Title

Objective and quantitative estimation of the optimal timing for epiretinal membrane surgery on the basis of metamorphopsia

Abbreviated title

Optimal timing for ERM surgery

Authors

Yuki Kanzaki, MD, PhD,[1] Shinichiro Doi, MD, PhD,[1] Ryo Matoba, MD, PhD,[1] Sayumi Kanzaki, MD,[1] Shuhei Kimura, MD, PhD,[1] Mio M. Hosokawa, MD, PhD,[1] Yusuke Shiode, MD, PhD,[1] Ippei Takasu, MD, PhD,[2] Yuki Morizane MD, PhD[1]

Institutional Affiliations

[1]Department of Ophthalmology, Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama University, 2-5-1 Shikata-cho Kita-ku, Okayama City, Okayama 700-8558, Japan

[2]Department of Ophthalmology, Takasu Eye Clinic, 1-4 Ekimotomachi Kita-ku, Okayama City, Okayama 700-0024, Japan

Corresponding author

Yuki Morizane, MD, PhD

Department of Ophthalmology, Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama University, 2-5-1 Shikata-cho Kita-ku, Okayama City, Okayama 700-8558, Japan

Telephone: +818 6235 7297

Fax: +818 6222 5059

E-mail: moriza-y@okayama-u.ac.jp

Competing interests

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Keywords

en face optical coherence tomography, epiretinal membrane, maximum depth of the retinal folds, M-CHARTS, metamorphopsia

Brief summary statement

We examined the relationship between maximum depth of retinal folds (MDRF) and metamorphopsia in epiretinal membrane (ERM) and showed that MDRF is an objective and quantitative biomarker of metamorphopsia. Our results suggest the quality of vision could be maintained if ERM is removed when the preoperative MDRF is 69-118 μm.

Abstract

Purpose: To establish an objective and quantitative biomarker of metamorphopsia in epiretinal membranes (ERMs) and determine the optimal timing for ERM surgery.

Methods: Retrospectively, 172 eyes with ERM were reviewed. Retinal folds due to tangential traction by ERM were visualized by en face optical coherence tomography (OCT). The maximum depth of retinal folds (MDRF) within the parafovea was quantified. Metamorphopsia was quantified by M-CHARTS. The change in the distance between the retinal vessels after ERM surgery and the preoperative total depth of retinal folds between the vessels were quantified using en face OCT and OCT angiography.

Results: Significant correlations were observed between preoperative MDRF and M-CHARTS scores before and at 6 months after surgery (r=0.617 and 0.460, respectively; $P<0.001$) and change in the distance between the retinal vessels after ERM surgery and preoperative total depth of retinal folds between the vessels (r=0.471, $P=0.013$). The preoperative MDRF values at which M-CHARTS scores were 0.5 before and 6 months after surgery were 69 μm and 118 μm, respectively.

Conclusion: MDRF is an objective and quantitative biomarker of metamorphopsia in ERM. To maintain patients' quality of vision, ERM surgery may be performed when the preoperative MDRF ranges between 69 and 118 μm.

Introduction

Epiretinal membrane (ERM) is a common type of fibrocellular proliferation found on the internal limiting membrane (ILM), and it is significantly associated with aging.[1–4] The major symptoms of ERM are believed to result from retinal traction and include reduced visual acuity, metamorphopsia, and aniseikonia.[5–10] Among these subjective symptoms, metamorphopsia is the most important because it is the earliest evident symptom[11] and shows a stronger association with the quality of vision (QOV) than do other visual parameters in ERM patients.[6]

Major problems associated with ERM surgery include the lack of consensus criteria regarding indications for the surgery and the fact that metamorphopsia remains even after ERM and ILM peeling in approximately 70% of patients.[5,12] Because there is no treatment for ERM other than ERM and ILM peeling, it is necessary to determine the optimal timing for ERM surgery to prevent metamorphopsia from exceeding a level that would significantly impair the patient's daily life. To achieve this goal, an objective and quantitative biomarker of metamorphopsia is desirable. Unfortunately, however, no such biomarker has been established to date.

Recently, we focused on the depth of retinal folds caused by ERM as an objective and quantitative biomarker reflecting the tangential retinal traction force applied by ERM,[13–16] and we found that the preoperative maximum depth of retinal folds (MDRF) within the parafovea was significantly related to preoperative metamorphopsia measured by M-CHARTS,[17] a subjective quantitative test.[14] However, it remains unclear whether MDRF can be a quantitative and objective biomarker of metamorphopsia in ERM patients.

Therefore, the aim of the present study was to determine the relationships between pre- and postoperative metamorphopsia and the preoperative MDRF in ERM patients, as well as the relationship between changes in metamorphopsia and MDRF over the natural course of ERM. Furthermore, we quantitatively determined the optimal timing for ERM surgery based on the relationships between pre- and postoperative metamorphopsia and the preoperative MDRF.

Methods

Study design and ethical considerations

This was a retrospective, consecutive, observational study. All investigative procedures adhered to the tenets of the Declaration of Helsinki. The study was approved by the Ethics Committee of Okayama University Hospital, Okayama, Japan. Each patient was informed about the study and provided written informed consent for participation.

Subjects

We retrospectively reviewed the charts of a consecutive series of 172 eyes of 160 patients with idiopathic ERM who visited Okayama University Hospital or Takasu Eye Clinic from June 1, 2017 through November 30, 2019. We excluded eyes with secondary ERM associated with ocular diseases such as age-related macular degeneration, diabetic retinopathy, retinal vein occlusion.

