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Predicting Visual Recovery in Long-Standing Macular Holes: Surgical Strategies and Role of Optical Coherence Tomography Biomarkers

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Background: Macular hole (MH) duration is a prognostic indicator of posttreatment visual outcomes. The aim was to evaluate chronic (≥12 months) MH treatment using extended internal limiting membrane (ILM) peeling.

Material/Methods: Medical records of patients with chronic MH treated with pars plana vitrectomy, ILM peeling (up to vascular arcades), and 20% SF_6 tamponade were reviewed. Spearman correlation coefficient (*r*) examined relationships between MH duration and best-corrected visual acuity (BCVA).

Results: Fifty patients were included (72.0% women; mean age, 73 years); mean (SD) MH duration was 19.1 (8.8) months. Most (76.0%) patients had a preoperative MH diameter >400 µm (mean [SD], 569.2 [164.6] µm). The MH was closed within 1 week in 46 (92.0%) patients. A significant improvement from baseline in BCVA was observed by month 1 after treatment (mean [SD] logMAR, 0.96 [0.38] vs 0.66 [0.25]; $P<0.001$). A moderate positive correlation was observed between MH duration and posttreatment BCVA (logMAR; $r=0.40$; $P<0.01$). Improvements in mean logMAR values through month 24 were similar when patients were stratified by MH diameter (≤400 vs >400 µm; $P>0.05$; all time points). Significant differences between patients with baseline MH diameter of ≤650 µm vs >650 µm were observed for BCVA (logMAR; $P\leq0.03$; all time points).

Conclusions: Twenty-four month follow-up revealed a steady increase in visual acuity, with no symptom worsening. Vitrectomy, extended ILM peeling, and gas tamponade is effective for chronic MH closure, including for holes of up to 650 µm in diameter. A MH diameter >650 µm was associated with poorer BCVA results after treatment.

Keywords: **Ophthalmologic Surgical Procedures • Retinal Perforations • Visual Acuity • Vitrectomy**

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Introduction

A macular hole is a full-thickness retinal defect in the fovea that decreases visual acuity, and it has an estimated annual age-adjusted incidence of approximately 8 per 100 000 individuals [1,2]. Macular holes typically occur in the elderly, more often in women, and can lead to substantial central visual impairment (ie, blurry/distorted vision) [1,3]. This condition negatively affects patient quality of life, including the inability to perform daily tasks, such as reading and driving [3], and can result in decreased independence, social interactions, and personal- and work-related productivity (ie, economic impact). Since the introduction in 1991 of vitrectomy with gas tamponade to repair macular holes [4], the use of vitrectomy with internal limiting membrane (ILM) peeling and gas tamponade has been considered a standard technique, providing high success rates of more than 85% [5-7]. However, several prognostic indicators have been identified that can negatively affect visual outcomes during treatment of macular holes, including large preoperative size (>400 µm) [8], longer duration of the condition, high myopia, and trauma-related etiology [6,9-14]. For example, in the European Vitreoretinal Society macular hole study, including 4138 eyes, the anatomical closure success rate was higher for smaller full-thickness macular holes (eg, stages 1 or 2 vs stage 3; odds ratio=0.35, P=0.001) and for those of shorter duration (not defined; odds ratio=0.94, *P*<0.001) [6].

Additional techniques have been introduced to treat these challenging types of macular holes, such as ILM inverted flap, platelet-rich plasma, amniotic membrane transplant, and retinal transplant, to help improve success rates, with techniques varying by surgeon [15-21]. However, these investigational techniques require specially prepared materials and/or specialized techniques and provider training, which can limit their widespread accessibility for patients, with a high risk of complications.

A macular hole is considered to be a traction-related condition [8], and there has been continued investigation of various ILM peeling techniques, including the degree of ILM removal to mobilize the retina for closure, to improve postsurgical functional outcomes, such as anatomy and visual acuity [20]. Previous studies have affirmed several ways in which application of ILM peeling aids in macular hole closure [20,22]. It has been suggested that the longer the duration of a macular hole, the larger its size, and thus extended ILM peeling must be performed to adequately mobilize the retina for closure [23]. The successful use of extended ILM peeling to treat large macular holes was first reported in 2009 [23]. Although several prognostic factors have been identified for difficult-to-treat macular holes, studies evaluating surgical techniques have generally concentrated on the macular hole diameter, given its perceived greater effect on visual outcomes vs duration of the condition, which can be perceived as a subjective parameter [24].

