

Natural progression of lamellar macular holes in high myopia: a long-term follow-up study

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Abstract

Background

To determine the long-term prognosis of lamellar macular holes (LMH) in highly myopic eyes.

Methods

This was a retrospective observational study. Patients with LMH associated with high myopia (>6 dioptres) were examined at regular 6-month intervals for a minimum of 36 months to detect for any structural and functional deterioration. Assessment included visual acuity checking, fundal examination, and optical coherence tomography (OCT) scanning. The risk factors for visual deterioration and progression to full-thickness macular hole (MH) were analysed using Kaplan-Meier survival analysis. The main outcome measures included the changes in mean best-corrected visual acuities, evidence of lamellar hole progression on OCT scans and complication rates of full-thickness macular hole (FTMH), and foveal detachment (FD) development.

Results

A total of 37 highly myopic eyes with optical coherence tomography confirmed LMH were recruited from 36 patients. The mean age was 63.4 ± 9.8 years and the mean spherical equivalent refractive error was -9.01 ± 3.6 D with axial length of 27.74 ± 1.45 mm. The mean follow-up duration was 57.6 ± 10.9 months. The mean baseline visual acuity was $0.272 \log\text{MAR} \pm 0.22$. A gradual decline in visual acuity was noted, and the change reached statistical significance from 36 months onwards. Visual acuity was $0.648 \pm 0.41 \log\text{MAR}$ at 36 months ($p = 0.034$) and 0.604 ± 0.455 at 48 months ($p = 0.046$). Twelve eyes (32.4%) had foveoschisis at baseline. Coexistence of a lamellar macular hole with foveoschisis was shown to be a risk factor for the development of a FTMH or FD ($p = 0.002$).

Conclusion

LMH in highly myopic eyes was generally stable, while a small proportion of patients progressed to full-thickness MH. Patients with coexisting LMH, foveoschisis, and vitreomacular traction had a higher risk of visual decline and progression to full-thickness MH.

Background

Lamellar macular hole (LMH) is a vitreoretinal disorder first described in the literature by Gass in 1975.(1) Witkin et al.(2) were among the first to describe the diagnostic criteria for LMH, which include an irregular foveal contour, a break in the inner fovea, dehiscence of the inner foveal retina from the outer retina, and the absence of a full-thickness foveal defect with intact foveal photoreceptors. Various features of

idiopathic LMH have been described based on optical coherence tomography (OCT) examinations, including the presence of an intact photoreceptor layer, presence of epiretinal membrane (ERM), intraretinal cysts, or foveoschisis (3–7).

LMH is a common macular abnormality in highly myopic eyes. The incidence of LMH in myopic eyes ranges from 4.8–20.7%. (8, 9) In myopic eyes, the clinical course of LMH is more complicated than that of idiopathic LMH given the presence of an adherent vitreous cortex, complex anteroposterior and tangential traction force, rigid internal limiting membrane (ILM), and posterior staphyloma. (7, 10) A certain proportion of LMHs in myopic eyes may progress to full-thickness macular holes (FTMH) or macular holes with retinal detachment over time. (11–13) LMH in highly myopic eyes has been shown to be highly associated with macular retinoschisis (MRS). (8, 9, 11, 14) In the presence of myopic traction maculopathy (MTM), foveal retinoschisis with foveal detachment indicates a high chance of progression to FTMH. (9) Currently, few studies have investigated the evolution of LMH in high myopia in the long term.

In the literature, LMH in high myopia is reported to have varying complication rates. Tanaka et al. reviewed 24 eyes in 21 consecutive patients with lamellar holes and high myopia. (15) With a mean follow-up of 19.2 months, 96% of these LMHs remained very stable with their BCVA maintained at the baseline level during the 44-month follow-up; only one eye progressed to FTMH after 17 months and had decreased vision. Rino et al. reported a more progressive course of LMH over a longer observation period. In the presence of atypical ERM, a significant reduction in residual foveal thickness (RFT) and greater involvement of the outer retinal layers were observed. (16) Of the 40 eyes they studied, one case of LMH which was associated with MRS developed FTMH over a mean follow-up period of 45 months, suggesting that MRS could be related to the development of FTMH. Similarly, Hsia et al. reported progressive changes in the LMH-related parameters in highly myopic eyes over a long-term assessment period, including worsening vertical and horizontal LMH diameters and reductions in residual foveal thickness. (17) These results contradict our belief that LMH associated with high myopia is a relatively benign condition.

In this study, we monitored the evolution of LMH in patients with LMH and highly myopic eyes and recorded their structural and functional outcomes in the long term. The aim of the current study was to report the complication rates of LMH in highly myopic eyes, and investigate the risk factors associated with structural and functional ocular deterioration.

