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REVIEW

Yellow Subthreshold Micropulse Laser in Retinal Diseases: An In-Depth Analysis and Review of the Literature

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ABSTRACT

Yellow subthreshold micropulse laser (YSML) is a retinal laser capable of inducing a biologic response without causing thermal damage to the targeted tissue. The 577-nm YSML is delivered to the retina abiding by different protocols in which wavelength, power, duration, spot size and number of spots can be properly set to achieve the most effective and safe treatment response in various chorioretinal disorders. The ultrashort trains of power modulate the activation of the retinal pigment epithelium cells and intraretinal cells, such as Müller cells, causing no visible retinal scars. Subthreshold energy delivered by YSML stimulates the production of the heat-shock proteins, highly conserved molecules that protect cells against any sort of stress by blocking apoptotic and inflammatory pathways that cause cell damage. YSML treatment allows resorption of the subretinal fluid in central serous chorioretinopathy and intraretinal fluid in various conditions including diabetic macular edema, postoperative cystoid macular edema and other miscellaneous conditions. YSML also seems to modulate the development and progression of reticular pseudodrusen in dry age-related macular degeneration. The aim of this review is to discuss and summarize the safety and efficacy of YSML treatment in retinal diseases.

Keywords: Micropulse laser; Photocoagulation; Retinal laser; Yellow laser photocoagulation; Yellow subthreshold laser

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Key Summary Points

Conventional laser photocoagulation delivers continuous waves of energy, which gets dissipated and absorbed as heat within the target tissue and produces visible burns associated with retinal scars and scotomas.

Over the past 30 years, there has been ongoing development and increasing interest in looking for an effective and safer alternative to continuous wave laser.

Subthreshold laser, which adopts several wavelengths, has been conceived to preserve retinal pigment epithelium from laser burns while effectively targeting the underlying disease by regulating heat-shock proteins and cytokine expression within the tissue.

Yellow subthreshold laser treatment appears to be a safe and effective therapeutic option for several diseases, including diabetic macular edema, central serous chorioretinopathy and other miscellaneous conditions.

A more accurate standardization of yellow subthreshold laser setting protocols is still desired, and further randomized, prospective studies with longer follow-up are warranted to confirm the role in chorioretinal diseases.

INTRODUCTION

Conventional threshold laser photocoagulation, first developed between 1950 and the 1970s, became a valuable treatment option for several retinal diseases over the last decades [1]. Its exact mechanism of action remains unknown, but several studies in animal models have demonstrated a local rise in preretinal and intraretinal oxygen tensions within areas overlying the photocoagulation spots [2, 3]. The energy delivered by laser treatment affects ocular tissues depending on wavelength, impulse duration, power and effective tissue energy absorption.

Conventional laser photocoagulation delivers energy to the target area as continuous waves (CW) throughout the entire pulse duration. Light energy gets dissipated as heat, and pigmented tissue absorbs the energy wavelengths. Heat absorption leads unequivocally to a rise in tissue temperature, leading often to collateral damage to the neighboring areas [2, 3]. In the past decades, coagulative necrosis and visible grayish/whitish burns within the target tissue were considered necessary to achieve successful treatment results [4]. Unfortunately, this was often associated with development of retinal scars, laser-related scotomas and complications such as subretinal neovascular membranes and subretinal fibrosis [5].

For these reasons, over the past 30 years, there have been ongoing development and increasing interest in looking for an effective and safer alternative to CW laser known as subthreshold laser therapy. This procedure provides therapeutic effects for several chorioretinal diseases while avoiding the typical laser-related damaging effects [1, 6].

Several subthreshold laser wavelengths have been adopted, ranging from green at 532 nm, yellow at 577 nm and 810 nm at near-infrared spectrum ranges [1, 6, 7]. This review aims to specifically analyze and summarize indications, efficacy and safety of the yellow subthreshold micropulse laser (YSML) treatment in retinal diseases.

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

METHODS OF LITERATURE SEARCH

We carried out a review of literature regarding the efficacy and safety of YSML in retinal diseases using PubMed and Embase database up to August 2022 with the following terms: conventional laser, laser treatment, micropulse laser, navigated laser, subthreshold laser, yellow subthreshold laser and combination of the terms. All relevant publications written in

English were sourced, including prospective and retrospective clinical studies and laboratory experimental studies. We included case reports only if they contributed new and relevant information about efficacy and safety of YSML.

YSML APPLICATION STRATEGY

In YSML, the standard wave of energy is chopped into series of repetitive micropulses (ON-time) that persist between 0.1 and 0.5 s and are separated by relatively long off-times. This allows for heat dissipation and reduces the typical threshold laser side effects.

The ratio between ON-time and total exposure time (ON + OFF) is called the duty cycle (DC) and represents the effective laser delivery time, which can be adjusted individually to achieve fine control and efficient spatial confining of photothermal effects [8].

The single spots on the retina are invisible, either ophthalmoscopically or using any current retinal multimodal imaging technique. Moreover, they are not characterized by any microperimetric retinal sensitivity reduction [8, 9].

Single-spot repetitive series of short duration micropulses, instead of a CW laser pulse, were demonstrated to deliver a total amount of energy insufficient to cause tissue damage [10].

Of note, substantial differences exist in protocols of subthreshold laser delivery on which wavelength, power, duration, spot size and number of spots can be set differently to achieve the most effective and safe treatment response. Moreover, Navilas® Laser System is an advanced focal/panretinal photocoagulation device revolutionizing the treatment of vision-threatening retinal diseases by integrating diagnostics with laser therapy and allowing pre-planned, computer-guided treatments.

Some physicians use a fixed power for laser applications, and some prefer different strategies based on the least invasive setting producing a visible lesion, defined as "threshold." Duty cycle and power are then reduced accordingly to lower the applied energy to a "subthreshold" target [11]. Of course, if laser settings are too low, the treatment will be subtherapeutic, and in case settings are too high, there is a high risk of damaging the retinal pigment epithelium (RPE) and/or the neural retina.

