FOVEAL MICROSTRUCTURE IN MACULAR HOLES SURGICALLY CLOSED BY INVERTED INTERNAL LIMITING MEMBRANE FLAP TECHNIQUE

HISAKO HAYASHI, MD, SHOJI KURIYAMA, MD

Purpose: To evaluate reconstructive foveal anatomical change in surgically closed macular hole (MH) by pars plana vitrectomy with inverted internal limiting membrane flap technique.

Methods: Spectral domain optical coherence tomography was used to evaluate foveal microstructures in 20 eyes of 19 patients who underwent pars plana vitrectomy with inverted internal limiting membrane flap technique to achieve MH closure. Eyes had idiopathic large MH with a diameter >500 μm (n = 7), MH in high myopia (axial length >26.5 mm) without retinal detachment (RD; n = 7), and with RD caused by the MH (n = 6).

Results: The 6-month postoperative spectral domain optical coherence tomography examination revealed restoration of the inner segment and outer segment junction in 3 of 7 idiopathic large MH eyes (43%), 2 of 7 highly myopic MH eyes without RD (29%), and 1 of 6 highly myopic MH eyes with RD (17%), and detected the external limiting membrane in 4 of 7 idiopathic large MH eyes (57%), 3 of 7 highly myopic MH eyes without RD (43%), 1 of 6 highly myopic MH eyes with RD (17%).

Conclusion: Inverted internal limiting membrane flap technique results in more satisfactory anatomical improvements in patients with idiopathic large MH eyes and highly myopic MH eyes without RD than with highly myopic MH eyes with RD. This might suggest that the foveal photoreceptor layer in MH with RD is destroyed and not recoverable even after retinal reattachment with surgical closure of the MH.

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Idiopathic macular hole (MH) can be closed successfully with vitreous surgery.[1–3] However, idiopathic MH with a minimum diameter >500 μm or MH in highly myopic eyes cannot be easily closed during a single vitreoretinal surgery and sometimes requires additional operations.[4,5]

Michalewska et al[6] reported that the inverted internal limiting membrane (ILM) flap technique for idiopathic large MH improves the postoperative closure rate and visual function. Subsequently, we reported that this new technique is effective for the treatment of MH with or without retinal detachment (RD) in highly myopic eyes.[7] More recently, Michalewska et al[8] also reported that the ILM flap technique is an effective addition to surgical options for treating myopic MHs.

Optical coherence tomography (OCT) has become the gold standard for the diagnosis of MH and for confirming the anatomical closure of the MH after surgery. Several studies using spectral domain OCT (SD-OCT) have reported structural changes in the photoreceptor layers of eyes with surgically closed MH, such as varying degrees of disruption of the junction between the photoreceptor inner segment and outer segment (IS/OS) and of the external limiting membrane (ELM).[9–19] However, there are few reports about anatomical change in the photoreceptor layers of eyes with MHs closed by the inverted ILM flap technique.

From the Department of Ophthalmology, Otsu Red Cross Hospital, Shiga, Japan.

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Reprint requests: Shoji Kuriyama, MD, Department of Ophthalmology, Otsu Red Cross Hospital, 1-1-35 Nagara, Otsu, Shiga 520-0046, Japan; e-mail: kuriyama@otsu.jrc.or.jp

The purpose of this study was to evaluate reconstructive anatomical change in foveal microstructure using SD-OCT and to investigate the differences among the types of MH surgically closed by the inverted ILM flap technique.

Patients and Methods

There were a total of 22 participants in this retrospective and interventional case study. All patients had vitreous surgery with the inverted ILM flap technique at Otsu Red Cross Hospital from January to December 2012. These investigations in this study adhered to the tenets of the Declaration of Helsinki. Because this was a study that retrospectively reviewed medical records, the Institutional Review Board/Ethics Committee of Otsu Red Cross hospital where this study was conducted waived the need for approval of this research.

