Title

FUNCTIONAL AND ANATOMICAL SIGNIFICANCE OF THE ECTOPIC INNER FOVEAL LAYERS IN EYES WITH IDIOPATHIC EPIRETINAL MEMBRANES

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Functional and anatomical significance of the ectopic inner foveal layers in eyes with idiopathic epiretinal membranes: surgical results at 12 months.

Short title: Surgical significance of the ectopic inner foveal layers.

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Key Words: Epiretinal Membrane; Macular Pucker; Ectopic inner foveal layers; Pars Plana Vitrectomy; Optical coherence tomography.

Summary statement: This study analyzed the outcomes of pars plana vitrectomy with epiretinal membrane peel in eyes with and without ectopic inner foveal layers. The presence of ectopic inner foveal layers was associated with lower preoperative and postoperative visual acuity, and should be considered a negative prognostic factor for postoperative anatomical and functional recovery.

Abstract

Purpose: To describe the functional and anatomical outcomes of pars plana vitrectomy (PPV) with epiretinal membrane (ERM) and internal limiting membrane (ILM) peel in eyes with and without ectopic inner foveal layers (EIFL).

Methods: In this retrospective multicenter study were enrolled patients diagnosed with idiopathic ERMs who underwent PPV with ERM and ILM peel, with a minimum follow-up of 12 months. Preoperative and postoperative spectral domain optical coherence tomography (SD-OCT) scans were qualitatively and quantitatively evaluated. The association of the EIFL and other SD-OCT parameters with preoperative and postoperative best corrected visual acuity (BCVA) was analyzed.

Results: One-hundred and eleven eyes of 107 patients were included. Preoperatively, the EIFL were present in 56 out of 111 eyes (50.4%). The presence of EIFL was significantly associated with lower preoperative and postoperative BCVA ($p<0.001$). EIFL thickness was negatively correlated with preoperative BCVA ($r=0.58$, $p<0.001$). Postoperatively, the EIFL persisted in 51 out of 56 eyes (91%) with stage 3 and 4 ERMs. EIFL thickness decreased significantly after surgery ($p<0.001$), but postoperative EIFL thinning had no direct effect on postoperative change in BCVA. At 12 months from surgery, EIFL thickness maintained a significant negative correlation with BCVA ($r=0.55$, $p<0.001$).

Conclusions: The presence of EIFL should be considered a negative prognostic factor for postoperative anatomical and functional recovery.

Introduction

Pars Plana vitrectomy (PPV) with membrane peeling is the standard treatment for symptomatic idiopathic epiretinal membranes (ERMs). However, despite high anatomical success rates, the postoperative visual prognosis is often elusive.[1-4] Consequently, considerable efforts have been made to identify reliable prognostic biomarkers that may predict postoperative visual outcome.[5,6]

Recent advancements with spectral-domain optical coherence tomography (SD-OCT) technology, including remarkably greater A scan speeds, have led to faster data acquisition and higher resolution. As a result, SD-OCT imaging provides a powerful tool for both preoperative and postoperative ERM evaluation.

Several biomarkers have been proposed as predictors of postoperative best corrected visual acuity (BCVA) in idiopathic ERMs, including the integrity of both the ellipsoid and interdigitation zone bands, and the length of photoreceptor outer segment.[3,7-9] However, the prognostic value of such factors remains controversial, as the evaluation of outer retinal integrity may be limited due to SD-OCT imaging artifacts that are common with the analysis of idiopathic ERMs.[10]

As the analysis of outer retinal alterations may be insufficient to predict postoperative visual outcome, attention has shifted to the study of the inner retina, the primary affected site of ERM-associated mechanical stress.[11-18] The presence of continuous ectopic inner foveal layers (EIFL) in the central foveal region was recently described with SD-OCT in eyes with idiopathic ERMs. EIFL formation may represent an important sign of ERM progression, and it is the centerpiece of a newly proposed SD-OCT staging scheme for idiopathic ERMs.[19] Although the presence of EIFL was significantly associated with lower preoperative BCVA, the prognostic value of the EIFL on postoperative BCVA has not yet been properly studied.[19]

To investigate the postoperative clinical significance of the EIFL, this study performed an in-depth analysis of both functional and anatomical surgical results in a consecutive cohort of patients diagnosed with idiopathic ERMs who underwent PPV with ERM and internal limiting membrane (ILM) peel.

Methods:

Study design.

This study was approved by the Institutional Review Boards of the University of California Los Angeles, the Fundación Oftalmológica Nacional Hospital and the Ramon y Cajal University Hospital. This research project adhered to the tenets of the Declaration of Helsinki and was designed in compliance with the Health Insurance Portability and Accountability Act regulations.

A retrospective, observational, and consecutive review of the clinical records of patients diagnosed with idiopathic ERMs and evaluated by three retina specialists (J.P.H, F.J.R, and M.S.F) between January 1, 2010 and January 31, 2016 at the Stein Eye Institute, the Fundación Oftalmológica Nacional Hospital and the Ramon y Cajal University Hospital, was performed. Cases were identified by a medical billing record search, using the International Statistical Classification of Diseases and Related Health Problems, Ninth Revision diagnosis code 362.56 for macular pucker. Inclusion criteria included the presence of idiopathic unilateral or bilateral ERM treated with PPV and membrane peeling, with a minimum follow up of 12 months. Exclusion criteria are listed in Table 1.

Ophthalmological evaluation and SD-OCT imaging.

Comprehensive ophthalmologic exams including BCVA and intraocular pressure assessment, slit-lamp biomicroscopy, fundus examination, and SD-OCT imaging were performed in all patients before surgery and at 1, 6 and 12 months after surgery.

BCVA was recorded at each visit, reported in Snellen fraction and then converted into logarithm of the minimal angle of resolution (logMAR) values for statistical analysis.

In all cases, SD-OCT images were obtained with the Spectralis OCT with eye-tracking dual-beam technology (Heidelberg Engineering GmbH, Heidelberg, Germany) and analyzed with the Heidelberg Eye Explorer (version 1.8.6.0) using the HRA/Spectralis Viewing Module (version 5.8.3.0).

Spectralis SD-OCT scans were used for all quantitative measurements and qualitative evaluation of ERMs. At each visit, all eyes were imaged with at least 2 type of SD-OCT scan patterns: 19 B-scans administered over an area of 20 X 15 degrees with each B-scan spaced 242 µm apart and a single high-definition horizontal B-scan at 30 degrees. In addition, some of the included eyes underwent high-density scanning over a macular area of either 15 X 10 degrees with 97 B-scan each spaced 31 µm apart, or 15 X 5 degrees with 131 B-Scan spaced 11 µm apart.

On SD-OCT, all retinal layers were identified according to the IN●OCT Consensus.[20]

EIFL were identified with SD-OCT and were defined according to Govetto et al: presence of continuous hyporeflective and hyperreflective bands, extending from the inner nuclear layer (INL) and inner plexiform layer (IPL) across the foveal region and visible in all SD-OCT scans centered in the fovea, as illustrated in figure 1.[19]

The thickness of the EIFL in the central foveal region were measured manually with the ‘‘caliper’’ function of the Heidelberg Spectralis, adjusted to an aspect ratio of 1:1 mm, by tracing a vertical line from the outer margin of the INL to the inner margin of the ILM.[19] Mean central foveal thickness (CFT) values were obtained automatically by the Heidelberg software.

With SD-OCT, ERMs were defined as single, irregular, and hyperreflective lines above the ILM, often associated with underlying retinal wrinkling and with the presence of hyporeflective spaces between the ERM and ILM. All ERMs were classified according to the 4-grade staging system by Govetto et al., as illustrated in figure 1.[19]

Cystoid macular edema (CME) was defined with SD-OCT as the presence of multiple hyporeflective intraretinal cystoid spaces.

