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INTERNAL LIMITING MEMBRANE PEELING VERSUS NONPEELING TO PREVENT EPIRETINAL MEMBRANE DEVELOPMENT IN PRIMARY RHEGMATOGENOUS RETINAL DETACHMENT

A Swept-Source Optical Coherence Tomography Study With a New Postoperative Classification System

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Purpose: To determine whether internal limiting membrane peeling in primary rhegmatogenous retinal detachment prevents epiretinal membrane (ERM) development. Secondarily, we propose a classification system for postoperative ERMs.

Methods: Retrospective, interventional, comparative case series. Consecutive eyes with primary rhegmatogenous retinal detachment (n = 140) treated by a single surgeon. The presence of postoperative ERMs was assessed with swept-source optical coherence tomography.

Results: An ERM was detected in 26 eyes (46.4%) in the nonpeeling group and in one eye (1.8%) in the internal limiting membrane peeling group ($P \leq 0.001$). The median visual acuity significantly improved in both groups ($P \leq 0.001$). Inner retinal dimples were observed in 41.1% of eyes in the internal limiting membrane peeling group versus 0% in the nonpeeling group ($P \leq 0.001$), and they were not correlated with visual acuity (r = 0.011; $P = 0.941$). Based on swept-source optical coherence tomography findings, we identified three different types of ERMs: 7 (26.9%) were classified as Type 1, 12 (46.1%) as Type 2, and 7 (26.9%) as Type 3. Superficial retinal plexus deformations observed on optical coherence tomography angiography and en face images were detected in 100% of Type 3 ERMs, 41.6% of Type 2, and 0% of Type 1 ($\chi^2 = 14.3$; $P = 0.001$). Interestingly, all of the patients who presented these alterations also had metamorphopsia.

Conclusion: Internal limiting membrane peeling in primary rhegmatogenous retinal detachment seems to prevent postoperative ERM development. Swept-source optical coherence tomography analysis is helpful to define and classify different types of ERMs and to establish the surgical indication for their removal.

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Internal limiting membrane (ILM) peeling in rhegmatogenous retinal detachment (RRD) is usually indicated when a coexisting macular hole (MH) is present in emmetropic or highly myopic eyes.[1,2] Internal limiting membrane peeling has also been proposed to prevent epiretinal membrane (ERM) formation in eyes treated with retinectomy for severe proliferative vitreoretinopathy.[3] Recently, several studies have

suggested that ILM peeling can prevent postvitrectomy ERM development in primary noncomplicated RRD.[4–6]

The reported incidence of ERM development after vitrectomy to repair a primary RRD range from 9% to 34%,[4–8] although the real incidence rate of postvitrectomy ERM remains unknown given the heterogeneity of criteria used to define and/or detect an ERM. At present, no uniform criteria have been established. Likewise, the criteria for surgical removal of postoperative ERMs are not well defined.

In this context, we used swept-source optical coherence tomography (SS-OCT) to retrospectively compare a consecutive series of eyes treated with and without ILM peeling for RRD. The main aim was to determine the role of ILM peeling in preventing postoperative ERM development after primary vitrectomy in RRD. In addition, given the lack of clear diagnostic criteria for postoperative ERMs, a second aim was to develop a new classification system for ERMs based on SS-OCT findings. Implementation of this new system could improve the criteria used to establish the surgical indication and timing of ERM removal.

Methods

This study was conducted at Bellvitge University Hospital (Barcelona, Spain). Patient data confidentiality is protected by the Spanish law, and all patient data were anonymized for this analysis. Both the study and the present article were approved by the Clinical Research Ethics Committee of Bellvitge University Hospital. All patients signed an informed consent form before surgery.

To identify eligible patients, we reviewed the medical records of all patients diagnosed with primary RRD and treated surgically by a single surgeon (L.A.) between the years 2010 and 2016. Inclusion criteria were as follows: 1) diagnosis of primary RRD; 2) absence of proliferative vitreoretinopathy or, if present, $<$C1; and 3) $\geq$6 months of follow-up. Exclusion criteria were as follows: 1) emmetropic or myopic patients with RRD and a coexisting MH; 2) presence of an ERM detected during the initial vitrectomy performed to repair the RRD; 3) presence of diabetic retinopathy; and 4) presence of any maculopathy such as age-related macular degeneration or macular edema secondary to retinal vein occlusion.

Internal limiting membrane peeling was systematically performed in all primary RRD cases starting in the year 2013. Before that year, ILM peeling was not used. Therefore, all consecutive cases from 2013 onward that met the study inclusion criteria were included in the ILM peeling group. The non-ILM peeling group consisted of consecutive patients treated surgically from 2010 through the end of 2012.

In all cases, surgery was performed under retrobulbar anesthesia with 23-gauge posterior vitrectomy (Stellaris PC; Bausch & Lomb, Bridgewater Township, NJ). If no posterior vitreous detachment was present, the posterior hyaloid was separated from the optic disk. Triamcinolone acetonide was not used during the surgical procedure. We systematically removed the posterior hyaloid without the use of triamcinolone but with the assistance of a blue dye. After injecting the blue dye, it was easy to check whether a complete posterior vitreous detachment had been successfully induced. In case of some residual attachment of the posterior hyaloid to the optic disk, we used the same blue dye to separate the remaining vitreous, and then, we reinjected more dye to perform the ILM peeling. Brilliant blue G was combined with trypan blue (Membrane Blue Dual; D.O.R.C. International, Zuidland, the Netherlands) and injected over the posterior pole and removed after 1 minute. Internal limiting membrane peeling was carefully performed in the macular area with 23-gauge end-gripping forceps (Bausch & Lomb). Internal limiting membrane peeling was performed after the vitrectomy, the induction of the posterior vitreous detachment, and the removal of the dye excess. In cases of macular detachment, ILM peeling was performed under perfluorocarbon liquid. The subretinal fluid was drained through the existing retinal tears with the assistance of perfluoro-n-octane (PFO, HPF8; Al.chi.mi.a. Srl, Ponte San Nicolò, Padova, Italy) or after peripheral retinotomy. Laser endophotocoagulation was performed around the retinal tears, and the perfluoro-n-octane was removed. A fluid–air exchange was performed using a soft-tip cannula and gas tamponade with 20% SF6 or 12% C3F8 (Al.chi.mi.a. Srl). An additional 2.5-mm width encircling band was used in eyes that had retinal tears in other quadrants, giant retinal tears, or predominantly inferior RRD. Sclerotomies were sutured with Vicryl 7/0 to prevent gas leakage.

