Original Article

Indistinct retinal outer layers in the walls of the idiopathic full-thickness macular hole - A potential predictive biomarker for surgical outcomes

Rushik Patel, Kushal Delhiwala, Bakulesh Khamar

Purpose: To evaluate the absence of external limiting membrane (ELM) and ellipsoid zone (indistinct retinal outer layers, I-ROL) in the walls of idiopathic full-thickness macular holes (FTMHs) circumferentially on optical coherence tomography (OCT) and its correlation with surgical outcome. **Methods:** In this retrospective observational study, OCT images of patients undergoing vitrectomy for FTMHs with at least 3-months of postoperative follow-up were analyzed for preoperative circumferential extent of I-ROL. Derived macular hole indices such as hole form factor (HFF), macular hole index (MHI), tractional hole index (THI), and hole diameter ratio (HDR) were also calculated. The circumferential extent of I-ROL was correlated with derived hole indices as well as anatomical closure, foveal architecture, and restoration of ELM following surgery. **Results:** All nine eyes (eight patients) with FTMH (mean size: 610.11 ± 122.95 microns) in the study showed I-ROL in ≥1 quadrant. The mean HFF, MHI, THI, and HDR values were 0.72 ± 0.09, 0.35 ± 0.05, 0.71 ± 0.24, and 0.53 ± 0.14, respectively. All eyes achieved type-1 hole closure with improvement in best-corrected visual acuity to 0.58 ± 0.32 LogMAR from 0.81 ± 0.26 LogMAR. Regular foveal architecture was achieved in six eyes. Out of these, five eyes had I-ROL in ≥2 quadrants, and one eye had I-ROL in <2 quadrants (P = 0.0476). Restoration of ELM was seen in aforementioned six eyes (complete = 5, partial = 1). Out of the five eyes with complete ELM restoration, four had a circumferential extent of I-ROL in ≥2 quadrants (P = 0.0476). Complete restoration of ELM was associated with the complete restoration of the ellipsoid zone in three eyes. **Conclusion:** Preoperative circumferential extent of I-ROL in FTMH walls can be a potential predictive OCT marker for the type of closure, postoperative foveal architecture, and ELM restoration.

Key words: External limiting membrane, idiopathic full-thickness macular hole, indistinct retinal outer layers, Muller cells, type-1 closure

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Idiopathic full-thickness macular hole (FTMH) is characterized by neurosensory retinal defect involving the fovea.[1] It is formed by a disruption of the Muller cell cone and the external limiting membrane (ELM) secondary to mechanical stress exerted by anteroposterior and tangential tractional forces.[2] Surgical intervention relieves these forces and helps in the approximation of FTMH walls, thereby leading to hole closure.[3,4] Improvement in our understanding with regard to the development of FTMH and advances in optical coherence tomography (OCT) machines have led to the identification of preoperative OCT parameters that can help to predict surgical outcomes in FTMH. Some of these well-known parameters include minimum linear diameter, basal diameter, macular hole index (MHI), hole form factor (HFF), tractional hole index (THI), hole diameter ratio (HDR), and area indices.[5-11] Among them, MHI and THI can predict type-1 closure.[11] Following type-1 closure, reconstruction of the foveal ELM is known to help in predicting subsequent foveal photoreceptor layer restoration and the potential for better visual outcomes.[12] On baseline OCT, the ELM band is known to extend within the walls surrounding the FTMH, whereas the EZ band may stop at the edge of the walls.[13] We noticed the absence of both bands (ELM and EZ) in the walls of the FTMH in a patient who showed type-1 closure following vitrectomy.[14] This prompted us to evaluate the relationship between the extent of absent ELM and EZ bands (henceforth referred to as indistinct retinal outer layers, I-ROL) circumferentially within the walls of the FTMH and the type of closure achieved following surgery in this preliminary study.

