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RETINAL DISORDERS

Persistent macular holes — what is the best strategy for revision?

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Abstract

Purpose This study aims to analyze the success rate and functional outcome after revision surgery of persistent idiopathic full-thickness macular holes in a large patient cohort and to identify the optimal tamponade strategy and the value of new adjunctive manipulation techniques for persistent macular hole (pMH) closure.

Methods Retrospective, comparative, non-consecutive case series of all revisional surgeries for idiopathic pMH between 2011 and 2019 at the Eye Clinic Sulzbach were identified. Of 1163 idiopathic MH surgeries, 74 eyes of 74 patients had pMH. Of those, group 1 (n = 38) had vitrectomy with tamponade alone (20% sulfur hexafluoride gas, 15% hexafluoroethane gas, silicone oil 5000, Densiron®), while group 2 (n = 36) included tamponade with adjuvant manipulation (internal limiting membrane (ILM) translocation, subretinal fluid injection, epiretinal amniotic membrane, free retina graft, or autologous blood). Main statistical outcomes were anatomic closure rate, visual acuity (VA), minimum linear diameter (MLD), and base diameter (BD).

Results Overall total anatomical success rate was 81.1% and mean VA improved 3.5 lines from LogMAR 1.03 ± 0.30 to 0.68 ± 0.38 ($p < .001$). Preoperative MLD or BD had no effect on total anatomic success ($p = 0.074$, $p = 0.134$, respectively). When comparing the two groups, slightly better anatomic success rates were achieved in group 1 (84.2%) compared to that in group 2 (77.8%) ($p = 0.68$). Final VA in group 1 (LogMAR 0.67 ± 0.39) outperformed group 2 (LogMAR 0.86 ± 0.38) ($p = 0.03$).

Conclusions Revisional surgery for persistent idiopathic MH with tamponade alone had comparable anatomical closure but better VA outcomes, compared to tamponade with adjuvant manipulation.

Keywords Macular hole surgery · Persistent macular hole · Refractory macular hole · Subretinal fluid injection · Epiretinal amniotic membrane · ILM translocation

Key messages

What was known:

- As anatomic closure or even restoration of the foveal architecture is more difficult to achieve in persistent macular holes (pMH), it is still under debate which is the best surgical approach.

What is new:

- Revision surgery for idiopathic pMH achieves anatomic success in over 80% of patients along with an average 3.5 lines improvement in visual acuity
- There is no advantage for any particular tamponade for visual acuity or anatomic closure of pMH
- New adjuvant manipulation techniques aiming centripetal hole closure do not seem advantageous over tamponade alone

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Introduction

Vitrectomy for idiopathic full-thickness macular holes (MHs) is one of the most successful procedures in the vitreoretinal subspecialty nowadays, with primary closure rates exceeding 90% along with significant visual acuity improvement [1, 2]. A small percentage of surgery fails, however, especially in large MHs. In these persistent MHs, anatomic and functional success is more difficult to achieve. Many studies report repeat vitrectomy with gas tamponade to be successful, but closure rates stand well below the results reported after primary surgery, and with relatively poor final visual acuity [3, 4].

Limited surgical options are available once the posterior hyaloid has been removed and structures for tractional relief or a guide rail for glial cell bridging (e.g., an inverted ILM flap) are missing [5, 6].

To overcome these challenges, several strategies have been described to achieve MH closure. A recent meta-analysis reports the clear tendency towards longer-acting gas tamponades for reoperations [4]. A simple fluid-gas exchange, however, can only attach, but not approximate the hole edges, which is particularly relevant for large persistent MHs.

Hence, several adjunctive procedures have been proposed to achieve a centripetal effect for hole edge approximation and to improve bridging. These new adjuvant manipulation approaches comprise grafting techniques with free autologous ILM [7–10], centripetal hole approximation through induced macular detachment [11–13], an amniotic membrane [14, 15], neurosensory retina from the periphery [16, 17], or autologous blood products [18, 19].

Although there are numerous studies on different tamponades [4, 20–23] and the various adjunctive procedures, only a few comparative studies are available [3]. A recent meta-analysis overviewing 22 studies failed to determine a successful revision technique, due to heterogeneity and small sample sizes of the available studies [4].

Therefore, the aim of this study was to analyze the success rate and functional outcome after revision surgery of persistent idiopathic full-thickness MHs in a large patient cohort and to identify the optimal tamponade strategy and the value of new adjunctive manipulation techniques for MH closure.

Methods

Study design

In this retrospective, comparative, non-consecutive single-center case series, we reviewed the medical records of all patients who underwent their first surgical revision of a persistent idiopathic full-thickness macular hole between 2011 and 2019 at the Eye Clinic Sulzbach by 4 experienced surgeons. The study was approved by the Ethics Committee of the Medical Association of Saarland (Nr. 243/14) and adheres to the tenets of the Declaration of Helsinki. Informed consent was obtained.

Patients and examinations

We reviewed the records of 1163 patients with idiopathic full-thickness MH who had undergone macular hole surgery with standard three-port 23G pars plana vitrectomy including ILM peeling (within the vascular arches of at least 2 pupil diameters) and gas tamponade between 2011 and 2019.

Inclusion criteria of failed primary idiopathic macular hole surgery were cases with sufficient data on preoperative and postoperative visual acuity (VA) and anatomical characteristics based on spectral domain optical coherence tomography (SD-OCT, Spectralis 2, Heidelberg Engineering, Heidelberg, Germany) measurements, and available follow-up data of at least 4 weeks. If multiple postoperative follow-up time points were available, then the last available follow-up was used for VA-related and OCT-related analysis.

Exclusion criteria were other surgeries than the previous vitrectomy and visually relevant secondary diagnoses, as well as MH of other origin (e.g., trauma, retinal detachment). All eyes were already pseudophakic and had no cataract surgery between the initial MH vitrectomy and this first revision pMH vitrectomy.

The mean interval between the initial surgery and the revision surgery was 6.7 months (range 2–17 months). All patients underwent preoperative and postoperative comprehensive ophthalmic examination including visual acuity (VA) with Snellen charts, slit-lamp, and dilated fundus examination, and OCTDecimal VA scores were converted to LogMAR for subsequent analysis. OCT scans were performed with high-resolution volume scans with a scanning density spacing of 60–80 µm of the MH prior and after the revision MH surgery.

