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REVIEW

A Review of Subthreshold Micropulse Laser for Treatment of Macular Disorders

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ABSTRACT

Micropulse laser treatment is an alternative to the conventional continuous-wave laser for the treatment of retinal or macular diseases. In contrast to the conventional laser, the therapeutic effect of the subthreshold micropulse laser is not accompanied by thermal retinal damage. This fact is of particular importance when a treatment near the fovea is required. Micropulse treatment is applied in indications such as central serous chorioretinopathy (CSC), diabetic macular edema (DME), or macular edema due to retinal vein occlusion (RVO). This review outlines and discusses the published literature of subthreshold micropulse laser treatment for CSC, DME, and macular edema after RVO.

Keywords: Central serous chorioretinopathy; Diabetic macular edema; Micropulse laser; Ophthalmology; Retinal vein occlusion; Subthreshold laser

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INTRODUCTION

Traditional laser photocoagulation has been used to treat different retinal diseases for many years [1–5]. Here, the endpoint is a visible whitening of the retina due to thermal damage of the retinal pigment epithelium (RPE) and the inner retina. However, apart from the favored therapeutic effect, the treatment can lead to undesirable side effects like visual field defects, epiretinal fibrosis, and choroidal neovascularization (CNV) in the area of the laser scar [6–10]. The mechanisms which are responsible for the therapeutic effect are still poorly understood.

Scarring seems not to be necessary to achieve a therapeutic effect. It might be the stimulation of the RPE alone and not the destroying of the photoreceptors that is needed to reach a therapeutic effect of laser photocoagulation [11]. The laser energy stimulates the RPE, which leads to repair of the inner blood retinal barrier [12]. A modification of the gene expression initiated by the wound healing response after laser photocoagulation could be responsible for the beneficial effect of laser photocoagulation. Sublethally injured RPE cells induce an up- and downregulation of various factors [pigment epithelium-derived factor (PEDF), vascular endothelial growth factor (VEGF) inhibitors,

VEGF inducers, permeability factors, etc.] which restores the pathologic imbalance. RPE cells destroyed by thermal heat are not capable of inducing this biologic activity [13, 14]. Inagaki et al. [15] showed that sublethal photothermal stimulation with a micropulse laser induces heat shock protein expression in RPE cells without cellular damage in a model of human RPE.

In subthreshold micropulse laser (SML), diffusion of heat to surrounding tissues is minimized and thereby scarring is prevented.

The neural retina can be spared by applying the minimum laser irradiance (watts per square meter) needed to raise the temperature of the RPE, but without exceeding the protein denaturation threshold. This leads to the required activation of the RPE cells, but the thermal wave will only reach the neural retina at temperatures beneath the protein denaturation threshold. Since the RPE and the neural retina are close together, the laser pulse has to be in the microsecond range and not in the millisecond range like the traditionally used supra threshold laser. For safety reasons it is not possible to deliver the required energy in one short enough laser pulse. A single laser pulse would require so much energy that there would be a high risk of bubble formation and micro-explosions, accompanied by retinal hemorrhages [16]. Those side effects can be avoided by using a repetitive series of very short pulses with low energy instead of a continuous-wave laser pulse [17–19].

The micropulse operating mode and terminology were described by Dorin [20]. In the traditional continuous-wave mode, a single laser pulse of 0.1–0.5 s delivers the preset laser energy. In the micropulse mode, a train of repetitive short laser pulses delivers the laser energy within an "envelope" whose width is typically 0.1–0.5s. The normal length of each pulse is 100–300 μs. The "envelope" includes "ON" time, which is the duration of each micropulse, and "OFF" time, which is the time between the micropulses. The "OFF" time is important since here the originated heat can cool down. The sum of the "ON" and "OFF" times is the period T and its reciprocal $1/T$ is the frequency (pulses per second) f in hertz (Hz). The duty cycle in percent is the ratio between "ON" time and the period T.

DIFFERENT LASERS AVAILABLE WITH MICROPULSE MODE

810-nm Diode Laser

The commercially available diode lasers emit at a wavelength of 810 nm, which is in the near-infrared range of the spectrum. A feature of the 810-nm wavelength is its deep penetration into the choroid, but it is not clear if this characteristic is relevant in micropulse treatment. For all indications requiring a treatment near the foveal avascular zone, the 810-nm laser has the advantage that the laser energy will relatively spare the inner neurosensory retina and affect mainly the deeper layers [21–24]. The deep penetration is a possible benefit especially for central serous chorioretinopathy (CSC) since the choroid may play a role in the pathogenesis of CSC. A potential disadvantage of the 810-nm laser is a possible sensation of pain during treatment with a diode laser [24, 25], although this is a rare problem in the micropulse mode.

577-nm Yellow Laser

Another laser type which is available for micropulse treatment is the 577-nm yellow laser. The yellow laser has the advantage that xanthophyll, the pigment which is located in the inner and outer plexiform layers of the macula, absorbs the yellow light only minimally so treatment near the fovea is relatively safe [26].

APPLICATIONS FOR SUBTHRESHOLD MICROPULSE LASERS

In this article we will review the applications for micropulse laser in macular diseases, namely CSC, diabetic macular edema (DME), and retinal vein occlusion (RVO). We will give an overview of the available literature and outline

the current evidence for micropulse laser treatment in each field.

The literature search was performed in English language in the PubMed database. We used pairings of the terms "micropulse", "laser", "subthreshold", and "central serous chorioretinopathy", "chorioretinopathy", "central serous retinopathy", or "diabetic macular edema", "macular edema" and "retinal vein occlusion", "branch retinal vein occlusion", "central retinal vein occlusion". Additionally, the references of the resultant articles were checked for publications missing in the primary search. Until February 2017 we found 18 articles [27–44] concerning micropulse laser in CSC; no articles were excluded and all articles are listed in Table 1. As a result of the high number of publications related to DME and micropulse treatment, we only listed the 11 prospective studies [45–55] in Table 2. We found four studies [56–59] investigating micropulse laser for RVO, which are all listed in Table 3.

As a result of different study designs, uneven inclusion and exclusion criteria, different laser types, treatment parameters, and various outcome measures, a direct comparison of the studies is limited. We looked for similarities referring to the outcome measures for making comprehensive conclusions regarding the treatment outcome. In Tables 1, 2, and 3, all studies are listed, but individual studies were excluded from the calculations as a result of missing information or prior treatment. The studies had a high variety regarding the follow-up visits. If available, after calculation of the decrease in central retinal thickness (CRT) in optical coherence tomography (OCT) in all individual studies, a weighted average value was calculated on the basis of the number of patients in each study. The best corrected visual acuity (BCVA) was not consistently presented in the different studies. To compare the BCVA, we converted all visual acuity data to Early Treatment Diabetic Retinopathy Study (ETDRS) letters equivalent using the formula ETDRS letters = 85 + 50 × log (Snellen fraction) [60]. If a large enough number of studies provided information about a control group, we additionally analyzed the control group regarding CRT, BCVA, and treatment outcome.

This article was based on previously conducted studies and did not involve any new studies of human or animal subjects performed by any of the authors.

CENTRAL SEROUS CHORIORETINOPATHY (CSC)

In CSC a serous detachment of the neurosensory retina leads to decreased vision [61]. The acute form of CSC is often self-limiting so that treatment is not always necessary. But some patients develop the chronic form of CSC with impending permanent structural damage and vision loss [62–64]. For patients with extrafoveal leakage, a continuous-wave laser photocoagulation is a treatment option. Studies showed an acceleration of subretinal fluid (SRF) resolution but no change in final visual acuity or recurrence rate after conventional laser. Furthermore, adverse events like CNV, scotomas, enlargement of the laser spot, and reduction of contrast sensitivity can occur [3, 62, 65–67]. Another treatment option is photodynamic therapy (PDT) which is used also in juxtafoveal or subfoveal leakage. But even with reduced treatment settings, complications like RPE atrophy, choroidal hypoperfusion, transient reduction of macular function, and CNV can occur [68–71].

