

# Outer retina reconstruction following inverted internal limiting membrane flap technique for large macular holes

Ogugua N. Okonkwo, Adekunle O. Hassan, Michael E. Gyasi<sup>1</sup>, Olufemi Oderinlo

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## Abstract:

**PURPOSE:** The aim of this study is to investigate the outer retina reconstruction using postoperative spectral domain optical coherence tomography (SD OCT) in large diameter macular holes (MHs) treated with the inverted internal limiting membrane (ILM) flap technique.

**METHODS:** A retrospective study of 14 consecutive eyes that had vitrectomy and inverted ILM flap technique for MHs with a base diameter of 400  $\mu$  or greater. Preoperative and postoperative SD OCT images were assessed for MH closure and for outer retina presence; represented by the external limiting membrane (ELM) and ellipsoid zone (EZ), in the subfoveal and parafoveal areas.

**RESULTS:** The average MH base diameter was 963  $\mu$ . Postoperative SD-OCT revealed an absence of the outer retina in six eyes, a continuous (regular) presence of the outer retina in four eyes, and a discontinuous (interrupted) presence in four eyes. There was an inverse relationship between MH size and presence or absence of ELM and EZ. A larger MH base diameter size was associated with a higher probability of an absent ELM and EZ ( $P = 0.04$ ). Eyes in which an outer retina was present postoperatively achieved 6/18 and better vision compared to eyes without ( $P = 0.08$ ).

**CONCLUSION:** The outer retina in some large MHs treated with ILM flap technique can undergo reconstitution and remodeling which improves over time. The average size for MHs with complete reconstitution was 652  $\mu$ , 855  $\mu$  for those with interrupted reconstitution, and 1242  $\mu$  for eyes with no outer retina reconstruction. This suggests that MHs having a size within the limit of the no outer retina reconstitution MH group may be candidates for other surgical techniques in which postoperative outer retina presence is expected.

## Keywords:

Internal limiting membrane, macular hole, optical coherence tomograph, vitrectomy

## INTRODUCTION

The closure of idiopathic macular holes (MHs) following conventional vitrectomy surgery is related to the preoperative MH diameter, with MHs smaller than 400  $\mu$  demonstrating higher anatomical success rates, and lesions larger than 400 or 500  $\mu$  having poorer anatomical closure rates.<sup>[1]</sup> The inverted internal limiting membrane (ILM) flap technique has been shown to have superior anatomical and visual results when compared to conventional ILM peel technique for large sized idiopathic MHs, myopic MHs and MH retinal detachments.<sup>[2-5]</sup> Some authors report outcomes close to or even

equal to 100% anatomical success rates using the inverted ILM flap technique. The inverted ILM flap technique has grown in popularity and therefore has become an important surgical technique for the repair of this category of large sized MHs. The safety of this technique has been further improved with the introduction of the temporal inverted ILM flap.<sup>[6]</sup> However, in several cases of successful closure of the MH, the outer retina may not be present as is desired and seen in successfully closed smaller size MH repaired with the conventional ILM peel technique.<sup>[1,7]</sup> The presence of the outer retina is an important outcome of successful intervention following MH repair.<sup>[7-9]</sup>

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Department of Ophthalmology,  
Eye Foundation Retina  
Institute, Ikeja, Lagos, Nigeria,  
<sup>1</sup>Department of Ophthalmology,  
St Thomas Eye Hospital,  
Accra, Ghana

## Address for correspondence:

Dr. Ogugua N. Okonkwo,  
27 Isaac John Street,  
GRA, Ikeja, Lagos, Nigeria.  
E-mail: o\_okonkwo@yahoo.  
com

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The postoperative absence of the outer retina implies that the MH though closed anatomically may be limited functionally since the outer retina is an important component for visual function.<sup>[8,10,11]</sup> Such large MHs may require other yet to be determined intervention that offers superior outcomes in reconstructing the outer retinal layers. We propose that further categorization of such large diameter MHs based on the preoperative anatomical size will be helpful to identify those eyes with less probability of postoperative reconstruction of the outer retina after attempted repair using the inverted ILM flap technique.

