately result in the downregulation of inflammation, a reduction in apoptosis, and the inhibition of neovascularization. In contrast to photocoagulation, which necessitates the death of treated cells, photostimulation aims to preserve the viability of these cells to facilitate the restoration of the diseased region. The increased awareness of this mechanism has contributed to the development of non-damaging and minimally damaging retinal

laser techniques. Notably, this mechanism is not disease-specific and is hypothesized to be effective in diverse retinal disorders.

Another proposed mechanism relates to the processes of repair following laser damage. In this mechanism, it is not the laser-irradiated cells that play a therapeutic role; rather, it is the surviving RPE cells surrounding them. In vitro studies have shown that after laser photocoagulation, RPE cells can proliferate to repair induced lesions [36]. Animal experiments revealed that following laser-induced loss of local photoreceptor and RPE cells, neighboring undamaged cells can migrate to fill in the lesion [37–41]. When the lesion is small enough and light, it can be completely refilled [37].

Additionally, there has been a noteworthy development in our understanding of the mechanisms underlying laser-induced cellular damage. Research findings indicate that, when pulse durations are less than 20 μ s, the predominant mechanism of cell damage is cavitation induced by photodisruption [42]. However, in pulse durations exceeding 50 μ s, photothermal damage (photocoagulation) emerges as the predominant mechanism [43].

The evolution of understanding of the mechanism of retinal laser therapy has led to the realization that laser-induced damage might not be necessary for all retinal laser treatments. Consequently, how to achieve a therapeutic effect while minimizing unwanted retinal damage has become a hot topic for research investigation, and the concept of subthreshold or subvisible retinal laser therapy has gradually gained traction. In contrast to conventional CW suprathreshold lasers, which can result in full-thickness retinal scarring with visible burns right after the irradiation, subthreshold laser-treated areas are not ophthalmoscopically visible. However, it may be identified through fluorescein angiography, which can allow visualization of its changes to the RPE, choriocapillaris, and outer retina [29]. In this review, we will focus on discussing novel retinal laser therapies based on these new therapeutic mechanisms (Table 1), especially subthreshold retinal laser therapy, and we will also discuss novel laser delivery techniques.

Table 1. Comparisons between different laser treatments.

Type	Mechanism	Cell Death	Wavelength	Power Setting	Duration	Pulsed Laser	Foveal Treatment	Repeat Treatment	Clinical Application	Advantages	Disadvantages
SMPL	Photostimulation of RPE	No	810 nm 577 nm	Titration; Fixed; Guiding system	0.1–0.3 ms	Yes	Yes	Yes	DME, CSCR, RVO, RP, DR, AMD, ...	Foveal treatment; Non-damaging; Allows repeated treatment; Higher safety; Wide application (not disease-specific therapeutic mechanisms of photostimulation)	Controversy over titration; Invisible laser spot; Might need multiple treatments
SRT	Mainly through photodisruption of RPE; Might have photostimulation on RPE	Yes, RPE cell	532 nm/527 nm/514 nm (higher melanin absorption)	Titration based on microbubble formation	<5 μ s (1.7 μ s)	Yes	No	Yes	DME, CSCR, SRF, ...	Selectively disrupt RPE cells; Allow repeated treatment;	Limited commercially available instruments; Lack of direct optical feedback

Table 1. Cont.

Type	Mechanism	Cell Death	Wavelength	Power Setting	Duration	Pulsed Laser	Foveal Treatment	Repeat Treatment	Clinical Application	Advantages	Disadvantages
2RT	Photodisruption of RPE	Yes, RPE cells	532 nm	Titration based on microbubble formation	3 ns	No; Single laser pulse	No	Yes	AMD, DME, CSCR	Selectively disrupt RPE cells; Minimal heat transfer outside the cell; Allow repeated treatment;	RPE “explosion” might cause subretinal hemorrhages; Limited photo-stimulation effect
PUT	Photo-mediated acoustic microcavitation bubbles within the absorbing tissue (eg, microvessels)	Yes	532 nm	0 to 1.4 μ J/pulse for rabbits; Can be OCT or photoacoustic guided	1–10 ns	Yes	Possibly	Yes	Not yet clinically approved	Selectively destroy the new vessel due to high optical absorption contrast between blood vessels and surrounding tissues; Low energy requirement	Still under development; More research is needed

subthreshold micropulse laser (SMPL); selective retina therapy (SRT); retinal rejuvenation therapy (2RT); photo-mediated ultrasound therapy (PUT); central serous chorioretinopathy (CSCR); diabetic macular edema (DME); retinal vein occlusion (RVO); retinitis pigmentosa (RP); diabetic retinopathy (DR); age-related macular degeneration (AMD); subretinal fluid (SRF); optical coherence tomography (OCT).

3. Novel Retinal Laser Therapy

3.1. Subthreshold Micropulse Laser (SMPL)

SMPL has been developed to selectively photothermally stimulate the RPE cell without causing damage to the overlying neurosensory retina, thus allowing for macular treatment and repeated applications [44]. It delivers laser energy in a train of short, repetitive pulses, measured in microseconds. Each pulse is characterized by an “on and off” time frame. The “off time” is crucial for the tissue to cool-down between pulses, thereby reducing heat accumulation and enabling the average power to be set at a much lower level than in most conventional CW lasers, which are often limited by a minimum power of around 50 mW [30]. A previous study demonstrated that the temperature rise induced by CW lasers and SMPLs of the same average energy is equivalent [45]. Thus, when an equal temperature rise is achieved, the pulse pattern of SMPLs allows for a more dramatic temperature (100,000 °C/s) change in a single pulse than CW lasers (100 °C/s), making MPLs a more effective treatment [46]. Additionally, the brief laser pulse in SMPL reduces the transfer of heat to untargeted tissue, leading to a more selective therapeutic effect with higher safety. Meanwhile, the reduced diffusion of heat into the choroid attenuates the pain caused by laser-stimulated pain receptors in the choroid [47]. In SMPL, the pulse length and duty cycle are closely related to tissue warming and heat diffusion. The short pulse lengths and low duty cycle permit maximal thermal localization in RPE cells [48].

