Retinal Layer Measurements After Successful Macula-Off Retinal Detachment Repair Using Optical Coherence Tomography

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Purpose. Optical coherence tomography (OCT) was used to analyze the thickness of various retinal layers of patients following successful macula-off retinal detachment (RD) repair.

Methods. Optical coherence tomography scans of patients after successful macula-off RD repair were reanalyzed with a subsegmentation algorithm to measure various retinal layers. Regression analysis was performed to correlate time after surgery with changes in layer thickness. In addition, patients were divided in two groups. Group 1 had a follow-up period after surgery of up to 7 weeks (range, 21–49 days). In group 2, the follow-up period was >8 weeks (range, 60–438 days). Findings were compared to a group of age-matched healthy controls.

Results. Correlation analysis showed a significant positive correlation between inner nuclear-outer plexiform layer (INL-OPL) thickness and time after surgery ($P = 0.0212$; $r^2 = 0.1551$). Similar results were found for the ellipsoid zone–retinal pigment epithelium complex (EZ-RPE) thickness ($P = 0.005$; $r^2 = 0.2215$). Ganglion cell-inner plexiform layer thickness (GCL-IPL) was negatively correlated with time after surgery ($P = 0.0064$; $r^2 = 0.2101$). For group comparison, the retinal nerve fiber layer in both groups was thicker compared to controls. The GCL-IPL showed significant thinning in group 2. The outer nuclear layer was significantly thinner in groups 1 and 2 compared to controls. The EZ-RPE complex was significantly thinner in groups 1 and 2 compared to controls. In addition, values in group 1 were significantly thinner than in group 2.

Conclusions. Optical coherence tomography retinal layer thickness measurements after successful macular-off RD repair revealed time-dependent thickness changes. Inner nuclear-outer plexiform layer thickness and EZ-RPE thickness was positively correlated with time after surgery. Ganglion cell-inner plexiform layer thickness was negatively correlated with time after surgery.

Keywords: OCT, retinal detachment, image analysis, subsegmentation

Rhegmatogenous retinal detachment (RRD) is a sight-threatening disease that is characterized by a separation of the neurosensory retina from the retinal pigment epithelium. Recently, Mitry et al.[1] systematically reviewed all population-based epidemiology studies of RRD published between January 1970 and January 2009. The median annual incidence rate of RRD was calculated to be 10.5 per 100,000 of population within the United States. Even after successful RRD surgery, visual recovery can be incomplete or prolonged. Besides poor visual acuity (VA), patients can suffer from color vision defects, or metamorphopsia.[2–4] The reason for this lack or delay of visual recovery is still unknown, especially since retinal morphology appears relatively normal in many of those patients. The invention of optical coherence tomography (OCT) facilitated imaging of retinal changes that were not clinically observable by fundus biomicroscopy.[5] Further improvement in OCT technology led to the development of spectral-domain OCT (SD-OCT) which had increased resolution and speed.[6] Spectral-domain OCT images allow identification of various retinal layers that can be distinguished by special software algorithms for thickness measurements.[7] In this study, SD-OCT was used to measure thickness of various retinal layers in eyes after successful macular-off RRD repair. Findings were correlated to time after surgery and, in addition, compared to a group of healthy, age-matched controls.

Methods

Patients with pseudophakic macula-off RRD were evaluated after successful surgery with complete retinal reattachment. All patients were treated with pars plana vitrectomy (PPV), encircling band, and SF6 gas tamponade. Snellen best-corrected VA was measured pre- and postoperatively. Values

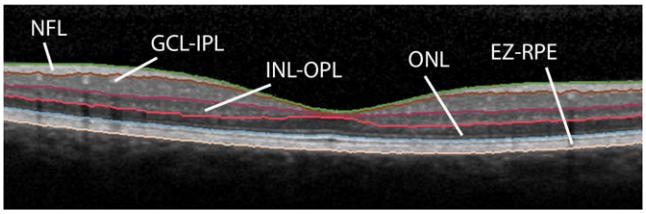

Figure 1. Vertical SD-OCT scan centered on the fovea. The automatic segmentation algorithm outlined several boundaries indicating different retinal layers.