Given the role of duration of a macular hole in prognosis, repair ideally would be performed as early as possible, for instance within 1 to 4 months of symptom onset [25]. However, in the community setting, circumstances can delay treatment, including patient delay in seeking diagnosis and/or treatment, misdiagnosis, and limited access to resources, such as a vitreoretinal surgeon. Thus, there is a need to identify a "simple" surgical intervention to restore visual acuity that can be broadly used, including for macular holes of long duration. The aim of this study was to evaluate a classic technique of macular hole surgery that is easily performed and does not require specialized equipment, resources, such as autologous platelet-rich concentrate, or techniques, such as inverted ILM flap and autologous retinal transplant, that can improve visual acuity in patients for whom the macular hole is considered difficult to treat due to a duration ≥12 months. Anatomic and functional outcomes were assessed following the use of a classic surgical procedure that included an extended ILM peeling technique alongside evaluation of potential relationships between posttreatment outcomes and baseline characteristics such as macular hole duration.

Material and Methods

A retrospective chart review was conducted of consecutive patients with a chronic (≥12-month duration) idiopathic macular hole in their emmetropic eye who were treated at a single center between 2019 and 2022 by a single ophthalmic surgeon. Patients were excluded if they had an atrophic macular hole, defined by its morphology on optical coherence tomography (OCT) examination; myopia or hyperopia in the affected eye prior to surgery; had undergone previous incisional vitreoretinal surgery in the affected eye; had glaucoma or other macular-related pathologies, such as wet age-related macular degeneration, dry age-related macular degeneration, and macular atrophy, in either eye; or had clinically significant, such as obstruction of fundus details, cataracts in the macular hole-affected (study) eye. The study was conducted according to the tenets of the Declaration of Helsinki and local ethics guidelines. All patients provided written informed consent for data to be analyzed retrospectively in an anonymized fashion and published.

The treatment protocol was standardized across patients. Following retrobulbar anesthesia, a 3-port, 23-gauge pars plana vitrectomy was conducted (Enhancing Visual Acuity Phaco-Vitrectomy system; D.O.R.C. BV, Zuidland, the Netherlands). The epiretinal membrane, if present, and/or ILM were stained for

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1.5 min with MembraneBlue-Dual. This was the dye of choice because it stains both the ILM and epiretinal membrane for combined removal. Peeling of the ILM was conducted using a pinch technique with 23-gauge, end-gripping oblique forceps with extended peeling up to the vascular arcades (3 disc diameters [DD]) and optic disc margin.

For patients who requested simultaneous lens exchange in the affected eye, phacoemulsification with implantation of a foldable intraocular lens was performed via a 1.8-mm corneal incision. Sutures were placed on sclerotomes when there was a risk of postoperative hypotony. In all cases, an intraocular gas tamponade (20% sulfur hexafluoride [SF_6]) was added, with no face-down postoperative posturing required. Patients were advised to avoid face-up posturing for 3 to 4 days after surgery to maintain contact between the gas tamponade and macula.

All patients underwent a complete ophthalmic examination, including best-corrected visual acuity (BCVA), intraocular pressure, and OCT scanning (DRI OCT-1 Triton, Topcon Corporation, Tokyo, Japan) prior to surgery (baseline), 1 week after treatment, and at 1, 6, 12, and 24 months after treatment. BCVA was measured using the logarithm of the minimum angle of resolution (logMAR). Patients were further stratified by chronic macular hole diameter (≤400 µm vs >400 µm and ≤650 µm vs >650 µm). Data were analyzed using IBM SPSS (Statistical Package for the Social Sciences), version 25 (IBM, Armonk, NY, USA). The Mann-Whitney U test was used for between-group comparisons, due to the unequal and small sample sizes. An analysis of variance with repeated measures was used to test whether there were statistically significant differences in visual acuity between time periods. Sphericity of variance was evaluated using the Mauchly test. The assumption of sphericity of variance was not met ($P<0.001$); therefore, the Greenhouse-Geisser correction was applied to compare differences across time points. The significance threshold used was 0.05. Spearman correlation analyses (coefficient [r]) were conducted to explore potential relationships between macular hole diameter or duration and BCVA.