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Patients were examined on Days 1 and 7, Months 1, 3, 6, and 12, and every 6 months to 12 months thereafter. Optical coherence tomography scans were performed starting with the 1-month follow-up visit and at all subsequent appointments. Starting in the year 2013, SS-OCT equipment became available in our department: The first unit was a prototype (Atlantis; Topcon Corporation, Tokyo, Japan), which was later replaced with the final commercial version (Triton; Topcon Corporation). In this study, the presented results were based on findings obtained with this SS-OCT equipment. Although data obtained with other equipment (SD-OCT, Topcon 3D OCT- 2000; Topcon Corporation) were available for all patients, these data were not included in this study to assure data homogeneity. Patients discharged from the hospital before SS-OCT became available were rescheduled for SS-OCT examination. For the analysis, we used the SS-OCT image obtained in the last follow-up visit.

A 3D scan pattern and a radial scan pattern consisting of 12 linear B-scans with a length of 12 mm centered on the fovea were used for the SS-OCT analysis. The SS-OCT equipment had a 1,050-nm wavelength and a speed of 100,000 A-scans per second with a 20-μm lateral resolution and a 2.6-μm in-depth resolution. For the en face and OCT angiography (OCTA) analysis, we used a 6 × 6-mm cube (with eye tracking in the latest version) to improve the quality of the captured images with fewer artifacts. Patients who complained about metamorphopsia were examined with an Amsler's grid, and we tried to analyze visual acuity and metamorphopsia in conjunction with the findings observed in OCTA and en face images. To describe anatomical landmarks, we used the terminology proposed by the International Nomenclature for Optical Coherence Tomography Panel.[7]

Patient clinical and demographic characteristics and follow-up data were recorded in the IBM-SPSS statistics program, v. 22 (IBM, Inc, Armonk, NY). This same program was used to perform the statistical analysis. The Student *t* test was used to evaluate differences in mean values, the Mann–Whitney *U* test for medians (independent samples), and the chi-square test for percentage differences. Median differences between the baseline and final visual acuity in the same group were evaluated with the Wilcoxon signed-rank test. Bivariate, multivariate, and logistic regression analyses were also performed. The Kruskal–Wallis nonparametric test was used to calculate differences in medians among three groups. We also performed "post hoc analysis" after the Kruskal–Wallis test to identify which groups (types of ERMs) presented differences in retinal thickness and visual acuity.

Results

A total of 140 patients were included in the study, 70 in the ILM peeling group and 70 in the non-ILM peeling group. The main characteristics of the sample are summarized in Table 1. The percentage of phakic patients was significantly higher in the nonpeeling group (75.7% vs. 48.6%, $\chi^2 = 14.8$; $P = 0.001$). There were no significant between-group differences neither in the number of RRD-involved quadrants nor in the presence of giant retinal tears. The macula was detached in 70% and 64.3%, respectively, of patients in the peeling and nonpeeling groups ($\chi^2 = 0.52$; $P = 0.472$). No significant between-group differences were observed in use of an encircling band, drainage retinotomy, or gas tamponade during the surgical procedure. However, the use of perfluorocarbon liquid was significantly more common in the ILM peeling group (74.3% vs. 55.7%, $\chi^2 = 5.30$; $P = 0.021$).

The RRD recurrence rate was 15.7% in the ILM peeling group versus 18.6% in the nonpeeling group ($\chi^2 = 0.20$; $P = 0.654$). The median follow-up was 15.9 months in the ILM peeling group versus 48.8 months in the nonpeeling group ($Z = -8.92$; $P \leq 0.001$). During follow-up, cataract surgery was more common in the nonpeeling group (61.4% vs. 18.6%, $\chi^2 = 26.8$; $P \leq 0.001$).

At baseline, the median Snellen visual acuity was 20/2000 in the ILM peeling group and 20/200 in the nonpeeling group. This difference could be due to a higher percentage of macula-off cases and a higher percentage of three and four involved quadrants in the ILM peeling group although with no statistical significance (Table 1). At the final follow-up, the median Snellen visual acuity was 20/25 in the ILM peeling group and 20/20 in the nonpeeling group.

For the statistical analysis, visual acuity was transformed to logarithm of the minimum angle of resolution (logMAR) values. At baseline, the median logMAR visual acuity was statistically better in the nonpeeling group (1.0 vs. 2.0, $Z = -2.72$; $P = 0.007$). However, at the final follow-up, this difference was no longer significant (0.0 vs. 0.1, $Z = -0.708$; $P = 0.479$). The median logMAR visual acuity significantly improved in both groups ($P \leq 0.001$) (Table 2).

We did not find statistical significance between macular involvement (on/off) at baseline and ERM development in both groups of patients ($P = 0.162$). Likewise, we did not find statistical significance between macular involvement at baseline and ERM development in the ILM peeling group ($P = 0.270$) and in the nonpeeling group ($P = 0.515$).

Table 1. Main Characteristics of the Patients Included in the Study

	ILM Peeling, n = 70	No ILM Peeling, n = 70	Chi-square/Student's *t* Test/Mann–Whitney *U* Test	*P**
Mean age, years (SD)	60.2 (12.5)	60.5 (12.4)	0.14	0.887
Sex, n (%)				
Female	22 (31.4)	24 (34.3)		
Male	48 (68.6)	46 (65.7)	0.13	0.719
Eye, n (%)				
Right	32 (45.7)	46 (65.7)		
Left	38 (54.3)	24 (34.3)	5.67	0.017†
Myopia ≥6.0 dp, n (%)	23 (32.9)	25 (35.7)	0.12	0.722
Lens status n (%)				
Aphakic	0 (0)	2 (2.9)		
Phakic	34 (48.6)	53 (75.7)		
Pseudophakic	36 (51.4)	15 (21.4)	14.8	0.001†
RRD quadrants, n (%)				
One	14 (20)	11 (15.7)		
Two	34 (48.6)	43 (61.4)		
Three	11 (15.7)	7 (10)		
Four	11 (15.7)	9 (12.9)	2.50	0.475
Macula, n (%)				
On	21 (30)	25 (35.7)		
Off	49 (70)	45 (64.3)	0.52	0.472
Giant retinal tears, n (%)	2 (2.9)	3 (4.3)	0.20	≥0.999
Encircling band, n (%)	21 (30)	17 (24.3)	0.57	0.447
PFCL, n (%)	52 (74.3)	39 (55.7)	5.30	0.021†
Retinotomy, n (%)	17 (24.3)	9 (12.9)	3.02	0.082
Gas tamponade, n (%)				
SF6	52 (74.3)	49 (70)		
C3F8	9 (12.9)	15 (21.4)	3.25	0.354
RRD recurrence, n (%)	11 (15.7)	13 (18.6)	0.20	0.654
Cataract surgery, n (%)	13 (18.6)	43 (61.4)	26.8	≤0.001†
Median follow-up, months (range)	15.9 (6–45)	48.8 (6–102)	−8.92	≤0.001†

*The Student *t* test was used to evaluate differences in mean values, the Mann–Whitney *U* test for medians, and the chi-square test for percentage differences.
†Statistically significant *P* value.
PFCL, perfluorocarbon liquid.