were converted to logMAR VA for statistical comparisons. Spectralis OCT (Heidelberg Engineering, Heidelberg, Germany) was used to perform high-resolution crosshair OCT scan centered on the fovea. Scans were performed with ART (automated real time) mean function, and 50 frames were averaged to reduce noise. Scans were then retrospectively reviewed by a single observer (MM) for quality and centration. Phacic eyes were excluded to avoid any influence of cataract formation on OCT image quality. Also, eyes with remaining subretinal fluid, epiretinal membranes, obvious scar tissue, proliferative vitreoretinopathy, macular holes, intraretinal cystic spaces, or any other obvious macular changes were excluded from further analysis. In addition, highly myopic eyes (more than −5 diopters [D]) have been excluded to rule out that OCT layer thinning was caused only by myopia. Also, all patients with recurrent macula-off RRD were excluded from this study. Special analysis software was used to perform automatic OCT subsegmentation of retinal layer boundaries.[8] The automatic segmentation algorithm is based on the graph-based optimal net-surface problem that was applied to volumetric OCT datasets by Garvin and colleagues.[9] The method allows simultaneous searching for multiple interacting surfaces and the specification of surface smoothness and intersurface distance feasibility constraints. To further improve the segmentation quality and robustness, additional soft smoothness constraints were applied to incorporate prior shape information.[10] Five different retinal layers could be identified by the algorithm: (1) nerve fiber layer (NFL); (2) ganglion cell layer-inner plexiform layer complex (GCL-IPL); (3) inner nuclear layer-outer plexiform layer complex (INL-OPL); (4) outer nuclear layer (ONL); (5) ellipsoid zone–retinal pigment epithelium complex (EZ-RPE). (Ellipsoid zone was formerly known as photoreceptor inner-outer segment band.[11]) Thickness measurements were performed on a vertical B-scan of 3-mm length centered on the fovea. Mean layer thickness values have been calculated out of all OCT A-scans within the B-scan for all retinal layers. Figure 1 shows an example of retinal subsegmentation indicating the five different layers and the area of measurement.

Similar to OCT measurements in patients, subsegmentation was performed in a group of 21 healthy, age-matched controls. All subjects in the control group received a complete eye exam including OCT to rule out any retinal disease or other ophthalmic problem that might interfere with study data. In addition, eyes with myopia $\geq$ 5 D were excluded for the same reasons as in the patient group. For comparison with healthy controls, patients were divided into two subgroups regarding their follow-up period after surgery. In group 1, follow-up was <8 weeks but more than 21 days post surgery to assure that SF6 gas has disappeared from the macular area before OCT examination. Less than 8 weeks follow-up in group 1 was chosen to allow observation of early changes in retinal layers after vitrectomy. In group 2, all other patients with a follow-up of >8 weeks were included. Optical coherence tomography retinal layer measurements were then compared between groups and controls. In addition, visual recovery was compared between groups.

Table 1. Study Demographics

	Group 1	Group 2	Controls
Mean age ± SD, y	63.8 ± 11.3	61.9 ± 10.4	63.8 ± 14
Female, %	31	37	43
Mean duration of macular involvement, d ± SD	8.2 ± 8.1	8.5 ± 8.9	NA
Mean preOP logMAR VA ± SD	1.54 ± 0.63	1.33 ± 0.7	NA

preOP, preoperative.

Statistical Methods

Statistic software (IBM SPSS Statistics 20.0, IBM, Armonk, NY, USA; and GraphPad Prism 3, GraphPad Software, Inc., La Jolla, CA, USA) was used to perform statistical analyses. Pearson product-moment correlation was calculated to correlate changes in retinal layer thickness with time after surgery. In addition, correlation was tested between postoperative logMAR VA and mean retinal layer thickness values and between postoperative logMAR VA and preoperative duration of presumed macular detachment (anamnestic duration of corresponding visual symptoms).

A Kolmogorov-Smirnov test was done to test for normal distribution. Since data were not normally distributed, a Mann-Whitney test was used to search for significant differences between groups 1 and 2 and between each group and controls. P values < 0.05 were considered statistically significant.