Results

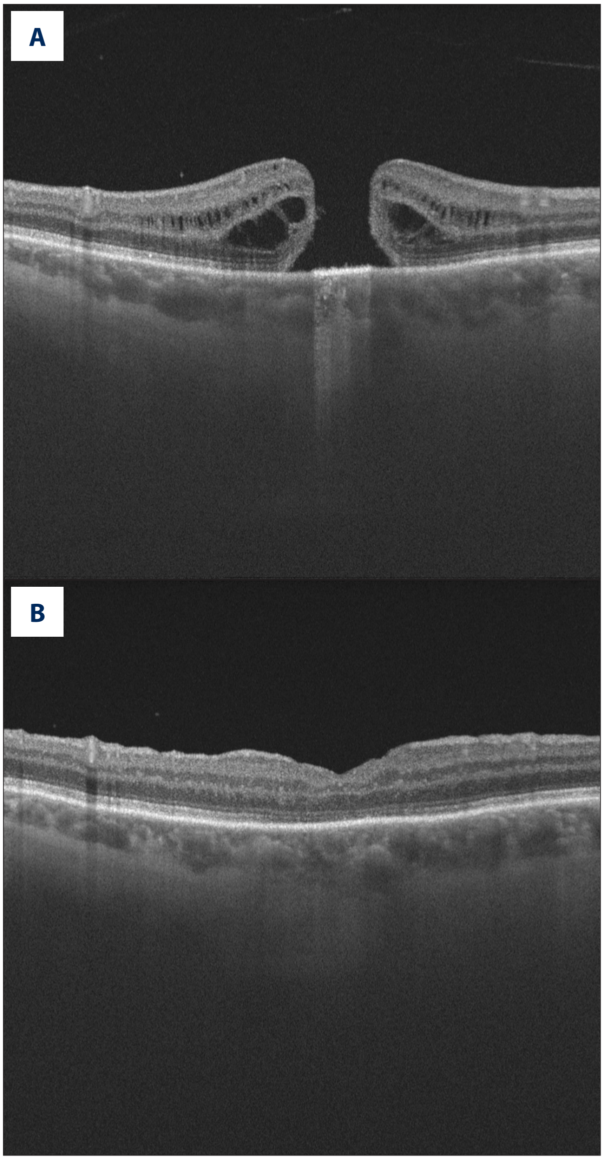
A total of 50 patients (50 eyes) with a chronic macular hole having a duration of ≥12 months (mean duration, 19.1 months) were included in the analysis (**Table 1**). The majority (76.0%) of patients had a chronic macular hole diameter of >400 µm at baseline (**Table 1**). A moderate positive correlation was observed between macular hole diameter and duration ($r=0.50$; $P<0.001$) and between macular hole diameter and preoperative visual acuity (logMAR; $r=0.47$; $P=0.001$). Additionally, there was a moderate positive correlation between macular hole duration and preoperative visual acuity (logMAR; $r=0.52$; $P<0.001$).

Table 1. Patient demographic and baseline characteristics.

Parameter	Patients (N=50)
Age, y	
Mean (SD)	73 (7)
Median	69
Range	65-85
Women, *n* (%)	36 (72.0)
Preoperative BCVA in affected eye, logMAR	
Mean (SD)	1.0 (0.4)
Range	0.5-1.6
Macular hole duration, months	
Mean (SD)	19.1 (8.8)
Range	12-43
Macular hole diameter, µm	
Mean (SD)	569.2 (164.6)
Range	247-822
Macular hole diameter, n (%)	
Small to medium (≤400 µm)	12 (24.0)
Duration of macular hole, mean (SD), months	12.8 (1.1)
Large to extra-large (>400 µm)	38 (76.0)
Duration of macular hole, mean (SD), months	21.0 (9.2)

BCVA – best-corrected visual acuity; logMAR – logarithm of the minimum angle of resolution.

