• Clinical Research •

Short-term effectiveness of intelligent navigated laser photocoagulation versus subthreshold micropulse laser in patients with chronic central serous chorioretinopathy

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Abstract

● **AIM:** To compare the short-term effectiveness of intelligent navigated laser photocoagulation and 577-nm subthreshold micropulse laser (SML) treatment in patients with chronic central serous chorioretinopathy (cCSC).

● **METHODS:** This observational retrospective cohort study included 60 consecutive patients who underwent intelligent navigated laser photocoagulation (*n*=30) or 577-nm SML treatment (*n*=30) for cCSC between Jan. 2021 and Oct. 2022. During 3mo follow-up, all patients underwent assessments of best correct visual acuity (BCVA) and optical coherence tomography (OCT).

● **RESULTS:** The operation of laser treatment was successful in all cases. At 1mo, BCVA improved significantly more in the intelligent navigated laser photocoagulation group compared to the SML group (*P*<0.05). The change was not significantly different at 3mo (*P*>0.05). Central macular thickness (CMT) in the intelligent navigated laser photocoagulation group was lower than in the SML group at 1mo (*P*<0.05). The subfoveal choroidal thickness (SFCT) in two groups were all significantly improved at 3mo (all *P*<0.05). The change between two groups was not significantly different at 1mo or at 3mo (*P*>0.05).

● **CONCLUSION:** Intelligent navigated laser photocoagulation is superior to SML for treating cCSC, leading to better improvements in vision and CMT for short term.

● **KEYWORDS:** intelligent navigated laser photocoagulation; subthreshold micropulse laser; central serous chorioretinopathy; optical coherence tomography
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INTRODUCTION

Central serous chorioretinopathy (CSCR) is a chorioretinal disease characterized by serous neurosensory detachment, primarily affecting men in their 40s and 50s, although cases have also been observed in older adults. Males had a higher incidence with 72%-88% than females[1]. Because of atrophy of the photoreceptors and retinal pigment epithelium (RPE), visual prognosis is relatively worse among patients with chronic CSCR (cCSCR) than those with acute disease[2-3]. CSCR is often characterized by multifocal areas of leakage on fluorescein angiography (FA) and diffuse RPE changes on optical coherence tomography (OCT). Fluid collection is thought to be influenced by RPE dysfunction and enhanced vascular choroidal hyperpermeability[4-5]. Impairments in RPE function can permit fluid diffusion into the subretinal space, which normally helps to maintain the outer blood-retinal barrier[1], and the presence of subretinal fluid (SRF) is a common hallmark of CSCR. However, chronic SRF accumulation is linked to long-term vision loss and irreversible photoreceptor impairment[6-7]. To avoid such impairments in photoreceptor function, complete resolution of SRF should be the primary goal of CSCR treatment.

Treatment for cCSCR aims to resolve the serous neuroretinal detachment and the underlying accumulation of SRF while preserving the outer neurosensory retinal layers, as even a modest amount of SRF can cause irreparable damage to photoreceptors. For these chronic cases, commonly performed treatments include conventional focal laser treatment, photodynamic therapy (PDT), and administration of intravitreal anti-vascular endothelial growth factor (VEGF)[8]. Recently, intelligent navigated laser photocoagulation has been used to expedite the resolution of SRF accumulation in patients with CSCR[9], with evidence suggesting that the treatment is both safe and effective in cases of cCSCR.

Subthreshold micropulse laser (SML) treatment may represent an alternative treatment option for cCSCR. The use of SML for CSCR was first described in 2008[10-11], with subsequent studies reporting that SML was as effective as traditional laser treatment, although it was less dangerous than PDT or laser photocoagulation[12-13]. Nonetheless, the mechanisms by which SML treatment exerts its effects remain poorly understood.

Guo *et al*[14] showed that SML treatment can promote resolution of SRF accumulation and visual improvement. In our previous study, complete resolution of SRF after intelligent navigated laser photocoagulation was achieved in 13 (68%) of 19 eyes at 3mo[15]. To date, no controlled study has compared intelligent navigated laser photocoagulation with SML for cCSCR. In this retrospective study, we aimed to compare the short-term effects of intelligent navigated laser photocoagulation and 577-nm SML treatment in patients with cCSCR.