The presence of a discontinuous ellipsoid band in the foveal region was considered a sign of ellipsoid zone disruption, while the appearance of a roundish or diffuse hyperreflective area between the ellipsoid zone and the interdigitation zone in the central fovea was defined as the *Tsunoda* or “cotton ball” sign, representing tractional elevation of the photoreceptors.[20]

All SD-OCT images were quantitatively and qualitatively evaluated by three independent and masked observers (A.G., F.J.R and M.S.F), and disagreements were resolved with the intervention of a fourth observer (D.S. or J.P.H.).

Surgical procedures.

All patients underwent a standard, three port 23-Gauge PPV with ERM and ILM peeling performed by three vitreo-retinal surgeons (J.P.H., F.J.R, and M.S.F) with the Constellation vision system (Alcon, Fort wort, TX, USA).

Combined phacoemulsification and intraocular lens implantation procedures were performed at the discretion of the surgeon.

Core vitrectomy was performed in all cases and, after the creation of posterior vitreous detachment, Grieshaber ILM forceps (Alcon, Fort Wort, TX, USA) were used to peel both ERM and ILM up to the vascular arcades. Depending on surgeons' preferences, in some cases intraocular Kenalog (Bristol-Myers Squibb, Irvine, CA, USA) or Brillant blue G (DORC, Zuidland, The Netherlands) was applied over the retinal surface to enhance retinal surface visualization during ILM peeling. At the end of the surgery, partial air-fluid exchange was performed in all cases, and subconjunctival vancomycin and dexamethasone were injected over the sclerotomy sites.

All patients were evaluated at 1, 6 and 12 months after surgery, and potential post-operative complications were recorded at any time point during the follow up period.

Statistical analysis.

Descriptive statistics were first calculated for all variables of interest. Mean and standard deviation values were calculated for continuous variables, while frequency and percentage were calculated for categorical variables. Kruskal-Wallis test was used to compare the statistically significant difference in continuous measurements among all subgroups, Chi-square test was used to compare proportions among the study population. Pearson correlation was used to explore the association among continuous functional and morphometric variables. The association of SD-OCT parameters with BCVA was assessed by means of univariate and multivariate linear or logistic regression, as appropriate. Structural Equation Modeling was used to fit mediation analyses and to assess whether EIFL affects BCVA directly or only indirectly, i.e. through CFT increase. Linear mixed models with subjects as random intercept and time as a random slope were used to investigate predictors of change in BCVA during follow-up. Covariates included in univariate and multivariate models were baseline BCVA and CFT, and change in CFT and EIFL thickness from baseline. All analyses were conducted using Stata 14.2 software (StataCorp, College Station, TX, USA).

Results

We reviewed the clinical records of 1135 patients diagnosed with ERMs, of which 1024 were excluded owing to the presence of one or more exclusion criteria. At the end of the selection process, we enrolled 107 patients (111 eyes), of which 52 were males (44.4%) and 55 were females (55.6%) with a mean age of 70 ± 8.9 years (range 45-93). Four out of 107 patients (3.7%) underwent bilateral PPV (figure 2), while combined phacoemulsification was performed in 13 out of 111 eyes (11.7%).

Preoperatively, stage 2 ERMs were diagnosed in 55 out of 111 eyes (49.5%), stage 3 ERMs were diagnosed in 42 out of 111 eyes (37.9%), and stage 4 ERMs were diagnosed in 14 out of 111 eyes (12.6%). Stage 1 ERMs were not identified in the study population. Characteristics of the included eyes at presentation are summarized in table 2.

Preoperatively, the presence of EIFL was confirmed in 56 out of 111 eyes (50.4%), in which the mean EIFL thickness was 191.7 ± 75.5 µm (range 76-420 µm). However, in 6 out of 14 stage 4 ERMs (42.8%) EIFL thickness measurements were unreliable due to the remarkable preoperative disruption of the retinal layers, and these eyes were therefore excluded from preoperative thickness analysis.

Preoperatively, differences in BCVA and CFT were significant among the three ERM stages, as stage 3 and 4 ERMs were characterized by lower BCVA and thicker CFT, if compared to stage 2 ERMs ($p < 0.001$, table 2).

Preoperative correlation of BCVA with SD-OCT parameters.

Preoperatively, BCVA was correlated with both CFT (r=0.61) and EIFL thickness (r=0.58, figure 3, A). However, CFT was strongly correlated with EIFL thickness (r=0.69, figure 3, B), meaning that these variables shared an effect on BCVA. This may be explained by the fact that the EIFL are an important determinant of increased CFT.

Mediation analysis was used to disentangle direct effects of EIFL thickness on BCVA from any indirect effects mediated by CFT. In this model, the effect of CFT on BCVA was a decrease of 0.047 logMAR per 100 µm ($p=0.030$), and EIFL thickness accounted for one half of this reduction (coefficient: 0.502, $p<0.001$). Moreover, the direct effect of EIFL on BCVA was a decrease of 0.062 logMAR per 100 µm (p<0001). Therefore, the total effect of EIFL thickness on BCVA was a decrease of 0.086 logMAR per 100 µm ($p<0.001$).

In multiple forward regression analysis of factors including CFT, EIFL thickness, ellipsoid layer status and presence of CME, only EIFL thickness ($p<0.001$) and the disruption of the ellipsoid zone ($p=0.012$) were significantly associated with worse preoperative BCVA.

Postoperative visual outcomes and association with EIFL and other SD-OCT parameters.

In the postoperative period BCVA improved significantly in all ERM subgroups, but differences between stages 2, 3 and 4 ERMs remained significant ($p<0.001$), as summarized in table 3 and illustrated in figure 4, A. The preoperative presence of EIFL was strongly associated with lower postoperative BCVA ($p<0.001$).

Postoperative BCVA changes were greatest in the first month after surgery especially for stage 3 and 4 ERMs, reflecting a ceiling effect. However, in stage 4 ERMs postoperative improvements in BCVA reached a plateau at six months after surgery, while in both stages 2 and 3 ERMs BCVA continued to improve until the end of the follow up period, as illustrated in figure 4, A.

Better preoperative BCVA and thicker preoperative CFT were robustly associated with greater postoperative BCVA improvement in multivariate analyses ($p<0.001$).

At 12 months from surgery, EIFL thickness maintained a significant negative correlation with BCVA ($r=0.55$, $p<0.001$). In a mediation model, the effect of CFT on BCVA at 12 months was a decrease of 0.055 logMAR per 100 µm ($p=0.049$), and EIFL thickness accounted for one third of this reduction (coefficient: 0.353, $p<0.001$). At 12 months, the direct effect of EIFL on BCVA was much stronger and accounted for a decrease of 0.124 logMAR per 100 µm (p<0001).

However, neither the preoperative presence of EIFL nor preoperative EIFL thickness were associated with the postoperative change in BCVA in both univariate and multivariate regression analysis ($p>0.100$). Moreover, while postoperative CFT reduction was associated with BCVA improvement ($p<0.001$), the postoperative decrease in EIFL thickness was not ($p=0.284$).

Postoperative anatomic outcomes and secondary findings.

CFT improved significantly after surgery in all ERM stages ($p<0.001$, figure 4, B). Similarly, EIFL thickness decreased significantly in stage 3 and 4 ERM in the postoperative period ($p<0.001$, figure 4, C).

EIFL persisted in the large majority of the cases, being present in 51 out of 56 eyes with stage 3 and 4 ERMs (91%) at 12 months from surgery, as illustrated in figure 5, A. Only in 5 out of 56 eyes (9%) the EIFL regressed by the end of the follow up period, as illustrated in figure 5, B. Preoperative differences in CFT, EIFL thickness and BCVA between eyes with and without postoperative EIFL regression were not significant.