In SMPL treatments, the 810 nm infrared diode laser and the 577 nm yellow laser are the most frequently employed [49]. Typically, SMPL [50] employs a repetition rate of 500 Hz, with a duty cycle of 5% to 15%. It delivers 100 to 300 ms bursts with pulse durations of 0.1 to 0.3 ms. Given that SMPL utilizes a subthreshold power with an invisible laser spot during treatment, a multispot laser modality is generally employed, with the spacing set to 0 to stimulate a maximum number of cells [44]. Since the therapeutic range of SMPL is wide (can be greater than 15 watts), it is possible to apply a fixed laser setting to all patients without causing laser-induced retinal damage [29]. The International Retinal Laser Society also proposed the use of fixed laser parameters for SMPL in 2020 [51]. Conversely, the Subthreshold Laser Ophthalmic Society’s guidelines for subthreshold laser therapy in

retinal diseases recommend a titration and a power setting of 50% of threshold power [52]. The controversy surrounding the determination of laser intensity through titration has been a point of debate. As previously stated, the therapeutic effects produced by retinal lasers are closely related to the increase in tissue temperature caused by the lasers. And this temperature rise is directly influenced by light absorption, which may vary due to the heterogeneous distribution of melanosomes within and between RPE cells, across species and fundus regions, and variations in choroidal and retinal vasculature [53]. In light of this theory, it is noteworthy that even if titration is employed, different regions of the retina within the same individual may require varied laser intensities to achieve equivalent therapeutic outcomes. In addition, there is no standardized protocol for titration, including the area of application, the use of CW or pulsed laser, and the appropriate intensity level according to the threshold value [50]. Furthermore, the subjective titration process may be affected by the treatment environment and the experience of the operator.

Donati et al. [54] compared the efficacy of two treatment regimens for diabetic macular edema (DME): a fixed treatment and a variable treatment that used titration with a subthreshold yellow micropulse laser. This study encompassed 39 eyes, and the findings indicated the efficacy of both treatments. However, the fixed treatment was regarded as more suitable, as it reduced treatment time and the potential for errors arising from improper titration during the transition from CW to micropulse mode (however, no such error was reported in this study). While Donati's findings suggest that fixed-parameter treatment may be safe and effective, a recent study indicates that the necessary laser parameters may vary depending on the circumstances. In the study on the efficacy of SMPL in treating acute and chronic CSCR, the lowest effective SMPL power for treatment differed, with a lower power requirement observed for chronic CSCR [55]. These findings highlight the necessity of establishing standardized laser parameters. A typical type of SMPL called the low-intensity/high-density subthreshold diode micropulse laser (SDM) has been developed, with the notable feature of completely avoiding laser-induced retinal damage (non-discernable by anytime and by any known means, such as fluorescein angiography (FA), fundus autofluorescence (FAF), and spectral-domain optical coherence tomography (SD-OCT) whilst retaining its effectiveness [56] (Figure 2). SDM treatment generally utilizes a low duty cycle of 5%, with the power set to strictly avoid laser-induced retinal damage (low-intensity) while ensuring complete and confluent coverage of the diseased retina (high-density) [46].

SMPL treatment has been utilized in the management of a range of retinal diseases, with diabetic macular edema (DME) and central serous chorioretinopathy (CSCR) being the most extensively studied.

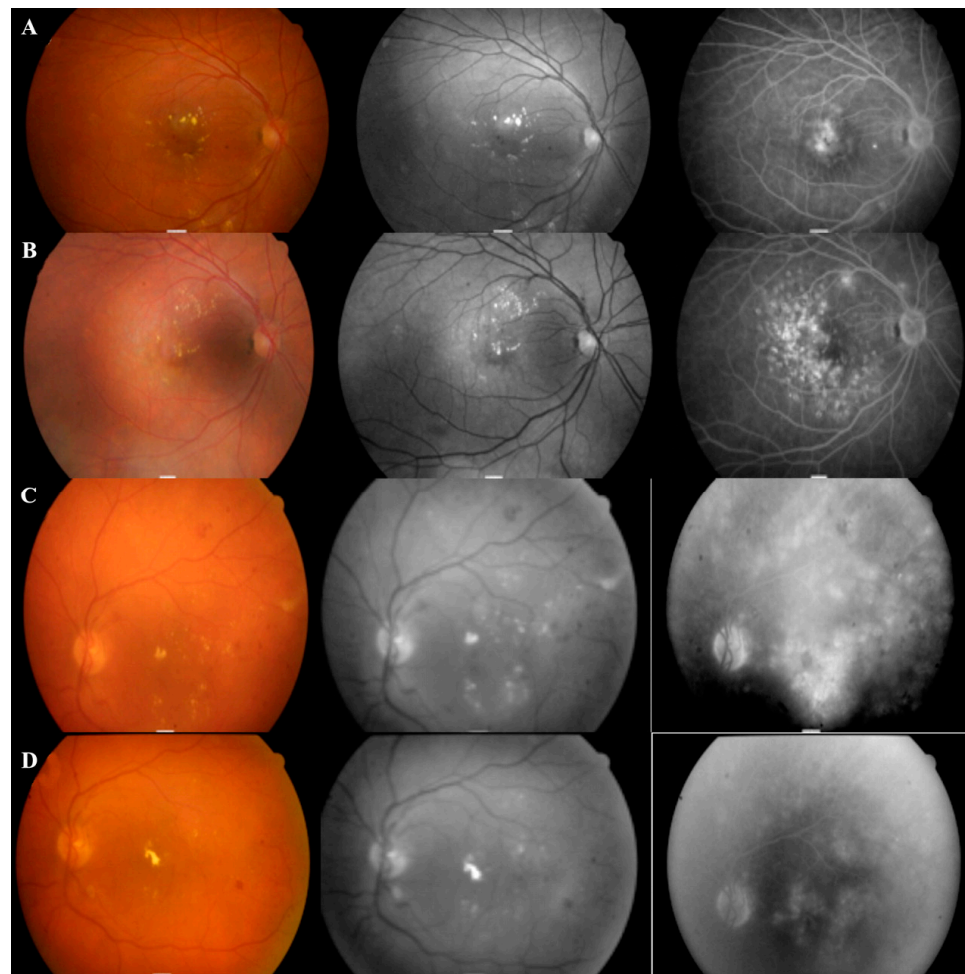


Figure 2. Baseline fundus color photography, red-free photography, and fluorescein angiography (FA) (A) of an mETDRS group patient; (B) of the same patient 3 months after mETDRS treatment, showing barely visible burns in the color photograph, although the laser scars can be easily identified in FA; (C) of an HD-SDM group patient before treatment; and (D) of the same patient after HD-SDM treatment, showing that even in FA, micropulse treatment remains nonvisible. Reprinted (adapted) with permission from [57]. Licensed under CC BY 4.0.