Methods

This retrospective observational case series included patients with idiopathic FTMH who underwent 23-G pars plana vitrectomy with brilliant blue G dye (0.05%)-assisted internal limiting membrane (ILM) peeling and 14% perflouropropane gas tamponade under local anesthesia between March 2020 and September 2021 and who followed up for at least 3 months postoperatively. The exclusion criteria included eyes having coexistent ocular pathology, previously treated for vitreoretinal diseases, and operated for FTMH with ILM

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insertion technique. The study was performed according to the declaration of Helsinki. Preoperative work-up included best-corrected visual acuity (BCVA), intraocular pressure, slit-lamp evaluation, and dilated fundus examination. The FTMH was evaluated at baseline by using 6- and 9-mm length scans on swept-source OCT (Topcon DRI Triton, Tokyo, Japan). Twelve radial equal meridian scans centered on the fovea were taken. The resultant angle between two adjoining scans is 15°. This helps in evaluating the circumferential extent of I-ROL [Fig. 1]. Same scan protocols were repeated to look for postoperative outcomes at 2 months and thereafter. The size of the FTMH was determined as proposed by International Vitreomacular Traction Study.[15] Preoperative OCT images were evaluated by two trained retina specialists for 1) the absence of EZ and ELM bands (I-ROL) and their circumferential extent along the FTMH walls [Fig. 2a and b], and 2) preoperative measurements of minimum linear diameter, basal diameter, and MH height in microns. From these values, derived hole indices such as HFF, MHI, THI, and HDR were calculated as described in previous studies.[6-8,11]

Postoperative OCT images were evaluated for the type of hole closure and foveal architecture.[16] Fisher's exact test was used for determining the correlation between the preoperative circumferential extension of I-ROL and postoperative foveal architecture following hole closure. Fisher's exact test was also used for determining the correlation between I-ROL and postoperative restoration of ELM. Pearson correlation coefficient was used for determining the correlation between the circumferential extent of I-ROL and derived hole indices.

Results

The study included nine eyes with FTMH in eight patients (seven females) with a mean age of 64.33 ± 4.24 years. One female had bilateral FTMH. The mean size of the FTMH was 610.11 ± 122.95 microns. Preoperative baseline characteristics of the studied eyes are summarized in Table 1. All nine eyes showed the existence of I-ROL, the circumferential extent of which was 1 quadrant in four eyes, 2 quadrants in one eye, 3 quadrants in one eye, and 4 quadrants in three eyes. Values of derived macular hole indices were 1) HFF: 0.72 ± 0.09, 2) MHI: 0.35 ± 0.05, 3) THI: 0.71 ± 0.24, and 4) HDR: 0.53 ± 0.14. Two months following surgery, type-1 closure of the FTMH was seen in all nine eyes on OCT. This was associated with an improvement in BCVA from 0.81 ± 0.26 LogMAR to 0.58 ± 0.32 LogMAR.

Regular foveal architecture was achieved in six eyes. Out of these, five eyes had I-ROL in ≥2 quadrants, and one eye had I-ROL in <2 quadrants (P = 0.0476) [Table 2]. All six eyes showed restoration of ELM (complete = 5, partial = 1). Regular foveal architecture was not observed in three eyes where ELM was not restored.

Restoration of ELM was seen in six eyes (complete = 5, partial = 1). Out of the five eyes with complete ELM restoration, four had a circumferential extent of I-ROL in ≥2 quadrants, whereas one eye with partial ELM restoration also showed a circumferential extent of I-ROL in ≥2 quadrants. Complete restoration of ELM was associated with the complete restoration of EZ in three of the aforementioned four eyes having I-ROL in ≥2 quadrants [Fig. 2c and d]. Three eyes showed a lack of restoration for both ELM and EZ [Fig. 2e]. Preoperative and postoperative OCT scans of nine eyes are summarized in Figs. 3 and 4.

No correlation was observed between I-ROL and MHI, whereas there was a positive correlation between I-ROL and HFF and between I-ROL and THI, and negative correlation between I-ROL and HDR [Table 3].

Table 1: Baseline characteristics of patients with FTMH having preoperative existence of I-ROL