Bandello et al. [72] presented the first pilot study investigating SML treatment for CSC in 2003. They reported a high treatment success with complete resorption of SRF in five out of five eyes within 1 month and no recurrence of SRF during follow-up of 2–6 month after non-visible subthreshold micropulse diode laser (810 nm) treatment. No evidence of RPE or retinal changes was discernible at fluorescein angiography (FA) or fundus biomicroscopy after laser treatment.

Table 1 shows all identified studies investigating micropulse laser treatment for CSC. In Table 4, the treatment outcome after SML, PDT, and observation for CSC is presented.

Treatment Response

Most studies defined a treatment response as a reduction in CRT measured in spectral domain

Table 1 Overview of the studies investigating subthreshold micropulse laser treatment for central serous chorioretinopathy

Authors	Year	Eyes	Disease duration	Laser type and parameters	Study design
Ricci et al. [27]	2004	1 eye	Chronic, ≥6 months	Iris Medical Oculight SLx 810 nm, Ø not shown, 10% DC, 0.5 s, power: 500 mW	Case report, SML after ICG injection
Ricci et al. [28]	2008	7 eyes	Chronic, ≥6 months	Iris Medical Oculight SLx 810 nm, Ø 112.5 µm, 10% DC, 0.5 s, power: 500 mW	Prospective, interventional, non-comparative case series, SML after ICG injection
Chen et al. [29]	2008	26 eyes Group 1: Source leakage without RPE atrophy, $n = 6$ Group 2: Source leakage with RPE atrophy, $n = 9$ Group 3: Diffuse RPE decompensation with indeterminate source leakage, $n = 11$	Chronic, >4 months	Iris Medical Oculight SLx 810 nm, Ø 125 µm, 15% DC, 0.2 s, power: titration	Prospective, non-comparative, interventional case series
Lanzetta et al. [30]	2008	24 eyes	Chronic, >3 months	Iris Medical Oculight SLx 810 nm, Ø 200 µm, 15% DC, 0.2 s, power: 1000–2000 mW, mean 1350 mW	Prospective, interventional, non-comparative case series
Gupta et al. [31]	2009	5 eyes	Chronic, ≥4 weeks	Iris Medical Oculight SLx 810 nm, Ø 125 µm, 15% DC, 0.2 s, power: titration	Retrospective, non-comparative, case series
Koss et al. [32]	2011	52 eyes SML: $n = 16$ BCZ: $n = 10$ Observation: $n = 26$	Chronic, >3 months	Iris Medical Oculight SLx 810 nm, Ø 125 µm, 15% DC, 0.2 s, power: titration	Prospective, comparative, nonrandomized interventional case series
Roisman et al. [33]	2013	15 eyes SML: $n = 10$ SHAM: $n = 5$	Chronic, >6 months	Opto FastPulse 810 nm, Ø 125 µm, 15% DC, 0.3 s, power: 1.2× threshold	Prospective, randomized, double-blind, sham-controlled pilot trial, cross over after 3 months
Malik et al. [34]	2015	11 eyes	Chronic, >3 months	Iris Medical Oculight SLx 810 nm, Ø not shown, 5% DC, 0.2–0.3 s, power: 750–1000 mW	Retrospective, interventional, non-comparative case series
Kretz et al. [35]	2015	62 eyes SML: $n = 20$ HdPDT: $n = 24$ Observation: $n = 18$	Chronic, >3 months	Iris Medical Oculight SLx 810 nm, Ø 75–125 µm, 15% DC, 0.3 s, power: average 1500 mW	Prospective, randomized, interventional, comparative trial

Table 1 continued

Authors	Year	Eyes	Disease duration	Laser type and parameters	Study design
Elhamid [36]	2015	15 eyes	Chronic, >3 months	Iridex IQ577 577 nm, Ø 200 µm, 10% DC, 0.2 s, power: titration	Prospective, interventional, non-comparative clinical study
Scholz et al. [37]	2015	38 eyes	Chronic, >6 weeks	Quantel Medical Supra Scan 577 nm, Ø 160 µm, 5% DC, 0.2 s, power: 50% of threshold	Retrospective, non-comparative case series
Kim et al. [38]	2015	10 eyes	Chronic, >6 months	Quantel Medical Supra Scan 577 nm, Ø 100 µm, 15% DC, 0.2 s, power: 50% of threshold	Retrospective, non-comparative case series
Gawęcki [39]	2015	1 eye	Chronic, (disease duration not defined)	Model not mentioned 577 nm, Ø 160 µm, 5% DC, 0.2 s, power: 550 mW	Retrospective case report
Yadav et al. [40]	2015	15 eyes	Chronic, >3 months	Quantel Medical Supra Scan 577 nm, Ø 100 µm, 10% DC, 0.2 s, power: 50% of threshold	Retrospective, non-comparative case series
Breukink et al. [41]	2016	59 eyes (All eyes received HdPDT, 10 eyes with persistent SRF after up to 2 HdPDT sessions received SML)	Chronic, (disease duration not defined)	Iris Medical Oculight SLx 810 nm, Ø 125 µm, 5% DC, 0.2 s, power: ≤1800 mW	Prospective, interventional non-comparative, case series
Özmert et al. [42]	2016	33 eyes SML: $n = 15$ HfPDT: $n = 18$	Chronic, >6 months	Quantel Medical Supra Scan 577 nm, Ø 160 µm, 5% DC, 0.2 s, power: titration	Retrospective, comparative case series
Ambiya et al. [43]	2016	10 eyes	≥3 months without signs of RPE atrophy or diffuse leakage	Navilas 577 nm, Ø 100 µm, 5% DC, 0.1 s, power: 30% of threshold	Prospective, interventional noncomparative, case series
Scholz et al. [44]	2016	100 eyes SML: $n = 42$ HdPDT: $n = 58$	Chronic, ≥6 weeks	Quantel Medical Supra Scan 577 nm, Ø 160 µm, 5% DC, 0.2 s, power: 50% of threshold	Retrospective, comparative, interventional case series