The efficacy and safety of SMPL in the treatment of DME have been confirmed by numerous studies [58–63]. SMPL has demonstrated equal or superior efficacy to conventional laser photocoagulation in the treatment of DME, accompanied by a reduced incidence of retinal damage [63–67]. However, a slightly higher number of laser treatments may be required [68]. Several studies have been conducted to compare the efficacy of anti-VEGF and SMPL therapy in the treatment of DME, though the results have been inconsistent [69–71]. The variability in outcomes may be attributed to the central macular thickness (CMT) before treatment, as evidenced by a study [71] that found SMPL therapy to be more efficacious than anti-VEGF injection in DME patients with relatively better visual acuity and central CMT ≤ 350 μm . Conversely, SMPL therapy exhibited minimal effectiveness when the CMT was higher than 350 μm . On the other hand, the combination of the anti-VEGF and SMPL treatment has been shown to reduce the number of anti-VEGF injections, with equal or superior efficacy in comparison to anti-VEGF monotherapy [72–75]. In addition, a study using novel imaging techniques like OCT angiography (OCTA) showed that SMPL not only optimizes the RPE function in DME patients but also improves their retinal vascularity [76].

SMPL is also widely utilized in the treatment of central serous chorioretinopathy (CSCR). CSCR is a common macular disease that is characterized by an accumulation of

serous fluid beneath the neurosensory retina. The retinal pigment epithelium (RPE) cells can transfer subretinal fluid (SRF) to the choroidal vessels. Given that SMPL functions by photostimulating the RPE, it may represent a highly promising treatment for CSCR. A meta-analysis involving 11 studies with 834 eyes showed that SMPL had similar efficacy and better safety compared to other treatment modalities for chronic CSCR [77]. Due to the self-healing tendency of CSCR, there is less research on the treatment of acute CSCR with SMPL. The present studies demonstrate that early treatment with SMPL results in enhanced visual acuity and contrast sensitivity, a shortened disease course, and a reduced likelihood of CSCR developing into chronic and recurrent CSCR [78–80]. Despite the existence of numerous clinical studies investigating the application of SMPL for the treatment of CSCR, controversy remains around the effectiveness of the approach, especially when compared with photodynamic therapy (PDT) [81–84]. This discrepancy in outcomes between different experiments may be attributable to variations in laser parameter settings. Moreover, SMPL has been reported to be effective in the treatment of CSCR with point source leakage, while a less favorable response was noted in cases with diffuse leakage [85]. In the treatment of CSCR, SMPL can be applied in three different ways [86]: (1) minimal treatment, which covers the dye leakage area in FA or indocyanine green angiography (ICGA); (2) SD-OCT-based treatment, with the aim of covering the SRF area; (3) panmacular treatment to stimulate a large area of RPE cells. Given the frequent necessity of macular treatment in CSCR treatment, the use of SDM was preferred to ensure maximum efficacy with minimal damage [87,88].

In addition to DME and CSCR, SMPL treatment has also been found to be effective in many other retinal diseases, including macular edema secondary to branch retinal vein occlusion (BRVO) [89,90], severe nonproliferative diabetic retinopathy (NPDR), proliferative diabetic retinopathy (PDR) [91–94], retinitis pigmentosa (RP) [95], persistent subfoveal fluid (PSF) after rhegmatogenous retinal detachment (RRD) surgery [96–98], age-related macular degeneration (AMD) [99,100], serous retinal detachment associated with tilted disc syndrome [101], refractory postoperative cystoid macular edema [102], dome-shaped macula in myopic eyes [103], and persistent macular thickening after epiretinal membrane peeling [104]. Furthermore, SMPL has been shown to have the potential to prevent neovascular conversion in dry age-related macular degeneration (AMD) [105,106]. Given that the mechanism of action of SMPL is primarily through photostimulation, a mechanism that is not disease-specific, there is a possibility that SMPL may be used in the treatment of a wide range of retinal diseases, including less-studied retinal disorders with limited structured research. Due to the non-disease-specific therapeutic mechanism of SMPL and its high safety profile, it may be practical for the treatment of rare diseases. However, it should be noted that since SMPL primarily functions by stimulating the RPE, its efficacy may be diminished in cases of widespread RPE loss.

3.2. Selective Retina Therapy (SRT)

SRT uses a pulsed laser with short pulses to target RPE cells while sparing the surrounding tissues. It normally utilizes a green wavelength such as 514, 527, or 532 nm to achieve higher melanin absorption. The duration of the laser pulse is usually less than 5 μ s [107]. The only commercially available laser is a Q-switched, frequency-doubled Nd:YLF laser that emits repetitive 1.7 μ s laser pulses 15 to 30 times at a repetition rate of 100 Hz [46]. The absorption of a short pulse by melanosomes in RPE cells results in a sharp increase in temperature, leading to the formation of microbubbles (microcavitation) around melanosomes in RPE cells; the expansion of these bubbles can mechanically disrupt the cellular membranes, leading to selective damage to the irradiated RPE cells, which is known as photodisruption [108,109]. As previously stated, the mechanisms of cell death

induced by varying laser pulse durations are not the same. The short duration of the laser in SRT resulted in the death of RPE cells primarily through photodisruption (pulse duration $< 20 \mu\text{s}$) [42]. The short laser pulse also reduces heat diffusion out of the cell, and the low repetition rate provides sufficient cooling time. Together, these factors enable the disruptive effect of SRT to be confined to the RPE cell while sparing surrounding tissues. As the neural retina remains unaffected, the laser spots are not visible under ophthalmoscopy during the treatment; detection is only possible through FA and FAF [110,111]. This is markedly distinct from photocoagulation, where the longer pulse duration results in cell death primarily through thermal denaturation, while the heat diffusion is pronounced. The potential therapeutic mechanism of SRT relies on the adjacent surviving RPE cells to repair the laser-damaged area by proliferation and migration, thereby reconstituting the monolayer structure of the RPE [112]. Furthermore, SRT has been demonstrated to modify the release of cytokines from RPE, including VEGF, platelet epithelium-derived factor (PEDF), pro-inflammatory cytokines, and matrix metalloproteinases (MMPs). The alternation of these cytokines may improve the molecular diffusion rate through Bruch's membrane (BM), thereby achieving the therapeutic effect [109].