From this perspective, EndPoint Management (EpM) protocol was thought to set a proper therapeutic window and titration procedure and to standardize subthreshold parameters. In the EpM algorithm, laser power is titrated to induce a barely visible spot, which allows defining the corresponding energy at 100%. It was demonstrated that no tissue damage could be detected below 30% of the EpM energy [12].

Potential YSML-Induced Biologic Mechanisms

Several lines of evidence claim that threshold burns may not be necessary to achieve photocoagulative therapeutic benefits [12].

From this perspective, subthreshold laser has been conceived to preserve RPE while effectively targeting the underlying disease by regulating heat-shock proteins (HSPs) and cytokine expression within the tissue [7].

HSPs are a group of ubiquitary, highly conserved molecules that can be triggered by a variety of stressful stimuli to protect cells against any sort of stress by blocking apoptotic and inflammatory pathways that cause cell damage [13]. Destructive suprathreshold energy is unnecessary to achieve biologic response and to maximize anti-inflammatory HSP release. In fact, it was recently shown that HSP expression begins when just above 20% EpM energy is released within the tissue [12, 14]. Furthermore, it was demonstrated that the still-viable cells induce a gene expression leading to a healing response to sublethal laser insults rather than the laser-killed cells [15, 16].

In addition, subthreshold energy stimulates cells to restore the blood-retinal barrier, which is now known to be regulated by the retinal glial cell population [17, 18]. It downregulates a series of local growth factors, inhibitors and permeability factors that were shown to be causative of underlying pathologic pathways elicited by retinal chronic hyperglycemia [17, 18].

Table 1 Safety and efficacy profile of YSML for diabetic macular edema in clinical studies

References	Study	F-UP	*No.* eyes	BCVA	CMT	Side effects
Citirik et al. [29]	R	2MO	70	Improved (CMT < 300 μm)	Decreased (CMT < 300 μm)	None
Citirik et al. [30]	P	6MO	80	Improved	Decreased	None
Donati et al. [31]	R	12MO	39	Stabilized	Decreased	None
Filloy et al. [32]	R	12.5MO	23	Stabilized	Decreased	None
Frizziero et al. [33]	R	16.6MO (SD ± 6.5)	134	Improved	Decreased	None
Hamada et al.[34]	P	6MO	10	Stabilized	Decreased	None
Kikushima et al. [35]	R	12MO	35	Stabilized	Decreased	None
Kwon et al.[36]	R	7.9MO (SD ± 1.6)	14	Improved	Decreased	None
Latalska et al. [37]	P	6MO	75	Stabilized	Decreased	None
Passos et al. [38]	R	3MO	56	Improved	Stabilized	None
Valera-Cornejo et al. [39]	P	3MO	33	Stabilized	Stabilized	None
Vujosevic et al. [40]	P	12MO	37	Improved	Stabilized	None
Vujosevic et al. [41]	P	6MO	53	Stabilized	Stabilized	None
Vujosevic et al. [42]	P	6MO	35	Improved	Stabilized	None

R retrospective, *P* prospective, *F-UP* follow-up, *No.* number, *MO* months, *BCVA* best-corrected visual acuity, *CMT* central macular thickness, *SD* standard deviation

Because of all the aforementioned characteristics, YSML allows treating lesions with large numbers of spots and offers the possibility to treat and retreat all retinal areas, including the fovea. Furthermore, it was shown to grant color vision preservation and maintain contrast sensitivity [19] compared to conventional photocoagulation [9].

CLINICAL APPLICATIONS

YSML and Diabetic Macular Edema

Conventional laser treatment in diabetic macular edema (DME) is routinely performed according to the modified Early Treatment Diabetic Retinopathy Study (ETDRS) protocol [20]. It was demonstrated to be effective in reducing vision loss incidence, but at the same time it is a destructive treatment associated with tissue impairment and many side effects, including choroidal neovascularization, permanent photoreceptors loss, laser scars and subretinal fibrosis [21–24].

Beneficial therapeutic effects are believed to be promoted by the destructive burn of oxygen-consuming photoreceptors and retinal pigmented cells that, in turn, produce pro-angiogenic mediators [8].

This long-standing belief has been slowly controverted by a better understanding of the inducible changes in retinal gene expression even with "lighter" laser treatments and by growing evidence of papers showing promising morpho-functional outcomes with much more

gentle, subvisible, micropulse treatment [25, 26].

Many patients with early DME display no symptoms at all and often have excellent visual acuity. Indeed, the risks of performing conventional photocoagulation in such eyes are objectionable and the same can apply to intravitreal drugs injections [27].

Currently, the treatment of clinical and subclinical DME, which comprises the largest number of diabetic patients with macular involvement, also includes YSML [28].

Safety and Efficacy of YSML

Most of the literature on safety and efficacy and YSML in DME is based on evaluation of best-corrected visual acuity (BCVA) and central macular thickness (CMT) outcomes after treatment. A summary of the data collected is reported in Table 1.

The mean follow-up of all the studies ranged between 2 and 16.6 months [29–42]. Overall, a worsening of both BCVA and CMT was not observed in any of the cohorts evaluated [29–42]. In particular, a significant CMT decrease and BCVA improvement in two thirds were demonstrated [29–37] and in half of the studies [29, 30, 33, 36, 38, 40, 41], respectively, whereas a stabilization of these features was described in the remaining cases throughout the entire follow-up [31, 32, 34, 35, 37–42].

No visible retinal or choroidal lesions were described in any studies on either fundus examination or fundus imaging [fundus autofluorescence (FAF), fluorescein angiography (FA) or color fundus photograph]. On optical coherence tomography (OCT), no integrity or reflectivity changes of the outer retina (external limiting membrane, inner segment/outer segment junction, RPE) were described. No side effects were reported [29–42].

An interesting stratification of the data was done in two studies by Citirik et al., who allocated the study subjects into different groups according to their initial CMT: group 1 ranged between 250 and 300 μm, group 2 between 301 and 400 μm and group 3 had a baseline CMT > 401 μm [29, 30]. The results indicated that the anatomical severity of DME may affect the YSML outcome, with a statistically significant improvement of BCVA and CMT observed only in the group 1 patients with a baseline CMT < 300 μm. The cause of YSML lack of response in patients with severe anatomical disease is not known; however, it was speculated that severe edema could dilute and reduce the concentration of cytokines released by YSML-stimulated RPE cells that might be responsible for the beneficial effects of the treatment [29].