Ophthalmologic examinations

All patients underwent comprehensive ophthalmologic examinations, including assessments using a 5-m Landolt C acuity chart, slit-lamp biomicroscopy, and swept-source (SS) optical coherence tomography (OCT; SS-OCT; Triton; Topcon Corporation, Tokyo, Japan). M-CHARTS (Inami, Tokyo, Japan) was used to quantify the degree of metamorphopsia.[17] The M-CHARTS score was obtained by examining

M-CHARTS for the vertical and horizontal directions and calculating the average of the values.[7,8,14]

Analysis of SS-OCT images

SS-OCT images were obtained in both B-scan and three-dimensional (3D) modes (6 × 6-mm area, 512 × 512 A-scans). Image analysis software (IMAGEnet6, Version 1.22 software, Topcon Corporation, Tokyo, Japan) was used to construct en face and OCT angiography (OCTA) images. Based on the retinal layer boundary information, IMAGEnet6 can align the 3D OCT volume scan data along a specific retinal layer boundary and generate en face and OCTA images at an arbitrary depth.

Measurement of the MDRF

We measured MDRF within a 3-mm-diameter circle centered at the fovea (parafoveal area in the ETDRS chart) as previously described.[13-15] Briefly, we flattened the 3D OCT volume scan data at the level of ILM and visualized the black lines corresponding to the retinal folds due to retinal traction by ERM on the en face image below the ILM level. Then, we measured the depth from the ILM just before the deepest retinal fold within parafoveal area disappeared, i.e. MDRF is the distance between the

two planes of en face images: one on the level of the ILM and another which through the bottom of the deepest retinal fold within parafoveal area. (see Fig. 1 and the Video, Supplemental Digital Content 1, which demonstrates how to measure MDRF).

Staging of ERM progression

According to the staging of ERM progression by Govetto et al.,[18] preoperative cases were classified on the basis of OCT B-scan images.

Quantitative assessment of the relationship between the change in the depth of retinal folds and the amount of retinal vessel displacement after ERM surgery

It has been reported that the retinal vessel displaces when retinal traction is released by ERM surgery.[19–21] Since the retinal folds visualized in the en face image are the result of retinal shrinkage caused by retinal traction by ERM, we hypothesized that the displacement of the retinal vessel by ERM surgery was caused by the smoothing out of the retinal folds by ERM surgery. To clarify the relationship between the depth of the retinal folds smoothed out by ERM surgery and the amount of retinal vessel displacement, we measured the change in the distance between two vessel branch points and the sum of the depths of all retinal folds between the vessel branch points (the total retinal fold

depth). For patients who underwent ERM surgery, we performed 3D imaging of the retina before and 1 month after ERM surgery. Then, we constructed both en face images to visualize the retinal folds and OCTA images of the superficial retinal vessels (Fig. 2). The en face and OCTA images were superimposed for simultaneous visualization of the retinal folds and superficial retinal vessels. On each superimposed preoperative OCT image (Fig. 2), we selected a cluster of retinal folds (hereafter referred to as “the fold cluster”) consisting of multiple retinal folds with the same major axis direction. Subsequently, we selected two vessel branch points, such that the selected fold cluster was located between the two vessel branch points, and the direction of the line connecting the two vessel branch points was approximately perpendicular to the major axis of the selected fold cluster. Then, the total retinal fold depth in the fold cluster was calculated by measurement of the depth of each fold that constituted the cluster and summation of the measured values. We also measured the distance between the two vessel branch points. On each superimposed postoperative OCT image, we measured the total retinal fold depth in the fold cluster and the distance between the vessel branch points before surgery. To calculate the change in the total retinal fold depth in the fold cluster and the amount of retinal vessel displacement after ERM surgery, we subtracted the postoperative total retinal fold depth and the preoperative distance between the

vessel branch points from the preoperative total retinal fold depth and the postoperative distance between the vessel branch points, respectively. For each eye, we investigated a couple of fold clusters and corresponding vessel branch points. Finally, we examined the relationship between the change in the total retinal fold depth and the amount of retinal vessel displacement after ERM surgery.

Surgical procedure

The indication for ERM surgery was determined based on decreased visual acuity (less than 20/20) or a complaint of metamorphopsia. All surgeries were performed using a 25-gauge microincision vitrectomy system (Constellation; Alcon Laboratories, Inc., Fort Worth, Texas, USA). After core vitrectomy, ERM was removed as much as possible. ILM was removed after staining with 0.25 mg/mL Brilliant Blue G solution (Coomassie BBG 250; Sigma-Aldrich, St. Louis, MO). At a minimum, the area of ILM peeling was larger than the parafoveal area and selected at the discretion of the surgeon.[13–15] Among patients with phakic eyes, those aged >50 years or showing a cataract density higher than Grade 2 according to the Emery–Little classification received simultaneous cataract surgery and intraocular lens implantation. All surgeries were performed by one of two surgeons (Y.M. and I.T.).

Statistical analysis

All statistical analyses were performed using SPSS version 25.0.0.0 (IBM Corporation, Armonk, NY, USA). Spearman's rank correlation test was used to analyze the following relationships: the preoperative MDRF and the mean preoperative M-CHARTS score, the preoperative MDRF and the mean M-CHARTS score at 6 months after ERM surgery, and the change in the total retinal fold depth and the amount of retinal vessel displacement after ERM surgery. The relationship between the preoperative MDRF and ERM staging was analyzed using a one-way analysis of variance. The Kruskal–Wallis test was used to compare MDRF and mean M-CHARTS scores before and at 1, 3, and 6 months after ERM surgery. A *P*-value of <0.05 was considered statistically significant.

Results

Relationship between the pre- or postoperative M-CHARTS score and preoperative MDRF

We examined the relationships between the pre- or postoperative M-CHARTS score and the preoperative MDRF in 74 eyes of 72 patients (mean age, 68.1 ± 8.3 years;

28 men and 44 women) who underwent vitrectomy with ERM and ILM peeling. Of the 74 eyes, 63 eyes (85.1%) simultaneously underwent cataract surgery. The results revealed that both the pre- and postoperative M-CHARTS score and the preoperative MDRF were significantly correlated ($y = 0.0083x - 0.069$; $r = 0.617$; $P < 0.001$; Fig. 3A and $y = 0.0048x - 0.065$, $r = 0.460$, $P < 0.001$, Fig. 3B, respectively). According to the equations of the regression line, the pre- and postoperative MDRF values corresponding to the threshold at which metamorphopsia interferes with daily life, an M-CHARTS score of 0.5,[10,12,14] were 69 μm and 118 μm, respectively.