Patients with idiopathic MH (diameter >500 μm) and with MH in high myopia (axial length >26.5 mm with or without RD) were included in this study. The diagnosis of MH was made by the presence of a full-thickness neurosensory defect confirmed by SD-OCT (Spectralis HRA + OCT; Heidelberg Engineering, Heidelberg, Germany). The minimum and maximum MH diameters were measured by SD-OCT. All patients underwent comprehensive ophthalmologic examinations, including measurement of axial length, best-corrected visual acuity (BCVA) using the 5-m Landolt C acuity chart, dilated indirect and contact lens slit-lamp biomicroscopy, and SD-OCT. Axial length was measured preoperatively by A-scan and B-scan ultrasonography. The inclusion criterion was the minimum MH diameter of >500 μm or an axial length of >26.5 mm in an eye with MH. The exclusion criteria were secondary MH (i.e., posttraumatic hole, because of cystoid macular edema resulting from inflammation, macular pucker), a history of another ocular surgery except for cataract surgery, and presence of MH not closed after surgery.

The surgical procedure was performed in all cases by the same surgeon and treated with conventional 23-gauge or 25-gauge 3-port pars plana vitrectomy (PPV) with the inverted ILM flap technique and sulfur hexafluoride (SF_6) gas tamponade. For this procedure, a posterior vitreous detachment was first created, followed by the removal of the residual thin premacular posterior cortex. The inverted ILM flap technique was basically performed according to the report of Michalewska et al.[6] Briefly, the ILM was peeled off in a circular fashion for ~2 disk diameters around the MH after the indocyanine green staining procedure (0.125% solution of indocyanine green). During the circumferential peeling, the ILM was not removed completely from the retina but was left attached to the edge of the MH. A rolled segment of the peeled ILM was hanging in the vitreous cavity. The ILM was then massaged gently over the MH from all sides until the ILM became inverted. If an epiretinal membrane was present, it was peeled off with the same procedure used for the ILM. The MH was covered with the inverted ILM and epiretinal membrane flap. After fluid–air exchange, the air was then replaced through the use of 20% SF_6 gas. Cataract surgery and intraocular lens implantation were performed simultaneously in patients with cataract or those older than 50 years. Patients were instructed to maintain a prone position postoperatively for at least a week.

In the follow-up visit at 1 week and 1, 2, 3, and 6 months postoperatively, all patients underwent visual acuity measurement, slit-lamp examination, indirect ophthalmoscopy, and SD-OCT imaging of foveal microstructure. Tracking system that enables accurate and repeatable alignment of OCT was used for the follow-up. Successful anatomical closure was defined as the absence of a neurosensory defect over the fovea.[20] The BCVA was expressed in decimal acuity and converted to the logarithm of the minimum angle of resolution (logMAR) units for statistical analyses. To evaluate the surgical effects, the preoperative and postoperative BCVAs (logMAR value) were analyzed using the paired t-test and Student's t-test. A $P < 0.01$ was considered significant.

Microstructural imaging analysis of the fovea was performed using SD-OCT. A recovered foveal microstructure in the photoreceptor layer was evaluated as a recovery of the continuous back-reflection lines corresponding to the IS/OS junction and the ELM line; distinct and continuous IS/OS junction or ELM line defined as IS/OS (+) or ELM (+), respectively; and disruption or loss of IS/OS junction or ELM line defined as IS/OS (−) or ELM (−), respectively. The postoperative photoreceptor state, that is, IS/OS junction and ELM line, was compared between types of MH by SD-OCT imaging.

Results

Twenty eyes of 19 patients with MH closed surgically by the inverted ILM flap technique were followed up by SD-OCT for at least 6 months and were enrolled. Three eyes of three patients (idiopathic large MH, one eye; highly myopic MH without RD, one eye; highly myopic MH with RD, one eye) were excluded from this study because the MH closure was not observed with SD-OCT. The characteristics of the 20 eyes are summarized in Table 1. There were 7 men and 12 women among the 19 patients. The mean age of the patients was 67.0 ± 10.7 years (range, 42–85 years). The mean preoperative BCVA (logMAR value) was 0.72 ± 0.44. Seven eyes had idiopathic large MH. The mean minimum diameter of idiopathic MHs and highly myopic ones was 640 ± 98 μm (range, 505–818 μm) and 404 ± 280 μm (range, 100–821 μm), respectively. The mean maximum diameter of idiopathic MHs and highly myopic ones was 1,068 ± 167 μm (range, 870–1,347 μm) and 824 ± 551 μm (range, 294–1,850 μm), respectively. Seven eyes had MH in high myopia without RD, and 6 eyes had that with RD caused by the MH. The postoperative follow-up time ranged from 6 months to 18 months. In highly myopic MHs, five eyes without RD and three eyes with RD were reported in our previous manuscript.[7]