SUBJECTS AND METHODS

Ethical Approval This study adhered to the tenets of the Declaration of Helsinki. This study was approved by the Nanjing Medical University Affiliated Eye Hospital Review Board. The approval number is 2021006. As a retrospective study, the informed consent waiver was approved by the Nanjing Medical University Affiliated Eye Hospital Institutional Review Board.

Patients In this retrospective study, we examined data for 60 eyes of 60 patients with cCSCR treated at Nanjing Medical University Affiliated Eye Hospital from January 2021 to Oct 2022. Data was gathered from hospital records. The diagnosis of CSCR was based on the results of fundus examination, OCT and FA. The inclusion criteria were as follows: symptomatic CSCR for ≥6mo and recurrent CSCR with a history of cCSCR. In both groups of patients included in the study, leak points were outside the avascular area of the fovea. The following conditions were met in order to be excluded: high myopia, systemic treatment with exogenous corticosteroids, pregnancy, inability to undergo relative fundus examination, and prior treatments such as polypoidal choroidal vasculopathy (PCV), choroidal neovascularization (CNV), intravitreal injection treatment with VEGF and PDT.

Study Design Sixty patients underwent ophthalmic examinations, including slit-lamp microscopy examination, measurement of best-corrected visual acuity (BCVA), Goldmann tonometry, and spectral-domain OCT (Spectralis HRA+OCT, Heidelberg Spectralis; Heidelberg Engineering GmbH, Heidelberg, Germany) of the macula at baseline and at each follow-up visit. FA (Spectralis HRA+OCT; Heidelberg Engineering, Germany) was performed to determine the leakage site and exclude other maculopathies at baseline and at the 3-month after treatment. SD-OCT and fundus autofluorescein assessments (FAF; Spectralis HRA+OCT; Heidelberg Engineering, Germany) were also performed at baseline and data were collected 1 to 3mo after treatment. Central foveal thickness (CMT) was defined as the distance from the inner surface of the neurosensory retina to the inner portion of the RPE at the fovea. Subfoveal choroidal thickness (SFCT) was measured *via* subfoveal localization using enhanced depth imaging[11].

Intelligent Navigated Laser Photocoagulation An image of the posterior pole was taken before laser photocoagulation using the NAVILAS® laser system (532-nm double-pulsed YAG laser, OD-OS GmbH Germany). The treatment was planned based on early FA pictures that revealed a leaky area, and all laser treatments were performed by a single physician (Zhou F). An initial test burn away from the macular region was performed to identify the parameters for laser shots. After creating a barely visible laser effect on fundus image, the laser spot was applied. The laser parameters were set as follows: grayish white burn, energy, 64.6±7.9 mW (50-90 mW); spot size, 113.5±14.6 μm (100-150 μm); and pulse duration, 84.3±10.7ms (70-100ms). On the overlay image, one to ten laser spots of 100-150 μm per leakage point were marked, along with a barrier to protect the fovea and optic nerve. All patients underwent color fundus photograph after laser treatment. An additional feedback window in the laser software displayed the immediate laser effect at the end of the pulse. If focal leakage of the same lesion was apparent on FA at the 3-month, treatment was repeated (Figure 1).

Subthreshold Micropulse Laser All treatments were operated by a single doctor (Zhou F) using a 577-nm yellow laser system (Supra 577Y Laser System, France). An AreaCentralis lens was used to apply the laser (Volk Optical, Mentor, OH, USA). The micropulse laser power was derived for each eye from the test burn. A 160 μm spot diameter, a 523.5±89.4 mW power (400-650 mW), and a 200ms duration with a 5% duty cycle were used for subthreshold treatment in the micropulse mode. The titration was carried out on a normal retina that was not inside the vascular arcades. Using a monospot micropulse model, titration began at a power of 400 mW, which was subsequently increased until a detectable minimal graying reaction was observed (*i.e.*, threshold burn). The laser power of the single threshold burn was reduced by half, resulting in no observable retinal alterations. The power level for the laser typically ranged from 400-650 mW. Laser pulses were administered in a 3×3 pattern over the whole area exhibiting CSCR, including the leakage point on FA and the foveal center. We also applied micropulse yellow laser on the area of serous retinal detachment (Figure 2).