Relationship between ERM severity and the preoperative MDRF

To clarify the relationship between ERM severity and the preoperative MDRF, we investigated preoperative MDRF at each ERM stage[18] in 146 eyes of 139 patients (mean age, 69.6 ± 8.5 years; 64 men and 75 women). The preoperative MDRF was significantly greater in eyes with stages 3 + 4 (100.7 ± 34.6 μm) than in eyes with stages 2 and 1 (56.9 ± 37.6 and 39.8 ± 24.7 μm, respectively; $P < 0.001$ for both; Fig. 3C). The preoperative MDRF in eyes with stage 2 was significantly greater than that in eyes with stage 1 ($P = 0.037$; Fig. 3C).

Time course of changes in the MDRF and metamorphopsia after ERM surgery

As shown in Fig. 4, the mean MDRF was 88.3 ± 37.8 μm before surgery. MDRF became 0 μm at 1 month after ERM surgery ($P < 0.001$) and remained the same until 6 months after the surgery (Fig. 4A). The preoperative M-CHARTS score (0.7 ± 0.5) was significantly decreased at 1 month after ERM surgery (0.4 ± 0.5, $P = 0.007$) and remained unchanged until 6 months (M-CHARTS scores at 3 and 6 months, 0.4 ± 0.4 and 0.4 ± 0.4, respectively; $P = 0.680$ and 0.655, respectively; Fig. 4B). The results showed that 68.9% of eyes (51/74 eyes) had some degree of residual metamorphopsia at 6 months after ERM surgery; the degree of residual metamorphopsia at 6 months after the surgery was 54.5% of the preoperative metamorphopsia.

Correlation between the change in the retinal fold depth and the amount of retinal vessel displacement after ERM surgery

We examined 27 retinal fold clusters in 12 patients (mean age, 66.8 ± 7.6 years; one man and 11 women) and found a significant correlation between the change in the total retinal fold depth and the amount of retinal vessel displacement after ERM surgery ($y = 0.4482x + 67.9$, $r = 0.471$, $P = 0.013$, Fig. 5).

Two representative cases are shown in Fig. 6.

Discussion

In this study, we aimed to develop metamorphopsia-based criteria for the indications for ERM surgery and examined the usefulness of MDRF, which reflects the retinal traction force exerted by ERM, as a quantitative and objective biomarker of metamorphopsia. We obtained three important results. First, preoperative MDRF displayed a significant positive correlation with both pre- and postoperative metamorphopsia and ERM staging. Second, the time course of changes in MDRF after ERM surgery demonstrated a trend similar to that of postoperative changes in metamorphopsia. Third, the change in the total retinal fold depth significantly correlated with the amount of retinal vessel displacement.

Our postoperative en face images revealed that the retinal folds completely disappeared after ERM + ILM peeling. Because the retinal folds are caused by tangential traction on the retina,[22–24] complete disappearance of these folds indicates that the tangential traction on the retina has been completely released. Furthermore, the significant positive correlation between the amount of retinal vessel displacement and the total retinal fold depth after ERM surgery (Fig. 5) suggests that ERM surgery

releases the tangential traction on the retina and returns the displaced retinal surface tissue to its original position. Interestingly, while ERM surgery significantly improved the structure of the retinal surface at 6 months after surgery, metamorphopsia remained in 68.9% of patients. The degree of this residual metamorphopsia was 54.5% of the preoperative level (Figs. 3B and 4B). This result is consistent with those of previous studies reporting that metamorphopsia remained even after ERM surgery,[5,12] indicating that not only the release of retinal traction but also the resolution of the complex pathology caused by retinal traction is necessary to eliminate postoperative metamorphopsia.

Since there is no effective treatment for complete resolution of the intraretinal pathology caused by ERM, clinicians need to think about the optimal timing for ERM surgery. We thought it would be better to determine the timing for ERM surgery based on the relationships between the degree of pre- and postoperative metamorphopsia and the patient's QOV. Specifically, ERM with a degree of metamorphopsia that does not affect the preoperative QOV does not require surgery. However, surgery is necessary if metamorphopsia reaches a stage where it begins to affect daily life. On the other hand, in terms of postoperative QOV, we thought it would be useful to determine the timing for

ERM surgery such that the residual postoperative metamorphopsia would not affect the daily life of patients. Kinoshita et al. reported that an M-CHARTS score of 0.3 to 0.5 is the threshold for clear perception of metamorphopsia, and Arimura et al. reported that 81.3% ERM patients with an M-CHARTS score of <0.5 experienced no difficulty in daily life.[10,12,14] Subsequently, for example, if an M-CHARTS score of 0.5 is set as the cutoff value, the preoperative MDRF at which a preoperative metamorphopsia is 0.5 is calculated by the relationship between the preoperative M-CHARTS score and the preoperative MDRF ($y = 0.0083x - 0.069$ in Fig. 3A), equaling a preoperative MDRF value of 69 μm. Similarly, the preoperative MDRF value corresponding to a postoperative M-CHARTS score of 0.5 was calculated by the relationship between the postoperative M-CHARTS score and the preoperative MDRF ($y = 0.0048x - 0.065$ in Fig. 3B), equaling a value of 118 μm. Our calculations indicate that to maintain a patient's QOV, ERM surgery should be performed when the preoperative MDRF value is between 69 and 118 μm (Fig. 7). This range corresponds to stage 2 or higher in the staging classification by Govetto et al. (Fig. 3C).[18] Representative cases of ERM surgery that exhibited preoperative MDRF values between 69 and 118 μm and >118 μm are shown in Fig. 6. Further prospective studies are required to determine the effectiveness of this criterion.