Interventions

All patients underwent a transconjunctival 23-gauge pars plana vitrectomy (DORC EVA, Zuidland, Netherlands) with staining of the posterior pole (Membrane Blue Dual®, DORC, Zuidland, Netherlands) to identify ILM residues, fluid-air exchange, and internal tamponade (with instruction to posture face down in case of gas tamponade). The exact procedure including the type of tamponade (20% sulfur hexafluoride gas (SF_6), 15% hexafluoroethane gas

(C_2F_6), silicone oil 5000 (Sil 5000), or Densiron®) and the optional use of adjuvant manipulation techniques (free ILM flap translocation (f-ILM), subretinal fluid application (SRF-Appl), 6-mm epiretinal amniotic membrane [15] (EAM, AmTrix®, Horus Pharma, Saint-Laurent-du-Var, France), free retina flap (Free Retina), or application of autologous blood (AB-Appl)) were documented. The decision on which technique was used for pMH repair did not follow any specific criteria in this real-life study and was therefore at the surgeon's experience and discretion.

Definitions and analysis

The minimum linear diameter (MLD) was defined as the minimum horizontal diameter across the widest horizontal high-resolution SD-OCT volume scan. The outer base diameter (BD) was measured at the level of the retinal pigment epithelium (RPE). The total anatomical success was defined as central continuity of neurosensory retina with sealed hole edges over RPE (closure) or atrophic closure (attached hole edges but bare central RPE). No success was defined as elevated neurosensory retinal hole edges with bare central RPE (open). All scan analyses were performed by one senior grader.

For the comparative group analysis on the effect of the closure rate and visual gain of adjuvant manipulation versus tamponade alone, patients were distributed into group 1 (tamponade alone: SF_6, C_2F_6, Sil 5000, Densiron) and group 2 (tamponade with adjuvant manipulation: f-ILM flap, SRF-Appl, EAM, free retina, AB-Appl).

The statistical analysis was performed with the R Software (Version 3.6.3, R Core Team, 2020). Group analyses were performed with Welch-t-tests or analysis of variances (ANOVAs). Frequencies between conditions were compared using $\chi 2$-tests. A *p*-value of < 0.05 was considered significant.

Results

In total, 1163 primary idiopathic macular hole surgeries were identified, of which 74 underwent revisional surgery due to persistent idiopathic MH (pMH) and met all inclusion criteria. Of the total of 74 eyes of 74 patients, the mean age was 70.7 ± 8.4 years (range 47–84 years). All eyes were pseudophakic and had an ILM peeling previously. The number of female patients (n = 56) was significantly higher than that of male patients (n = 18) (75.68%, 95% CI [64.31, 84.90], p < 0.001). Six eyes were high myopes (axial length ≥ 6 dpt or ≥ 26.5 mm) which had no influence on the success rate (p = 0.318). During the average follow-up time of 295 days (range 30–1901 days), none of the eyes showed complications such as retinal breaks, retinal detachment, fibrinous exudates, or endophthalmitis.

Overall success rate

The overall demographic data and outcome parameters are shown in Table 1. The total anatomic success rate (complete anatomic closure and atrophic closure) was 81.1% (n = 60/74). Female patients showed a statistically not significant lower success rate than male patients (79% vs. 89%, p = 0.54), but a statistically not significant stronger improvement in visual acuity improvement (3.0 lines vs. 1.9 lines, p = 0.28) despite the disadvantage of an initially a statistically not significant larger hole size (MLD 507 ± 195 µm vs. 390 ± 220 µm, $\Delta M = -177$, 95% CI [−2, 237], p = 0.06). Younger patients (≤ 65 years, n = 19) achieved a statistically not significant better total anatomical success rate compared to medium age (66–75 years, n = 28) and oldest patients (> 75 years, n = 27) (94% vs. 83% vs. 72%, respectively) (p = 0.207). We did not observe any differences in preoperative MLD or BD regarding total anatomic success (p = 0.074,

Table 1 Clinical characteristics of all patients (n = 74)

	Anatomical success (60/74)		No closure (n = 14)	Total (n = 74)	*p*-value*
	Complete closure (n = 51)	Atrophic closure (n = 9)			
Gender (female/male)	38/13	6/3	12/2	56/18	0.538
Mean (SD) age in years	70.1 ± 8.6	69.9 ± 8.6	73.2 ± 7.2	70.7 ± 8.4	0.464
Mean (SD) MLD preoperative in µm	446 ± 185	516 ± 286	573 ± 207	479 ± 206	0.108
Mean (SD) BD preoperative in µm	1320 ± 303	1174 ± 470	1080 ± 728	1190 ± 480	0.465
Mean (SD) preoperative VA in logMAR	1.03 ± 0.31	1.06 ± 0.26	1.04 ± 0.3	1.03 ± 0.3	0.973
Mean (SD) postoperative VA in logMAR	0.64 ± 0.38	0.89 ± 0.27	1.11 ± 0.27	0.76 ± 0.4	< 0.001
Mean (SD) line improvement of VA	3.87 ± 3.25	1.69 ± 1.81	− 0.77 ± 3.09	2.72 ± 3.56	< 0.001

MLD, minimum linear diameter; *BD*, base diameter; *MH*, macular hole; *VA*, visual acuity; *LogMAR*, logarithm of the minimum angle of resolution

*p-values are based on a one-way ANOVA (complete closure vs. atrophic closure vs. no closure) p = 0.134, respectively). A post hoc analysis showed no statistically significant difference among the surgeons.

Overall visual gain

Overall, 51% patients achieved a VA increase of ≥ 3 lines, albeit only 33% achieving VA suitable for reading (0.5 logMAR). With total anatomical success, mean VA improved by 3.5 lines (p < 0.001), while in complete closure, VA even increased by 3.9 lines, compared to 1.7 lines in eyes with atrophic closure. Eyes where anatomical closure could not be achieved, lost 0.8 lines (Table 1). Younger patients (≤ 65 years, n = 19) achieved a statistically not significant greater visual acuity improvement compared to medium age (66–75 years, n = 28) and oldest patients (> 75 years, n = 27) (3.5 vs. 2.6 vs. 2.3 line improvement) (p = 0.66), and statistically not significant better final visual acuity (p = 0.56). Overall, 42% of the younger patients achieved reading visual acuity (0.5 logMAR).