Methods

Study Design and Ethical Approval

This was a retrospective observational trial approved by the Clinical Research Ethics Committees of the New Territories East Cluster (CRE-2012.322). Written informed consent was obtained from all participants. This study adhered to the tenets of the Declaration of Helsinki. Patients with myopic LMH were enrolled in this retrospective study from July 2013 to August 2014 in the Prince of Wales Hospital in

Hong Kong. Patients with myopia (spherical equivalents of an eye >-6.00 dioptres (D) or an axial length greater than 26.5 mm) who were clinically suspected to have or were diagnosed with LMH using biomicroscopy were identified during their clinic visits. Patients with LMH confirmed by OCT findings were enrolled. LMH with or without retinoschisis was diagnosed and included in the study using the criteria suggested by the International Vitreomacular Traction Study Group: 1) irregular foveal contour; (2) defects in the inner fovea; (3) separation between the inner and outer retinal layers in the fovea; (4) absence of full-thickness foveal defects. (18) The exclusion criteria included patients with media opacities hindering reliable OCT examination or patients who refused regular follow-up examinations.

All patients were assessed at baseline, at 1, 3, and 6 months, and at 6-month intervals thereafter for at least 36 months. At baseline, patients underwent a comprehensive ocular examination, including measurements of their best-corrected visual acuity (BCVA), refractive error (spherical equivalent), axial length, dilated macular examinations with a 90-D lens for any apparent macular hole, epiretinal membrane, chorioretinal atrophy, or vitreous detachment. The patients' BCVAs, visual symptoms, and macular and fundal findings were recorded at every visit. They were followed up every 6 months for repeated OCT monitoring. Spectral domain OCT structural scans were obtained using Spectralis OCT (Heidelberg Engineering, Heidelberg, Germany). To improve the image quality in high myopia cases, optics options for high myopia and extremely long eyeballs were adopted. OCT examinations were performed through a dilated pupil. In each patient, a horizontal averaged image consisting of 100 repeated scans and a 3-dimensional macular scan (area of 4.5×6 mm) were created. The lamellar hole morphology, including the inner diameter of the lamellar hole opening, the outer diameter, the residual foveal thickness, and the choroidal thickness, were measured by two independent researchers (E.M. and F.L.) (Figure 1). The mean values were then adopted for analysis. Any associated macular features were also documented. Foveoschisis was defined as separation of the neurosensory retina into two or more layers in the foveal area. Foveal detachment without a hole was defined as retinal detachment confined to the macular area, but without macular hole. (19)

Outcomes and statistical methods

The main outcome parameters in this study included visual acuity changes and the incidence of complications including foveal detachment, FTMH, and the development of MH retinal detachment. Continuous variables were compared using a paired *t*-test for parametric distributions. The Chi-square test and Fisher's exact test were used for the categorical variables. Statistical analysis was performed using SPSS software (v. 20.0; IBM SPSS, Armonk, NY, USA). A *P* value <0.05 was considered statistically significant.

Results

Patients demographics

37 eyes from 36 patients with high myopia associated with lamellar holes were included. The mean age of the patients was 63.4 ± 9.8 years (range, 41–75 years). The mean axial length was 27.74 ± 1.45 mm

(range, 25.55 to 31.04). The mean refractive error was -9.01 ± 3.6 D (range, -6 D to -15 D) in the phakic patients. The baseline mean visual acuity was 0.272 ± 0.22 logMAR (range, -0.04–1.0).

After a mean follow-up duration of 57.6 months, a gradual decline in visual acuity was noted in all cases. The mean visual acuity reduction was statistically significant from 36 months onwards. The mean visual acuity was 0.64 ± 0.41 logMAR at 36 months ($p=0.034$) and 0.604 ± 0.455 logMAR at 48 months ($p=0.046$), respectively (Table 1). The mean choroidal thickness for these patients was 128 ± 78 mm, which was slightly reduced to a mean of 104 ± 11 mm at 48 months ($p=0.093$, paired t -test).

Analysis According to FS and Vitreomacular Traction (VMT) Status

The majority of eyes presented with ERM at baseline (97%; 36/37). Among these eyes, 51% had contractile ERM, whereas 49% had non-contractile ERM. The proportion of cases with non-contractile ERM or contractile ERM did not differ much over time. At 24 months, 50% of cases were found to have non-contractile ERM. Sixteen eyes (43.2%) had foveoschisis in their initial OCT. Among the cases with foveoschisis, 31% (5/16) also had VMT on their OCT scans. The remaining eyes without initial foveoschisis remained stable throughout the follow-up.

Patients were divided into two groups in order to analyse the visual acuity changes based on the presence of foveoschisis. The visual acuity in the simple LMH group remained stable over time (Figure 2), but the visual acuity for patients in the group with LMH associated with FS dropped significantly to 0.71 ± 0.44 logMAR at 48 months ($p=0.05$) and 0.63 ± 0.31 logMAR at 60 months ($p=0.021$).

Morphology of the LMH

The mean RFT was 176.21 ± 44 mm at baseline, 182.43 ± 64 mm at 12 months, and 160.55 ± 65 mm at 48 months, respectively. A decreasing trend was observed in the RFT, but it did not reach statistical significance ($p=0.233$, paired t -test). Similar observations were noted when RFT was evaluated in the simple LMH group and LMH with FS group ($p=0.096$ and $p=0.658$ respectively at 48 months compared to baseline).