Parameters	Numbers and percentages
Age (years) (mean±SD)	64.33±4.24
Gender (male/female)	1/7
Lens status (phakic/pseudophakic)	4/5
Preoperative logMAR BCVA (mean±SD) (range)	0.81±0.26 (0.60–1.48)
Size of idiopathic FTMH (μ) (mean±SD) (range)	610.11±122.95 (493–867)
Large FTMH	9 (100%)
Vitreomacular traction (eyes, percentage)	4 (44%)
Cystoid changes in the walls of FTMH (eyes, percentage)	9 (100%)
Hyper-reflective spots on RPE at base of FTMH (eyes, percentage)	8 (89%)
CSS under the roof of FTMH (eyes, percentage)	2 (22%)
HFF (mean±SD) (range)	0.72±0.09 (0.57–0.85)
MHI (mean±SD) (range)	0.35±0.05 (0.29–0.45)
THI (mean±SD) (range)	0.71±0.24 (0.43–1.15)
HDR (mean±SD) (range)	0.53±0.14 (0.34–0.73)
Circumferential extent of I-ROL (eyes):	4
1 quadrant	1
2 quadrants	1
3 quadrants	3
4 quadrants	
LogMAR BCVA post FTMH closure (mean±SD) (range)	0.58±0.32 (0.18–1.0)
Type-1 closure pattern of FTMH (eyes, percentage)	9 (100%)
Restoration of distinct ROL post FTMH closure (eyes, percentage)	6 (66.66%)
Closure with regular foveal contour and restoration of ELM (eyes)	6
Closure with regular foveal contour and full restoration of ELM and full restoration of EZ (eyes)	3
Closure with regular foveal contour and full restoration of ELM with partial restoration of EZ (eyes)	2
Closure with regular foveal contour and partial restoration of ELM with partial restoration of EZ (eyes)	1

FTMH=Full-thickness macular hole, I-ROL=Indistinct retinal outer layers, BCVA=Best-corrected visual acuity, RPE=Retinal pigment epithelium, CSS=Cone shaped structure HFF=Hole form factor, MHI=Macular hole index, THI=Tractional hole index, HDR=Hole diameter ratio, I-ROL=Indistinct outer retinal layers, ELM=External limiting membrane, EZ=Ellipsoid zone

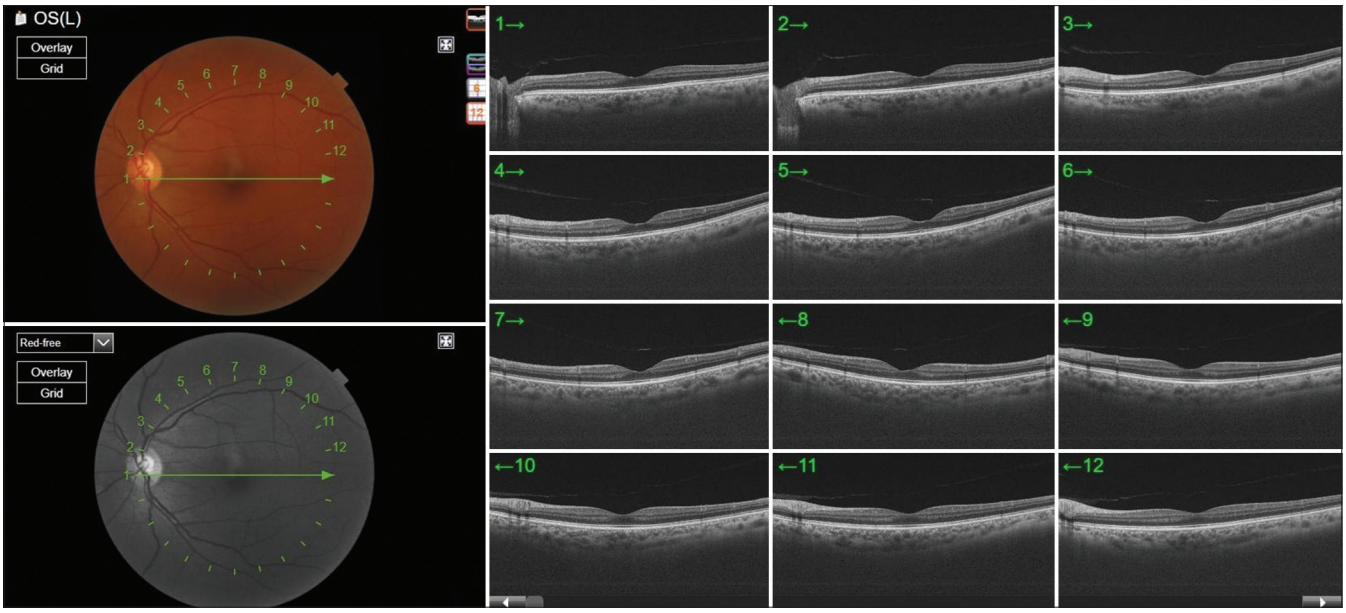

Figure 1: Image showing the method to measure/ estimate the circumferential extent of the I-ROL on the OCT b scan. IT shows 12 radial equal meridian scans centered on the fovea.The resultant angle between two adjoining scans is 15 degrees. This helps in evaluating circumferential extent of I-ROL