Subgroup analysis of tamponades

Of 74 patients, one-half was treated traditionally with tamponade only (group 1, n = 38), while the other half received one of the new adjuvant manipulation techniques to promote MH edge approximation and/or bridging (group 2, n = 36).

To analyze the effect of tamponades only on functional and structural outcome in pMH surgery, we conducted a subgroup analysis of group 1, shown in Table 2. The tamponade types included SF6 (n = 11), C2F6 (n = 20), SIL 5000 (n = 3), and Densiron (n = 4) (Fig. 1). At baseline, prior to pMH revision surgery, there was no difference in VA (p = 0.071) and MLD (p = 0.368) between the tamponades. To assess the influence of different tamponades on visual acuity improvement, we conducted an ANOVA which yielded no differing improvements in visual acuity by different tamponades (p = 0.860). Thus, the current analysis yielded no indication that different tamponades have an influence on the functional outcome. To assess the influence of MLD, BD, and tamponades on total anatomical success, we conducted a logistic regression. Neither MLD (OR = 1.00, 95% CI [0.99, 1.00], p = 0.130) nor BD (OR = 1.00, 95% CI [1.00, 1.00], p = 0.628) had an influence on total anatomic success. In addition, tamponades did not improve the prediction of total anatomic success (p = 0.444).

Subgroup analysis of adjuvant manipulations

To analyze the effect of adjuvant manipulation on functional and structural outcome in pMH surgery, we conducted a subgroup analysis of group 2 (see Table 3). These included free ILM flap translocation (n = 12), induced macular detachment (n = 12), epiretinal amniotic membrane (n = 7), free retinal translocation (n = 2), and application of autologous blood (n = 3) (Figs. 2 and 3).

Free ILM flaps and epiretinal amniotic membrane grafts showed a statistically not significant high rate of complete closure and VA gains of 3.9 and 3.3 lines, respectively. Autologous free ILM grafts obtained reading vision in 42%.

Of interest, all amniotic membrane grafts achieved an initial complete closure (success rate 100%) despite a large initial hole size, however, with 2 cases showing a slow-progressive reopening resulting in atrophic closure and VA loss 2 months later. The induced macular detachment group achieved an average MH closure rate, but a low visual acuity gain. This correlated with distinct pigment epithelial irregularities in postoperative OCT even in successful cases. Interestingly, the group with autologous blood still showed a visual acuity increase despite the low closure rate, while the patients with free retina flap showed no increase in visual acuity (Table 3).

Comparative analysis of tamponades alone versus tamponades with adjuvant manipulations

Group 1 had a better mean preoperative VA (logMAR 0.92 ± 0.29) when compared to group 2 (logMAR 1.15 ± 0.25, p = 0.001), while this relationship was reverse for MLD, with group 2 having a larger preoperative pMH

Table 2 Structural and functional outcome depending on tamponades (group 1, n = 38)

	SF_6 (n = 11)	C_2F_6 (n = 20)	Sil 5000 (n = 3)	Densiron (n = 4)	*p*-value
Mean (SD) MLD preoperative in µm	323 ± 231	446 ± 194	442 ± 199	448 ± 166	0.368
Anatomical success of MH closure (complete/atrophic) (n = 28/4)	90.9% (9/1)	80.0% (15/1)	100% (3/0)	75% (1/2)	0.693
Mean (SD) postoperative VA in logMAR	0.50 ± 0.40	0.68 ± 0.40	1.10 ± 0.10	0.75 ± 0.19	0.113
Mean (SD) line improvement of VA	2.63 ± 3.08	2.72 ± 3.70	2.59 ± 3.28	3.05 ± 3.27	0.860

MLD, minimum linear diameter; *MH*, macular hole; *VA*, visual acuity; *LogMAR*, logarithm of the minimum angle of resolution; *SF6*, 20% sulfur hexafluoride gas; C_2F_6, 15% hexafluoroethane gas; *Sil 5000*, silicone oil 5000

