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1 2 3 4	Microstructural macular changes after pars plana vitrectomy for primary rhegmatogenous retinal detachment. Maurizio Mete <sup>1</sup> , Emilia Maggio <sup>1</sup> , Francesca Ramanzini <sup>2</sup> , Massimo Guerriero <sup>3</sup> , Giulia Airaghi <sup>1</sup> , Grazia Pertile <sup>1</sup>
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27 28	<b>Keywords:</b> Air tamponade; Ellipsoid zone; External limiting membrane; Optical coherence tomography (OCT); Pars-plana vitrectomy; Retinal detachment.
29	

#### 30 ABSTRACT

- 31 Purpose. To describe the foveal microstructural changes after pars-plana vitrectomy (PPV)
- 32 with air tamponade for reghmatogenous retinal detachment (RRD).
- 33 Methods. External limiting membrane (ELM) and ellipsoid zone (EZ) integrity, cystoid macular
- 34 edema (CME) and subretinal fluid blebs (SBs) presence were analyzed with optical
- 35 coherence tomography (OCT) in 59 eyes undergone surgery for RRD, divided between
- macula-on (n=30) and macula-off (n=29) and followed up 6 months. The association between
- 37 ELM and EZ recovery and best-corrected visual acuity (BCVA) was investigated. Predictive
- 38 factors for ELM and EZ recovery were also identified.
- Results. The nterval between symptoms and surgery didn't significantly differ between the
   groups. Macula-on patients showed ELM and EZ integrity. In macula-off patients, ELM and
   EZ were namely restored in 89.7% and in 86.2% of cases. Final BCVA was higher when ELM
- 42 and EZ were restored. Significant associations were found at several time points between
- 43 ELM/EZ recovery and macular preoperative involvement and EMC development, and
- 44 between BCVA and preoperative BCVA and EZ recovery. EMC and SBs development were
- 45 equally distributed between the groups.
- 46 Conclusion. Prompt surgery for macula-off RRD usually allows a progressive recovery of
   47 outer retinal layers. Thus, a high visual gain can be achieved, regardless of macular
   48 involvement.
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#### 62 INTRODUCTION

Retinal detachment (RD) is defined as the separation of neurosensory retina from underlying retinal pigment epithelium (RPE). Retinal apposition to the RPE is essential for supporting

vision, and RD involving the foveal center can lead to significant visual loss.

66 Rhegmatogenous RD (RRD) is the most frequent form of RD, where a retinal break allows the

67 fluid passage from the vitreous chamber into the subretinal space, resulting in retinal

- separation. RRD can occur at any age, with a peak prevalence of 13 cases per 100000
   amongst individuals aged 60 to 70 years. Pars plana vitrectomy (PPV) has been increasingly
- adopted for the treatment of RRD, with recent advances in its techniques having improved its

71 outcomes. Several factors, such as RD duration, macular involvement, proliferative

- vitreoretinopathy (PVR), epiretinal membrane (ERM) development, cystoid macular edema
- 73 (CME) occurrence, retinal fold formation and pigment migration, seem to affect postoperative
- functional outcomes <sup>1, 2</sup>. Regardless of these macroscopic features, poor visual recovery can
- also occur in retinas of normal appearance, suggesting the existence of microstructural
- alterations not detectable upon fundus examination. The advent of high-resolution spectral-
- domain optical coherence tomography (SD-OCT) has allowed macular microstructural

abnormalities detection and a better understanding of the discrepancies between anatomical

and functional surgical outcomes.