Table 1 continued

Authors	FU	Treatment response	Central retinal thickness	Best corrected visual acuity	Safety	Laser sessions
Ricci et al. [27]	8 weeks	1 week: SRF was reduced (1/1) 8 weeks: Complete resolution (1/1)	Not shown	BL: 0.3 logMAR 1 week: 0.0 logMAR 8 weeks: −0.1 logMAR	No signs of laser treatment were visible on FA	1
Ricci et al. [28]	Minimum 12 months	Response*: 2 weeks: 7/7 (100%) 8 weeks: 7/7 (100%) Complete*: 5/7 (71%) *12 months: no recurrence in patients with complete resolution of SRF. No worsening of SRF in patients with incomplete recovery	Not shown	2 weeks: all patients showed improvement 12 months: no worsening of the BCVA Change: +0.19 logMAR Significant increase of BCVA after 12 months ($p < 0.05$)	No laser lesions were visible via funduscopic examination and on FA	1
Chen et al. [29]	Minimum 6 months (9.5 ± 2.6 months)	FFU response: Group 1: 6/6 (100%) Group 2: 8/9 (89%) Group 3: 5/11(46%) All eyes: 19/26 (73%) FFU complete: Group 1: 6/6 (100%) Group 2: 8/9 (89%) Group 3: 5/11 (46%) All eyes: 19/26 (73%)	Group 1: BL: 339 ± 67 μm FFU: 136 ± 26 μm Group 2: BL: 342 ± 84 μm FFU: 139 ± 34 μm Group 3: BL: 340 ± 121 μm FFU: 192 ± 103 μm Significant CRT decrease in all patients ($p < 0.001$)	Group 1: BL: 0.18 ± 0.08 logMAR FFU: 0.00 ± 0.00 logMAR Group 2: BL: 0.38 ± 0.19 logMAR FFU: 0.07 ± 0.06 logMAR Group 3: BL: 0.41 ± 0.28 logMAR FFU: 0.24 ± 0.22 logMAR Significant BCVA increase in all patients ($p = 0.01$)	No patients developed laser-related scotoma	1–3
Lanzetta et al. [30]	3–36 months (mean 14 months)	Response: 1 month: 16/24 (67%) FFU: 18/24 (75%) Complete: 1 month: 9/24 (38%) FFU: 17/24 (71%)	BL: 328 μm (range 162–720 μm) 1 month: 197 μm (range 93–403 μm) FFU: 168 μm (range 107–340 μm) Significant CRT decrease at 1 month ($p = 0.0003$) and FFU ($p < 0.0001$)	BL: 20/32 Snellen 1 month: 20/25 Snellen FFU: 20/25 Snellen No significant increase in BCVA at 1 month ($p = 0.64$) or FFU ($p = 0.062$)	−5/24 eyes showed RPE changes at the site of SML spots No complications	1–5

Table 1 continued

Authors	FU	Treatment response	Central retinal thickness	Best corrected visual acuity	Safety	Laser sessions
Gupta et al. [31]	Minimum 6 months	FU response: 5/5 (100%) FU complete: 4/5 (80%)	Not shown	Improvement in BCVA in all patients	No complications mentioned	1–2
Koss et al. [32]	10 months	FU response: not shown FU complete: not shown Leakage activity in FA 10 months: SML: 2/16 (12.5%) BCZ: 6/10 (60%) Observation: 24/26 (92%) SML leads to significantly more leakage activity reduction than BCT ($p = 0.0239$) and observation ($p = 0.0054$)	SML: BL: 419 ± 59 μm 6 weeks: 387 ± 94 μm 6 months: 329 ± 69 μm 10 months: 325 ± 93 μm BCZ: BL: 393 ± 84 μm 6 weeks: 355 ± 114 μm 6 months: 334 ± 59 μm 10 months: 355 ± 73 μm Observation: BL: 388 ± 59 μm 6 weeks: 396 ± 57 μm 6 months: 388 ± 63 μm 10 months: 415 ± 53 μm Significant decrease in CRT at ($p = 0.0098$) but not after BCZ or observation	SML: BL: 45.4 ± 7.2 ETDRS 6 weeks: 47.8 ± 6.8 ETDRS 6 months: 50.5 ± 7.3 ETDRS 10 months: 51.6 ± 7.0 ETDRS BCZ: BL: 44.1 ± 10.8 ETDRS 6 weeks: 41.9 ± 11.3 ETDRS 6 months: 42.4 ± 13.6 ETDRS 10 months: 43.5 ± 14.5 ETDRS Observation: BL: 46.4 ± 6.1 ETDRS 6 weeks: 46.3 ± 6.9 ETDRS 6 months: 44.9 ± 5.1 ETDRS 10 months: 44.3 ± 5.2 ETDRS SML better than BCZ ($p = 0.000047$) and observation ($p = 0.0054$) at 10 months	No ocular adverse events, i.e., intraocular inflammation, bleeding, or IOP rise, were observed	1–3
Roisman et al. [33]	Minimum 6 months	Not shown	SML: BL: 420 ± 112 μm 1 month: 307 ± 55 μm 3 months: 265 ± 98 μm SHAM: BL: 350 ± 61 μm 1 month: 351 ± 94 μm 3 months: 290 ± 78 μm No significant decrease in CRT at 3 months after SML ($p = 0.091$) or SHAM treatment ($p = 0.225$)	SML: BL: 35.4 ± 11.6 ETDRS 1 month: 44.4 ± 8.1 ETDRS 3 months: 47.9 ± 8.0 ETDRS SHAM BL: 26.6 ± 6.8 ETDRS 1 month: 26.8 ± 7.6 ETDRS 3 months: 25.6 ± 8.9 ETDRS Significant BCVA increase at 3 months after SML ($p = 0.008$) but not after SHAM treatment ($p = 0.498$)	No laser scars observed at funduscopic examination or on FA	1–2

Table 1 continued

Authors	FU	Treatment response	Central retinal thickness	Best corrected visual acuity	Safety	Laser sessions
Malik et al. [34]	Minimum 2 months (2–12 months)	FU response: 8/11 (72%) FU complete: not shown	BL: 414 ± 137 μm FFU: 316 ± 97 μm Significant CRT decrease after SML ($p = 0.0046$)	BL: 39.2 ± 15.1 ETDRS FFU: 45.5 ± 12 ETDRS	No evidence of RPE damage in FAF or in FA	1–2
Kretz et al. [35]	4 months	4-month response (reduction of leakage activity): SML: 12/20 (60%) HdPDT: 16/24 (67%) Observation: 7/18 (38%) Significant reduction of leakage activity in both treatment groups compared to the control group	Change BL/4 months: SML: −69.7 μm HdPDT: −109.8 μm Observation: −89 μm	Change BL/4 months: SML: +6.7 ETDRS HdPDT: +8.5 ETDRS Observation: +1.5 ETDRS	No evidence of secondary RPE damage in FAF after both treatments	1–3
Elhamid [36]	6 months	Response: 3 months: 15/15 (100%) Complete: 3 months: 11/15 (73%) 6 months: 13/15 (86%)	BL: 390 ± 46 μm 6 months: 264 ± 24 μm Significant CRT decrease after SML ($p < 0.05$)	BL: 0.67 ± 0.10 Snellen 6 months: 0.85 ± 0.10 Snellen Significant BCVA increase after SML ($p < 0.05$)	No sign of laser-induced lesions	1–2
Scholz et al. [37]	Minimum 6 weeks (mean 5 ± 3 months)	Response: 6 weeks: 24/38 (63%) 3 months: 20/23 (87%) 6 months: 11/14 (79%) FFU: 28/38 (74%) Complete: 6 weeks: 5/38 (13%) 3 months: 7/23 (30%) 6 months: 2/14 (14%) FFU: 9/38 (24%)	BL: 402 ± 139 μm 6 weeks: 309 ± 86 μm FFU: 287 ± 75 μm Significant CRT decrease after SML ($p < 0.001$)	BL: 0.36 ± 0.24 logMAR 6 weeks: 0.33 ± 0.24 logMAR FFU: 0.30 ± 0.25 logMAR Significant BCVA increase after SML ($p = 0.039$)	No laser burns were detected with any imaging modality	1–3