The limitations of this study include its retrospective nature, the small sample size, and the relatively short follow-up period. Due to these limitations, although we found that the optimal timing for ERM surgery is when the MDRF is between 69-118 μm, there are some cases that do not meet this criterion. Therefore, we currently believe that it is important to consider both preoperative M-CHARTS score and the criterion of MDRF to determine the indication for ERM surgery. To improve this criterion, prospective cohort studies with a larger number of patients are needed. The other limitation of this study is that only metamorphopsia was examined and other symptoms of ERM, such as aniseikonia and decreased contrast sensitivity, were not evaluated.

In summary, we demonstrated that MDRF is useful as an objective and quantitative biomarker of metamorphopsia and that patients' QOV could be maintained if ERM surgery is performed when the preoperative MDRF is between 69 and 118 μm.

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Figure Legends

Fig. 1. Measurement of the parafoveal maximum depth of retinal folds (MDRF) using en face images. En face optical coherence tomography (OCT) images (**A**, **B**, **D**, **E**, **G**, and **H**) and B-scan OCT images (**C**, **F**, and **I**) at the internal limiting membrane (ILM) level (**A**, **B**, and **C**), 33.8 μm below the ILM level (**D**, **E**, and **F**), and 106.6 μm below the ILM level (**G**, **H**, and **I**), respectively are shown. The white line (**C**, **F**, and **I**) indicates the depth at which the en face OCT images（**A**, **B**, **D**, **E**, **G**, and **H**）were constructed. The dotted arrow (**B**) indicates the scan section of the B-scan images in **C**, **F**, and **I**. The white arrowheads（**B** and **C**) indicate the epiretinal membrane (ERM). The white dotted circle (**E**) indicates the parafoveal area, and the white arrows indicate the retinal folds caused by retinal traction due to ERM. The black arrow (**H** and **I**) indicates the deepest retinal fold in the parafoveal area. The deepest retinal fold disappeared in the en face OCT image constructed at a level deeper than that in this image. Therefore, MDRF in this case was 106.6 μm.

Fig. 2. Measurement of the amount of retinal vessel displacement after epiretinal membrane surgery. Pre- and postoperative en face optical coherence tomography (OCT) images (**A** and **E**), optical coherence tomography angiography (OCTA) images (**B** and **F**), superimposed images (**C** and **G**), and schematic diagrams (**D** and **H**), respectively. First,

select a fold cluster consisting of several retinal folds (surrounded by the white dotted line in **A**). Next, select two vessel branch points, P1 and P2; the selected fold cluster is located between these two vessel branch points, and the direction of the line segment connecting the two points is perpendicular to the long axis of the fold cluster (**B** and **C**). L is the distance between P1 and P2 (**D**). P1' and P2' (**F** and **G**) are the postoperative positions of P1 and P2, and L' is the distance between P1' and P2' (**H**). The difference in the distance between L and L' is defined as the amount of retinal vessel displacement.

Fig. 3. Relationships of the preoperative maximum depth of retinal folds (MDRF) with the pre- (**A**) or postoperative (**B**) M-CHARTS score and the epiretinal membrane stage (**C**). *$P < 0.05$.

Fig. 4. Time course of changes in the maximum depth of retinal folds (MDRF) (**A**) and the M-CHARTS score (**B**) after epiretinal membrane surgery. N.S., not significant; pre-op, preoperative; post-op, postoperative. *$P < 0.05$.

Fig. 5. Relationship between the change in the total retinal fold depth in the cluster of retinal folds and the amount of retinal vessel displacement after epiretinal membrane surgery.

Fig. 6. Representative cases involving a 69-year-old woman (**A**-**H:** case1) and a 71-year-old woman (**I**-**P:** case 2) who underwent epiretinal membrane (ERM) surgery are shown. The M-CHARTS scores before and at 6 months after surgery were 0.6 and 0 in case 1 and 1.6 and 1.3 in case 2, respectively, while the corresponding best-corrected visual acuity values were 20/50 and 20/20 in case 1 and in 20/17 and 20/17 case 2, respectively. Optical coherence tomography (OCT) images obtained before and at 6 months after surgery are shown. En face OCT images at the ILM level (**A**, **B**, **E**, **F**, **I**, **J**, **M**, and **N**), and en face OCT images obtained 20 μm below the internal limiting membrane (ILM) level (**C**, **G**, **K**, and **O**) are shown. The white dotted arrow (**B**, **F**, **J**, and **N**) indicates the scan section of the B-scan images (**D**, **H**, **L**, and **P**). The white arrowheads (**B**, **D**, **J**, and **L**) indicate ERM. The white arrows (C and K) indicate the retinal folds caused by ERM. The maximum depth of retinal folds was 91 μm in case 1 and 161.2 μm in case 2, respectively. The postoperative en face images (**E**, **F**, **M**, and **N**) and the B-scan image (H

and P) show that ERM was removed by surgery, with complete disappearance of the retinal folds. The black arrowheads (F and N) indicate the boundaries of ILM peeling.

Fig. 7. Optimal timing for epiretinal membrane (ERM) surgery based on pre- and postoperative metamorphopsia. MDRF, maximum depth of retinal folds.

Supplemental Digital Content 1. Video explaining how to measure the maximum depth of retinal fold with en face imaging.mp4