First, we performed bivariate analysis (chi-square test) to determine presumed associations between different variables (age, sex, macular involvement, encircling band, number of involved quadrants, perfluorocarbon liquid, retinotomy, giant retinal tear, and myopia) and the presence of ERM. None of these variables showed statistical significance related with the development of ERM. The logistic regression analysis, with the purpose of finding risk factors for the development of postoperative ERM, did not reveal statistical significance: age ($P = 0.472$), sex ($P = 0.390$), macular involvement ($P = 0.644$), encircling band ($P = 0.375$), number of involved quadrants ($P = 0.117$), use of perfluorocarbon liquid ($P = 0.604$),

Table 2. Visual Results of the Patients Included in the Study

	Baseline LogMAR Visual Acuity (Snellen Equivalent)	Final LogMAR Visual Acuity (Snellen Equivalent)	Wilcoxon Signed-Rank Test	*P**
ILM peeling median (range)	2.0 (0–3) (20/2,000 [20/20–20/20,000])	0.1 (0–3) (20/25 [20/20–20/20,000])	−6.09	≤0.001†
No ILM peeling median (range)	1.0 (0–3) (20/200 [20/20–20/20,000])	0.0 (0–3) (20/20 [20/20–20/20,000])	−3.76	≤0.001†
Mann–Whitney *U* test	−2.72	−0.708		
P value‡	0.007‡	0.479		

*Median differences between the baseline and final VA in the same group were evaluated with the Wilcoxon signed-rank test.
†Statistically significant *P* value.
‡The Mann–Whitney *U* test was used to evaluate differences in medians of independent samples.

Table 3. Swept-Source Optical Coherence Tomography Results

	ILM Peeling, n = 56 (80%)	No ILM Peeling, n = 56 (80%)	Chi-square or Student's *t* Test	*P**
ERM, n (%)	1 (1.8)	26 (46.4)	30.5	≤0.001†
ELM disruption, n (%)	6 (10.7)	13 (23.2)	3.10	0.078
EZ disruption, n (%)	6 (10.7)	13 (23.2)	3.10	0.078
Retinal dimples, n (%)	23 (41.1)	0 (0)	28.9	≤0.001†
CRT (μ), mean (SD)	273.4 (48.9)	284.3 (104.6)	0.713	0.477
CCT (μ), mean (SD)	185.1 (102.7)	144.9 (73.4)	−2.43	0.016†

*The Student *t* test was used to evaluate differences in means and the chi-square test for percentage differences.
†Statistically significant *P* value.
CCT, central choroidal thickness; ELM, external limiting membrane; EZ, ellipsoid zone.

retinotomy ($P = 0.160$), giant retinal tear ($P = 0.624$), and myopia ($P = 0.638$). According to this model, it has correctly classified 78.6% of individuals. The analysis was performed step by step to evaluate confounding variables.

We have also used bivariate analysis (chi-square test) to evaluated the possible associations between the variables (age, sex, baseline visual acuity <20/40, macular involvement, encircling band, number of involved quadrants, perfluorocarbon liquid, retinotomy, giant retinal tear, and myopia) and the final visual acuity <20/40. Some of these variables had been included previously as predictors of ERM development. According to the results, the baseline visual acuity <20/40 ($\chi^2 = 13.0$; $P \leq 0.001$), RRD recurrence ($\chi^2 = 8.5$; $P = 0.004$), and macula-off ($\chi^2 = 8.41$;

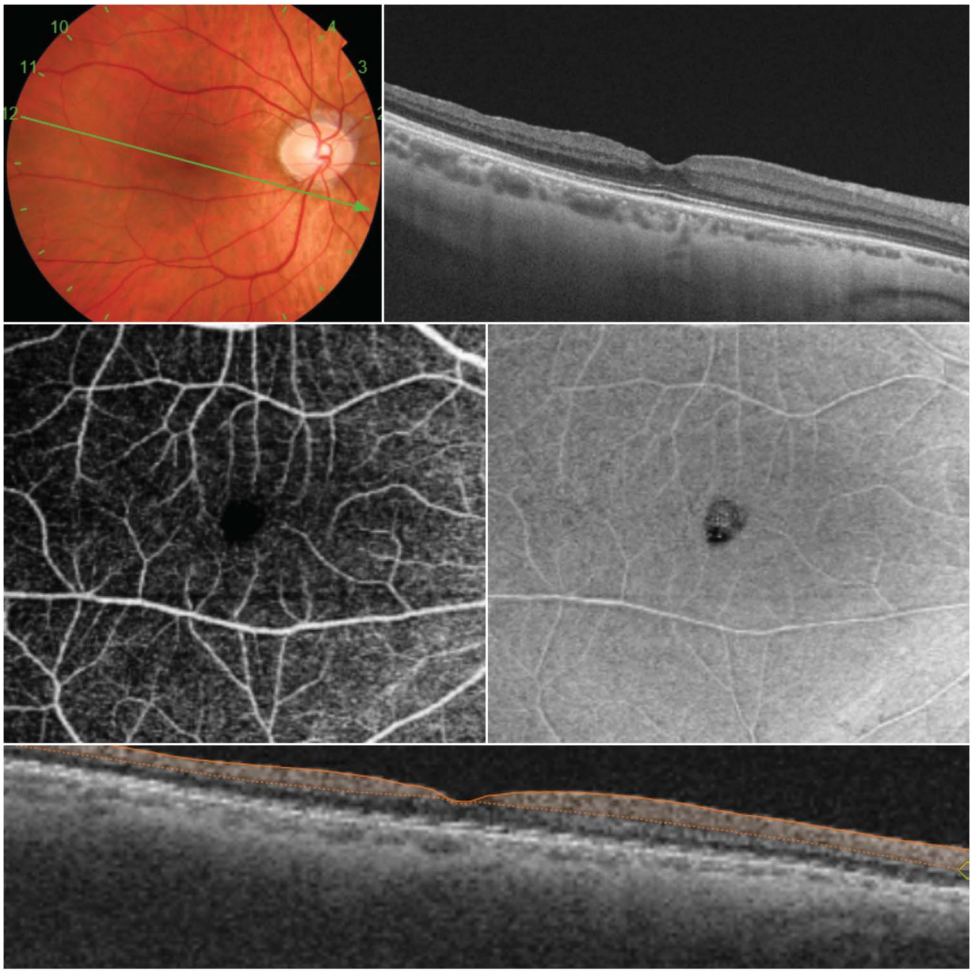

Fig. 1. Patient in the ILM peeling group without inner retinal dimples. Female, 54 years old, visual acuity: 20/20 without metamorphopsia. Fundus photograph (top left) and SS-OCT (top right) without evidence of ERM at the 12-month follow-up. Optical coherence tomography angiography (middle left) and en face imaging (middle right) of the superficial retinal plexus showing no alterations in the ILM peeling area. B-scan corresponding with the OCTA and en face (bottom).