Given that only a single SRT system is available for commercial use, clinical research employing SRT is limited in scope. The existing clinical studies with small sample sizes have demonstrated the safety of SRT in DME [112–114], CSCR [115–119], persistent subretinal fluid following RRD surgery [120], and subretinal fluid (SRF) associated with choroidal nevus. For DME, two studies demonstrated improvement solely in BCVA [113,114], while one study indicated only an improvement in CMT [112]. In clinical studies employing SRT to treat CSCR, a consistent improvement in BCVA was observed [115–119], with slightly less than or more than half of the patients achieving complete resolution. Re-treatment of under-treated areas identified by FA immediately after the first treatment accelerated the resolution [118].

One of the major drawbacks of SRT is the lack of direct optical feedback. The inability to directly observe the laser spot during treatment makes it difficult to assess whether the laser-induced destruction of RPE cells was achieved, which is necessary for the therapeutic effect. Since the photodisruption of RPE is achieved through the formation of microbubbles, the generation of microbubbles can be monitored to assess whether photodisruption is taking place. Generally, microbubble formation can be monitored in four ways: optoacoustic (photoacoustic) [114,121,122], light reflection [123], small bandwidth interferometry [124], and broad bandwidth interferometry-OCT [125,126].

The R: GEN [127] is the only commercially available SRT laser. It integrates a 527 nm Q-switched, frequency-doubled Nd: YLF laser with Dual Dosimetry technology to measure reflectometry (back-scattered light) and photoacoustic signal (thermo-elastic pressure waves) to offer real-time titration of laser energy delivery to the RPE. The efficacy and safety of R: GEN has been evidenced in two clinical studies employing SRT treating CSCR [121,128].

Another novel microsecond laser system, named “Spectralis Centaurus” [129], which combines a 532 nm wavelength laser with an OCT system, has recently been introduced to the SRT treatment. This system was integrated with an upgraded diagnostic SPECTRALIS system, enabling the combination of beam control for treatment planning with real-time optical coherence tomography (OCT) overexposure protection of the photoreceptors. This system enables precise control of energy deposition, along with optical monitoring of tissue response, thereby enabling selective limitation of cell death to the RPE in SRT treatment. The findings of both the animal study [130,131] (incorporated porcine eyes), and the clinical study (comprised three DR patients) [132,133] demonstrated a high degree of sensitivity and specificity when statistical evaluation was conducted on the real-time

feedback-controlled dosimetry (RFD) stimulation pattern for the dosimetry algorithm. Furthermore, the safety and efficacy of the Spectralis Centaurus system for treatment purposes have also been substantiated.

3.3. Retinal Rejuvenation Therapy (2RT, Subthreshold Nanosecond Laser, SNL)

2RT typically employs a single, ultra-short, laser pulse with a duration of 3 ns and a spot size of 400 μm diameter. The laser beam is emitted by a 532 nm Q-switched frequency-doubled Nd: YAG laser. The power is adjusted according to titration with appropriate dosimetry methods (usually around 0.15–0.45 mJ). The laser–tissue interaction and therapeutic mechanism of 2RT are similar to SRT. However, the ultra-short single pulse generates a more dramatic temperature change in the RPE cells, leading to a more explosive mechanical destruction of the RPE cell. Even though the ultra-short pulse does not permit heat to transfer outside the cell, thereby preserving the integrity of adjacent structures such as BM and retinal photoreceptors [134], violent RPE “explosions” can cause physical damage beyond the RPE, often evidenced by subretinal hemorrhages due to ruptures of BM [29]. Moreover, given the markedly restricted heat transfer in 2RT, the photostimulation of RPE may be constrained, which could result in a limitation of the therapeutic benefits. In addition to the photodisruptive effect, several cytokines, including anti-angiogenic factors, PEDF, and HSPs, were elevated [134,135]. Inflammation was observed following 2RT treatment but was minor when compared with CW lasers [134]. In an animal model of AMD, treatment with 2RT can reduce the thickness of the thickened BM, probably by modulating the expression of MMPs within the RPE to alter the turnover of extracellular matrix components of the BM [134].

Subthreshold 2RT has been utilized in the treatment of various retinal diseases, yet not all outcomes have been satisfactory. A clinical trial involving 50 patients found that 2RT reduced drusen burden and improved macular function without retinal damage [136]. Despite the success of this studies, the results of a large, 36-month, multicenter, randomized, sham-controlled clinical study, named the Laser Intervention in Early Stages of Age-Related Macular Degeneration (LEAD) study [137], demonstrated less favorable results. In LEAD, subthreshold 2RT did not slow the progression of intermediate AMD (iAMD), which remained unchanged in the 24-month observational extension study [138]. However, a post hoc analysis revealed that 2RT treatment appeared to slow the progression of disease in the subgroup without the coexistence of reticular pseudodrusen (RPD) while accelerating disease progression in the subgroup with RPD. The low treatment density (12 laser spots) may have constrained the low therapeutic efficiency, given the limited photostimulation effect of 2RT. High treatment densities may initially improve the retinal function and best-corrected visual acuity (BCVA), but these benefits may dissipate over time, reverting to pre-treatment levels [139]. At the same time, the high treatment density also resulted in short-term changes to the retinal structure, which recovered at 3 months post-treatment. Further studies are needed to adjust the effect of 2RT in the treatment of AMD.

Subthreshold 2RT has also been tested in two pilot trials treating DME [140,141]. The findings indicated that in the treatment of DME, 2RT yielded comparable [140] or superior [141] enhancements in BCVA when compared to conventional laser therapy. However, no discernible differences were observed between the two treatment modalities in terms of their impact on CMT [140,141]. No adverse events were documented in either trial.

