Foveal Photoreceptor Deformation as a Significant Predictor of Postoperative Visual Outcome in Idiopathic Epiretinal Membrane Surgery

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PURPOSE. The purpose of this study was to determine whether the outer nuclear layer (ONL) deformation detected by spectral-domain optical coherence tomography (SD-OCT) is correlated with visual acuity before and after surgery in patients with idiopathic epiretinal membrane (ERM).

METHODS. Forty-four eyes of 44 patients who underwent vitreous surgery for treatment of ERM were included. All patients underwent comprehensive ophthalmologic evaluations including measurement of best corrected visual acuity (BCVA) and SD-OCT before and after surgery. The central foveal thickness (CFT), foveal ONL thickness, juxtafoveal ONL plus outer plexiform layer (OPL) thickness, photoreceptor outer segment thickness, and size of the disrupted interdigitation zone (IZ) line were measured. We defined the “photoreceptor deformation index” (PDI) as the ratio of foveal ONL thickness to the juxtafoveal ONL plus OPL thickness.

RESULTS. Multiple regression analysis showed that the only significant predictor of preoperative mean logarithm of the minimum angle of resolution (logMAR) BCVA was preoperative CFT ($P < 0.0001$). Preoperative PDI ($P < 0.0001$) and disrupted IZ diameter ($P = 0.0242$) were positively correlated with logMAR at 3 months after surgery. PDI ($P < 0.0001$) and disrupted IZ diameter ($P = 0.0351$) were also positively correlated with logMAR BCVA at 6 months after surgery. The only significant predictor of logMAR at 12 months after surgery was preoperative PDI ($P < 0.0001$).

CONCLUSIONS. Preoperative PDI was most significantly correlated with postoperative BCVA. These results suggest that PDI is a novel parameter predicting visual outcome after surgery in eyes with ERM.

Keywords: epiretinal membrane, optical coherence tomography, vitreoretinal surgery

Epiretinal membrane (ERM) may have adverse effects on vision ranging from mild distortion and metamorphopsia to severe visual loss. Idiopathic ERM is most commonly encountered in individuals 50 years of age or older.1–4 Surgical removal of the ERM is a standard method for improving vision, but successful removal of the ERM does not always yield satisfactory functional results.5–7 Appropriate management of patients presenting with ERM relies on ophthalmologists distinguishing between patients who will benefit from surgery and those who will not.

Optical coherence tomography (OCT) has become the gold standard for diagnosing ERM and for evaluating retinal anatomic changes before and after surgery.8,9 In eyes with ERM, structural changes in the photoreceptor layer, such as various degrees of disruption of the photoreceptor inner segment ellipsoid zone (EZ)(10,11) (previously called photoreceptor inner and outer segment junction) and increased foveal thickness, have been identified using time domain OCT and higher-resolution spectral-domain OCT (SD-OCT). Recent SD-OCT studies have indicated prognostic factors in patients with ERM, such as foveal morphology,12–14 photoreceptor outer segment (OS) thickness,15 disruption of the EZ line,16,17 condition of the interdigitation zone (IZ) [also called cone outer segment tip, or COST](11,18,19) and parallelism of retinal layers.20 However, in clinical practice, it is still difficult to predict postoperative visual outcome before surgery, even taking into account all of these factors.

Previous OCT studies using time domain OCT or SD-OCT did not evaluate the deformation of foveal photoreceptors, which possibly may affect surgical outcome. The purpose of this study was to determine whether the deformation of the outer nuclear layer (ONL) is correlated with best corrected visual acuity (BCVA) before and after ERM surgery. We also examined correlation between visual outcome and other parameters that were already reported, such as preoperative BCVA, foveal retinal thickness, ONL thickness, OS thickness, and disrupted IZ diameter, and evaluated the usefulness of the novel parameter in comparison with previously reported parameters.

METHODS
This was a retrospective, observational study which adhered to the tenets of the Declaration of Helsinki, and this retrospective review of existing patient data was approved by the Institutional Review Board at Kyoto University Graduate School of Medicine.
Participants

Candidates in this retrospective interventional case study were consecutive patients with idiopathic ERM but without any other macular abnormality such as age-related macular degeneration or glaucoma, who underwent vitrectomy at the Kyoto University Hospital from December 2008 through March 2013, and were followed for at least 1 year. Glaucomatous eyes were defined by the presence of evident diffuse or localized rim thinning on stereo disc photography regardless of the presence of glaucomatous visual field defects. Eyes with high myopia (axial length > 26.5 mm) were excluded. Eyes with secondary ERM (e.g., due to retinal detachment, diabetic retinopathy, venous occlusion, uveitis, or trauma) were excluded from this study. Eyes with other ocular pathologies that could have interfered with the functional results, such as dense cataract, also were excluded.