Table 1 continued

Authors	FU	Treatment response	Central retinal thickness	Best corrected visual acuity	Safety	Laser sessions
Kim et al. [78]	Minimum 3 months	There were 2 patients who had recurrent CSC. One at 6 months, one at 10 months. One patient had persistent SRF for 3 months despite total of 4 laser sessions	BL: 349 ± 53 μm 3 months: 251 ± 29 μm FFU: 261 ± 38 μm Significant CRT decrease at 3 months ($p = 0.009$) and FFU ($p = 0.009$)	BL: 0.21 ± 0.21 logMAR 3 months: 0.06 ± 0.09 logMAR FFU: 0.04 ± 0.06 logMAR Significant BCVA increase at 3 months ($p = 0.020$) and FFU (p = 0.012)	No laser scar was detected in color fundus photographs, SDOCT, or near-infrared images	1–5
Gawęcki [39]	Not specified	Response: 0/1 Complete: 0/1	After 1st treatment: no change After 2nd treatment: "significant amount of SRF present in the macular area"	BL: 0.63 decimal FU 1st*: no change FU 2nd*: 0.32 decimal treatment*	FAF showed hyperfluorescent punctate areas referring to multispot SML pattern	2
Yadav et al. [40]	Minimum 4 weeks (4–19 weeks)	FU: Response: 15/15 (100%) Complete: 6/15 (40%)	CRT not shown SRF (high): BL: 232 μm FU: 49 μm Significant decrease in SRF ($p < 0.001$)	Change: 1 line BL: 20/40 Snellen FU: 20/30 Snellen Significant BCVA increase ($p = 0.015$)	No evidence of RPE or retinal damage on SDOCT, FA, or on FAF	1
Breukink et al. [41]	8–118 weeks	After mean 8.7 weeks, (range: 4–18 weeks) Complete after: 1st HdPDT: 37/59 (63%) 2nd HdPDT: 7/19 (37%) 1st SML: 1/10 (10%)	Not shown	BL (all): 0.28 logMAR FFU (all): 0.16 logMAR No difference in eyes after HdPDT or SML		1–2 HdPDT 1 SML
Özmert et al. [42]	Minimum 12 months	SML: Response: 13/15 (87%) Complete: 12/15 (80%) HfPDT: Response: 14/18 (78%) Complete: 13/18 (72%)	SML: BL: 287.3 ± 126 μm 12 months: 138.0 ± 40 μm HfPDT: BL: 242.8 ± 80 μm 12 months: 156.9 ± 60 μm Significant CRT decrease after SML ($p = 0.003$), but not after hfPDT ($p = 0.098$)	SML: BL: 67.3 ± 14.2 ETDRS 12 months: 71.5 ± 21.4 ETDRS HfPDT: BL: 60.7 ± 16.3 ETDRS 12 months: 64.4 ± 24.9 ETDRS No significant increase in both groups SML: $p = 0.285$, hfPDT: $p = 0.440$	No visible retinal scarring	1–2

Table 1 continued

Authors	FU	Treatment response	Central retinal thickness	Best corrected visual acuity	Safety	Laser sessions
Ambiya et al. [43]	6 months	Response: 1 month: 10/10 Complete: 1 month: 4/10 (40%) 3 month: 6/10 (60%) 6 months: 6/10 (60%)	BL: 298 ± 129 µm 1 month: 200 ± 72 µm 3 months: 179 ± 53 µm 6 months: 215 ± 90 µm Significant CRT decrease at 6 months ($p = 0.03$)	BL: 73.3 ± 16.1 ETDRS 1 month: 73.1 ± 16.3 ETDRS 3 months: 75.8 ± 14.0 ETDRS 6 month: 76.9 ± 13.0 ETDRS No significant increase in BCVA ($p = 0.59$)	No evidence of laser spots via funduscopic examination, on SDOCT, and on FAF No complications	1–2
Scholz et al. [44]	6 weeks	SML 6 weeks: Response: 33/42 (79%) Complete: 15/42 (36%) HdPDT 6 weeks: Response: 34/58 (59%) Complete: 12/58 (21%) SML showed higher treatment response than HdPDT ($p = 0.036$)	SML: BL: 445 ± 153 µm 6 weeks: 297 ± 95 µm HdPDT: BL: 398 ± 88 µm 6 weeks: 322 ± 93 µm Significant decrease in both groups (SML: $p < 0.001$, hdPDT: $p < 0.001$) CRT decrease better after SML ($p = 0.041$)	SML: BL: 0.39 ± 0.24 logMAR 6 weeks: 0.31 ± 0.27 logMAR HdPDT: BL: 0.35 ± 0.24 logMAR 6 weeks: 0.31 ± 0.24 logMAR Significant BCVA increase after SML ($p = 0.003$), but not after HdPDT ($p = 0.07$)	No laser spots detectable by funduscopic examination or on FA	1

BCVA best corrected visual acuity, *BCZ* bevacizumab (intravitreal), *BL* baseline, *CRT* central retinal thickness, *CSC* central serous chorioretinopathy, *DC* duty cycle, *ETDRS* Early Treatment Diabetic Retinopathy Study Group letters, *FA* fluorescein angiography, *FAF* fundus autofluorescence, *FU* follow-up, *FFU* final follow-up, *HdPDT* half dose photodynamic therapy, *HfPDT* half fluence photodynamic therapy, *ICG* indocyanin green, *IOP* intraocular pressure, *logMAR* logarithm of the minimum angle of resolution, *OCT* optical coherence tomography, *RPE* retinal pigment epithelium, *SDOCT* spectral domain OCT, *SML* subthreshold micropulse laser, *SRF* subretinal fluid, *Ø* spot size

Table 2 Overview of the studies investigating subthreshold micropulse laser treatment for diabetic macular edema

Authors	Year	Eyes	Inclusion criteria	Laser type and parameters	Study design
Fazel et al. [45]	2016	68 eyes SML: $n = 34$ CL: $n = 34$	DME* CRT <450 μm Without PDR Without previous IVT or any retinal laser	Quantel Medical 810 nm, Ø 50–100 μm, 0.1 s, power: adjusted Quantel Medical 810 nm, Ø 75–125 μm, 15% DC, 0.0003 s, power: 2× threshold	Prospective, single-blind, randomized clinical trial
Inagaki et al. [46]	2015	53 eyes 810 nm: $n = 24$ 577 nm: $n = 29$	DME*, type II with or without NPDR/PDR No IVT or laser within the last 3 months Patients with isolated local FA dye were excluded	Iris Medical IQ577 577 nm, Ø 200 μm 15% DC, 0.2 s, power: 2× threshold, (mean 204 mW) Iris Medical OcuLight SLX, 810 nm, Ø 200 μm 15% DC, 0.2 s, power: 2× threshold, (mean 955 mW)	Prospective, non-randomized, interventional case series Additional micro-aneurysm closure in both groups at BL
Vujosevic et al. [47]	2015	53 eyes 810 nm: $n = 27$ 577 nm: $n = 26$	DME* <400 μm, type I/II diabetes No macular therapy, IVT, laser, ppV previously	Iris Medical IQ577 577 nm, Ø 100 μm, 5% DC, 0.2 s, power: 250 mW, HD treatment Iris Medical OcuLight SLX, 810 nm, Ø 125 μm, 5% DC, 0.2 s, power: 750 mW, HD treatment	Prospective, masked, randomized, comparative pilot study
Othman et al. [48]	2014	220 eyes Group 1 Primary treatment ($n = 187$) Group 2 Secondary treatment ($n = 33$)	DME* without PDR and foveal ischemia Group 1 without prior treatment, BCVA at least 20/80 Group 2 with prior CL, BCVA at least 20/200	Iris Medical OcuLight SLX 810 nm, Ø 75–125 μm, 15% DC, 0.3 s, power: 650–1000 mW confluent	Prospective, single-center, nonrandomized, interventional case series