At the 1-week posttreatment follow-up, 46 (92.0%) patients had closure of the macular hole. A representative case is shown in **Figure 1**. Four patients (baseline macular hole diameters 711, 720, 734, and 822 µm) had a flat-open macular hole anatomy after surgery (ie, edges are flat against the retinal pigment epithelium but it is not covered by a retinal layer in the middle; therefore, restoration of retina in the fovea is not complete). A flat-open retinal configuration is considered by some healthcare providers to be a type of macular hole closure [26,27]. However, due to the lack of restoration of the retinal contour and the low level of postsurgical visual acuity improvement typically achieved with this type of closure [26,27], in the present study, we considered a flat-open macular hole anatomy to be a surgical failure. A significant improvement from baseline in BCVA was observed by month 1 after treatment (mean [SD] logMAR, 0.96 [0.38] vs 0.66 [0.25]; $P<0.001$). Time after treatment had a significant effect on visual acuity (logMAR) results (**Figure 2**; $P<0.001$ across time periods). A moderate positive



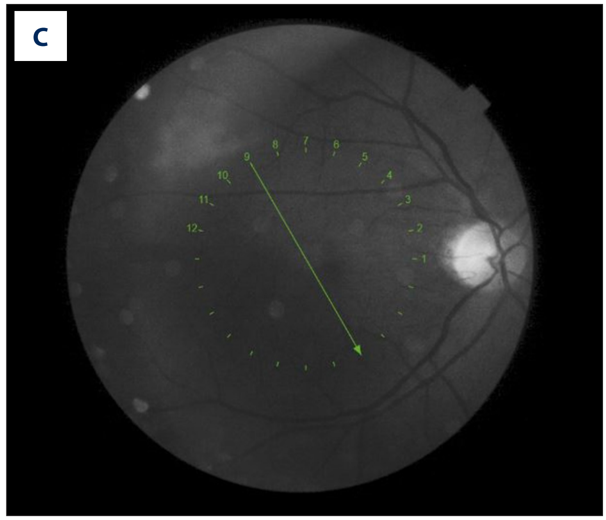


Figure 1. Case example of a patient presenting with a full-thickness macular hole measuring 576 μm in diameter on optical coherence tomography (OCT) scanning (**A**) with postoperative outcomes at 1 week showing macular hole closure by OCT scanning (**B**) and fundus photography (**C**).

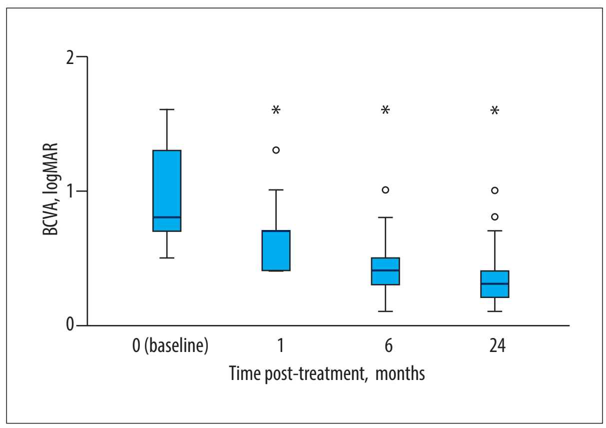


Figure 2. Box plot showing best-corrected visual acuity (BCVA) over time (N=50); *P*<0.001, pairwise comparison across time periods.* Horizontal lines on the bars indicate the median values; circles and asterisks represent outliers and extreme outliers, respectively. logMAR – logarithm of the minimum angle of resolution.* Mauchly sphericity test showed that the assumption of sphericity was not met (*P*<0.001). Therefore, the Greenhouse-Geisser correction was applied to the analysis of variance determination, and results showed statistically significant differences between time periods ($F(1.68; 82.13)=145.23$; *P*<0.001; $\eta^2=0.75$).

correlation was observed between macular hole diameter and visual acuity (logMAR) at month 24 after treatment (*r*=0.38; *P*<0.01) and between macular hole duration and visual acuity (logMAR) at month 24 after treatment (*r*=0.40; *P*<0.01).