Another independent variable that was extensively found to affect the therapy outcome was the timing of response. Indeed, it was shown that the vast majority of patients with DME were characterized by a significant CMT shrinkage within the first 3 months of therapy and that from the 4th month onwards no further CMT reduction could be observed [43, 44] In other words, if no improvement is achieved within the first 4 months, waiting longer is unlikely to result in any significant beneficial YSML effect.

Kikushima et al. and Vujosevic et al. drew a comparison of morphologic and visual function safety parameters between YSML versus the subthreshold micropulse infrared (810 nm) laser, which is a widely adopted wavelength in published studies to test subthreshold laser efficacy [35, 45]. No significant differences were found in terms of either efficacy outcomes or safety profile between the two SLTs, suggesting the two lasers to be comparable in treating mild center involving DME [35, 45].

To date, there is great variability in the choice of laser power, titration, DC and pulse duration for DME eyes [31, 46]. A group of experts recently published the YSML consensus guideline settings for DME suggesting a DC of 5%, pulse duration 200 ms, spot size 150–200 μm with no spacing between spots and titration power of 50% of threshold power [11, 46].

Donati et al. evaluated efficacy and safety of morphologic and functional outcomes of diabetic patients affected by mild center involving DME treated with two different settings of yellow subthreshold laser: a fixed and a variable regimen delivered with the same DC (5%) [31]. The main considered outcomes were BCVA and CMT changes in both groups. Fixed regimen

consisted of 100 μm spot size, 250 mW power and a variable number of confluent spots based on the center involving DME extension. Regarding the variable regimen, instead, micropulse laser power was selected starting with a 200-μm CW test burn in non-edematous areas outside the vascular arcades. The preferential starting power was 70 mW, slowly increased by 10–20 mW until a hardly visible burn was seen, at which point the laser was switched to micropulse mode multiplying the test burn power by 4 and keeping the spot size of 200 μm. Both YSML treatment regimens were found equally effective in terms of BCVA stabilization and center involving DME reduction [31].

To support the safety of YSML, Wells-Gray et al. performed an observational study investigating the integrity of individual cones after YSML treatment using high-resolution retinal imaging [47]. Cones that were evident before the treatment remained visible, whereas cones that were initially hidden by the DME became even more distinguishable after treatment. In addition, total retinal thickness displayed a statistically significant thinning in 50% of the patients, and no subject showed any sort of photoreceptor impairment after the therapy [47].

Optical coherence tomography angiography (OCTA) was also used to investigate parameters that could be potentially affected in DME patients after YSML treatment [41, 48]. The area of foveal avascular zone, number of microaneurysms (MAs), cyst area and presence of capillary network alterations were investigated within the superficial capillary plexus (SCP) and deep capillary plexus (DCP). The most peculiar finding of this study was the early decrease of MA number within the DCP, considered a hallmark of DR [49]. Leaking MAs are believed to be one of the main causes of DME development; therefore, their reduction within the DCP may ultimately lead to an inner nuclear layer (INL) thickness decrease and consequently DME shrinkage [50, 51].

Of note, YSML is not directly targeted to MAs, as it is instead the modified conventional ETDRS laser treatment, which determines MA clotting. Indeed, the RPE is considered the main site of action of YSML, but the exact mechanism leading to MA closure is still unknown [51].

Two relatively recent papers assessing retinal thickness changes after repeated YSML sessions in DR patients demonstrated an important INL thickness reduction as a result of Müller cell (MC) downregulation and return to normal size [40, 52].

Furthermore, Midena et al. demonstrated a marked reduction of diabetes-induced glial fibrillary acidic protein (GFAP), an important biomarker of MCs activity, following YSML [17]. The association of all these molecular findings suggests that YSML induces morpho-functional recovery of MCs with a substantial reduction of their inflammatory pathologic biomarkers [17, 52].

YSML Versus Intravitreal Injections

Anti-VEGF injections have emerged as the first-choice treatment for DME [53]. As widely demonstrated in clinical trials and real-life studies, protracted series of anti-VEGF injections are proven to efficiently manage DME [53]. However, the cost of recurrent injections and ophthalmologic check-ups imposes a significant economic burden on these patients and seriously hinders provision of optimal treatment [54].

Currently, in real-life routine practice, ophthalmologists may also consider other choices for DME management, including YSML.

Several studies in the literature have compared YSML with anti-VEGF therapy for DME. A summary of the data collected is reported in Table 2.

The mean follow-up of the studies shown ranged between 6 and 24 months [55–64]. Most of the studies reported indicated a common positive result for the usefulness of YSML, which appeared to have complimentary effects to the anti-VEGF therapy [55–64]. Their combined use was demonstrated, in fact, to significantly reduce the number of anti-VEGF injections while preserving or even improving morpho-functional outcomes. BCVA improvement and a CMT decrease were illustrated in two thirds [55, 56, 58–61, 63] and in half of the studies considered [55, 58–61], respectively, and a stabilization of these features was described in

Table 2 Yellow subthreshold laser treatment impact on number of anti-VEGF injections for in clinical studies

References	Study	F-UP	*No.* eyes	BCVA	CMT	*No.* injections
Akkaya et al. [57]	R	9MO	76	Improved	Decreased	Decreased
Altinel et al. [58]	R	12MO	80	Improved	Stabilized	Decreased
Ecsedy et al. [59]	R	6MO	30	Stabilized	Stabilized	Decreased
El Matri et al. [60]	R	12MO	98	Improved	Decreased	Decreased
Elhamid et al. [61]	P	12MO	20	Improved	Decreased	Decreased
Kanar et al. [62]	P	12MO	28	Improved	Decreased	Decreased
Khattab et al. [63]	P.	18MO	54	Improved	Decreased	Decreased
Lai et al. [64]	R	24MO	164	Stabilized	–	No differences
Moisseiev et al. [65]	R	12MO	38	Improved	Stabilized	Decreased
Tatsumi et al. [66]	P	24MO	51	Stabilized	Stabilized	No differences

R retrospective, *P* prospective, *F-UP* follow-up, *No.* number, *MO* months, *BCVA* best-corrected visual acuity, *CMT* central macular thickness, *VEGF* vascular endothelial growth factor, *DME* diabetic macular edema

the remaining cases throughout the entire follow-up [56, 57, 62–64].