80 In our center, PPV with air tamponade represents the technique of choice in case of

81 uncomplicated primary RRD. Gas or silicon oil are usually used in case of a supposed risk of

82 RD recurrence (giant retinal tears, PVR stage higher than B). The aims of this study are to

83 investigate microstructural changes after primary uncomplicated RRD repair and to identify

- 84 both preoperative and postoperative factors that could affect healing processes and functional
- 85 outcomes.
- 86

## 87 **METHODS**

88 PATIENT SELECTION

89 This is a retrospective study based on a review of consecutive patients' medical records who 90 were affected by uncomplicated primary RRD and underwent PPV with air tamponade at 91 IRCCS Sacro Cuore-Don Calabria Hospital in Verona (Italy) between 2017 and 2019. Patients having undergone baseline as well as 1, 3 and 6-month follow-up postoperative visits were 92 93 included. Exclusion criteria were: axial length > than 26 mm; previous retinal surgery; 94 inadequate imaging due to low quality; any ocular condition that could influence best-corrected 95 visual acuity (BCVA), with the exception of lens opacity; and the absence of a complete 6-month 96 follow-up. All procedures adhered to the tenets of the Declaration of Helsinki. This study was 97 approved by the Institutional Review Board Committee of IRCCS Sacro Cuore-Don Calabria 98 Hospital and by the Ethical Committee of Verona and Rovigo (reference number: Prot. Negrar-99 2020 K).

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101 Patients were divided into two groups (macula-on and macula-off) according to macular 102 involvement in the RRD. At baseline and at each follow-up visit, a complete ophthalmic 103 examination was performed, including BCVA measurement, slit-lamp biomicroscopy, intraocular pressure (IOP) evaluation, dilated fundus examination with a 90 diopters indirect
lens and SD-OCT evaluation (Spectralis HRA-OCT, Heidelberg Engineering GmbH,
Heidelberg, Germany). At baseline, axial length was also measured in phakic eyes (IOLMaster;
Carl Zeiss Meditec, Jena, Germany). A Snellen Chart was used for the assessment of BCVA
and converted into the logarithm of minimum angle of resolution (LogMAR) for statistical
analysis purposes. The semi-quantitative scale "counting fingers" was transposed into logMAR
2 and "hand motion" into logMAR 3 (Holladay 2004).

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112 RRD duration was also considered and was defined as the length of time between the onset 113 of central or peripheral vision loss, and surgery as opposed to the length of time between clinical evaluation and surgery. Macular microstructural changes were evaluated by OCT. 114 The hyperreflective outer retinal bands (external limiting membrane (ELM) and ellipsoid zone 115 (EZ)) were defined according to the International Nomenclature for OCT panel classification. 116 The ELM was defined as a discrete hyperreflective band at the outermost border of the outer 117 nuclear layer, located above the inner segment/outer segment (IS/OS) junction. The EZ line 118 was defined as the second hyperreflective band above the RPE. The following OCT features 119 120 were recorded at each visit: (1) external limiting membrane (ELM) integrity, (2) ellipsoid zone (EZ) integrity, (3) the presence of cystoid macular edema (CME), (4) the presence of an 121 epiretinal membrane (ERM), and (5) the presence of subretinal fluid blebs (SBs). The integrity 122 of the foveal ELM and EZ was assessed as follows: line not visible or disrupted in at least one 123 124 scan (band defect) and continuous line in both the horizontal and vertical scans (intact band). 125 The same analysis was always performed also in fellow eyes to minimize potential bias arising from artefacts. The eye-tracking dual-beam technology (TruTrack<sub>TM</sub> Active Eye 126 Tracking Software, Heidelberg Engineering, Heidelberg, Germany) mitigated eye movement 127 artefacts and ensured point-to-point correlations between the OCT scan and fundus images. 128 The "automatic real-time" (ART) function provided by the software was used to reduce noise 129 and increase image guality. With ART activated, multiple frames (B-scans) of the same 130 scanning location being performed during the scanning process, and only scans with elevated 131 ART (range 90–100) being considered. Follow-up visits were scheduled at 1, 3 and 6 months 132 133 after the operation.

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#### 136 SURGICAL TECHNIQUE

137 All patients underwent the same surgical technique. General or local anesthesia was chosen

138 according to both the patient preference and the anesthesiologist's indication. Local

anesthesia was induced by retrobulbar nerve block. A 23-gauge PPV was performed using

140 EVA (Dutch Ophthalmic Research Centre, DORC, The Netherlands) or Constellation (Alcon,

141 USA) platform. Cataract surgery was also performed during the same procedure, on a case-

142 by-case basis as required. Patients underwent complete vitrectomy and peripheral vitreous

shaving. A posterior hyaloid separation from the retina was obtained if needed.