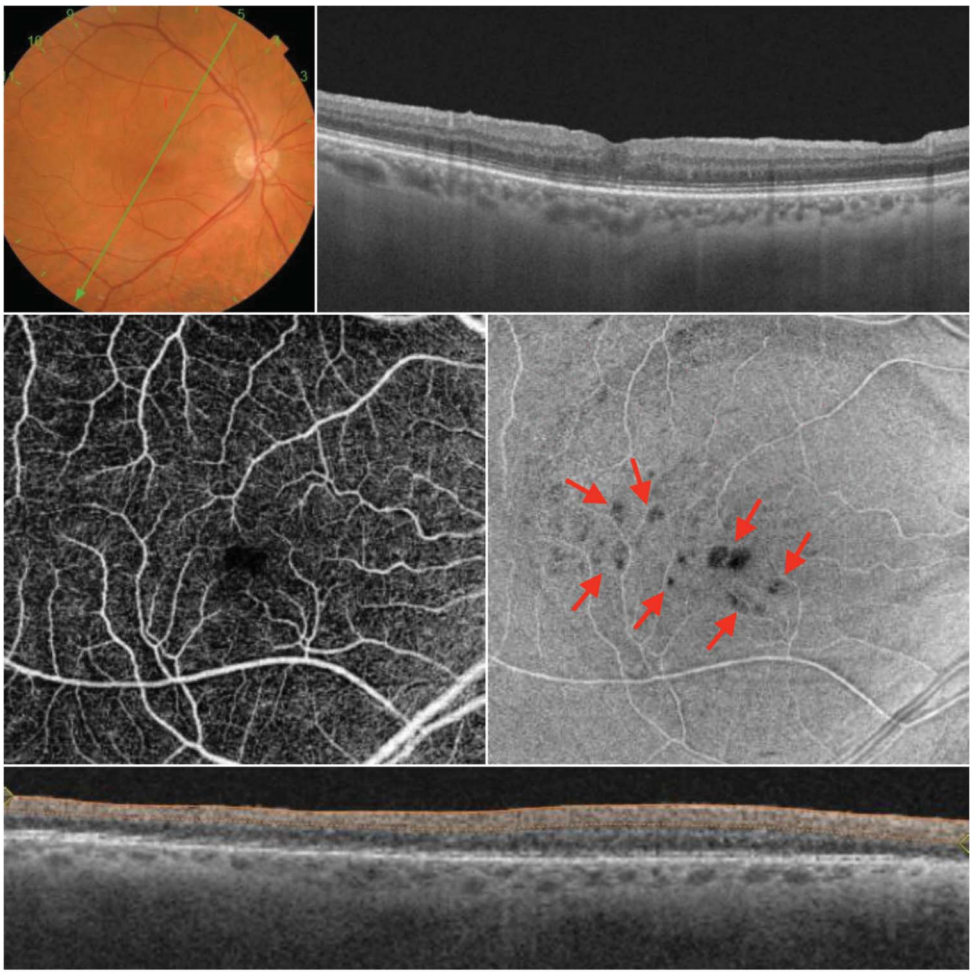

Fig. 2. Patient in the ILM peeling group with inner retinal dimples. Male, 68 years old, visual acuity: 20/25 without metamorphopsia. Fundus photograph (top left) and SS-OCT (top right) without evidence of ERM at the 6-month follow-up. Optical coherence tomography angiography (middle left) showing no alterations and en face imaging (middle right) of the superficial retinal plexus showing inner retinal dimples within the ILM peeling area (red arrows). B-scan corresponding with OCTA and en face (bottom).

$P = 0.004$) showed a statistically significant association with the final visual acuity <20/40. These variables were studied as presumed predictors in the logistic regression analysis following the same procedure explained previously with ERM. In this model, the baseline visual acuity <20/40 (odds ratio = 5.23; $P = 0.006$), myopia (odds ratio = 0.33; $P = 0.020$), and RRD recurrence (odds ratio = 0.17; $P = 0.001$) were significant predictors of the final visual acuity <20/40.

Metamorphopsia was clinically detected and confirmed with an Amsler's grid in 12 patients (17.1%) in the nonpeeling group compared with none in the ILM peeling group ($P \leq 0.001$). Metamorphopsia was associated with an ERM and visual acuity <20/40 in all these patients. Apart from the ERM, we did not find any predictor for metamorphopsia.

Swept-source OCT including OCTA and en face was performed in 56 patients (80%) in both groups of patients (Table 3). The rest of the patients could not be examined with this equipment because it was not available in our department until 2013, such as stated before, and not all patients could be rescheduled to perform the SS-OCT. With this technique, ERM was detected in one patient in the ILM peeling group (1.8%) versus 26 patients in the nonpeeling group (46.4%) ($\chi^2 = 30.5$; $P \leq 0.001$).

Spectral-domain OCT was performed in all patients in both groups. With this equipment, ERM was also detected in one patient in the ILM peeling group (1.4%) and in two additional patients in the nonpeeling group (28 patients, 40%) ($P \leq 0.001$). These 2 patients were found in the remaining 20% of patients where the SS-OCT could not be performed. Then, no significant differences were observed in the ERM detection between the SS-OCT and the SD-OCT equipments.

Following data were only obtained with the SS-OCT. Optical coherence tomography angiography and en face images were helpful to identify the dimple distribution on the retinal surface and the deformations of the vascular retinal plexus in eyes with ERMs. Superficial plexus deformation shown on OCTA was produced by the traction exerted by the ERM on the retinal vessels and complemented the information given by the structural SS-OCT.

