

# Macular hole edge morphology predicts restoration of postoperative retinal microstructure and functional outcome

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## Research article

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# Abstract

**Background:** To investigate the association between iOCT feature in macular hole (MH) surgery and the restoration of the retina microstructure and visual outcomes.

**Methods:** This was a case series study including fifty-three eyes of 53 patients with macular hole were recruited. According to the morphological characteristics of the hole edge as imaged by iOCT after ILM peeling, all patients were divided into three groups: foveal flap group, hole-door group, and negative group. The restoration of the retina microstructure and postoperative visual outcomes of the MH surgery were compared between these groups.

**Results:** All of the eyes had MH closure after vitrectomy. The postoperative BCVA was significantly improved compared with the preoperative BCVA ( $P < 0.001$ ). Based on the features of the hole edge as reveal by iOCT, the negative group included 24 eyes, the fovea flap group included 14 eyes, and the hole-door group included 15 eyes. The hole-door group and foveal flap group had significantly better final visual acuity and postoperative restoration of the ELM than the negative group ( $P = 0.002$ ,  $P = 0.012$ ). For the group in which the MHD was  $\leq 400 \mu\text{m}$ , there were no significant differences in ELM restoration, EZ restoration, or BCVA among the three groups ( $P = 0.516$  and  $P = 0.179$  respectively). For the MHD  $> 400\text{-}\mu\text{m}$  group, the hole-door group and fovea flap group had significantly better final visual acuity and restoration of ELM than the negative group ( $P = 0.013$ ,  $P = 0.005$ ).

**Conclusion:** This study describes a novel intraoperative sign using iOCT. This sign can provide useful predictive information for postoperative restoration of the retinal microstructure and visual outcomes of MHs, especially large ones

## Introduction

Idiopathic full-thickness macular holes (MHs) can lead to decreased central vision and metamorphopsia. [1-4] Currently, the standard surgical procedure includes pars plana vitrectomy (PPV), internal limiting membrane (ILM) peeling, intraocular gas tamponade, and postoperative positioning to ensure satisfactory anatomic outcomes with MH closure rates of 90%. [1-4] Recent studies, using spectral domain optical coherence tomography (SD-OCT) to image retinal microstructure, reported favorable visual outcomes after MH surgery, especially as it relates to restoration of the external limiting membrane (ELM) and the ellipsoid zone (EZ). [5,6] Several studies have indicated that the recovery of the ELM might be the most critical factor for visual function improvement in the early postoperative period. [7,8]

Researchers used OCT measurements in attempts to evaluate prognostic factors in MH surgery, including minimum and base hole diameter (MHD), hole form factor, macular hole index, and tractional hole index. [9-12] However, the results have been variable due to the poor reproducibility of the OCT measurements. Recent studies have proved the feasibility and usefulness of intraoperative OCT (iOCT) in vitreoretinal surgery. [13-15] iOCT was said to have added valuable information related to surgical anatomic features and the surgical procedure, and it directly impacted the surgical procedure. Other recent studies have

shown the feasibility of real time iOCT in PPV surgery. [14-15] The DISCOVER study reported that the majority of surgeons preferred viewing static images rather than analysis details. Therefore, non-real time iOCT still has important clinical value in vitreoretinal surgery. [13] Several authors have recently shown iOCT to be useful in patients undergoing membrane peeling in MH surgery. [16,17] Moreover, alterations in MH geometry on iOCT have been visualized that may have important implications for postoperative care and positioning. [16,17] However, the relationship of these intraoperative changes with the MH closure rate and anatomic normalization have not been well analyzed.

In this study, we used iOCT after ILM peeling during vitrectomy for MH to describe morphological changes at the edges of MHs. With iOCT imaging, we identified three types of MHs based on the morphology of the hole edge after ILM peeling. We then analyzed the postsurgical association of the hole edge types with the restoration of retinal microstructure and postoperative visual outcomes

## **Materials And Methods**

### **Study Design**

This is a retrospective study of consecutive patients undergoing 23-gauge PPV for MH by a single surgeon (L.J-S) at Affiliated Eye Hospital of Wenzhou Medical University from July 2015 to July 2018. All patients gave written informed consent prior to the surgery. All procedures were approved by the institutional review board of the Affiliated Eye Hospital of Wenzhou Medical University and adhered to the Declarations of Helsinki.