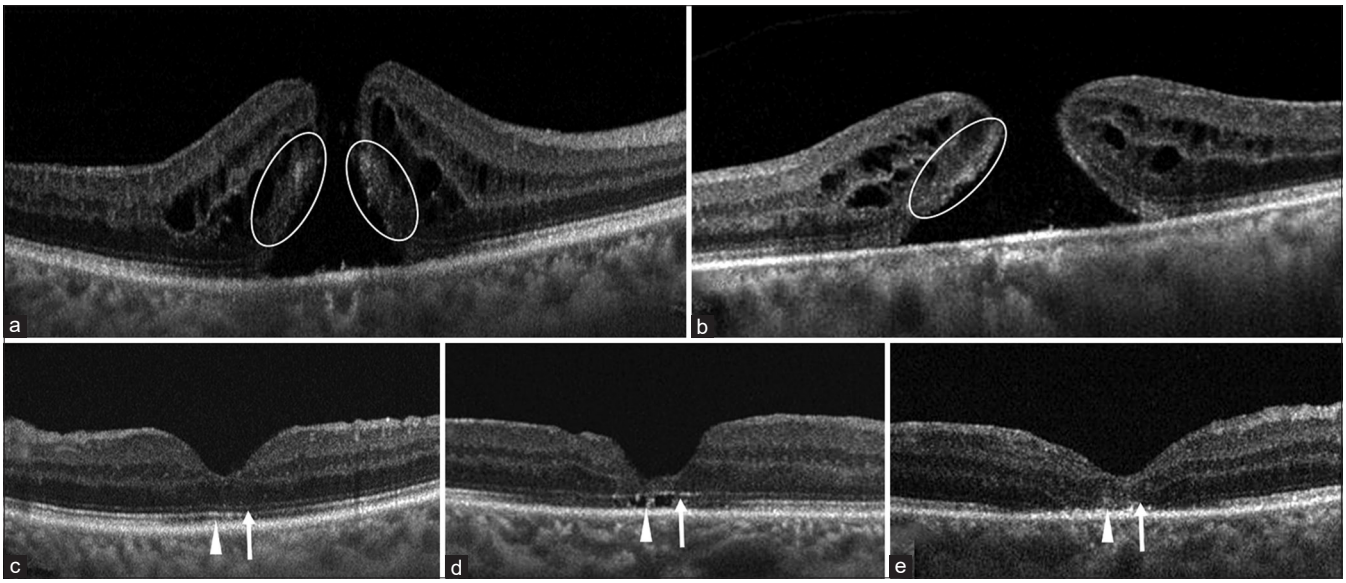

Figure 2: Representative optical coherence tomography images of the full-thickness macular hole (FTMH) showing preoperative existence of indistinct retinal outer layers (I-ROL) in the walls (oval marked areas) on both sides (a) and one side (b). Representative postoperative optical coherence tomography images showing changes in the external limiting membrane (ELM, white arrows) and ellipsoid zone (EZ, white arrowheads) following FTMH closure with complete restoration of both ELM and EZ (c), complete restoration of ELM and partial restoration of EZ (d), and no restoration of both ELM and EZ (e)

Discussion

In this study, we observed that eyes with FTMH having preoperative existence of I-ROL achieved type-1 closure postoperatively. This was noticed despite the values of HFF, MHI, and THI being lower than 0.9, 0.5, and 1.41 respectively, while HDR value being >0.6 in three of nine eyes.[6-8,10] THI primarily represents anteroposterior traction, whereas HFF and MHI consider both anteroposterior tractions.[10] Higher values of these indices are considered predictive of good anatomical closure following surgery. Similarly, HDR primarily represents tangential traction, and eyes with a preoperative HDR value of < 0.6 have a higher chance of achieving type-I closure.[11] Based on the above understanding, elimination of tractional components following surgery should increase the chances of predominantly type-1 closure. However, some indices such as MHI, THI, and HDR have been found to predict type-1 closure, whereas outer diameter and DHI have been found to predict type-2 closure.[10] A previous study also showed 100%

