Predictors of 3-month and 1-year visual outcomes after vitrectomy with subretinal tissue plasminogen activator injection for submacular hemorrhage

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SMH visual outcome after subretinal tPA

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Keywords
age-related macular degeneration, early displacement, macular hole, retinal macroaneurysm, submacular hemorrhage, subretinal tissue plasminogen activator, vitrectomy

Summary Statement
In eyes with submacular hemorrhage, visual acuity significantly improved 3 months after vitrectomy with subretinal tissue plasminogen activator injection. The 1-year visual acuity correlated with recurrence of submacular hemorrhage. Early displacement correlated with the contrast-to-noise ratio of submacular hemorrhage. Complicating macular holes (10%) could be closed via a second vitrectomy.

ABSTRACT

Purpose: To investigate factors associated with 3-month or 1-year best-corrected visual acuity (BCVA) after vitrectomy with subretinal tissue plasminogen activator (tPA) injection for submacular hemorrhage (SMH) and to identify the predictors of early displacement.

Methods: This prospective cohort study included consecutive eyes with SMH complicating neovascular age-related macular degeneration (nAMD) or retinal macroaneurysm (RMA) that underwent vitrectomy with subretinal tPA injection and were followed up for at least 3 months. We identified parameters correlated with 3-month BCVA, 1-year BCVA, and 2-week displacement grade (0–3).

Results: Twenty-nine eyes of 29 patients (73.1 ± 8.4 years; nAMD, 25 eyes) were included. Logarithm of the minimum angle of resolution (logMAR) BCVA improved 3 months after the surgery (baseline, 0.76 [20/115] ± 0.35; 3-month, 0.51 [20/65] ± 0.32; $P = 0.006$). In multivariable analyses, 1-year logMAR BCVA correlated with age ($P = 0.007$, $\beta = 0.39$) and SMH recurrence within 1 year after surgery ($P < 0.001$, $\beta = 0.65$). Two-week displacement grade correlated with the contrast-to-noise ratio (CNR) of SMH ($P = 0.001$, $\beta = -0.54$). Macular hole occurred in three eyes (10%) with small SMH size and was closed in all eyes via additional vitrectomy with an inverted internal limiting membrane flap technique.

Conclusions: The recurrence of SMH negatively affected the 1-year visual outcome after vitrectomy with subretinal tPA injection for SMH. The CNR was a useful predictor of early SMH displacement but not of 1-year BCVA. Further research is necessary to determine the optimal treatment to prevent SMH recurrence.

INTRODUCTION

Submacular hemorrhage (SMH) is one of the most severe vision-threatening complications. It mainly occurs in cases of neovascular age-related macular degeneration (nAMD), including its subtype of polypoidal choroidal neovascularization (PCV), and retinal macroaneurysm (RMA).[1] Subretinal hemorrhage is toxic to the photoreceptors and causes irreversible retinal destruction within 24 hours after onset in rabbit eyes.[2] In humans, a 24-month observation study showed that the best-corrected visual acuity (BCVA) worsened in 80% of the eyes with SMH, with a mean final BCVA of 20/1, 250 (range: 20/100 to light perception), indicating an extremely poor prognosis.[3]

Various treatments have been tried for SMH, including intravitreal gas injection with or without tissue plasminogen activator (tPA),[4-6] intravitreal anti-vascular endothelial growth factor (VEGF) injection,[7, 8] and pars plana vitrectomy with subretinal tPA, with or without air injection.[9-12] Each treatment has its advantages and disadvantages, and treatment is chosen according to the individual patient's status. The common goal of each treatment is disappearance or displacement of SMH from the macula as early as possible. Recently, it was reported that the contrast-to-noise ratio (CNR) of SMH, based on an optical coherence tomography (OCT) image, was a useful predictor of early displacement of SMH after simple intravitreal SF_6 gas injection.[6] We hypothesized that the CNR could be a predictor of displacement after vitrectomy with subretinal tPA injection and might affect the BCVA because it potentially represents the standing period of SMH or strength of its toxicity to the retina.

Some studies have demonstrated that the BCVA improved after vitrectomy with subretinal tPA injection.[11, 13, 14] However, to our knowledge, the effects of various parameters on long-term BCVA have not yet been determined. Thus, this study aimed to identify the predictors of early displacement among various parameters, including the CNR of SMH, and to investigate the factors associated with 3-month or 1-year BCVA after vitrectomy with subretinal tPA injection for SMH.

MATERIALS AND METHODS

This prospective cohort study was approved by the ethics committee of Kyoto University Graduate School of Medicine (Kyoto, Japan). All the study protocols adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from all participants.