### **Patient Selection**

All patients with MH who underwent 23-gauge PPV were included in the study. MH was defined as a full-thickness retinal defect in the foveal neurosensory retina as visualized by SD-OCT. Exclusion criteria included previous vitreoretinal surgery, history of penetrating trauma, high myopia, final follow-up period less than 6 months, and eyes that underwent PPV for MH without iOCT or using other techniques, e.g., inverted ILM flap technique, during the study period.

According to the morphological characteristics of the hole edge as imaged by iOCT after ILM peeling, all patients were divided into three groups. In the foveal flap group, iOCT imaged a preoperative foveal flap that adhered to the hole edge after ILM peeling. In the hole-door group [23], iOCT revealed vertical pillars of tissue that projected into the vitreous cavity from the edges of the hole. In the negative group, iOCT imaged neither foveal flap nor hole-door features.

### **Surgical Technique**

Each surgery was performed under retrobulbar anesthesia in patients receiving 23-gauge PPV. After core vitrectomy, posterior vitreous detachment was induced using the suction power of a 23-gauge vitrectomy cutter in the optic disc area. The posterior hyaloid membrane was cut except for the macular area. After staining the posterior pole with indocyanine green (0.025 mg/ml) for 5 seconds, the ILM was grasped

with ILM forceps and peeled off for approximately two-to-three disc diameters around the MH. Air-fluid exchange was followed by C3F8 endotamponade.

All eyes underwent examination for best corrected visual acuity (BCVA) by Snellen chart. BCVA was expressed as the logarithm of the minimum angle of resolution (logMAR). All preoperative and postoperative OCTs were done using a commercially available SD-OCT device (Spectralis HRA OCT; Heidelberg Engineering, Heidelberg, Germany). Diameters of MH were defined as the shortest distances between the edges of the broken ends of the neuroepithelia on the largest cross-section and were quantified based on a horizontal scan through the center of the hole. iOCT images were obtained with the Optovue iVue OCT System (Optovue, Inc., Fremont, CA, USA). The scanning speed was 26,000 times/min, the vertical resolution was 5  $\mu\text{m}$ , the horizontal resolution was 11.4  $\mu\text{m}$ , and the wavelength was 830 nm. Images acquired before and after ILM peeling were analyzed for qualitative changes. The primary outcome measures were anatomic success and restoration of the photoreceptor layer of the MH as documented by SD-OCT. The functional outcome of surgery was evaluated by BCVA at the last follow-up.

The postoperative BCVA and anatomical morphology of photoreceptor layer observed on SD-OCT images obtained in the postoperative follow-up period were compared among the three MH groups. Moreover, the restoration of the photoreceptor layer was assessed via the reconstruction of the continuous back reflection line corresponding to the EZ and the ELM. Two independent observers (H.C, J.F) evaluated the images, with a consensus used to resolve disagreements. All data were analyzed using the SPSS 22.0 statistical software (SPSS Inc, Chicago, IL), and P-values  $\leq 0.05$  were considered to be statistically significant. The descriptive analysis was used for all the ocular parameters discussed in the current study. One-way analysis of variance with post-hoc examination was used for the preoperative BCVA or postoperative BCVA among the three groups throughout the study period. The Chi-squared test was applied to evaluate differences in macular hole closure and restoration of the ELM and EZ.

## Results

One eye each of 53 patients matched the study criteria and were included in the analysis. The mean age of the patients was  $66.0 \pm 6.50$  years (range 47-78 y), and 36 patients were female, and 17 were male. The preoperative BCVA for all subjects was  $1.10 \pm 0.77$ , and the mean MHD was  $420.19 \pm 170.79$   $\mu\text{m}$ .

Based on the features of the hole edge as reveal by iOCT, the negative group included 24 eyes, the fovea flap group included 14 eyes, and the hole-door group included 15 eyes (Table 1). At the baseline examination, there was no significant difference among the three groups regarding age ( $p = 0.151$ ), sex ( $p = 0.252$ ), axial length ( $p = 0.615$ ), duration of MH ( $p = 0.735$ ), mean preoperative BCVA ( $p = 0.287$ ), or MHD ( $p = 0.268$ ).