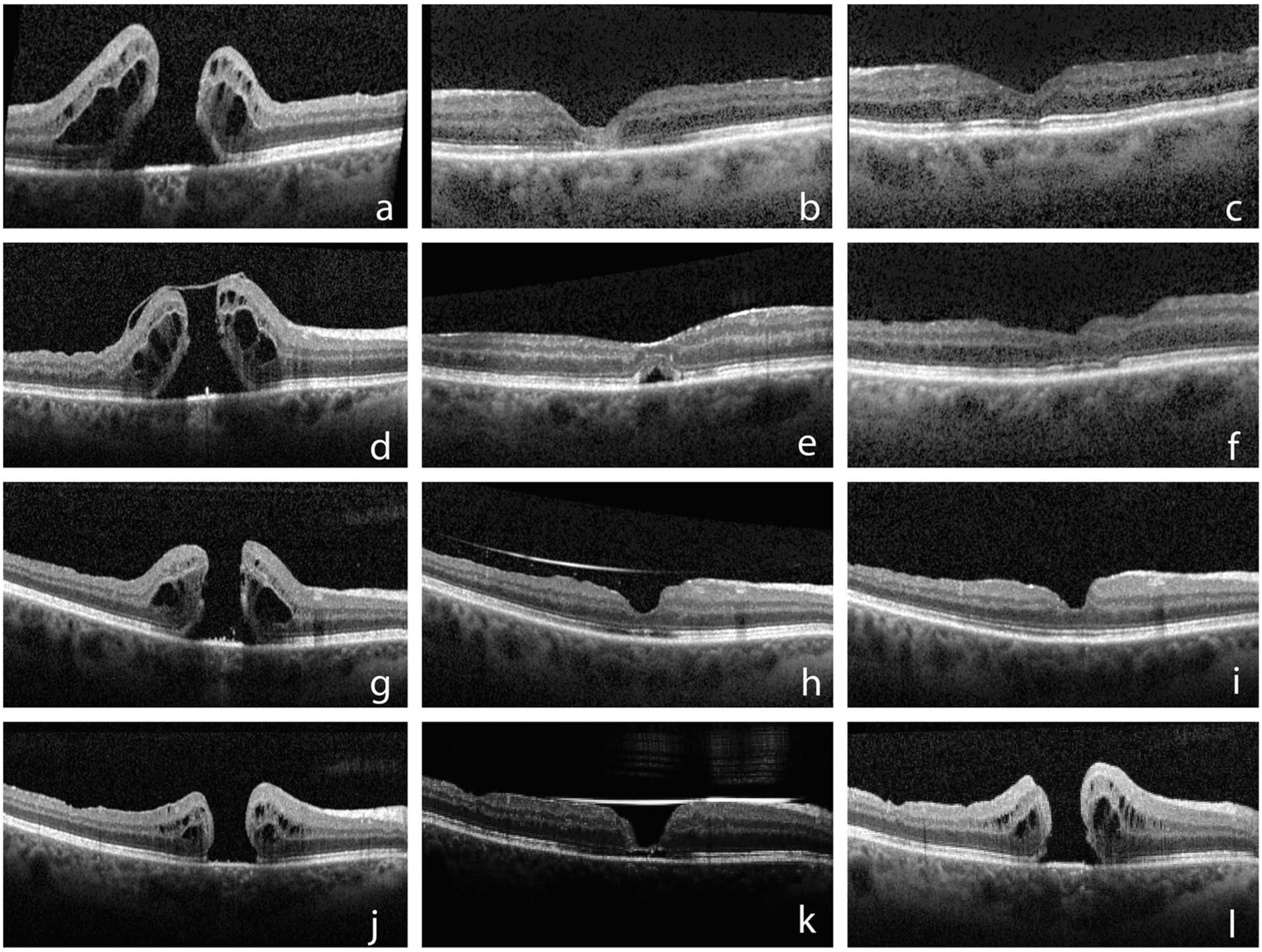

Fig. 1 OCT examples of group 1 with tamponade only. C2F6 tamponade preoperatively (**a**), after 4 months (**b**) and after 16 months (**c**) with good restoration of ellipsoid zone and 6-line improvement. Silicone oil 5000 tamponade preoperatively (**d**, note the inverted ILM flap from previous surgery), before (**e**) and after (**f**) silicone oil release with anatomic closure, but only 1-line improvement. Heavy silicone oil tamponade (Densiron) preoperatively (**g**), before (**h**), and after (**i**) silicone oil release with full restoration of ellipsoid zone and 8-line improvement. Example of heavy silicone oil tamponade (**j**) with incomplete closure (**k**) and reopening after silicone oil removal (**l**)

than group 1 (see Table 4, Fig. 4). A higher anatomic success rate was shown for group 1 with tamponade alone (84.2%) compared to that for group 2 with adjuvant manipulation (77.8%), albeit this was not statistically significant ($p = 0.682$). The final VA was higher in group 1 (LogMAR 0.67 ± 0.39) compared to that in group 2 (LogMAR 0.86 ± 0.38, $p = 0.030$). However, when comparing only large holes (> 500 µm), there was no difference in final VA

Table 3 Structural and functional outcome depending on manipulation techniques (n = 36)

	f-ILM (n = 12)	SRF-Appl (n = 12)	EAM (n = 7)	Free retina (n = 2)	AB-Appl (n = 3)	*p*-value
Mean (SD) MLD preoperative in µm	468 ± 106	606 ± 168	494 ± 210	964 ± 180	464 ± 61	< 0.001
Anatomical success of MH closure (complete/atrophic) (n = 23/5)	75% (9/0)	75% (8/1)	100% (5/2)	50% (0/1)	66.7% (1/1)	0.131
Mean (SD) postoperative VA in logMAR	0.75 ± 0.4	0.92 ± 0.41	0.86 ± 0.41	1.15 ± 0.21	0.9 ± 0.26	0.224
Mean (SD) line improvement of VA	3.9 ± 4.8	2.2 ± 4.1	3.3 ± 2.8	0	2.3 ± 1.5	0.707

MLD, minimum linear diameter; *MH*, macular hole; *VA*, visual acuity; *LogMAR*, logarithm of the minimum angle of resolution; *f-ILM*, free ILM flap translocation; *SRF-Appl*, subretinal fluid application; *EAM*, epiretinal amniotic membrane; *Free Retina*, free retina flap; *AB-Appl*, application of autologous blood