Of note, only two studies reported no significant differences within the cohorts treated with anti-VEGF therapy and anti-VEGF + YSML in terms of number of injections needed [62, 64].

All these studies highlighted the advantages of performing YSML in mild DME cases, including the easy administration, laser treatment management and lower costs of the procedure [55–64].

The efficacy of YSML over anti-VEGF therapy was also evaluated in terms of OCTA changes in a retrospective analysis carried out by Karasu et al. [65]. Data of 44 eyes of 44 patients with DME refractory to anti-VEGF were reported in a 6-month single-center follow-up study. A significant decrease ($p < 0.05$) occurred in the SCP, choriocapillaris and DCP, which caused a substantial decrease in vessel densities. In parallel, BCVA improved and CMT decreased significantly [65].

YSML Versus Conventional Laser

Laser photocoagulation was suggested as preferential therapy for DME after ETDRS, much before the anti-VEGF era [66]. Contrast sensitivity reduction, accidental foveal impairment, poor color vision and expansion of macular scars were common complications of laser photocoagulation, which led this procedure to take a backseat over the years [67].

The efficacy and safety of YSML were compared to conventional retinal laser photocoagulation by Chhablani et al. who conducted a 3-month prospective randomized study including 30 eyes of 20 patients who received either YSML or standard CW laser [67]. All patients underwent microperimetry, thickness measurements and visual acuity examinations. While both treatment arms achieved a stabilization of BCVA, the main differences between the two groups involved retinal volume and sensitivity. These two parameters were demonstrated to be heavily and negatively impaired by CW therapy, whereas positively preserved when treated with YSML [67].

Li et al. quantitatively investigated the combined effect of YSML with panretinal laser photocoagulation (PRP) on 86 eyes of 86 patients previously diagnosed with severe nonproliferative diabetic retinopathy (NPDR) with a center involving DME [68]. Several OCTA parameters, including foveal avascular zone (FAZ), capillary density (CD), CMT, choriocapillary flow area (ChF) and BCVA, were evaluated

during a 6-month observational retrospective study. Overall, BCVA remained stable throughout the entire follow-up. CMT, macular edema, blood flow and capillary density were characterized by a decreasing trend, whereas FAZ tended to increase during the 6-month period [68].

A limitation of these studies includes the relatively small sample sizes and short-term follow-ups unable to highlight the effects of DME recurrences. In addition, visual function examinations such as visual field test were not performed. From this perspective, further prospective studies with more patients would help to better understand the compared effect of YSML with conventional laser.

YSML After Pars Plana Vitrectomy

Application of YSML in patients who previously underwent pars plana vitrectomy (PPV) for tractional DME was explored by Bonfiglio et al. [69]. They reported data of a consecutive comparative prospective study on 95 eyes of 95 patients in which 54 eyes were treated 6 months after PPV with YSML and 41 eyes were assigned to the control group only for observation. In the treatment group, mean BCVA increased and CMT decreased in parallel more significantly than in the control group. In addition, vessel densities evaluated with OCTA in the SCP and DCP were substantially higher and FAZ significantly smaller in the YSML group. No adverse effects were described in YSML patients [69].

YSML and Central Serous Chorioretinopathy

Several treatment strategies have been proposed for central serous chorioretinopathy (CSC) including observation, diuretics, anti-VEGF intravitreal injections, photodynamic therapy (PDT) and different kind of laser treatments [70]. The goals of an ideal treatment should consider the subretinal fluid (SRF) resolution, vascular permeability alteration restoration and photoreceptor and RPE cell recovery [71, 72].

Safety and Efficacy of YSML

To assess the efficacy of YSML in chronic CSC, special focus was placed on the SRF and CMT reduction and BCVA variation after treatment. A summary of the data collected is reported in Table 3.

Overall, a BCVA improvement was reported [73–91], except for one study displaying a visual acuity stabilization [92].

All the studies that explored a SRF variation showed a reduction of the fluid [73–92]. No visible retinal or choroidal lesions were described in any study, and no side effects were reported [73–92]. Wood et al. hypothesized that, since laser energy of visible wavelengths is mainly absorbed by the RPE, the efficacy of YSML could be related to RPE cell vitality and trophism [9].

Chen et al. further subcategorized the cohort of patients based on three phenotypes classified according to FA: (1) focal point of iuxtafoveal leakage with no RPE atrophy, (2) focal point of iuxtafoveal leakage with RPE atrophy and (3) diffuse RPE impairment with indistinct source of iuxtafoveal leakage. They reported an increasing trend of fluid reabsorption and decreasing SRF recurrence in patients with limited RPE atrophy and focal leakage [93].

Other anatomic features have been investigated as predictors of higher YSML effectiveness.

In particular, Kiraly et al. demonstrated the amount of SRF to be an important biomarker in predicting treatment response by observing worse outcomes in cases with greater SRF [82]. They also investigated the role of pigment epithelium detachments (PEDs), concluding that wider PEDs correlated with poor response to YSML [82].

Several OCT parameters were demonstrated to influence the YSML response.

Altinel et al. observed 39 eyes of 39 patients for 24 months, focusing on the ellipsoid zone (EZ) band integrity and analyzing its correlation with YSML success status [94]. The eyes were allocated into three groups: complete remission, partial remission and failure. Baseline EZ was found significantly intact in 71.4% of eyes in the complete remission group, and these rates were progressively inferior in the partial remission and failure groups, with 38.5% and 25%, respectively [94].