### MH closure, iOCT features, and visual acuity change after surgery

All of the eyes had MH closure after vitrectomy. Type 1 MH closure occurred in 52 eyes, and Type 2 MH closure occurred in one eye. The postoperative BCVA was for all subjects was  $0.44 \pm 0.46$ , which was

significantly improved compared with the preoperative BCVA of  $0.93\pm 0.47$  ( $P<0.001$ ). The restoration of ELM and EZ was present 6 months after surgery in 77.4% (41 of 53) and 37.7% (20 of 53) respectively of the patients after surgery.

### **iOCT features and visual acuity change after surgery among the three groups**

The baseline and final visual acuity and anatomic outcomes between the three groups are summarized in Table 1. There was no significant difference in the rate of MH closure among the three groups at 6 months postoperatively.

The postoperative visual acuity at 6 months was  $0.68\pm 0.60$  in the negative group,  $0.24\pm 0.15$  in the hole-door group, and  $0.25\pm 0.15$  in the foveal flap group. The hole-door group and foveal flap group had significantly better final visual acuity than the negative group ( $P=0.002$ ). The ELM was restored by 6 months after surgery in 58.3% (14 of 24) of the patients in the negative group, 93.3% (14 of 15) in the hole-door group, and 92.9% (13 of 14) in the foveal flap group. Postoperative restoration of the EZ was present at 6 months in 33.3% (8 of 24) of the patients in the negative group, 33.3% (5 of 15) in the hole-door group, and 50% (7 of 14) in the foveal flap group. The negative group had significantly poorer restoration of the ELM than the other two groups ( $P=0.012$ , Table 1).

### **Macular hole size, BCVA, and microstructural changes of the fovea after surgery**

Subgroup analysis divided patients into groups in which the MHD was  $\leq 400\ \mu\text{m}$  (Table 2) or  $>400\ \mu\text{m}$  (Table 3). By six months after surgery, for the group in which the MHD was  $\leq 400\ \mu\text{m}$ , the ELMs were completely restored in all three MH groups (Table 2). At the same time, restoration of the EZ was achieved in 77.8% (7 of 9) of the patients in the negative group, 62.5% (5 of 8) in the hole-door group, and 50% (4 of 8) in the foveal flap group. There were no significant differences in ELM restoration, EZ restoration, or BCVA among the three groups ( $P=0.516$  and  $P=0.179$  respectively).

For the MHD  $>400\text{-}\mu\text{m}$  group, the ELM was restored by 6 months after surgery in 33.3% (5 of 15) of the patients in the negative group, 85.7% (6 of 7) in the hole-door group, and 100% (6 of 6) in the foveal flap group (Table 3). Postoperative restoration of the EZ at 6 months occurred in 13.3% (2 of 15) of the patients in the negative group, 28.6% (2 of 7) in the hole-door group, and 33.3% (2 of 6) in the foveal flap group. The negative group had significantly poorer restoration of the ELM than the other two groups ( $P=0.017$ ,  $P=0.002$ ), while there was no significant difference for EZ restoration among the three groups ( $P=0.569$ ). The hole-door group and the foveal flap group had significantly better final visual acuity than the negative group ( $P=0.013$ ).

### **Representative Case Examples**

**Fig. 1** Case 1: A representative foveal flap case. **(a)** The MH foveal flap was evident in the preoperative SD-OCT images (arrow) of a 63-year-old woman. **(b)** iOCT showed that the foveal flap (arrow) was preserved after ILM peeling. **(c)** Postoperatively at 6 months, SD-OCT showed hole closure with recovery of the ELM and EZ. The BCVA was 0.6.

**Fig. 2** Case 2: A representative hole-door case. **(a)** The preoperative SD-OCT image showed a MH without a foveal flap in a 60-year-old woman. **(b)** iOCT showed vertical pillars of tissue at the edges of the hole projecting into the vitreous cavity (arrow) after ILM peeling. **(c)** Postoperatively at 6 months, SD-OCT showed hole closure with full recovery of the ELM and EZ. The BCVA was 0.4.

**Fig. 3** Case 3: A representative negative case. **(a)** The preoperative SD-OCT image showed a MH without a foveal flap in a 67-year-old woman. **(b)** iOCT showed neither foveal flap nor vertical pillars of tissue at the edges of the hole after ILM peeling. **(c)** Postoperatively at 6 months, SD-OCT showed hole closure without restoration of the ONL. The bridging tissue was hyperreflective. The BCVA was 0.15.