In the postoperative period a shallow, hyperreflective layer of inner retinal tissue over the foveal region developed in 24 out of 55 stage 2 ERMs (46.1%). The morphology of this tissue as seen with SD-OCT was similar to the EIFL, but without continuity with the INL, as illustrated in figure 6. This finding had no effect on post-operative BCVA in univariate or multivariate models ($p>0.100$)

At the end of the follow up period, a shallow foveal depression was present in 23 out of 55 eyes with stage 2 ERMs (41.8%), 10 out of 42 eyes with stage 3 ERMs (23.8%) and only 1 out of 14 eyes with stage 4 ERM (7.1%). These rates were significantly different between the 3 groups ($p=0.020$). The restoration of the foveal depression was not associated with better postoperative BCVA in univariate or multivariate models ($p>0.100$).

CME resolved in 24 out of 27 eyes (88.9%) after surgery, and persisted until the end of the follow up in only 3 out of 27 eyes (11.1%).

At the end of the follow-up period, the cotton ball sign persisted only in 1 out of 32 eyes (3.1%).

No serious intra- or postoperative complications were registered over the follow-up period. However, the new onset of postoperative CME was recorded in 6 out of 84 eyes (7.1%). The postoperative CME had microcystoid morphology, it was mainly located in the INL and persisted until the end of the follow up period in 2 out of 84 eyes (2.9%), despite treatment with topical ketorolac tromethamine (Acular, Parsippany-Troy Hills, NJ, USA).

Finally, 11 out of 53 phakic eyes (20.7%) developed visually significant cataract in the postoperative period, of which 9 (81.8%) underwent cataract extraction before the end of the follow up period. The development of visually significant cataract was taken into account in all the statistical analysis performed.

Discussion

The timing of surgery in eyes with idiopathic ERMs can be challenging with poor consensus even among experienced vitreoretinal surgeons. The evaluation of the severity of the ERM and the prognosis with surgical removal can be elusive.[19] Therefore, the identification of reliable prognostic biomarkers is critical to improve the ability of clinicians to predict postoperative outcomes in patients with idiopathic ERMs.

This study explored the clinical significance of the EIFL in a cohort of 111 eyes diagnosed with idiopathic ERMs treated with PPV, ERM and ILM peel, and found a significant association between the preoperative presence of EIFL and lower preoperative and postoperative BCVA over a 1-year follow up period.

Recently, there has been a greater number of published SD-OCT studies investigating inner retinal alterations in idiopathic ERMs, and the role of the inner retina in visual acuity loss has been studied more closely. In fact, increasing evidence suggests that outer retinal disruption may be insufficient to fully explain vision loss in the setting of ERM formation.[11-18]

In this regard, we described the development of continuous EIFL in a subset of idiopathic ERMs, and correlated the incidence of this anatomical finding with lower preoperative BCVA.[19] The present study further supports our previous observations demonstrating a significant correlation between EIFL thickness and lower BCVA at presentation. Such results are coherent with the work of Joe et al., who first suggested that an “abnormal inner retinal thickening” in the foveal region may be a major determinant of visual acuity in patients with idiopathic ERMs.[11]

However, to estimate the direct effect of inner retinal alterations on visual function may be challenging due to the strong correlation between inner retinal thickness and CFT, which makes such analysis prone to bias.

Previous reports have already described independent associations between inner retinal thickness and visual acuity in idiopathic ERMs, but inner retinal parameters were often measured using automated software, which may have provided inaccurate layer segmentation.[15,16,22]

In the present study the effect of EIFL thickness on BCVA was separated from that of CFT with mediation analysis, and remained significant after further multivariate logistic regression. Such results suggest a negative direct effect of EIFL thickness on BCVA, independently from CFT and other confounders.

EIFL thickness was significantly reduced in the postoperative period. This reduction was prominent up to 6 months but minimal between 6 and 12 months after surgery. However, mediation analysis showed no direct effect of postoperative EIFL thinning on postoperative BCVA changes.

This fact raises questions on the mechanisms of EIFL-related vision loss and limited functional recovery after surgery. In fact, the negative correlation between EIFL thickness and BCVA at presentation may suggest that the ectopic retinal tissue may act as a physical barrier which interposes between the afferent light and photoreceptors, obstructing or degrading the projected visual image on the foveal cones. The extent of this optical obstruction may be greater with increasing EIFL thickness.

However, the presence of inner retinal tissue covering the foveal region does not fully explain vision loss, as suggested by the good visual function frequently observed in patients with foveal plana, a congenital condition characterized by the persistence of inner retinal layers over the central fovea.[23]

Therefore, further alterations in retinal microstructures may occur in the presence of EIFL. The chronic displacement of the inner retina may cause damage and deformations of photoreceptors and other retinal neural cells, compromising normal neural transmission and contributing to the visual alterations and metamorphopsia in eyes with ERM.[11,19,24] This fact may be especially relevant in stage 4 ERMs, characterized by complete foveal disorganization and lower postoperative functional outcomes.

The chronic disruption of foveal microanatomy may not be fully reversible after ERM peel, as illustrated in figure 7. In the present study, the likelihood to restore the foveal depression at 12 months from surgery decreased progressively at increasing ERM stage and was rarely encountered in advanced stage 4 ERMs. This result is consistent with other reports describing poor anatomical restoration after ERM peel, and may be the reflection of deeper retinal alterations associated with the presence of EIFL.[25]

After surgery, the EIFL persisted in the vast majority of eyes diagnosed with stage 3 and 4 ERM, a fact which may explain the lower postoperative anatomical restoration observed in this subset of patients and the lower visual outcomes.

The persistence of EIFL in the absence of traction supports the hypothesis that other molecular reactions, possibly mediated by Müller cells, may contribute to their formation, together with the mechanical displacement of inner retinal tissue driven by the ERM.[19] Müller cell activation may also be responsible for the postoperative formation of inner retinal bridging tissue over the fovea in a subset of eyes with stage 2 ERMs, which may represent a reparative reaction after surgery.

Finally, the present study explored the prognostic value of our SD-OCT classification of ERMs, which was a useful and practical tool in the prediction of postoperative outcomes. In fact, differences in functional and morphometric outcomes remained significant between the three ERM stages, with stage 2 and 4 ERMs at opposite ends.

Limitations of this study include its retrospective nature, and the lack of high-density macula raster scanning for all cases. Although high-density SD-OCT imaging was performed in most of the included eyes, the central fovea may have been missed by the standard 20 X 15-degree macular raster or the single high-definition horizontal B-scan, causing the misclassification of some ERMs.

Strengths of our study include adequate follow up and good size of the study population, consistent surgical technique among the three surgeons and the use of SD-OCT eye tracking systems in all cases, which allowed precise analysis of postoperative anatomical changes. Although longer follow-up would have increased the strength of this study, it has been shown that both visual acuity and SD-OCT parameters stabilize at 12 months from surgery, suggesting that a 1-year follow up is adequate to assess postoperative results.[26]

In conclusion, to the best of our knowledge this is the first report investigating the surgical significance of the EIFL in eyes with idiopathic ERMs. This study reported significantly lower postoperative visual and anatomical restoration in idiopathic ERMs with EIFL over a 1-year follow-up period. The thickness of the EIFL had a strong negative correlation with both preoperative and postoperative BCVA. However, postoperative EIFL thinning had no direct effect on postoperative BCVA change, suggesting that once EIFL is established, its change has no independent effect on surgical visual outcome. Accordingly, EIFL formation may produce irreversible retinal damage, and the presence of EIFL should be considered a negative prognostic factor for postoperative anatomical and functional recovery.