Table 2 continued

Authors	Year	Eyes	Inclusion criteria	Laser type and parameters	Study design
Venkatesh et al. [49]	2011	46 eyes SML: $n = 23$ CL: $n = 23$	DME* without PDR No prior medical or laser treatment within the last 6 months	Iris Medical OcuLight SLX, 810 nm, Ø 125 µm, 10% DC, 2 s, power: 80–130 mW Zeiss Visulas Nd:YAG LC 532 nm, Ø 50–100 µm, 0.1 s, power: 90–180 mW	Prospective, randomized interventional study
Lavinsky et al. [50]	2011	123 eyes ND-SLM: $n = 39$ HD-SLM: $n = 42$ CL: $n = 42$	DME* with CRT ≥250 µm No prior macular laser or IVT for DME No panretinal laser within last 4 months	Opto FastPulse 810 nm, Ø 125 µm, 15% DC, 0.3 s 0.3 s, power: 1.2× threshold ND-SML: 2 invisible burn widths apart HD-SML: Confluent invisible burn Iridex, Nd:YAG LC 532 nm, Ø 75 µm, 0.05–0.1 s, power: titration mETDRS grid	Prospective, randomized, controlled, double-masked clinical trial
Ohkoshi and Yamaguchi [51]	2010	43 eyes	DME* with CRT ≤600 µm without PDR Type II Patients with isolated local FA dye were excluded No prior medical or laser treatment within last 6 months	Iris Medical OcuLight SLX 810 nm, Ø 200 µm, 15% DC, 0.2–0.3 s, power: 520–100 mW confluent	Prospective, nonrandomized interventional study
Nakamura et al. [52]	2010	28 eyes	DME* No prior laser or surgical therapy within last 6 months	Iris Medical OcuLight SLX 810 nm, Ø 200 µm, 15% DC, 0.2 s, power: titrated, grid pattern was used	Prospective

Table 2 continued

Authors	Year	Eyes	Inclusion criteria	Laser type and parameters	Study design
Vujosevic et al. [53]	2010	62 eyes SML: $n = 32$ CL: $n = 30$	DME*, type II No prior medical/laser/surgical treatment within last 6 months	Coherent Novus Omni laser, 514 nm, Ø 100 µm, 0.1 s, power: 80–100mW mETDRS grid CL Iris Medical OcuLight SLX 810 nm, Ø 125 µm 5% DC, 0.2 s, power: 750mW	Prospective, randomized clinical trial (retreatment after 3 months if: CMT ≥250 µm or CMT reduction ≤50% or BCVA decrease >5 ETDRS letters)
Figueira et al. [54]	2009	84 eyes SML: $n = 44$ CL: $n = 40$	Both eyes DME*, type II, <80 years without PDR No prior laser treatment	Iridex Oculite GLx argon green 514 nm, Ø 100–200 µm 0.1 s, power: titration Iris Medical OcuLight SLX 810 nm, Ø 125 µm 15% DC, 0.3 s, power: titration	Prospective, randomized, controlled, double-masked trial
Laursen et al. [55]	2004	23 eyes SML: $n = 12$ (Diffuse, $n = 6$; focal: $n = 6$) CL $n = 11$ (Diffuse, $n = 6$; focal, $n = 5$)	DME* without PDR Without prior LC Without retinal surgery	Iris Medical OcuLight SLX 810 nm, Ø 125 µm 5% DC, 0.1 s, power: titration Novus 200 argon green 514 nm, Ø 100 µm, 0.1 s, power: titration	Prospective, randomized

Authors	FU (months)	Central retinal thickness	Best corrected visual acuity	Safety	Additional treatments
Fazel et al. [45]	4	810 nm SML: BL: 373 ± 56 µm 4 months: 344 ± 60 µm 810 nm CL: BL: 355 ± 53 µm 4 months: 350 ± 54 µm SML superior to CL ($p = 0.001$; 4 months)	810 nm SML: BL: 0.59 ± 0.3 logMAR 4 months: 0.52 ± 0.3 logMAR 810 nm CL: BL: 0.58 ± 0.3 logMAR 4 months: 0.60 ± 0.3 logMAR SML superior to CL ($p = 0.015$; 4 months)	No laser scars after SML Laser scars after CL	Not mentioned

Table 2 continued

Authors	FU (months)	Central retinal thickness	Best corrected visual acuity	Safety	Additional treatments
Inagaki et al. [46]	12	810 nm: BL: 488 ± 176 μm 3 month: 404.5 μm 6 months: 394.4 μm 12 months: 361.8 μm 577 nm: BL: 417 ± 113 μm 3 months: 345.8 μm 6 months: 340.6 μm 12 months: 335.2 μm No significant difference between groups after 12 months	810 nm: BL: 0.59 ± 0.41 logMAR 3 months: 0.57 logMAR 6 months: 0.53 logMAR 12 months: 0.54 logMAR 577 nm: BL: 0.31 ± 0.31 logMAR 3 months: 0.32 logMAR 6 months: 0.32 logMAR 12 months: 0.28 logMAR BCVA stable in both groups, intergroup differences were not evaluated	No laser scars in either group	810 nm: 12.5% Re-SML, 4.2% IVT (bevacizumab) 5–577 nm: 3.4% Re-SML
Vujosevic et al. [47]	6	810 nm: BL: 340 ± 36 μm 6 months: 335 ± 55 μm 577 nm: BL: 358 ± 46 μm 6 months: 340 ± 56 μm Significant decrease for 577 nm group at 6 months ($p = 0.009$) and not for 810 nm ($p = 0.45$) No significant difference between the groups at 6 months	810 nm: BL: 78.6 ± 7.5 ETDRS 3 months: 79.3 ± 6.8 ETDRS 6 months: 77.3 ± 8.2 ETDRS 577 nm: BL: 79.7 ± 6.1 ETDRS 3 months: 79.4 ± 7.6 ETDRS 6 months: 78.7 ± 7.4 ETDRS No significant difference of BCVA between groups at 3 months ($p = 0.3$) and at 6 months ($p = 0.62$)	No laser scars or visible secondary effects of laser spots in either group	810 nm: 85.2% Re-SML 5–577 nm: 88.5% Re-SML

Table 2 continued

Authors	FU (months)	Central retinal thickness	Best corrected visual acuity	Safety	Additional treatments
Othman et al. [48]	12	810 nm: Primary treatment (1) BL: 353 ± 80 µm 4 months: 257 ± 51 µm 12 months: 215 ± 27 µm 810 nm: Secondary treatment (2) BL: 429 ± 69 µm 4 months: 356 ± 64 µm 12 months: 263 ± 59 µm In both groups, CRT decrease was significant at 4 and 12 months ($p < 0.05$)	810 nm: primary treatment (1) BL: 0.21 logMAR 4 months: 0.15 logMAR 12 months: 0.18 logMAR 810 nm: secondary treatment (2) BL: 0.50 logMAR 4 months: 0.44 logMAR 12 months: 0.46 logMAR In group 1, *BCVA* improved at 4 months ($p = 0.017$) and was stable at 12 months for 85% of the eyes In group 2, no significant BCVA change was observed	Laser marks seen as pigmentary changes were noted 3.3% via funduscopic examination and 5.7% via FA	Group 1: 23% Re-SML (median 2 × SML) 11.7% IVT (triamcinolone) 3.2% ppV Group 2: 33% IVT (triamcinolone)
Venkatesh et al. [49]	6	810 nm SML: BL: 299 ± 50 µm 3 months: 287 ± 53 µm 6 months: 275 ± 63 µm 532 nm YAG CL: BL: 313 ± 47 µm 3 months: 296 ± 34 µm 6 months: 287 ± 33 µm No difference between SML and CL ($p = 0.064$)	810 nm SML: BL: 0.41 ± 0.3 logMAR 3 months: 0.41 ± 0.3 logMAR 6 months: 0.43 ± 0.3 logMAR 532 nm YAG CL: BL: 0.33 ± 0.2 logMAR 3 months: 0.36 ± 0.2 logMAR 6 months: 0.41 ± 0.3 logMAR No difference between SML and CL ($p = 0.77$) for BCVA. Better preservation of retinal sensitivity in SML group	In mfERG: 810 nm SML: 4/23 eyes with focal void regions 532 nm YAG-CL: 18/23 eyes with focal void regions	Not mentioned