Table 4. Proposed Epiretinal Membrane Types and the Characteristics Observed in the Study Sample

	ERM Type 1, n = 7 (26.9%)	ERM Type 2, n = 12 (46.1%)	ERM Type 3, n = 7 (26.9%)	Chi-square or Kruskal–Wallis Test	P*
Inner retinal layer thickening, n (%)	0 (0)	11 (91.6)	7 (100)	21.6	≤0.001†
Inner retinal surface wrinkling, n (%)	1 (14.3)	6 (50)	2 (28.6)	2.64	0.266
ONL thickening, n (%)	0 (0)	1 (8.3)	5 (71.4)	12.7	0.002†
ELM disruption, n (%)	0 (0)	1 (8.3)	1 (14.3)	1.01	0.601
EZ disruption, n (%)	0 (0)	1 (8.3)	1 (14.3)	1.01	0.601
Intraretinal cysts, n (%)	0 (0)	0 (0)	5 (71.4)	16.8	≤0.001†
Subretinal fluid, n (%)	0 (0)	0 (0)	1 (14.3)	2.82	0.244
Retinoschisis, n (%)	0 (0)	3 (25)	4 (57.1)	5.85	0.054
Lamellar MH, n (%)	0 (0)	1 (8.3)	0 (0)	1.21	0.545
CRT (μ), median (range)	266 (235–296)	311 (259–368)	349 (305–452)	12.5	0.002†
CCT (μ), median (range)	177 (87–210)	143 (26–345)	138 (72–173)	1.27	0.530
Superficial retinal plexus deformation (OCTA), n (%)	0 (0)	5 (41.6)	7 (100)	14.3	0.001†
Superficial retinal plexus deformation (en face), n (%)	0 (0)	5 (41.6)	7 (100)	14.3	0.001†
Age (years), median (range)	68 (51–81)	62.5 (51–82)	60 (50–80)	0.80	0.668
LogMAR visual acuity median (range) (Snellen equivalent)	0 (0–0.4) (20/20 [20/20–20/50])	0.2 (0–0.9) (20/32 [20/20–20/160])	0.5 (0.2–0.8) (20/63 [20/32–20/125])	10.1	0.006†
Metamorphopsia, n (%)	0 (0)	5 (41.6)	7 (100)	14.3	0.001†
ERM surgical removal, n (%)	0 (0)	5 (41.6)	7 (100)	14.3	0.001†

*The chi-square test was used to evaluate differences in percentages. The Kruskal–Wallis nonparametric test was used to calculate differences in medians among three groups.
†Statistically significant *P* value.
CCT, central choroidal thickness; ELM, external limiting membrane; EZ, ellipsoid zone; ONL, outer nuclear layer.

Disruptions of the external limiting membrane and the ellipsoid zone were not significantly different between groups (23.2% vs. 10.7%, $\chi^2 = 3.10$; $P = 0.078$ for both). The Pearson correlation analysis showed that external limiting membrane and ellipsoid zone disruption were both positively correlated with the final visual acuity ($r = 0.369$; $P \leq 0.001$). We do not have an explanation for the higher frequency of these disruptions in the nonpeeling group, but it does not seem that these anatomical changes were related to the presence or absence of an ERM.

Inner retinal dimples were present in 41.1% of the eyes in the ILM peeling group versus 0% of eyes in the nonpeeling group ($\chi^2 = 28.9$; $P \leq 0.001$) (Figures 1 and 2). The Pearson correlation coefficient showed that inner retinal dimples were not correlated with visual acuity ($r = 0.011$; $P = 0.941$).

We decided to study the choroidal thickness as SS-OCT usually shows high accuracy in its measurement. No significant between-group differences in central retinal thickness (CRT) were observed ($t = 0.713$; $P = 0.477$); however, central choroidal thickness was significantly thinner in the nonpeeling group ($t = -2.43$; $P = 0.016$). It may be due to the slightly greater number of myopic patients included in the nonpeeling group although with no statistical significance (Table 1).

Based on the characteristics identified on SS-OCT findings, we identified three different types of ERM (Table 4 and Figures 3–5):

1. Type 1. Highly epimacular reflective band without other relevant alterations.
2. Type 2. Highly epimacular reflective band with thickening of the inner retinal layers. Commonly, Type 2 ERMs may also present inner retinal surface wrinkling and superficial retinal plexus deformation on OCTA and en face images.
3. Type 3. Highly epimacular reflective band with inner retinal layer thickening and superficial retinal

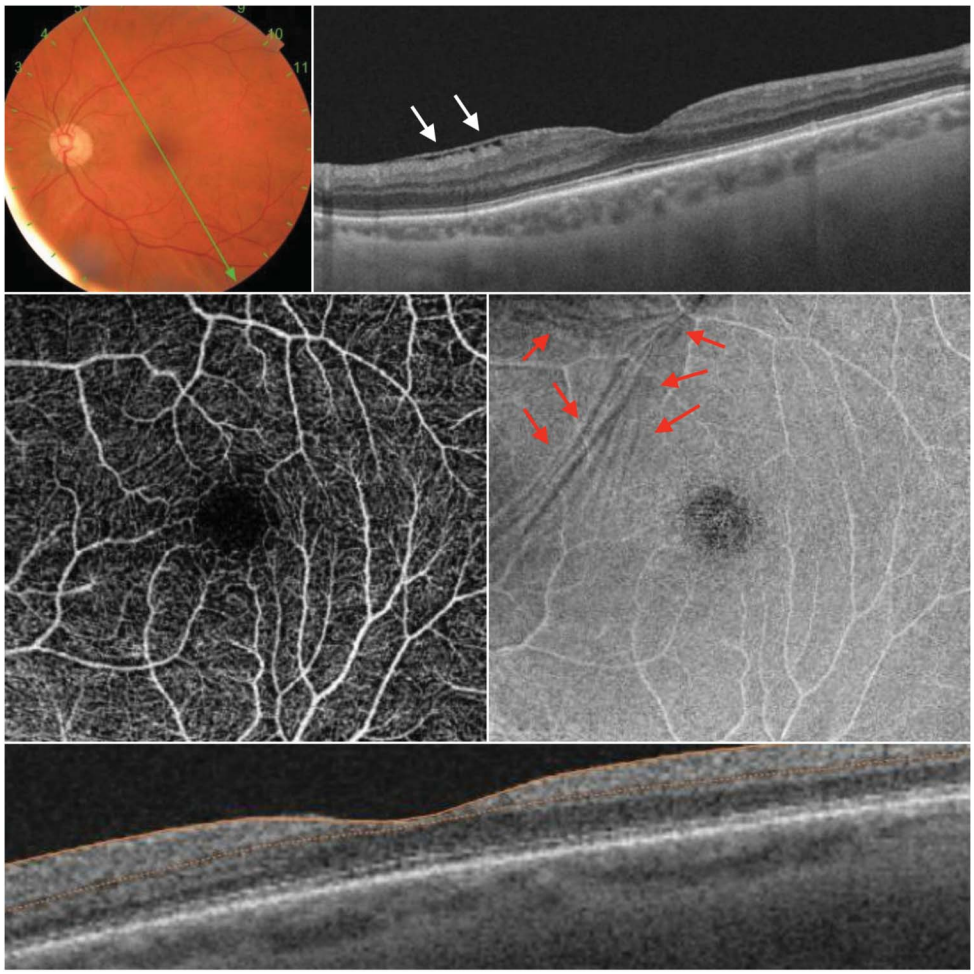

Fig. 3. Patient in the nonpeeling group with ERM Type 1. Female, 51 years old, visual acuity: 20/20 without metamorphopsia. Epiretinal membrane not apparent in the fundus photograph (top left) but visible on the SS-OCT scan (top right) at the 6-month follow-up (white arrows). Optical coherence tomography angiography (middle left) and en face imaging (middle right) of the superficial retinal plexus showing no deformation of the inner retinal layers. B-scan corresponding with OCTA and en face (bottom). En face image shows some wrinkles (red arrows).

