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Title

Predictive factors of outcome of selective retina therapy for diabetic macular edema.

Running Title

Predictive factors of SRT for DME

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Abstract

*Purpose***:** To investigate the predictive factors of clinical outcome of Selective Retina Therapy (SRT) for diabetic macular edema (DME).

Methods: This retrospective study included 22 eyes of 22 patients (15 males and 7 females), who were treated with SRT for DME at the department of Ophthalmology of Osaka City University Hospital, and observed at least 6 months after the treatment. The mean age was 64 years (range 40-81). 13 of the 22 eyes (59%) had a treatment history other than SRT before. SRT laser (527 nm, 1.7 μs, 100 Hz) was used for treatment. Changes of the best corrected visual acuity (BCVA) (logMAR) and central macular thickness (CMT) in optical coherence tomography (OCT) were examined at baseline, 3-month follow-up, and 6-month follow-up. Factors associated with the rate of change in CMT at 3 and 6 months after SRT were examined.

*Results***:** The mean BCVA (logMAR) were 0.26±0.31, 0.22±0.27 and 0.23±0.29 at baseline, 3 months and 6 months, respectively (P=0.15 at 3 months, 0.40 at 6 months; compared to baseline). The mean CMT were 502±163, 493±204 and 416±185 μm at baseline, 3 months and 6 months, respectively (P=0.69 at 3 months, 0.01 at 6 months; compared to baseline). The multivariate analysis found a significant negative association with previous macular photocoagulation (p = 0.03) at 3 months, and positive association with history of insulin use (p = 0.02) and previous panretinal photocoagulation (p = 0.03) at 6 months after SRT.

*Conclusion***:** The CMT was significantly decreased at 6 months after SRT in DME. A history of insulin use and panretinal photocoagulation may positively, a history of macular photocoagulation may negatively affect the outcome of SRT, which must be considered when determining the therapeutic indications for SRT.

Keywords: macular edema, diabetic retinopathy, laser therapy, Retinal pigment epithelium

Introduction

Diabetic macular edema (DME) is an ocular complication of diabetes, and is one of the critical conditions that may cause serious visual impairment [1,2]. Factors that contribute to the development of DME include elevated vascular permeability, impaired perfusion due to vascular occlusion, retinal pigment epithelium (RPE) damage, and traction by the posterior vitreous membrane.

Treatments for DME have included retinal photocoagulation, vitreous surgery, and sub-tenon triamcinolone injection [3-9]. Although laser photocoagulation was previously considered as a gold standard of DME treatment, intravitreal injections of anti-vascular endothelial growth factor (anti-VEGF) have proven to be more effective than grid macular coagulations in maintaining visual function and are now regarded as the first-choice treatment for DME [10-13]. However, the half-life of anti-VEGF agents in the vitreous body is 2.9-3.9 days [14, 15], and the therapeutic effect demonstrated in clinical trials lasts only 1–2 months per treatment, and thus administration must be frequently repeated.

Selective retinal therapy (SRT) was developed as a laser procedure in which the RPE is selectively damaged without affecting the neural retina and choroid [16-18]. In this procedure, a microsecond (1.7 µs) pulsed laser is used to induce an instantaneous temperature rise at just the melanosomes within RPE cells, which leads to the formation of microbubbles around these melanosomes. Their temporary expansion results in a cell volume expansion and eventually mechanical cellular disruption without an increase of temperature in the surrounding tissue. In recent SRT systems, an optoacoustic technique is integrated to enable irradiations with pulse energies close above bubble formation threshold (lit). In the previous studies, SRT has been reported to be effective for CSCR and DME, etc [18-22].

The accumulation of extracellular fluid observed in DME is caused by the breakdown of the inner and outer blood-retinal barriers, which can be affected by systemic conditions including diabetes and hypertension [2]. Clinical outcome of DME treatment may also be influenced by various clinical and pathological factors, such as previous treatments and morphological features. Therefore, in

this study, we carried out a retrospective investigation to evaluate the factors which may affect the therapeutic effectiveness of SRT on DME at 3 and 6 months after the treatment.

Materials and Methods

Subjects

This study was approved by the ethics committee of our hospital, carried out on the basis of the Declaration of Helsinki, and registered with University hospital Medical Information Network (UMIN) (No. 000010471). Written informed consent was obtained from all patients prior to enrolment. This study investigated 22 eyes in 22 DME patients (15 eyes of 15 men and 7 eyes of 7 women), who underwent SRT in the Department of Ophthalmology at Osaka City University Hospital between March 2013 and March 2017 and were followed-up for at least 6 months. The mean age of patients was 64.2 years (range, 40–81 years). Table 1 shows baseline characteristics of the patients. 13 of these 19 eyes (59%) had undergone treatment before SRT, consisting of macular photocoagulation in 8 eyes (36%), panretinal photocoagulation (PRP) in 13 eyes (59%), sub-Tenon triamcinolone injection (STTA) in 4 eyes (18%), anti-VEGF therapy in 7 eyes (32%), and vitreous surgery in 13 eyes (59%). Diabetic retinopathy was classified as mild nonproliferative retinopathy in 5 eyes (23%), moderate or severe preproliferative retinopathy in 3 eyes (14%), and proliferative retinopathy in 13 eyes (59%). Previous antihypertensive treatment, history of smoking, duration of diabetes, and history of insulin use were ascertained from medical questionnaires. There was no change in treatment for diabetes during study period for all patients.

Inclusion and exclusion criteria

The inclusion criterion for SRT was clinically significant macular edema according to ETDRS criteria giving rise to subjective symptoms such as central scotoma, metamorphopsia, and reduced visual acuity [3]. Patients with a central macular thickness (CMT) >250 μm measured by optic coherence tomography (OCT) were included.

