RETINAL SURFACE WRINKLING AS AN INDICATOR FOR INTERNAL LIMITING MEMBRANE PEELING DURING VITRECTOMY FOR RETINAL DETACHMENT

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Purpose: To assess the validity of retinal surface wrinkling (RSW) as an indicator to select patients relevant for internal limiting membrane peeling during vitrectomy for rhegmatogenous retinal detachment, to prevent postoperative visual decline due to epiretinal membrane growth.

Methods: This was a prospective, interventional case series of 78 consecutive eyes that underwent initial vitrectomy to repair rhegmatogenous retinal detachments and were followed for 6 months. The presence/absence of RSW was evaluated presurgically on en face optical coherence tomographic images. The internal limiting membrane was peeled if RSW was identified. The main outcome measure was the prevalence of postsurgical epiretinal membrane growth that caused a visual decline of 0.2 or more in logarithm of the minimum angle of resolution unit.

Results: The internal limiting membrane was peeled for RSW appearance in 22 eyes (28.2%). Mild epiretinal membranes developed in 8 of the 56 internal limiting membrane–unpeeled eyes (10.3% of total, 6 eyes at stage 1 in the classification of Govetto); however, visual decline occurred in none of them with the mean visual acuity of these 8 eyes maintained at 20/0.08 ± 0.11 in logarithm of the minimum angle of resolution unit (≈20/16).

Conclusion: Visual decline due to epiretinal membrane growth after rhegmatogenous retinal detachment repair was entirely prevented by peeling the internal limiting membrane in about 30% of cases selected for the presence of RSW.

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Internal limiting membrane (ILM) peeling has been advocated as prophylaxis for epiretinal membrane (ERM) growth after vitrectomy for rhegmatogenous retinal detachment (RRD). Because visual acuity does not always recover to normal after removal of ERMs that have developed after repair of macula-sparing RRDs, the prevention of postsurgical ERM growth would be beneficial for the maintenance of favorable vision, especially in macula-sparing cases.

On the other hand, there have been arguments regarding ILM peeling because of its adverse effects on visual function as well as anatomical changes induced. Although the visual acuity and visual field are maintained after ILM peeling, some previous reports have detected deterioration in the microperimetry and focal electroretinogram after ILM peeling. Microstructural studies have also suggested that the damaged retinal structure might not recover after ILM peeling.

To avoid the possible adverse events while preventing visual deficits due to postsurgical ERM growth, ILM peeling is desirable to be performed in selected cases that are likely to develop a vision-threatening ERM. However, no distinct methods based on pre-operative or intraoperative observation have been elucidated to predict the development of ERMs.

In a previous histological study, “surface wrinkling retinopathy” was shown to be related to ERM formation in eye bank eyes. A similar phenomenon is found during vitrectomy for RRD and in optical coherence tomographic (OCT) images of eyes with RRDs.
particularly by en face analyses. Surface wrinkling is also referred to as a clinical sign to define proliferative vitreoretinopathy Grade B,\textsuperscript{23,24} whereas fine wrinkling is often confirmed on the macula of eyes with RRDs in an acute phase. In the current study, we hypothesized that the fine retinal surface wrinkling (RSW) in the macular area is an early sign for predicting ERM growth after RRD repair and conducted a prospective study to assess the validity of selecting patients relevant for ILM peeling based on the presence of RSW. This study was designed to follow each patient for at least 1 year after the initial vitrectomy for RRDs, and we report here the results at six-month follow-up.

**Methods**

**Study Design**

This was a prospective, interventional case series study of 78 consecutive eyes that underwent initial vitrectomy to repair RRDs from December 6, 2017, to February 30, 2020, in the National Hospital Organization Tokyo Medical Center (UMIN Clinical Trials Registry identifier: UMIN000030292, registered on December 6, 2017). All patients provided written informed consent to participate in the study when surgeries were planned. The study protocol adhered to the tenets of the Declaration of Helsinki, and the Institutional Review Board of the National Hospital Organization Tokyo Medical Center approved the study protocol (approval number: R17-099).