Changes in preoperative and postoperative visual acuity are shown in Figure 1. For the 20 eyes with initial MH closure, the mean BCVA was significantly improved from 0.72 ± 0.43 logMAR units before surgery to 0.35 ± 0.31 after surgery ($P < 0.01$, paired *t*-test). In addition, the BCVAs of 7 idiopathic large MH eyes, 7 highly myopic MH eyes without RD, and 6 highly myopic eyes with RD were improved from 0.85 ± 0.23, 0.36 ± 0.14, and 0.84 ± 0.61 before surgery to 0.30 ± 0.26, 0.25 ± 0.22, and 0.53 ± 0.36 after surgery, respectively. The improvement in BCVA was significant in idiopathic large MH eyes ($P = 0.0007$) but not significant in highly myopic MH eyes with ($P = 0.03$) or without ($P = 0.05$) RD ($P < 0.01$, paired *t*-test).

Table 1. Patient Baseline Clinical Characteristics

Factors	All Cases (n = 20)
Mean age ± SD, years	67.0 ± 10.7
Range	42–85
Sex, n (%)	
Male	7 (37)
Female	12 (63)
Mean BCVA ± SD, logMAR	0.72 ± 0.43
Type of MH, n (%)	
Idiopathic MH	7 (35)
High myopia without RD	7 (35)
High myopia with RD (MHRD)	6 (30)
Mean MH diameter (±SD)	
Idiopathic (n = 7)	
Minimum diameter, μm	640 ± 98
Maximum diameter, μm	1,068 ± 167
Highly myopic (n = 7)	
Minimum diameter, μm	404 ± 280
Maximum diameter, μm	824 ± 551
Lens status, n (%)	
Phakic	10 (50)
Intraocular lens	10 (50)

MHRD, retinal detachment due to MH; SD, standard deviation.

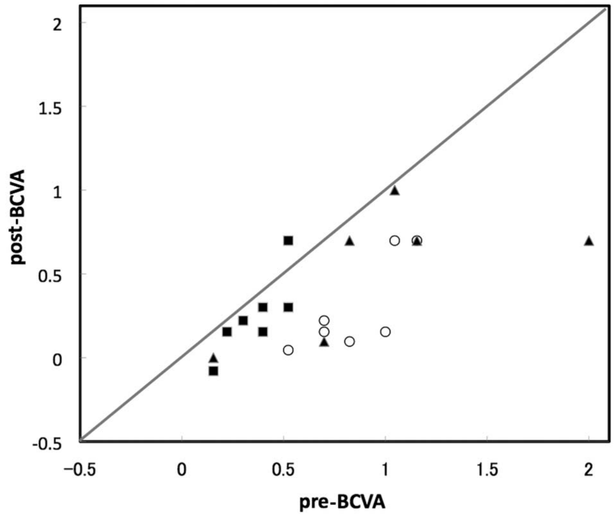

Fig. 1. Changes in preoperative and postoperative visual acuity of the eyes with MH. The mean BCVA was significantly improved from 0.72 ± 0.43 logMAR units before surgery to 0.35 ± 0.31 after surgery ($P < 0.01$). The improvement of BCVA was significant in idiopathic large MH eyes ($P = 0.0007$) but not significant in highly myopic MH eyes with ($P = 0.03$) or without ($P = 0.05$) RD ($P < 0.01$). Best-corrected visual acuity was measured using the Landolt C acuity chart at baseline and at the final visit. Best-corrected visual acuity was converted into logarithm of the minimal angle of resolution (logMAR) values. Open circles (○), eyes with idiopathic MH; solid squares (■), eyes with highly myopic MH; solid triangles (▲), eyes with RD caused by the MH.