Besides AMD and DME, 2RT has also been utilized in the treatment of both acute and chronic CSCR [142] and Doyme honeycomb retinal dystrophy (DHRD) [143], with some degree of reported effectiveness and safety. In a recent study, Nguyen et al. utilized a nanosecond laser to remove the RPE cells in rabbits, thereby establishing a laser-induced RPE deficiency model for the investigation of stem cell therapy [144]. This application

suggests that 2RT may have the potential to be employed in stem cell therapy by assisting in the removal of unhealthy RPE cells and thereby facilitating the engraftment of transplanted cells.

4. Innovations in Laser Delivery

4.1. Semiautomated Multispot Laser (MSL)

Diseases such as DR and BRVO may require large areas of laser treatment or even PRP, and subthreshold laser techniques such as SDM also need to cover larger treatment areas. In such cases, the conventional monospot laser modality is often associated with pain, a prolonged duration, and the requirement of multiple outpatient visits. Furthermore, the absence of real-time feedback in subthreshold laser treatment may result in undertreatment or overtreatment under conventional laser delivery systems. The semi-automated multispot laser (MSL) is a proposed solution to these issues. Four MSLs are currently in clinical use: pattern scanning laser (PASCAL), Valon, Visulas 532s VITE, and Navilas, Teltow, Germany. Among these, PASCAL has the most extensive usage.

PASCAL comprises a semiautomated scanning laser system that utilizes a frequency-doubled Nd:YAG laser, capable of delivering multiple laser shots in rapid succession to the retina with a single foot pedal application. It utilizes a 532 nm (green) wavelength, with some versions also offering 577 nm (yellow) and 638 nm options [145]. PASCAL can deliver patterns that vary in both shape and size. The short pulse duration (10–20 milliseconds) facilitates the rapid application of multiple laser spots, thereby enhancing patient comfort and reducing treatment time [146,147]. A single-session treatment has been shown to be clinically equally efficacious as multiple-session treatments in controlling PDR [148]. Favorable regression rates in PDR patients have been described in previous studies that employed PASCAL for PRP [148–150]. No adverse effects, such as visual field defects, were reported in the aforementioned studies or other studies that applied the PASCAL system [151,152].

While Valon and Visulas 532 VITE have similar functionality to PASCAL, Navilas has been integrated with a retinal navigation system with digital fundus imaging that can be used for color fundus photography, red-free and infrared imaging, and FA. The pretreatment FA with the treatment strategy can be overlaid on top of the post-treatment images, allowing the calculation of treatment accuracy [153]. The NAVILAS system has been shown to offer a safer and more precise alternative to conventional manual techniques in the context of photocoagulation treatments for DR [153]. A study comparing PASCAL with Navilas for panretinal photocoagulation (PRP) showed that Navilas achieves more uniform laser burns with less pain during shorter treatment [154].

Considering the aforementioned findings, MSL has been demonstrated to exhibit a reduced propensity for patient discomfort when compared to conventional laser modalities. This reduction in discomfort leads to an enhancement in the patient's tolerance for laser treatment. Furthermore, MSL necessitates a reduced number of treatment sessions while achieving a greater number of laser spots, thereby compensating for its comparatively lower fluency. This results in a more efficient treatment process, consequently reducing the treatment time. Concurrently, when employed in conjunction with EpM, MSL ensures the efficacy of the treatment while mitigating the risk of laser-induced damage through a more precise control of laser energy. In addition, when integrated with a laser navigation system, MSL facilitates more precise targeting, thereby achieving therapeutic effects with minimal unnecessary damage.

4.2. Endpoint Management (EpM)

EpM [155] is a titration protocol that adjusts laser power and duration to achieve subthreshold effects by analyzing the visible threshold. The protocol is grounded in a computational model of retinal photothermal damage, which can be employed to facilitate power settings for diverse levels of tissue effect. EpM can be applied to laser treatments that rely on the photothermal effect. When the duration of a laser pulse is greater than 50 μ s, the predominant mechanism of cell damage is photothermal damage [43], which can be described by Arrhenius's law and first-order reaction kinetics [155]. This theory, when integrated with the standard titration dose, enables the EpM software to map the calculated Arrhenius values to linear steps in pulse energy. And the optimal therapeutic window is identified as pulse energies ranging from 20% to 40% for 20 ms pulses, a range that allows for the activation of heat shock proteins (HSPs) without causing damage to the RPE [107]. However, this model is derived from burns applied to the retina of rabbits [155], which possess significantly different retinal pigmentation from humans. Additionally, researchers [29] have noted that the titration, which is the most critical component for power setting, is based on a subjective clinical evaluation of photocoagulation laser burn, thereby making the technique subjective. Furthermore, the therapeutic window of CW lasers, like the PASCAL (0.010 watts), is too narrow a target to consistently hit clinically. These factors may, at least in part, account for the observed variability in outcomes among clinical studies employing EpM technology.

EpM can be combined with other laser techniques to achieve subthreshold treatment, which can be regarded as a type of non-damaging retina therapy (NRT). The most common application is the combination of EpM with MSLs, such as the PASCAL system, for diseases like DME and PDR. One study [156] utilized a 577 nm PASCAL Streamline laser with EpM titration, achieving enhancements in visual acuity, reductions in retinal and choroidal thickness, and decreases in SRF in patients with CSCR and macular telangiectasia (MacTel). In this study, 30% EpM energy with high spot density was applied without any retinal damage observed by clinical observation, OCT, fundus autofluorescence, or FA at one-year follow-up, and no adverse effects were reported.

A prospective, single-center, paired, randomized controlled trial involving 56 eyes with NPDR was conducted to compare the efficacy and safety of subthreshold PRP using EPM with conventional threshold PASCAL PRP [91]. The findings indicated that subthreshold EPM PRP is noninferior to the conventional threshold PASCAL PRP during 12-month follow-up and could serve as an alternative treatment for severe NPDR.