The inclusion criterion was an initial vitrectomy to repair RRDs. The exclusion criteria were RRDs associated with a macular hole, proliferative vitreoretinopathy except for Grade A, any preexisting or coexisting ocular or macular conditions that might affect visual function and high myopia accompanied by posterior staphyloma. Both fovea-on and fovea-off cases were included, but eyes with RRDs that involved the entire area of the posterior pole within the vascular arcade were excluded because of the difficulty of the RSW assessment in the detached retina. Eyes were excluded from the analyses if presurgical en face OCT images had not been obtained with adequate quality, which were required for the assessment of the presence of RSW as described below.

**Patients and Observations**

Each patient underwent ophthalmologic examinations on the day of diagnosis of RRD, and the baseline data were collected as listed in Table 1. The decimal best-corrected visual acuity (BCVA) was measured using the Landolt chart and was converted into the logarithm of the minimum angle of resolution (logMAR) unit for statistical analyses. OCT images were obtained by the five-line raster protocol and the three-dimensional (3D) mapping (macular cube protocol) using the Cirrus HD-OCT system (Carl Zeiss Meditec, Dublin, CA). Best-corrected visual acuity measurements and OCT scans were performed again on the day of surgery if the eye was not treated on the day of diagnosis. The same data as the baseline observation were collected at each postoperative visit at 1, 3, and 6 months.

Various characteristics of the ocular condition were recorded, as listed in Table 2. Combined surgery with cataract extraction or scleral buckling and repeated surgery for redetachment were also raised as parameters for these analyses. Vitreous hemorrhage was not included in these factors because presurgical en face images could not be obtained with an adequate quality in eyes with vitreous hemorrhage.

**Surgical Intervention**

Surgeries were performed by one of the three experienced vitreoretinal surgeons (K.A., K.W., and T.M.). The surgical methods were the standardized procedures of microincision vitreous surgery using a 25- or 23-gauge system, including core vitrectomy, induction of posterior vitreous detachment if absent, release of vitreous traction at the retinal tears or holes, and shaving of the peripheral vitreous. Then, the
posterior pole was observed using a magnifying contact lens to identify and remove residual vitreous cortex, if any, that was visualized by triamcinolone acetonide.

After confirming that there was no vitreous cortex remaining on the macula, the ILM was peeled around the fovea if RSW had been detected based on the definition shown below. The ILM was preserved if RSW was not present. The ILM was peeled facilitated by triamcinolone acetonide or brilliant blue-G. Sulfur hexafluoride or air was used for tamponade in all patients except for one whose fellow eye was blind; silicone oil was selected for that patient and was removed after three months. Photocoagulation was performed for retinopexy in all cases, and cryopexy was not used. Perfluorocarbon was not used in any of the cases.

Definition of Retinal Surface Wrinkling

Retinal surface wrinkling was defined as fine wrinkling observed on the surface of the attached retina in the macular area. The fovea may or may not have been involved by RSW. The presence of RSW was determined by en face OCT images obtained presurgically. The en face images were generated from the macular cube scans (512 · 128), and the vitreoretinal interface slab was used for the assessment, with the boundaries adjusted at 3 μm above and 33 μm below the ILM layer. Because quantitative analysis of the wrinkling was not available, the assessment results were based on the agreement of at least two of the three investigators (K.A., K.W., and T.M.).

Definition of Epiretinal Membrane and Epiretinal Membrane With Visual Decline

In this study, the ERM was defined as a highly reflective thin layer covering the inner surface of the macula observed on the OCT images recorded with a horizontal and vertical 5-line raster protocol centered on the fovea. Mild membrane formation without the loss of the foveal pit, which was classified as stage 1 by Govetto et al., was also considered as ERM growth. When wrinkling was presented postoperatively on the retinal surface by en face imaging, it was termed “postsurgical RSW” (Table 3). This postsurgical RSW was distinguished from ERM growth because it was not necessarily accompanied by ERM formation defined on the 5-line raster OCT images.