The postoperative SD-OCT examination revealed IS/OS (+) in 0, 1, and 3 of 7 idiopathic large MH eyes (0, 14, and 43%) at 1, 3, and 6 months, respectively; 0, 1, and 2 eyes MH eyes in high myopia without RD (0, 14, and 29%) at 1,3, and 6 months, respectively; and 0, 1, and 1 eyes MH eyes in high myopia with RD (0, 17, and 17%) at 1, 3, and 6 months, respectively. Similarly, ELM (+) was detected in 1, 2, and 4 of 7 idiopathic large MH eyes (14, 29, and 57%) at 1, 3, and 6 months, respectively; 0, 1, and 3 of 7 MH eyes in high myopia without RD (0, 14, and 43%) at 1, 3, and 6 months, respectively; and in 0, 1, and 1 of 6 MH eyes in high myopia with RD (0, 17, and 17%) at 1, 3, and 6 months, respectively (Table 2). Eventually, the number of eyes with defects of both IS/OS and ELM at 6 months was 3 (43%), 4 (57%), and 5 (83%) in idiopathic large MH, highly myopic MH without RD, and highly myopic MH with RD, respectively. Complete restoration of the IS/OS junction was not observed without complete restoration of the ELM. Foveal hyperreflective lesions were found in 6 eyes (30%).

The SD-OCT images of the foveal photoreceptor layer were divided into 3 groups according to the integrity of the 2 back-reflection lines representing the photoreceptor IS/OS junction and the ELM (Figure 2): eyes with restored IS/OS junction and restored ELM

Table 2. Photoreceptor Layer State

	IS/OS (+)			ELM (+)		
	1 Month, n (%)	3 Months, n (%)	6 Months, n (%)	1 Month, n (%)	3 Months, n (%)	6 Months, n (%)
Idiopathic large MH (n = 7)	0 (0)	1 (14)	3 (43)	1 (14)	2 (29)	4 (57)
MH in high myopia without RD (n = 7)	0 (0)	1 (14)	2 (29)	0 (0)	1 (14)	3 (43)
MHRD (n = 6)	0 (0)	1 (17)	1 (17)	0 (0)	1 (17)	1 (17)

MHRD, retinal detachment due to MH.

(6 eyes); eyes with disrupted IS/OS junction but restored ELM (2 eyes); and eyes with both disrupted IS/OS junction and ELM (12 eyes). The mean postoperative BCVA at 6 months did not differ significantly among the 3 groups (0.20 ± 0.27, 0.18 ± 0.05, and 0.45 ± 0.33, respectively).

Case 1

A 63-year-old woman presented with idiopathic large MH. The minimum MH diameter was 689 μm (Figure 3A). Preoperative BCVA was 0.09. After surgery with the inverted ILM flap technique, MH was completely closed at 1 month (Figure 3B). The foveal hyperreflective lesion was observed in the entire intraretinal layer (asterisk). There were also disruptions of the IS/OS junction (between solid triangles) and ELM line (between open triangles). The visual acuity was 0.1. Six months after surgery, SD-OCT showed a disrupted IS/OS junction (between solid triangles) with a restored ELM accompanied by foveal detachment (Figure 3C). The visual acuity was 0.2.

Case 2

A 53-year-old woman presented with MH in high myopia without RD. The minimum MH diameter was 100 μm (Figure 4A). Preoperative BCVA was 0.6. After surgery with the inverted ILM flap technique, MH was completely closed at 1 month (Figure 4B). The foveal hyperreflective lesion was observed in the

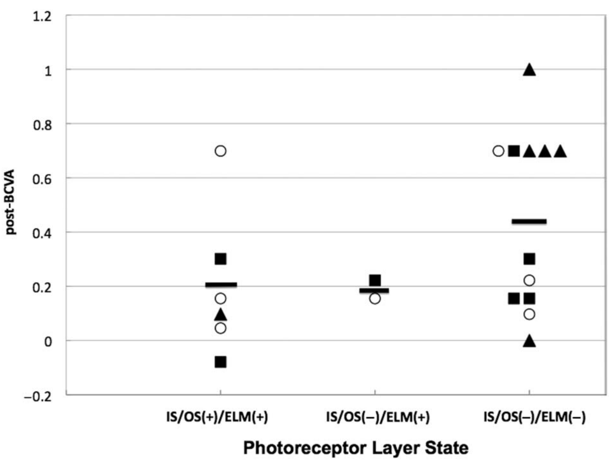

Fig. 2. Scattergrams and graphs showing the postoperative visual acuity and photoreceptor layer state of the eyes with MH. The SD-OCT images of the foveal photoreceptor layer were divided into 3 groups: restoration of both the IS/OS junction and the ELM (6 eyes); disruption of the IS/OS junction but with a restored ELM (2 eyes); and disruption of both the IS/OS junction and the ELM (12 eyes). The mean postoperative BCVA at 6 months did not differ significantly among groups ($P > 0.01$). Post-BCVA, postoperative BCVA. Open circles (○), eyes with idiopathic MH; solid squares (■), eyes with highly myopic MH; solid triangles (▲), eyes with RD caused by the MH; Bar, mean postoperative BCVA in each eye.