Fig. 1

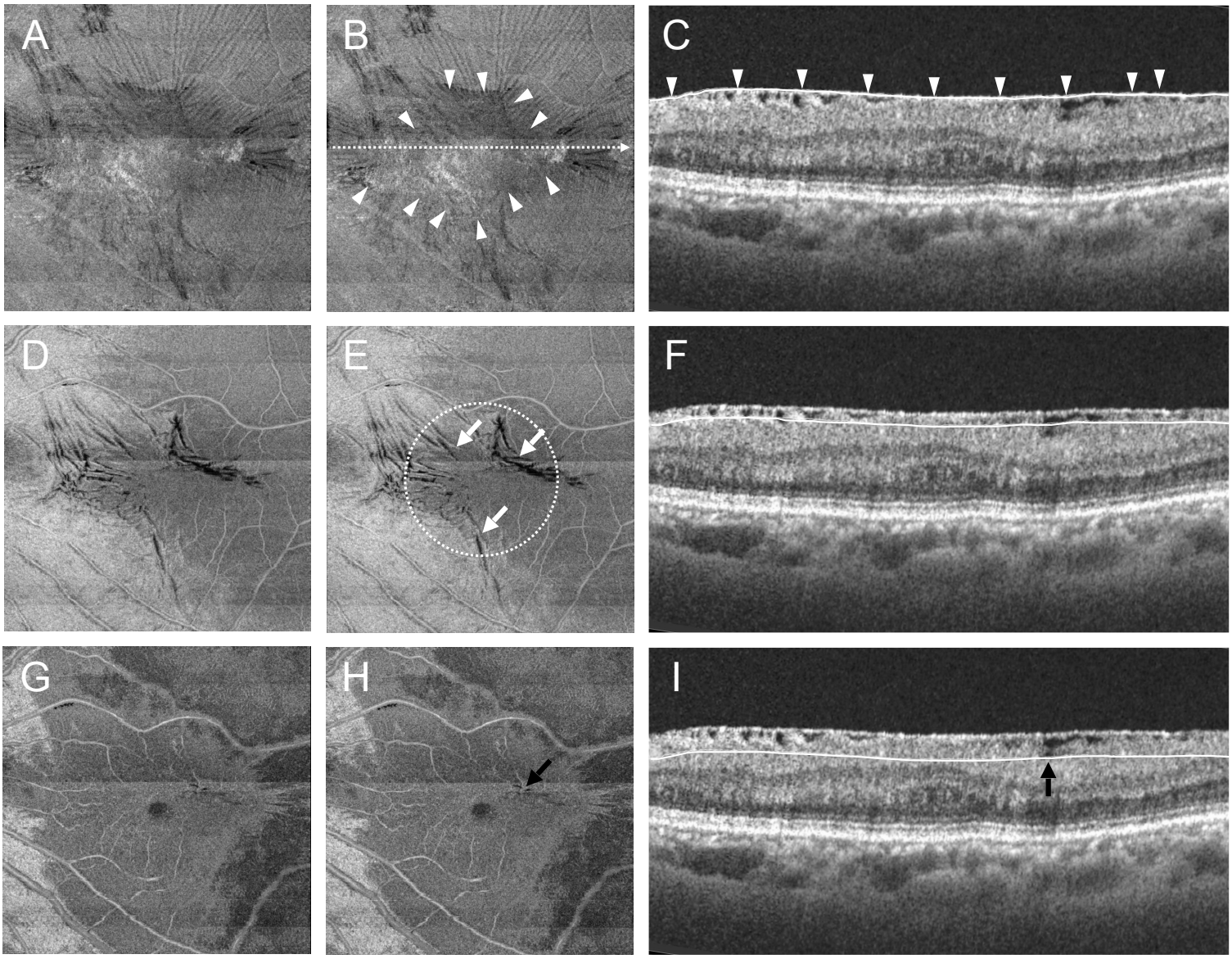


Fig. 2

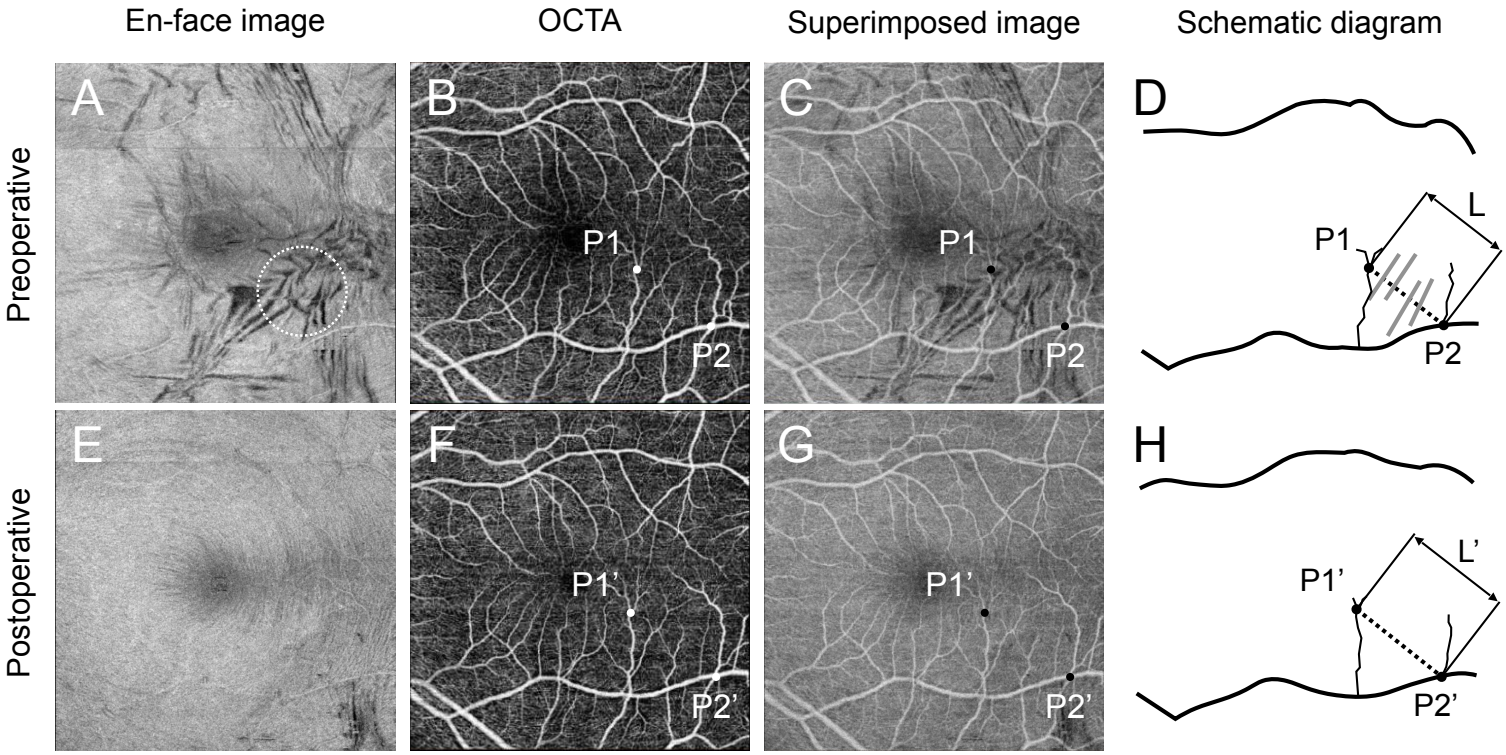

En-face image
OCTA
Superimposed image
Schematic diagram
Preoperative
Postoperative
A
B
C
D
E
F
G
H
P1
P2
P1'
P2'
L
L'