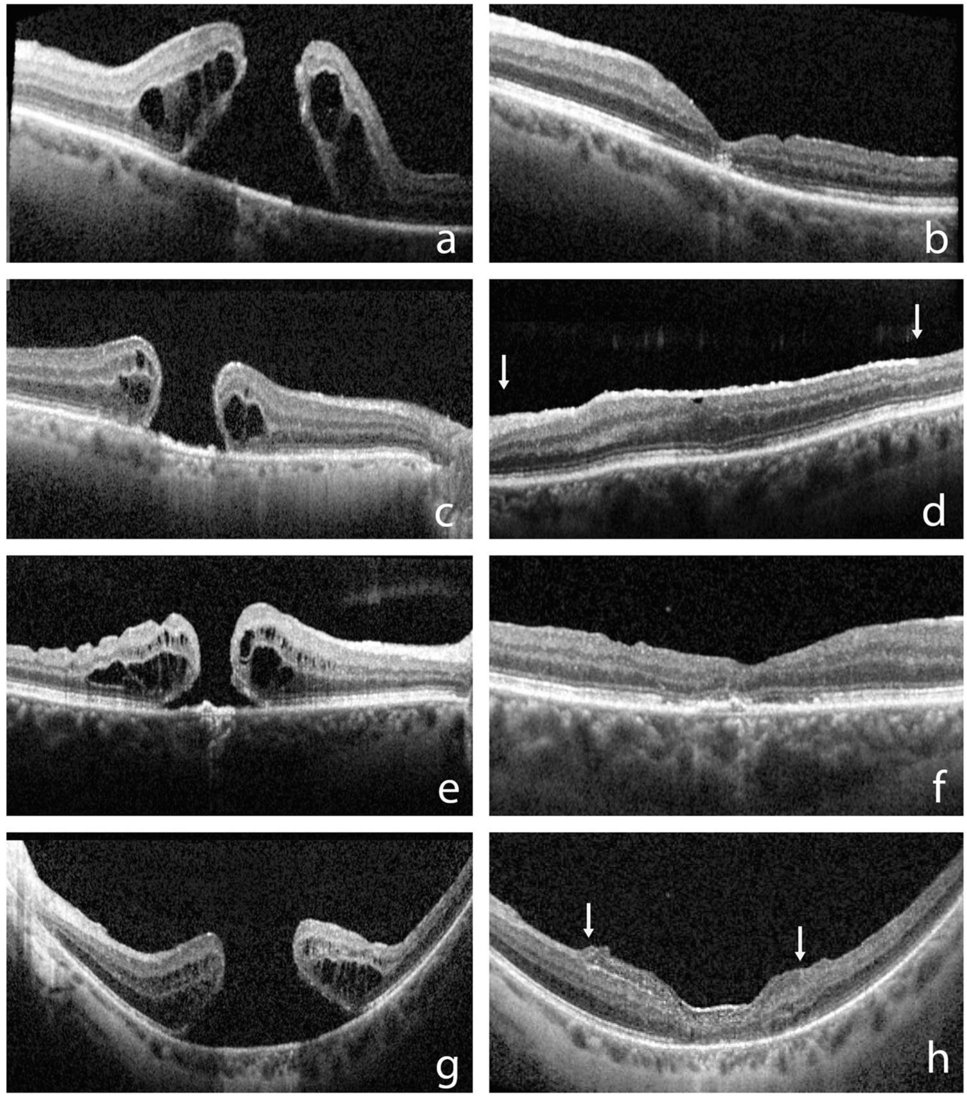

Fig. 2 OCT examples of group 2 with additional adjuvant manipulation techniques. Free ILM flap transplantation preoperatively (**a**) and after 7 months (**b**) with 2-line improvement, but still deranged ellipsoid zone (ILM flap still visible subretinally). Amniotic membrane transplantation before (**c**) and after 4 months (**d**) with 6-line improvement and restored external limiting membrane (arrows mark the edges of the epiretinal amniotic membrane). Induced macular detachment before (**e**) and after 8 months (**f**) with 2-line visual loss despite anatomical success (note the deranged foveal architecture and pigment epithelium clumping). Free retina transplantation before (**g**) and after 2 months (**h**) without visual change despite anatomical closure (arrows mark the edges of the transplanted retina flap)

($p = 0.254$) or anatomic success ($p = 0.490$) between the groups.

Discussion

This large single-center study on surgical revision of idiopathic pMHs could show an anatomical closure rate of 81%, with a mean VA improvement of 3.5 lines. Comparing tamponades with or without adjuvant manipulation techniques, neither advantage for new adjuvant manipulation techniques over tamponades nor advantage for any particular tamponade for visual acuity or anatomic closure of pMH could be determined.

Our results are in accordance to published literature [3]. In a fixed-effects meta-analysis model comprising 520 eyes from 22 studies, the pooled estimates for anatomical closure of persistent MHs were 78% [4]. However, these study cohorts included only a small number of patients (mean $n = 20$) and showed a considerable variation between 49 and 89% success [19, 24–29].

Anatomic closure or even restoration of the foveal architecture is more difficult to achieve in pMHs and may result in an atrophic closure in up to 29% [26, 28]. Interestingly, we found no correlation between initial pMH size and atrophic closure.

Despite a good anatomical closure rate, only 33% of our patients achieved reading vision and 51% obtained 3-line improvement, which is similar to other studies [10, 27, 28]. A recent meta-analysis reported the weighted mean improvement at 2.5 lines [4]. Incomplete ellipsoid zone (EZ) restoration might explain the limited functional recovery in many cases of successful closure [30, 31].

Age, initial hole size, and myopia could not be identified as additional risk factors for an unfavorable outcome.

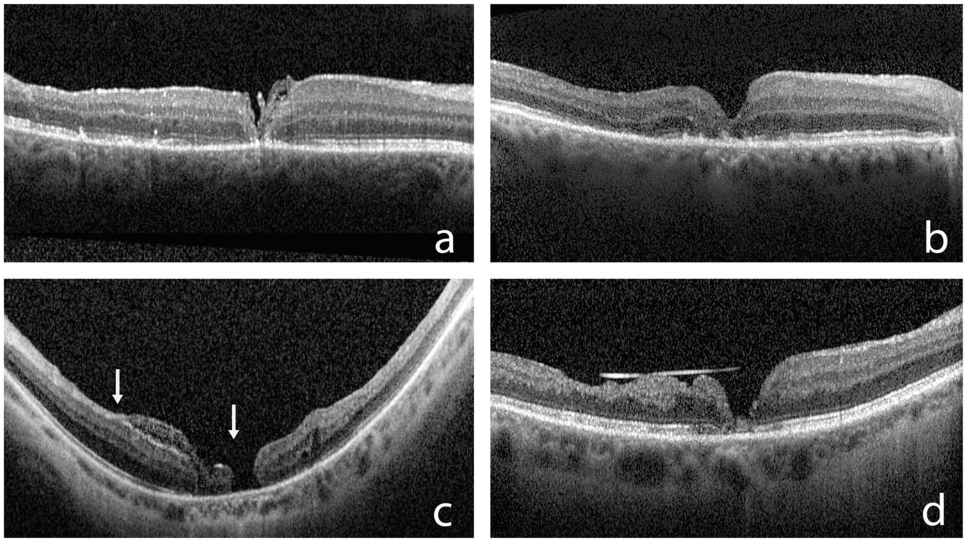

Fig. 3 OCT examples of typical findings of clinical relevance. Free ILM flap (**a**) is visible up to 2 months with beginning bridging of glial tissue. In later stages, the ILM flap becomes completely resolved. (**b**) Induced macular detachment shows typical pigment epithelium clumping and deranged ellipsoid zone with poor visual improvement despite an acceptable closure rate even in very large MH. (**c**) Free retina transplant shows necrotic melting of the graft after 6 months without any signs of glial bridging and poor visual results (arrows mark the edges of the graft). (**d**) Heavy silicone oil tamponade (Densiron) often results in only atrophic MH closure with moderate visual improvement

This is consistent with studies on primary surgery [4] but was not yet confirmed for revision surgery on pMH.