## Discussion

Several authors have recently used iOCT to show MH geometry changes after ILM peeling. [16,17] However, the relationship of the intraoperative findings with the MH closure rate and anatomic normalization were not thoroughly analyzed. We found three types of iOCT features at the hole edge that were evident after ILM peeling. The morphological characteristics imaged by iOCT are closely related to the prognosis of MH surgery. Thus, the hole-door and foveal flap structures imaged by iOCT during surgery served as positive predictors of MHs that acquired better anatomic and functional results after surgery than did the group in which these features were absent.

Though the nature of the foveal flap is still unknown, it is considered to be an early stage operculum. [18,19] With the development of posterior vitreous detachment, the foveal flap becomes separated from the retinal tissue as an operculum. Histopathological results suggest that the foveal flap is a part of the retinal tissue. [20,21] One report stated that good anatomic and functional outcomes were achieved by preserving the foveal flap for the treatment of MH. [22] While preservation of the flap can be achieved by the surgeon using a microscope during the procedure, the use of iOCT may be helpful for making more objective assessments during surgery. We used iOCT to observe the morphology of the foveal flap after ILM removal. Further, iOCT confirmed that all flaps were preserved during the surgery. Subsequent analysis showed that these patients had a better prognosis compared to the negative patients for whom no foveal flap or door-hole was present. We believe that the fovea flap can cover the defect in the inner retina and facilitate hole closure. This then results in a better restoration of photoreceptors at the fovea. To the best of our knowledge, this study is the first to use iOCT to describe the feature of foveal flaps after ILM peeling and demonstrate the beneficial effect on the prognosis after MH surgery.

Patients who were negative or who did not have a fovea flap, iOCT also showed vertical pillars of tissue at the edges of the hole projecting into the vitreous cavity after ILM peeling in 15 patients. This phenomenon is similar to the “hole-door” feature described in previous literature [23], they conclude hole-door sign can predicts postoperative Type 1 closure of MH. In our study, we found that patients with this phenomenon had a better recovery of the foveal microstructure and a better visual outcome compared with the negative group, even though there was no difference in the closure rate. Kumar and Yadav [23] considered that the tissue pillars could be composed of redundant retinal tissue, subclinical epiretinal

membranes, or small residual pieces of the ILM attached to the edges of the hole. They suggested that the mechanism of closure could be similar to the inverted ILM flap surgical approach in which the pillars provide mechanical support to bridge the gap and more quickly cover up the defects in the inner retina. [24-27]

Visual recovery after MH closure may depend on the recovery of the retinal microstructure in the fovea, particularly the outer retina. [5-8] The authors reported that the restoration of the ELM and the EZ lines over the closed MH was associated with better BCVAs. However, the presence of hyperreflective bridging tissue at the closed MH indicated that the MH was closed with scar tissue or migrated glial tissue, including collagen components derived from Müller cells. The restoration of the ELM in the hole-door and foveal flap groups was higher than in the negative group. Correspondingly, the both groups had better postoperative visual acuity than the negative group. Our research shows that the favorable visual outcomes after MH surgery were related to restoration of the ELM, and this is similar to previous reports. [5-8] This observation indicated that the recovery of the ELM might be the most critical component for visual function improvement in the early stage after MH surgery.

The size of the hole was also closely related to the prognosis of MH surgery. [28] Regarding preoperative MH size, Liu et al reported that simply dividing patients into those with MHs  $>400\ \mu\text{m}$  and those with MHs  $\leq 400\ \mu\text{m}$  was more clinically significant for the prognosis after MH surgery. [8] Our study shows that the intraoperative feature at the hole edge may be the best predictor of prognosis for those with MHD  $>400\ \mu\text{m}$ . For those in which the MHD was  $\leq 400\ \mu\text{m}$ , there were no significant differences between the postoperative ELM, EZ restoration, and BCVA of the three groups.

Real time iOCT is a newly developed technology in the field of ophthalmic imaging. The 3-year results of the DISCOVER study found that 69% of posterior segment surgeons preferred viewing images on the display screen, and that percent increased from year 1 to subsequent years.[13] These may be related to greater OCT detail and subtle changes on screen review than in real time. Therefore, non-real time iOCT still has important clinical value in MH surgery.