Glaucomatous eyes were defined as the distance between the vitreoretinal interface and the inner border of the retinal pigment epithelium (RPE) at the center of the fovea. Foveal ONL thickness was defined as the distance between the vitreoretinal interface and the external limiting membrane (ELM) at the center of the fovea. Juxtafoveal ONL plus OPL thickness was defined as the distance between the inner border of the OPL and the ELM 500 μm from the center of the fovea (white arrows). OS thickness was defined as the distance between the outer border of the EZ and inner border of the RPE.

SD-OCT Evaluation of Photoreceptor Features

SD-OCT was performed 3, 6, and 12 months after surgery. Horizontal and vertical line scans through the center of the fovea were obtained at a 30° angle, after which we obtained volume scans (10° × 30°). In this study, we used horizontal and vertical B-scan images through the fovea for analysis. Eyes with poor image quality or no central foveal scans were excluded. If both images were eligible, we selected one image at random. Using preoperative images, we measured the central foveal thickness (CFT), foveal ONL thickness, juxtafoveal ONL plus outer plexiform layer (OPL) thickness, OS thickness, diameter of the disrupted IZ line and EZ line by using the digital caliper tool built into the OCT system. The border of EZ or IZ disruption was defined as the line on the grayscale image along which EZ or IZ reflectivity had diminished by 2 standard deviations from the reflectivity of the EZ or IZ in the unaffected peripheral macula.21
measurements. OS thickness was defined as the distance between the inner border of the retinal pigment epithelium and the external limiting membrane (ELM) at the center of the fovea. Foveal ONL thickness (center of the fovea) was defined as the distance between the juxtafoveal OPL and ELM interfaces. Juxtafoveal ONL plus OPL thickness (average of two white arrows) was defined as the distance between two points of each B-scan image). OPL and ONL are seen as hyporeflective and hyperreflective layer, respectively. Structural continuum of the inner retinal layers over the central fovea in healthy eyes has been known.22 In such cases, inner retinal layers were included in foveal ONL measurements. OS thickness was defined as the distance between the outer border of the EZ and the inner border of the RPE. We defined the “photoreceptor deformation index” as a/b.

Schemas of photoreceptor deformation indexes in eyes with ERM and normal eyes are presented in Figure 2. Inner border of juxtafoveal OPL may be sometimes unclear. In such cases, several points where the border of OPL could be identified were chosen and connected to create a segmentation line, and then OPL+ONL thickness was measured.

**Statistical Analysis**

Comparisons between preoperative and postoperative BCVA values and photoreceptor deformation indexes were evaluated by Mann-Whitney U test. Correlations among CFT, ONL thickness, OS thickness, diameter of disrupted EZ and IZ lines, photoreceptor deformation indexes, and BCVA values were evaluated using Spearman rank correlation coefficient. Independent variables for multiple regression analysis were determined using stepwise selection. A P value of <0.05 was considered statistically significant. All analyses were performed using a commercial software program (SPSS software version 20.0; SPSS, Inc., Chicago, IL, USA).

**RESULTS**

**Preoperative and Intraoperative Characteristics**

Images obtained from 44 eyes from 44 patients (16 men and 28 women; mean age: 67.7 ± 7.6 years) and 35 normal eyes of 35 subjects (13 men and 22 women; mean age: 69.8 ± 8.1 years) were suitable for analysis in this study. Table 1 summarizes patients’ characteristics prior to surgery. Mean preoperative logMAR BCVA was 0.278 ± 0.204, and mean symptom duration was 20.6 months. In eyes with ERM, mean ONL thickness of the fovea was 368 ± 88 μm, and mean OS thickness was 59 ± 10 μm, both of which were significantly greater than in normal eyes (P < 0.0001 and P = 0.0441, respectively). In six eyes, inner retinal layers were included in foveal ONL measurements because of structural continuum of the inner retinal layers.22 Mean disrupted IZ diameter was 357 ± 176 μm. Mean photoreceptor deformation index was significantly higher in eyes with ERM than in normal eyes (2.66 vs. 0.95, respectively; P < 0.0001). Photoreceptor deformation index did not significantly correlate with age (P = 0.6226) and had no association with sex (P = 0.4366) in normal eyes. Half of the eyes (22 eyes) had cotton-ball sign, a highly reflective foveal region reported by Tsunoda et al.23 before surgery. The ILM was peeled in 26 eyes, and 0.05% ICG was used to dye ILM in 10 eyes.