The study adhered to the tenets of the Declaration of Helsinki and was approved by the Cantonal Ethics Committee Berne. Informed consent was obtained prior to the inclusion of subjects.

Results

Forty-three charts of patients with pseudophakic macula-off RRD between January 2009 and June 2011at the Department of Ophthalmology, Inselspital, Bern, Switzerland have been reviewed. Thirty-four patients were eligible for inclusion. In addition, 21 age-matched controls were included. For comparison, 18 patients were included in group 1 with a follow-up period of up to 7 weeks (range, 21–49 days), and 16 patients were in group 2 with a follow-up of >8 weeks (range, 60–438 days). The mean duration of presumed macular detachment (duration of corresponding visual symptoms) was 8.4 ± 8.6 days (8.2 ± 8.1 days in group 1 and 8.5 ± 8.9 days in group 2; differences not significant). Demographics of the study population are shown in Table 1.

Correlation analysis showed a significant positive correlation between INL-OPL thickness and time after surgery ($P = 0.0212$; $r^2 = 0.1551$). Similar results were found for EZ-RPE complex thickness, which also significantly increases over time ($P = 0.005$; $r^2 = 0.2215$). In contrast, GCL-IPL thickness was negatively correlated with time after surgery ($P = 0.0064$; $r^2 = 0.2101$). Figure 2 shows the corresponding regression plots.

Table 2 shows mean retinal layer thickness measurements and corresponding P values in both groups and controls. Figure 3 shows corresponding bar plots, indicating differences in retinal layer thickness between groups and controls. Figure 4 shows the corresponding box plots of all measured retinal layers in both groups and controls.

Mean postoperative logMAR Snellen VA improved from 1.44 (Snellen equivalent approximately 20/500) to 0.65 (Snellen

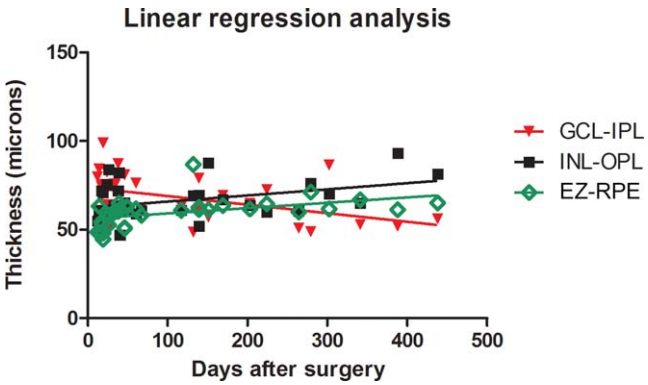

FIGURE 2. Linear regression plot showing changes in retinal layer thickness over time after surgery.

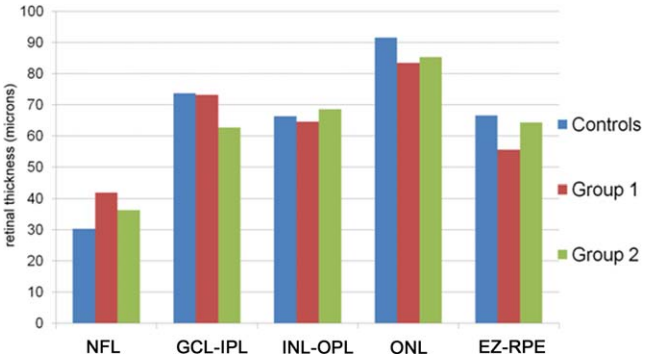

FIGURE 3. Bar plot indicating differences in retinal layer thickness between group 1, group 2, and healthy controls.

equivalent approximately 20/80) ($P < 0.001$). In group 1, logMAR VA improved from 1.54 (Snellen equivalent approximately 20/600) to 0.74 (Snellen equivalent approximately 20/100) ($P < 0.001$) and in group 2 from 1.33 (Snellen equivalent approximately 20/400) to 0.56 (Snellen equivalent approximately 20/70) in group 2 ($P < 0.001$). No significant correlation could be found for postoperative logMAR VA and any mean retinal layer thickness. In addition, no significant correlation was found between the presumed duration of macular detachment (duration of corresponding visual symptoms) and postoperative logMAR VA. (Nonsignificant results are not presented.)