The other parameters related to the morphology of LMH remained stable during the follow-up period; these parameters and their changes are reported in Table 2.

As regards EZ disruptions, 16% (6/37) of eyes were found to have EZ disruptions at baseline, which increased to 22% (8/37) eyes at 12 months and to 35% (13/37) at 60 months. ($p<0.001$ chi-square test).

Complication Development Rate

Of the 37 eyes, 5 (13.5%) developed a foveal detachment (Figure 3), 4 eyes (10.8%) evolved into a full-thickness macular hole (FTMH), and 3 eyes (8.1%) had MH-associated retinal detachment (Figure 4). All of these five eyes with adverse outcomes had FS and VMT coexisting with LMH at baseline. The mean axial length (AL) of these four eyes was 29.21 mm, whereas the mean AL of the whole cohort was 27.96

mm. In addition, one patient developed a total rhegmatogenous retinal detachment due to a peripheral retinal break.

The survival analysis graph showed that the presence of FS was a risk factor for the development of FD and FTMH (Kaplan-Meier survival log-rank test, $p=0.002$) (Figure 5).

Discussion

Natural course of LMH in myopic eyes

Currently, studies on the natural history of LMH in high myopia are limited(15, 16, 20-23). In contrast to myopic eyes, LMH has a stable clinical course in normal eyes.(7, 23, 24) Thoedossiadis and associates(23) examined the natural course of LMH in non-myopic eyes. Visual acuity was stable in 78% of cases over a mean follow-up of 37.1 months. Experts in the field generally agree that LMH in non-myopic eyes is a stable condition without much progression over time.(25) However, LMH in highly myopic eyes often coexists with MTM, which complicates patient outcomes due to the presence of complex tractional forces around the macular region.(26) Hence, LMH in myopic eyes likely represents a distinct entity, with different morphological features compared to the degenerative or tractional types described by Govetto et al.(6)

The available studies on LMH in highly myopic eyes had varying conclusions. Rino et al. showed in their series that myopic LMH with posterior staphyloma progresses during the lifetime of a patient.(16) On the other hand, Tanaka et al(15) concluded in their long-term study that LMH in high myopia is a stable condition which seldom progresses into FTMH. Similarly, LMH was found to be stable in visual and anatomic outcomes over a long-term period in pathological myopia cases.(7) In the current study, LMH in the myopic eye was found to be an unstable condition. The majority of cases, with or without foveoschisis, showed evidence of visual declines and progressive EZ disruptions over time. This study also identified the presence of foveoschisis and vitreomacular traction as risk factors for the development of FD and FTMH.

Pathogenesis of FS in causing FTMH

Myopic retinoschisis (MRS) is considered one of the most frequent complications of MTM.(8, 9, 14, 27) Clinical studies on MRS revealed that 4.8-29.2% of myopic eyes had both LMH and MRS.(8, 9, 15). LMH, on the other hand, was considered a potential intermediate phase before the development of FTMH in highly myopic eyes.(11) In concordance with previous studies,(11, 15, 16) this study revealed the presence of foveoschisis as a risk factor for the development of FTMH or foveal detachment in the long term. This echoes our understanding of the pathogenesis of FTMH in highly myopic eyes. The presence of FS indicates the presence of a prominent anteroposterior vitreomacular traction force. In addition, macular retinoschisis itself promotes a tangential or multidirectional traction force, which increases the risk of foveal detachment or FTMH. (10) In the LMH without foveoschisis group, the structural parameters of LMH remained stable, but the visual function and EZ integrity did decline over time.

However, surgical intervention was seldom required in this LMH group, as the risk of developing foveoschisis or impending macular holes was smaller compared to the group with co-existing FS.

Surgical decision on operating on FS eyes with lamellar holes

Both the timing and techniques for the surgical treatment of LMH remain controversial. Witkin et al. believe that there is no evidence showing the benefit of surgical intervention in non-myopic eyes.(28) In contrast, vitrectomy with removal of the ERM-ILM complex has been shown in other studies to be beneficial in terms of functional and anatomical improvements.(4, 29-32) Macular surgeries in highly myopic eyes, however, remain a challenge for many surgeons. In these pathological myopic eyes, the ILM appears thin, sticky, and strongly adheres to the retina. In addition, chorioretinal atrophy limits the contrast for the membrane peeling procedure. These factors increased the chances of an iatrogenic retinal break and macular injuries. Hence, it is a well-accepted consensus that observation and conservative approaches for LMH related to high myopia are necessary, given its static visual acuity. However, the timing of ILM peeling in the presence of myopic FS or worsening FS is a difficult decision. The thin residual central foveal tissue is likely to be damaged during the operative procedure and may lead to iatrogenic FTMH. The reported rates of FTMH development ranged from 16.7% to 20.8% after ILM peeling in FS eyes.(33) Foveal-sparing ILM peeling procedures were therefore introduced to avoid FTMH development.(33-35) However, this technique remains surgically challenging, and there is no consensus on the size of the residual ILM area. From the results of our study, the authors suggest considering earlier surgical interventions for LMH in myopic eyes when there is co-existence of FS.