Ophthalmological exclusion criteria were:

1) loss of sight in one eye;

2) optic media that is insufficiently transparent to acquire fundus images or obtain other imaging findings from the eye to be treated;

3) presence of inflammatory intraocular disorders, including infectious disorders;

4) intraocular surgery or laser treatment within 6 months;

5) intravitreal injection within 3 months;

6) presence of comorbidity reducing visual acuity of the eye to be treated or that may require medical or surgical treatment during the study period;

7) ophthalmic impairment in the eye to be treated that would confuse interpretation of the effectiveness of treatment in the judgement of an investigator or subinvestigator;

8) scarring or atrophy of the central fovea indicating that reduced visual acuity of the eye to be treated would not be recoverable;

9) vitreous traction or epiretinal membrane in the eye to be treated visible on biological optical microscopy or OCT that would significantly affect central visual acuity in the judgement of an investigator or subinvestigator;

10) neovascularization of the iris or vitreous haemorrhage in the eye to be treated;

11) signs of infectious blepharitis, keratitis, scleritis, or conjunctivitis in the eye to be treated, or currently undergoing treatment for serious systemic infectious disease.

Systemic exclusion criteria were:

1) systemic inflammatory disease;

2) haemorrhagic diathesis, or other condition of currently undergoing anticoagulant therapy judged to entail a high risk of serious haemorrhage during treatment;

3) pregnancy or the possibility of pregnancy;

4) a history of untreated or poorly controlled hypertension, diabetes, or other systemic disease judged to have a significant effect on treatment;

5) a systemic condition judged as rendering it impossible to attend hospital for continued treatment.

Clinical observations

All patients underwent the following ophthalmic observations at baseline and at 3 and 6 months after the treatment: the best corrected visual acuity (BCVA) measurement, slit-lamp microscopy, funduscopy, OCT(SPECTRALIS®; Heidelberg Engineering GmbH, Heidelberg, Germany), color fundus photography, fundus autofluorescence, and fluorescein angiography (FA) (SPECTRALIS®). For the BCVA analysis, decimal visual acuities were converted to logarithmic minimum angle of resolution (logMAR) values.

SRT method

The SRT laser used in this study was a Q-switched frequency-doubled neodymium-doped yttrium lithium fluoride laser (Nd:YLF) operating at a wavelength of 527 nm (Medical Laser Center Lübeck, Lübeck, Germany). The pulse duration was 1.7 µs, and 30 pulses per irradiation site were applied with a repetition rate of 100 Hz. A 1.05× magnification Mainster central field contact lens was used, and the slit lamp optics was adjusted such that the irradiation diameter on the retina was approximately 200 µm [20].

The extent of irradiation was determined by identifying the location of the macular edema before SRT using FA and OCT. The area of the edema was covered in a grid pattern, with the spacing between spots of about one spot diameter (200 µm) and sparing the central 500-µm area. Because the irradiated locations are ophthalmoscopically invisible, microbubble generation within the RPE and resulting cell destruction were estimated from the optoacoustic (OA) value, as described in a previous report [22]. The OA value is a number which is calculated from the ultrasonic waves generated during microbubble formation leading to cell disintegration. The pressure waves are recorded by an ultrasonic transducer embedded in the contact lens. According to the study, the OA value indicating 50% probability of RPE cell disruption (Effective Dose (ED) 50) is 70, and the one indicating 90% probability (ED90) is 112 as a result of calculating the leakage as positive on FA in the used system.

Outcome measures

Visual acuity, OCT, and FA were performed before treatment and 3 and 6 months later, as well as changes in BCVA. Central macular thickness (CMT) and fluorescein leakage during FA were also investigated. With regard to BCVA, changes of logMAR ≥0.2 were considered significant. A change in CMT ≥15% compared with the pre-treatment baseline was regarded as significant as previously described [23]. SRT was considered effective if CMT decreased significantly compared to baseline, and as ineffective if this was not the case. As factors that might influence the rate of change in CMT 3 and 6 months after SRT, we evaluated sex, age (≥65 years vs. <65 years), previous hypertension, smoking history, history of diabetes, history of insulin use, previous cataract surgery (crystalline lens/intraocular lens), stage of diabetic retinopathy (proliferative vs. nonproliferative), previous treatment (macular photocoagulation, panretinal photocoagulation, anti-VEGF therapy, or vitreous surgery), baseline BCVA, baseline CMT, type of DME (diffuse vs. other), ellipsoid zone (EZ) abnormality, and foveal avascular zone (FAZ) abnormality. The type of DME was classified into focal and diffuse based on the leakage using FA following previous reports [24]. EZ abnormality was evaluated within 500 μm of the central fovea in the horizontal plane on OCT, and then graded as follows: 0, normal (no disruption of EZ); 1, abnormal (some disruption of EZ); or 2, absent (EZ not visible). FAZ abnormality was graded as 0-4 using FA in accordance with the Early Treatment Diabetic Retinopathy Study (ETDRS) charts [21].

Statistical analysis

Changes in BCVA (logMAR) and CMT from baseline were assessed using a paired t-test. With respect to the association between the effectiveness of SRT and the various parameters, univariate analyses were performed.

In order to assess the associations between the changes of CMT after SRT treatment and clinical factors among SRT treated patients, we performed a univariable linear regression analyses with the change value of CMT at 6 months as the function of each clinical characteristic. Furthermore, the multivariable linear regression models were utilized with adjustment for baseline CMT value to

reduce the effect of confounding by baseline CMT (the association between the change of CMT and baseline CMT was examined with adjustment for stage of DR). Similar regression analyzes were conducted with the 3 months CMT change values as the dependent variable.

These analyses were performed with 2-sided 5% significance level using R version 3.6.0 (https://cran.r-project.org/) and IBM® SPSS® Statistics 24.0 (IBM Japan, Ltd., Tokyo, Japan).