**Postoperative Changes of BCVA and Foveal Deformation Index**

Mean logMAR BCVA values at 3, 6, and 12 months after surgery were 0.136 ± 0.188, 0.075 ± 0.193, and 0.057 ± 0.209, respectively. Mean logMAR BCVA values at 3, 6, and 12 months postoperatively were improved significantly compared with mean preoperative logMAR BCVA values (P < 0.0001 for all) (Figs. 3, 4). Mean photoreceptor deformation indexes at 3, 6, and 12 months after surgery were 1.99, 1.87, and 1.72, respectively. Mean photoreceptor deformation indexes at 3, 6, and 12 months postoperatively decreased significantly compared with mean preoperative photoreceptor deformation indexes (P = 0.0020, <0.0001, and <0.0001, respectively) (Fig. 4).
Relationship Between Preoperative OCT Parameters and BCVA

Table 2 shows correlations between preoperative OCT parameters and logMAR BCVA before and after surgery. Preoperative logMAR BCVA was positively correlated with CFT ($P < 0.0001$), foveal ONL thickness ($P < 0.0001$), and photoreceptor deformation index ($P < 0.0001$). Preoperative logMAR BCVA was negatively correlated with OS thickness ($P = 0.0066$). Preoperative photoreceptor deformation index positively correlated with logMAR BCVA at all time points after surgery ($P < 0.0001$ for all) (Fig. 5). However, preoperative photoreceptor deformation index showed no significant correlation with improvement of BCVA at 12 months after surgery ($P = 0.1850$). Preoperative logMAR BCVA and foveal ONL thickness also showed positive correlation with logMAR BCVA at each time point examined. Disrupted IZ diameter was positively correlated with BCVA postoperatively but not preoperatively. Disrupted EZ diameter did not correlate with BCVA at each time point. There were no relationships between cotton-ball sign and preoperative/postoperative logMAR BCVA. Symptom duration showed no significant correlation with OCT parameters and logMAR BCVA at each time point.
Juxtafoveal ONL plus OPL thickness analysis was 0.336.

The only significant predictor of preoperative logMAR BCVA was photoreceptor deformation index, diameter of disrupted IZ line, OS thickness, ICG staining, and ILM peeling) and preoperative/postoperative logMAR BCVA values. Multiple regression analysis showed that the only significant predictor of preoperative logMAR BCVA was photoreceptor deformation index (P < 0.0001; standard regression coefficient = 0.706). Model R² for this analysis was 0.499. Preoperative photoreceptor deformation index (P < 0.0001) and disrupted IZ diameter (P = 0.0242) were positively correlated with logMAR BCVA at 3 months after surgery. Photoreceptor deformation index (P < 0.0001) and disrupted IZ diameter (P = 0.0351) were also positively correlated with logMAR BCVA at 6 months after surgery. The only significant predictor of logMAR BCVA at 12 months after surgery was preoperative photoreceptor deformation index (P < 0.0001; standard regression coefficient = 0.468). Model R² for this analysis was 0.336.

**DISCUSSION**

Results of this study showed that photoreceptor deformation index, a new parameter that provides a quantitative method for evaluating deformation of the foveal ONL, was significantly correlated with BCVA at each time point before and after surgery. Most importantly, multiple regression analysis showed that preoperative photoreceptor deformation index was most significantly correlated with BCVA postoperatively. These results suggest that photoreceptor deformation index is a novel parameter predicting visual outcome after surgery in eyes with ERM.