The ERM was considered as “ERM with visual decline” if the BCVA had dropped by 0.2 logMAR unit or more after the ERM detection, compared with the best value of the BCVAs during the follow-up until the ERM detection.
Statistical Analyses and Outcome Measures

The main outcome measure was the prevalence of postsurgical ERM growth in the total cohort and was interpreted as a measure to evaluate the validity of selecting patients relevant for ILM peeling (Table 3). The prevalence was assessed in two categories: (1) any ERM and (2) ERM growth with visual decline. All cases were divided into one of the following two groups (Tables 1–3): cases with RSW (Group 1) and cases without RSW (Group 2). Because the same criterion was applied for both the indication of ILM peeling and the definition of the two groups, the cases in Groups 1 and 2 were equivalent to those treated with and without ILM peeling, respectively.

To assess the visual outcomes and safety of the ILM-peeling procedure, BCVAs at baseline and at the 6-month visit were compared between Groups 1 and 2. Groups 1 and 2 were also compared in terms of baseline data, various ocular characteristics, and surgical procedures to evaluate the association of each factor with the presence of RSW.

To evaluate the predictive factors of ERM growth, cases in Group 2 (ILM unpeeled) were subdivided into cases with and without postsurgical ERM growth, and the aforementioned factors (baseline data, various ocular characteristics, and surgical procedures) were compared between the two subgroups. The same analysis was also performed between other subdivided groups with and without postsurgical RSW determined by en face images. These analyses were conducted only among cases in Group 2 to avoid the statistical confounding with the effect of ILM peeling to prevent ERM growth.

Table 2. Comparison of Ocular Conditions Between Patients With and Without RSW

| Ocular Condition                              | Total Cases (n = 78), n (% | Group 1: RSW (+), ILM-Peeled (n = 22), n (%) | Group 2: RSW (−), ILM-Unpeeled (n = 56), n (%) | P  |
|-----------------------------------------------|---------------------------|----------------------------------------------|-----------------------------------------------|----|
| Pseudophakia                                  | 17 (21.8)                 | 6 (27.3)                                    | 11 (19.6)                                     | 0.545 |
| Combined with cataract surgery                | 57 (73.1)                 | 17 (77.3)                                   | 40 (71.4)                                     | 0.778 |
| Combined with scleral buckling                | 2 (2.6)                   | 0 (0.0)                                     | 2 (3.6)                                       | >0.999 |
| Foveal detachment                             | 25 (32.1)                 | 7 (31.8)                                    | 18 (32.1)                                     | >0.999 |
| Posterior vitreous detachment                 | 65 (83.3)                 | 19 (86.4)                                   | 46 (82.1)                                     | 0.749 |
| Residual vitreous cortex                      | 32 (41.0)                 | 8 (36.4)                                    | 24 (42.9)                                     | 0.799 |
| Tractinal/atrophic                            | 69/9 (88.5/11.5)          | 21/1 (95.5/4.5)                             | 48/8 (85.7/14.3)                              | 0.432 |
| Large tear (>3 clock hours)                   | 3 (3.8)                   | 1 (4.5)                                     | 2 (3.6)                                       | >0.999 |
| Location of retinal tears/holes (superior/inferior/both) | 62/8/8 (79.4/10.3/10.3) | 15/3/4 (68.2/13.6/18.2) | 47/5/4 (83.9/8.9/7.1) | 0.246 |
| Quadrants (1/2/3/4) with retinal tears/holes | 57/14/6/1 (73.1/17.9/7.7/1.3) | 16/4/2/0 (72.7/18.2/9.1/0.0) | 41/10/4/1 (73.2/17.9/7.1/1.8) | >0.999 |
| Quadrants (1/2/3/4) with RRD                  | 18/51/8/1 (23.1/65.3/10.3/1.3) | 5/14/3/0 (22.7/63.7/13.6/0.0) | 13/37/5/1 (23.2/66.1/8.9/1.8) | 0.899 |
| Repeated surgery for recurrence               | 1 (1.3)                   | 0 (0.0)                                     | 1 (1.8)                                       | >0.999 |