Results

Figure 1 and 2 shows a typical case of DME treated with SRT. The mean number of irradiations in one SRT was 47.4 ± 17.4 (range, 25-86). Per patient, the mean number of irradiations with <ED50 (OA <70) was 7.6 ± 7.0 (15.8% ± 14.9%), the mean number of irradiations with ≥ED50 but <ED90 (70 ≤ OA < 112) was 15.0 ± 12.0 (26.4% ± 17.3%), and the mean number of irradiations with ≥ED90 (OA ≥112) was 24.3 ± 11.7 (57.8% ± 22.2%) (Figure 3).

Mean BCVA (logMAR) was 0.26 ± 0.31 before SRT, 0.22 ± 0.27 after 3 months, and 0.23 ± 0.29 after 6 months, with no significant difference (3 months, $p = 0.15$; 6 months, $p = 0.40$) (Figure 4a). Individually, after 3 months BCVA had improved in 9% of patients and was unchanged in 91%, and after 6 months had improved in 18%, was unchanged in 77%, and had worsened in 5% (Figure 5a).

Mean CMT was 502 ± 163 μm before SRT, 493 ± 204 μm after 3 months, and 416 ± 185 μm after 6 months, showing a significant decrease after 6 months (3 months, $p = 0.69$; 6 months, $p = 0.01$) (Figure 4b). Individually, after 3 months CMT had decreased in 14% of patients, was unchanged in 68%, and had increased in 18%, and after 6 months had decreased in 50%, was unchanged in 45%, and had increased in 5% (Figure 5b).

Comparison of the leakage in FA showed that, 3 months after SRT, leakage was decreased in 27% and unchanged in 73% of cases compared to the baseline; at 6 months after SRT, leakage was decreased in 27%, unchanged in 68% and increased in 5% of cases (Figure 5c).

The Table 2 and 3 shows univariate and multivariate analysis of factors associated with the rate of change in CMT at 3 and 6 months after SRT. The multivariate analysis found a significant negative

association with previous macular photocoagulation (p = 0.03, odds ratio 0.064, 95% confidence interval 0.005 – 0.816) at 3 months, and positive association with history of insulin use (p = 0.02, odds ratio -6.65, 95% confidence interval -11.84 – -1.46) and previous panretinal photocoagulation (p = 0.03, odds ratio -7.03, 95% confidence interval -13.32 – -0.75) at 6 months after SRT.

During this study, no patient developed cerebral infarction, myocardial infarction, or other systemic disease, or intraocular inflammation, haemorrhage, or other event attributable to laser irradiation.

Discussion

DME is a chronic condition that persists or recurs in many patients, and repeated treatments are often required for a long time. In fact, 13 of the 22 eyes in our study had previously undergone other treatment for DME. Anti-VEGF therapy is presently the first line treatment for DME, which shows a prompt and remarkable effect, hence SRT is not the first-choice therapy for DME patients. However, the reduction of DME after a single SRT was evident 6 months after the treatment, which suggests that the effect of SRT can be maintained for a long-term in the patients who respond to the treatment.

This study found that the mean CMT in DME patients was significantly decreased 6 months after SRT with an overall improvement rate of 50%. Given that 59% of our cases (13 of the 22 eyes) had previously undergone treatment with anti-VEGF therapy or vitrectomy, this indicates that SRT may induce reduction of macular edema for both naïve and treated cases. Previous studies showed that SRT reduces macular edema in both treatment-naïve and previously treated DME [18, 19]. Our findings are consistent with those results.

A significant negative association was found with previous macular photocoagulation at 3 months after SRT, but no association was found at 6 months. This can be interpreted such that previous macular photocoagulation may delay the effect of SRT leading to resolution of edema. Different from conventional photocoagulation, SRT laser generates microbubbles within the RPE, breaking down the RPE cells alone without damaging photoreceptor cells [25-27], which could be indirectly confirmed with the measured OA values as presented. One possible mechanism for the reduction

of edema is an acceleration of a drainage function of submacular RPE by the reconstructed monolayer structure through the proliferation of RPE cells. Conventional macular photocoagulation for DME causes degeneration of the RPE and retinal tissues by thermal denaturation, which may cause scarring of the retina. Hens the potential of RPE wound healing, consisted mainly of migration and proliferation of cells, in the retina undergone macular grid photocoagulation might be different from the monolayer without scar formation and it might cause the delay of functional reepithelialization after treatment. Our investigation also identified history of insulin use and previous PRP associated with the reduction of CMT at 6 months after SRT. Insulin use may generally reduce the level of blood glucose, thus can be consequently associated with HbA1c. However, HbA1c did not show significant association with the reduction of CMT, thus blood glucose level or stability does not seem to be the main explanation of this high association between insulin use and CMT reduction. On the other hand, Insulin has been reported to stimulate wound healing of different cell/tissue types through activation of different kinase pathways responsible to cell migration and proliferation [28]. For RPE cells, too, insulin showed a weak to moderate stimulatory effect on proliferation of human RPE cells if applied alone [29]. This could be a possible mechanism of the positive association between insulin use and CMT reduction after SRT, in which RPE wound healing is one of the initial key therapeutic processes.

PRP is performed generally for the proliferative or severe pre-proliferative DR, in order to improve retinal oxygenation [30]. Therefore, the obtained statistic result could be interpreted that SRT might reduce macular edema more effectively in the retina with better intraretinal oxygen supply. Although association between the extent of retinal oxygenation and the response of RPE cells to laser irradiation in diabetic patients has not been well investigated yet to date, hyperbaric oxygen has shown positive therapeutic effects in the process of wound healing in the foot ulcer of diabetic patients [31].