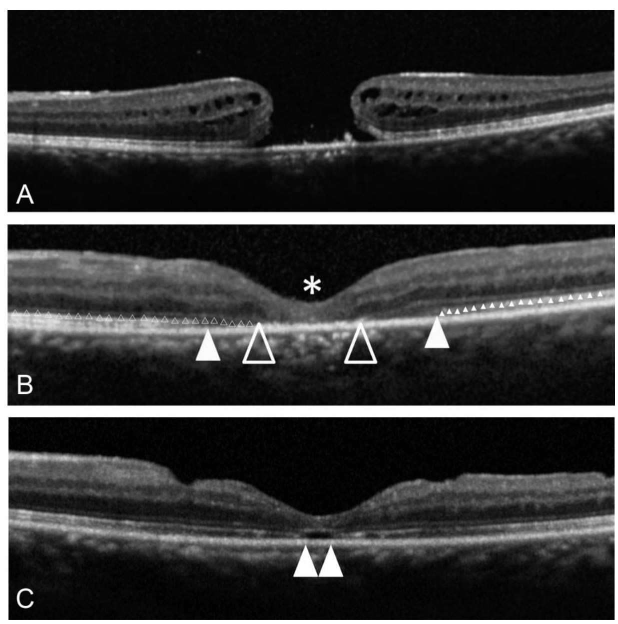

Fig. 3. Optical coherence tomography images of idiopathic large MH. A 63-year-old woman presented with idiopathic large MH. **A.** The minimum MH diameter was 689 μm. **B.** The SD-OCT image obtained 1 week after surgery showed the foveal hyperreflective lesion in the inner retina (asterisk), a disrupted IS/OS junction (between large solid triangles), and a disrupted ELM line (between large open triangles). Small solid triangles and small open triangles indicate the IS/OS junction line and the ELM line, respectively. **C.** The SD-OCT image obtained 6 months after surgery showed a disrupted IS/OS junction (between solid triangles) with a restored ELM accompanied by a foveal detachment.

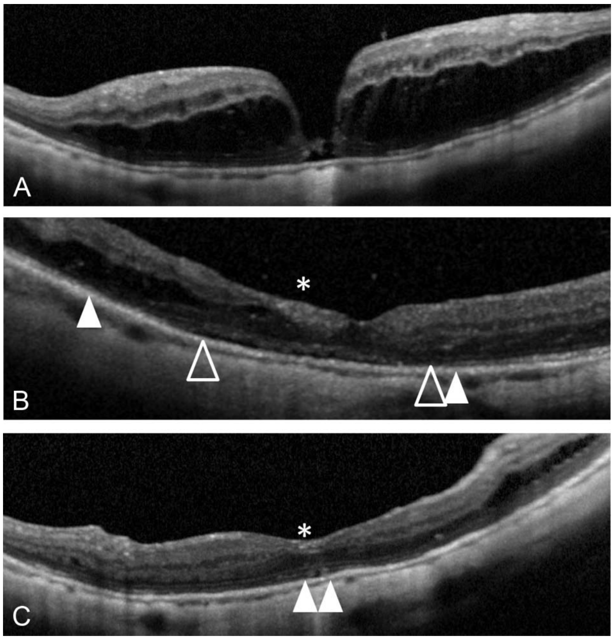

Fig. 4. Optical coherence tomography images of MH with retinoschisis in high myopia. A 53-year-old woman presented with MH in high myopia without RD. **A.** The minimum MH diameter was 100 μm. Preoperative best-corrected visual acuity was 0.6. **B.** After surgery with the inverted ILM flap technique, MH was completely closed at 1 month. The foveal hyperreflective lesion was observed in the inner retina (asterisk). There were also disruptions of the IS/OS junction (between solid triangles) and the ELM line (between open triangles). The visual acuity was 0.5. **C.** Six months after surgery, SD-OCT showed a disrupted IS/OS junction (between solid triangles) with a restored ELM. The foveal hyperreflective lesion was still observed in the inner retina (asterisk). The visual acuity was 0.5.