We propose photoreceptor deformation index represents the degree of photoreceptor deformation in eyes with ERM. ONL contains the photoreceptor cell bodies of both rods and cones. In eyes with ERM, thickening of the ONL is greatest at the center of the fovea (Figs. 1–5), suggesting that the centripetal force toward the foveal center is transmitted from the ERM to the foveal photoreceptor cell bodies. Thus, photoreceptor deformation index appears to reflect how shrinkage of the ERM causes disarrangement to the photoreceptor cell bodies. In support of this proposal, we previously reported that the regularity of the spatial arrangement of the rod cone mosaic is disrupted in eyes with ERM by using adaptive optics scanning laser ophthalmoscopy.21

Predictors of Preoperative/Postoperative BCVA by Using Multiple Regression Analysis

Table 3 shows results of multiple regression analysis of preoperative and intraoperative parameters (BCVA before surgery, CFT, foveal ONL thickness, photoreceptor deformation index, diameter of disrupted IZ line, OS thickness, ICG staining, and ILM peeling) and preoperative/postoperative logMAR BCVA values. Multiple regression analysis showed that the only significant predictor of preoperative logMAR BCVA was photoreceptor deformation index (P < 0.0001; standard regression coefficient = 0.706). Model R² for this analysis was 0.499. Preoperative photoreceptor deformation index (P < 0.0001) and disrupted IZ diameter (P = 0.0242) were positively correlated with logMAR BCVA at 3 months after surgery. Photoreceptor deformation index (P < 0.0001) and disrupted IZ diameter (P = 0.0351) were also positively correlated with logMAR BCVA at 6 months after surgery. The only significant predictor of logMAR BCVA at 12 months after surgery was preoperative photoreceptor deformation index (P < 0.0001; standard regression coefficient = 0.468). Model R² for this analysis was 0.336.

**Table 2.** Relationship Among Optical Coherence Tomography Parameters and Visual Acuity Before and After Epiretinal Membrane Surgery

<table>
<thead>
<tr>
<th>Parameter</th>
<th>BCVA Before Surgery</th>
<th>BCVA 3 Months After Surgery</th>
<th>BCVA 6 Months After Surgery</th>
<th>BCVA 12 Months After Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCVA before surgery</td>
<td>-</td>
<td>P &lt; 0.0001</td>
<td>r = 0.593</td>
<td>P = 0.0008</td>
</tr>
<tr>
<td>CFT</td>
<td>P &lt; 0.0001</td>
<td>r = 0.669</td>
<td>P = 0.0247</td>
<td>r = 0.263</td>
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<tr>
<td>Foveal ONL thickness</td>
<td>P &lt; 0.0001</td>
<td>r = 0.561</td>
<td>P = 0.0128</td>
<td>r = 0.150</td>
</tr>
<tr>
<td>Juxtafoveal ONL plus OPL thickness</td>
<td>P &lt; 0.0001</td>
<td>r = 0.315</td>
<td>P = 0.0372</td>
<td>r = 0.0069</td>
</tr>
<tr>
<td>Photoreceptor deformation index</td>
<td>P &lt; 0.0001</td>
<td>r = 0.059</td>
<td>P = 0.0003</td>
<td>r = 0.056</td>
</tr>
<tr>
<td>Diameter of disrupted IZ line</td>
<td>P = 0.0802</td>
<td>r = 0.267</td>
<td>P = 0.0051</td>
<td>r = 0.0013</td>
</tr>
<tr>
<td>Diameter of disrupted EZ line</td>
<td>P = 0.1483</td>
<td>r = 0.222</td>
<td>P = 0.1342</td>
<td>r = 0.0415</td>
</tr>
<tr>
<td>OS thickness</td>
<td>P = 0.0221</td>
<td>r = 0.344</td>
<td>P = 0.3855</td>
<td>r = 0.154</td>
</tr>
</tbody>
</table>

**Table 3.** Multiple Regression Comparison Between Preoperative Parameters and Visual Acuity Before and After Surgery in Eyes With Epiretinal Membrane