The spectral domain optical coherence tomogram (SD OCT) provides near histological section of the retina and makes it possible to determine the microstructure of both the inner and outer layers of the retina and foveomacular area.<sup>[7,12,13]</sup> Several studies have considered OCT evaluation of preoperative and postoperative features of MHs.<sup>[1,4,7]</sup> In smaller size MHs treated with conventional ILM peel surgery, closure of the MH in a majority of the cases is usually followed by reconstitution of the outer retinal layers, mainly the external limiting membrane (ELM) and ellipsoid zone (EZ) also known as the inner segment/outer segment junction.<sup>[1]</sup> Though there are several reports on the retinal microstructure following MH surgery, there are fewer reports on the outer retina following inverted ILM flap technique for larger size MHs. The purpose of this study is to investigate the outer retinal layer reconstitution following MH surgery using the inverted ILM flap technique for idiopathic MHs with a base diameter of 400  $\mu$  and larger measured using the SD OCT. We seek to show the predictive value of idiopathic MH size on achieving outer retinal reconstruction following an inverted ILM flap technique.

## METHODS

A retrospective interventional case series involving SD OCT (Optovue) reviews of preoperative and postoperative images of 14 consecutive eyes of 14 patients that had an inverted ILM flap technique for repair of idiopathic MH with a base diameter of 400  $\mu$  or greater was done. Since the study only involved a retrospective review of case records and images, the institutional review board waived the need for ethical approval. The research was performed according to the principles of the Helsinki declaration.

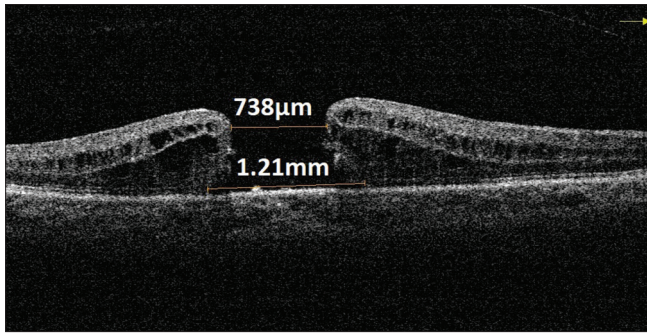
All patients had been diagnosed to have an idiopathic MH after a clinical assessment at the institute's retina clinic. None of the eyes had undergone physical trauma. The clinical assessment involved a Snellen visual acuity, intraocular pressure assessment, slit-lamp biomicroscopy, digital fundus photography, and SD OCT (Optovue) assessment of the macula. A MH was diagnosed when there was a full-thickness defect in the foveomacular area. The MH base diameter was determined using the SD OCT, as illustrated in Figures 1-3. The MH base diameter was used for size determination since the emphasis of the study was on the outer retina, and for purposes of uniformity and reproducibility of MH dimensions. After surgery, a MH was deemed to have closed when SD

OCT demonstrated the presence of tissue covering the entire area of the previous defect, as shown in Figures 4 and 5. One surgeon, ONO, performed all fourteen surgeries between April 2015 and January 2017.