Table 3. Postsurgical ERM Growth Among Patients Treated With and Without ILM Peeling Based on RSW Appearance

| Ocular Condition                              | Total Cases (n = 78), n (%) | Group 1: RSW (+), ILM-Peeled (n = 22), n (%) | Group 2: RSW (−), ILM-Unpeeled (n = 56), n (%) | P  |
|-----------------------------------------------|---------------------------|----------------------------------------------|-----------------------------------------------|----|
| Postsurgical ERM                              | 8 (10.3)                  | 0 (0.0)                                      | 8 (14.3)                                      | 0.097 |
| Postsurgical ERM with visual decline          | 0 (0.0)                   | 0 (0.0)                                      | 0 (0.0)                                       | N/A  |
| Postsurgical RSW on en face OCT               | 27 (34.6)                 | 0 (0.0)                                      | 27 (48.2)                                     | <0.001 |

OCT, optical coherence tomography.
Statistical analyses were performed with IBM SPSS Statistics, version 24.0 (IBM Corp, Armonk, NY). $P < 0.05$ was considered statistically significant. Continuous values are expressed as the mean ± SD, and categorical data are described as the prevalence and proportion (percent). The Unpaired $t$-test (Welch) and Fisher exact test were performed for the comparison of continuous and categorical data, respectively. $P$ values were derived from two-sided tests in all analyses.

Results

One hundred patients among 106 who met the inclusion criteria completed the 6-month follow-up. Six patients dropped out during the follow-up. Twenty-two patients among them were excluded from the current analyses because presurgical en face images with an adequate quality were not available. Consequently, 78 eyes of 78 patients were included in the analyses. The BCVA at baseline of the excluded cases was significantly worse ($P < 0.001$) than that of the included cases because the prevalence of foveal detachment ($P = 0.001$) was associated with the unavailability of presurgical en face images in the excluded cases (see Table, Supplemental Digital Content, http://links.lww.com/IAE/B383, which illustrates the comparisons of the baseline data and the ocular conditions between the included and excluded cases). None of the other factors showed difference between the included and excluded cases.

The ILM was peeled in 22 patients (Group 1, 28.2%) based on the presence of RSW and was preserved in 56 patients (Group 2, 71.8%) (Tables 1–3). The baseline data and BCVAs at 6 months are compared between the 2 groups in Table 1. The preoperative values of the two groups showed no statistically significant difference in terms of age, refraction, BCVA, or duration between the onset and the day of surgery. The postoperative BCVA did not differ significantly between the two groups at 6 months. OCT images and en face images of three representative cases with RSW are shown in Figure 1.

Comparison results of ocular conditions between patients with and without RSW are presented in Table 2. None of the ocular conditions were associated with the presence or absence of RSW.

An ERM developed during the follow-up period in eight patients (Table 3). All of the eight patients with ERM growth had been treated without ILM peeling (Group 2), and none of them presented visual decline throughout the follow-up period. Detailed findings of the cases with ERM growth are presented in Table 4. Serial OCT images of a representative case of ERM growth are shown in Figure 2. The ERM had developed by the 3-month visit in 4 patients (Cases 1, 3, 5, and 8) and between 3- and 6-month visits in 4 patients postoperatively, and those ERMs did not affect BCVAs, with the mean BCVA maintained at $-0.08 \pm 0.11$ in the logMAR ($\approx 20/16$) among those 8 cases, and the decimal BCVA of each patient maintained at 0.9 ($\approx 20/22$) or better except for one patient who had a fovea-involving RRD with unknown onset (Case 7). Consequently, no patient in this study was affected by vision-threatening postsurgical ERM growth that required additional surgery.