When stratified by chronic macular hole diameter, patients with a diameter ≤400 μm (small to medium) and patients with a diameter >400 μm (large to extra-large) had improvements in BCVA (logMAR) over time (**Figure 3**). Of note, there were no significant differences between these subgroups in mean logMAR values for BCVA improvement for all time points through month 24 (*P*>0.05 for all [**Figure 3**]). However, significant differences between patients with a baseline macular hole diameter of ≤650 μm vs >650 μm were observed for BCVA (logMAR; **Figure 4**; *P*≤0.03 at all time points), including at month 24 (mean [SD] logMAR, 0.24 [0.11] vs 0.46 [0.35]; *P*=0.001).

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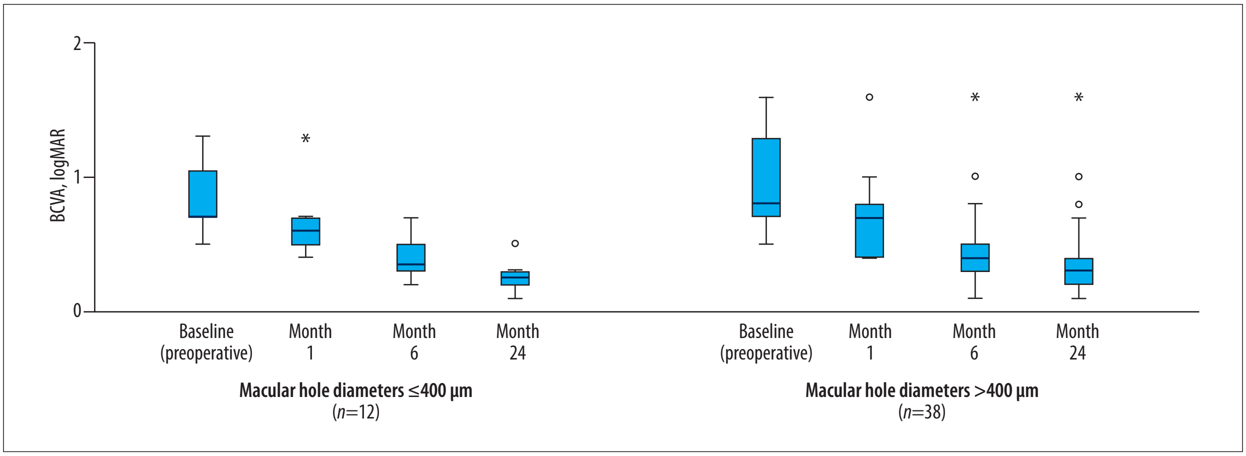

Figure 3. Box plot showing best-corrected visual acuity (BCVA) over time in patients stratified by baseline macular hole diameter with threshold of 400 µm. Horizontal line is the median value; circles and asterisks represent outliers and extreme outliers, respectively. logMAR – logarithm of the minimum angle of resolution.