Data Collection Comprehensive eye examinations such as OCT and FA were collected 1 to 3mo after treatment. Patients underwent complete eye examination at baseline and at all

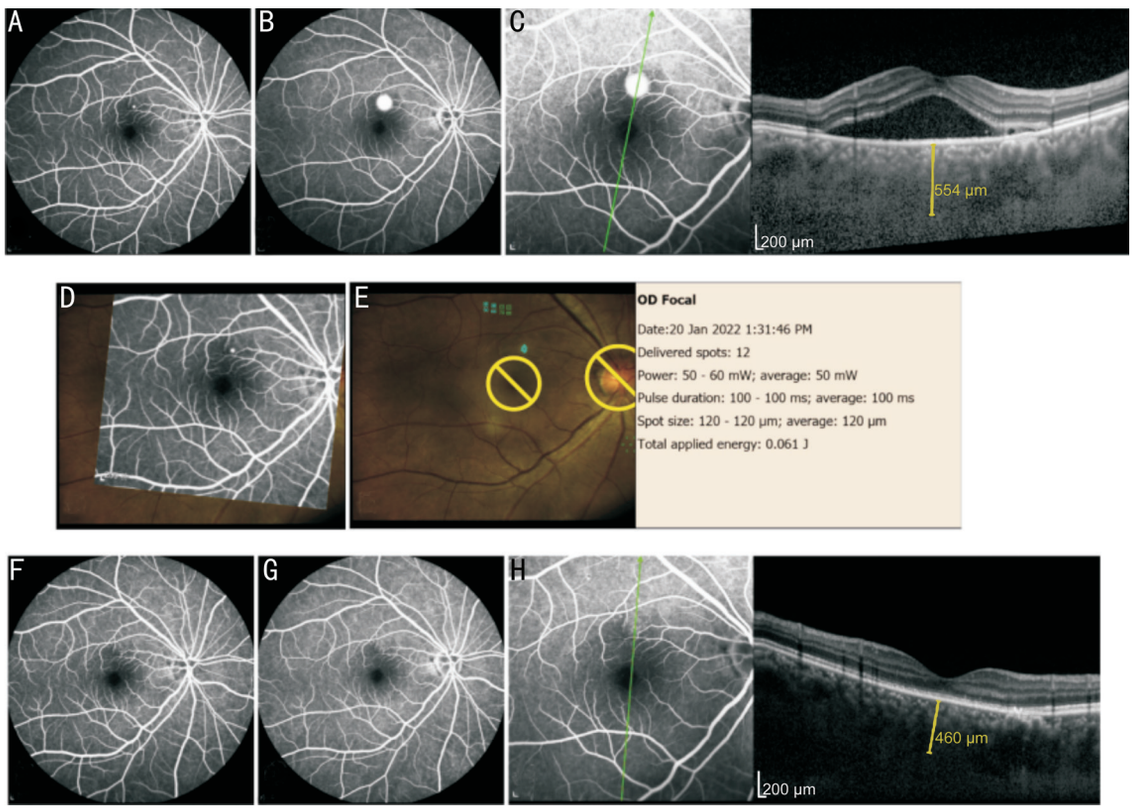

Figure 1 Findings from a 49-year-old man with cCSCR for 7mo A: FA showed an inkblot on early-phase. B: In the late phase, there was an increase in hyperfluorescence. C: OCT showed obvious subretinal fluid and the retina dipping above pigment epithelial detachment with slight fibrin. D: The color fundus photograph was automatically superimposed with the chosen FA image displaying focal leakage. E: NAVILAS® laser photocoagulation was programmed on the actual fundus image to six single laser spots on the leak point and performed with the following parameters: spot size: 120 μm; power: 50-60 mW; pulse duration: 100ms. F: At 3mo, focal leak point in the early stage on FA has disappeared. G: The focal leak point in the late stage on FA has also disappeared. H: OCT showed no SRF. cCSCR: Chronic central serous chorioretinopathy; FA: Fluorescein angiography; OCT: Optical coherence tomography; SRF: Subretinal fluid.