144 Perfluorocarbon liquid (PFCL) was used to reattach the retina. Subretinal fluid was drained

145 through retinal breaks during fluid-air exchange. The procedure was completed using 360°

146 endolaser photocoagulation around retinal breaks and on the peripheral retina. Postoperative

- 147 positioning was determined according to the retinal breaks position.
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#### 150 STATISTICAL ANALYSIS

Demographic and clinical data were summarized using descriptive statistics, variability and precision measures and plots. Statistical tests were used based on the type of variables, test assumptions and sample dimension. All parameters were reported with 95% confidence intervals. Statistical models were adjusted for covariates if necessary.

T-test and Wilcoxon rank-sum test were used to compare continuous variables in independent groups whereas one-way analysis of variance was adopted to compare continuous variables stratified in more than two groups. The Chi-square test and the Fisher test were used to compare categorical variables.

159 Multivariate linear regression models and multivariate logistic models were used to model 160 continuous and binary dependent variables respectively.

A p-value of less than 5% was considered as statistically significant. Data were analyzed by
 STATA vers. 15 (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX:
 StataCorp LLC.).

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## 167 **RESULTS**

- 168 Fifty-nine patients met the inclusion criteria. Macula-on group included 30 patients, while
- 169 macula-off group comprised 29 patients. Demographic and the baseline characteristics of
- patients are summarized in Table 1. The two groups were homogeneous with no statistically
- 171 significant differences at baseline other than BCVA. Phacoemulsification was performed
- together with PPV in 13 cases (22%) from within the entire cohort. The median interval
- 173 between symptoms being reported and surgery was 4 days for both groups and so was not
- 174 significantly different (p = 0.85).
- 175 In the macula-on group, the mean BCVA was 0.24 (SD 0.18) logMAR (20/35) at baseline,
- 176 and 0.14 (SD 0.16) logMAR (20/28), 0.13 (SD 0.21) logMAR (20/27) and 0.14 (SD 0.25)
- 177 logMAR (20/28) at 1, 3 and 6 months after surgery, respectively. In the macula-off group,
- 178 BCVA was 1.33 (SD 0.18) logMAR (20/400) at baseline, and 0.36 (SD 0.40) logMAR (20/45),
- 179 0.31 (SD 0.42) logMAR (20/40) and 0.20 (SD 0.25) logMAR (20/32) at 1, 3 and 6 months after
- 180 surgery, respectively. The difference in BCVA between the macula-on and macula-off groups
- 181 was statistically significant at baseline (p < 0.01), and at 1 month (p = 0.01) and 3 months (p = 1.02
- 182 0.05) after surgery, while there was no significant difference in BCVA between groups at 6
- 183 months after surgery (p = 0.33) (fig. 1).

In the macula-on group, no ELM or EZ defects were detected at any time point. In the 184

185 macula-off group, the number of eyes showing complete recovery of both the ELM and EZ at