Participants

This study included consecutive eyes with SMH involving the fovea, complicating nAMD or RMA, which underwent vitrectomy with subfoveal tPA injection by the same surgeon (M. Miyata) at Kyoto University Hospital between June 2018 and June 2022, and which were followed up for at least 3 months. Our policy was to select subretinal tPA injection for large SMH and poor BCVA. Prior to the surgery, we performed BCVA assessment using a Landolt chart, intraocular pressure measurement, slit-lamp biomicroscopy, fundus ophthalmoscopy, measurement of the axial length using partial coherence interferometry (IOLMaster®; Carl Zeiss Meditec, Dublin, USA), OCT (Spectralis®, Heidelberg Engineering, Heidelberg, Germany), and color fundus photography (TRC-NW8F, Topcon, Tokyo, Japan; and/or Optos® 200Tx or

California, Marlborough, USA). Patients were followed up postoperatively using the aforementioned examinations. The analyzed parameters were assessed 2 weeks (range, 1–2 weeks), 3 months (range, 2–3 months), and 1 year (range, 8 months–12 months) after surgery. We obtained the onset date from the patients' episodes and calculated the days between the onset and surgery as the disease duration. Furthermore, we obtained information regarding anticoagulant or antiplatelet drug intake.

The exclusion criteria were as follows: (1) thick sub-internal limiting membrane hemorrhage in the fovea that precludes obtaining analyzable OCT images around the fovea, (2) severe dementia preventing an adequate examination and prone position, or (3) no available OCT images or BCVA data 3 months after the surgery.

Treatments

As early as possible, we performed 27-gauge pars plana vitrectomy in the peripheral cortical gel with inducing posterior vitreous detachment using the Constellation Vision System® (Alcon Laboratories, Fort Worth, USA) under local anesthesia provided by 4% lidocaine eye drops and 2% lidocaine injection in the sub-Tenon's capsule; subsequently, subretinal injection of 0.1–0.3-mL (corresponding to 4,000–12,000 IU) monteplase (Cleactor®; Eisai Co, Tokyo, Japan) was administered via a 38-gauge cannula (PolyTip® Cannula 27g/38g, MedOne, Sarasota, USA) attached with a 15-cm high pressure extension tube (MedOne) and 1-mL silicon oil syringe (MicroDose™ Injector, MedOne) connecting the Constellation Vision System for all eyes. For the subretinal injection, we essentially inserted the cannula at a retinal site devoid of SMH and superior from the SMH after small-range internal limiting membrane (ILM) peeling as necessary. Subretinal air injections were additionally performed after the subretinal monteplase injection in consecutive eyes since April 2020. At the end of the surgery, intravitreal 25% SF6 gas injection was used to exchange air after a fluid/air exchange of approximately 50% of the vitreous cavity (Figure 1). In phakic eyes, phacoemulsification and intraocular lens implantation were performed prior to vitrectomy. We instructed the patients to maintain a prone position for 1 or 2 days after surgery. An intravitreal injection of an anti-VEGF agent, mainly 2 mg aflibercept (Eylea®, Bayer, Leverkusen, Germany), was administered intraoperatively or a few days after surgery, followed by a pro re nata regimen of anti-VEGF therapy or sometimes verteporfin photodynamic therapy (vPDT; Visudyne®, Novartis AG, Basel, Switzerland). When SMH recurred after the initial surgery, we performed either vitrectomy with subretinal monteplase and intravitreal 25% SF_6 gas injection, simple intravitreal injection of 0.4–0.6 mL 100% SF_6 gas without vitrectomy, or intravitreal anti-VEGF injection in accordance with the SMH status and patient's wishes. As a previous study also showed that low CNR of SMH and small SMH height on OCT images predicted good displacement using simple intravitreal SF6 gas injection,[6] we selected the treatment mainly based on the OCT images.

Morphological Analysis

Sensory foveal thickness, central retinal thickness (CRT), and central choroidal thickness (CCT) were measured via an OCT B-scan through the fovea using OCT

built-in software, by one investigator (M. Miki). Sensory foveal thickness was defined as the distance between the surface of the ILM and outer border of the sensory retina, excluding the SMH. CRT was defined as the distance between the ILM surface and outer border of the retinal pigment epithelium, including the SMH. CCT was defined as the distance between Bruch's membrane and outer border of the choroid. In accordance with a previous report,[11] preoperative SMH size was graded by one investigator (M. Miyata) as 1, small (within the arcades); 2, large (reaches the arcades); 3, extensive (beyond the arcades); and 4, massive (beyond the equator, involving two retinal quadrants, or both); furthermore, displacement of SMH was graded 2 weeks (range, 1–2 weeks) after surgery. Grade 0 represented almost no displacement; grade 1 represented displacement beyond the arcade and residual subretinal hemorrhage involving the fovea; grade 2 represented displacement beyond the arcade and residual subretinal hemorrhage within the arcade but not at the subfovea; and grade 3 represented displacement beyond the equator. The occurrence of complicating macular hole (MH) within 1 week postoperatively was recorded. Furthermore, SMH recurrence in the macular area within 3 months (0–3 months) and 1 year (0–12 months) post-surgery was recorded.