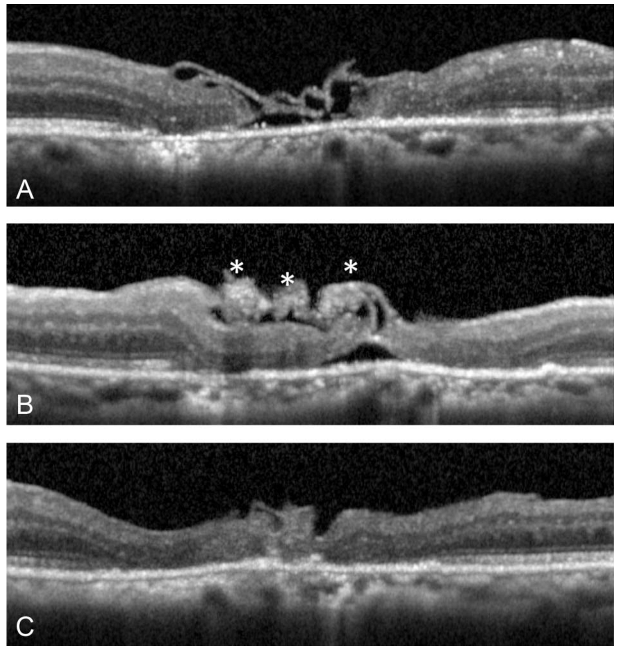

Fig. 5. Optical coherence tomography images of idiopathic large MH. A 73-year-old woman presented with idiopathic large MH. The minimum MH diameter was 818 μm. Preoperative BCVA was 0.07. By the primary vitrectomy with the inverted ILM flap technique, the epiretinal membrane and ILM were inverted. **A.** One month after surgery, the MH was not closed completely, and a thin ILM tissue covered the MH. **B.** Three months after surgery, MH was closed. Retinal layers at the margins of the MH approached and connected with one another forming a thin line of hyperreflective tissue (asterisks). **C.** After 6 months, the MH closed completely, and the loss of the photoreceptor layer was reduced. Postoperative BCVA improved to 0.2.

inner retina (asterisk). There were also disruptions of the IS/OS junction (between solid triangles) and ELM line (between open triangles). The visual acuity was 0.5. Six months after surgery, SD-OCT showed a disrupted IS/OS junction (between solid triangles) with a restored ELM (Figure 4C). The foveal hyperreflective lesion was still observed in the inner retina (asterisk). The visual acuity was 0.5.

Case 3

A 73-year-old woman presented with idiopathic large MH. The minimum MH diameter was 818 μm. Preoperative BCVA was 0.07. By the primary PPV with the inverted ILM flap technique, the epiretinal membrane and ILM were inverted. One month after surgery, the MH was not closed completely, and a thin layer of ILM tissue covered the MH (Figure 5A). Three months after surgery, the MH was closed. Retinal layers at the margins of the MH approached and connected with one another forming a thin line of hyperreflective tissue (Figure 5B). After 6 months, the MH closed completely and the loss of photoreceptor layer was reduced (Figure 5C). Postoperative BCVA improved to 0.2.