Patients who have undergone vitreous surgery exhibit increased clearance of anti-VEGF therapy and the multiple injections of anti-VEGF agents have also been reported to increase the incidence

of endophthalmitis and other ocular complications [32, 33]. In the patients with a history of vascular infarction-related disease, the anti-VEGF therapy may also increase the risk of cerebral or myocardial infarction. Particularly in diabetic patients, the risk of infarction-related disease increases with the progression of diabetes, and the continuous usage of anti-VEGF agents for long-term must be performed with caution [34, 35]. Since no systemic effects of SRT has been reported to date, this treatment may have an advantage over anti-VEGF therapy for systemic safety.

Although anti-VEGF therapy is highly effective in reducing macular edema, about a half of patients show no improvement in visual function [36]. This may be because DME is a multifactorial disorder that is not caused by VEGF alone. The main effect of anti-VEGF therapy is to regulate an excess permeability of the retinal vessels and reducing leakage into the neuronal retina [37]. The therapeutic mechanism of SRT is considered, as described above, to lie primarily on the restored RPE function including drainage function [18, 19]. SRT thus may improve macular edema via a different mechanism from those of other treatment modalities, and it suggests that SRT may be a useful alternative or concomitant treatment of other treatment modalities with different therapeutic mechanisms, especially because SRT is free of any adverse effect.

Recently, other different types of minimally-invasive retinal laser treatment procedures, such as subthreshold micropulse laser (SML) treatment, were also reported to be effective in treating eyes with DME [38-40]. It might be thus also interesting to elucidate in future studies the differences in clinical results and determining factors among these different interventions. However, so far SRT is the only sub-visible treatment modality with an individual and accurate spot-by-spot dosing control.

In conclusion, SRT is one of the treatment modalities to reduce DME over 6 months of follow-up. SRT may be affected by history of insulin use and photocoagulation, and our results suggested that this must be taken into consideration when determining the indications for SRT. This study was limited by the inclusion of only a small number of patients and by a non-randomized study design. Further prospective studies with a larger number of patients will be useful to confirm the factors associated with the outcomes of SRT.

Acknowledgments

None.

Compliance with ethical standards

Conflict of interest

The authors declare that they have no conflict of interest.

Ethical approval

This study was approved by the ethics committee of our hospital, carried out on the basis of the Declaration of Helsinki, and registered with University hospital Medical Information Network (UMIN) (No. 000010471).

Informed consent

Written informed consent was obtained from all patients prior to enrolment.

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combined with yellow (561-577-nm) direct photocoagulation for diabetic macular edema. Jpn J Ophthalmol 59:21–8

Tables

Table 1 Patient characteristics at baseline

Characteristics		
Number	22 Cases (22 eyes)	
Sex	Male 15, Female 7	
Age; Mean (Range)	64.2 (40 - 81)	
Hypertension (%)	13 (59)	
Smoking (%)	13 (59)	
Duration of diabetes; Median, (Range)	10 (3 – 30)	
HbA1c; Median (Range)	6.9% (5.8 - 9.0)	
Insulin use (%)	10 (45)	
Intraocular lens (%)	12 (54)	
Proliferative diabetic retinopathy (%)	14 (64)	
Macular photocoagulation (%)	8 (36)	
Previous PRP (%)	13 (59)	
STTA (%)	4 (18)	
Anti-VEGF therapy (%)	7 (32)	
Vitreous surgery (%)	13 (59)	
BCVA (logMAR); Mean, (Range)	0.26 (0.82 - -0.18)	
CMT: Mean, (Range)	502 µm (241 - 776)	
Type of macula edema (%)	focal	11 (50)
	diffuse	11 (50)
Abnormality of ellipsoid zone (%)	normal	9 (37)
	abnormal	10 (42)
	absent	3 (21)
Abnormality of foveal avascular zone (FAZ) (using FA)(%)	grade 0	5 (11)
	grade 1	5 (32)
	grade 2	5 (16)
	grade 3	4 (32)
	grade 4	3 (11)

Table 2 Univariate analysis of factors associated with the rate of change in CMT

	3M				6M			
	CI	95%CI		p Value	CI	95%CI		p Value
Age	1.10	(-2.73 -	4.93)	0.56	2.18	(-1.8 -	6.15)	0.27
Sex (Male: Female)	0.15	(-5.83 -	6.13)	0.96	-1.57	(-7.88 -	4.74)	0.61
Duration of diabetes (Years)	2.57	(-1.76 -	6.90)	0.23	-2.17	(-6.83 -	2.50)	0.34
HbA1c (%)	-0.73	(-5.62 -	4.16)	0.76	3.42	(-1.53 -	8.38)	0.17
Hypertension	0.44	(-5.22 -	6.11)	0.87	0.47	(-5.54 -	6.48)	0.87
Smoking	1.95	(-3.65 -	7.54)	0.48	0.66	(-5.35 -	6.67)	0.82
History of Insulin use	0.70	(-4.89 -	6.29)	0.80	-6.60	(-11.68 -	-1.52)	0.01
Ocular characteristics								
Phakia: Intraocular lens	1.68	(-3.86 -	7.22)	0.53	-2.38	(-8.22 -	3.45)	0.41
Stage of DR (nPDR: PDR)	-0.09	(-5.88 -	5.70)	0.98	-3.73	(-9.63 -	2.17)	0.20
History of DR treatment								
Macular photocoagulation	6.57	(1.66 -	11.49)	0.01	1.96	(-4.12 -	8.05)	0.51
Panretinal photocoagulation	-1.62	(-7.24 -	3.99)	0.55	-4.61	(-10.23 -	1.02)	0.10
Anti-VEGF therapy	-0.78	(-6.75 -	5.19)	0.79	-1.57	(-7.88 -	4.74)	0.61
Vitrectomy	2.14	(-3.44 -	7.72)	0.43	-2.54	(-8.44 -	3.36)	0.38
Baseline BCVA (logMAR)	-0.14	(-3.42 -	3.14)	0.93	-1.64	(-5.04 -	1.76)	0.33
Type of macular edema (focal: diffuse)	4.36	(-0.82 -	9.55)	0.10	2.45	(-3.35 -	8.26)	0.39
Ellipsoid zone	3.26	(-4.71 -	11.24)	0.40	3.67	(-4.79 -	12.12)	0.38
Baseline CMT	-0.50	(-4.57 -	3.56)	0.80	-0.92	(-5.22 -	3.38)	0.66
FAZ grade	-2.26	(-1.74 -	6.27)	0.25	-2.18	(-6.46 -	2.09)	0.30