- 186 1, 3 and 6 months after surgery is shown in figure 3. ELM and EZ foveal defects both
- decreased progressively up to 6 months after surgery. At the end of follow-up, the ELM was 187
- 188 restored in 89.7% of the patients studied, while EZ reached completion in 86.2% of cases (fig. 2). Figure 3 also provides examples of macula-on and macula-off cases, in which the
- 189
- 190 progressive recovery of the ELM and EZ was observed during follow-up.
- 191 The analysis of the relationship between visual outcomes and outer retinal layers revealed a
- higher mean BCVA when the ELM and EZ were restored. No significant relationship was 192
- 193 found between BCVA and ELM or EZ status 1 month after surgery (p = 0.33), and although a
- 194 clinical difference was reported 3 months after surgery, it was not statistically significant (p =
- 195 0.07). However, a statistically significant difference was found 6 months after surgery (p =
- 196 0.04) (fig. 4).
- 197 After surgery, 6 macula-off patients (20.7%) and 5 macula-on patients (16.7%) developed
- 198 CME, with no statistically significant difference between groups (p = 0.69). CME was
- 199 observed in 3 of 13 patients (23.1%) who underwent phacoemulsification and PPV, and in 6
- of 46 cases (13.1%) in which PPV alone was performed. CME occurrence was significantly 200
- more frequent when phacoemulsification and PPV were both performed (p = 0.04). In the 201
- 202 majority of cases, CME reabsorption was achieved within 3 months of topical 1%
- 203 prednisolone acetate tapering administration. In three cases, CME was still present at the end 204 of follow-up.
- 205 Three macula-off patients (10.3%) and 4 macula-on patients (13.3%) presented with SBs, 206 with no significant difference between groups (p = 0.72). ERM formation was not detected in 207 either group.
- 208 Of the patients that did not undergo phacoemulsification, clinically relevant cataract onset was 209 observed in 1 macula-off (3.5%) and in 2 macula-on patients (6.7%).
- 210 Only 1 case of RRD recurrence was observed in the macula-off group, which was due to PVR 211 development.
- 212 Multivariate logistic regression models revealed the following significant associations. 1 month 213 after surgery, ELM restoration was directly associated with preoperative macular non-
- involvement (odds ratio, OR = 45.13, p = 0.05), while it was inversely associated with age 214
- (OR = 0.83, p = 0.02) and EMC development (OR = 0.3, p = 0.04). At 3 months, ELM 215
- restoration was directly associated with preoperative macular non-involvement (OR = 17.27, p 216
- = 0.03), while it was inversely associated with EMC development (OR = 0.03, p = 0.02). The 217
- 218 model could not reach statistical convergence for the 6-month follow up data, due to the
- extremely low number of ELM disruption cases. As expected, 1 month after surgery, EZ 219
- 220 restoration was strongly associated with preoperative macular non-involvement (OR = 71.23,
- 221 p = 0.01). At 3 months, EZ restoration was strongly associated with preoperative macular
- 222 non-involvement (OR = 27.11, p = 0.01), while it was inversely associated with EMC

223 development (OR = 0.05, p = 0.03). A marginal inverse association with age was also found 224 (OR = 0.88, p = 0.07). As for ELM, the model could not reach statistical convergence for the 225 data regarding EZ recovery at 6 months. 1 month after surgery, BCVA was directly associated 226 with baseline BCVA (beta coefficient,  $\beta = 0.10$ ; p = 0.05) and inversely associated with EMC 227 development ( $\beta$  = 0.28; p = 0.03). At 3 months, BCVA was directly associated with baseline 228 BCVA ( $\beta$ = 0.13; p = 0.03) and with EZ recovery ( $\beta$  = -0.35; p = 0.03). BCVA at 6 months was 229 directly associated with EZ recovery only ( $\beta = -0.30$ ; p = 0.04). No significant associations 230 were found with SBs, RRD duration and RRD recurrence. Preoperative macular involvement 231 was not significantly associated with final BCVA ( $\beta$  = 0.01; p = 0.98), confirming the results of 232 the direct comparison between macula-on and macula-off BCVA at 6 months. No statistically 233 significant association was found between preoperative macular involvement and RRD 234 duration (OR = 1.00, p = 0.84).