Table 3 Safety and efficacy profile of yellow subthreshold micropulse laser in chronic central serous chorioretinopathy

References	Study	F-UP	No. eyes	BCVA	SRF reduction	CMT	Side effects[a]
Altinel et al. [75]	R	24MO	39	Stabilized	Yes	Decreased	None
Ambiya et al. [76]	P	6MO	10	Improved	Yes	Decreased	None
Arsan et al. [77]	P	17.82MO (SD ± 0.42)	39	Improved	–	Decreased	None
Chhablani et al. [78]	R	10MO (Range 5–36)	101	Improved	–	Decreased	None
Elhamid et al. [79]	P	6MO	15	Improved	–	Decreased	None
Gawecki et al. [80]	R	2MO	51 patients	Improved	Yes	Decreased	None
Gawecki et al. [81]	R	6MO	32 patients	Improved	Yes	Decreased	None
Isik et al. [82]	R	11.4MO (SD ± 8.5)	58	Improved	Yes	Decreased	None
Kim et al. [83]	R	3MO	10	Improved	–	Decreased	None
Kim et al. [84]	R	3.7YRS (SD ± 0.8)	27	Improved	Yes	Decreased	None
Kiraly et al. [85]	P	6MO	31 patients	–	Yes	Decreased	None
Long et al. [86]	R	6MO	34	Improved	–	Decreased	None
Prasuhn et al. [87]	P	1MO	27	Improved	Yes	Decreased	None
Scholz et al. [88]	R	5MO (SD ± 3.7)	38	Improved	Yes	Decreased	None
Schworm et al. [89]	P	6MO	42	Improved	Yes	Decreased	None
Uzlu et al. [90]	R	6MO	20	Improved	–	Decreased	None
Yadav et al. [91]	R	4W (Range 4–19)	15	Improved	Yes	Decreased	None
Zeng et al. [92]	R	3MO	58	–	Yes	–	None
Zhou et al. [93]	P	3MO	54	Improved	Yes	Decreased	None
Zhou et al. [94]	P	6MO	110 Patients	Improved	Yes	Decreased	None

P/R prospective/retrospective, *F-UP* follow-up, *No.* number, *MO* months, *W* weeks, *YRS* years, *BCVA* best-corrected visual acuity, *SRF* sub-retinal fluid, *CMT* central macular thickness, *SD* standard deviation

[a]Development of choroidal neovascularization, allergic reaction, laser scar, scotoma

Hyperreflective dots were also found in all the retinal layers, and subretinal fibrinous exudates were seen more commonly in the failure group than in the complete remission group ($p > 0.05$) [94]. These findings suggest that hyperreflective dots may help predict the need for early YSML treatment.

There is only one report in the literature showing the use of 577-nm YSML to successfully treat a patient with chronic CSC with subretinal fibrin deposition with complete

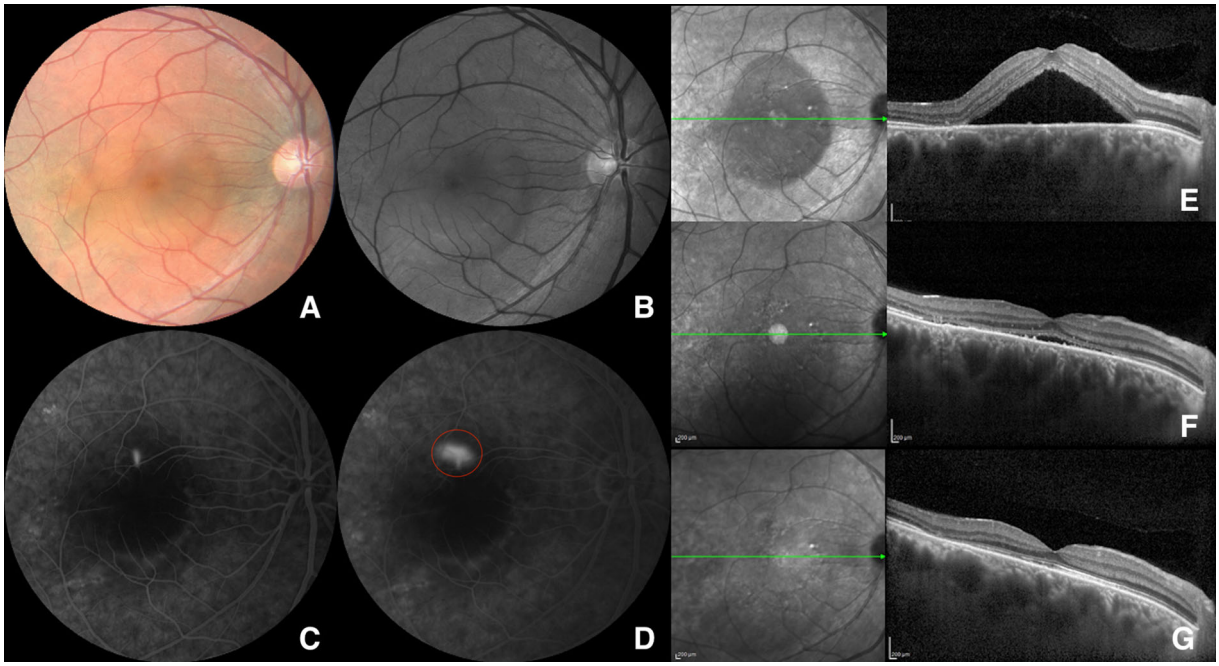

Fig. 1 Multimodal imaging of a 41-year-old patient with an 11-month history of chronic central serous chorioretinopathy (cCSC) treated with yellow subthreshold micropulse laser (YSML). **A–B** Baseline color fundus photography (**A**) and red-free light picture (**B**) show neurosensory retinal detachment in the macular area. **C–D** Early and late phase fluoresceine angiography displays the characteristic ink-blot pattern with a single point leakage that gradually increases in size over time. The area of leakage (red circle, **D**) is the target of YSML. **E–G** Tracked spectral domain optical coherence tomography scans with corresponding near infrared images acquired with enhanced depth imaging mode at baseline (**E**) and at 1 month (**F**) and 6 months (**G**) after YSML show resolution of the subretinal fluid over time

subretinal fluid and fibrin reabsorption and no visible retinal damage [95].

A representative case of chronic CSC successfully treated with YSML is shown in Fig. 1.