plexus deformation on OCTA and en face images. Other alterations commonly observed in Type 3 ERMs include the presence of outer retinal nuclear layer thickening and intraretinal cysts.

All cases presented a highly epimacular reflective band. The inner retinal layer thickening was different between the three types of ERMs ($\chi^2 = 21.6$; $P \leq 0.001$), showing higher percentage in ERM Type 2 (91.6%) and 3 (100%). The outer nuclear layer thickening and the presence of intraretinal cysts were also significantly different ($\chi^2 = 12.7$; $P = 0.002$ and $\chi^2 = 16.8$; $P \leq 0.001$, respectively) between the three groups, being more common in ERM Type 3 (71.4% in both items). The median of CRT showed differences between the three types of ERMs (K-W = 12.5; $P = 0.002$). Superficial retinal plexus deformations observed on OCTA and en face images were detected in 100% of Type 3 ERMs, 41.6% of Type 2, and 0% of Type 1 ($\chi^2 = 14.3$; $P = 0.001$). Interestingly, all of the patients who presented these alterations also had metamorphopsia. Comparing the median of logMAR visual acuity among ERMs, we observed significant differences between them (K-W = 10.1; $P = 0.006$).

We also performed "post hoc analysis" after the Kruskal–Wallis test to identify which groups (types of ERMs) presented differences in CRT and logMAR visual acuity. In this step, we obtained a pairwise analysis for both variables. The CRT evidenced significant differences between ERM Type 1 and 2 ($P = 0.017$) and Type 1 and 3 ($P < 0.001$), but they were not observed between ERM Type 2 and 3 ($P = 0.116$). Considering logMAR visual acuity, pairwise analysis showed significant differences among ERM Type 1 and 3 ($P = 0.001$), but they were not observed between ERM Type 1 and 2 ($P = 0.740$) and Type 2 and 3 ($P = 0.074$).

Of the 26 ERMs detected in the nonpeeling group, 7 (26.9%) were classified as Type 1, 12 (46.1%) as Type 2, and 7 (26.9%) Type 3. Surgical removal of the ERM was indicated in 12 eyes with ERMs (46.1%) due to visual acuity <20/40 and metamorphopsia, in 7 (100%) of the Type 3 ERMs, and in 5 (41.6%) of the Type 2 ERMs. Importantly, in the ILM peeling

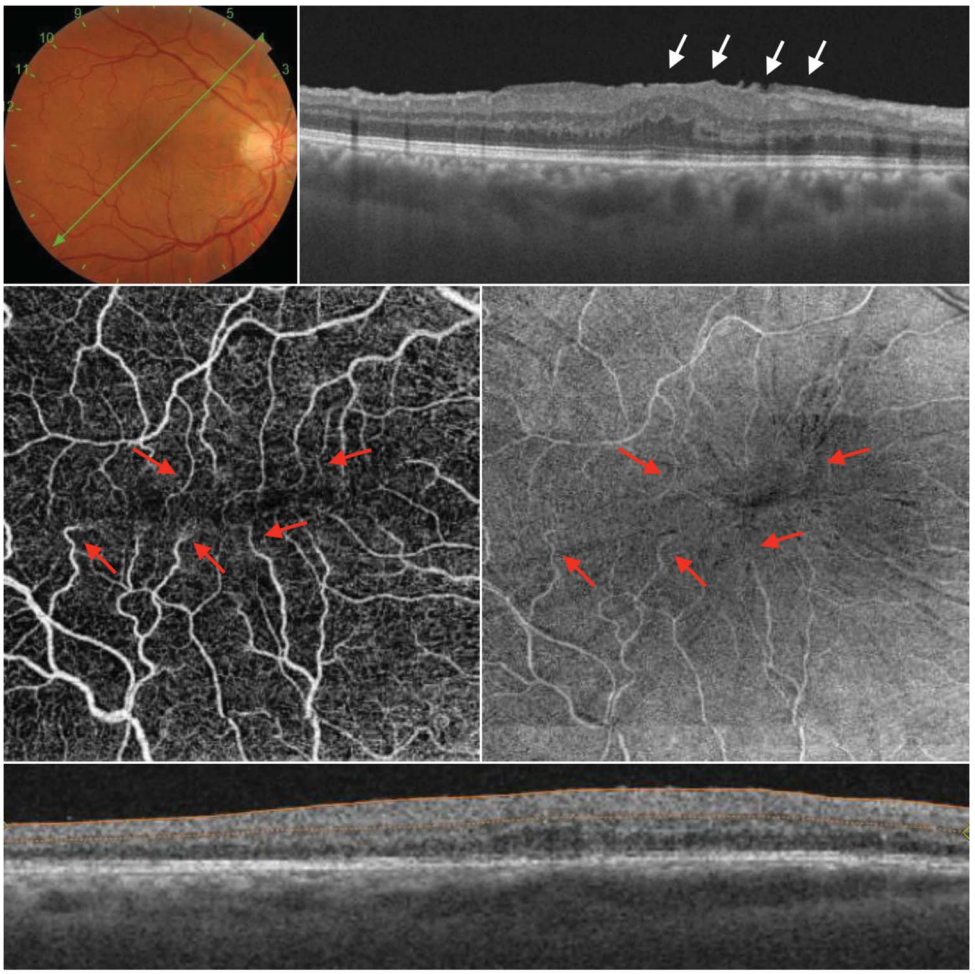

Fig. 4. Patient in the nonpeeling group with ERM Type 2. Male, 50 years old, visual acuity: 20/50 with metamorphopsia. Epiretinal membrane not readily apparent in the fundus photograph (top left) but clearly visible on the SS-OCT scan with macular thickening (top right) at the 3-month follow-up (white arrows). Optical coherence tomography angiography (middle left) and en face imaging (middle right) of the superficial retinal plexus showing deformation of the inner retinal layers (red arrows). B-scan corresponding with OCTA and en face (bottom).

group, only one ERM (Type 1) was detected at the 6-month follow-up. Moreover, this ERM was asymptomatic and did not require surgical removal.