DISCUSSION

Optical coherence tomography retinal subsegmentation revealed various changes in layer thickness after successful macula-off retinal detachment surgery.

Correlation analysis revealed a significant positive correlation between INL-OPL thickness and time after surgery ($P = 0.0212$; $r^2 = 0.1551$). Similar results were found for EZ-RPE complex thickness, which also significantly increased over time ($P = 0.005$; $r^2 = 0.2215$). Ellipsoid zone reorganization within these retinal layers might explain this recovery in thickness. Intraretinal edema after surgery might play a role in the early period after surgery but does not explain thickening several weeks after the event. In contrast, GCL-IPL thickness was negatively correlated with time after surgery ($P = 0.0064$; $r^2 = 0.2101$). Similar findings could be observed when comparing groups with healthy controls. The ganglion layer-inner plexiform layer complex showed no significant difference in group 1 but was significantly reduced in group 2 (>8 weeks post surgery) compared to controls. Ganglion cell damage with consecutive cell loss might contribute to this delayed decrease of GCL-IPL thickness. In a rabbit model of retinal detachment, Faude and colleagues[12] were able to show an incomplete but severe loss of ganglion cell axons and considerable ganglion cell death, particularly in the detached retina. Further studies are needed to confirm cell loss in the ganglion cell layer and inner plexiform layer after macula-off RD. These cells might be good targets for neuroprotective rescue therapies in the future to preserve vision.

Nerve fiber layer thickness was significantly increased in group 1 (<7 weeks post surgery) compared to controls. One possible explanation might be that NFL edema is a direct result of vitreoretinal surgery or is due to relative retinal ischemia associated with retinal detachment. In group 2, NFL was still significantly thicker compared to controls, but less thickened compared to group 1. It seems that NFL thickening is only temporary after RRD surgery. Brazitikos et al.[13] showed that 6 months after vitrectomy for macular surgery NFL thickness has not significantly changed. These findings are in agreement with our observation that NFL thickness was significantly thinner in group 2 compared to group 1.

Cell loss due to apoptosis might explain the observed thinning in the ONL. Xie et al.[14] showed caspase-3 activation in a rat model for retinal detachment. Furthermore, they showed a decrease in caspase-3 activation when treating animals with intravitreal injections of erythropoietin (EPO) to inhibit apoptosis and protect photoreceptors. In their study, the ONL was significantly thicker in rats treated with EPO compared to untreated animals.[15] The loss of outer nuclear layer thickness in RD might contribute to delayed and incomplete visual recovery in cases with macular involvement.

It is obvious that macular involvement in RD leads to severe disturbance of the photoreceptor layer that becomes visible in OCT by disturbance of the EZ. Tilting and disorganization of photoreceptors have been reported previously. Delolme et al.[16] found microstructural changes within the photoreceptor

TABLE 2. Mean Retinal Layer Thickness Measurements in the Macula

	NFL	GCL-IPL	INL-OPL	ONL	EZ-RPE
Controls ± SD	30.28 ± 2.6	73.71 ± 4.3	66.31 ± 6.8	91.58 ± 7.9	66.6 ± 1.2
Group 1 ± SD	41.89 ± 9.0	73.16 ± 12.0	64.53 ± 10.0	83.39 ± 12.8	55.55 ± 6.2
	$P < 0.0001$*			$P = 0.0011$*	$P < 0.0001$*
	$P < 0.001$†				$P = 0.001$†
Group 2 ± SD	36.24 ± 6.9	62.63 ± 11.5	68.51 ± 11.1	85.32 ± 15.3	64.26 ± 6.7
	$P < 0.0001$*	$P = 0.003$*		$P = 0.025$*	$P = 0.001$*
		$P = 0.021$†			

All values in micrometers.
* Statistically significant difference compared to controls.
† Statistically significant difference between groups 1 and 2.