This study has the following limitations. It was a retrospective study and involved a small number of cases, which limited the statistical strength of the analysis. In addition, the imaging system used in this study was not integrated into the microscope, which may have impacted the overall functionality of iOCT in these cases.

## Conclusions

In conclusion, we described a novel intraoperative sign using iOCT. This sign can provide useful predictive information for postoperative restoration of the retinal microstructure and visual outcomes of MHs, especially large ones. Our results also provide useful insights into the pathophysiology of ILM peeling in MH surgery.

# Abbreviations

iOCT: Intraoperative Optical Coherence Tomography;

MH: Macular Hole;

EZ: Ellipsoid Zone;

ELM: External Limiting Membrane;

BCVA: Best Corrected Visual Acuity.

# Declarations

## Acknowledgements

Not applicable.

## Authors' contributions

JWT contributed to the concept and study design. Patients were enrolled by LJS, CH, ZL. PDM collected the data and interpreted the data. CH drafted the manuscript. All the authors were involved in the critical revision of the manuscript, supervision of the manuscript, and final approval before submission.

## Funding

None.

## Availability of data and materials

The datasets for the analysis of the current study are readily available from the corresponding author on reasonable request.

## Ethics approval and consent to participate

The study followed the tenets of the Declaration of Helsinki and was approved by the Ethics Committee of the Eye Hospital of Wenzhou Medical University, and written informed consent was obtained from all patients.

## Consent for publication

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

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## Tables

**Table 1** Characteristics of the negative, hole-door, and foveal flap MH groups

	Groups			P
	Negative (N=24)	Hole-door (N=15)	Foveal flap (N=14)	
Male/female, no	5/19	7/8	5/9	0.252
Age, (years)	68.13±5.86	62.33±15.54	63.00±7.30	0.151
Axial length, (mm)	23.36±0.77	23.53±0.94	23.33±1.27	0.615
Duration of MH, (months)	3.07±1.92	2.87±1.51	3.00±1.71	0.735
Preoperative BCVA	1.06±0.56	1.34±1.17	0.89±0.44	0.287
Preoperative MHD	463.35±174.04	391.47±165.32	380.07±166.61	0.268
Macular hole closure	23 (95.8%)	15 (100%)	14 (100%)	0.717
ELM restoration	14 (58.3%)	14 (93.3%)	13 (92.9%)	0.012
EZ restoration	8 (33.3%)	5 (33.3%)	7 (50%)	0.587
Postoperative BCVA	0.68±0.60	0.24±0.15	0.25±0.15	0.002

MH: macular hole; BCVA: best corrected visual acuity; MHD: minimum hole diameter; ELM: external limiting membrane; EZ: ellipsoid zone;

**Table 2.** Functional and anatomical outcomes in the MHD ≤400 mm group

	Groups			P
	Negative (N=24)	Hole-door (N=15)	Foveal flap (N=14)	
Preoperative BCVA	0.77±0.28	1.71±1.53	0.90±0.57	0.110
Preoperative MHD	289.56±69.41	285.75±110.94	252.63±72.19	0.636
Macular hole closure	9 (100%)	8 (100%)	8 (100%)	/
ELM restoration	9 (100%)	8 (100%)	8 (100%)	/
EZ restoration	7 (77.8%)	5 (62.5%)	4 (50%)	0.516
Postoperative BCVA	0.30±0.12	0.16±0.14	0.23±0.18	0.179