The best surgical approach or the ideal choice of tamponade is still under debate. A recent meta-analysis showed that a longer-acting tamponade is preferred for persistent MHs (air 0.2%, SF6 15%, C2F6 15%, C3F8 48%, silicone oil 11%) [4]. We could not confirm this in the present study due to the comparable anatomical success rate and visual gain between the different tamponades. However, possibly, short-acting gas tamponade SF6, which showed an anatomical success of 91%, may be sufficient to adhere MH edges, but cannot sufficiently promote bridging of the fovea and restoration of the ellipsoid zone [32].

The silicone oil tamponade Densiron showed a more frequent atrophic closure and foveal architecture remained deranged. This is consistent with other studies that could not show silicone oils to be advantageous [24, 33, 34]. Only two studies with Densiron showed an exceptionally high anatomical and functional success rate [23, 35].

Evaluating new adjuvant manipulation techniques to approximate and bridge the pMH edges could reveal that free ILM flaps and epiretinal amniotic membrane grafts showed a high rate of complete closure and high VA gains of 3.9 and 3.3 lines. We obtained a high anatomical and functional success rate of epiretinal amniotic membrane with a rapid restoration of the foveal architecture and EZ. Furthermore, autologous free ILM grafts obtained reading vision in 42%. In comparison to published literature, autologous ILM graft transplants of 30 eyes in 3 studies showed a high closure rate, but rather moderate visual improvement [8–10]. Only 17% reached a final VA of ≥ 20/63 [10].

While a large number of small case series with promising data are available, there is only one comparative multicenter study, suggesting that an ILM flap and nerve fiber

Table 4 Comparison of structural and functional outcomes of groups 1 and 2

	Group 1, no manipulation (n = 38)	Group 2, with manipulation (n = 36)	*p*-value
Mean (SD) MLD preoperative in µm	415 ± 205	546 ± 188	0.005
Anatomical success of MH closure (complete/atrophic) (n = 51/9)	84.2% (28/4)	77.8% (23/5)	0.682
Mean (SD) VA postoperative in logMAR	0.67 ± 0.39	0.86 ± 0.38	0.030
Mean (SD) line improvement of VA	2.6 ± 3.3	2.9 ± 3.9	0.744

MLD, minimum linear diameter; *MH*, macular hole; *VA*, visual acuity; *LogMAR*, logarithm of the minimum angle of resolution

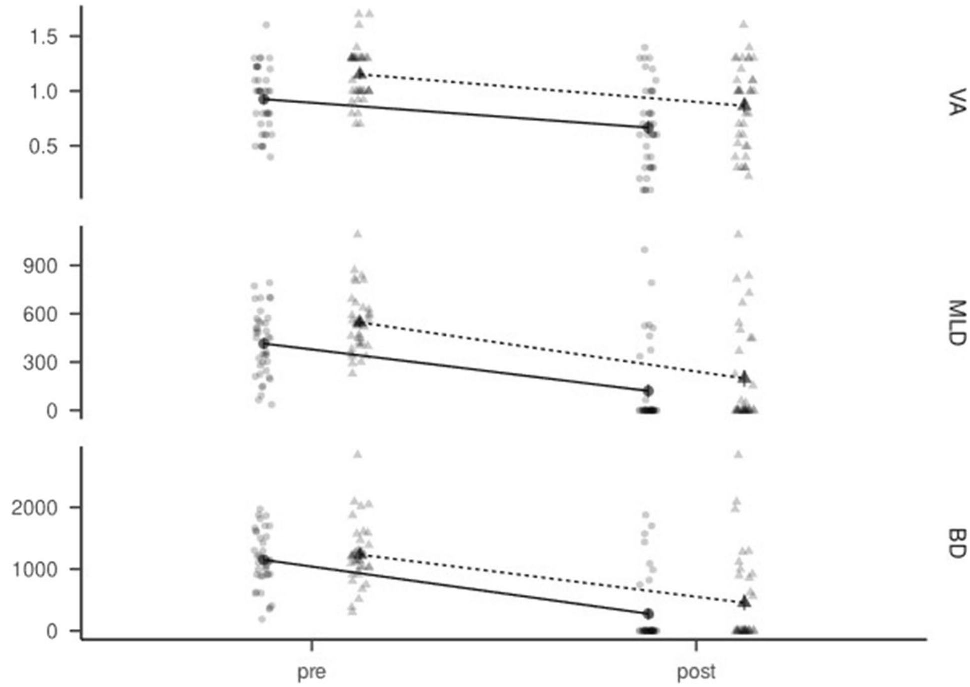

Fig. 4 Comparison analysis between group 1 and group 2. Visual acuity (VA), minimum linear diameter (MLD), base diameter (BD) before and after revisional persistent macular hole surgery separated by group 1 (without manipulation, solid line, and circles) and group 2 (with manipulation, dashed line, and rectangles). Gray points and rectangles in the background show individual values; black points and lines indicate mean and 95% CI (standard error)

layer incisions might be more effective in the treatment of idiopathic pMH [3].

Induced macular detachment by application of subretinal fluid has been described to release adhesions between the retracted retina and adjacent retinal pigment epithelium and may approximate the edges of even very large holes [13]. Previous studies have described a satisfying hole closure rate, but only a moderate increase in visual acuity [13, 36]. The largest study reported a 2.2-line improvement [13]. This is consistent with our study. As a possible explanation for the below-average visual improvement, we found parafoveal RPE clumping in the postoperative OCT. This may suggest that induced macular detachment causes a relevant stress on the RPE and outer retina [37].