YSML Versus Photodynamic Therapy

The PLACE Trial confirmed photodynamic therapy (PDT) to be superior to high-density subthreshold laser (HDSL) treatment for chronic CSC in terms of patients' percentage with complete SRF resorption, BCVA increase and higher mean retinal sensitivity increase on microperimetry [96]. HDSL treatment protocol consisted of a DC of 5%, spot size of 125 μm, power starting from 1800 mW with lowering of 300 mW if any retinal discoloration was visible and pulse duration of 200 ms. PDT consisted of half-dose verteporfin (3 mg/m^2) infused over 10 min followed by laser activation for 83 s [97].

Considering that PDT is an invasive procedure that can rarely carry risks of collateral retinal damage, several authors suggest YSML as a competitive alternative for chronic CSC [75, 97]. Moreover, in the last 2 years there has been a verteporfin shortage worldwide that still represents a problem in many countries [98].

PDT and YSML have different mechanisms of action. While YSML targets the RPE, the treatment effect of PDT is believed to be the result of remodeling of the choroidal vascular endothelium through the formation of free radicals after photoactivation, resulting in occlusion, thrombosis and choroidal hypoperfusion in the treated areas [99].

Roca et al. treated leakage sites identified by FA and/or ICGA in a cohort of 92 eyes followed up for 12 months with either YSML or PDT. The first consisted of a DC of 5%, spot sizes from 100 to 200 μm, power from 320 to 660 mW and

pulse duration of 200 ms; the latter consisted in half-dose verteporfin (3 mg/m^2) infused over 10 min, followed by laser activation for 83 s. The authors described a significant CMT decrease from baseline in both YSML and PDT groups [100]. BCVA paralleled this improvement only in patients treated with YSML with a gain of $\geq$ 3 lines. Contrarily, in the PDT group after the 12-month follow-up, only 19% of eyes had such a visual acuity increase, with the vast majority (73%) recuperating no more that two lines from baseline BCVA. Notably, no adverse events attributable to the YSML were observed, whereas one eye within the half-dose PDT group developed choroidal neovascularization 4 weeks after the treatment and was treated with three intravitreal bevacizumab injections [100].

Ntomoka et al. retrospectively assessed 45 eyes of 39 patients who underwent either one of the two treatments with a minimum follow-up of 6 months [101]. PDT was performed over areas of choroidal hyper-permeability on ICGA by injecting a normal dose of verteporfin infused over 8 min followed by laser activation for 83 s. YSML was carried out in confluent spots directed to areas of focal leakage in the earliest phase of FA with a DC of 5%, spot size of 100 μm, pulse duration of 200 ms and 30% threshold power. The group treated with YSML demonstrated a significantly greater increase in BCVA compared to PDT [101]. The trend was confirmed anatomically, with a CMT decrease significantly higher in the YSML group as well. In addition, 13 (59%) eyes treated with sub-threshold laser showed complete SRF reabsorption compared to only 5 (21%) in the PDT cohort [101].

In a study with a long-term follow-up, Scholz et al. made a comparison by retrospectively analyzing 100 patients with a mean follow-up of 2.6 years (SD ± 3.3), of which 42 received YSML while the rest were treated with PDT [102]. Hyperfluorescent areas on mid-phase ICGA and the corresponding "hot spots" on mid-phase FA were treated. YSML treatment protocol consisted of a DC of 5%, spot size of 160 μm, pulse duration of 200 ms, 50% threshold power and PDT consisting of half-dose verteporfin (3 mg/m^2) infused over 10 min followed by laser activation for 83 s. Results observed showed similar anatomic outcomes with comparable CMT decrease ($p < 0.05$) and SRF resorption ($p > 0.05$) within the two treatment arms; BCVA, instead, improved more in the YSML group ($p > 0.05$). They noted a significant difference between the two groups in treatment response regarding the duration, more or less than 1 year, of the disease. Indeed, a significant higher number of patients with a disease duration < 1 year showed treatment response to YSML (92% vs. 58%). Another OCT variable demonstrated to have an impact on both treatment responses was central retinal thickness (CRT): non-responders showed a statistically significant lower CRT at baseline compared to responders (337 ± 81 μm vs. 442 ± 131 μm). Regarding safety, only the PDT group displayed side effects: one patient developed CNV, and one patient suffered from a moderate allergic reaction to verteporfin with tachycardia, dyspnea, flushing and hypotension [102].

Altinel et al. retrospectively compared 52 eyes of 46 patients over 8.42 (± 3.34 SD) months [92]. They found that the YSML group was characterized by longer SRF resolution duration and a slower trend of BCVA improvement compared to the fellow group. EZ band integrity was explored as well, with higher SRF resolution rates observed in both treatment arms when EZ was intact [92].

Ozmert et al. retrospectively evaluated 33 eyes of 30 patients during a 12-month follow-up [103]. Their results reached similar findings: mean BCVA ($p > 0.05$), CMT and SRF ($p < 0.05$) outcomes improved significantly with YSML treatment, consisting of a DC of 5%, spot size of 160 μm, pulse duration of 200 ms and 50% threshold power [103].

Ho et al. investigated alterations in choriocapillaris blood flow with OCTA and choroidal volume with en-face OCT [104]. Eighteen patients were randomized into YSML and PDT groups. YSML was set with a DC of 5%, spot size of 200 μm, pulse duration of 200 ms and power of 340–400 mW, whereas PDT was performed with half-dose verteporfin (3 mg/m^2) infused over 10 min followed by laser activation for 83 s. Results were extremely positive: flow deficit areas with suspected choriocapillaris

hypoperfusion were found in all CSC cases at baseline, and a progressive reduction of such areas was found in both YSML and PDT groups ($p < 0.05$), with the latter showing better results. Mean choroidal volume decreased as well at all time points (1, 3 and 6 months), but only in the PDT arm [104].

Van Rijssen et al. prospectively analyzed 29 eyes of 29 patients from the PLACE trial cohort for 8 weeks to assess whether choroidal vascularity index (CVI) changes could be responsible for therapeutic efficacy of both PDT and YSML [105]. No significant correlations were demonstrated between CVI and the two treatment options, leading the authors to conclude that any CVI change may not be primarily responsible for the treatment effect [105].