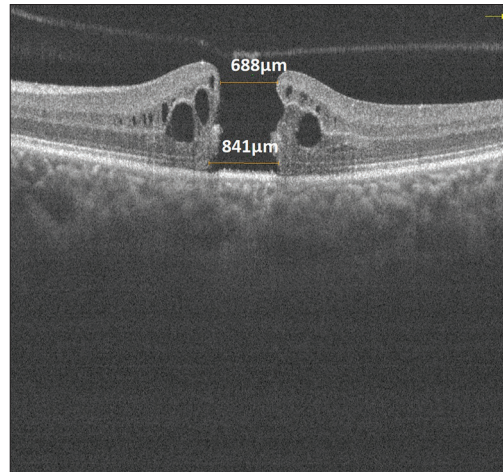
The surgical technique involved a 23G pars plana vitrectomy in all 14 eyes. After a core vitrectomy, triamcinolone crystals were used to highlight residual vitreous. Complete vitreous separation was performed. Duo blue (a combination of Brilliant Blue G and Trypan Blue) was used to stain both ILM and any epiretinal membrane present, by applying the cold dye from a close position within the vitreous cavity onto the surface of the retina in a fluid filled eye with infusion turned off for approximately 60 s. The infusion was reopened, and the excess dye was irrigated out from the vitreous cavity. This provided sufficient staining and visualization of the ILM. An ILM flap was initiated about 1-2-disc diameters away from the MH margin and peeled to a position close to the edge of the MH. The mobilized flap was then folded (inverted) over the MH and left to lie over it. In the earlier cases ( $n = 4$ ), an effort was made to reduce the size of the ILM flap by trimming the edge of the ILM flap using the vitreous cutter in a low vacuum mode. This step was not undertaken in the latter cases ( $n = 10$ ) as the size of the flap was made smaller (by peeling a smaller area of ILM) and required no trimming. An air fluid exchange completed the surgery. The tamponade agent used was SF6, C3F8, or air. In the initial cases, SF6 (16%) or C3F8 (10%) gas was used (depending on which gas was available at the time of surgery). Air was used in the last four eyes. Face down position was adopted for 3–5 days in the initial cases ( $n = 3$ ), but in the latter cases ( $n = 11$ ), only 1 day of supervised face down positioning was required. All the patients gave written informed consent before the surgery was performed.

Postoperatively, the patients were examined on day 1, week 1, and month 1 and at any other clinic visit including months 3 and whenever the patients attend the clinic. The postoperative examination involved an assessment of the best Snellen visual acuity, intraocular pressure, slit-lamp examination, and dilated funduscopy. SD OCT (Optovue) evaluation involving a scan through the center of the fovea was performed at months one and at subsequent visits to assess for MH closure. Furthermore, two of the patients had a postoperative OCT angiography examination. The postoperative visual acuity was categorized into the numbers of Snellen line gain or loss.

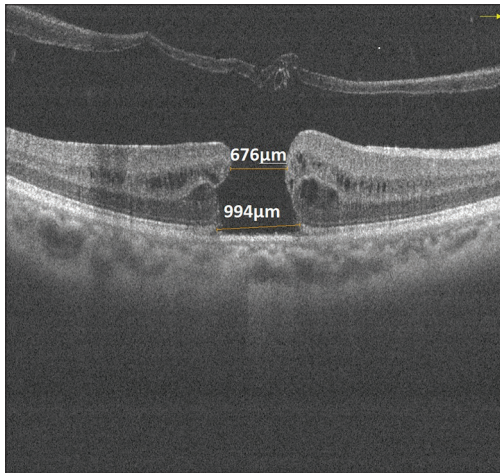
In consideration of the outer retina structure, the presence (P) or absence (A) of the EZ and the ELM in the subfoveal and parafoveal area was considered. If there was no presence of the EZ or ELM in the subfoveal and parafoveal area, this was taken as "Absent; (A)" as illustrated in Figure 6. If there was a presence of both the EZ and the ELM in the subfoveal area and this was continuous with the parafoveal component of the layers, this was categorized to be "Present Continuous; (PC)" or regular; in which case there is a continuity between the subfoveal and parafoveal component of both layers as illustrated in Figure 7. When the EZ and ELM was present



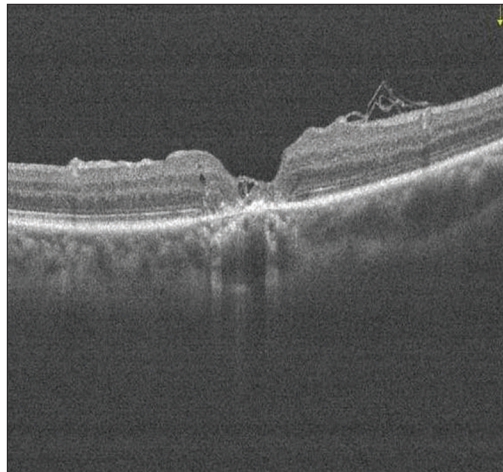
**Figure 1:** This is a 24-month-old chronic macular hole measuring 1.21 mm in its base diameter, which was closed with using the inverted internal limiting membrane flap technique and 16% SF6 gas tamponade