Fig. 3

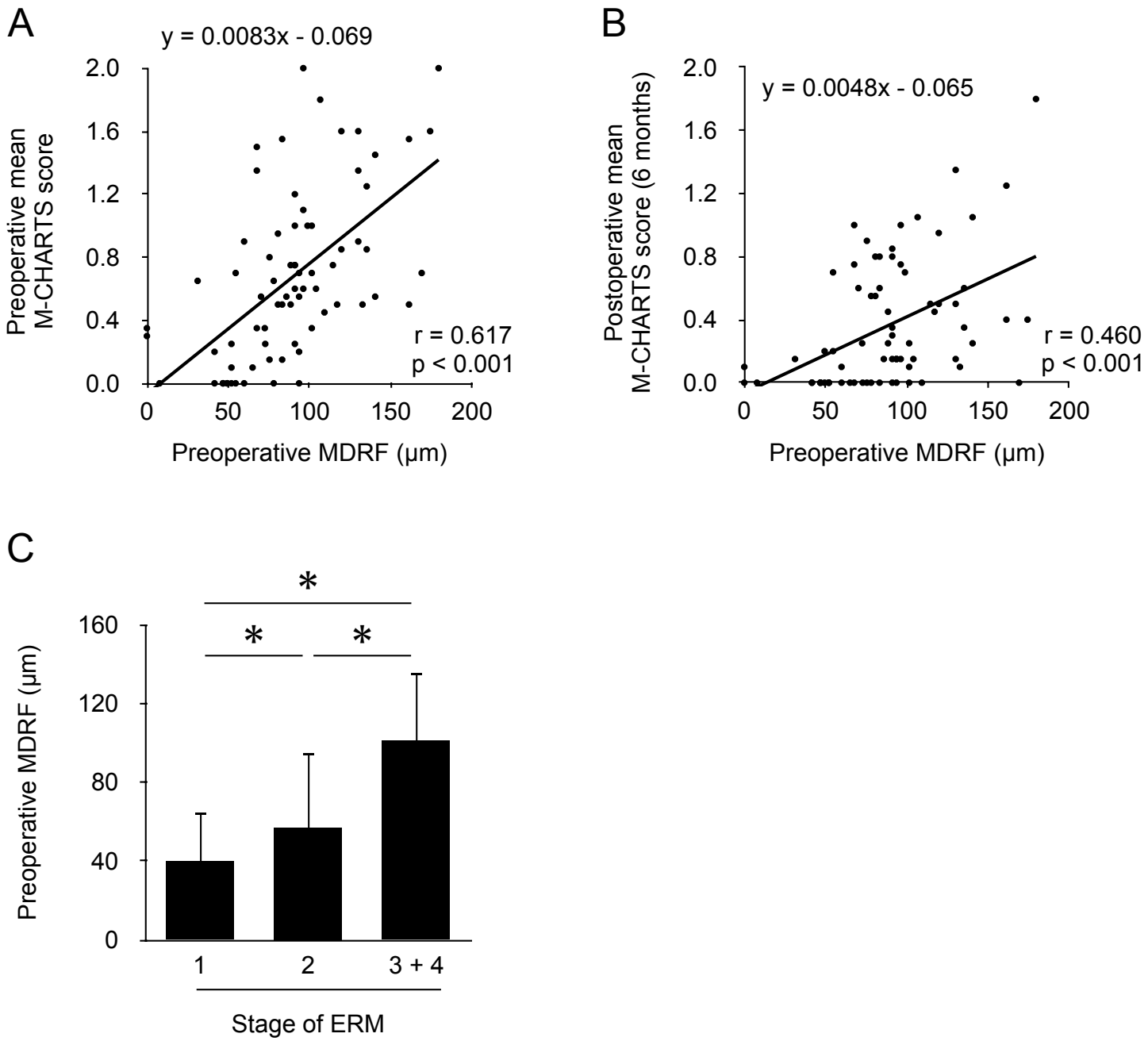

A
y = 0.0083x - 0.069
Preoperative mean M-CHARTS score
2.0
1.6
1.2
0.8
0.4
0.0
0
50
100
150
200
Preoperative MDRF (μm)
r = 0.617
p < 0.001
B
y = 0.0048x - 0.065
Postoperative mean M-CHARTS score (6 months)
2.0
1.6
1.2
0.8
0.4
0.0
0
50
100
150
200
Preoperative MDRF (μm)
r = 0.460
p < 0.001
C
*
*
*
Preoperative MDRF (μm)
160
120
80
40
0
1
2
3 + 4
Stage of ERM