However, our hypothesis should be the subject of further prospective investigations, which are necessary to confirm our results, further validate the proposed ERM staging scheme and reduce the risk of bias. Additional clinicopathological studies are also needed to better understand the pathophysiology of EIFL development prior to developing rational preventive and interventional strategies.

We hope that our results and proposed ERM classification scheme will stimulate and encourage the design of future research, which will ultimately improve the management of these lesions.

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FIGURE CAPTIONS

Figure 1: Spectral-Domain optical coherence tomography staging scheme of epiretinal membranes.

Stage 1. Mild epiretinal membrane with few anatomical modifications. The foveal depression is preserved, and all retinal layers are well identified. **Stage 2.** Epiretinal membrane with more advanced anatomical changes. The foveal depression is loss, but all retinal layers are still well defined. **Stage 3.** Continuous ectopic inner foveal layers cover the whole foveal floor (white arrows). Like in stage 2 epiretinal membranes, the foveal depression is lost and all retinal layers are well defined. **Stage 4.** Advanced epiretinal membrane with complete foveal disorganization. Thick ectopic inner foveal layers cover the foveal area (white arrows), there is no foveal depression and all retinal layers are disrupted.

Figure 2: Multimodal imaging of a patient diagnosed with stage 2 epiretinal membrane in one eye and stage 3 epiretinal membrane in the fellow eye.

A. Right eye. Preoperatively, blue reflectance and multicolor imaging show mild wrinkling on the retinal surface from membrane contracture. A Stage 2 epiretinal membrane is diagnosed with spectral-domain optical coherence tomography. The cotton ball sign is visible in the outer retina (white arrow). At 1 month from surgery, the cotton ball sign is reduced, but there is no restoration of foveal microanatomy. At 12 months from surgery, the cotton ball sign is resolved and a shallow foveal depression appears. There is no continuity between parafoveal inner retinal layers. **B. Left eye.** Preoperatively, blue reflectance and multicolor imaging evidence severe wrinkling of the retinal surface due to a thick epiretinal membrane. A stage 3 epiretinal membrane is diagnosed with spectral domain optical coherence tomography due to the presence of continuous ectopic inner foveal layers in the central fovea (black arrow). At 1 month from surgery, thick ectopic inner foveal layers persist over the outer nuclear layer. At 12 months from surgery the ectopic inner foveal layers persist, although significant thinning is observed. There is still continuity of inner retinal layers over the fovea, and a shallow foveal depression is present.

Figure 3: Preoperative correlations between best corrected visual acuity and central foveal thickness with ectopic inner foveal layers thickness.

A. Best correcte visual acuity. Preoperatively, there was a strong inverse correlation of best corrected visual acuity and ectopic inner foveal layers thickness (r=0.58). **B. Central foveal thickness.** Preoperatively, there was a robust direct correlation between the thickness of the ectopic inner foveal layers and central foveal thickness (r=0.69).

Figure 4: Functional and anatomical modifications after surgery.

A. Best corrected visual acuity. In all epiretinal membrane stages, best corrected visual acuity improved in the postoperative period. Higher visual acuity changes from baseline are observed in epiretinal membranes stages 3 and 4. In stage 4 epiretinal membranes, best corrected visual acuity tended to stabilize after 6 months from surgery. Best corrected visual acuity differences between the three epiretinal membrane stages remained significant during the follow-up period ($p<0.001$). **B. Central foveal thicknes**. Central foveal thickness decreased significantly in all epiretinal membrane stages, with a prominent effect in the first month after surgery. Central foveal thickness differences between epiretinal membranes stages 3 and 4 were minimal after 6 months from surgery. Central foveal thickness differences between stage 2 versus stages 3 and 4 epiretinal membranes remained significant over the follow-up period ($p<0.001$). **C. Ectopic inner foveal layers thickness**. Similarly to central foveal thickness, ectopic inner foveal layers thickness decreased significantly in all epiretinal membrane stages, with a prominent effect in the first month after surgery.

Figure 5: Anatomical variations of the ectopic inner foveal layers in the postoperative period.

A. Persistence of the ectopic inner foveal layers. In this stage 4 epiretinal membrane, thick ectopic inner foveal layers are visible at presentation. The cotton ball sign is present. Over the follow up period, retinal and ectopic inner foveal layers thickness decrease significantly, but the ectopic inner foveal layers persist up to 12 months after surgery. At the end of the follow-up period, residual chronic cystoid macular edema and the cotton ball sign are visible. **B. Regression of the ectopic inner foveal layers.** In this stage 3 epiretinal membrane, thick ectopic inner foveal layers are identified at presentation, as well as a prominent cotton ball sign in the outer retina, accompanied by a shallow foveolar detachment. Over the follow up period, the ectopic inner foveal layers progressively regressed. At 12 months from surgery, the foveal depression is restored and the fovea is free from ectopic inner foveal layers. The cotton ball sign is no longer visible.

Figure 6: Postoperative anatomical changes in a stage 2 epiretinal membrane.

At presentation, no ectopic inner retinal tissue is observed in this stage 2 epiretinal membrane. At 1 month from surgery, a thin and hyperreflective bridge of inner retinal tissue develops over the outer nuclear layer in the absence of traction (white arrows). The thickness of this tissue increases over the follow up period, while the parafoveal inner nuclear layer approximates to the foveal center (black arrows). However, differently from the ectopic inner foveal layers, there is no apparent continuity with the parafoveal inner nuclear layer.

Figure 7: Preoperative and postoperative changes of foveal morphology.

A. At presentation, no epiretinal membrane is present. The foveal depression is wide and no inner retinal tissue is visible over the foveal center. Signs of mild vitreomacular traction can be appreciated over the foveal floor. After 21 months, a thick stage 4 epiretinal membrane has developed. At 1 month from surgery both retinal and ectopic inner foveal layers thickness significantly decreased. At 12 months, a shallow foveal depression can be appreciated, although thin ectopic inner foveal layers are still present over the foveal floor. Note the significant alteration of the foveal anatomy, if compared to baseline. **B.** At presentation, no epiretinal membrane is present. The foveal depression is appreciable, although shallow. No inner retina is visible over the foveal floor. After 18 months, a stage 3 epiretinal membrane developed, with thick ectopic inner foveal layers over the fovea, and the appearance of the cotton ball sign in the outer retina. At 1 month from surgery, thick ectopic inner foveal layers can still be seen in the central fovea, although retinal thickness significantly decreased. The cotton ball sign disappeared. At 12 months from surgery, there is no restoration of the foveal microanatomy and the ectopic inner foveal layers thickness remained grossly unchanged. Note the remarkable differences in the foveal structure compared to baseline.