**Figure 2:** This is a 2-month-old macular hole measuring 0.841 mm in its base diameter; which was closed using the inverted internal limiting membrane flap technique and 10% C3F8 gas tamponade



**Figure 3:** This is a 5-month-old macular hole measuring 0.994 mm in its base diameter; which was closed using the inverted internal limiting membrane flap technique and 10% C3F8 gas tamponade



**Figure 4:** This is the postoperative optical coherence tomography image of a closed 1.50 mm based diameter, 12-month-old macular hole. Observe hyperreflective tissue within the foveal depression and piece of floating internal limiting membrane tissue on the parafoveal retina

in the subfoveal area, but both or one layer was not entirely continuous with the parafoveal extent of the layers, this was categorized as “Present Broken; (PB)” or discontinuous or irregular. This is illustrated in Figure 8.

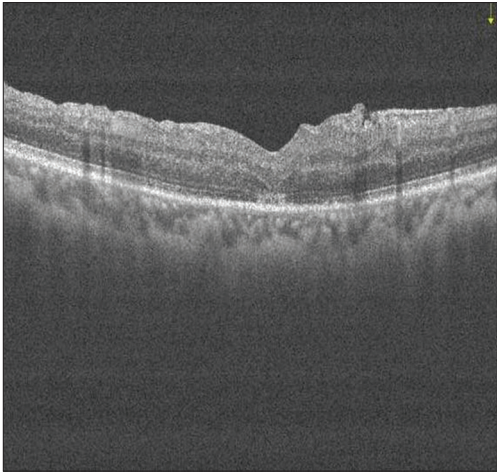
The preoperative measurement of MH size, including the MH base diameter with OCT, has been found to provide a prognostic factor for postoperative visual outcome and anatomical success rate after MH surgery.<sup>[14]</sup> An OCT-based anatomic classification system for MHs has been developed by the international vitreomacular traction study (IVTS) group.<sup>[15]</sup> The IVTS group subclassified full-thickness MH by size of the hole as determined by OCT and the presence or absence of VMT. The classification was into small (<250 microns), medium (>250–400 microns), or large (>400 microns).<sup>[15]</sup> Therefore, to determine the correlation of preoperative MH base diameter size with postoperative outer retina presence or absence, the large MHs were further categorized into two based on the base diameter size. Category B MHs were MHs with base size 401–1000 µ and Category C, 1001 µ, and above. Correlation of the MH size with the presence or absence of the outer retina layers was analyzed using the Fisher’s exact test in which a  $P < 0.05$  was taken to be significant.

## RESULTS

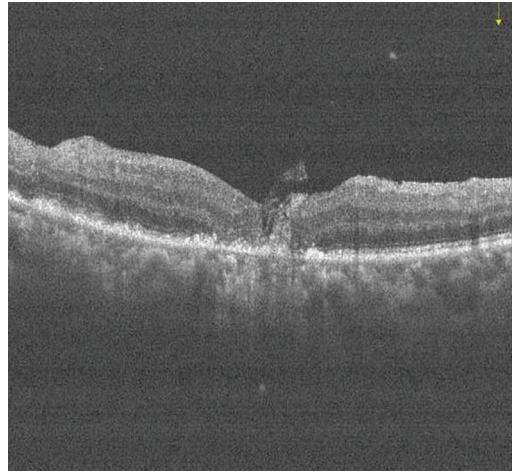
The patient demographics, MH characteristics, tamponade used, the outcome of surgery, and OCT features are shown in Table 1.

There were slightly more females (57%). Five eyes were myopic with a refraction ranging from 0.75Ds to 5.50DS (average-3.50DS). The MH symptom duration ranged from 1 to 60 months (average 16 months). The mean duration of follow-up for all study participants was 11.6 months. The preoperative Snellen visual acuity ranged from CF to 6/24 and a summary of this is shown in Table 2.