Contrast-to-Noise Ratio

As previously reported,[6] we analyzed the gray value of the SMH region beneath the fovea to that of the vitreous cavity region in an OCT image taken through the fovea, using ImageJ (National Institutes of Health, Bethesda, MD) (Figure 2) and calculated the CNR using the following formula (1):

$$\mathrm{CNR} = (f - b)/\sqrt{{\delta_f}^2 + {\delta_b}^2} \quad , \ldots (1)$$

where f and b are the mean gray values of the foreground (SMH) and background (vitreous cavity), respectively. δf and δb are standard deviations. CNR may represent the solidity of SMH. A lower CNR correlated with early displacement of the SMH after simple intravitreal SF_6 gas injection.

Statistical Analysis

Data are presented as means ± standard deviations, where applicable. We converted BCVA into the logarithm of the minimum angle of resolution (logMAR) values for analyses. BCVA of counting fingers, hand motion, light perception, and no light perception were arbitrarily assigned logMAR values of 2.6, 2.7, 2.8, and 2.9, respectively in accordance with a previous report.[15] Two unpaired comparative analyses were performed using the Mann−Whitney U test, chi-square test, or chi-square trend test where applicable. The change in logMAR BCVA at baseline, 2 weeks, 3 months, and 1 year after surgery was analyzed using analysis of variance (ANOVA) with repeated measures and post hoc analysis with Bonferroni correction. Univariable correlation analyses between the 3-month or 1-year logMAR BCVA and the studied parameters were performed using Spearman's correlation coefficient. Furthermore, correlation between the 2-week displacement grade and baseline or intraoperative parameters was analyzed using Spearman's correlation coefficient. Multivariable correlation analyses were performed using 3-month or 1-year logMAR

BCVA or 2-week displacement as the dependent variable and studied parameters with *P*-values <0.10 in Spearman's correlation coefficient analyses as the independent variables. All statistical analyses were conducted using SPSS (version 27.0; IBM, Armonk, NY, USA). Statistical significance was set at *P* <0.05.

RESULTS

In total, 29 eyes of 29 patients (age, 73.1 ± 8.4 years) were examined, after excluding two eyes with thick subILM hemorrhage, two eyes of patients with severe dementia, and 12 eyes with insufficient data (Table 1). Among them, 24 eyes of 24 patients were observed for 1 year after surgery. Disease duration from onset to surgery was 12.7 ± 14.4 days (range, 1–69 days). SMH was associated with nAMD in 25 eyes and RMA in four eyes. The number of eyes with SMH size of 1 (small), 2 (large), 3 (extensive), and 4 (massive) was nine, 14, five, and one, respectively. Anticoagulant or antiplatelet drug intake was associated with eight eyes (28%). According to ANOVA with repeated measures, logMAR BCVA improved significantly during the 1-year observation period (baseline, 0.76 [Snellen equivalent, 20/115] ± 0.35; 2-week, 0.84 [20/138] ± 0.53; 3-month, 0.51 [20/65] ± 0.32; and 1-year, 0.59 [20/78] ± 0.65; *P* = 0.024) in the 24 eyes with 1-year follow-up. Post hoc analyses with Bonferroni correction revealed that the 3-month BCVA improved compared to baseline BCVA (*P* = 0.006) and 2-week BCVA (*P* = 0.01). However, the 1-year BCVA did not differ from baseline BCVA (*P* >0.999). Intraoperative subretinal air injection was performed in 16 consecutive eyes from April 2020, except for one eye in which MH was observed before the air injection and after tPA injection. SMH recurred in three (10%) of 29 eyes within 3 months and in five (17%) of 24 eyes within 1 year after surgery. There were no significant differences in baseline or intraoperative parameters between eyes with and without recurrence within 1 year after the initial surgery (Supplementary Table). We performed subretinal tPA reinjection, simple intravitreal SF_6 gas injection, and anti-VEGF therapy for one, two, and two eyes, respectively. In all eyes, SMH disappeared at the 1-year time-point after the initial surgery.

In univariable analyses, the 3-month logMAR BCVA correlated with age (*P* = 0.02, r = 0.45), baseline logMAR BCVA (*P* = 0.009, r = 0.48), and baseline sensory foveal thickness (*P* = 0.01, r = −0.46); in multivariable analyses, it correlated with age (*P* = 0.008, β = 0.45), SMH size (*P* = 0.04, β = −0.38), and anticoagulant or antiplatelet drug intake (*P* = 0.03, β = −0.34) (Table 2). In univariable analyses, 1-year logMAR BCVA correlated with age (*P* = 0.008, r = 0.53), SMH recurrence within 3 months after surgery (*P* = 0.01, r = 0.50), and SMH recurrence within 1 year after surgery (*P* = 0.002, r = 0.61), and in multivariable analyses, it correlated with age (*P* = 0.007, β = 0.39) and SMH recurrence within 1 year after surgery (*P* <0.001, β = 0.65) (Table 2). Furthermore, in univariable analyses, 2-week displacement grade correlated with age (*P* = 0.02, r = −0.43) and CNR (*P* = 0.001, r = −0.61), and in multivariable analyses, it correlated with CNR (*P* = 0.001, β = −0.54) (Table 3).