Figure 1

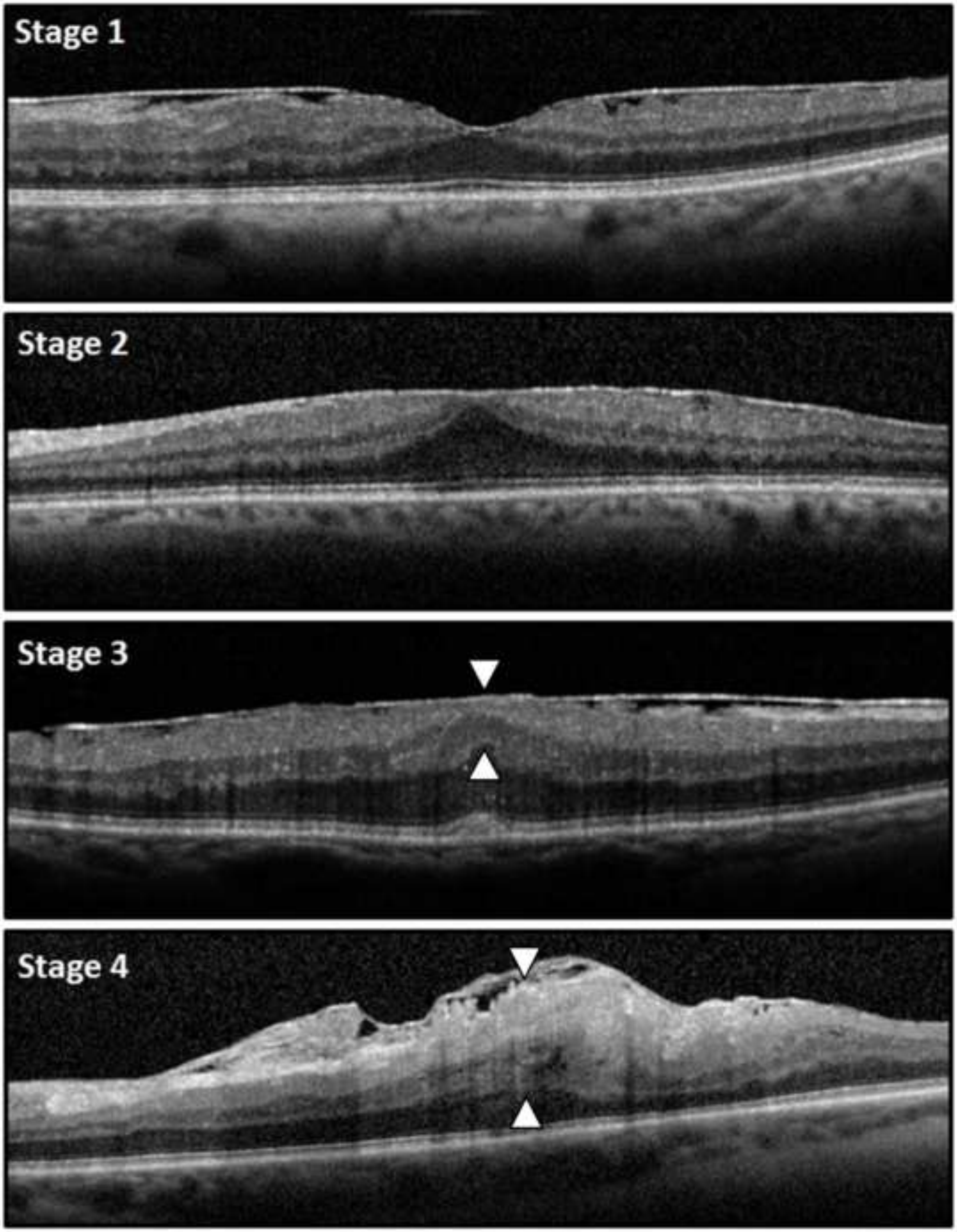


Figure 2

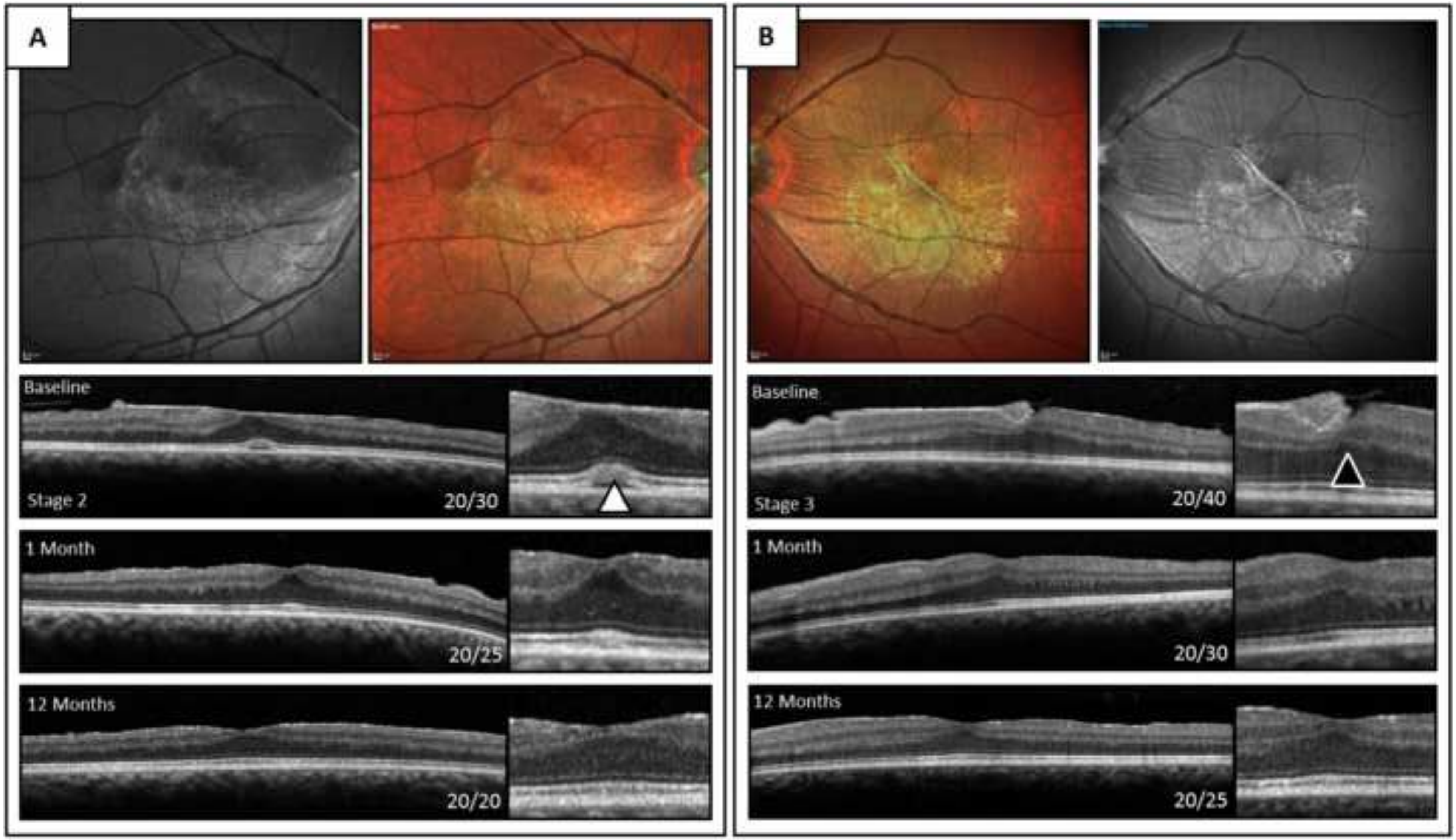
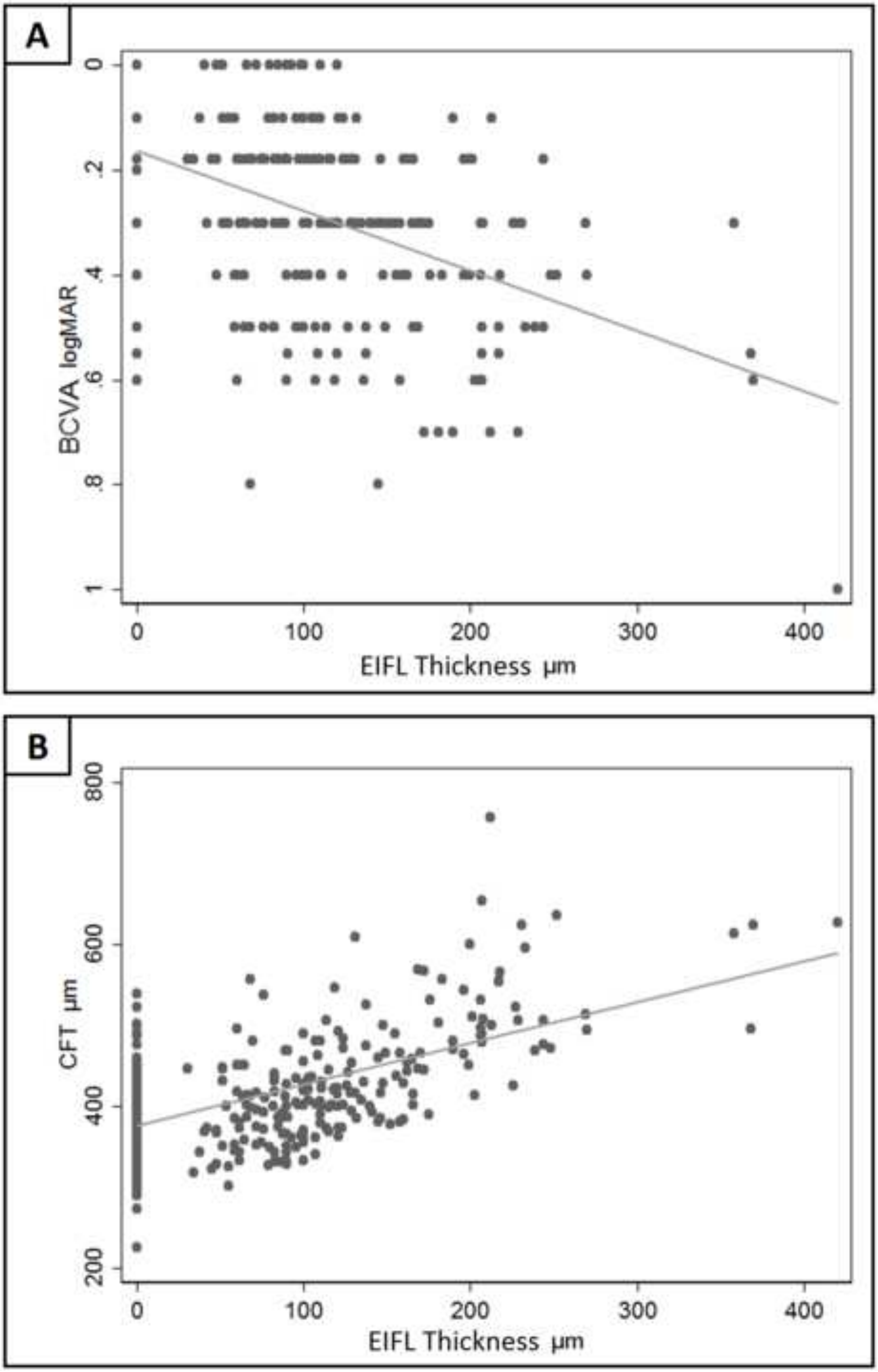