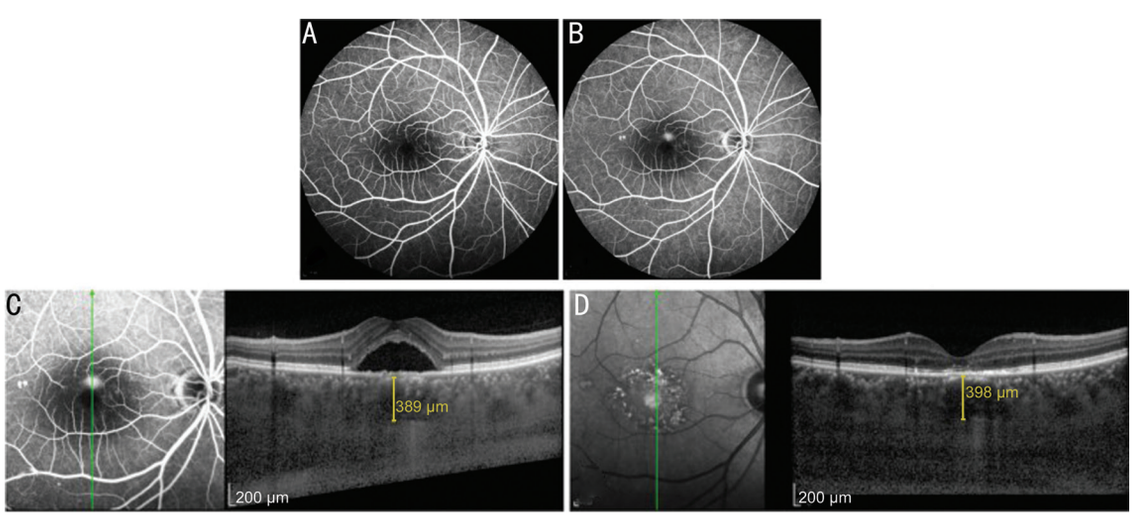

Figure 2 A 35-year-old man with cCSCR for 13mo who received SML Early-phase (A) and late-phase (B) FA images obtained at baseline showing pin-point leakage with a smokestack pattern of fluorescein leakage. Baseline OCT image showing fluid accumulation involving the fovea (C). OCT image obtained at 3mo showing complete absorption of the subretinal fluid (D). cCSCR: Chronic central serous chorioretinopathy; SML: Subthreshold micropulse laser; FA: Fluoresceien angiography; OCT: Optical coherence tomography.

visits after treatment. Data regarding the SRF resolution rate, BCVA, CMT and SFCT were collected and compared between the treatment groups.

Statistical Analysis Descriptive statistics were calculated for each variable. Data are expressed as the mean±standard deviation (SD). Comparisons of categorical variables between the 2 groups were performed using the Fisher exact test. The Mann-Whitney *U* test was used to analyze the changes in

BCVA at baseline and follow-up at 1 and 3mo. Differences in CMT and SFCT between the two groups were also examined using the Mann-Whitney *U* test. Statistical analyses were performed using SPSS version 22 (IBM, Armonk, NY, USA). Statistical significance was set at $P<0.05$.

RESULTS

Baseline Demographic and Clinical Data This retrospective comparative study included 60 eyes of 60 patients with cCSCR who were treated with either 577 nm SML or intelligent navigated laser photocoagulation. The intelligent navigated laser photocoagulation group included 30 eyes of 30 patients [23 men (76.7%) and 7 women (23.3%); mean age, 49±8.1y; age range, 31-63y]. The SML group included 30 eyes of 30 patients [25 men (83.3%) and 5 women (16.7%); mean age, 47±7.3y; age range, 33-53y].