Regarding intraoperative or early-postoperative complications, MH occurred in three eyes (10%). In all of them, the associated disease was nAMD. Although the sample size of the MH group was too small, SMH size was significantly smaller in the MH-group compared to the no-MH group (*P* = 0.02, Table 4). In all three eyes

with MH, the MH was not closed only by maintaining the prone position for several days after the initial surgery; however, it was closed in all three eyes within a few days of additional vitrectomy with an inverted ILM flap technique and intravitreal SF_6 gas tamponade. Additionally, macula-on rhegmatogenous retinal detachment occurred in one eye 10 days after the initial surgery as other severe complications. However, it was attached via vitrectomy.

DISCUSSION

This study showed that BCVA improved significantly 3 months after vitrectomy with subretinal tPA injection for SMH and that the 1-year BCVA correlated with SMH recurrence, whereas the 3-month BCVA did not. Despite intraoperative or immediate postoperative administration of anti-VEGF therapy for nAMD, SMH recurred in some patients. A previous study suggested that SMH occurred regardless of the timing of anti-VEGF therapy and was likely to be the result of mechanisms other than loss of effective VEGF inhibition.[16] Although SMH is difficult to control, it is important to maintain BCVA during the long-term period. Further studies are necessary to determine the best treatment for preventing SMH recurrence after surgery.

Our findings showed that the recurrence of SMH was the key point to follow up in patients after vitrectomy with subretinal tPA injection. We considered how recurrence could be prevented and the response required in the event of recurrence. First, adequate control of the cause could prevent recurrence. For PCV, the most common cause of SMH,[1] regression of polypoidal lesions is desirable, because cluster type PCV (many polypoidal lesions) poses a high risk of SMH (hazard ratio [HR], 3.4).[17] The EVEREST II study compared 24-month treatment outcomes between anti-VEGF monotherapy and vPDT combined with anti-VEGF therapy; the combination therapy was superior to monotherapy in terms of complete polypoidal lesion regression (56.6% vs. 26.7%, P <0.001).[18] It was also reported that vPDT followed by anti-VEGF therapy reduced the risk of SMH (HR, 0.24) as compared to PDT (HR, 0.65) or anti-VEGF therapy alone (HR, 0.41).[17] Thus, employing vPDT with anti-VEGF therapy as early as possible may be effective in reducing the risk of recurrence in the quiescent phase after anti-VEGF monotherapy. In regard to RMA, a previous study showed that photocoagulation and anti-VEGF therapy were effective in RMA regression;[19] however, there is no literature comparing the treatment methods. Secondly, what should we do, if SMH recurs? To the best of our knowledge, no recent study has focused on the treatment of SMH recurrence. We considered that SMH recurrence should be treated in the same manner as that for initial SMH because the treatment objective remains the same, that is, protecting the macula from hemorrhagic toxicity. We performed subretinal tPA reinjection, simple intravitreal SF6 gas injection, and anti-VEGF therapy for one, two, and two recurrent eyes, respectively. Although SMH disappeared at the 1-year time-point in all eyes, the visual outcome was not desirable. The validity of treatments based on our policy is unclear. Since these are the results of a small case-series, further large cohort studies are necessary on treatments for SMH recurrence.

In three of 29 eyes (10%), MH occurred after surgery in the present study. The MH occurrence rate was similar to that in previous reports (4/22, 18%[20]; 1/24, 4%[11]). The latter study suggested administering the subretinal injection closer to the inferior arcade, with the injection directed toward the inferior retina to prevent MH.[11]

Another report claimed that a relatively small SMH had a high risk of MH.[12] We found that small SMH size was a risk factor for MH. Furthermore, although the MH group's sample size was too small (n = 3), the duration from onset to surgery was longer in the MH group than in the no-MH group (26.7 ± 36.7 vs 11.1 ± 9.9 days) and sensory foveal thickness was thinner in the MH group than in the no-MH group (73.0 ± 30.9 vs 102.7 ± 78.6 μm). A long disease duration or thin fovea may thus be risk factors for MH. However, there is no need for hesitation in performing vitrectomy with subretinal tPA injection for fear of complicating MH, even in eyes with high risk, because additional vitrectomy can achieve MH closure, as shown in all eyes with MH in our study and in a previous report;[20] furthermore, MH occurrence did not correlate with 3-month or 1-year BCVA.