Table 2 continued

Authors	FU (months)	Central retinal thickness	Best corrected visual acuity	Safety	Additional treatments
Lavinsky et al. [50]	12	810 nm ND-SML: BL: 379 (279–619) μm 3 months: 332 (223–610) μm 6 months: 316 (215–627) μm 12 months: 311 (207–599) μm 810 nm HD-SML: BL: 371 (297–879) μm 3 months: 301 (203–698)μm 6 months: 291 (201–577) μm 12 months: 226 (187–513) μm 532 nm YAG mETDRS CL: BL: 370 (269-710) μm 3 months: 306 (209–512) μm 6 months: 290 (208–501) μm 12 months: 249 (199–475) μm HD-SML, CL were superior to ND-SLM group ($p < 0.001$) No difference between HD-SDM and CL groups ($p = 0.75$)	810 nm ND-SML: BL: 0.70 (0.4–1.3) logMAR 3 months: 0.80 (0.4–1.3) logMAR 6 months: 0.80 (0.4–1.3) logMAR 12 months: 0.80 (0.3–1.3) logMAR 810 nm HD-SML: BL: 0.90 (0.3–1.3) logMAR 3 months: 0.70 (0.2–1.3) logMAR 6 months: 0.60 (0.2–1.3 logMAR 12 months: 0.52 (0.2–1.3) logMAR 532 nm YAG mETDRS CL: BL: 0.80 (0.3–1.3) logMAR 3 months: 0.75 (0.3–1.3) logMAR 6 months: 0.70 (0.2–1.3) logMAR 12 months: 0.65 (0.3–1.3) logMAR HD-SML with significant BCVA increase 12 months ($p = 0.009$), ND-SML and CL group: No improvement	SML: No laser scars or visible laser burns after SML, although some very light laser-induced lesions could be identified CL: laser scars after CL	810 nm ND-SML: 21% re-SML (once) 77% Re-SML (twice) 810 nm HD-SML: 38% Re-SML (once) 13% Re-SML (twice) 532 nm CL: 32% Re-CL (once) 24% Re-CL (twice)
Ohkoshi and Yamaguchi [51]	12	810 nm SML: BL: 342 ± 119 μm 3 months: 301 ± 124 μm 6 months: 292 ± 122 μm 12 months: 290 ± 123 μm CRT reduction was significant at 3 months ($p = 0.05$) and stable afterwards	810 nm SML: BL: 0.12 ± 0.2 logMAR 3 months: 0.12 ± 0.2 logMAR 6 months/12 months: N/A Stable BCVA until 12 months	No laser scars, no evidence of laser treatment After 1 year, one patient showed pigmentary changes	19% re-SML (once) 7% 1× grid CL 2% 1× CL of microaneurysm 2% IVT 4% ppV

Table 2 continued

Authors	FU (months)	Central retinal thickness	Best corrected visual acuity	Safety	Additional treatments
Nakamura et al. [52]	3	810 nm SML, CFT changes: BL: 481 ± 110 µm 3 months: 388 ± 127 µm Significant CFT reduction at 3 months ($p = 0.004$)	810 nm SML BL: 0.47 ± 0.2 logMAR 3 months: 0.40 ± 0.2 logMAR Significant BCVA improve at 3 months ($p = 0.03$)	No laser scars, no evidence of laser treatment	Not mentioned
Vujosevic et al. [53]	12	810 nm SML: BL: 358 ± 94 µm 3 months: 341 ± 114 µm 6 months: 346 ± 113 µm 12 months: 312 ± 76 µm 514 nm argon CL: BL: 378 ± 95 µm 3 months: 338 ± 72 µm 6 months: 327 ± 77 µm 12 months: 310 ± 87 µm No significant difference between CL and SML	810 nm SML: BL: 0.21 ± 0.30 logMAR 3 months: 0.23 ± 0.29 logMAR 6 months: 0.24 ± 0.32 logMAR 12 months: 0.24 ± 0.25 logMAR 514 nm argon CL: BL: 0.29 ± 0.30 logMAR 3 months: 0.32 ± 0.33 logMAR 6 months: 0.29 ± 0.27 logMAR 12 months: 0.30 ± 0.30 logMAR No significant difference between CL and SML	SML: No signs of laser treatment via funduscopic examination and on FA CL: laser scars after CL	Number of treatments: SML: 2.03 ± 0.75 CL: 2.10 ± 1.0
Figueira et al. [54]	12	810 nm SML: BL: 249 ± 59 µm 12 months: 291 ± 104 µm 514 nm Argon CL: BL: 255 ± 62 µm 12 months: 284 ± 105 µm No significant differences between CL and SML ($p = 0.81$)	810 nm SML: BL: 78.4 ± 8.1 ETDRS 12 months: 71.8 ETDRS 514 nm argon CL: BL: 78.0 ± 7.8 ETDRS 12 months: 70.70 ETDRS No significant differences between CL and SML ($p = 0.88$)	SML: 13.9% of the treated eyes showed laser scars CL: 59% of the treated eyes showed laser scars	Not mentioned

Table 2 continued

Authors	FU (months)	Central retinal thickness	Best corrected visual acuity	Safety	Additional treatments
Laursen et al. [55]	5–8	Focal LC/diffuse LC Central retinal thickness 810 nm SML focal LC ($n = 6$): BL: 275 µm 3 months: 250 µm 6 months: 256 µm 810 nm SML diffuse LC: ($n = 6$) BL: 293 µm 3 months: 318 µm 6 months: 341 µm 514 nm argon focal LC (n = 5) BL: 325 µm 3 months: 338 µm 6 months: 330 µm 514 nm argon diffuse LC ($n = 6$): BL: 272 µm 3 months: 308 µm 6 months: 90 µm In all patients with focal edema CRT decrease significant ($p = 0.02$)	BL BCVA cannot be extracted! 810 nm SML focal LC ($n = 6$) 3 months: +2.8 ETDRS 6 months: +3.5 ETDRS 810 nm SML diffuse LC ($n = 6$) 3 months: −0.8 ETDRS 6 months: −1.6 ETDRS 514 nm Argon focal LC: ($n = 5$) 3 months: +4.6 ETDRS 6 m: +3.5 ETDRS 514 nm argon diffuse LC ($n = 6$): 3 months: −1.7 ETDRS 6 months: +0.6 ETDRS No significant differences between groups	No laser complications were observed in both groups	Not mentioned

BL baseline, *CL* conventional laser, *CRT* central retinal thickness, *DC* duty cycle, *DME* diabetic macular edema, *ETDRS* Early Treatment Diabetic Retinopathy Study Group letters, *FA* fluorescein angiography, *FU* follow-up, *HD-SLM* high density subthreshold micropulse laser, *logMAR* logarithm of the minimum angle of resolution, *IVT* intravitreal drug therapy, *mfERG* multifocal electroretinography, *mETDRS* modified ETDRS (Early Treatment Diabetic Retinopathy Study Group) Grid, *ND-SLM* normal density subthreshold micropulse laser, *NdYAG* neodymium–yttrium–aluminum garnet laser, *PDR* proliferative diabetic retinopathy, *ppV* pars plana vitrectomy, *OCT* optical coherence tomography, *SML* subthreshold micropulse laser, *Ø* spot size

* Clinically significant DME

Table 3 Overview of the studies investigating subthreshold micropulse laser treatment for macular edema after branch retinal vein occlusion