Table 1 summarized the baseline demographic and clinical characteristics of the two groups, which exhibited no significant differences in mean BCVA (logMAR; 0.44±0.19 *vs* 0.45±0.22, $P=0.863$), CMT (520.78±124 *vs* 504.64±155 μm, $P=0.614$), SFCT (485.69±89.34 *vs* 476.86±78.64 μm, $P=0.833$).

Changes in Subretinal Fluid At the 1-month after treatment, the rate of complete SRF resolution was lower in the SML group (43.3%) than in the intelligent navigated laser group (53.3%). At 3mo, the SML group also exhibited a lower rate of complete SRF resolution than the intelligent navigated laser group (73.3% *vs* 76.7%; Figure 3).

Changes in Visual Acuity In the intelligent navigated laser group, the logMAR BCVA improved from 0.44±0.19 at baseline to 0.23±0.16 at 1mo ($P<0.05$) and to 0.19±0.12 at 3mo ($P<0.01$). In the 577-nm SML group, there was a logMAR BCVA improvement of 0.38±0.20 and 0.21±0.13 at 1mo and 3mo, respectively, after 577-nm SML. There was significant difference in the change in logMAR BCVA at the 1-month follow-up between the two treatment groups ($P<0.05$). When comparing the 2 groups, the change in logMAR BCVA from baseline was not significantly different at 3mo ($P>0.05$; Figure 4).

Changes of Central Macular Thickness In the intelligent navigated laser group, significant decreases in mean CMT were observed at both the 1- and 3-month. CMT had decreased from 520.78±124 at baseline to 247.15±64.34 μm at 1mo ($P<0.001$) and to 231.23±55.61 μm at 3mo ($P<0.001$). In the SML group, the mean CMT significantly decreased from 504.64±155 at baseline to 330.21±98.32 at 1mo ($P<0.01$). While CMT also decreased to 240.25±101.33 at 3mo ($P<0.001$), this difference was also significant. There was significant difference in the change in CMT at 1mo between the two treatment groups ($P<0.05$). However, this difference was not significant at 3mo ($P>0.05$; Figure 5).

Changes of Subfoveal Choroidal Thickness In the SML group, SFCT decreased from 485.69±89.34 at baseline to 53.08±79.47 μm at 1mo ($P>0.05$) and 415±74.92 μm at 3mo ($P<0.05$). This difference was significant between the two treatment groups at 3mo. In the intelligent navigated laser photocoagulation group, SFCT decreased from 476.7±78.64 at baseline to 455.7±59.76 μm at 1mo ($P>0.05$) and 430.1±71.28 μm at 3mo ($P<0.05$). However, there was no significant difference in the change in SFCT between the two treatment groups at 1mo ($P>0.05$) or 3mo ($P>0.05$; Figure 6).

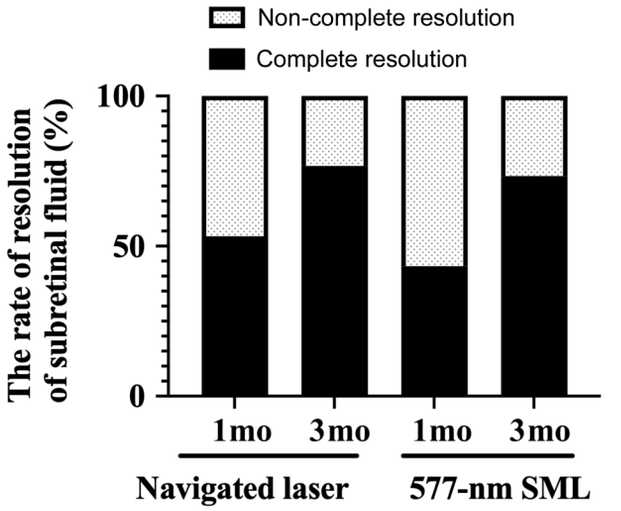

Figure 3 At 1mo, the intelligent navigated laser group had a higher rate of complete SRF resolution (53.3%) than the SML group (43.3%). The intelligent navigated laser group also had a higher rate of complete SRF resolution than the SML group at the 3-month (76.7% *vs* 73.3%) SRF: Subretinal fluid; SML: Subthreshold micropulse laser.