A
Baseline
Stage 2
20/30
1 Month
20/25
12 Months
20/20
B
Baseline
Stage 3
20/40
1 Month
20/30
12 Months
20/25

Figure 3



A
0
.2
.4
.6
.8
1
BCVA logMAR
0
100
200
300
400
EIFL Thickness μm
B
800
600
400
200
CFT μm
0
100
200
300
400
EIFL Thickness μm

Figure 4

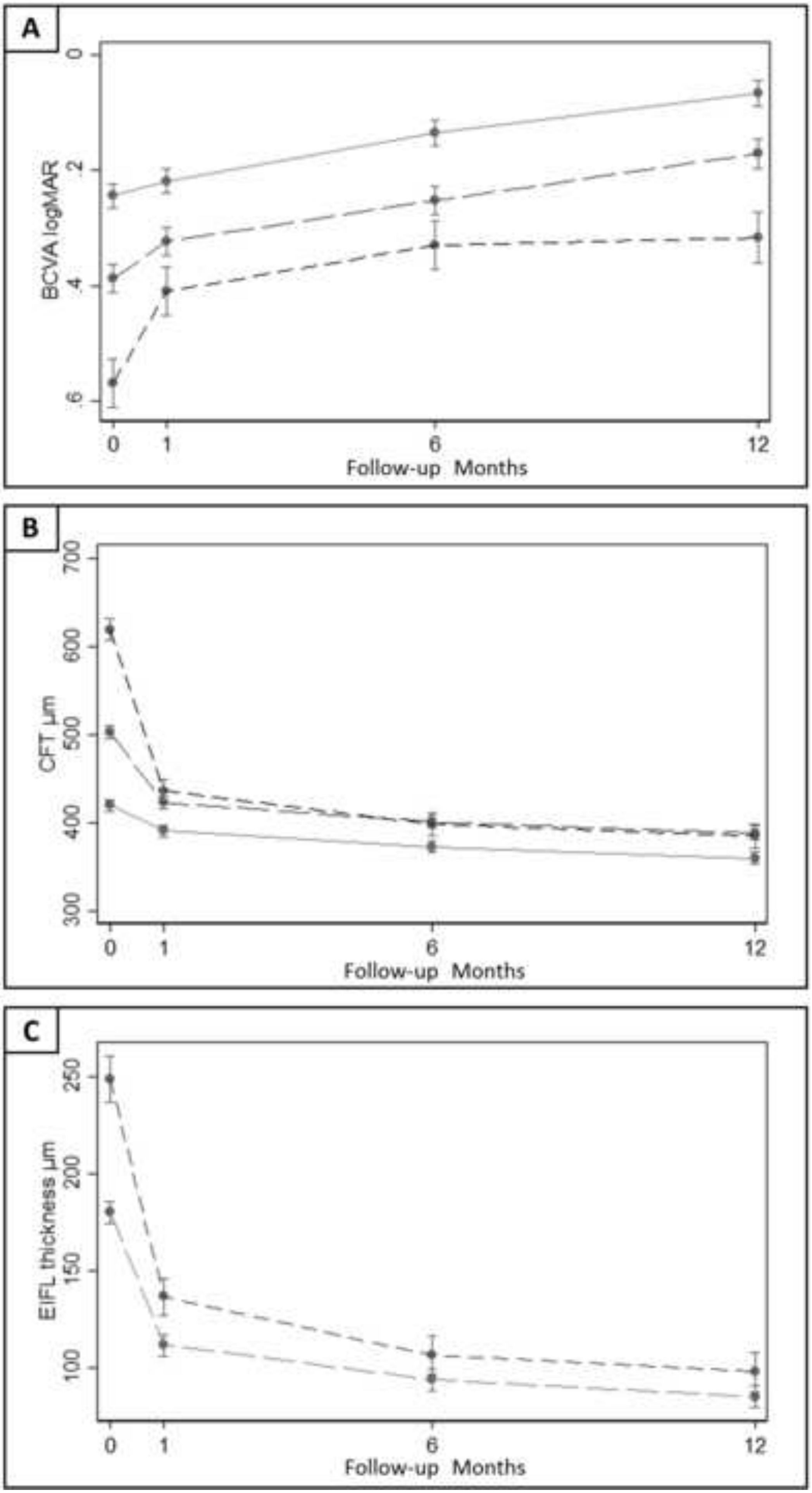

A
BCVA logMAR
0
.2
.4
.6
0
1
6
12
Follow-up Months
B
CFT µm
700
600
500
400
300
0
1
6
12
Follow-up Months
C
EIFL thickness µm
250
200
150
100
0
1
6
12
Follow-up Months