Unexpectedly, the baseline CNR of the SMH did not correlate significantly with postoperative BCVA (3-month, $P = 0.96$; 1-year, $P = 0.60$). However, CNR correlated significantly with the 2-week displacement of SMH. A previous report of simple intravitreal SF_6 gas injection showed that the 1-week displacement grade correlated with CNR and SMH height.[6] In our study, the 2-week displacement grade similarly correlated with CNR, but not with CRT, including the SMH height. To predict early displacement of SMH after vitrectomy with subretinal tPA injection, CNR was useful, regardless of the SMH height.

In the present study, unexpectedly, subretinal air injection was not significantly correlated with 2-week displacement ($P = 0.51$, r =0.13). Previous reports showed the effectiveness of subretinal air injection for displacement of SMH from the fovea.[10, 11] We also experienced good displacement of SMH to the equator via subretinal air injection in most cases. However, in some cases, tPA injected far from the fovea might not reach the subfoveal clot because the clot around the subfovea was too solid. For eyes with high CNR, which represents SMH solidity, subretinal air injection might not be effective for SMH displacement from the fovea because the subfoveal clot might not be dissolved sufficiently. Subretinal air injection plays an important role in making a path from the macula to the equator; expands the retinal detachment and creates space for the displaced SMH. It might be difficult to displace a subfoveal clot with high CNR regardless of using subretinal air injection. Further large cohort studies are necessary.

This study has some limitations. First, the sample size was small. SMH requiring vitrectomy with subretinal tPA injection is quite rare.[21] A retrospective study showed that the incidence rate of SMH with loss of vision was 1 per 1,283 intravitreal anti-VEGF injections (0.08%).[22] A larger sample size might convert some parameters with marginal significance to those with significance. Second, we started giving additional subretinal air injection part way through the study. However, we have routinely performed this treatment since April 2020; therefore, selection bias should be small. Third, five patients (17%) dropped out 1 year from 3 months after surgery. There might be patients with a good course among the patients who dropped out. Fourth, we measured BCVA using a Landolt chart and not the standardized ETDRS chart. Thus, the BCVA values might be slightly different between the present study and those from previous studies. Fifth, grading was performed by one investigator. Ideally, two investigators should independently judge the grade and a third senior grader should provide the final judgement when the two investigators disagree. Sixth, we considered nAMD and RMA together as the associated diseases.

However, the associated disease did not correlate with 1-year BCVA (P = 0.57) or 2-week displacement (P = 0.10).

In conclusion, SMH recurrence negatively affected the 1-year visual outcomes after vitrectomy with subretinal tPA injection for SMH. The CNR was a useful predictor of early SMH displacement but not of 1-year BCVA. Further research is necessary to determine the optimal treatment to prevent SMH recurrence.

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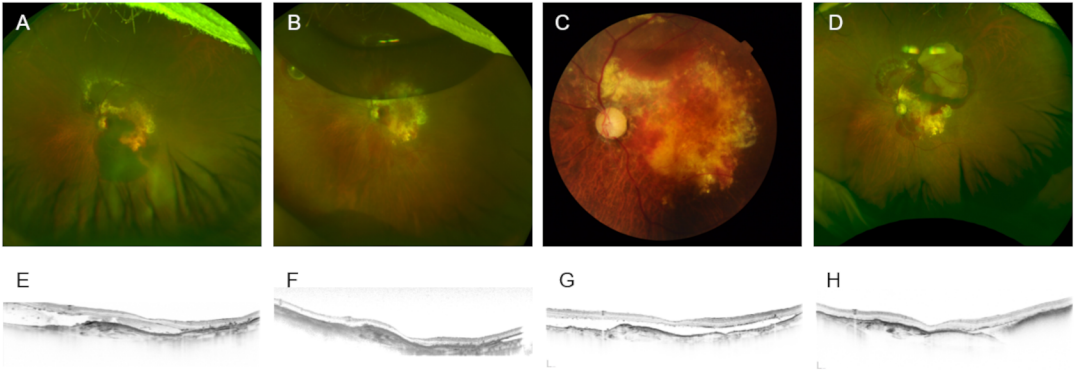
FIGURE LEGENDS

Figure 1. Representative images of recurrence of submacular hemorrhage.
Color fundus photography (A–D) and optical coherence tomography (OCT) (E–H) images of the left eye of a woman in her 70s.
(A, E) Images obtained preoperatively. Submacular hemorrhage (SMH) involving the fovea is visible and the contrast-to-noise ratio (SMH) is low. Best-corrected visual acuity (BCVA) was 20/133.
(B, F) Images obtained 2 days after surgery. The SMH is displaced beyond the fovea. Residual subretinal air is visible at the nasal upper midperiphery. An intravitreal injection of 2 mg aflibercept was administered.