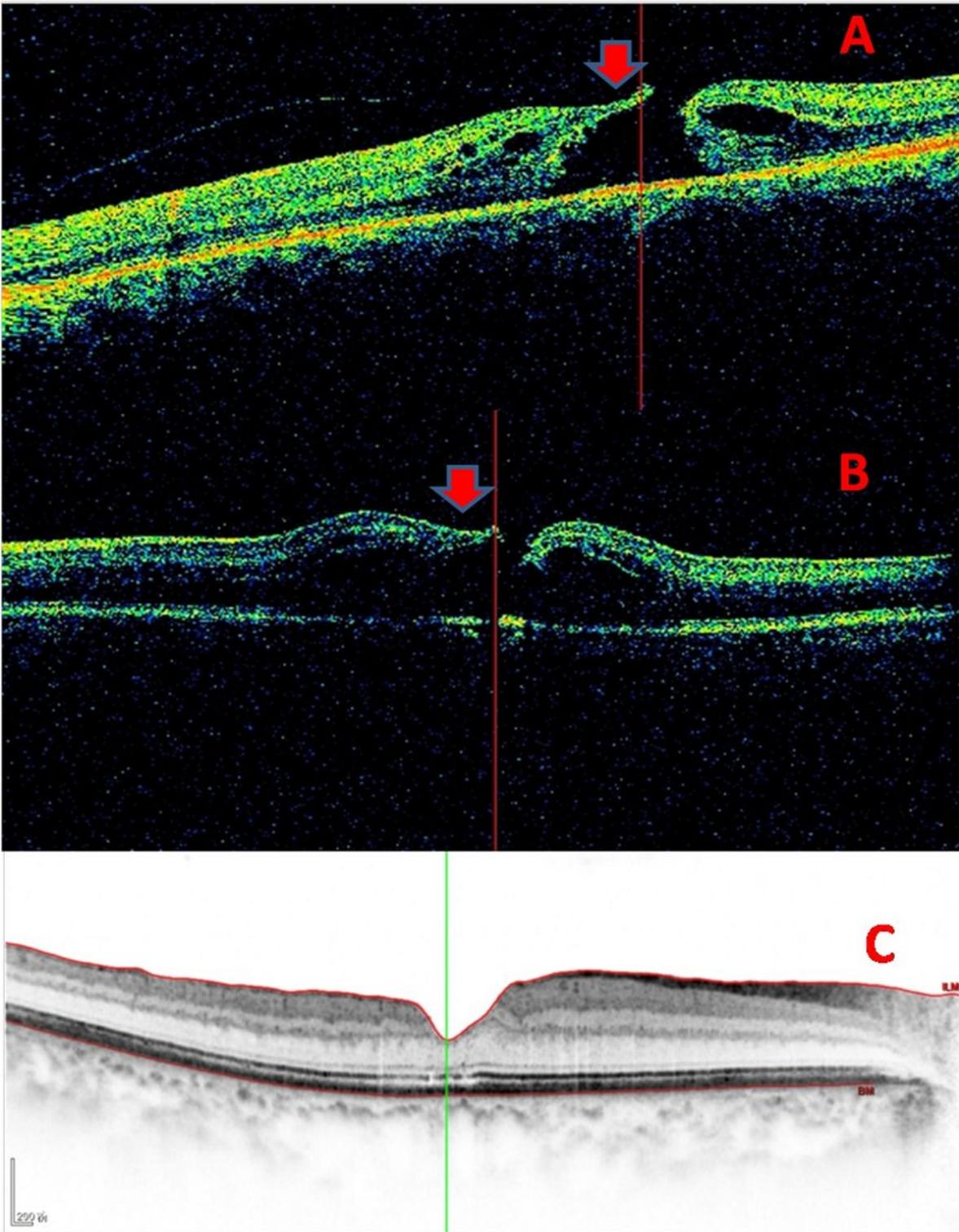
MHD: minimum hole diameter; ELM: external limiting membrane; EZ: ellipsoid zone; BCVA: best corrected visual acuity;

**Table 3.** Functional and anatomical outcomes in the MHD >400 mm group

	Groups			P
	Negative (N=15)	Hole-door (N=7)	Fovea-flap (N=6)	
Preoperative BCVA	1.24±0.62	0.92±0.26	0.89±0.21	0.205
Preoperative MHD	575.07±118.08	512.29±132.22	550.00±65.11	0.496
Macular hole closure	14 (93.3%)	7 (100%)	6 (100%)	0.750
ELM restoration	5 (33.3%)	6 (85.7%)	6 (100%)	0.005
EZ restoration	2 (13.3%)	2 (28.6%)	2 (33.3%)	0.569
Postoperative BCVA	0.93±0.65	0.34±0.17	0.28±0.10	0.013