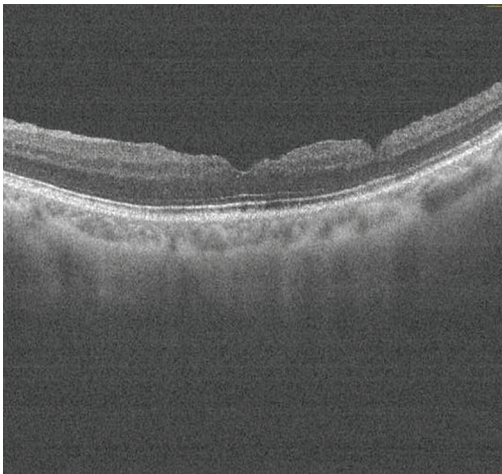
With respect to tamponade agent, details of all the tamponade is shown in Table 1. We observed that air could be used effectively with the inverted ILM flap technique as a tamponade for large size MHs measuring up to 1450 µ.



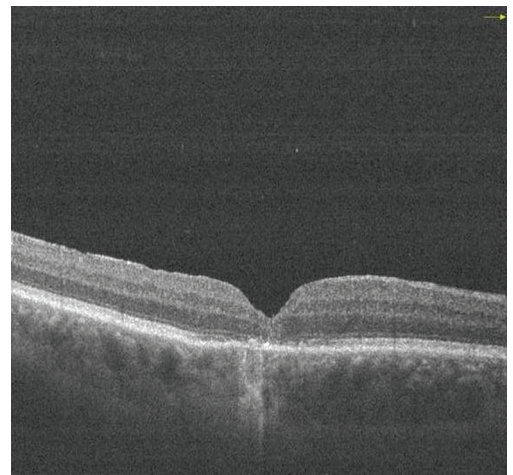
**Figure 5:** This is the postoperative optical coherence tomography appearance of a closed macular hole



**Figure 6:** This is the postoperative optical coherence tomography of a closed macular hole with "A" absence of outer retina, seen as the absence of ellipsoid zone and external limiting membrane in the subfoveal area



**Figure 7:** This is the postoperative optical coherence tomography appearance of a closed macular hole with "PC" continuous presence and regularity of subfoveal and parafoveal ellipsoid zone and external limiting membrane



**Figure 8:** This is the postoperative appearance of a closed macular hole with "PB" discontinuous presence, broken (interrupted) and irregular ellipsoid zone and external limiting membrane

There was a complete closure of the MH in all 14 eyes translating to a 100% single operation anatomical success. One eye had a 5-Snellen line gain in vision while two eyes had a 4-Snellen line gain in vision. Other eyes had significant visual benefits, as shown in Table 3. In four eyes, vision remained unchanged from preoperative level. No eye lost vision from initial preoperative level.

A representative scatter plot in LogMAR conversion of preoperative versus postoperative Snellen visual acuity is shown in Figure 9.

In respect of postoperative outer retina reconstruction of ELM and EZ, there were six eyes with Absent (A) outer retina; 4 eyes each with PC and PB outer retina outcomes.

Table 1 includes the MH size correlation with the presence or absence of outer retina and includes the preoperative vision and postoperative visual outcome. The average MH size for

all the 14 MHs was 965  $\mu$ . Average MH size for the six A eyes was 1242  $\mu$ . The average MH size for PB was 855  $\mu$  and for PC was 652  $\mu$ . Figures 6-8 illustrates representative OCT images of three eyes with A, PC, and PB outer retina outcomes. Analysis of MH base diameter size and outer retina reconstruction was done, based on MH categorization into B and C as shown in Table 1. Amongst MHs with base diameter size between 400 and 1000 (category = B), of 8 eyes there was 1 A (12.5%), 4 PC (50.0%) and 3 PB (37.5%). For MH > 1000 (category = C), of 6 eyes there was 5 A (83.3%) 1 PB (17.7%) and 0 PC. The *P* value = 0.048 (*P* < 0.05) indicating a significant correlation between the MH base size and postoperative presence or absence of the EZ and ELM. Since it was noticed that Category C MHs recorded more A (83.3%) than PC or PB, it suggests that the larger base diameter MHs were more likely to have a postoperative absence of the outer retina (EZ and ELM).