<table>
<thead>
<tr>
<th>Dependent Variable</th>
<th>Preoperative Parameter</th>
<th>Regression</th>
<th>P Value</th>
<th>Standard Regression Coefficient</th>
<th>Overall R²</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCVA before surgery</td>
<td>CFT (a)</td>
<td>-0.4647+0.0015*(a)</td>
<td>&lt;0.0001</td>
<td>0.706</td>
<td>0.499</td>
</tr>
<tr>
<td>BCVA 3 months after surgery</td>
<td>Photoreceptor deformation index (b)</td>
<td>-0.4985+0.1922*(b)+0.0003*(c)</td>
<td>&lt;0.0001</td>
<td>0.611</td>
<td>0.516</td>
</tr>
<tr>
<td>BCVA 6 months after surgery</td>
<td>Size of disrupted IZ line (c)</td>
<td>0.0242</td>
<td>0.274</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BCVA 12 months after surgery</td>
<td>Photoreceptor deformation index (b)</td>
<td>-0.6565+0.2318*(b)+0.0003*(c)</td>
<td>&lt;0.0001</td>
<td>0.673</td>
<td>0.622</td>
</tr>
<tr>
<td>BCVA 12 months after surgery</td>
<td>Size of disrupted IZ line (c)</td>
<td>0.0351</td>
<td>0.249</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations are as in Table 2.

* Values in boldface are statistically significant.
significant predictors of postoperative BCVA. These results suggest that preoperative BCVA and CFT are not strong prognostic factors.

Shiono et al.\textsuperscript{15} reported that preoperative OS thickness yielded the highest regression coefficient with postoperative BCVA, suggesting that OS thickness may be a predictor of postoperative BCVA in patients with ERM. In the current study, preoperative logMAR BCVA was negatively correlated with preoperative OS thickness. However, we found that the correlation between preoperative OS thickness and postoperative BCVA was marginal. Although these opposing results may be due to different study populations, OS thickness does not appear to be a major prognostic factor compared with photoreceptor deformation index. It is possible that the photoreceptor cell body, rather than OS, has a close association with visual function in eyes with ERM.

Several researchers have reported that the length of the preoperative IZ (or COST) line defect can predict BCVA after ERM surgery.\textsuperscript{18,19} Consistent with those reports, we also found that the disrupted IZ diameter was positively correlated with postoperative BCVA, although we found no significant correlation with preoperative BCVA. Multiple regression analysis revealed that the disrupted IZ diameter was correlated with logMAR BCVA at 3 and 6 months after surgery. These results suggest that the status of the preoperative IZ line is also a useful prognostic factor. However, visibility of the IZ line depends on the intensity and direction of the laser light that reaches the photoreceptor layer, so care must be taken during its evaluation.

Multiple regression analysis showed that preoperative photoreceptor deformation index was more significantly correlated with postoperative BCVA than previously reported prognostic factors such as preoperative BCVA, CFT, OS thickness, and disrupted IZ diameter. In addition, preoperative photoreceptor deformation index was the only significant predictor of logMAR BCVA at 12 months after surgery, and patients with lower photoreceptor deformation index resulted in better visual outcome. These results suggest that photoreceptor deformation index is most useful to predict visual outcome of ERM surgery and that foveal photoreceptor cell bodies play one of the most important roles in the improvement of visual function in eyes with ERM. Contraction or shrinkage of an ERM may cause not only retinal thickening but also various degrees of distortional force in the photoreceptor cell bodies, leading to irreversible functional impairment. However, it also should be stated that preoperative photoreceptor deformation index showed no significant correlation with improvement of BCVA. It implies that photoreceptor deformation index may fail to identify the patients who would benefit most from surgery and is rather a useful measure for severity of retinal distortion and subsequent limited visual prognosis of patients.

This study has several limitations. First, this was a retrospective study and the ILM was peeled at the surgeon's discretion. However, multiple regression analyses have revealed that neither ILM peeling nor ICG staining were significant predictors of postoperative BCVA. Second, we did not evaluate ONL thickness alone at 500 μm from the center of the fovea; instead, we measured the combined thicknesses of the OPL and ONL. This is because standard SD-OCT images acquired along the optical axis typically do not show axons of the photoreceptor nuclei or Henle's fiber layer; thus, accurate measurement of ONL thickness is challenging except at the center of the fovea.\textsuperscript{25} Further studies are necessary to evaluate “pure ONL” deformation by using a method reported by Lujan et al.\textsuperscript{25} Despite these limitations, the current study revealed highly significant correlations between the photoreceptor deformation index and visual acuity before and after ERM surgery. Considering the strength of these results, we believe that the photoreceptor deformation index is a strong indicator of mechanical stress on foveal structures and a prognostic factor for postoperative BCVA in patients with idiopathic ERM.

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\section*{References}