ERM associated with LMH

The pathogenesis and role of ERM in the development of FTMH in highly myopic eyes are not fully understood. In conjunction with many reported series,(2, 4, 23, 29) ERM was identified in most cases in the current study.

Regarding the formation of ERM, the abnormal vitreous-retinal interface and the presence of posterior vitreous adherence in myopic eyes play important roles in the pathogenesis of ERM.

This hypothesis was further supported by a histological study; reports on the histological composition of ERM in idiopathic LMH showed a component of glial cells from vitreous collagen.(3, 36, 37) Tanaka et al. reported that 17 of 24 myopic eyes affected by LMH (70.83%) were associated with ERM. Similarly, Rino et al. reported that ERMs, especially atypical contractile ERMs, were commonly associated with LMH in eyes with pathological myopia. Different types of ERMs, including convention and atypical ones, have been reported to be highly prevalent in myopic lamellar holes.(3, 5, 38) Witkin and associates(2) reported that the contraction of the perifoveal complex of ERM and the existing anteroposterior vitreous traction can lead to the formation and progression of LMH. Theodossiadis et al. reported that ERM contributed to the enlargement of the LMH. (23) However, the role of ERM in causing LMH progression is not well understood. Our study reported that nearly all cases (94%) were associated with ERM, but this study did not find any association between the morphology of ERM and changes in the residual foveal thickness or

visual acuity. In our study, ERM did not add to the risk of visual decline, RFT thinning, or FTMH development. Further studies investigating both the microscopic composition of ERM in myopic eyes and the long-term macroscopic morphology changes are advised.

Study strengths and weaknesses

Our study provides a good documentation of the natural progression of LMHs in highly myopic eyes due to its regular monitoring and long-term follow up period. It provided a glimpse into the course of disease by being one of the longest follow-up studies compared to the concurrent literature. Due to the surgical complexity and slow progression of the disease status, many patients with high myopia and LMH in our study adopted a non-surgical conservative approach, which allowed us to monitor the respective changes over time. Serial monitoring using OCT scans was performed, and comparisons can be made since the scans were applied with reference to patients' previous scans. In contrast to previous studies,(4, 15, 16, 23) our study showed that LMHs in myopic eyes are potentially progressive in nature, and the risk of deterioration to FD or FTMH increases with the coexistence of foveoschisis and VMT. However, this study has a relatively small sample size. Prospective studies with larger sample sizes are recommended to investigate the natural course of this disorder and to identify other potential risk factors related to the progression of LMH.

Conclusion

In myopic eyes, simple LMH without foveoschisis was shown to be a relatively benign condition, but there was a risk of slow visual decline and progressive EZ disruption over the long-term. LMH with FS in myopic eyes, especially with evidence of VMT, was observed to have a progressive natural course, and these patients had a higher risk of developing FD or FTMH. The timing of surgical procedures for maculopathies which are associated with high myopia remains a challenge; however, surgery can be advised at an earlier stage when, in addition to LMH, there is evidence of foveoschisis and vitreomacular traction.

Abbreviations

Axial length (AL), best-corrected visual acuity (BCVA), epiretinal membrane (ERM), Ellipsoid zone (EZ), foveoschisis (FS), foveal detachment (FD), full-thickness macula hole (FTMH), inner limiting membrane (ILM), lamella macular hole (LMH), Optical coherence tomography (OCT), myopic tractional maculopathy (MTM), macular retinoschisis (MRS), residual foveal thickness (RFT), vitreomacular traction (VMT).

Declarations

Ethics approval and consent to participate

This retrospective trial was approved by the Clinical Research Ethics Committees of the New Territories East Cluster (CRE-2012.322), the Hospital Authority Hong Kong. Written informed consent was obtained

from all participants for participation in the study. The study was performed in accordance with the Declaration of Helsinki.

Consent to publish

Written informed consent was obtained from all participants for publication purpose.

Availability of data and materials

All data generated and analysed during the current study are included in this published article.

The original datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests:

The authors have no conflicts of interest to declare.

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Authors' contribution:

All authors listed here are qualified for authorship. This is to certify all the authors gained credit by fulfilling substantial contributions to conception and design, acquisition and analysis of data; drafting and revising the article and approval of version to be published. FL and EM acquired and analysed the data. MH, HS, and SM contributed to drafting and revising the article. LC, MB, and TL contributed to conception and design of the study. CT and AY revised the article and approved the final version to be published. All authors have read and approved the manuscript.