A clinical trial with a small sample size (10 eyes) of DME patients reported that PASCAL (577 nm wavelength) treatment with EpM at 50% of the threshold is safe and effective for the treatment of DME and preserves macular sensitivity [157]. For the combination therapy combined laser and anti-VEGF treatment, one retrospective study demonstrated that PASCAL with EpM therapy can reduce the number of anti-VEGF injections without compromising visual acuity or macular thickness [158]. Another prospective multicenter, open-label, nonrandomized interventional study [159] with 42 DME patients indicated that the combination of a PASCAL-EpM grid laser (40% threshold power) did not decrease the number of injections. However, a mixed regression analysis revealed that the EpM group required 0.94 fewer injections. While the results of the aforementioned trials suggest that EpM in combination with PSCAL is safe and effective for the treatment of DME and has the potential to reduce the number of anti-VEGF injections, a more recent study has yielded different results. Forty-four patients with DME refractory to anti-VEGF treatment were enrolled in this study [160], following PASCAL with EpM treatment. OCTA alterations with decreased BCVA were identified. At the 6-month follow-up, OCTA revealed that vascular densities (VDs) of the choroidal capillaries, superficial capillary plexus (SCP),

and deep capillary plexus (DCP) exhibited varying degrees of decline across different regions. The observed variance in outcomes across studies can be attributed, in part, to the inherent limitations of the EpM technique discussed previously. Algorithmic refinements and novel dosimetry techniques may enhance the reliability of this technique. Concurrently, further prospective studies are necessary to enhance understanding of the effectiveness and longitudinal outcomes of EpM in treating retinal diseases. A further challenge in the implementation of EpM is that, in cases involving large treatment areas, the one-time titration may not maintain the intended therapeutic effect across the entire area. As previously stated, the uneven distribution of pigments within individuals can lead to discrepancies in the treatment outcomes achieved by the same laser settings. In addition, uneven media opacities, pigmentation variation in the retina and choroid, and other factors may also lead to localized variations in light absorption in clinical applications, resulting in inconsistencies in therapeutic effects. To address the issue, the development of advanced techniques, such as real-time feedback and the automatic detection of pigments, may be beneficial.

4.3. Navigated Laser Treatment

The necessity for targeted treatment of lesions that are difficult to directly visualize under ophthalmoscopy, such as retinal non-perfusion, is a common occurrence in the clinical practice of retinal laser therapy. The advent of wide-field FA and wide-field OCTA have facilitated this process in recent years. However, localizing the target region under ophthalmoscopy by retinal vessels or other retinal references (e.g., hemorrhage, exudates) remains challenging. This may present not only a challenge for the clinician but may also result in prolonged treatment time and increased patient discomfort. For many years, research has been conducted to enhance laser treatment through a navigation system. From the advent of angio-mounted slit lamp systems [161–163] to the subsequent development of computer-based systems for real-time image acquisition and overlapping under slit-lamp [164], concerted efforts have been made in the field. Nevertheless, the long system reaction time and slow tracking speed hinder the application of these systems in clinics [165].

The Navilas system, introduced in 2009, marked a significant breakthrough in this domain. This system integrates a digital imaging system with a laser system and incorporates an eye-tracking technology to compensate for eye movements during treatment [165] (Figure 3). Navilas employs a scanning slit-based instrument, rather than a slit lamp, for the treatment, a notable difference from other laser systems. It provides a 50° field of view for focal laser treatment and an 85° field of view for panretinal treatment [166]. As aforementioned, Navilas has been demonstrated to be a precise, effective, and safe modality for the treatment of DME and PDR [166–170].

Besides the integrated imaging system, Navilas can also align external images from OCT [171], OCTA [172], and ICGA [173] with a live fundus view. This functionality serves to broaden its application in precise treatment for a range of conditions, including the treatment of large neovascular trunk in neovascular AMD [172], CSCR [174], and retinopathy of prematurity (ROP). Furthermore, the distinctive operating mode of the Navilas has been demonstrated to provide a highly effective instrument for remote retinal laser therapy [175,176].

In comparison with traditional retinal laser therapy, navigated retinal laser treatment has been shown to offer enhanced precision with less pain. For instance, in the treatment of microaneurysms in the DR, Navilas has been demonstrated to have a higher microaneurysm hit rate than manual treatment [153]. Furthermore, it facilitates the accessibility of laser retinal treatments through its support for remote retinal laser treatments. Additionally, it provides a precise treatment record with real retinal images, which is a notable advance-

ment over the conventional laser treatment method, where the operator must manually draw the record. Despite the numerous advantages of navigated retinal laser therapy over conventional laser therapy, limitations persist. In cases where patients demonstrate poor fixation or are unable to maintain ocular stability for other reasons, laser treatment facilitated by a navigation system may be more time-consuming or even unfeasible, as the system is incapable of accurate targeting.



Figure 3. Navilas fundus imaging and laser treatment device applying a slit-based camera and touchscreen monitor for imaging, planning, and treating fundus changes. Reprinted (adapted) with permission from [166]. Licensed under CC BY 4.0.

4.4. Targeted Retinal Photocoagulation (TRP)

TRP refers to the targeted application of laser treatment to the diseased retina to achieve therapeutic effects while avoiding undesirable damage. This approach aligns with the minimal invasive concept of modern medicine. Typical applications include photocoagulation of feeder vessels in choroidal neovascularization (CNV), focal photocoagulation in the treatment of DME, and photocoagulation of the ischemic area of retinal vein occlusion (RVO) [177]. TRP has been utilized in clinical settings for a considerable period. However, recent endeavors have focused on its application in diseases that have traditionally been treated with PRP (Figure 4).