(C, G) Images 2.5 months after the surgery and 1 month after verteporfin photodynamic therapy with intravitreal injection of 0.5 mg ranibizumab. Subretinal fluid is observed; however, the SMH appears to be disappearing. BCVA improved to 20/40.
(D, H) Images 6 months after surgery. Submacular hemorrhage recurred in the macular area. BCVA worsened to 20/100. One-year BCVA was 20/667.

Figure 2. Analysis of contrast-to-noise ratio of submacular hemorrhage to the vitreous cavity.
We analyzed the gray value of the submacular hemorrhage region beneath the fovea (within the red circle) to that of the vitreous cavity region (within the green square) in an optical coherence tomography image through the fovea using ImageJ software.


A
B
C
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H

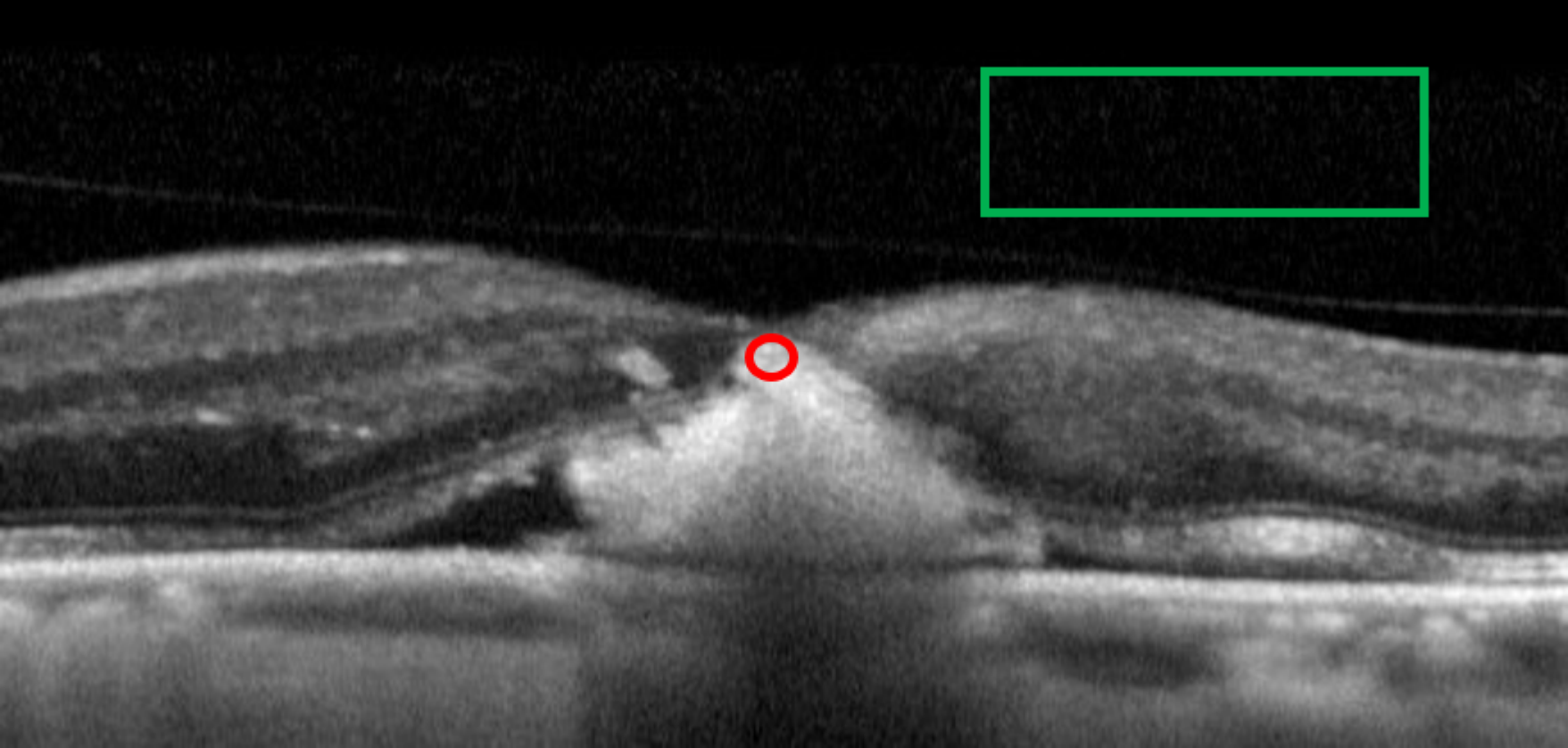

Table 1. Participants' characteristics		
Eyes, n (patient, n)		29 (29)
Age at surgery, years (range)		73.1 ± 8.4 (56–91)
Male sex, n (%)		14 (48)
Axial length, mm (range)		24.15 ± 0.65 (21.73–28.72)
Disease duration (onset–surgery date), days (range)		12.7 ± 14.4 (1–69)
LogMAR BCVA (Snellen)	Baseline	0.82 (20/132) ± 0.40
	2-week	0.85 (20/142) ± 0.52
	3-month	0.56 (20/73) ± 0.32
	1-year[a]	0.59 (20/78) ± 0.65
Associated disease, nAMD/RMA, n		25/4
Sensory foveal thickness at baseline, μm		99.6 ± 75.3
CRT at baseline, μm		630.5 ± 288.0
CCT at baseline, μm		215.4 ± 103.6
CNR of SMH at baseline		16.5 ± 12.5
SMH size, 1/2/3/4, n		9/14/5/1
Anticoagulant or antiplatelet drug intake, n (%)		8 (28)
Complicating MH occurrence, n (%)		3 (10)
Subretinal air injection, n (%)		16 (55)
Displacement grading 2 weeks after surgery, 0/1/2/3, n		0/6/3/20
SMH recurrence within 3 months after surgery, n (%)		3 (10)
SMH recurrence within 1 year after surgery, n (%)[a]		5 (17)

Data are presented as means ± standard deviations where applicable.
logMAR BCVA = logarithm of the minimal angle of resolution best-corrected visual acuity; nAMD = neovascular age-related macular degeneration; RMA = retinal macroaneurysm; CRT = central retinal thickness; CCT = central choroidal thickness; CNR = contrast-to-noise ratio; SMH = submacular hemorrhage; MH = macular hole