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Tables

Table 1:

Table 1: demographic and clinical information of these pathologically myopic eyes	
Mean age (years, +/-SD)	63.4 ± 9.8
Gender	13:23 (M:F)
Baseline best-corrected visual acuity (logMAR +/-SD)	0.272 ± 0.22
BCVA at 48 months	0.604 ± 0.45
Refractive error (spherical equivalence in diopters +/- SD)	-9.01 ± 3.6
Axial length (mm +/- SD)	27.74 ± 1.45
SD: standard deviation	

Table 2 shows the summary of the functional and morphological parameters of all LMHs cases included in our study and their changes over time.

	baseline	6 months	12 months	36 months	48 months
Visual acuity (mean +/- SD logMAR)	0.27 ± 0.22	0.36 ± 0.22	0.41 ± 0.20	0.648 ± 0.41 (p=0.034*)	0.604 ± 0.45 (p=0.046*)
Residual foveal thickness (µm)	176 ± 44	176 ± 57.3	182 ± 64.8	155 ± 66.2	160 ± 65 (p=0.233)
Perifoveal thickness (µm)	447 ± 117	452 ± 113	453 ± 142	490 ± 181	438 ± 147
Inner diameter (µm)	571 ± 201	628 ± 194	582 ± 174	709 ± 203	697 ± 259
Outer diameter (µm)	694 ± 307	662 ± 171	708 ± 319	756 ± 328	770 ± 409
SD: standard deviation; logMAR: log minimum angle of resolution; p value (paired t-test); *: statistically significant					