Authors	Year	Eyes	Inclusion criteria	Laser type and parameters	Study design
Parodi et al. [56]	2015	35 eyes Group 1: SML: $n = 18$ Group 2: IVT Bevacizumab (PRN after 3 initial injections) $n = 17$	ME to due BRVO CFT > 250 µm Without non-perfusion ≥ 5 disc areas All eyes were previously treated with conventional grid laser	Iris Medical OcuLight SLX 810 nm, Ø 125 µm, 15% DC, 0.3 s, power: titration	Prospective, randomized, interventional
Inagaki et al. [57]	2014	32 eyes Group 1: BCVA ≤20/40 $n = 15$ Group 2: BCVA >20/40 $n = 17$	ME due to BRVO (ischemic/ non-ischemic) CRT <600 µm No prior macular therapy (LC, IVT etc.) within last 6 months	Iris Medical OcuLight SLX, 810 nm, Ø 200 µm, 15% DC, 0.2 or 0.3 s, Power: 750–1500 mW (90%) for 0.2 s or 360–2000 mW (60%) for 0.3 s	Retrospective, single-center, nonrandomized, interventional case series
Parodi et al. [58]	2008	24 eyes Group 1: SML only $n = 13$ Group 2: SML + IVT Triamcinolone $n = 11$	ME due to BRVO CRT >212 µm No prior laser treatment Without non-perfusion ≥5 disc areas	Iris Medical OcuLight SLX, 810 nm Ø 125 µm 15% DC, 0.3 s Power: titration	Prospective randomized pilot clinical trial
Parodi et al. [59]	2006	36 eyes Group 1: SML grid $n = 17$ Group 2: Krypton grid $n = 19$	ME due to BRVO CRT >210 µm No prior laser treatment Without non-perfusion ≥5 disc areas	Iris Medical OcuLight SLX 810 nm Ø 125 µm, 10% DC, 0.2 s, power: titration Novus Omni Krypton Ø 100 µm, 0.1 s	Prospective, randomized clinical trial

Table 3 continued

Authors	FU (months)	Central retinal thickness	Best corrected visual acuity	Safety	Additional treatments
Parodi et al. [56]	12	SML group (CFT): BL: 485.5 μm 3 months: 472.0 μm 6 months: 475.0 μm 9 months: 475.0 μm 12 months: 445.0 μm IVT group (CFT): BL: 484.2 μm 3 months: 305.0 μm 6 months: 266.0 μm 9 months: 265.0 μm 12 months: 271.0 μm IVT group significantly better ($p = 0.001$)	SML group: BL: 0.92 logMAR 3 months: 0.89 logMAR 6 months: 0.89 logMAR 9 months: 0.94 logMAR 12 months: 0.99 logMAR IVT group: BL: 0.94 logMAR 3 months: 0.88 logMAR 6 months: 0.88 logMAR 9 months: 0.85 logMAR 12 months: 0.72 logMAR IVT group significantly better ($p = 0.0085$)	No laser scars	Not mentioned
Inagaki et al. [57]	12	Group 1: (BCVA ≤20/40 Snellen) BL: 409.3 μm 1 month: 394.3 μm 3 months: 371.3 μm 6 months: 313.5 μm 12 months: 303.5 μm Group 2: (BCVA >20/40 Snellen) BL : 373.3 μm 1 month: 353.5 μm 3 months: 313.1 μm 6 months: 294.1 μm 12 months: 320.1 μm Significant CRT decrease at 3, 6, and 12 months for both groups. No significant difference between the groups at any time point	Group 1: (BCVA ≤ 20/40 Snellen) BL: 0.59 logMAR 1 month: 0.54 logMAR 3 months: 0.54 logMAR 6 months: 0.58 logMAR 12 months: 0.51 logMAR Group 2: (BCVA >20/40 Snellen) BL: 0.13 logMAR 1 month: 0.09 logMAR 3 months: 0.13 logMAR 6 months: 0.09 logMAR 12 months: 0.12 logMAR	No laser scars	Group 1: $n = 8$ (53.3%) Group 2: $n = 3$ (17.6%)

Table 3 continued

Authors	FU (months)	Central retinal thickness	Best corrected visual acuity	Safety	Additional treatments
Parodi et al. [58]	12	SML only: BL: 429 μm 3 months: 364 μm 6 months: 320 μm 9 months: 290 μm 12 months: 278 μm SML + IVT (triamcinolone): BL: 476 μm 3 months: 269 μm 6 months: 276 μm 9 months: 260 μm 12 months: 283 μm Combined SML + IVT showed better response at 3 months ($p < 0.001$). No difference between groups from 9th month on	SML only: BL: 0.76 logMAR 3 month: 0.78 logMAR 6 months: 0.78 logMAR 9 months: 0.73 logMAR 12 months: 0.65 logMAR SML + IVT (triamcinolone): BL: 0.67 logMAR 3 months: 0.50 logMAR 6 months: 0.45 logMAR 9 months: 0.36 logMAR 12 months: 0.35 logMAR Combined SML + IVT showed significant better response at 9th and 12th months ($p < 0.009$, $p = 0.011$, respectively)	No Laser scars	Not mentioned
Parodi et al. [59]	24	SML grid: BL: 480 μm 6 months: 457 μm 12 months: 217 μm 18 months: 215 μm 24 months: 208 μm Krypton grid: BL: 454 μm 6 months: 252 μm 12 months: 226 μm 18 months: 229 μm 24 months: 217 μm Krypton showed better response at 3 months and 6 months ($p < 0.001$). SML showed better response from 12th month on ($p < 0.001$)	SML grid: BL: 0.70 logMAR 6 months: 0.70 logMAR 9 months: 0.55 logMAR 12 months: 0.51 logMAR 24 months: 0.49 logMAR Krypton grid: BL: 0.69 logMAR 6 months: 0.60 logMAR 9 months: 0.58 logMAR 12 months 0.57 logMAR 24 m: 0.56 logMAR No statistical difference between groups	No laser scars after SML	Not mentioned

BRVO branch retinal vein occlusion, *BL* baseline, *CFT* central foveal thickness, *CRT* central retinal thickness, *DC* duty cycle, *FA* fluorescein angiography, *IVT* intravitreal drug therapy, *logMAR* logarithm of the minimum angle of resolution, *ME* macular edema, *PRN* pro re nata, *SML* subthreshold micropulse laser

Table 4 Treatment outcome after SML, PDT, observation and conventional laser for CSC, DME, and BRVO

	Treatment	Change in CRT (μm)	Change in BCVA (ETDRS letters)
CSC	SML	−131 (range −69.7 to −204)[a]	6.34 (range −15 to 20)[d]
	PDT	−85 (range −76 to −109.8)[b]	3.87 (range 2 to 8.5)[b]
	Observation	−25 (range 26 to −89)[c]	0.67 (range −2.1 to 2.5)[c]
DME	SML	−74.9 (range −138 to 48)[e]	1.26 (range −6.6 to 19)[e]
	Conventional laser	−43.6 (range −145 to 28.7)[f]	−0.29 (range −7.3 to 7.5)[f]
BRVO	SML	−122.59 (range −272 to −40.5)[g]	2.98 (range −3.5 to 9.5)[g]

CSC central serous chorioretinopathy, *DME* diabetic macular edema, *BRVO* branch retinal vein occlusion, *BCVA* best corrected visual acuity, *CRT* central retinal thickness, *ETDRS* Early Treatment Diabetic Retinopathy Study Group letters, *PDT* photodynamic therapy, *SML* subthreshold micropulse laser

[a] 199 patients from 11 studies, 7 studies excluded from the calculations, one due to prior PDT treatment [37], six due to absence of information about the CRT

[b] 100 patients from 3 studies

[c] 49 patients from 3 studies

[d] 216 patients from 14 studies, two studies excluded due to prior PDT [37, 41], two due to absence of information about the concrete BCVA [28, 31]

[e] 613 patients from 11 studies

[e] 195 patients from 7 studies

[f] 80 patients from 3 studies, one study excluded from the calculation due to prior conventional laser treatment [56]

OCT (SDOCT). A complete resolution of SRF in SDOCT was defined as a complete treatment response. Two studies measured the leakage activity in FA as a parameter for treatment response [32, 35]. For simplicity reasons we do not distinguish between the different definitions for treatment response in our calculations. Few studies did not mention the amount of patients with treatment response. If we were able to work out the treatment response from the data shown in the paper, we quote the response; otherwise the studies were excluded from the calculations [33, 38]. One case report was excluded from the calculation because of prior bevacizumab treatment [39], and two studies were excluded since they included patients with prior PDT [37, 41]. Few studies mentioned only the response or the complete response, and those studies were included in the calculations.