Figure 5

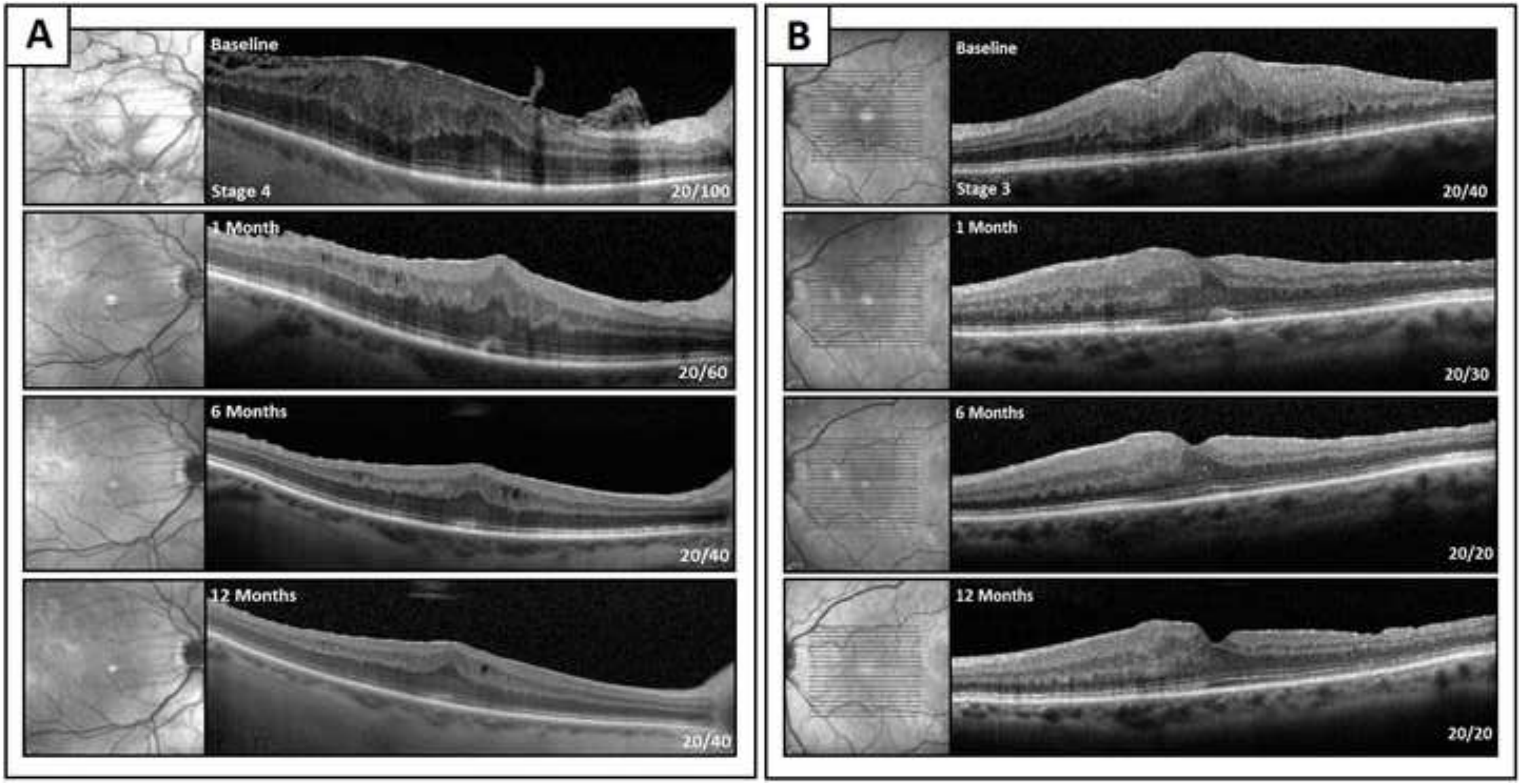

A
Baseline
Stage 4
20/100
1 Month
20/60
6 Months
20/40
12 Months
20/40
B
Baseline
Stage 3
20/40
1 Month
20/30
6 Months
20/20
12 Months
20/20