Figures

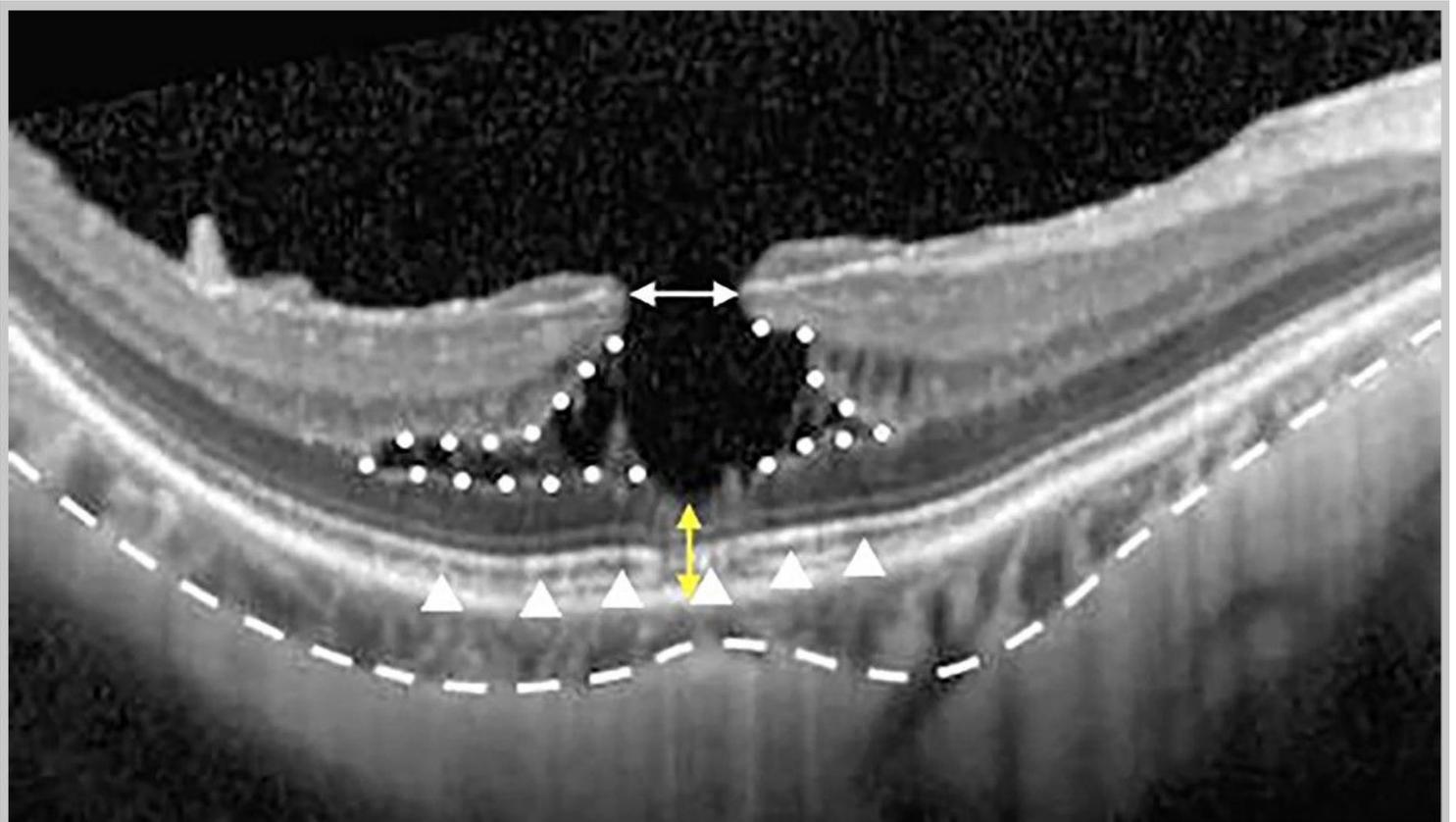


Figure 1

illustrates the measurement for the OCT parameters. There is a lamellar hole with foveoschisis and the presence of a contractile epiretinal membrane. The residual foveal thickness (yellow double headed arrow) is measured from the anterior border of remaining foveal tissue to the retinal pigment epithelium. The inner diameter of the lamellar hole is measured from the inner limiting membrane (white double headed arrow). The area of foveoschisis is demarcated by a dotted line, from which the maximum height is taken as the foveoschisis height. The ellipsoid zone integrity is assessed from the foveal scan cut (arrowheads). The choroidal thickness (dashed line) is measured manually by two investigators and the mean value generated for analysis.

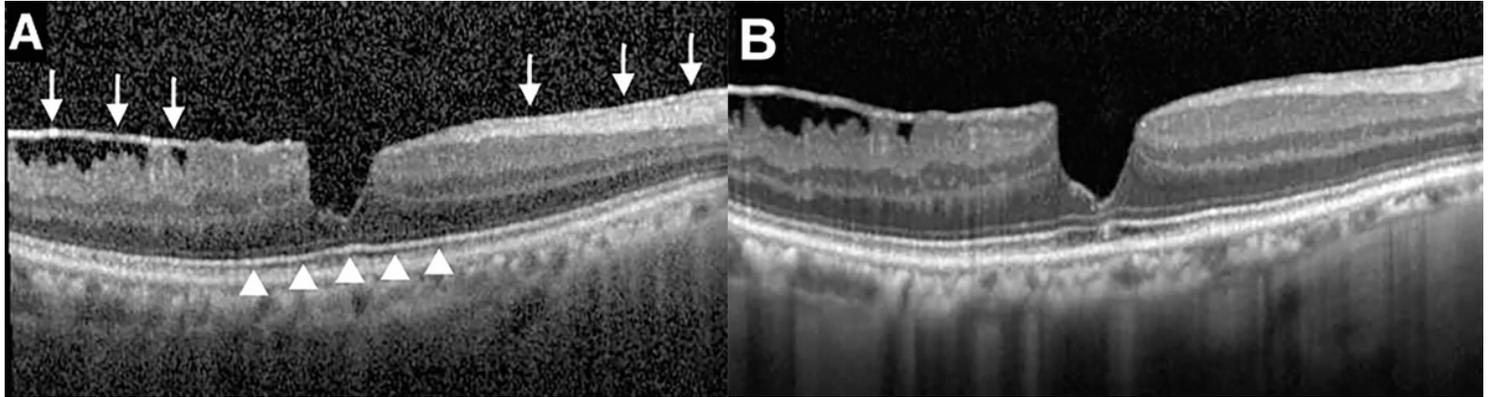


Figure 2

shows example of a relatively stable lamella hole. OCT images of 60-year-old man taken 48 months apart. A) The baseline OCT shows a LMH with an epiretinal membrane (arrows). There is no foveoschisis. The ellipsoid zone is intact (arrowheads). The residual foveal thickness is 155 μ m. The baseline VA was 0.18 logMAR. B) OCT at 48 months shows little change in OCT appearance. The residual foveal thickness is 128 μ m. The VA is 0.00 logMAR. This is an example of a stable LMH with no foveoschisis, showing no progression in OCT parameters and VA over 4 years.