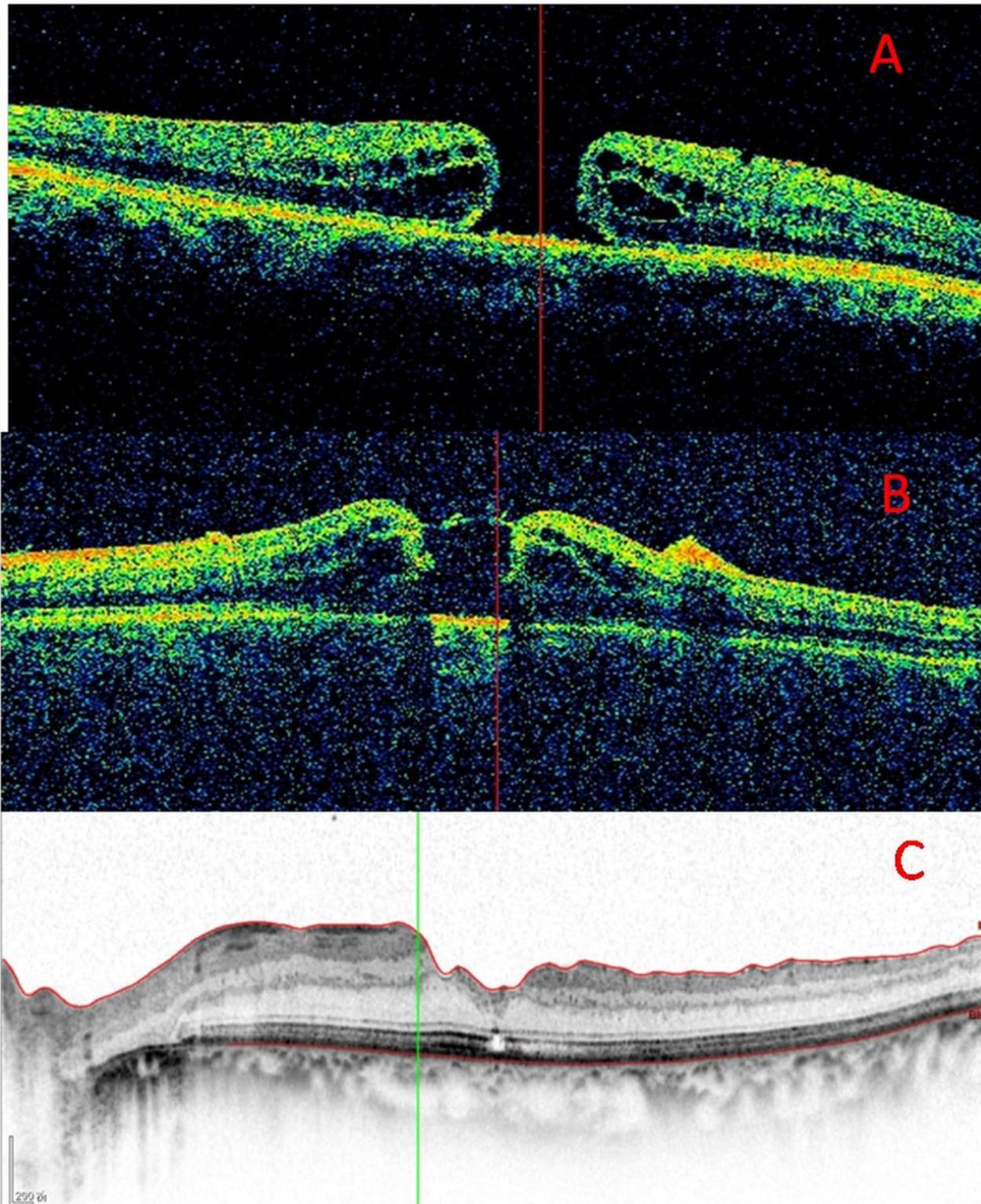
MHD: minimum hole diameter; ELM: external limiting membrane; EZ: ellipsoid zone; BCVA: best corrected visual acuity;