Table 1 Patient characteristics

Characteristics	Navigated laser (*n*=30)	577-nm SML (*n*=30)	*P*
Age (y)	49±8.1	47±7.3	0.783[b]
Gender			0.415[a]
Female	7	5	
Male	23	25	
Number of recurrences			0.674[a]
First	22	24	
Second	8	6	
Duration of symptoms (mo)	14.2±7.3	14.7±5.6	0.463[b]
BCVA (logMAR)	0.44±0.19	0.45±0.22	0.863[b]
CMT (μm)	520.78±124	504.64±155	0.614[b]
SFCT (μm)	485.69±89.34	476.86±78.64	0.833[b]

No significant differences between the two groups. SML: Subthreshold micropulse laser; BCVA: Best-corrected visual acuity; logMAR: Logarithm of the minimum angle of resolution; CMT: Central foveal thickness; SFCT: Subfoveal choroidal thickness. [a]Fisher exact test. [b]Mann-Whitney *U* test.

DISCUSSION

Treatment strategies such as laser photocoagulation and micropulse laser treatment have been reported as being effective[14-15]. As far as we know, this study is the first retrospective controlled trial on the comparison of

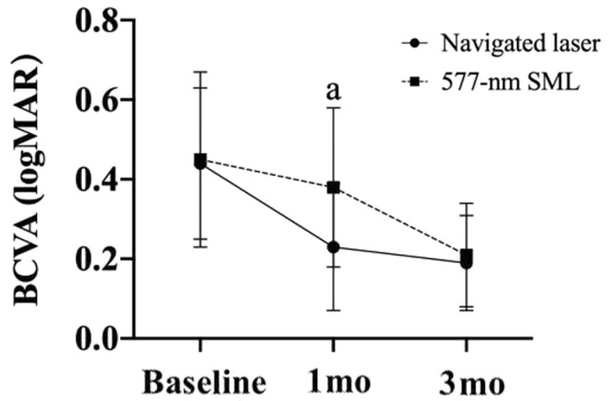

Figure 4 Changes in logMAR BCVA from baseline through the 3-month follow-up of patients with cCSCR treated with either intelligent navigated laser photocoagulation treatment or SML treatment [a]*P*<0.05. BCVA: Best-corrected visual acuity; logMAR: Logarithm of the minimum angle of resolution; cCSCR: Chronic central serous chorioretinopathy; SRF: Subretinal fluid; SML: Subthreshold micropulse laser.

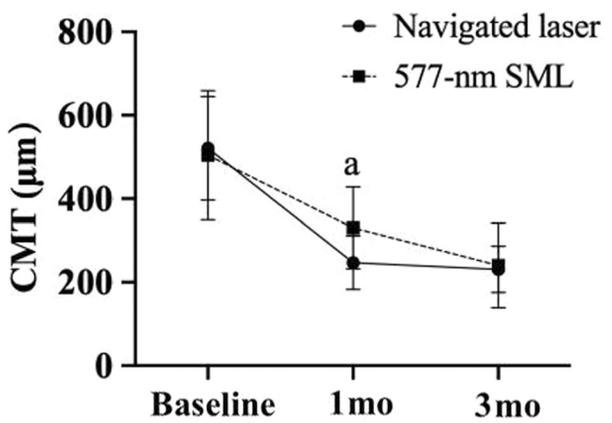

Figure 5 Changes in CMT from baseline through the 3-month follow-up of patients with cCSCR treated with either intelligent navigated laser photocoagulation treatment or SML treatment [a]Significant differences (*P*<0.05) between the 2 groups at 1mo *P*<0.05. CMT: Central foveal thickness; cCSCR: Chronic central serous chorioretinopathy; SML: Subthreshold micropulse laser.

intelligent navigated laser photocoagulation with 577-nm SML for cCSCR. In this study, we compared the short-term effectiveness of intelligent navigated laser photocoagulation and 577-nm SML treatment in patients with cCSCR for 3mo. Our findings indicated that both therapies were successful in restoring and improving visual function. However, intelligent navigated laser photocoagulation is superior to SML for treating cCSCR, leading to better improvements in vision and CMT within the first three months post-treatment.