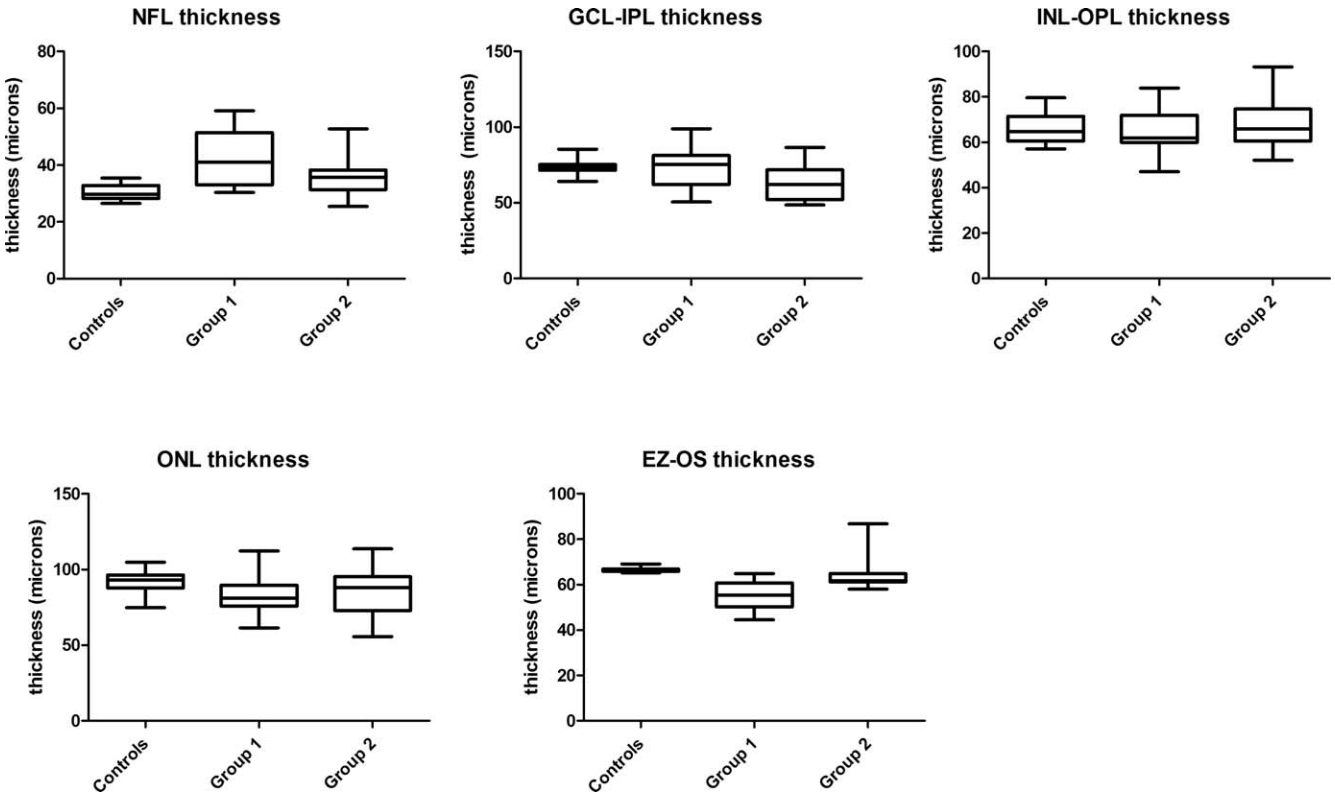

Figure 4. Box plots showing differences in retinal layer thickness between both groups and controls.

layer in 66.7% of their study population with macula-off RD. Disrupted inner segments/outer segments junctions were noted in 53.3% of the subjects. In OCT this disruption or disorganization appears as thinning within the EZ-RPE complex. Shimoda et al.[17] investigated restoration of photoreceptor outer segments after PPV for retinal detachment and found a gradual recovery of the ellipsoid zone (formerly known as IS/OS band) at the fovea after surgery. Postoperative visual acuity was correlated with a restored EZ in OCT.