Fig. 4

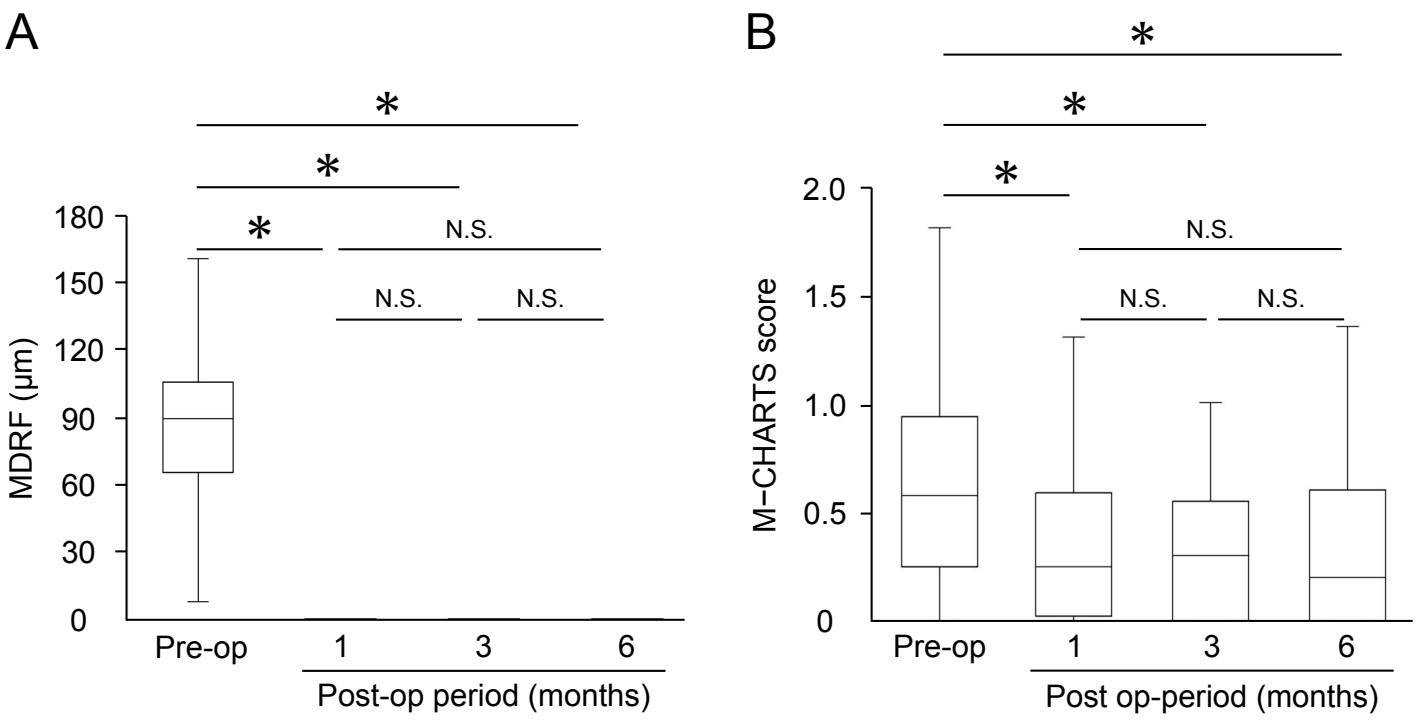

A
*
*
*
N.S.
N.S.
N.S.
180
150
120
90
60
30
0
MDRF (μm)
Pre-op
1
3
6
Post-op period (months)
B
*
*
*
N.S.
N.S.
N.S.
2.0
1.5
1.0
0.5
0
M−CHARTS score
Pre-op
1
3
6
Post op-period (months)

Fig. 5

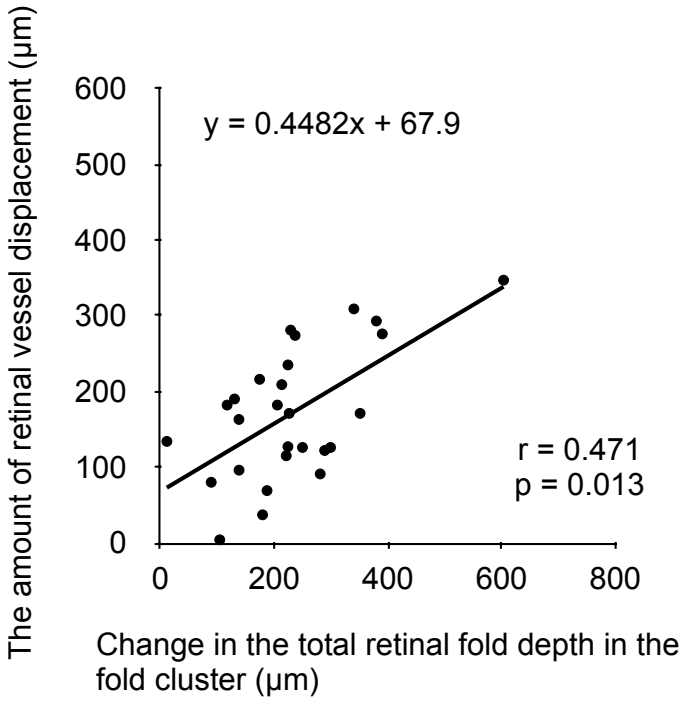

The amount of retinal vessel displacement (μm)
600
500
400
300
200
100
0
y = 0.4482x + 67.9
r = 0.471
p = 0.013
0
200
400
600
800
Change in the total retinal fold depth in the fold cluster (μm)