**Table 1: Demographics, macular hole characteristics, and outcome of surgery**

Age	Gender	Laterality	MH size (microns)	MH duration (months)	Preoperative VA	Tamponade agent used	Postoperative VA	MH category	ELM	EZ
58	Male	OS	400	1	6/36	SF6	6/9	B	PC	PC
56	Female	OS	500	4	6/36	SF6	6/36	B	PB	PB
59	Male	OS	640	3	6/60	C3F8	6/9	B	PC	PC
56	Male	OS	718	24	6/36	Air	6/18	B	PC	PC
73	Male	OS	777	2	6/24	Air	6/12	B	PB	PB
47	Female	OS	850	2	6/60	C3F8	6/36	B	PC	PC
53	Female	OS	900	60	6/36	Air	6/36	B	A	A
63	Female	OD	1000	5	6/36	C3F8	6/24	B	PB	PB
59	Male	OD	1100	6	6/36	C3F8	6/36	C	A	A
62	Male	OD	1140	3	6/60	SF6	6/12	C	PB	PB
68	Female	OD	1200	24	CF	SF6	6/36	C	A	A
76	Female	OD	1300	24	6/36	SF6	6/36	C	A	A
70	Female	OD	1450	60	6/36	Air	6/24	C	A	A
62	Female	OS	1500	12	6/36	SF6	6/18	C	A	A

MH=Macular hole; VA=Visual acuity; CF=Counting fingers; SF6=Sulphur hexafluoride gas; C3F8=Perfluoro propane gas; Category B=Base size 400-1000 μ; Category C=Base size>1000 μ; ELM=External limiting membrane; EZ=Ellipsoid zone; PC=Present continuous; PB=Present broken; A=Absent

**Table 2: Summary of preoperative Snellen visual acuity**

Preoperative snellen visual acuity	Number of eyes
Counting fingers	1
6/60	3
6/36	9
6/24	1
Total	14

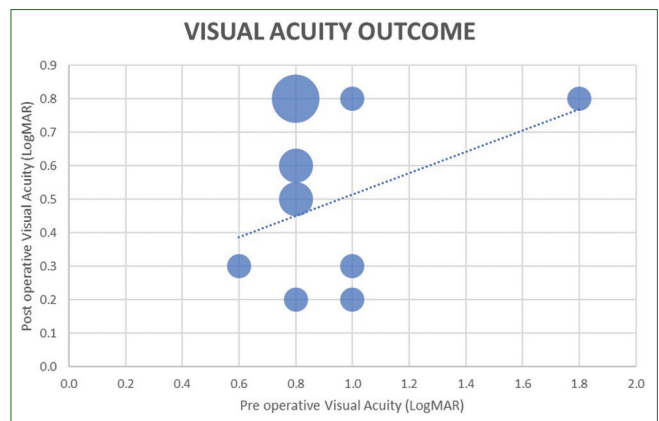
**Table 3: Summary of postoperative change in Snellen line**

Snellen acuity line change	Number of eyes
Same (no change)	4
1 line gain	3
2 line gain	4
4 line gain	2
5 line gain	1
Total	14

Correlating outer retina presence with postoperative change in visual acuity; there was a trend towards improved postoperative Snellen visual acuity in eyes with a present outer retina when compared with eyes with absent outer retina. Six (75%) of eight eyes with a presence of outer retina had an improvement in postoperative vision compared with three (50%) of 6 eyes with an absence of outer retina ( $P=0.33$ ). Furthermore, five (62.5%) of 8 eyes with outer retina presence had two or more-line improvement in Snellen acuity compared with 2 (33%) of 6 eyes with an absent outer retina. Finally, five (62.5%) of 8 eyes with outer retina presence had a postoperative vision of 6/18 or better, compared with 1 (16.7%) of 6 eyes with no outer retina presence ( $P=0.08$ ). Details of these findings are shown in Table 1.