We included 191 patients from 12 studies for the calculations of the treatment response and 176 patients from 11 studies for the complete response. A total of 156 (79.6%) of the 191 patients showed a treatment response at the last mentioned follow-up: 112 (63.6%) of the 176 patients had a complete resolution of SRF. Only two studies showed data concerning the improvement rate in an untreated control group: a complete resolution of SRF was seen in 2 (8%) out of 26 eyes at the last follow-up and a reduction in SRF in 7 (39%) out of 18 eyes.

Four studies had a control group consisting of patients receiving PDT treatment (half dose PDT in three studies and half fluence PDT in one). The treatment response could be calculated from 100 patients in three studies and the complete treatment response from 135 patients in three studies. A total of 64 (64%) of the 100 patients responded to PDT and 62 (46%) of 135 patients showed complete response.

Safety

The majority of studies described no visible retinal changes after the micropulse laser treatment. In six patients from two studies [30, 39] pigmentary changes at the level of the RPE were seen after SML but without any visual implications for the patients. Complications like scar

formation, visible laser burns, or CNV did not occur.

DIABETIC MACULAR EDEMA (DME)

DME is a frequent complication of diabetic retinopathy (DR) and the most common cause of visual impairment in patients with DR [5]. Since the ETDRS trial [1, 73] showed that laser photocoagulation reduced the risk of moderate visual loss by 50% in eyes with clinically significant macular edema, laser photocoagulation became the standard therapy for DME for many years. Depending on the kind of edema, the treatment pattern can be selected: a focal photocoagulation for localized areas of leakage and a grid pattern for a diffuse macular edema. Continuous-wave photocoagulation comes with potential side effects like epiretinal fibrosis, CNV, and enlargement of laser scars [7, 8, 74]. Table 3 shows only the prospective studies investigating micropulse laser treatment for diabetic macular edema. A total of 613 patients from 11 studies were included in the calculations. The inclusion and exclusion criteria varied between studies; some did not allow prior treatment at all, most of them only excluded patients with treatment in the prior 3–6 months. All listed studies were included in the calculations for change in CRT and BCVA. Seven studies had a control group consisting of 195 patients treated with conventional laser. The same calculations were performed for those studies.

Table 4 displays the treatment outcome after SML and conventional laser for DME.

Safety

In the majority of studies no laser scars occurred after SML. Four studies reported scar formation or pigmentary changes in a small amount of eyes after SML treatment [48, 50, 51, 54]. Retinal changes were only observed in eyes treated with duty cycles of 15%; lower duty cycles did not lead to scar formation in the listed studies.

Venkatesh [49] et al. reported focal void regions in multifocal electroretinogram in 4 out of 23 eyes after SML treatment with 10% duty cycle compared to 18 out of 23 eyes after conventional laser.

MACULAR EDEMA DUE TO RETINAL VEIN OCCLUSION (RVO)

Macular edema is a common complication of branch RVO (BRVO) [75]. Grid laser photocoagulation reduces the visual acuity loss after BRVO with macular edema [75]. Parodi et al. [59] reported a similar outcome in visual acuity improvement and resolution of macular edema after SML treatment compared to conventional laser, but without retinal changes after SML. Table 3 summarizes studies investigating SML treatment for macular edema after BRVO. In total 80 patients from three studies could be included in the calculations, and one study was excluded because of prior conventional laser treatment [56]. As a result of the small number of studies and the variety in control groups (bevacizumab, SML + triamcinolone, conventional laser), the control groups were not separately analyzed. Only one study [48] had a control group where patients were treated with anti-VEGF agents, the current standard therapy for macular edema due to BRVO.

Table 4 presents the treatment outcome after SML for macular edema after BRVO.

Safety

No study described complications like scar formation, visible laser burns, or CNV.

PROBLEMS AND CHALLENGES OF SML TREATMENT

Although the majority of the studies showed some efficacy of the SML treatment for CSC, DME, or BRVO, the treatment parameter differed significantly between the individual studies. No study compared the outcome of SML with different treatment parameters like higher or lower duty cycle. Concerning the treatment power, most authors titrated the power individually for each patient, but the

path was not consistent. The titration is probably the most challenging part of the SML treatment. Since the laser surgeon did not see an effect of the treatment, there is a high risk of undertreatment and treatment failure accordingly. A solution to this problem could be to use fixed laser parameters with the same power for all patients. But so far there is not enough published data to choose the best treatment power and to evaluate the safety and the treatment success of subthreshold micropulse treatment with fixed parameters. For the future, controlled trials comparing treatment outcome and safety of individual titrated SML treatment and SML treatment with fixed parameters would be desirable. Those studies should include safety follow-up with multimodal imaging including autofluorescence, OCT, and fundus photographies as well functional follow-up with microperimetry or multifocal electroretinogram.

CONCLUSION

For CSC, the presented studies showed a higher efficacy of the micropulse laser treatment for both morphology and visual function in comparison to no treatment or PDT. The decrease in CRT was highest after SML (−131 μm), followed by PDT (−85 μm) and the no-treatment group (−25 μm). Moreover, 64% of patients showed no SRF after SML compared to 46% after PDT and 8% after observation.

No study reported any complications after up to five SML treatment sessions, so even an early treatment could be considered for potentially better results. Chen et al. [29] showed that the SML treatment outcome was best in patients with source leakage without RPE atrophy. The investigated literature did not allow an evaluation of the best treatment parameter or the best laser wavelength.

Regarding the treatment of DME, the investigated studies showed efficacy also in morphology and function. The decrease in CRT and increase in BCVA after SML (−74.9 μm and +1.26 ETDRS letters) was better than after conventional laser (−43.6 μm and −0.29 ETDRS letters), but no study had a control group in which patients were treated with anti-VEGF agents. After the RISE and RIDE studies [76] and the approval of ranibizumab for the treatment of DME, anti-VEGF agents became the standard treatment for DME. Without any trial, comparing SML treatment with anti-VEGF agents, we do not know when SML treatment could be an alternative first-line treatment for DME. Nevertheless, SML might be an option in patients not responding sufficiently to, or who are not able to follow an anti-VEGF therapy (e.g., high costs, compliance problems due to frequent visits for the injections and ophthalmological controls). Chen et al. [77] had come to a similar result in their meta-analysis of randomized controlled trials comparing subthreshold micropulse diode laser photocoagulation and conventional laser. They reported a significantly better visual acuity and a similar decrease in CRT after SML compared to conventional laser. They underline the advantage of the SML treatment in terms of the affordability compared to the cost-intensive anti-VEGF therapy.

On the subject of macular edema after BRVO, SML treatment shows some efficacy as well. But in comparison to the current standard treatment, intravitreal anti-VEGF, SML was inferior to intravitreal bevacizumab [56]. However, similar to DME, SML treatment could be an option for adjunct treatment for selected patients.

In summary, in all three indications micropulse laser is an efficacious and safe treatment option. Owing to its higher efficacy and the excellent safety profile compared to PDT, it could become the first-line therapy in CSC, potentially even in acute cases.

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Data Availability. The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

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