Fig. 6

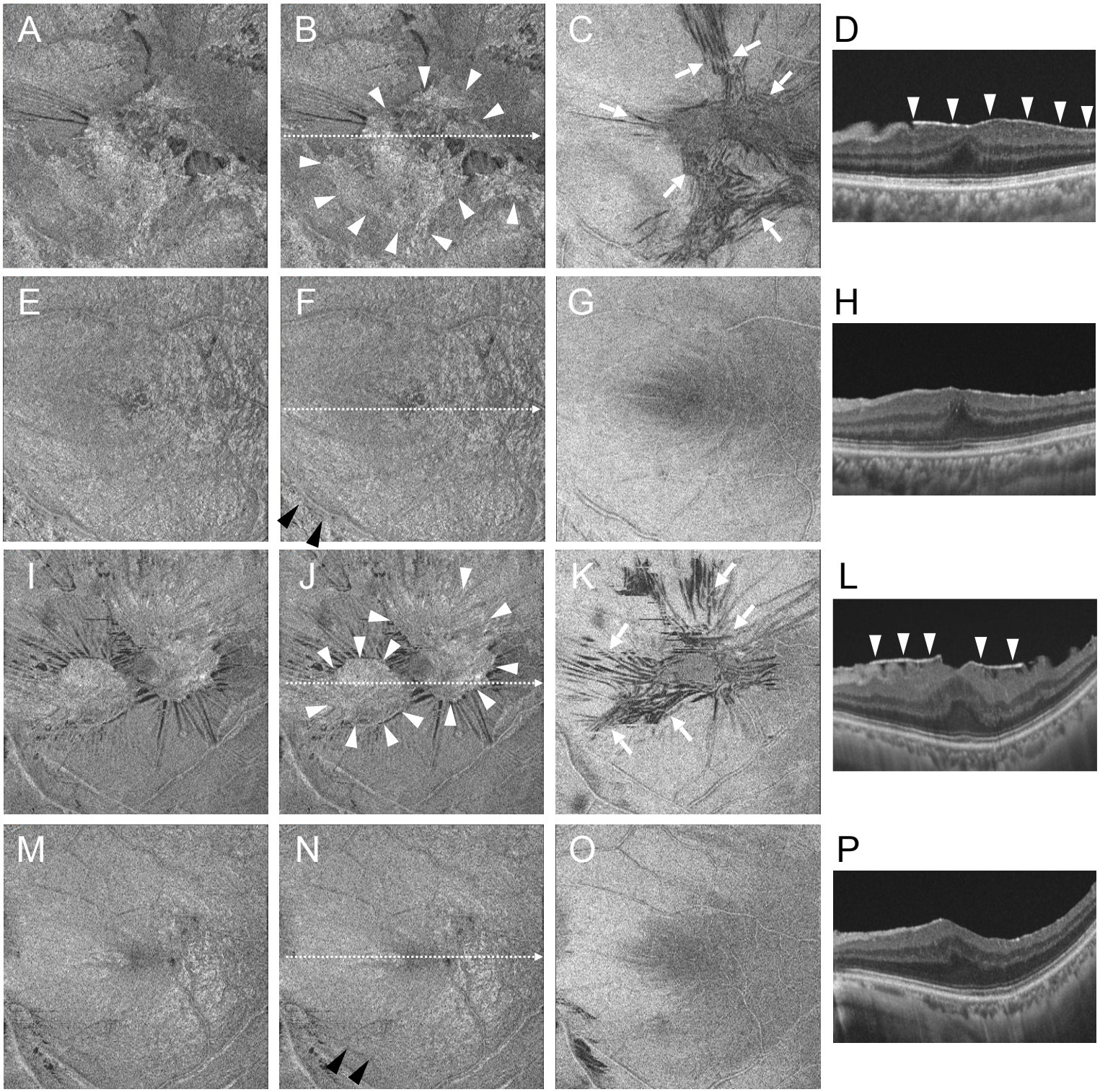
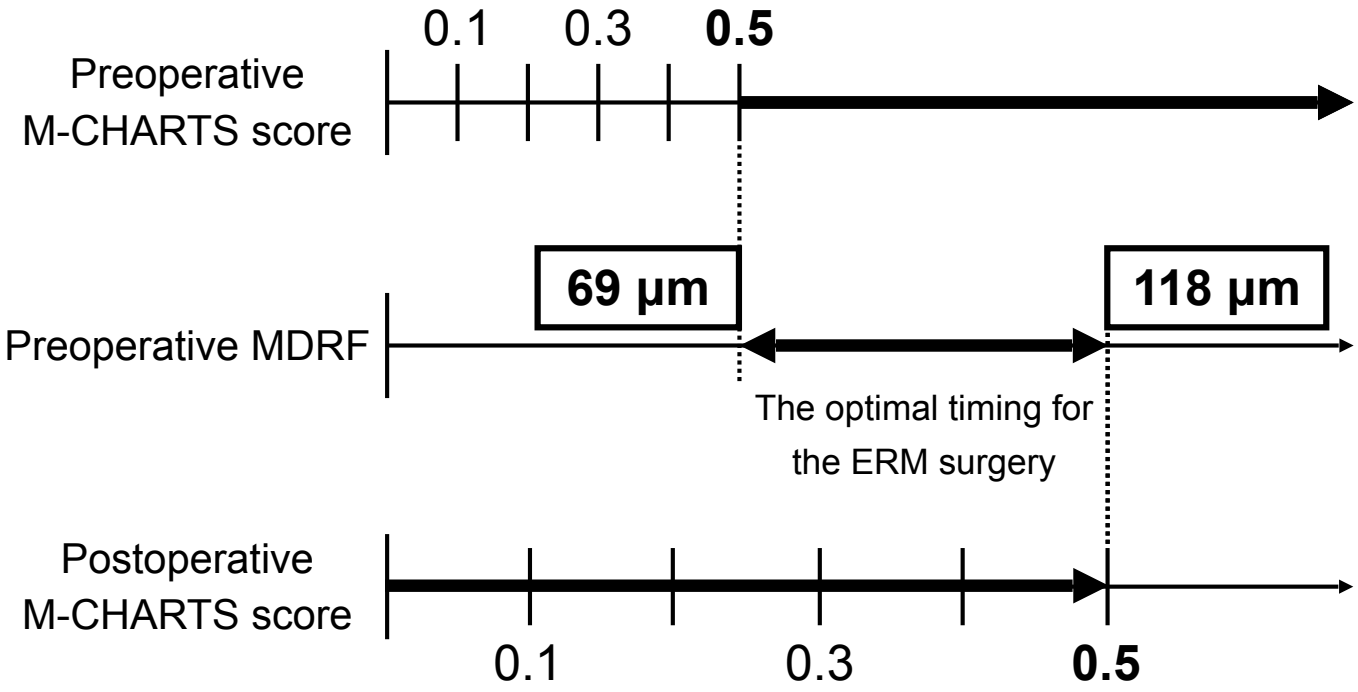


Fig. 7


0.1
0.3
0.5
Preoperative
M-CHARTS score
69 µm
118 µm
Preoperative MDRF
The optimal timing for
the ERM surgery
Postoperative
M-CHARTS score
0.1
0.3
0.5