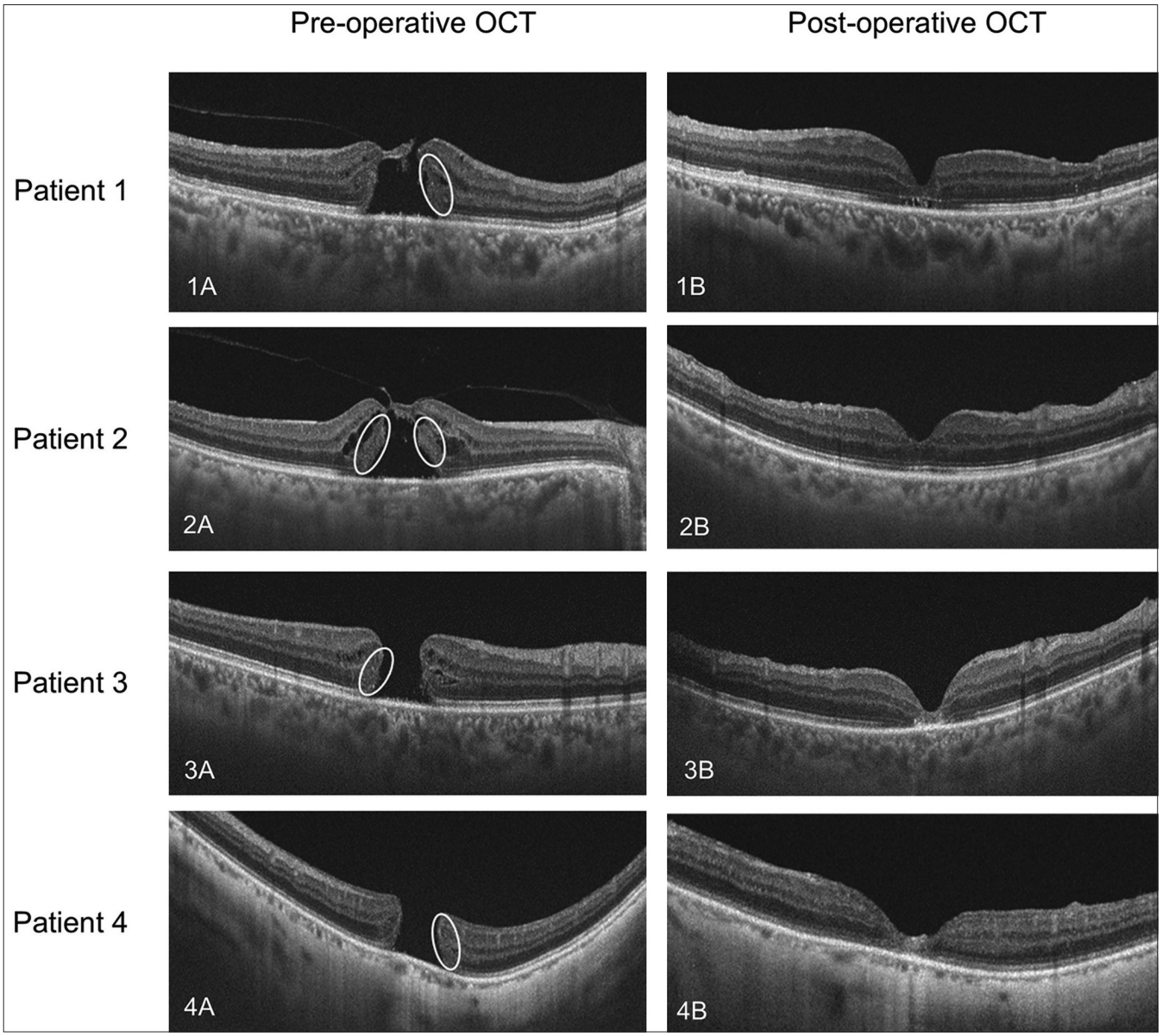

Figure 3: Pre- and post-operative OCT scans of first 4 cases. (1,2,3,4) A are preoperative images of 4 eyes. White oval demarcates I-ROL. AQ1(1,2,3,4) B are post operative images of 4 eyes

anatomical success with the inverted flap method in large FTMHs, irrespective of OCT indices.[17] This may be due to the use of linear measurements and lack of consideration for the postoperative restoration process during the calculation of these hole indices. Restoration of retinal layers following FTMH closure is a variable biological process and involves the formation of a temporary hyperreflective glial scar near and at ELM. This is mediated by the outer processes of the Müller cells of the foveal walls and parafovea, which seal the outer fovea and thereby contribute to the regeneration of outer layers at the fovea.[18] Centripetal contraction of Muller cell processes also leads to central displacement of photoreceptor cell somata near and at ELM.[19]