CI Confidence interval

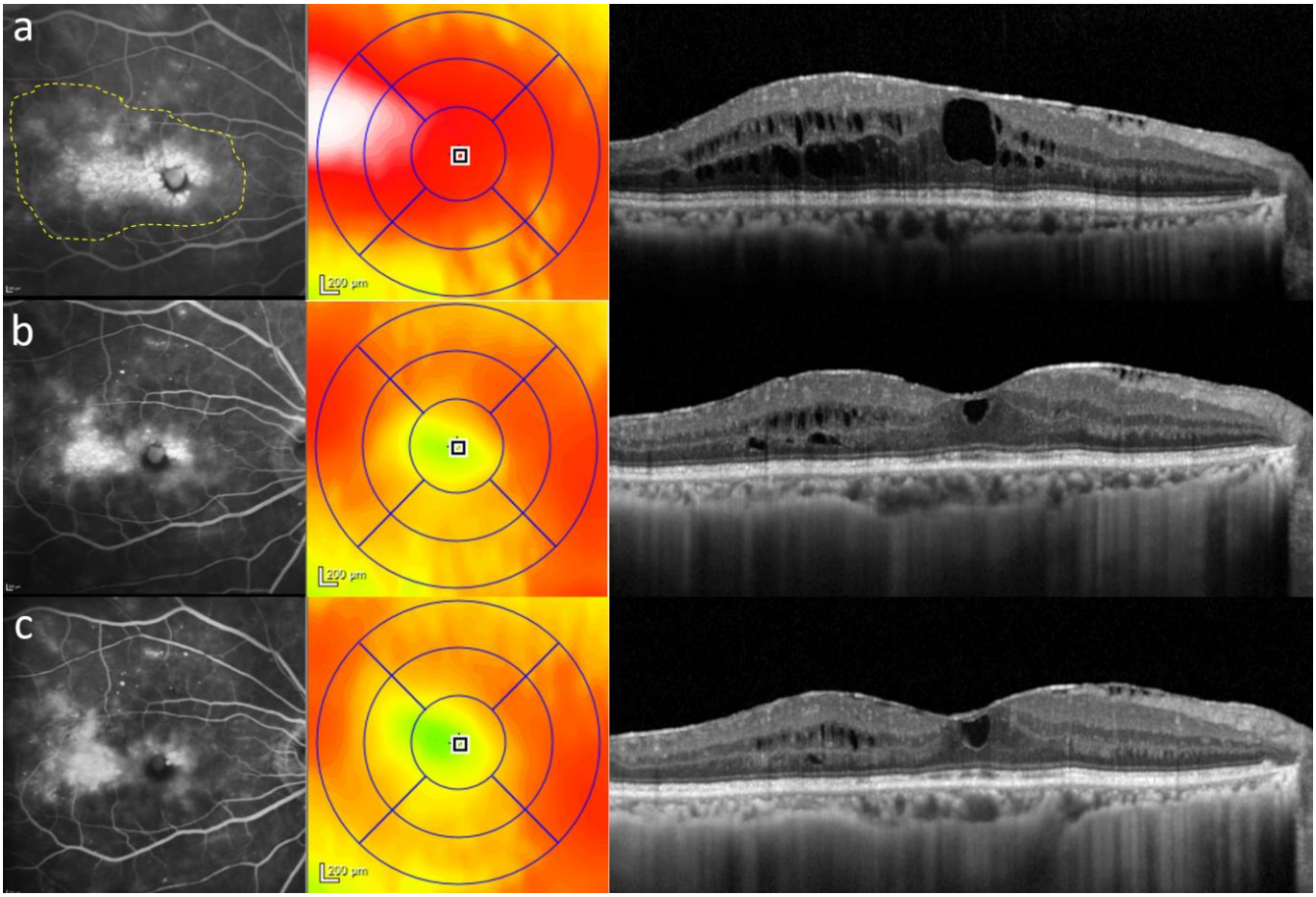
Table 3 Multivariate analysis of factors associated with the rate of change in CMT