Discussion

Because Kelly and Wendel[1] reported the efficacy of vitrectomy for idiopathic MH in 1991, PPV with ILM peeling has been the gold standard for MH surgery and currently achieve a success rate of >90%.[21] However, idiopathic large MH and highly myopic MH with or without RD represent different situations. These MHs show poorer closure rates and visual functions than idiopathic MH.[4,22,23] An important factor influencing postoperative outcome is variation in postoperative MH closure types.[4,5] The U-shape closure is associated with the best functional results. In ~19% to 39% of idiopathic MHs, flat MH margins with bare retinal pigment epithelium, described as W-type closure, flat-closed MHs, or flat-open MHs, are observed.[4,5,20] Although this situation is considered an anatomical success, visual acuity remains limited in these eyes. In high myopia, OCT often demonstrates that surgically closed MHs by ILM dissection have not only flat borders but also bare pigment epithelium (i.e., are flat-open MHs).[4,20] In these eyes, visual acuity is usually limited (0.02–0.2). Regarding closing MHs, the inverted ILM flap technique to fill the MH with proliferating cells might have more advantages than the ILM dissection technique to relax the retina.[7] In this study, none of the MHs closed after surgery showed a flat-open appearance. Kawano et al[24] reported observing outer foveal defects after successful vitreous surgery in approximately half of the eyes with idiopathic MH during the early postoperative period and one third of the eyes at 12 months postoperatively, suggesting that it takes a longer than expected time to recover the normal foveal anatomy after surgery. In this study, postoperative outer foveal defects were observed in only 1 case (Case 4), and these disappeared at 6 months. These results suggest that foveal anatomical structure in MHs recovers from surgical closure better when the inverted ILM flap technique is used than when the ILM peeling technique is used.

Wakabayashi et al[10] reported that reconstruction of the foveal ELM in the early postoperative period helps predict subsequent restoration of the foveal photoreceptor layer and the potential for better visual outcomes. In this study, ELM was reconstructed in idiopathic large MH and in highly myopic MH without RD better than in highly myopic MH with RD. The postoperative BCVA was better in idiopathic large MH and highly myopic MH without RD than in highly myopic MH with RD, and BCVA did not differ significantly between the latter two groups. Our results might support the conclusion of Wakabayashi et al that the presence of the ELM is a critical structural feature significantly correlated with improved postoperative BCVA. In MH with RD, the foveal photoreceptor layer was restored at 6 months in only 1 case. This might suggest that the foveal photoreceptor layer in MH with RD is destroyed and not recoverable even after retinal reattachment with surgical closure of the MH.

Michalewska et al[6] hypothesize that the inverted ILM flap technique stimulates proliferation of glial cells that produce an environment conductive to the movement of photoreceptors into direct proximity to the fovea.

However, Ko et al[25] first described the "moderately reflective lesion" seen on ultrahigh-resolution OCT images as glial cell proliferative events taking place at the foveal defect during MH closure. They divided these lesions into two subtypes: 1) larger lesions of foveal reflectivity that replaced the entire intraretinal foveal layer, and 2) smaller lesions of moderate reflectivity restricted to the inner foveal layers. In our cases, both subtypes were seen on SD-OCT images (Figures 3 and 4). Hyperreflective foveal lesions were detected in 6 cases (30%; larger lesions in 3 cases and smaller lesions in 3 cases). In the report of Wakabayashi et al,[10] a hyperreflective lesion replacing all intraretinal layers at the fovea was found in all cases that showed disruption of the IS/OS junction and the ELM line. In contrast, when the IS/OS junction and the ELM line were restored, the reflective lesion was at the inner retina above the ELM line or was absent. However, there was no such correlation between the subtypes of hyperreflective foveal lesions and the reconstruction of the foveal photoreceptor layer in our series. This result suggests that the process of foveal reconstruction might differ between idiopathic MH surgically closed by the ILM peeling technique and idiopathic large MH and highly myopic MH surgically closed by the inverted ILM flap technique.

In summary, we evaluated the reconstructive change in foveal anatomy in MH surgically closed by PPV with the inverted ILM flap technique. The improvement in BCVA was significant in eyes with idiopathic large MH but not in eyes with highly myopic MH with or without RD. The postoperative SD-OCT examination demonstrated that restoration of the ELM was better in idiopathic large MH and highly myopic MH without RD than in highly myopic MH with RD. Restoration of the IS/OS junction was incomplete in eyes without a completely restored ELM. The results of this study suggest that the inverted ILM flap technique can lead to anatomical improvements in patients with idiopathic large MH and highly myopic MH without RD. To determine the actual anatomical and functional efficacy of PPV with the inverted ILM flap technique for the treatment of MH in highly myopic MH with or without RD, further prospective studies involving a larger number of patients will be required.

Key words: internal limiting membrane, high myopia, macular hole, spectral domain optical coherence tomography, vitrectomy, inverted internal limiting membrane flap technique.

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