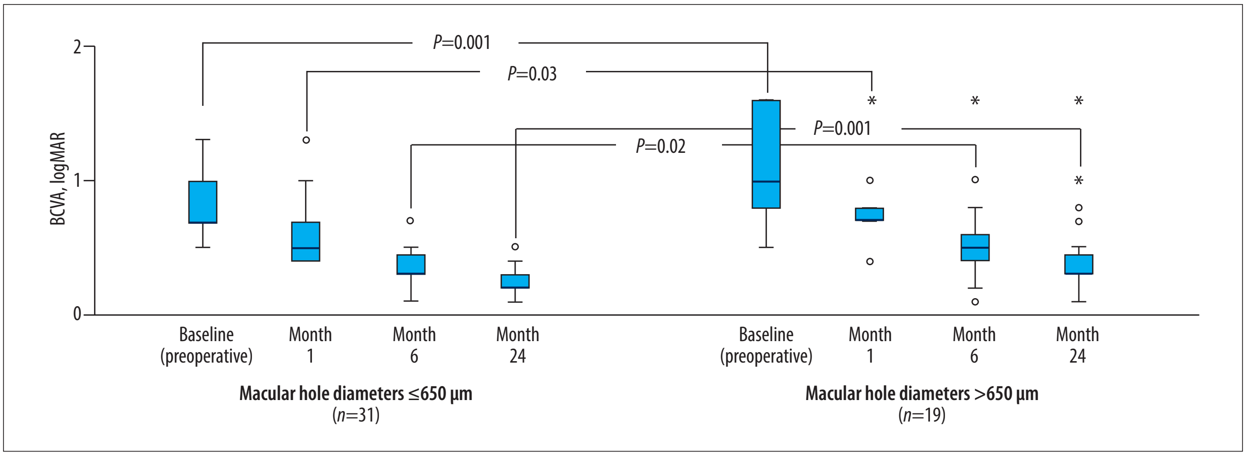

Figure 4. Box plot showing best-corrected visual acuity (BCVA) over time in patients stratified by baseline macular hole diameter with threshold of 650 µm. Horizontal line is the median value; circles and asterisks represent outliers and extreme outliers, respectively. logMAR – logarithm of the minimum angle of resolution.

Discussion

Vitrectomy and ILM peeling with gas tamponade has achieved idiopathic macular hole closure rates of 90% to 100% [28]; however, outcomes for some macular holes remain unsatisfactory, as macular hole size is inversely proportional to the closure rate with wide ILM peeling [29]. The use of vitrectomy and ILM peeling has approached these high closure success rates for a macular hole <400 µm, but success rates for a macular hole >400 µm have been lower (at 80% [13,14]). The present study of 50 patients, which used extended ILM peeling (3 DD) in combination with vitrectomy and gas tamponade, found a high closure success rate for macular holes of long duration (≥12 months) and size >400 µm, including those >650 µm.

Efforts have continued to identify surgical techniques that improve outcomes in macular holes classified as difficult to treat, such as those with chronic duration (ie, >6 months) and large macular holes (>400 µm). Although the benefits of ILM peeling, including use of extended ILM peeling (≥2 DD) [30-32] in the treatment of macular holes have been shown previously [20,30], consensus is lacking on the ideal width of the peel to maximize anatomical closure rates. For example, some studies have reported no statistically significant difference in idiopathic macular hole closure rates when comparing DD in classical ILM peeling (6 months: 0.75 DD [97.0%] vs 1.5 DD [97.0%] [33]) or extended ILM (1 year: 2 DD [82.5%] vs 4 DD [91.4%] [32]; 3 months: 2 DD [80%] vs 3 DD [65%] [34]). Our study supports that extended ILM peeling to a width of 3 DD in combination with the classical technique of vitrectomy is effective for chronic macular holes.

Studies typically have not had chronic duration as an inclusion criterion, but some have considered it in subgroup analyses, using a 6-month threshold to define "chronic" [31,34,35].

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Success rates for idiopathic macular holes in those with a duration of 6 to 12 months have been <85% [31,34,35]. It has been suggested that longer duration of the condition is a main contributor to lower closure rates [31,35]. The high closure success rate in the present study was within the range of success rates for procedures that have included the use of various inverted ILM flap techniques for large macular holes, as reviewed in Caporossi et al [20], including a temporal inverted ILM flap technique [36]. Comparative data with ILM peeling are limited; however, a large trial (N=620 eyes) in a mixed population with either idiopathic or myopic macular holes compared vitrectomy and gas tamponade plus either ILM peeling or an inverted ILM flap technique [37]. The closure success rate with the inverted ILM flap technique was higher than with ILM peeling (91.9% vs 78.8%, respectively; P=0.001), including for those ≥400 μm in diameter (95.6% vs 78.6%, respectively; P=0.001) [37]. A review by Caporossi et al concluded that the inverted ILM flap technique was more effective than classic ILM peeling for closure of large-diameter (>400 μm) macular holes but noted that there are several potential drawbacks, such as risk for flap detachment [20,37].