	3M				6M			
	CI	95%CI		p Value	CI	95%CI		p Value
Age	1.21	(-2.78 -	5.19)	0.53	2.38	(-1.72 -	6.49)	0.24
Sex (Male: Female)	0.17	(-5.98 -	6.32)	0.96	-1.54	(-8.00 -	4.93)	0.63
Duration of diabetes (Years)	2.56	(-1.90 -	7.01)	0.24	-2.19	(-6.96 -	2.58)	0.35
HbA1c (%)	-0.73	(-5.76 -	4.29)	0.76	3.41	(-1.66 -	8.49)	0.18
Hypertension	0.38	(-5.46 -	6.23)	0.89	0.35	(-5.83 -	6.54)	0.91
Smoking	1.88	(-3.97 -	7.73)	0.51	0.44	(-5.82 -	6.71)	0.88
History of Insulin use	0.68	(-5.07 -	6.42)	0.81	-6.65	(-11.84 -	-1.46)	**0.02**
Ocular characteristics								
Phakia: Intraocular lens	1.61	(-4.29 -	7.52)	0.57	-2.91	(-9.05 -	3.24)	0.34
Stage of DR (nPDR: PDR)	-0.81	(-8.24 -	6.62)	0.82	-7.05	(-14.16 -	0.06)	0.052
History of DR treatment								
Macular photocoagulation	6.77	(1.58 -	11.96)	**0.01**	1.76	(-4.67 -	8.18)	0.57
Panretinal photocoagulation	-2.65	(-9.27 -	3.98)	0.41	-7.03	(-13.32 -	-0.75)	**0.03**
Anti-VEGF therapy	-1.26	(-7.90 -	5.39)	0.70	-2.47	(-9.43 -	4.49)	0.47
Vitrectomy	2.08	(-3.73 -	7.88)	0.46	-2.79	(-8.88 -	3.30)	0.35
Baseline BCVA (logMAR)	0.14	(-4.00 -	4.28)	0.94	-1.82	(-6.11 -	2.47)	0.38
Type of macular edema (focal: diffuse)	4.69	(-0.70 -	10.09)	0.09	2.82	(-3.22 -	8.86)	0.34
Ellipsoid zone	3.88	(-4.64 -	12.40)	0.35	4.58	(-4.38 -	13.55)	0.30
Baseline CMT	-0.84	(-6.06 -	4.38)	0.74	-3.89	(-8.89 -	1.10)	0.12
FAZ grade	2.24	(-1.89 -	6.37)	0.27	-2.26	(-6.64 -	2.12)	0.29

CI Confidence interval

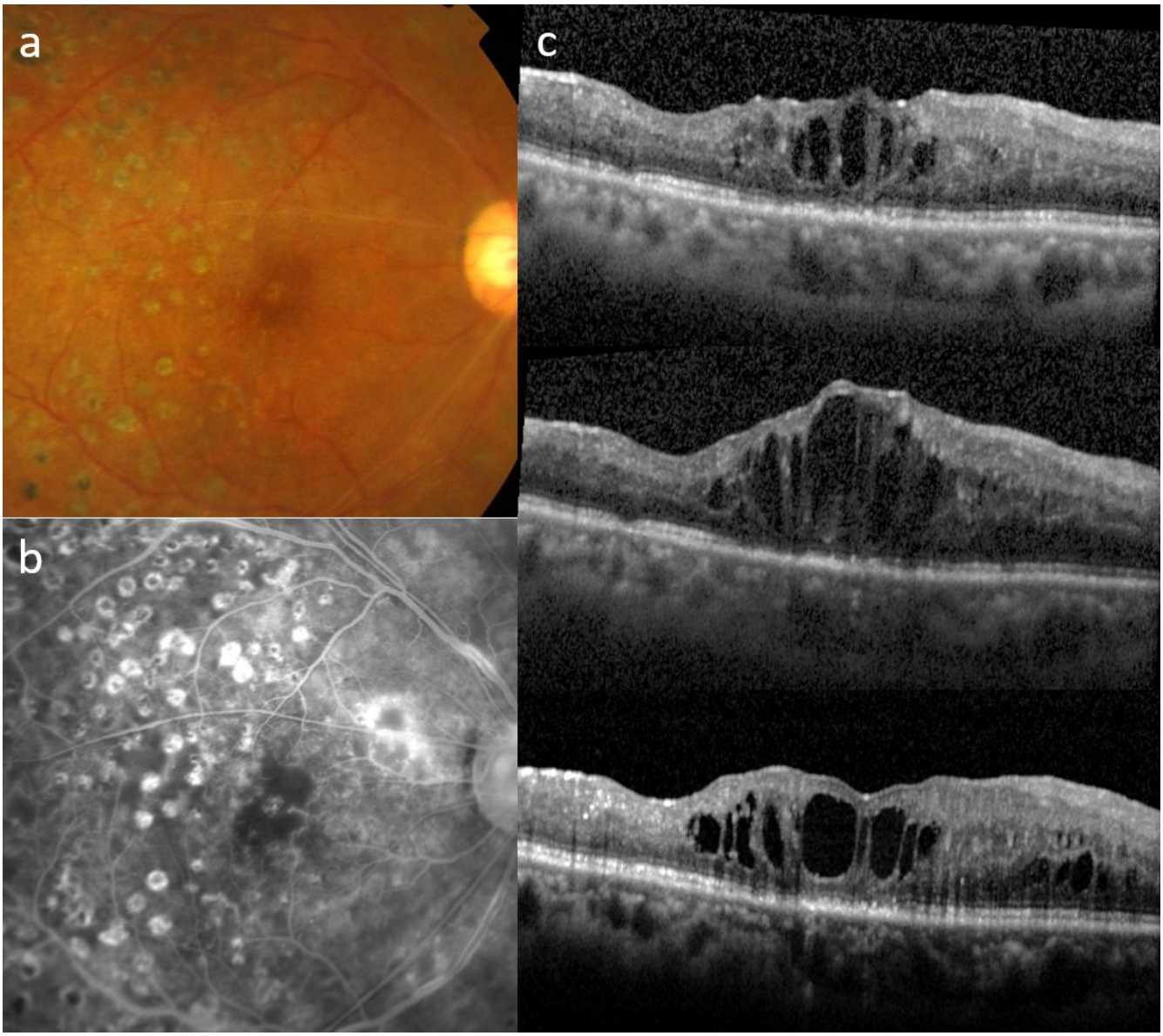
Figures

Fig.1 Example images from a 67-year-old woman with DME treated by SRT who had previously received one vitrectomy, two STTA, five anti-VEGF therapy and PRP.