In this study, five eyes having a circumferential extent of I-ROL in ≥2 quadrants, showed restoration of ELM, whereas among four eyes having I-ROL in <2 quadrants, only one eye showed restoration of ELM. This suggests that the presence and circumferential extent of I-ROL can be a good predictor of type-1 closure and restoration of ELM. ELM is the first among outer retinal layers to recover following FTMH closure.[20] This is followed by the gradual restoration of EZ with the prerequisite of an intact outer nuclear layer (ONL).[21,22] ELM is thought to be composed of Muller cells' terminal processes which surround photoreceptor cells.[23]

The Muller cell cone along with the Muller cells of foveal walls and parafovea provide structural stability to foveola and outer foveal layers, respectively.[24] Disruption of the Muller cell cone following anteroposterior traction is responsible for the initiation of FTMH formation.[25,26] As Muller cells are involved in the pathogenesis of FTMH and are also known to play an important role in the closure of the hole followed by restoration of ELM, we presume that I-ROL observed in the walls of FTMHs in this

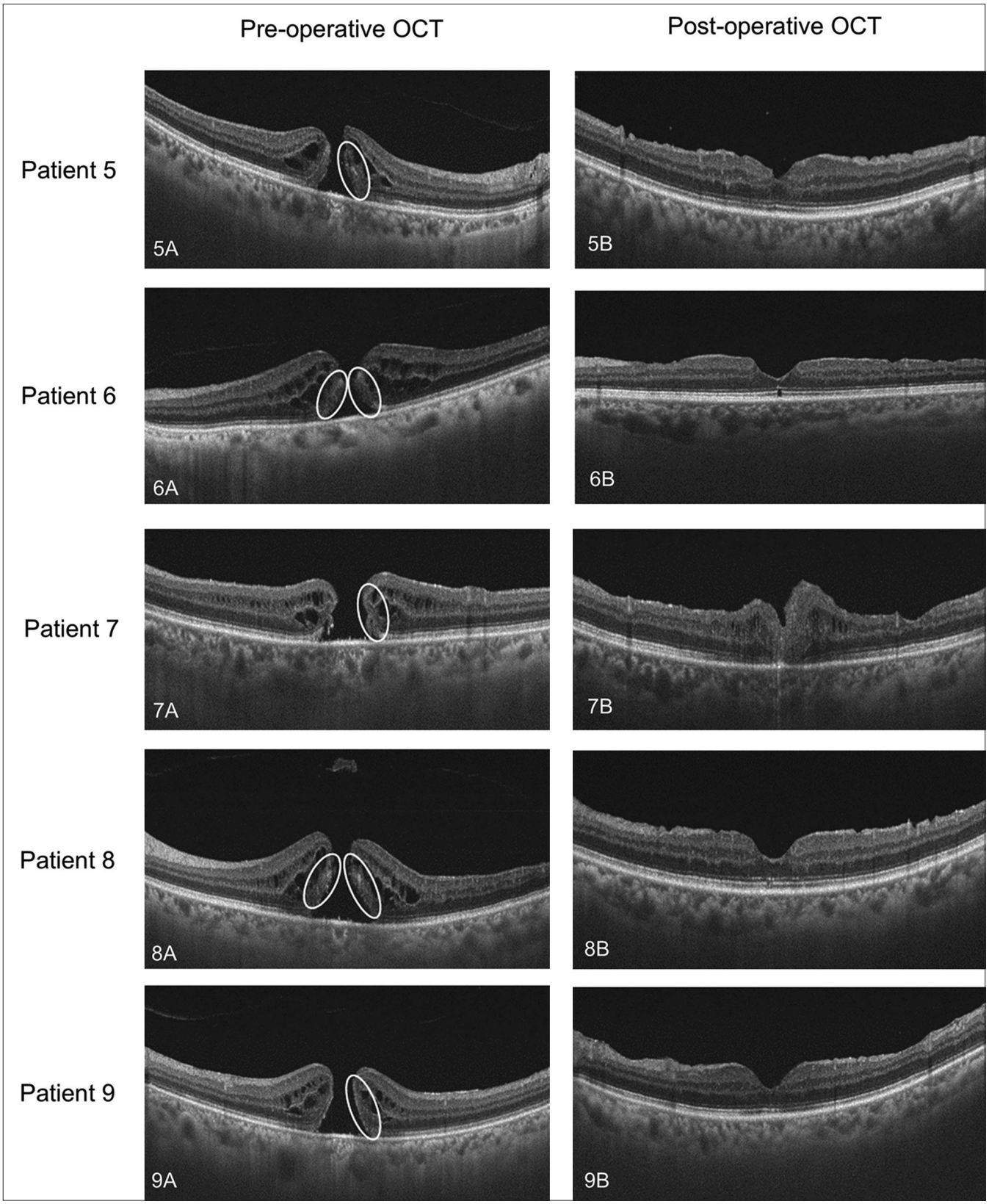

Figure 4: Pre- and post-operative OCT scans of next 5 cases. (5,6,7,8,9) A are preoperative images of 5 eyes. White oval demarcates I-ROL. AQ1 (5,6,7,8,9) B are post operative images of 5 eyes

study is likely to be activated Muller cells. The circumferential extent of I-ROL provides a quantitative estimate of Muller cells' response. This may explain the relationship between I-ROL in ≥2 quadrants and achieving regular foveal architecture following surgery. This again suggests that the existence of I-ROL may be related to Muller cells in the walls of FTMHs.

Table 2: Preoperative circumferential extent of I-ROL and anatomical outcome after FTMH surgery

Anatomical outcome (*N*=number of eyes out of 9)	Circumferential extent of I-ROL *n*=number of eyes			
	≥1 to<2 quadrants *n*=4	≥2 to<3 quadrants *n*=1	≥3 to<4 quadrants *n*=1	4 quadrants *n*=3
Closure with regular foveal contour with complete ELM+EZ restoration (*N*=3)	1	1	0	1