The present study adds to the literature in several important ways: (1) the results demonstrated that in a population with a chronic macular hole of ≥12 months, vitrectomy with extended ILM peeling (3 DD) plus gas tamponade closed the macular hole in >90% of patients within 1 week and improved BCVA; (2) it provided long-term follow-up of patients – through 24 months; (3) the population was explicitly defined by the duration of the macular hole rather than its size; (4) the surgical technique was effective in patients with a chronic macular hole of larger diameter (ie, 2 negative prognostic indicators of hole closure [8,9]); and (5) it supports that a diameter of >650 μm, rather than >400 μm, should be used to define a macular hole as difficult to treat. A similar technique of extended ILM peeling (to the arcades), in combination with vitrectomy and gas tamponade for extra-large macular holes, has been previously reported in a case series of 2 patients [23], a substantially smaller population than in the present study with 50 patients.

Not surprisingly, moderate correlations were observed between macular hole diameter and duration and between preoperative visual acuity and macular hole diameter or duration. These results are consistent with other data showing enlargement of macular hole diameter over time, and this expansion can be related to persistent tangential traction on the retina [38-40]. If traction increases over time, a larger area of ILM must be removed from the surface of the retina to relieve the tangential traction. In addition, the epiretinal membrane (a thin layer of scar tissue) should be removed to reduce tangential traction caused by its formation on the surface of the retina over time, which can interfere with the healing process and prevent proper macular hole closure. If the degree of ILM peeling is insufficient, the potential for success with surgery is compromised, and additional techniques must be considered.

In addition to favorable anatomic outcomes, visual acuity improved in this study through follow-up of 24 months. Improvements in BCVA were similar when patients were stratified by a preoperative macular hole diameter of ≤400 μm vs >400 μm. However, when expanding the stratification threshold to 650 μm, significant differences in BCVA through 24 months after treatment were observed between the ≤650-μm and >650-μm subgroups, with slightly poorer visual acuity observed in those with a larger macular hole diameter (>650 μm). Correlation analysis identified a relationship between poorer visual acuity at month 24 and larger baseline macular hole diameter or longer macular hole duration. In addition, because postsurgical macular hole repair by ganglion cells and Müller cells is typically completed by day 7, and gas reabsorption and recovery of visual acuity are prolonged with long-acting agents, SF_6 was considered a better choice than a long-acting gas tamponade (eg, octafluoropropane [C_3F_8]), which is usually preferred for large macular holes [41].

Limitations of this study include the retrospective and noncomparative nature of the analysis. In addition, the definition of "chronic" was based on patient medical history, and posttreatment follow-up was limited to 24 months. These limitations can affect the generalizability of the findings, due to potential bias, such as selection (ie, not representative of population), information (eg, chart accuracy/completeness), and insufficient control of confounding variables. However, several strengths outweigh the limitations of the study. These include the large cohort of consecutive patients included, the broad range of difficult-to-treat macular holes (>12-month duration and large size), which allows for generalizability of findings, and the use of a standardized treatment protocol. Although approximately one-quarter (28.0%) of patients requested simultaneous lens exchange (for comfort-related reasons and/or to eliminate the need for a future cataract procedure), this additional procedure was not considered to clinically affect visual outcomes during the study. A single expert surgeon performed all procedures, which allowed consistency across the standardized procedure and accurate determination of the macular hole closure success rate. Overall, the present study supports that extended ILM peeling, along with vitrectomy and gas tamponade, is an appropriate intervention strategy for chronic, large macular holes.

Conclusions

Despite the limitations of this retrospective, large case series, these data support that long-standing (ie, chronic) macular holes can be successfully treated using a classic technique of vitrectomy with extended ILM peeling and adequate 20% SF_6 tamponade. A

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macular hole of diameter >650 µm, rather than >400 µm, should be considered difficult to treat because visual acuity outcomes can be poor, even with successful closure. Additionally, because the technique used in this study does not require specialized equipment or substantial additional training, the procedure can be performed on challenging macular holes by a less experienced vitreoretinal surgeon, still with excellent results.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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