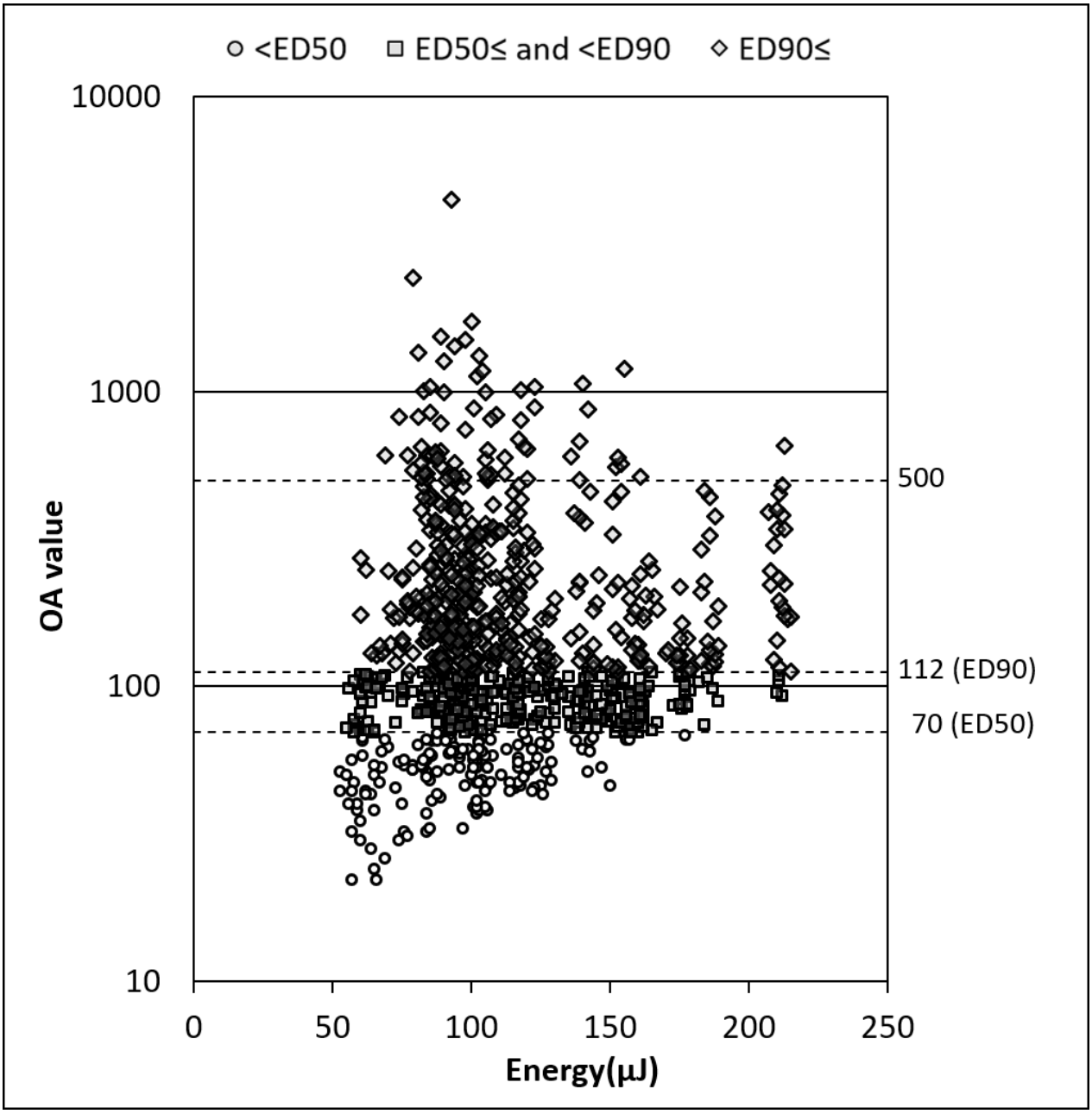
FA (left), retina thickness map of OCT (centre), horizontal line of OCT (right). a) Baseline; b) 3 months after SRT; c) 6 months after SRT. Extent of SRT irradiation (yellow dotted line). Totally 33 spots with energy range from 65 to 106 µJ were irradiated. CMT was 436 µm at baseline, decreasing to 308 µm at 3 months follow-up and 309 µm at 6 months follow-up of SRT.

Fig.2 Example images from a 62-year-old man with DME treated by SRT who had previously received one vitrectomy, three STTA, one macular photocoagulation using grid pattern and PRP.



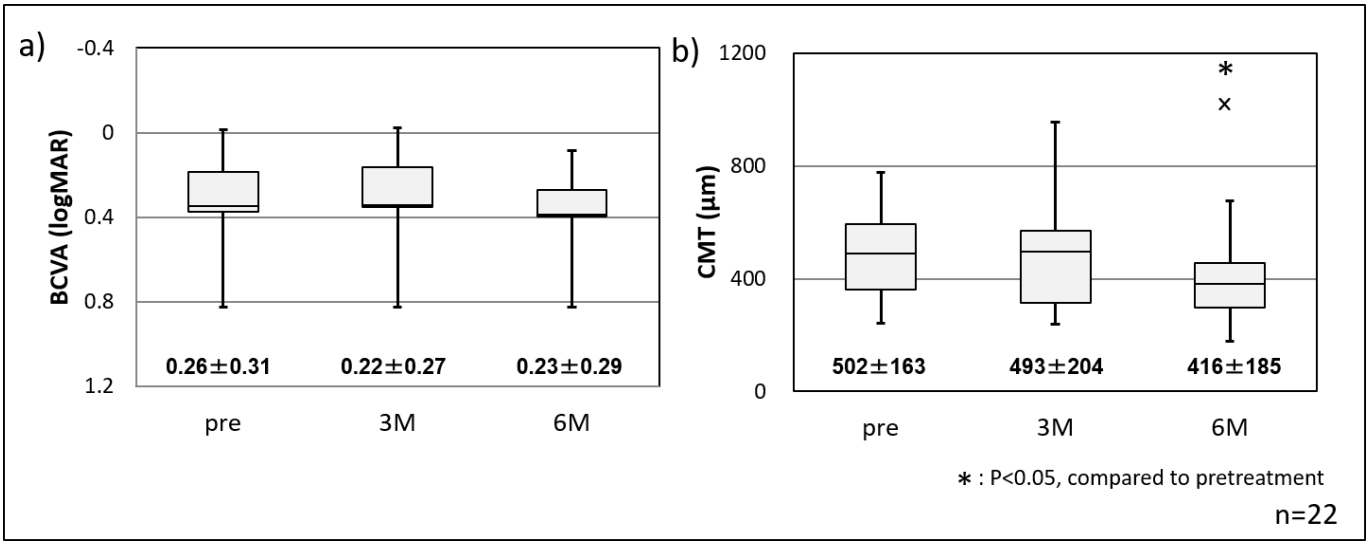
a) Fundus color photograph; b) FA; c) horizontal line of OCT baseline (top), 3 months after SRT (middle) and 6 months after SRT (bottom). Totally 51 spots with energy range from 84 to 12 μJ were irradiated. CMT was 372 μm at baseline, increasing to 585 μm at 3 months follow-up and 415 μm at 6 months follow-up of SRT.