YSML Versus Conventional Laser

The efficacy of YSML was also compared to conventional laser treatment.

Sun et al. carried out a prospective, double-masked, 12-week trial, randomizing 88 patients with a diagnosis of chronic CSC to one of the two lasers [106]. At the end of follow-up, YSML demonstrated non-inferiority to CW laser regarding BCVA improvement. In contrast, anatomical outcomes appeared to be more prominent in the cohort treated with threshold laser, which displayed a proportion of patients with complete SRF reabsorption of 81.82% compared to 63.63% of YSML [106].

Maruko et al. retrospectively investigated 28 patients over 3.4 months in the CW laser group and 2.2 months in the YSML group [107]. BCVA showed no improvement compared to baseline, whereas SRF resolution outcomes were equivalent between the two lasers (66% and 64% in CW laser and YSML, respectively). Importantly, despite comparable therapeutic effects, CW laser treatment resulted in RPE damage at the site of laser delivery in all eyes treated, while only one eye that underwent YSML developed some sort of RPE modification on FAF [107].

YSML Versus Eplerenone

Oral mineralocorticoid receptor inhibitors (MRIs) such as eplerenone and spironolactone were found to be associated with SRF resolution, choroidal thickening decrease and BCVA improvement in the short term [108].

However, Lotery et al., running a randomized, double-blind, placebo-controlled trial over a 12-month follow-up on 114 patients, assigned each patient to receive either eplerenone (57) or placebo (57) and found that MRI was not superior to placebo in BCVA improvement [109].

A few other studies in the literature compared eplerenone to YSML effectiveness.

Toto et al. retrospectively enrolled 36 eyes of 30 patients into subthreshold and eplerenone groups and followed them up for 3 months [110]. Mean BCVA, CMT and SRF improved significantly by the end of the follow-up ($p < 0.001$) in both cohorts. In particular, 55.6% and 66.7% of patients showed a complete reabsorption of SRF over the period of interest in the YSML and eplerenone groups, respectively [110].

Vignesh et al. retrospectively evaluated 48 eyes over a median follow-up of 8 months in YSL and 4.5 months in the eplerenone treatment arm [111]. Complete SRF resorption was observed in 12/28 (42.8%) eyes in YSML, a much higher proportion compared to eplerenone (4/20, 20%). BVCA paralleled the anatomical outcomes, showing a greater improvement in YSML versus eplerenone group (0.14 vs. 0.05 logMAR) [111].

No paper compared YSML's efficacy to spironolactone or evaluated its effects on CSC.

YSML in Miscellaneous Disorders

YSML in Age-Related Macular Degeneration

In the last decades, anti- VEGF injections dramatically decreased the incidence of vision loss due to CNV in neovascular age-related macular degeneration (AMD) [112]. Contrarily, no therapy is available to prevent dry AMD from progressing into its latest stage, geographic atrophy (GA) [113]. Reticular pseudodrusen (RPDs) are associated with an increased progression to both forms of late AMD [114, 115]. In this light, a therapy that targets RPD progression could be pivotal for AMD management. Considering that the RPE dysfunction was suggested as the main

causative element in RPD pathogenesis, a subthreshold laser that preserves and stimulates RPE function could play a crucial role [116, 117].

Querques et al. prospectively enrolled 20 eyes of 20 patients with a RPD finding secondary to a diagnosis of dry AMD and treated them with YSLT, following them up over a 3-month period [118]. No changes in BCVA were observed from baseline. YSML-treated areas did not display any sort of worsening in macular sensitivity, whereas RPD distribution and concentration appeared to be affected ($p < 0.05$). In particular, a significant increase of stage-1 RPDs [characterized by a diffuse deposition of hyperreflective material between the RPE and the inner/outer segments (IS/OS) boundary] was observed ($p < 0.05$) and associated with a decrease of stage 3 RPDs (featured by a thicker and conical appearance of deposited material passing through the IS/OS boundary). A statistically significant association was also found between RPD regression and ONL thickness increase ($p < 0.05$) [118].

Huang et al. focused their research on evaluating long-term outcomes of YSML on drusenoid PEDs [119]. A total of 21 eyes of 16 patients were consecutively included and followed up for a mean of 25.3 (SD ± 12.6) months and categorized in two groups based on presence (6 eyes) or absence (15 eyes) of drusenoid PED collapse after YSML treatment. Height, area and volume of dPEDs were positively correlated with the collapse, suggesting that larger lesions are more likely to collapse after YSML treatment. Moreover, the collapse group showed faster growth and regression rates of dPEDs compared to the natural course of these features, therefore reducing the RPE separation from the underlying Bruch's membrane/choriocapillaris complex and consequently mitigating the RPE damage. More importantly, at the end of the follow-up, BCVA was stable compared to baseline and similar within the two groups, suggesting that YSML could alleviate not only the natural course of the disease but also its related vision impairment [119].

Further prospective studies with larger sample size are needed to further confirm these data.

YSML in Pseudophakic Cystoid Macular Edema

Pseudophakic cystoid macular edema (PCME), also known as Irvine-Gass syndrome, is a major cause of unexpected postoperative vision loss [120, 121]. Surgical insults along with postoperative inflammation are widely shown to be the important risk factors for this condition, which commonly tends to resolve spontaneously [122]. However, for chronic presentations treatment is often mandatory, requiring steroidal or non-steroidal anti-inflammatory (NSAI) drugs or even anti-VEGFs or steroid intravitreal injections [123, 124].

Verdina et al. retrospectively included ten eyes of ten patients with refractory PCME to standard treatments, namely NSAI eyedrops, topical steroids, oral indomethacin, sub-Tenon triamcinolone injections and dexamethasone intravitreal implant [125, 126]. All underwent YSML and were followed up for 6 months. Five cases occurred after uncomplicated cataract surgery, two cases after complicated cataract surgery with posterior capsule rupture and three cases subsequent to retinal detachment. At the end of the follow-up, BCVA had improved significantly from baseline. Anatomic restoration was also demonstrated with complete resorption of cystoid macular edema and a statistically significant CMT reduction ($p = < 0.005$) [125, 126].