## DISCUSSION

The anatomical success following MH surgery has greatly improved over the years and this includes the category of difficult MHs with a large diameter and those associated with



**Figure 9:** A scatter plot of the preoperative versus the postoperative Log Mar equivalent of Snellen visual acuity

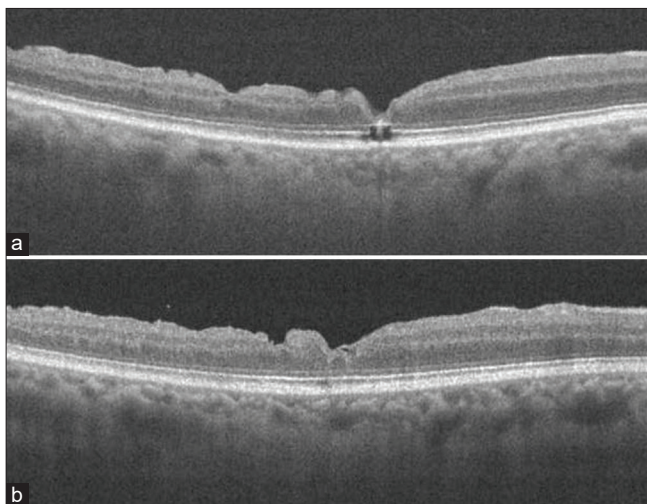
high myopia and retinal detachment.<sup>[2,5,16,17]</sup> Techniques that have been employed to manage such difficult cases include the inverted ILM flap technique, free ILM graft, autologous lens capsule with autologous blood, MH hydro dissection, and lastly autologous retina transplant.<sup>[5,18-20]</sup> Fortunately, these cases are not common. The inverted ILM flap technique has gained popularity because of successes reported by several authors. Michalewska *et al.* hypothesize that the inverted ILM flap technique stimulates the proliferation of glial cells that produce an environment conducive to the movement of photoreceptors into direct proximity to the fovea.<sup>[2]</sup> The outer retina has been shown to be a predictor of visual outcome as it contains the photoreceptors, which are essential for vision.<sup>[7,11,20-22]</sup> A reconstitution of the outer retina postoperatively in these large sized MH cases implies a functional improvement in vision is anticipated aside from anatomical success.

In our current review of 14 eyes, there was a reconstitution of the outer retina in eight eyes (57%). Four of these eyes (average MH base diameter of 652 μ) had a complete and continuous reconstruction of the outer retina layers while another

four (average MH base diameter of 855  $\mu$ ) had a broken, fragmented reconstruction of the outer retina. These eight eyes had a demonstrable anatomical and functional benefit since the outer retina was present on SD OCT examination. It is expected that over time there may be a further improvement in the microstructure including the outer retina of these eyes as shown by Kawano *et al.* and Michalewska *et al.* who noted that further improvement in the retina microstructure and outer retina occurred from between 6 months to 12 months postsurgery after the inverted ILM flap surgery.<sup>[9,23]</sup> We noticed that four (40%) out of the ten eyes that had 10 months or more of follow up showed a continued remodeling of the foveal microstructure postoperatively with significant improvement in the appearance of foveal microstructure and foveal contour. The most significant change was seen in patient 4 in who over a 16 month follow-up period, an obvious outer foveal defect gradually reduced in size and eventually disappeared. This is shown in Figure 10a and b.

Reports on the foveal microstructure following inverted ILM flap technique are few. Hayashi *et al.* noted that postoperative reconstruction of ELM appeared to occur after the inverted ILM flap technique in idiopathic MH and highly myopic MH, but not in highly myopic MHs associated with retina detachments.<sup>[4]</sup> In an earlier study, Wakabayashi *et al.* reported that reconstruction of the foveal ELM in the early postoperative period helps predict the subsequent restoration of the foveal photoreceptor layer and the potential for better visual outcomes.<sup>[21]</sup> We noticed that in the 14 eyes studied, the ELM and EZ appeared to be present or absent together. This assertion by Wakabayashi may explain this finding.