The poorest anatomical closure rate was achieved in eyes with autologous blood and free retina flap, but due to the small sample size, the relevance is limited. However, it is noticeable that both free retina grafts melted away within a few weeks without any signs of bridging or glial cell healing leading to poor final vision. Although a recent study with 41 patients reported a high anatomical closure rate, merely poor visual increase was observed [17].

Our data show that the new adjuvant manipulation techniques with the aim of promoting centripetal hole closure are not advantageous over tamponade alone. Even though tamponade alone had superior anatomic closure and VA outcomes compared to tamponade with adjuvant manipulation, these results should be interpreted with caution, as the initial MLD and BD compromise the statistical readout. Also, the surgeons may have been more likely to use adjuvant techniques because of the larger diameter of the pMH. However, it is noteworthy that the new techniques did not appear to contribute any discernible added value. This might be explained by the surgical learning curve and higher manipulation of retinal tissue compared to tamponade alone. In fact, we found parafoveal RPE clumping more frequently in postoperative OCT, although the rate of atrophic closure did not differ.

The limitations of the study were the retrospective nature, the therefore resulting lack of randomization, and the limited number of patients included. Therefore, the statistical significance, especially in the subgroups, is limited. Although multiple experienced surgeons were involved, this is to date the largest single-center study that allowed a preliminary subgroup analysis. However, more future comparative studies are needed to identify the best surgical maneuver for persistent MH.

In conclusion, we can show in a large patient collective that surgical revision of persistent MHs offers an acceptable anatomic and functional success rate. However, only one-third of patients achieve reading vision. Although silicone oil has a high anatomical success rate, functional improvement is poor, mainly due to the high number of atrophic closures. Due to the comparable closure rate and visual improvement, the use of a gas tamponade seems to be sufficient in most cases. Furthermore, new adjuvant manipulation techniques with the aim of promoting centripetal hole closure do not seem to bring a significant advantage over tamponade alone. However, it should be further investigated whether adjuvant techniques could have an advantage in a larger cohort.

Author contribution Conceptualization: Peter Szurman; methodology: Peter Szurman; formal analysis and investigation: Philip Wakili, Peter Szurman, Rudolf Siegel, Annekatrin Rickmann, and Boris Stanzel; writing—original draft preparation: Peter Szurman and Annekatrin Rickmann; writing—review and editing: Boris Stanzel, Rudolf Siegel, Annekatrin Rickmann, and Karl Boden.

Rudolf Siegel conducted the statistical analysis.

All authors have approved the submitted version.

Data availability All data are within the manuscript.

Code availability Not applicable.

Declarations

Ethics approval The study was approved by the Ethics Committee of the Medical Association of Saarland (Nr. 243/14) and adheres to the tenets of the Declaration of Helsinki.

Consent to participate All information is anonymized and the submission does not include images that may identify a person.

Consent for publication Informed consent was obtained.

Competing interests The authors declare no competing interests.

References

1. Haritoglou C, Gass CA, Schaumberger M, Gandorfer A, Ulbig MW, Kampik A (2002) Long-term follow-up after macular hole surgery with internal limiting membrane peeling. Am J Ophthalmol 134:661–666
2. Spiteri Cornish K, Lois N, Scott NW, Burr J, Cook J, Boachie C, Tadayoni R, La Cour M, Christensen U, Kwok AKH (2014) Vitrectomy with internal limiting membrane peeling versus no peeling for idiopathic full-thickness macular hole. Ophthalmology 121:649–655
3. Maguire MJ, Steel DH, Yorston D, Hind J, El-Faouri M, Jalil A, Tyagi P, Wickham L, Laidlaw AH (2020) Outcome of revision procedures for failed primary macular hole surgery. Retina (Philadelphia, Pa.) https://doi.org/10.1097/IAE.0000000000003072. Epub ahead of print
4. Reid GA, McDonagh N, Wright DM, Yek JTO, Essex RW, Lois N (2020) First failed macular hole surgery or reopening of a previously closed hole: do we gain by reoperating?-A systematic review and meta-analysis. Retina 40:1–15
5. Michalewska Z, Michalewski J, Adelman RA, Nawrocki J (2010) Inverted internal limiting membrane flap technique for large macular holes. Ophthalmology 117:2018–2025
6. Michalewska Z, Michalewski J, Dulczewska-Cichecka K, Adelman RA, Nawrocki J (2015) Temporal inverted internal limiting membrane flap technique versus classic inverted internal limiting membrane flap technique: a comparative study. Retina 35:1844–1850
7. Morizane Y, Shiraga F, Kimura S, Hosokawa M, Shiode Y, Kawata T, Hosogi M, Shirakata Y, Okanouchi T (2014) Autologous transplantation of the internal limiting membrane for refractory macular holes. Am J Ophthalmol 157:861-869.e1
8. Dai Y, Dong F, Zhang X, Yang Z (2016) Internal limiting membrane transplantation for unclosed and large macular holes. Graefe's Arch Clin Exp Ophthalmol 254:2095–2099
9. Ozdek S, Baskaran P, Karabas L, Neves PP (2017) A modified perfluoro-n-octane-assisted autologous internal limiting membrane transplant for failed macular hole reintervention: a case series. Ophthalmic Surg Lasers Imaging Retina 48:416–420
10. Pires J, Nadal J, Gomes NL (2017) Internal limiting membrane translocation for refractory macular holes. Br J Ophthalmol 101:377–382
11. Szigiato A-A, Gilani F, Walsh MK, Mandelcorn ED, Muni RH (2016) Induction of macular detachment for the treatment of persistent or recurrent idiopathic macular holes. Retina 36:1694–1698
12. Gurelik G, Sul S, Kılıç G, Özsaygılı C (2017) A modified foveal advancement technique in the treatment of persistent large macular holes. Ophthalmic Surg Lasers Imaging Retina 48:793–798
13. Meyer CH, Szurman P, Haritoglou C, Maier M, Wolf A, Lytvynchuk L, Priglinger S, Hillenkamp J, Wachtlin J, Becker M, Mennel S, Koss MJ (2020) Application of subretinal fluid to close refractory full thickness macular holes: treatment strategies and primary outcome: APOSTEL study. Graefe's Arc Clin Exp Ophthalmol 258:2151–2161
14. Rizzo S, Caporossi T, Tartaro R, Finocchio L, Franco F, Barca F, Giansanti F (2019) A human amniotic membrane plug to promote retinal breaks repair and recurrent macular hole closure. Retina 39(Suppl 1):S95–S103
15. Moharram HM, Moustafa MT, Mortada HA, Abdelkader MF (2020) Use of epimacular amniotic membrane graft in cases of recurrent retinal detachment due to failure of myopic macular hole closure. Ophthalmic Surg Lasers Imaging Retina 51:101–108
16. Thomas AS, Mahmoud TH (2018) Subretinal transplantation of an autologous retinal free flap for chronic retinal detachment with proliferative vitreoretinopathy with and without macular hole. Retina 38(Suppl 1):S121–S124
17. Grewal DS, Charles S, Parolini B, Kadonosono K, Mahmoud TH (2019) Autologous retinal transplant for refractory macular holes: Multicenter International Collaborative Study Group. Ophthalmology 126:1399–1408
18. Korobelnik J-F, Hannouche D, Belayachi N, Branger M, Guez J-E, Hoang-Xuan T (1996) Autologous platelet concentrate as an adjunct in macular hole healing. Ophthalmology 103:590–594
19. Purtskhvanidze K, Frühsorger B, Bartsch S, Hedderich J, Roider J, Treumer F (2018) Persistent full-thickness idiopathic macular hole: anatomical and functional outcome of revitrectomy with autologous platelet concentrate or autologous whole blood. Ophthalmologica. Journal international d'ophtalmologie. International journal of ophthalmology. Zeitschrift fur Augenheilkunde 239:19–26
20. Jonas JB, Jäger M (2003) Perfluorohexyloctane endotamponade for treatment of persisting macular hole. Eur J Ophthalmol 13:103–104
21. Oz O, Akduman L (2003) Successful surgical repair and good visual outcome of a recurrent macular hole of seven years duration. Eur J Ophthalmol 13:588–589
22. Lappas A, Foerster AMH, Kirchhof B (2009) Use of heavy silicone oil (Densiron-68) in the treatment of persistent macular holes. Acta Ophthalmol 87:866–870
23. Rizzo S, Genovesi-Ebert F, Vento A, Cresti F, Miniaci S, Romagnoli MC (2009) Heavy silicone oil (Densiron-68) for the treatment of persistent macular holes: Densiron-68 endotamponade for persistent macular holes. Graefe's Arch Clin Exp Ophthalmol 247:1471–1476
24. Hillenkamp J, Kraus J, Framme C, Jackson TL, Roider J, Gabel V-P, Sachs HG (2007) Retreatment of full-thickness macular hole: predictive value of optical coherence tomography. Br J Ophthalmol 91:1445–1449
25. D'Souza MJJ, Chaudhary V, Devenyi R, Kertes PJ, Lam W-C (2011) Re-operation of idiopathic full-thickness macular holes