A representative case of postsurgical CME successfully managed with a single YSML session in a patient operated on for a rhegmatogenous retinal detachment is shown in Fig. 2.

YSML in Radiation Retinopathy

Radiation retinopathy is a progressive and chronic vasculopathy secondary to exposure to radiation. Current treatment includes thermal laser photocoagulation, intravitreal anti-VEGF and steroid injections, and hyperbaric oxygen [127]. Despite treatments patients often may have progressive visual impairment secondary to ischemic retinal damage. Wong et al. reported a case of a 60-year-old man who developed retinopathy in his left eye 23 years after radiotherapy for nasopharyngeal carcinoma treated with YSML [128]. Baseline BCVA was 20/40, and

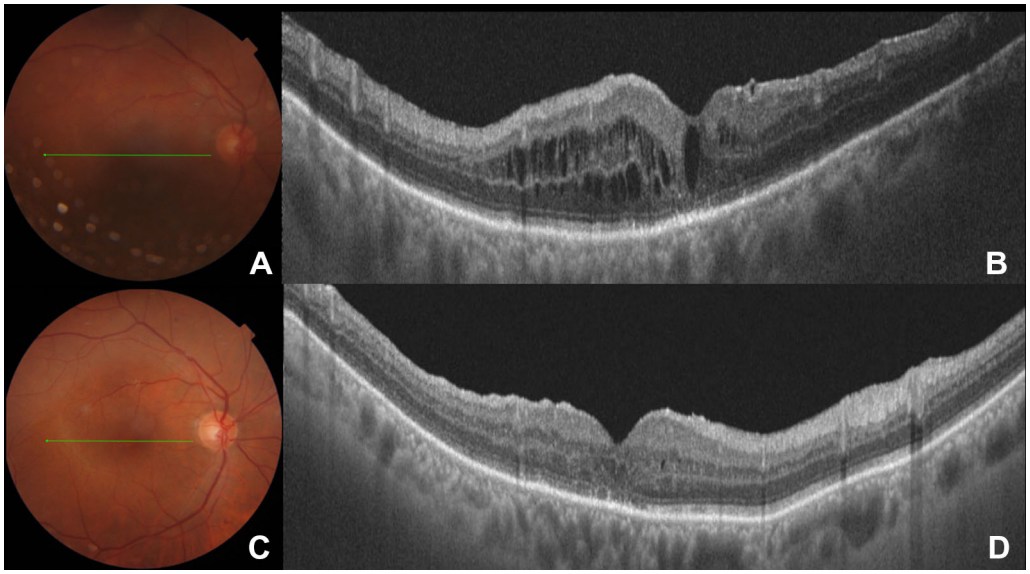

Fig. 2 Persistent post-surgical macular edema following a combined cataract and pars plana vitrectomy (PPV) surgery for rhegmatogenous retinal detachment (RD) successfully treated with yellow subthreshold micropulse laser (YSML). **A** Color fundus picture 3 months after combined cataract and PPV surgery for rhegmatogenous RD shows a reattached retina. **B** Spectral domain optical coherence tomography (SD-OCT) image shows persistent intraretinal cysts not responsive to any topical and/or oral medications including anti-inflammatory and steroids eye drops. **C** Color fundus picture 6 months after YSML session. **D** Corresponding tracked SD-OCT reveals resolution of the intraretinal fluid

FA showed macular leak compatible with CME, which was confirmed on OCT. Ten months after one single treatment, BCVA improved to 20/20, and OCT examination demonstrated complete reduction of the cystoid macular edema [128].

YSML in Branch Retinal Vein Occlusion

Several treatment modalities for branch retinal vein occlusion (BRVO) have been proposed over the years; among them, anti-VEGF is recognized as the treatment of choice for BRVO-induced CME [129].

Terashima et al. retrospectively enrolled 46 eyes of 46 patients with BRVO and allocated them to two groups: the first received intravitreal ranibizumab (IVR) + YSML, whereas the second underwent IVR monotherapy [130]. BCVA and CMT improved in both groups, and results did not differ significantly between the two. However, the number of intravitreal injections decreased significantly in the IVR + YSML group compared to the IVR-only cohort (2.3 ± 0.9 vs. 1.9 ± 0.9) at the end of the 6-month follow-up [130].

YSML in Idiopathic Macular Telangiectasia Type 1

Type 1 macular telangiectasia (MacTel) is an aneurysmal telangiectasia, most commonly unilateral and typically found in the temporal half of the macula. It commonly occurs in middle-aged males, and it is thought to be a variant of Coats' disease [131]. Therapeutic options consist of laser photocoagulation, intravitreal injections of steroids or anti-VEGF agents [132]. Kang et al. reported a case of a 54-year-old man with type 1 MacTel in the left eye [133]. BCVA was 20/800 at baseline, and spectral domain (SD)-OCT showed severe CME, for which he underwent two ineffective intravitreal injections of bevacizumab before receiving three YSML sessions. One month after the last treatment, SD-OCT demonstrated complete CME resorption and absence of any macular damage. However, after 1 year the treated area

showed focal atrophic changes, which the authors claimed to potentially be associated with the chronic CME but they could not exclude that it was triggered by repeated YSLT. Nevertheless, at 3-year follow-up BCVA still improved to 20/40 in the treated eye [133].

CONCLUSIONS

The YSML has progressively been recognized as an effective treatment option for several chorioretinal diseases. A growing body of evidence highlights its efficacy and safety in both short- and long-term follow-ups. Based on the literature, YSML can be considered a safe, cost-effective and non-invasive therapeutic procedure. It is less destructive with fewer potential adverse effects like CNV, RPE atrophy or choroidal ischemia compared to CW laser. Nevertheless, a more accurate standardization of laser setting protocols is still desired, and a better understanding of the underlying molecular mechanisms would be pivotal for the future advancement and optimization of this relatively new treatment approach. Further randomized prospective studies with longer follow-up and larger sample size studies are warranted to confirm its role in chorioretinal diseases management.

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