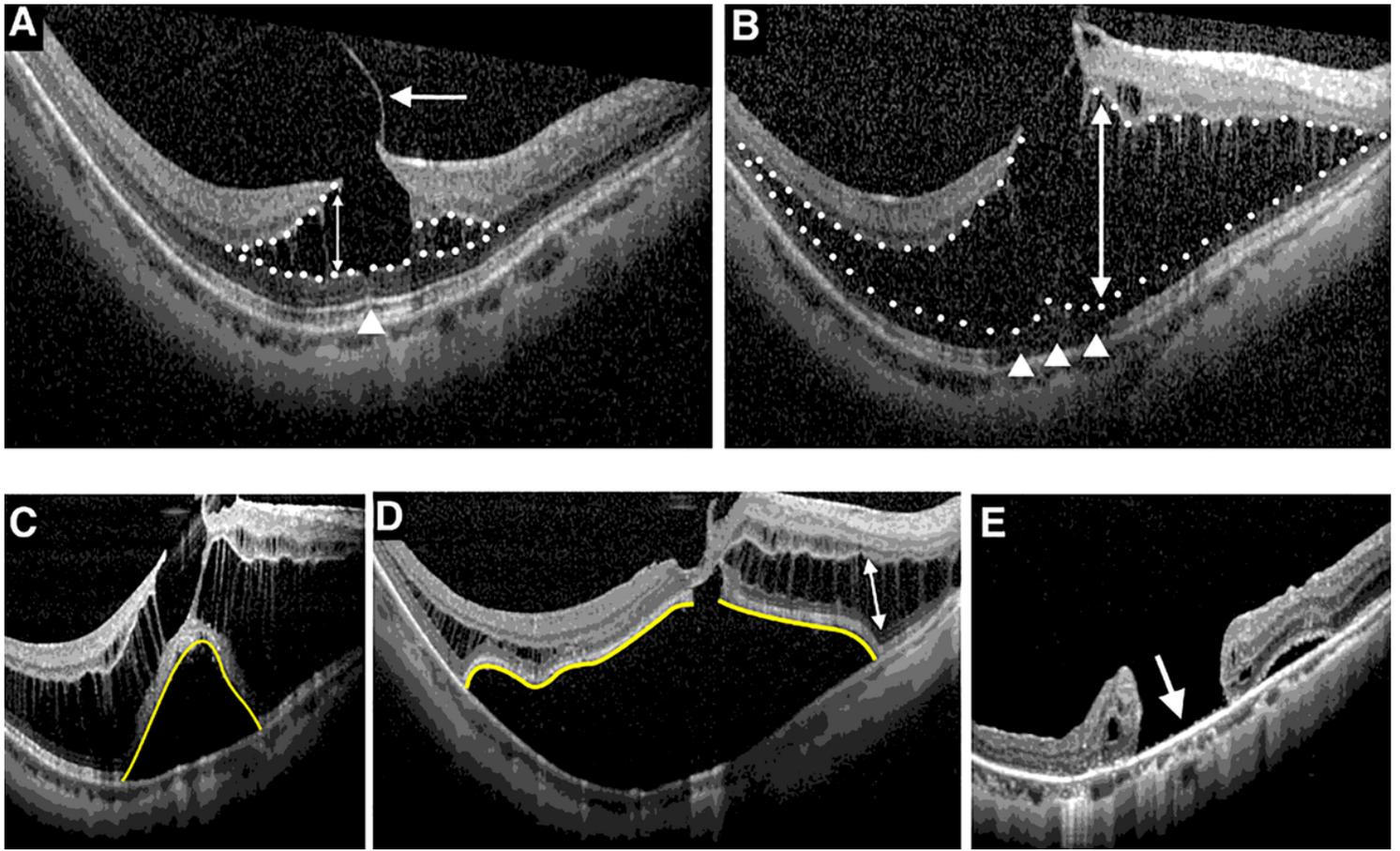


Figure 3

showing examples of LMH associated with FS progressing to FTMH: Serial OCT scans of a 53 year old lady. A) Baseline OCT shows a lamellar hole with foveoschisis (dotted line). The foveoschisis height (double headed arrow) is 188µm. The residual foveal thickness is 155µm. There is vitreomacular traction (single headed arrow). The ellipsoid zone is intact (arrowhead). Her VA was 0.3 logMAR. B) OCT at 12 months shows an increased foveoschisis height (double headed arrow) of 587µm. There is ellipsoid zone disruption (arrowheads). Her VA remained stable at 0.18 logMAR. C) OCT at 24 months shows progression to foveal detachment (yellow line). Her VA remained unchanged at 0.18logMAR. D) OCT shows macular hole retinal detachment (yellow line). The area of foveoschisis decreases, with a foveoschisis height (double headed arrow) of 178µm. The VA dropped to 0.50 logMAR. Cataract and macular hole surgery was done. Post-operatively the macular hole closed, and the VA was 0.54 logMAR. E) OCT at 7 months post-op shows re-opening of the macular hole (arrow), with a VA drop to 1.0 logMAR.