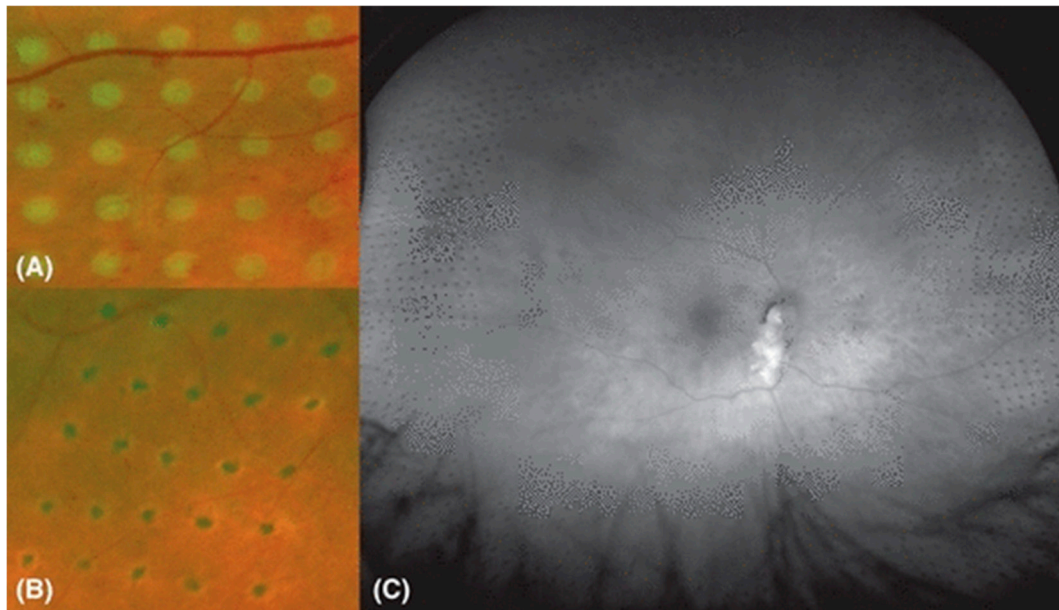


Figure 4. Scanning laser ophthalmoscopy (Optos) photographs of standard targeted retinal photocoagulation (TRP) treatment burns: (A) Color fundus photograph at 1 hr showing standard intensity of 20 ms TRP burns within a 5×5 array. (B) Color image of fundus photograph at 4 weeks showing well-localized and pigmented laser burns within an array. The laser burn spot spacing has increased because of healing of laser lesions and reduction in burn size over time. (C) Optos green-free fundus photograph at 12 weeks showing retinal coverage of TRP laser burns in peripheral retina. There are pretreatment laser titration burns visible nasal and superior to the optic disk. Reprinted (adapted) with permission from [178]. Licensed under CC BY 4.0.

The conversion of PRP to TRP is closely related to the development of ultra-wide-field (UWF) imaging techniques. In 2009, TRP was first documented in the treatment of two patients with PDR [179]. UWF FA, with a 200-degree field of view of the retina, was used to facilitate TRP to the ischemic area. A regression of retinal neovascularization was observed in both patients, with no occurrence of macular edema or visual loss during follow-up. However, one patient complained about the reduced peripheral visual field when utilizing the fellow eye as a control. The advent of navigated laser techniques has significantly contributed to the adoption of TRP. Subsequent studies have been conducted to investigate its efficacy and safety. These studies demonstrated that TRP is comparable to conventional PRP in controlling the progression of PDR [152,180,181]; it may also reduce the impact on CMT resulting from laser treatment [152,180,182]. While TRP may initially enhance visual fields following treatment [152], it has been observed to potentially result in the same visual impairment as conventional PRP over an extended period after treatment [180,182]. One issue with TRP is the absence of a universally accepted standard for this technique. The treatment area is not uniform, with some researchers targeting solely the ischemic regions and others expanding the treatment to encompass the intermediate zones of perfused and non-perfused retinas. Furthermore, extant studies are limited by their modest sample sizes. Further randomized trials with a refined design are necessary to ascertain the actual benefits of TRP.

5. Photo-Mediated Ultrasound Therapy (PUT)

Although novel laser treatment techniques have greatly improved the efficacy and safety of retinal laser treatments, it is important to note that most of these techniques target the RPE cells. This is because melanin within the RPE cells is the strongest absorber of light. While these techniques may indirectly reduce neovascularization through photo-

stimulation of the RPE, the treatment for neovascularization itself still relies on anti-VEGF therapy. Photodynamic therapy (PDT) has been demonstrated to target neovascularization. However, the systemic injection of photosensitizers limits the application of PDT in patients with certain systemic diseases. Moreover, it can result in choroidal infarction and acute, severe vision loss [183]. Additionally, photosensitizers present in the circulation system can render the skin and eyes sensitive to light post-treatment. PUT is a novel, selective, non-invasive, localized antivascular technique that is undergoing rapid development [184]. The utilization of a synergistic combination of nanosecond laser pulses and ultrasound bursts enables the PUT to effectively remove targeted microvessels through the process of cavitation [185] (Figure 5). The PUT demonstrates a unique capacity to selectively self-target either arteries or veins, given that strong cavitation occurs exclusively within an area of high absorption of both ultrasound and laser [184]. By integrating a nanosecond laser and ultrasound, the energy necessary to induce cavitation is significantly reduced compared to the energy requirements of laser or ultrasound alone [186]. Consequently, this approach minimizes the damage to surrounding tissue caused by ultrasound and laser. The efficacy of this technique has been investigated in animal models of retinal neovascularization [187] and choroidal neovascularization [188,189]. Recently, a novel integrated system combining PUT and spectral domain OCT (SD-OCT) was developed for real-time monitoring of cavitation [185]. This technique can further improve the safety and efficiency of PUT in treating neovascularization.