Our data also suggest that part of this disorganization might only be temporary since patients in group 2 showed significantly thicker EZ-RPE compared to group 1. However, values remained lower compared to controls. Our findings suggest that some kind of reparation process leads to reestablishment of order within the photoreceptors after successful reattachment surgery. It is also likely that some permanent photoreceptor loss will remain owing to apoptosis or necrosis. This might explain why EZ-RPE complex thickness does not recover completely.

To our knowledge, there are few published reports of the use of OCT to study retinal layers after macula-off retinal detachment repair. Sridhar et al.[18] performed spectral-domain OCT in a small number of patients with macula-off RD and also found outer nuclear layer atrophy and inner segment ellipsoid layer disruption that correlated to postoperative visual acuity. Joe et al.[19] investigated foveal microstructure of pre- and postoperative patients with macula-off RD. They found a higher incidence of disruption to the EZ and the external limiting membrane (ELM) at final follow-up if preoperative intraretinal separation and outer layer undulation were present. Another group analyzed outer retinal thickness and retinal sensitivity in macula-off RD after successful reattachment.[20] Outer retinal thickness was found to be significantly thinner after vitrectomy compared to scleral buckling. However, retinal sensitivity of the central 10° of the macula was higher after vitrectomy compared to scleral buckling.

In our study, retinal sensitivity has not been tested with microperimetry, but visual recovery was better in group 2 compared to group 1. Reformation of the EZ-RPE complex might explain the increase of thickness in group 2 and might also explain better visual recovery. Burton[21] investigated the influence of duration of macula-off retinal detachment on visual recovery and described a nonlinear regression model to estimate the trend in visual recovery, in which duration of macular involvement was the only modifying factor. In our groups, differences in duration of macula involvement were not significant and do not explain why VA was better in group 2 compared to group 1. Ross and Kozy[22] investigated visual recovery after macula-off detachment and found that within the first week after development of macula-off retinal detachment, delay in surgical repair does not adversely affect visual outcome. In our study, all eyes received surgery within 72 hours after diagnosis. Therefore, it is unlikely that delay of surgery caused any adverse effect on visual recovery.

From what we see in OCT analyses, the recovery of the EZ-RPE complex and the diminishing of NFL thickening are major changes after macula-off RRD that might contribute to visual recovery. Permanent loss of photoreceptors and thinning of the GCL-IPL complex and/or ONL layer might be predictors for a negative visual outcome. However, from our study data one cannot directly predict visual outcome following successful RRD repair based on retinal layer thickness measurements. It is a bit surprising that retinal layer thickness values were counterintuitively not associated with visual recovery in our study. This might be due to the fact that the study group was too small to prove a direct correlation between retinal layer thickness values and visual recovery. One further limitation is that no OCT measurements have been performed prior to RRD surgery to confirm that retinal layers were normal before

detachment. In addition, patients in groups 1 and 2 were not the same patients. Therefore, group comparison will not reveal real retinal layer thickness changes over time. In conclusion, OCT subsegmentation of different retinal layers after macula-off RRD revealed various findings. Main changes in retinal layer thickness after macula-off retinal detachments appear in the ganglion cell layer-inner plexiform layer complex, the outer plexiform layer, and the EZ-RPE complex. Data from this study might help to better understand pathologic processes in this disease and to target certain retinal layers for neuroprotection in the future to avoid severe vision loss after macula-off retinal detachment.