Comparison results among Group 2 patients in terms of each of the ocular conditions between patients with and without postsurgical ERM and between patients with and without postsurgical RSW are presented in Table 5. None of the ocular conditions were associated with postsurgical ERM or RSW development. The visual acuity at the 6-month visit showed a difference between patients with and without...
| Case | Age | R/L | Refraction (Diopters) | Location of Retinal Tears/Holes | Tractional/Atrophic | Quadrants with Retinal Tears/RRD | Posterior Vitreous Detachement | Residual Vitreous Cortex | Duration Between Onset and Vitrectomy (Days) | Duration Between Vitrectomy and ERM Detection (Days) | Stage of ERM at 6 Months* | BCVA (Baseline/ERM Detection/6 Months) (Snellen) |
|------|-----|-----|----------------------|-------------------------------|------------------|-------------------------------|-------------------------------|----------------------|------------------------------------------|---------------------------------------------|---------------------|-----------------------------------------------|
| 1    | 61  | R   | -0.5                 | On                            | Sup              | T                             | 1/1                           | +                    | -                                        | 1                                           | 98                  | 1/1, 20/20, 20/16, 20/16                        |
| 2    | 59  | R   | 0.0                  | On                            | Sup              | A                             | 1/2                           | -                    | +                                        | 10                                          | 164                 | 1/1, 20/20, 20/16, 20/16                        |
| 3    | 61  | R   | -7.0                 | On                            | Sup              | T                             | 1/2                           | +                    | -                                        | 14                                          | 52                  | 1/1, 20/20, 20/16, 20/16                        |
| 4    | 49  | R   | -4.0                 | Off                           | Sup              | T                             | 1/2                           | +                    | -                                        | 10                                          | 185                 | 1/1, 20/667, 20/22, 20/22                      |
| 5    | 43  | L   | 0.0                  | On                            | Sup              | A                             | 1/1                           | +                    | -                                        | 5                                           | 103                 | 1/1, 20/16, 20/16, 20/16                        |
| 6    | 22  | R   | -5.25                | Off                           | Inf              | T                             | 3/3                           | +                    | -                                        | 7                                           | 198                 | 1/1, 20/25, 20/22, 20/22                       |
| 7    | 64  | L   | -5.25                | Off                           | Sup              | A                             | 1/3                           | -                    | +                                        | Unknown                   | 190                 | 1/1, 20/63, 20/32, 20/32                      |
| 8    | 57  | L   | -3.25                | On                            | Both             | T                             | 4/2                           | +                    | +                                        | 5                                           | 30                  | 1/1, 20/20, 20/25, 20/16                      |

*Classification by Govetto et al.25

inf, inferior; sup, superior.
postsurgical RSW (P = 0.018), but the mean BCVA of patients with RSW was even better than that of patients without RSW; therefore, postsurgical RSW did not negatively affect the visual prognosis in these cases.

Discussions

The postsurgical development of an ERM is one of the concerns after vitrectomy for RRDs that might cause postsurgical visual impairment and distortion. In a previous report, the mean BCVA was 20/40 at 12 months after the removal of the ERMs that developed after repair of macula-on RRDs.11 Given the fact that visual recovery after subsequent ERM removal does not necessarily reach 20/20 among eyes treated for macula-on RRDs, a postsurgical ERM would be better prevented by a safe and valid procedure rather than being removed after visual impairment has occurred.