after initial surgery with internal limiting membrane peel. Br J Ophthalmol 95:1564–1567
26. Rao X, Wang N-K, Chen Y-P, Hwang Y-S, Chuang L-H, Liu I-C, Chen K-J, Wu W-C, Lai C-C (2013) Outcomes of outpatient fluid-gas exchange for open macular hole after vitrectomy. Am J Ophthalmol 156:326-333.e1
27. Patel R, Gopalakrishnan M, Rajesh B, Giridhar A (2017) Post-vitrectomy macular hole undergoing delayed closure after 28 months. Indian J Ophthalmol 65:882–884
28. Vishal MY, Babu N, Kohli P, Rajendran A, Ramasamy K (2018) Retrospective study of changes in ocular coherence tomography characteristics after failed macular hole surgery and outcomes of fluid-gas exchange for persistent macular hole. Indian J Ophthalmol 66:1130–1135
29. Yek JTO, Hunyor AP, Campbell WG, McAllister IL, Essex RW (2018) Outcomes of eyes with failed primary surgery for idiopathic macular hole. Ophthalmology Retina 2:757–764
30. Kitaya N, Hikichi T, Kagokawa H, Takamiya A, Takahashi A, Yoshida A (2004) Irregularity of photoreceptor layer after successful macular hole surgery prevents visual acuity improvement. Am J Ophthalmol 138:308–310
31. Baba T, Yamamoto S, Arai M, Arai E, Sugawara T, Mitamura Y, Mizunoya S (2008) Correlation of visual recovery and presence of photoreceptor inner/outer segment junction in optical coherence images after successful macular hole repair. Retina 28:453–458
32. Itoh Y, Inoue M, Rii T, Hiraoka T, Hirakata A (2012) Significant correlation between visual acuity and recovery of foveal cone microstructures after macular hole surgery. Am J Ophthalmol 153:111–9.e1
33. Nowroozzadeh MH, Ashraf H, Zadmehr M, Farvardin M (2018) Outcomes of light silicone oil tamponade for failed idiopathic macular hole surgery. J Ophthalmic Vis Res 13:130–137
34. Schaub F, Gözlügöl N, Goscinski C von, Enders P, Heindl LM, Dahlke C (2020) Outcome of autologous platelet concentrate and gas tamponade compared to heavy silicone oil tamponade in persistent macular hole surgery. Eur J Ophthalmol:1120672120903704
35. Cillino S, Cillino G, Ferraro LL, Casuccio A (2016) TREATMENT OF PERSISTENTLY OPEN MACULAR HOLES WITH HEAVY SILICONE OIL (DENSIRON 68) VERSUS C2F6. A PROSPECTIVE RANDOMIZED STUDY. Retina 36:688–694
36. Fotis K, Alexander P, Sax J, Reddie I, Kang CY, Chandra A (2019) Macular Detachment for the Treatment of Persistent Full-Thickness Macular Holes. Retina 39(Suppl 1):S104–S107
37. Szurman P, Roters S, Grisanti S, Aisenbrey S, Schraermeyer U, Lüke M, Bartz-Schmidt KU, Thumann G (2006) Ultrastructural changes after artificial retinal detachment with modified retinal adhesion. Invest Ophthalmol Vis Sci 47:4983–4989