Fig.3 SRT irradiation energy and optoacoustic values.



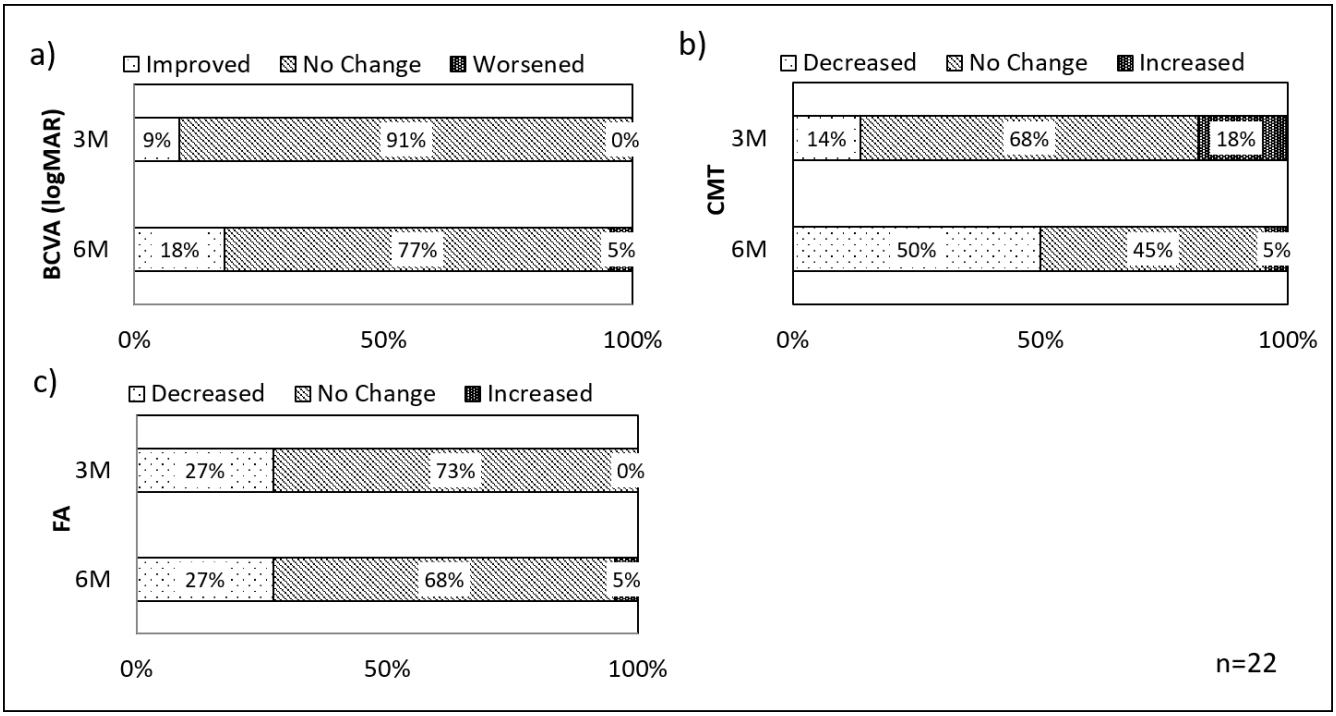
The scatter plot shows the correspondence between irradiation energy and optoacoustic value at each irradiation spot in all cases.

Fig.4 Time course of changes in BCVA, CMT and dye leakage on FA.



a) Boxplots showing BCVA (logMAR) before, 3 months (3M) and 6 months (6M) after SRT: The mean ± SD of BCVA was 0.26 ± 0.31, 0.22 ± 0.27, and 0.23 ± 0.29, at baseline, 3M, and 6M, respectively, where there were no significant differences among different points in time. b) Boxplots showing CMT before, 3 and 6 months after SRT: The mean ± SD of CMT was 502 ± 163 μm, 493 ± 204 μm, 416 ± 185 μm at baseline, 3 months, and 6 months, respectively, where a significant difference was shown between baseline and 6 months (* $p<0.05$).

Fig.5 Time course of individual changes in BCVA, CMT and leakage in FA.



a) Proportions of patients whose BCVA was improved, unchanged or worsened by ≥0.2 from baseline at 3M and 6M after treatment. The proportion of patients with improved BCVA was increased over time (9% at 3M to 18% at 6M). b) Proportion of patients whose CMT reduced ("improve"), unchanged, or increased ("worse") by ≥15% from baseline at 3M and 6M after treatment. The number of the patients with reduced CMT increased (from 14% to 50%) from 3M to 6M. c) Proportion of patients whose changes in dye leakage was decrease, unchanged, or increased on FA. There was almost no difference in the leakage on FA between 3M and 6M.