235

#### 236 **DISCUSSION**

237 Despite successful retinal reattachment, functional results can vary greatly among eyes

treated for RRD. With the SD-OCT introduction, several studies have demonstrated that outer

retinal layer defects correlate with low visual gain after surgery in patients with macular

#### 240 involvement <sup>3-8</sup>.

241 Wakabayashi was amongst the first to study SD-OCT foveal changes after RRD 242 surgery. They found that the postoperative recovery of the ELM may serve as a predictive factor for the subsequent restoration of the photoreceptor layer <sup>4</sup>. Shimoda observed a 243 gradual IS/OS line recovery after PPV with sulfur-hexafluoride (SF<sub>6</sub>) tamponade. Six months 244 after surgery, a disrupted IS/OS line was observed in 3 eyes (17%), a foveal detachment in 6 245 246 eyes (33%), and a continuous IS/OS line in 9 eyes (50%), with a significant association between BCVA and IS/OS line restoration <sup>5</sup>. Other studies reported similar postoperative ELM 247 and EZ recovery rates <sup>3, 6</sup>. Although we have reported a higher outer retinal band recovery 248 249 rate, our data suggest an association between outer retinal layer recovery and BCVA improvement after surgery. However, limitations of sample size have resulted in relatively few 250 251 EZ recovery cases in our study, especially at 6 months, which has affected the statistical 252 robustness of our findings (fig. 2, 4). 253 Park identified the detachment extent, macula-off duration, and ELM integrity as being 254 preoperative prognostic factors potentially influencing functional RRD surgery outcomes. 255 Postoperative EZ recovery was also found to impact the final visual outcome. The mean 256 macula-off duration was 18.44 ± 60.54 days. The final BCVA in patients with a macula-off 257 duration lasting less than a day, was significantly higher than in patients with a macula-off 258 duration lasting more than 7 days. However, there were no statistically significant differences 259 when compared with cases of macula-off duration lasting between 1 and 7 days<sup>8</sup>. Malosse 260 reported EZ and ELM defects in 100 (47.2%) and 64 (30.2%) eyes respectively, 1 month 261 after surgery and in 44 (17.4%) and 18 (7.1%) eyes respectively, 6 months after surgery. The 262 median macula-off duration was 5.0 days (range 1–90) and a multivariate analysis showed 263 that the duration of macular detachment was the only factor associated with ELM and EZ

damage at 6-months.<sup>7</sup>. While mean RRD durations, and ELM and EZ recovery rates that are

similar to our findings, other studies demonstrated that shorter delays in surgery correlate with
 better ELM and EZ recovery and BCVA improvement <sup>9-11</sup>. In addition, Narala have
 demonstrated a significant positive association between photoreceptor volume, BCVA and
 short surgery wait time <sup>12</sup>.

269 Studies on animal models show that cell apoptosis occurs within hours of RD induction, peaking at 2 to 3 days, and dropping at 7 days <sup>13, 14</sup>. Diederen found that visual acuity rapidly 270 271 worsened when the macular detachment lasted longer than 6 days, concluding that surgical repair can be undertaken within 7 days of macular detachment without negatively affecting 272 visual outcomes <sup>15</sup>. However, Frings reported a narrower time frame, observing worse final 273 274 visual outcomes from 3 days of macula-off RRD <sup>16</sup>. Taken together, these data support the importance of a prompt RRD surgical repair. Interestingly, we have not observed any 275 significant difference in the final BCVA between macula-on and macula-off patients. This 276 277 might suggest that the short interval between diagnosis and surgery allowed us to minimize 278 functional impairment even in cases of macula-off RRD. This is an intriguing point that could 279 prompt a revision of current practices where macula-on RRD patients are prioritized for 280 surgery over macula-off cases. As such, surgery timing should carefully consider RRD 281 duration.