SMH size: 1, small (within the arcades); 2, large (reaches the arcades); 3, extensive (beyond the arcades); 4, massive (beyond the equator, involving two retinal quadrants, or both)
[a] Data for 1-year logMAR BCVA are missing for five eyes.

Table 2. Correlation between 3-month or 1-year logMAR BCVA and the studied parameters

	3-month (n = 29)				1-year (n = 24)			
	Univariable Analysis		Multivariable Analysis		Univariable Analysis		Multivariable Analysis	
	P	r	*P*	β	*P*	r	*P*	β
Age	0.02*	0.45	0.008*	0.45	0.008*	0.53	0.007*	0.39
Sex (1, male; 2, female)	0.75	0.63	-	-	0.65	−0.10	-	-
Axial length	0.08	−0.33	0.16	−0.19	0.39	−0.18	-	-
Disease duration (onset ~ surgery date)	0.79	−0.53	-	-	0.17	−0.29	-	-
LogMAR BCVA at baseline	0.009*	0.48	0.19	0.25	0.37	0.19	-	-
Associated disease (1, RMA; 2, nAMD)	0.03*	−0.41	0.75	−0.05	0.57	−0.12	-	-
Sensory foveal thickness at baseline	0.01*	−0.46	0.94	−0.01	0.30	−0.22	-	-
CRT at baseline	0.51	0.13	-	-	0.70	−0.08	-	-
CCT at baseline	0.78	0.53	-	-	0.18	−0.29	-	-
CNR at baseline	0.96	−0.01	-	-	0.60	−0.11	-	-
SMH size	0.06	−0.36	0.04*	−0.38	0.90	0.03		
Anticoagulant or antiplatelet drug intake	0.06	−0.35	0.03*	−0.34	0.16	−0.30	-	-
MH (0, no; 1, complicating)	0.97	0.07	-	-	0.15	−0.31	-	-
Subretinal air injection (0, no; 1, performed)	0.26	−0.22	-	-	0.78	−0.06	-	-
Displacement grading 2 weeks after the surgery	0.16	−0.27	-	-	0.16	−0.30	-	-
SMH recurrence within 3 months after the surgery (0, absent; 1, present)	0.29	0.21	-	-	-	-	-	-
SMH recurrence within 1 year after the surgery (0, absent; 1, present)	-	-	-	-	0.002*	0.61	<0.001*	0.65

logMAR BCVA = logarithm of the minimal angle of resolution best-corrected visual acuity; RMA = retinal macroaneurysm; nAMD = neovascular age-related macular degeneration; CRT = central retinal thickness; CCT = central choroidal thickness; CNR = contrast-to-noise ratio; SMH = submacular hemorrhage; MH = macular hole;
* Statistically significant (*P* <0.05)

Table 3. Correlation between 2-week displacement and the baseline or intraoperative parameters (n = 29)