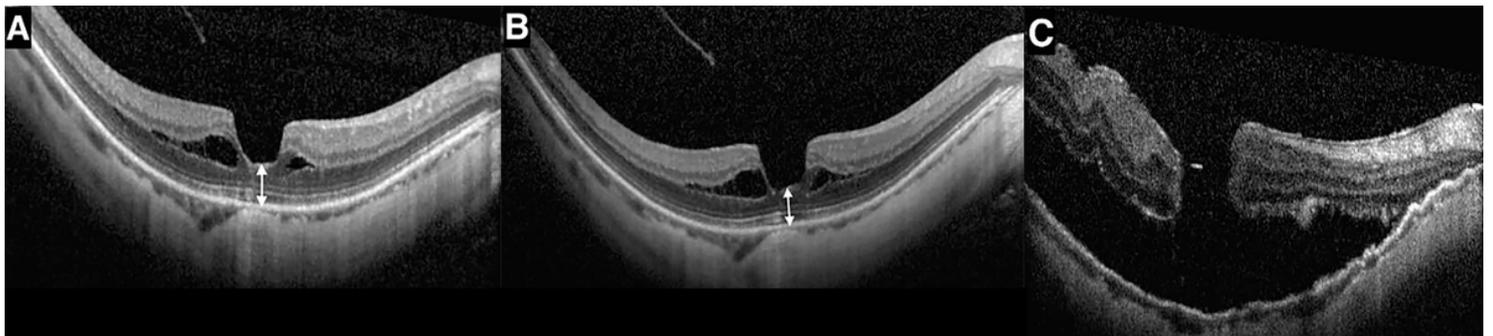


Figure 4

OCT images of a 63-year-old woman. A) Baseline OCT shows a lamellar hole with foveoschisis. The foveoschisis height is 105 μ m. The residual foveal thickness (double headed arrow) is 158 μ m. The VA was 0.78 logMAR. B) OCT at 24 months shows similar appearance of the lamellar hole. The foveoschisis height and residual foveal thickness (double headed arrow) remain largely stable at 121 μ m and 158 μ m respectively. Her VA was 0.78 logMAR, same as baseline. C) She presented with a drop in VA to 2.30 logMAR at 45 months, with OCT showing macular hole retinal detachment. Surgery was done, but the macular hole soon re-opened with inferior retinal detachment, which persisted despite a second surgery involving macular buckle. The latest VA was hand movement.

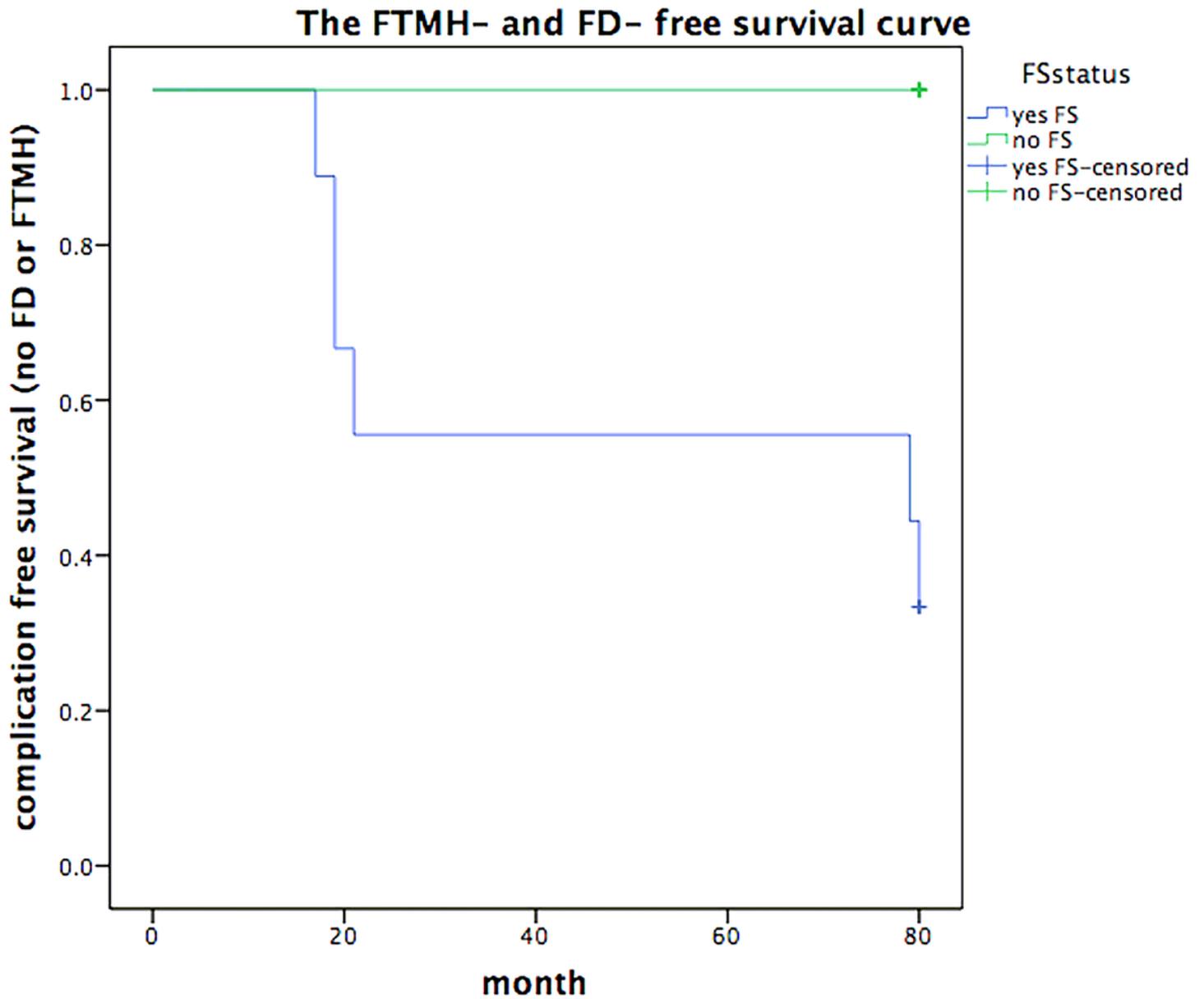


Figure 5

Survival analysis curve for progression to FTMH and FD using Kaplan-Meier survival Mantel-Cox log rank test ($p= 0.002^*$). (FTMH: full-thickness macular hole, FD: foveal detachment, *: statistically significant result)