282 Regarding complications, CME development occurred in about 6.5% of patients in our study, 283 with a similar prevalence the 2 groups. According to our regression models, it seemed to affect ELM and EZ healing processes and, at least in the first part of the follow-up, BCVA 284 recovery. In the majority of cases, topical steroids were able to resolve this complication by 285 286 the follow-up. Our data suggest that CME could slow and critically compromise both microstructural and functional recovery. In our series, patients who had undergone combined 287 surgery, showed a significantly higher CME prevalence during follow-up. Conversely, other 288 289 studies have not found any significant difference in CME prevalence between combined surgery and PPV alone <sup>17</sup>. Some publications have speculated that the breakdown of the 290 blood-aqueous-barrier due to cataract surgery and of the blood-retinal barrier due to 291 292 vitrectomy together could cause stronger ocular inflammatory responses in RRD eyes, 293 leading to a higher reoperation rate following combined surgery than after PPV alone <sup>18</sup>. 294 However, this hypothesis is not widely confirmed by the literature. Other authors have hypothesized that 360° retinopexy could increase CME risk <sup>19</sup>. In our surgical practice, 360° 295 296 retinopexy is performed in both combined surgery and in PPV alone. Further studies are required, on larger series, to confirm the higher EMC prevalence in cases of combined 297 298 surgery that were observed in our study. Moreover, cases of EMC that persist for more than 6 299 months after surgery should be monitored for any resolution at a later time point. Preoperative 300 and intraoperative factors should also be examined to better predict the postoperative EMC 301 risk in patients treated for RRD.

302 SBs are relatively common after scleral buckling procedures having been described since the 303 1980s <sup>20</sup>. They are confirmed by OCT in about 9% of buckling procedures <sup>21</sup>. Their 304 mechanism of formation has not yet been clarified, but they usually disappear spontaneously 305 within a year. Some authors have speculated that they could originate from vascular changes 306 resulting from cryotherapy used during scleral buckling procedures <sup>21</sup>, but it has been recently 307 demonstrated that they can also occur after PPV <sup>22, 23</sup>. However, in our study, no significant

- <sup>308</sup> difference in SBs prevalence was demonstrated between macula-on and macula-off RRDs <sup>4</sup>.
- 309 Another study has found that subfoveal located blebs may slow visual recovery, although the
- 310 final BCVA outcome is not affected <sup>3</sup>. In our study, BCVA recovery was not affected by SBs at
- any time point.
- 312

#### 313 CONCLUSIONS

The main limitations of this study arise from its retrospective nature. However, taken together, our data suggest that prompt surgery for macula-off RRD allows the recovery of outer retinal layers in the majority of cases. As a consequence, a high degree of visual gain can be achieved after surgery for RRD, regardless of macular involvement.

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## 396

#### **397 FIGURE CAPTIONS**

398

Fig.1. Best corrected visual acuity (BCVA) changes during the follow-up in macula-on and
 macula-off patients. BCVA is expressed as a logarithm of minimum angle of resolution
 (LogMAR). The difference between macula-on and macula-off patients was significant at
 baseline, and 1 and 3 months after surgery, whereas no significant difference was observed 6

403 months after surgery. Asterisks indicate a statistically significant difference between the two

404 groups (p < 0.05).

405

406 Fig. 2. External limiting membrane (ELM) and ellipsoid zone (EZ) recovery rate during the407 follow-up in macula-off patients.

408

409 Fig. 3. Follow-up in a case of macula-on (A-D) and another of macula-off (E-H)

410 rhegmatogenous retinal detachment (RRD). Both the ELM and EZ in the preoperatively

411 detached retina progressively recovered during the follow-up. Preoperative (A, E). 1 month

412 after surgery (B, F). 3 months after surgery (C, G). 6 months after surgery (D, H).

413

Fig. 4. The relationship between best corrected visual acuity (BCVA) and external limiting

415 membrane (ELM) and ellipsoid zone (EZ) recovery during the follow-up in macula-off patients.

No significant relationship was found at 1 month (p=0.33); however, a clinical difference that

417 was not statistically significant was found at 3 months (p=0.07), and a statistically significant 418 difference was found at 6 months after surgery (p = 0.04). ELM– EZ– = neither ELM nor EZ

418 difference was found at 6 months after surgery (p = 0.04). ELM- EZ- = neither ELM nor EZ 419 recovery; ELM+ EZ- = ELM recovery; ELM+ EZ+ = ELM and EZ recovery. Asterisks indicate

419 recovery, ELM+  $EZ^{-}$  – ELM recovery, ELM+  $EZ^{+}$  – ELM and EZ recovery. Astensis indice 420 a statistically significant difference between the two contiguous points (p < 0.05).