	Univariable Analysis		Multivariable Analysis	
	P	**r**	***P***	**β**
Age	0.02*	−0.43	0.08	−0.29
Sex (1, male; 2, female)	0.37	0.17	-	-
Axial length	0.22	−0.24	-	-
Disease duration (onset–surgery date)	0.76	−0.06	-	-
LogMAR BCVA at baseline	0.052	−0.36	0.27	−0.18
Associated disease (1, RMA; 2, nAMD)	0.10	0.31	-	-
Sensory foveal thickness at baseline	0.87	0.03	-	-
CRT at baseline	0.79	0.05	-	-
CCT at baseline	0.63	0.09	-	-
CNR at baseline	0.001*	−0.61	0.001*	−0.54
SMH size	0.34	−0.19	-	-
Anticoagulant or antiplatelet drug intake	0.48	−0.14	-	-
MH (0, no; 1, complicating)	0.24	0.22	-	-
Subretinal air injection (0, no; 1, performed)	0.51	0.13	-	-

logMAR BCVA = logarithm of the minimal angle of resolution best-corrected visual acuity; RMA = retinal macroaneurysm; nAMD = neovascular age-related macular degeneration; MH = macular hole; CRT = central retinal thickness; CCT = central choroidal thickness; CNR = contrast-to-noise ratio; SMH = submacular hemorrhage

* Statistically significant (P <0.05)

Table 4. Differences in baseline or intraoperative parameters between the no-MH and MH groups (n = 29)

	no-MH Group	MH Group	*P*-value
Eyes, n	26	3	
Age, years	65.1 ± 5.3	57.4 ± 9.6	0.33
Male sex, n (%)	12 (46)	2 (67)	0.50†
Axial length, mm	24.13 ± 1.59	24.36 ± 1.10	0.62
Disease duration (onset–surgery date), days	11.1 ± 9.9	26.7 ± 36.7	0.61
LogMAR BCVA at baseline	0.85 ± 0.40	0.51 ± 0.43	0.17
Association disease, nAMD/RMA	22/4	3/0	0.46†
Sensory foveal thickness, μm	102.7 ± 78.6	73.0 ± 30.9	0.57
CRT, μm	625.6 ± 294.3	673.0 ± 274.7	0.62
CCT, μm	217.4 ± 108.0	198.3 ± 64.0	0.94
CNR	17.0 ± 12.9	12.5 ± 9.4	0.39
SMH size, 1/2/3/4, n	6/14/5/1	3/0/0/0	0.02*††
Anticoagulant or antiplatelet drug intake, n (%)	6 (23)	2 (67)	0.18†
Subretinal air injection, n (%)	14 (54)	2 (67)	0.67†

Data are presented as means ± standard deviations where applicable.
MH = macular hole; logMAR BCVA = logarithm of the minimal angle of resolution best-corrected visual acuity; CRT = central retinal thickness; CCT = central choroidal thickness; CNR = contrast-to-noise ratio; SMH = submacular hemorrhage; RMA = retinal microaneurysm; nAMD = neovascular age-related macular degeneration.
SMH size: 1, small (within the arcades); 2, large (reaches the arcades); 3, extensive (beyond the arcades); 4, massive (beyond the equator, involving two retinal quadrants, or both)
†, chi-square test; ††, chi-square trend test; the others, Mann–Whitney U test
*Statistically significant (P <0.05)

Supplementary Table. Differences in baseline or intraoperative parameters between eyes with and without recurrence within 1 year after the initial surgery (n = 24)

	Eyes with recurrence	Eyes without recurrence	*P*-value
Eyes, n	5	19	
Age, years	75.4 ± 9.8	71.7 ± 8.4	0.49
Male sex, n (%)	3 (60)	10 (53)	0.77†
Axial length, mm	23.81 ± 0.55	24.22 ± 1.74	0.78
Disease duration (onset–surgery date), days	5.2 ± 4.1	15.6 ± 16.8	0.09
LogMAR BCVA at baseline	0.88 ± 0.20	0.73 ± 0.37	0.37
Associated disease, nAMD/RMA	5/0	18/1	0.60†
Sensory foveal thickness, μm	102.2 ± 94.1	106.3 ± 79.6	0.63
CRT, μm	534.8 ± 326.4	628.7 ± 270.6	0.41
CCT, μm	162.2 ± 73.5	238.3 ± 115.6	0.24
CNR	18.6 ± 16.0	16.9 ± 13.1	0.84
SMH size, 1/2/3/4, n	0/3/1/1	6/10/3/0	0.09††
Anticoagulant or antiplatelet drug intake, n (%)	1 (20)	6 (32)	0.61†
Subretinal air injection, n (%)	4 (80)	10 (53)	0.27†

Data are presented as means ± standard deviations where applicable.
MH = macular hole; logMAR BCVA = logarithm of the minimal angle of resolution best-corrected visual acuity; CRT = central retinal thickness; CCT = central choroidal thickness; CNR = contrast-to-noise ratio; SMH = submacular hemorrhage; RMA = retinal microaneurysm; nAMD = neovascular age-related macular degeneration.
SMH size: 1, small (within the arcades); 2, large (reaches the arcades); 3, extensive (beyond the arcades); 4, massive (beyond the equator, involving two retinal quadrants, or both)
†, chi-square test; ††, chi-square trend test; the others, Mann–Whitney U test
*Statistically significant (P <0.05)