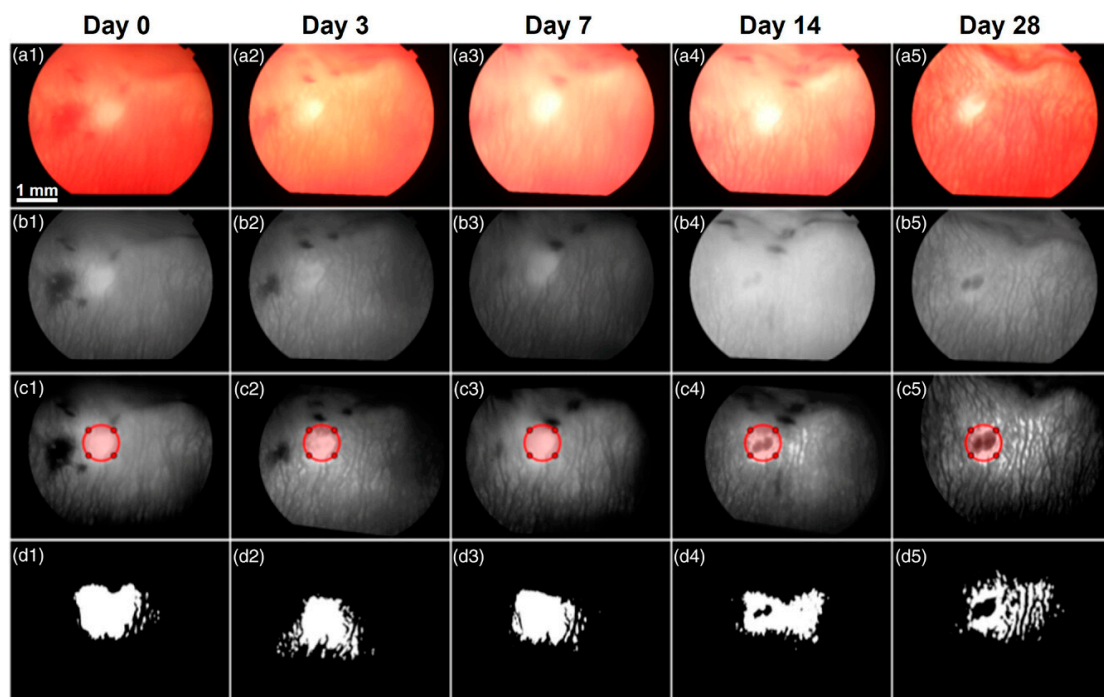


Figure 5. Representative PUT results in a rabbit CNV model. (a1–a5) Fundus photographs and (b1–b5) late-phase FA images taken at different observation time points, including Day 0 (immediately before PUT treatment and 2–4 weeks after M&V injection), and Day 3, Day 7, Day 14, and Day 28 after the treatment. (c1–c5) Registered late-phase FA images at different observation time points, where the red circles indicate the treatment area. (d1–d5) Binary images at different observation time points, showing the hyperfluorescent area consistent with the CNV leakage. Reprinted (adapted) with permission from [189]. Licensed under CC BY 4.0.

PUT is a developing technology that can combine imaging and therapeutic functions, enabling real-time observation of therapeutic targets via OCT to achieve optimal therapeutic results. It utilizes the pronounced contrast between the chorioretinal vessels and the

surrounding tissue for targeted treatment without the use of dyes, as in PDT. In addition, PUT enhances the efficiency of the treatment by integrating laser with ultrasound, thereby reducing the therapeutic energy of both modalities and, consequently, improving its safety profile. In contrast to other novel retinal lasers, which primarily act on the RPE, PUT targets the chorioretinal vasculature, suggesting its potential for the targeted treatment of retinal vascular diseases, such as retinal neovascularization and retinal angioma. Presently, commercialized photoacoustic imaging devices are available [190], which may facilitate the development and commercialization of this technique, although no clinical PUT system is currently approved for patient use.

6. Conclusions

Even with significant advancements in pharmacologic therapy, which have led to a decline in the reliance on laser treatments for retinal disorders, laser retinal therapy remains an indispensable modality, particularly given that pharmacologic treatment of retinal diseases typically necessitates multiple treatments with a frequent (e.g., monthly) treatment time.

The transition of a novel retinal laser technique from the laboratory to the clinic and, subsequently, to widespread use, is usually a long process. The paucity of commercially available laser equipment may be a contributing factor. For example, the SRT, despite its development in the 1990s, has only one commercially available system and research on this technique has been limited. Moreover, when compared with pharmacological treatments, conducting long-term, prospective, randomized controlled trials of a new retinal laser therapy is often more difficult, which complicates the assessment of its efficacy and safety. In addition, since laser treatment is largely reliant on the ability of the tissue to absorb light, differences in the distribution of melanin between and within individuals, and the subjective titration process, may affect treatment results, thus complicating the evaluation of the technique. Another challenge in the development of new laser technologies lies in their uneven accessibility across different regions, which may lead to an imbalanced distribution of research populations. As previously discussed, optimal laser parameters may vary among different populations. It is important to consider that applying laser parameters derived from studies conducted in developed regions to populations in areas with little or no related research may result in reduced treatment efficacy or increased adverse effects.

Advancements in artificial intelligence (AI) may hold the potential to address these challenges. The utilization of artificial intelligence (AI) in the domains of disease screening, grading, and prediction is a subject of extensive research in the field of retinal diseases, including AMD, DR, RVO, CSCR, and ROP [191]. In the domain of retinal treatment, the application of AI has been demonstrated in two distinct areas: laser treatment detection [192,193] and treatment design [194]. Specifically, AI offers a solution to the deficiencies in laser treatment design that arise from a lack of experience and skill. Furthermore, the integration of AI with a navigation system has the potential to enhance the precision of laser settings. The navigation system can collect real-time images of the retina, while an AI-assisted system can automatically detect color changes in the targeted retina. This method has the potential to mitigate errors arising from operator subjectivity during the titration process. In addition, during the treatment, AI may facilitate the automatic adjustment of laser power according to the distribution of pigments, thereby achieving specific therapeutic effects. This process can be supported by advanced algorithms such as EpM. The employment of AI in retinal laser treatment allows for enhanced precision and efficiency.

Despite the challenges, the advent of novel insights into the therapeutic mechanisms of laser therapy has prompted the evolution of laser technology toward subthreshold and

non-invasive treatment modalities. The development of modern imaging techniques and computer technology has led to significant advancements in laser delivery technology. In the future, the integration of multimodal imaging and artificial intelligence may further enhance the precision and efficiency of retinal laser treatment.

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Abbreviations

The following abbreviations are used in this manuscript:

SMPL	Subthreshold micropulse laser
SRT	Selective retina therapy
CW	Continuous wave
RPE	Retinal pigment epithelium
DR	Diabetic retinopathy
VEGF	Vascular endothelial growth factor
HSP	Heat shock protein
FA	Fluorescein angiography
FAF	Fundus autofluorescence
SD-OCT	Spectral domain optical coherence tomography
SDM	Subthreshold diode micropulse laser
DME	Diabetic macular edema
CSCR	Central serous chorioretinopathy
CMT	Central macular thickness
SRF	Subretinal fluid
AMD	Age-related macular degeneration
PASCAL	Pattern scanning laser
EpM	Endpoint management
NRT	Non-damaging retina therapy
TRP	Targeted retinal photocoagulation
PRP	Panretinal photocoagulation
RP	Retinitis pigmentosa
RVO	Retinal vein occlusion

ROP	Retinopathy of prematurity
CNV	Choroidal neovascularization
AI	Artificial intelligence
OCT	Optical coherence tomography
MacTel	Macular telangiectasia
PDT	Photodynamic therapy
MSL	Multispot laser
ICGA	Indocyanine green angiography
PUT	Photo-mediated ultrasound therapy

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