Several studies have shown that SML treatment was both safe and effective for CSCR, reporting complete resolution of SRF in 36%-100% of patients with cCSCR after treatment[11,16-17]. In 75%-94% of patients with cCSCR, intelligent navigated laser photocoagulation of the focal leaking site on FA results

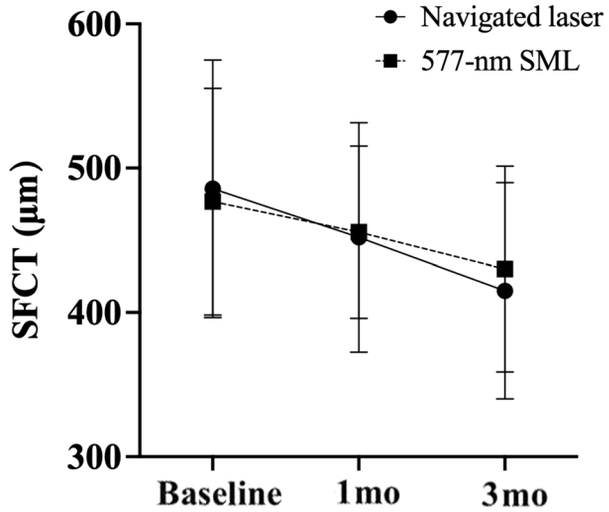

Figure 6 Plots showing SFCT change after treatment in two groups There was no significant difference at each visit between two groups (*P*>0.05). SFCT: Subfoveal choroidal thickness; SML: Subthreshold micropulse laser.

in complete absorption of the fluid. In our previous study, we reported subretinal fluid was completely resolved in 13 (68%) of 19 eyes at 3mo. In this study, 73.3% of SML-treated patients demonstrated no SRF at 3mo, while intelligent navigated laser photocoagulation showed 76.7% SRF absorption. The SML treatment enhances the transretinal pump to eliminate SRF by restoring RPE function to normal. Only a little amount of thermal energy is delivered to the choroid and neurosensory retina at the locations of leakage identified by FA, preventing injury to those tissues. Direct effects at the leakage sites are obtained on the RPE[18]. The effectiveness of intelligent navigated laser photocoagulation (53.3%) in achieving complete resolution of SRF was greater than that of SML treatment (43.3%) at 1mo. The significantly better anatomical and functional outcomes after intelligent navigated laser treatment may be attributed to the fact that the intelligent navigated laser targets the focal leakage point and closes the focal defect, which is caused by dysfunction of the outer blood-retina barrier in cCSCR. Intelligent navigated laser photocoagulation integrates fundus image and FA to identify the area to be treated. Photocoagulation with a 532-nm laser is then performed automatically by computer system in the planned area. Treatment also cuts the time to complete resolution in half, to an average of one month.

Our finding demonstrated that intelligent navigated laser photocoagulation for cCSCR can result in substantial anatomical and visual improvement 3mo after treatment[15]. No controlled study has shown that intelligent navigated laser photocoagulation can lead to better improvements in vision than SML. Recent studies have suggested that intelligent navigated laser photocoagulation is safe and effective for the treatment of CSCR. In addition to promoting complete

resolution of SRF over a short period of time, intelligent navigated laser photocoagulation can significantly improve BCVA. In this study, the effect of 577-nm SML and intelligent navigated laser photocoagulation treatment on chronic CSCR was compared. It was found that BCVA was increased and CMT was decreased in both groups at 1mo after treatment, but the improvement degree of intelligent navigated laser photocoagulation group was significantly better than that of SML group. At 3mo, BCVA was further increased and CMT was continuously decreased in the two groups. There was no significant difference between the two groups, indicating that the two treatments had similar effects. The difference between groups 1mo after treatment may be due to the delay in the effect of 577-nm micropulse laser compared with intelligent navigated laser photocoagulation. This finding is consistent with our previous study, which demonstrated that intelligent navigated laser photocoagulation is effective for cCSCR and can result in substantial anatomical and visual improvement[15].