The mean time from RRD surgery to ERM detection was 9.7 months in the nonpeeling group (range, 3–24 months).

In our study, we had no cases of full-thickness MH and only one case of an asymptomatic lamellar MH in the nonpeeling group that did not require surgical intervention.

Discussion

This study shows that ILM peeling in primary RRD may prevent the development of postoperative ERM. In our sample, only one patient who underwent ILM peeling (1.8%) developed an ERM, whereas 26 patients in the nonpeeling group (46.4%) developed an ERM, a highly significant difference.

Epiretinal membrane development after RRD surgery is a relatively common complication that may require a second vitrectomy to remove the ERM due to visual acuity loss and metamorphopsia. However, the true incidence of postvitrectomy ERMs has not been well established, mainly due to the lack of a well-defined classification system accurately diagnosis ERMs and to determine the indication for surgical removal. Table 5 provides a comparison of our study in the context of the main studies on this topic.

Katira et al retrospectively evaluated a series of 141 patients diagnosed with primary RRD and treated surgically (15 different surgeons) without ILM peeling. These authors found that 18 of the 141 patients (12.8%) developed a postoperative ERM (identified by biomicroscopy). Of those 18 patients, 6 (33.3%) underwent a second vitrectomy for macular pucker removal. The mean time elapsed from RRD surgery to membrane peeling surgery was 5.4 months.[8]

Martínez-Castillo et al prospectively evaluated a series of patients with primary RRD treated without ILM peeling. Of the 312 eyes in that study, 28 (9%) developed an ERM. Time-domain and SD-OCT were used in some cases to confirm the clinical diagnosis of an ERM. Surgical removal of the ERM was performed

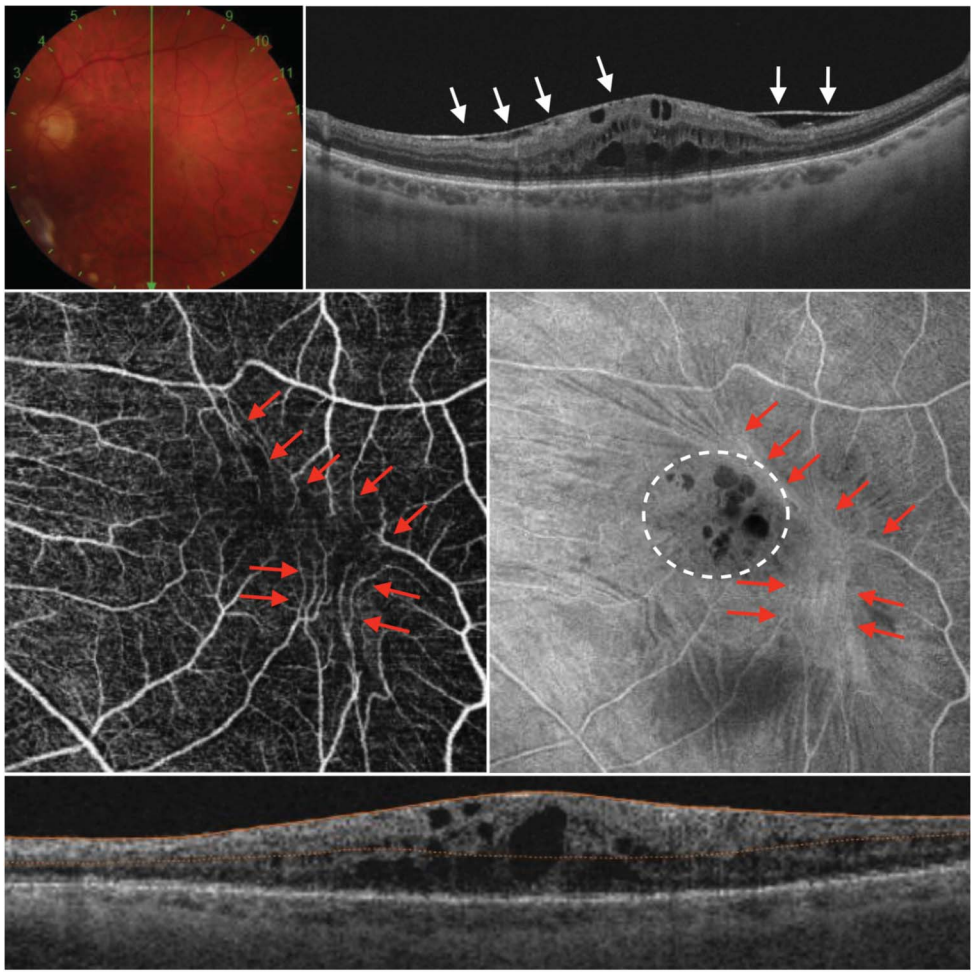

Fig. 5. Patient in the nonpeeling group with ERM Type 3. Male, 75 years old, visual acuity: 20/63 with metamorphopsia. Epiretinal membrane visible on the fundus photograph (top left) and on the SS-OCT scan (top right) showing intraretinal cysts at the 12-month follow-up (white arrows). Optical coherence tomography angiography (middle left) and en face imaging (middle right) of the superficial retinal plexus showing deformation of the inner retinal layers (red arrows). En face image clearly shows the distribution of the intraretinal cysts (white dotted circle). B-scan corresponding with OCTA and en face (bottom).

in 22 eyes. Most postoperative ERMs (57.1%) were diagnosed at the 3-month follow-up appointment.[9]

Role and Safety of Internal Limiting Membrane Peeling to Prevent Postoperative Epiretinal Membrane Development

The first study to compare ILM peeling versus nonpeeling in eyes diagnosed with RRD was performed by Rao et al.[4] In that study involving 62 eyes, 30 underwent ILM peeling and 32 did not. The postoperative macular pucker rate was 3.3% (1/30) in the peeling group versus 34.3% (11/32) in the nonpeeling group. However, it should be noted that the ERMs were diagnosed by clinical examination (no OCT was performed).[4]

Nam and Kim[5] retrospectively compared 135 patients with primary RRD treated by a single surgeon. Of the 135 cases, 70 underwent ILM peeling and 65 did not. The authors found no cases of ERM in the ILM peeling group versus 14 cases (21.5%) in the 65 patients in the nonpeeling group. Time-domain OCT was used for ERM detection. Epiretinal membrane diagnosis was made within 3 months after surgery in 12 of the 14 patients (85.7%). In 10 of these 14 patients (71.4%), ERM removal was performed within a mean of 22 weeks from the RRD surgery.[5]

Akiyama et al retrospectively evaluated 102 cases of RRD in which 58 eyes (56.8%) underwent ILM peeling. Postoperatively, 21 eyes (20.5%) developed an ERM (considered severe in 10 cases), all in the nonpeeling group. Internal limiting membrane peeling was significantly ($P < 0.001$) associated with ERM prevention. The average time elapsed between RRD surgery and ERM detection by SD-OCT was 3.4 months.[6]

The findings described previously seem to support the value of ILM peeling in primary RRD to help prevent ERM development. The results from this study further bolster this hypothesis given that fewer than 2% of patients who underwent ILM peeling developed an ERM versus close to 50% of patients in the nonpeeling group. Although follow-up was significantly longer in the nonpeeling group (48.8 months vs.