Kitaya *et al.* have demonstrated that irregularity of the photoreceptor layer after successful MH surgery may prevent visual acuity improvement.<sup>[11]</sup> They reported that the percentage of regular OCT images in the group with good visual acuity was significantly higher than that in the group with poor visual acuity. Our findings agree with this

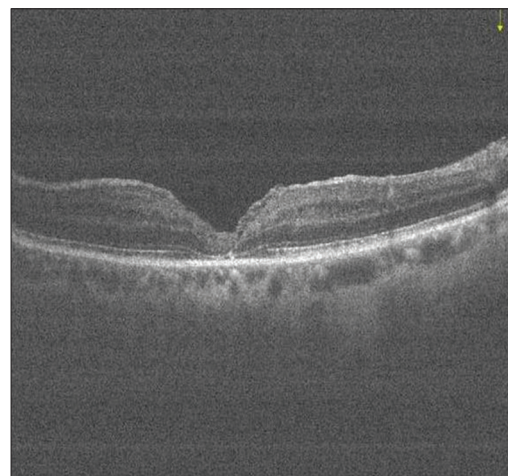


**Figure 10:** The postoperative outer foveal defect is shown (a); which is seen to resolve after 16 months of follow-up (b)

observation. In our study, of the 6 eyes in the group with postoperative visual acuity of 6/18 or better, 5 (83%) had a present EZ and only 1 eye had an absent EZ. Therefore, the postoperative reconstruction of the foveal microstructure including the outer retina does correlate with visual recovery and is perhaps the most significant factor affecting the postoperative visual acuity, but it is certainly not the only factor. To illustrate this point, there were some of the cases in this series with some degree of reconstruction of the ELM and EZ but with no improvement in vision. In one such case, we noticed the absence of the COST (cones outer segment tips line or IZ-interdigitation zone layer), as shown in Figure 11, which could be responsible for the lack of anticipated improvement in vision. This is one of the important ways in which the OCT is able to explain the reason for poorer than expected postoperative visual outcomes.

Another factor that may play a significant role in postoperative visual recovery is the duration of the MH. MHs with a history >6 months predictably have been shown to have poor visual recovery compared to those that present earlier.<sup>[11]</sup> This may in part account for the observation that the patients with the shortest symptom duration in our series regained the best postoperative vision of 6/9 and 6/12. The average duration for the three eyes with the best postoperative vision was 2 months, compared to approximately 16 months for the entire case series.

Some of the outer retina abnormalities detected on ultra-high-resolution optical coherence tomography of surgically closed MHs include outer foveal defects, persistent foveal detachment, and moderately reflective foveal lesions.<sup>[7]</sup> In our study, the incidence of outer foveal defect abnormalities using the SD-OCT (Optovue) for postoperative evaluation was 2 (14%) out of the 14 eyes. There was no eye with a persistent foveal detachment. Two eyes were noted to have suffered a defective COST. The reason for this COST defect is not clear but could be related to phototoxicity, toxicity from the dye, or surgery-induced trauma. These two eyes did not



**Figure 11:** This figure shows that there is a postoperative absence of the COST layer; though there is a presence of the outer retina

attain the expected or predicted postoperative visual acuity. It appears there may be a lower incidence of outer foveal defects following the inverted ILM flap technique compared to the conventional peel technique since our incidence of these abnormalities is far less than reported by Ko *et al.*<sup>[7]</sup>

The limitations of this study include its retrospective nature and the small sample size (given that this category of larger diameter MHs is a minority). A prospective randomized trial comparing the postoperative outer retina reconstruction after the various surgical techniques employed for the treatment of larger diameter MHs will provide further information in this area of study. Such research will ultimately help in deciding which technique is favored to provide the best functional and anatomical outcome in this category of large diameter MHs.

## CONCLUSION

There is growing need to further categorize large diameter MHs based on their size measured using OCT, into those with a higher probability for postoperative outer retina presence or reconstruction, and those in which outer retina reconstruction is not expected after available surgical techniques are used for closing them (the most popular of these techniques being the inverted ILM flap technique). The larger diameter MHs with no outer retina after inverted ILM flap technique will be candidates for other surgical options that may guarantee a better chance of outer retina presence; and this will be associated with improved visual outcomes. In our review of fourteen eyes, we found that six MHs without any reconstruction of the outer retina after surgery had an average base diameter of 1242 microns. This suggests that the inverted ILM flap technique may not be the ideal technique for MHs within or above this size. MHs sized within this range should be treated using other surgical technique that will improve the chance of postoperative outer retina presence.

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Nil.

## Conflicts of interest

There are no conflicts of interest.

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