Although the pathogenesis of CSCR remains unknown, significant angiographic data suggest that choroidal vascular hyperpermeability is the primary underlying mechanism. Expansion of choroid thickness indicates hyper-permeability alterations of the choroid and can be used as the indicator of disease activity[19-20]. Micropulse laser treatment can selectively target the RPE while preserving photoreceptors[21]. In the current study, we observed no significant differences in the SFCT change between the two groups. It is likely that SML just impacts RPE dysfunction without influencing hyperdynamic choroidal circulation and choroidal hyperpermeability, which have been thought to be the primary causes of CSCR. Maruko *et al*[22] also reported that using photocoagulation to treat CSCR did not change SFCT at 4wk. Our study also demonstrated that the median value of SFCT was not changed after intelligent navigated laser photocoagulation for 4wk. Whereas, the mean SFCT of two groups showed a statistically significant improvement at 3mo. We have found that the difference of SFCT at three months might be related to SRF resolution. This implies that choroidal thickness could be a significant factor in the pathogenesis of CSCR. The biological mechanisms underlying the decline in SFCT after navigational laser treatment are not fully understood and are being investigated in animal models in our new research.

No treatment-related side events were reported by any of the participants in either treatment group, consistent with previous findings. Importantly, choroidal neovascularization has also been described as a part of the natural course of cCSCR. SRF exposure can result in irreversible photoreceptor impairment, which is linked to impaired vision in cases of cCSCR. Significant changes in BCVA, CMT, and SFCT at 3mo were observed following both treatments. Despite the use of thermal lasers to target the RPE in patients with retinal diseases for several years, application of thermal energy is associated with some drawbacks, such as damage to adjacent tissues including the inner retina and photoreceptors. As a result, heat-related laser treatment is not recommended for subfoveal or juxtafoveal leaks, although it can be considered in patients with leaks further away from the macular fovea.

The limitation of this study is the short follow-up time and small number of patients. Additionally, the impact of intelligent navigated laser photocoagulation on long-term recurrence rates or final visual acuity remains unknown. Furthermore, although intelligent navigated laser photocoagulation demonstrated superior short-term effectiveness compared to SML treatment, it is important to acknowledge that the cost of intelligent navigated laser photocoagulation is high, rendering it unaffordable for some patients. Therefore, while intelligent navigated laser photocoagulation may offer better outcomes in terms of symptom duration reduction, the accessibility and affordability of this treatment modality remain significant challenges.

The results of this retrospective study suggest that intelligent navigated laser photocoagulation provides superior outcomes when compared with 577-nm SML treatment in patients with cCSCR at 1mo. Meanwhile, SML is comfortable for the patients and economically feasible compared with intelligent navigated laser photocoagulation. This finding provides key insight into the development of best practice guidelines for treating cCSCR. Intelligent navigated laser photocoagulation represents a potential treatment option for these patients given that it expedites the absorption of SRF and improves visual function without visible retinal damage. Nonetheless, the 577-nm SML treatment was considered safer because it did not appear to harm the RPE and could be used multiple times, even in situations of macular degeneration near the fovea. In conclusion, our research shows that patients with cCSCR can benefit from both 577-nm SML and guided laser photocoagulation therapies, the latter of which leads to better CMT reduction and faster SRF resolution.

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Authors' contributions: All authors conceived of and designed the experimental protocol. Zhou F collected the data. Zhou F, Wang CH, Zhou CC, and Liu S were involved in the analysis. Zhou F wrote the first draft of the manuscript. Yao J and Jiang Q reviewed and revised the manuscript and produced the final version. All authors read and approved the final manuscript.

Conflicts of Interest: Zhou F, None; **Wang CH,** None; **Zhou CC,** None; **Liu S,** None; **Yao J,** None; **Jiang Q,** None.

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