Closure with regular foveal contour with complete ELM and partial EZ restoration (*N*=2)	0	0	1	1
Closure with regular foveal contour with partial restoration of both ELM and EZ (*N*=1)	0	0	0	1
No restoration of ELM and EZ with irregular foveal architecture (*N*=3)	3	0	0	0

I-ROL=Indistinct retinal outer layers, FTMH=Full-thickness macular hole, ELM=External limiting membrane, EZ=Ellipsoid zone

Table 3: Correlation between circumferential extent of I-ROL and other derived hole indices

Derived hole index	Coefficient (Pearson's *r*)	*P*
HFF	0.372	0.324
MHI	-0.015	0.969
THI	0.612	0.080
HDR	-0.675	0.046

HFF=Hole form factor, MHI=Macular hole index, THI=Tractional hole index, HDR=Hole diameter ratio

Postoperative visual recovery in FTMH follows the restoration of ELM and/or EZ, which was found to be dependent on the circumferential extent of I-ROL in this study.[27,28] Thus, the circumferential extent of I-ROL may be a predictor of visual outcome following surgery.

Limitations of the present study include a small number of study eyes and the retrospective nature of the study. Moreover, there was a lack of control group with eyes having FTMH and preoperative presence of distinct ELM and EZ bands (absence of I-ROL). We did not come across eyes with the absence of I-ROL during our study period. In addition, the previously utilized OCT machine did not provide radial scan protocol. Furthermore, lack of long-term follow-up for assessing progressive changes in ROL and associated improvement in visual acuity was another limitation. Based on the findings of this study as well as the review and analysis of the literature, we believe that eyes having a large FTMH and the presence of I-ROL will have a better outcome (hole closure and restoration of outer retinal layers) compared to eyes without I-ROL. This can be confirmed with a prospective larger study.

Conclusion

To conclude, preoperative I- ROL within the walls of the FTMH and its circumferential extent on OCT can be a good predictive marker for the anatomical outcome of FTMH surgery and needs to be evaluated in a larger series with a long-term follow-up.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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