## Figures



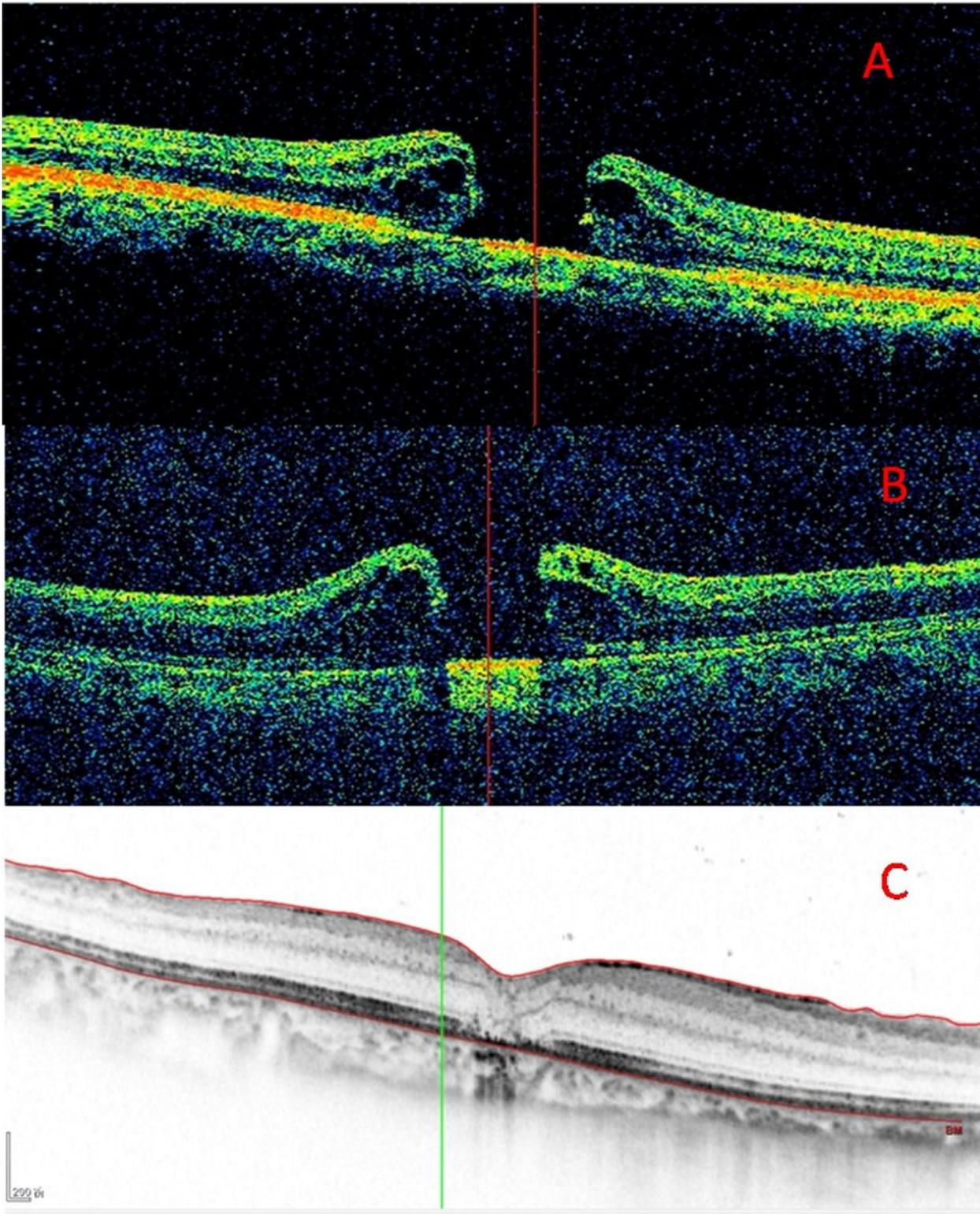
**Figure 1**

Case 1: A representative foveal flap case. (a) The MH foveal flap was evident in the preoperative SD-OCT images (arrow) of a 63-year-old woman. (b) iOCT showed that the foveal flap (arrow) was preserved after ILM peeling. (c) Postoperatively at 6 months, SD-OCT showed hole closure with recovery of the ELM and EZ. The BCVA was 0.6.



**Figure 2**

Case 2: A representative hole-door case. (a) The preoperative SD-OCT image showed a MH without a foveal flap in a 60-year-old woman. (b) iOCT showed vertical pillars of tissue at the edges of the hole projecting into the vitreous cavity (arrow) after ILM peeling. (c) Postoperatively at 6 months, SD-OCT showed hole closure with full recovery of the ELM and EZ. The BCVA was 0.4.



**Figure 3**

Case 3: A representative negative case. (a) The preoperative SD-OCT image showed a MH without a foveal flap in a 67-year-old woman. (b) iOCT showed neither foveal flap nor vertical pillars of tissue at the edges of the hole after ILM peeling. (c) Postoperatively at 6 months, SD-OCT showed hole closure without restoration of the ONL. The bridging tissue was hyperreflective. The BCVA was 0.15.