The effect of ILM peeling on preventing ERM growth after RRD repair has been reported by several groups.1–9 This procedure would be most effective with the best validity when applied to eyes at a high risk of postsurgical ERM growth because there are arguments regarding its potential adverse influence on visual function, although the changes are subtle and are not usually perceived by patients subjectively.12–15 Some authors have suggested risk factors for ERM growth after RRD repair such as foveal involvement26, the number, size, type, or location of retinal breaks3,10,27,28; residual vitreous cortex29; vitreous hemorrhage10; and the duration of foveal detachment.28 However, none of these factors have been established as predictors. In this study, no relationship was revealed between ERM growth and any of the ocular conditions (Table 5).

In an attempt to predict postsurgical ERM growth, we focused on a phenomenon reported as “surface wrinkling retinopathy” by Roth and Foos.22 They investigated 1,000 enucleated eyes of 500 autopsied subjects histologically and reported that wrinkling of the retinal surface, categorized as “surface wrinkling retinopathy,” was present in 5.4% of subjects in association with microscopic ERM formation.22 Based on their findings, we hypothesized that the wrinkling on the retinal surface is an early sign of postsurgical ERM growth and could be an indicator for ILM peeling during vitrectomy for RRDs. Because we were not sure whether the wrinkling should be considered “retinopathy,” we used the term “RSW,” which referred only to the morphological feature of this phenomenon.

In the current study, we applied ILM peeling to the selected eyes in which the appearance of RSW was confirmed on the macula. During the follow-up period, an ERM with visual decline developed in none of the total cases, whereas severe ERM formation requiring surgical removal has been reported to occur more frequently after vitrectomy for RRD: 9.4% when the mean BCVA was 20/141 at the time of ERM removal,2 15.4% with the criterion for surgical intervention being BCVA < 20/40,3 and 22.7% when severe ERM growth was defined as a BCVA decline of 0.2 or more in the logMAR (same as this study),4 corresponding to 7.3, 12.0, and 17.7 eyes expected in our cohort, respectively. This result implies that all potential cases at risk of vision-threatening ERM formation were successfully classified into Group 1 based on the RSW appearance, and ILM peeling prevented severe ERM growth in such cases.

The definition of RSW may overlap the surface wrinkling of proliferative vitreoretinopathy Grade B.23,24,30 However, most patients with RRD in this study were in an acute phase, having a clear onset of the symptom. The duration of the symptom showed no significant difference between the two groups
Therefore, the RSW in this study could be distinguished from proliferative vitreoretinopathy formation in most cases.

En face analyses revealed the presence of postsurgical RSW in 34.6% (Table 3). Because a postsurgical ERM or RSW was not observed in any eyes in Group 1, it should be noted that postsurgical RSW was identified in about half of the ILM-unpeeled eyes (48.2% of Group 2, Table 3), in which RSW had not been detected presurgically. Then, a question arises regarding the possibility that these cases with postsurgical RSW may develop an ERM with visual decline after the follow-up period of this study. To answer this question, we are continuing further monitoring of these cases.

The current study has limitations. One limitation is the relatively short follow-up period for 6 months. As mentioned above, we are conducting a further study to follow these patients for up to 12 months. However, it is noteworthy that visual impairment due to ERM growth after RRD repair has been recognized to usually occur within 3 to 6 months after vitrectomy.3,4,10,28 Another limitation is the lack of a control group to compare ILM-peeled and ILM-unpeeled cases under the same condition of RSW at baseline. We could not conduct a randomized control study because we believed that some patients with RSW would develop a severe postsurgical ERM if the ILM was not peeled; nevertheless, our results support the low prevalence of ERM formation with visual decline, which was better than the prevalence in previous reports of eyes treated without ILM peeling. A randomized clinical trial held somewhere else would hopefully provide definite insights into an indication for ILM peeling during vitrectomy for RRD.

In conclusion, the appearance of RSW at baseline could be a valid indicator to select cases at risk of ERM growth leading to visual decline after vitrectomy for RRD.
Key words: en face imaging, epiretinal membrane, optical coherence tomography, retinal surface wrinkling, rhegmatogenous retinal detachment, visual decline, vitrectomy.

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