Table 5. Main Studies Evaluating Postoperative Epiretinal Membrane Incidence Rate With and Without Internal Limiting Membrane Peeling

	Katira et al[8]	Martínez et al[9]	Rao et al[4]	Nam and Kim[5]	Akiyama et al[6]	Arias et al, 2018
N, total	141	312	62	135	102	140
ILM peeling (%)	—	—	30 (48.4)	70 (51.8)	58 (56.8)	70 (50)
Age (years), mean	62	65	66	48	58	60
ERM incidence (%)						
No ILM peeling	12.8	9	34.3	21.5	20.5	46.4
ILM peeling	—	—	3.3	0	0	1.8
ERM detection (m)						
Mean	5.4	?	?	2	16.5	9.7
Range	?	1–12	?	1–6	?	3–24
ERM removal (%)						
No ILM peeling	33.3	78.6	9.4	71.4	47.6	46.1
ILM peeling	—	—	0	0	0	0
OCT	—	TD/SD	—	TD	SD	SS
Mean follow-up (m)						
No ILM peeling	12	12	20.8	12	42.3	48.8
ILM peeling	—	—	14.2	12	17.6	15.9

SD, spectral-domain; TD, time-domain.

15.9 months), the mean time from RRD surgery to ERM detection was 9.7 months, which was more than sufficient to develop an ERM (in most published reports, ERMs are detected within the first 1–12 months after surgery; Table 5). Therefore, it seems unlikely that longer follow-up in the ILM peeling group would have resulted in a significant increase in the proportion of patients with ERMs.

The ILM plays a supporting role for cell proliferation. Histological analyses of the surface of peeled ILMs have shown the presence of hyalocytes, glial cells, and myofibroblasts adhering to the surface of the ILM.[10] The interaction between hyalocytes and glial cells is reported to promote the development of an ERM. Thus, ILM peeling may have a dual action in the prevention of ERMs by more completely eradicating persisting cells on the retinal surface and by removing the support necessary for their proliferation.[10]

Doubts about the safety of ILM peeling have been raised by several authors.[11–15] It has been found that many eyes that undergo ILM peeling develop inner retinal dimples that course along the path of the nerve fiber layer. The dimples seem to be the result of an interplay between trauma to the Müller cells along with the regenerative growth of the Müller cell processes.

Internal limiting membrane peeling does not seem to have a detrimental effect on postoperative visual acuity, although the real impact on the quality of vision remains unclear. Internal limiting membrane peeling may induce microscotoma formation.[16] In our study, inner retinal dimples were detected in more than 40% of eyes in the ILM peeling group versus none of the eyes in the nonpeeling group. The statistical analysis showed that the presence of these dimples does not seem to affect visual acuity, which was similar among eyes with and without inner retinal dimples.

Classification of Postoperative Epiretinal Membrane

Among the studies published to date, there is a wide variation in the percentage of eyes that developed ERM.[4–6,8,9] This variation could be attributable to several factors. However, it seems highly probable that the main cause of this heterogeneity is the lack of uniform criteria used to define an ERM. An additional issue is that the criteria used to define ERM in most of studies published to date were not well defined, thus making accurate comparisons difficult. Second, a wide variety of detection techniques were used among these studies, including fundus examination and different types of OCT, including time-domain OCT. Therefore, it seems highly likely that ERM was underdiagnosed in many studies. At present, current classifications are based on idiopathic ERMs but not postoperative ERMs.[17–19]

Hwang et al[17] proposed 5 ERM subtypes according to the foveal morphology observed on SD-OCT, identifying 2 major groups: 1) fovea-attached ERMs and 2) fovea-sparing (pseudohole type) ERMs. Konidaris et al[18] also classified ERMs into two major categories, but according to the presence or absence of posterior vitreous detachment. Stevenson et al[19] included CRT and inner segment ellipsoid zone integrity in their classification system.

Given the drawbacks of the current classification system, we have developed a more comprehensive classification based on the ERM characteristics shown on SS-OCT and we have identified three main types of post-RD ERMs.

Clinically, we found that Type 1 ERMs were asymptomatic; by contrast, all Type 3 ERMs and a large proportion (41%) of Type 2 ERMs induced metamorphopsia and caused visual acuity loss, thus requiring surgical removal. Interestingly, metamorphopsia was present in all cases in which superficial retinal plexus deformation was observed on OCTA and en face images. It is known that metamorphopsia is not an uncommon finding in RRD.[20]

The ERM may also play a role in the pathogenesis of secondary full-thickness MH formation after RRD.[21] We had no full-thickness MHs in our study.

Study Strengths and Limitations

This study has several important strengths: 1) a relatively large sample size, especially considering that the surgery was performed in all cases by a single surgeon; 2) the consequent absence of any surgeon-dependent influence on interpretation of the results; 3) a standardized postoperative SS-OCT analysis; 4) a long follow-up period; and 5) the proposed new classification for postoperative ERMs. The main limitations of this study are the nonrandomized study design and the lack of other functional examinations apart from visual acuity to evaluate ILM peeling safety.

Conclusions

The findings of this study suggest that ILM peeling in primary RRD can help prevent the development of postoperative ERM without significantly affecting visual acuity. In addition, the proposed classification scheme based on SS-OCT may help to better define the criteria to determine the indication and timing of surgical removal of the ERM.

However, more data are needed—particularly regarding safety, given the high percentage of cases that developed inner retinal dimples after ILM peeling —before this technique can be considered the standard approach to preventing postoperative ERM in all primary RRD cases. Large multicenter, randomized studies are needed to definitively resolve this important question.

Key words: epiretinal membrane, internal limiting membrane peeling, rhegmatogenous retinal detachment, swept-source optical coherence tomography.

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