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References

1. Mitry D, Charteris DG, Fleck BW, Campbell H, Singh J. The epidemiology of rhegmatogenous retinal detachment: geographical variation and clinical associations. *Br J Ophthalmol*. 2010;94:678–684.
2. Nork TM, Millecchia LL, Strickland BD, Linberg JV, Chao GM. Selective loss of blue cones and rods in human retinal detachment. *Arch Ophthalmol*. 1995;113:1066–1073.
3. Oshima Y, Yamanishi S, Sawa M, Motokura M, Harino S, Emi K. Two-year follow-up study comparing primary vitrectomy with scleral buckling for macula-off rhegmatogenous retinal detachment. *Jpn J Ophthalmol*. 2000;44:538–549.
4. Salicone A, Smiddy WE, Venkatraman A, Feuer W. Visual recovery after scleral buckling procedure for retinal detachment. *Ophthalmology*. 2006;113:1734–1742.
5. Puliafito CA, Hee MR, Lin CP, et al. Imaging of macular diseases with optical coherence tomography. *Ophthalmology*. 1995; 102:217–229.
6. Wojtkowski M, Srinivasan V, Fujimoto JG, et al. Three-dimensional retinal imaging with high-speed ultrahigh-resolution optical coherence tomography. *Ophthalmology*. 2005; 112:1734–1746.
7. Kajic V, Povazay B, Hermann B, et al. Robust segmentation of intraretinal layers in the normal human fovea using a novel statistical model based on texture and shape analysis. *Opt Express*. 2010;18:14730–14744.
8. Dufour PACL, Abdillahi H, Schröder S, De Zanet S, Wolf-Schnurrbusch U, Kowal J. Graph-based multi-surface segmentation of OCT data using trained hard and soft constrains. *IEEE Trans Med Imaging*. 2012;99:1–13.
9. Garvin MK, Abramoff MD, Wu X, Russell SR, Burns TL, Sonka M. Automated 3-D intraretinal layer segmentation of macular spectral-domain optical coherence tomography images. *IEEE Trans Med Imaging*. 2009;28:1436–1447.
10. Song QWX, Liu Y. Simultaneous searching of globally optimal interacting surfaces with shape priors. Paper presented at: Computer Vision and Pattern Recognition (CVPR) Conference; 2010; San Francisco, CA.
11. Spaide RF. Questioning optical coherence tomography. *Ophthalmology*. 2012;119:2203–2204.
12. Faude F, Francke M, Makarov F, et al. Experimental retinal detachment causes widespread and multilayered degeneration in rabbit retina. *J Neurocytol*. 2001;30:379–390.
13. Brazitikos PD, Katsimpris JM, Tsironi E, Androudi S. Retinal nerve fiber layer thickness evaluation after trypan blue-assisted macular surgery. *Retina*. 2010;30:640–647.
14. Xie Z, Chen F, Wu X, et al. Safety and efficacy of intravitreal injection of recombinant erythropoietin for protection of photoreceptor cells in a rat model of retinal detachment. *Eye (Lond)*. 2012;26:144–152.
15. Chen F, Xie Z, Wu X, et al. Intravitreal injection of soluble erythropoietin receptor exacerbates photoreceptor cell apoptosis in a rat model of retinal detachment. *Curr Eye Res*. 2012;37:1156–1164.
16. Delolme MP, Dugas B, Nicot F, Muselier A, Bron AM, Creuzot-Garcher C. Anatomical and functional macular changes after rhegmatogenous retinal detachment with macula off. *Am J Ophthalmol*. 153:128–136.
17. Shimoda Y, Sano M, Hashimoto H, Yokota Y, Kishi S. Restoration of photoreceptor outer segment after vitrectomy for retinal detachment. *Am J Ophthalmol*. 2010;149:284–290.
18. Sridhar J, Flynn HW Jr. Spectral-domain optical coherence tomography imaging of macula-off rhegmatogenous retinal detachment. *Clin Ophthalmol*. 2014;8:561–566.
19. Joe SG, Kim YJ, Chae JB, et al. Structural recovery of the detached macula after retinal detachment repair as assessed by optical coherence tomography. *Korean J Ophthalmol*. 2013; 27:178–185.
20. Baba T, Mizuno S, Tatsumi T, et al. Outer retinal thickness and retinal sensitivity in macula-off rhegmatogenous retinal detachment after successful reattachment. *Eur J Ophthalmol*. 2012;22:1032–1038.
21. Burton TC. Recovery of visual acuity after retinal detachment involving the macula. *Trans Am Ophthalmol Soc*. 1982;80: 475–497.
22. Ross WH, Kozy DW. Visual recovery in macula-off rhegmatogenous retinal detachments. *Ophthalmology*. 1998;105:2149–2153.

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