Figure 6

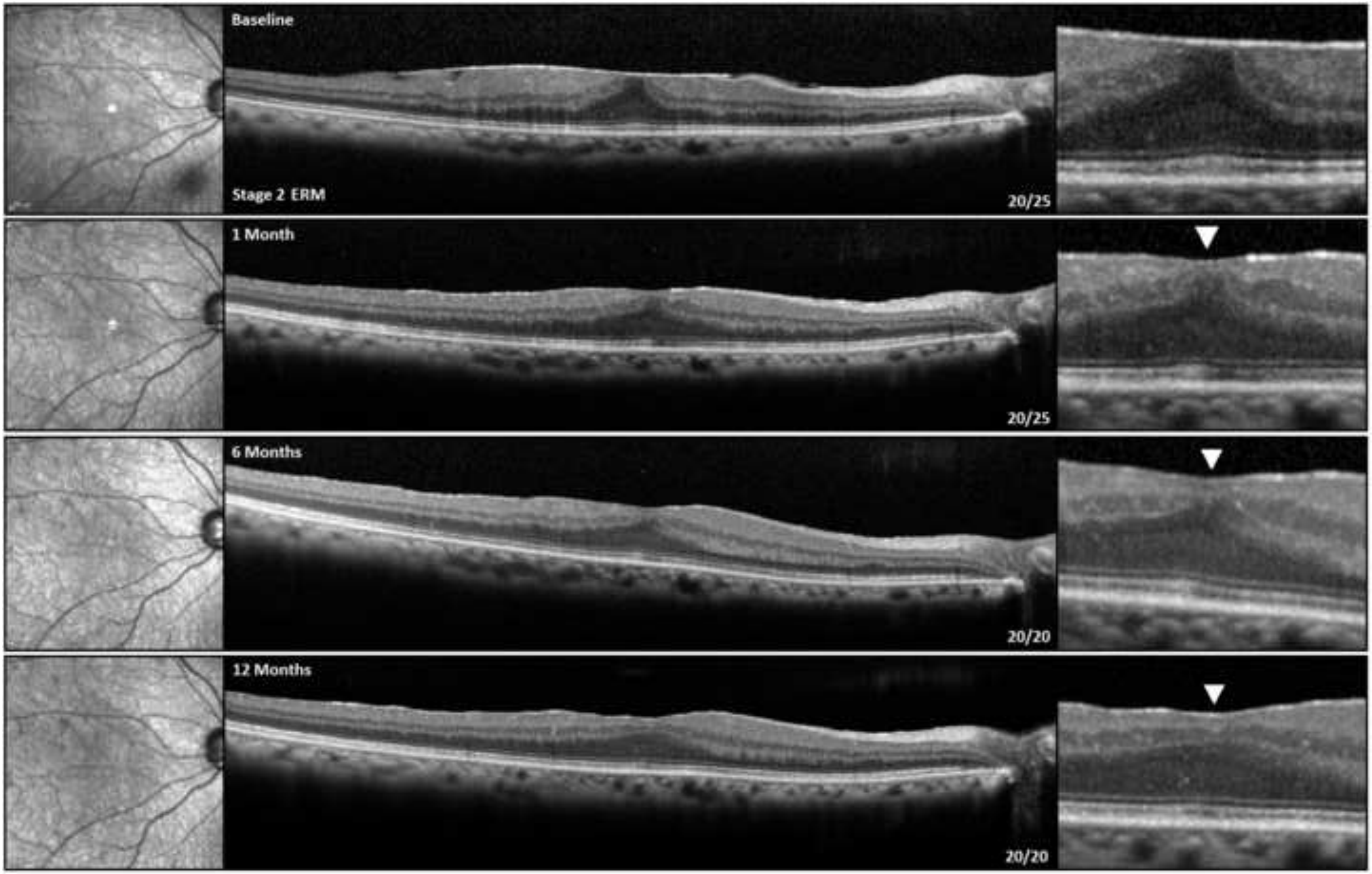

Baseline
Stage 2 ERM
20/25
1 Month
20/25
6 Months
20/20
12 Months
20/20

Figure 7

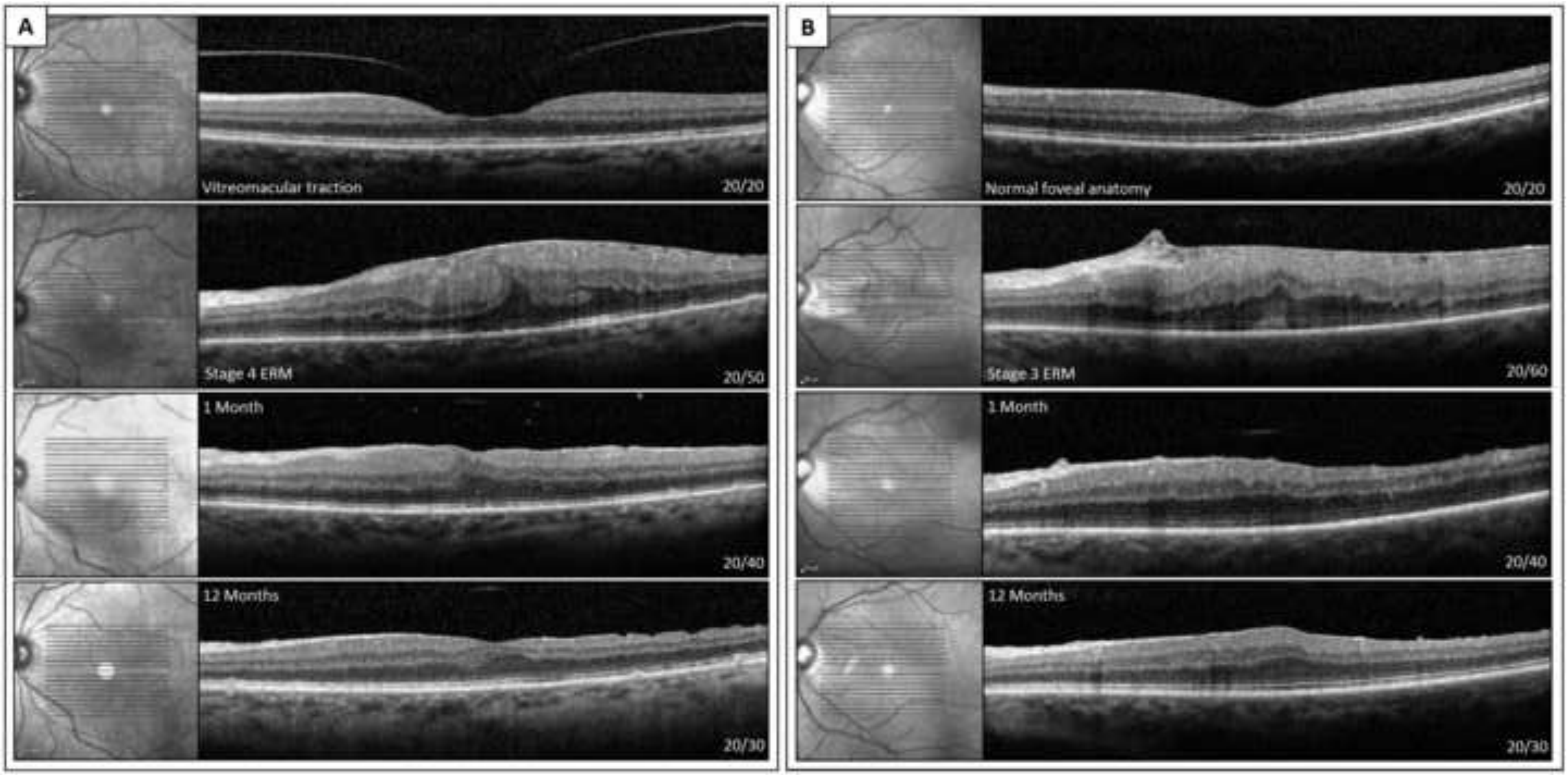

A
Vitreomacular traction
20/20
Stage 4 ERM
20/50
1 Month
20/40
12 Months
20/30
B
Normal foveal anatomy
20/20
Stage 3 ERM
20/60
1 Month
20/40
12 Months
20/30

Table 1. Exclusion Criteria

Exclusion Criteria	• Any previous intraocular surgery with the exclusion of uncomplicated phacoemulsification. • History of retinal detachment. • Intermediate or Advanced Age Related Macular Degeneration. • History of Choroidal neovascularization of any etiology. • Central Serous Chorioretinopathy. • Proliferative Diabetic Retinopathy. • Non Proliferative Diabetic Retinopathy with history of clinically significant diabetic macular edema. • Macular teleangectasias. • Tractional and Degenerative lamellar macular holes. • History of central or branch retinal vein occlusion and central or branch retinal artery occlusion. • Advanced Glaucoma, or optic neuropathy of any kind. • History of inflammatory eye disorders. • History of Irvine-Gass syndrome. • Visually significant cataract. • History of endophthalmitis or any other intraocular infection. • Retinal dystrophies. • Foveal hypoplasia/Fovea plana • History of ocular trauma. • Any other potential cause of vision loss other than epiretinal membranes.

Table 2: Preoperative characteristics of the included eyes.

ERM	BCVA	CFT	CME	Ellipsoid disruption	Pseudophakia	Cotton ball sign
Stage 2 (n=55)	0.24 ± 0.11 logMAR 20/35 Snellen	419.7 ± 45 µm	14/55 (25.4%)	10/55 (18.1%)	31/55 (56.4%)	21/55 (38.1%)
Stage 3 (n=42)	0.39 ± 0.13 logMAR 20/49 Snellen	501.9 ± 66 µm	6/42 (14.2%)	4/42 (9.5%)	20/42 (47.6%)	10/42 (23.8%)
Stage 4 (n=14)	0.57 ± 0.30 logMAR 20/74 Snellen	619.2 ± 90 µm	7/14 (50%)	6/14 (42.8%)	7/14 (50%)	1/14 (7.4%)
-p value	<0.001*	<0.001*	0.025†	0.019†	0.683†	0.039†

ERM: epiretinal membrane; BCVA; best-corrected visual acuity; CFT; central foveal thickness; CME: cystoid macular edema;

p-value: *Kruskal-Wallis test; †Chi-square test.

Table 3: Best corrected visual acuity changes in the postoperative period.

ERM	Baseline	1 Month	6 Months	12 Months
Stage 2 (n=55)	0.24 ± 0.11 logMAR 20/35 Snellen	0.22 ± 0.14 logMAR 20/33 Snellen	0.13 ± 0.15 logMAR 20/27 Snellen	0.06 ± 0.08 logMAR 20/23 Snellen
Stage 3 (n=42)	0.39 ± 0.13 logMAR 20/49 Snellen	0.32 ± 0.17 logMAR 20/42 Snellen	0.25 ± 0.16 logMAR 20/35 Snellen	0.17 ± 0.14 logMAR 20/30 Snellen
Stage 4 (n=14)	0.57 ± 0.30 logMAR 20/74 Snellen	0.41 ± 0.23 logMAR 20/51 Snellen	0.33 ± 0.26 logMAR 20/43 Snellen	0.31 ± 0.26 logMAR 20/41 Snellen
-p value	<0.001	<0.001	<0.001	<0.001

ERM: epiretinal membrane; p-value: Kruskal-Wallis test.