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Review

FIRST FAILED MACULAR HOLE SURGERY OR REOPENING OF A PREVIOUSLY CLOSED HOLE

Do We Gain by Reoperating?—A Systematic Review and Meta-analysis

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Purpose: To evaluate repeated surgery for idiopathic full-thickness macular hole that failed to close (FTC) after first surgery or reopened (RO) once originally closed.

Methods: Systematic review and meta-analysis. Pubmed.gov and Cochrane Library were searched for studies in English presenting outcomes of idiopathic full-thickness macular hole that FTC or RO (case reports/series of <5 cases excluded).

Outcome Measures: Anatomical closure, postoperative best-corrected visual acuity, intraoperative/postoperative complications, and patient-reported outcomes. Meta-analysis was performed on aggregate and available individual participant data sets using the *metafor* package in R.

Results: Twenty-eight eligible studies were identified. After reoperation, pooled estimates for anatomical closure were 78% (95% confidence interval 71–84%) and 80% (95% confidence interval 66–89%) for FTC and RO groups, respectively. On average, best-corrected visual acuity improved in both groups. However, only 15% (28 of 189 eyes) of FTC eyes achieved best-corrected visual acuity of ≥6/12. The pooled estimated probability of ≥2-line best-corrected visual acuity improvement was 58% in the FTC group (95% confidence interval 45–71%); meta-analysis was not possible in the RO group. The most common complication was cataract.

Conclusion: Reoperation for FTC or RO idiopathic full-thickness macular hole achieved a clinically meaningful visual acuity improvement in more than half of patients; high levels of vision (≥6/12), however, were uncommon.

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An idiopathic full-thickness macular hole (iFTMH) represents a defect of all neurosensory retinal layers involving the fovea and can result in metamorphopsia and reduced central vision.[1] The Beaver Dam Study found an FTMH prevalence of 0.3% in the population; the risk increased with age with a prevalence of 0.7% among persons aged 75 years and older and zero prevalence in the 43- to 54-year age group.[2] Optical coherence tomography–guided examination at 20-year follow-up of the Beaver Dam population found an FTMH prevalence of 0.4%.[3] There is greater incidence among women with a population-based study finding an incidence of 10.9 per 100,000 population per year in women compared with 4.3 per 100,000 population per year in men.[4]

Idiopathic full-thickness macular holes result from changes at the vitreomacular interface, which, in turn, lead to perifoveal cortical vitreous traction.[5] Clinical observations based on slit-lamp examination allowed Gass[6] to classify iFTMHs in four stages, based on the size of the macular hole and the status of the posterior vitreous, whether attached or detached. Using optical coherence tomography, the International Vitreomacular Traction Study Group proposed a classification for macular holes in terms of size (i.e., small, medium, or large), presence or absence of vitreomacular traction, and cause (primary [idiopathic] or secondary [subsequent to other anomalies, such as myopia or after trauma]).[7]

If untreated, most iFTMHs will progress in size and grade with increasing central visual loss.[8] Closure of FTMHs surgically was first described by Kelly and Wendel[9] who in 1991 aimed to reattach the retina around the macular hole by performing pars plana vitrectomy, peeling of epiretinal membranes at the macula, gas tamponade, and face-down positioning for 1 week after surgery. In subsequent years, internal limiting membrane (ILM) peeling gained popularity as an adjuvant maneuver to macular hole surgery (reviewed by Abdelkader and Lois[10]). Internal limiting membrane peeling is now used routinely for the treatment of most iFTMH; a systematic review and individual participant data (IPD) meta-analysis demonstrated superiority of ILM peeling versus no peel for the treatment of iFTMHs of any size both in terms of macular hole closure and visual acuity improvement.[11,12] Thus, ILM peeling increased the odds of primary and final macular hole closure (odds ratio 9.27, 95% confidence interval [CI] 4.98–17.24 and odds ratio 3.99, CI 1.63–9.75, respectively); this applied to any stage of macular hole, from 2 to 4.[11,12] The chance for an improvement in best-corrected visual acuity (BCVA) at 3 months after surgery was also increased by peeling the ILM (mean difference −0.09, 95% CI −0.17 to −0.02). Differences in BCVA were not observed at 6 or 12 months; this, however, could be explained by the fact that most patients in the no ILM peel group would have received by then ILM peeling given that, following ethical considerations and standard clinical practice, ILM peeling was allowed in the nonpeel group in all randomized controlled trials included if the hole had not closed following the primary procedure. Only one study included in this systematic review and IPD meta-analysis evaluated near vision[13]; this study did not find differences in near vision between ILM peeling and no peel groups.

Published rates of macular hole closure following a primary surgical procedure range from 70% to 100%.[10,13–16] A study using data from the national U.K. electronic database[17] found that over an 8-year period, further vitreoretinal surgery had been undertaken in 4.2% of primary macular hole repairs. Furthermore, it has been recognized that iFTMHs which initially closed after the primary surgery may later reopen.[18] For patients in whom primary macular hole closure failed and for those in whom macular hole reopening occurs, repeated surgery could be considered.

The aim of this study was to systematically review available evidence on functional and anatomical outcomes after repeated surgery 1) after primary surgical failure and 2) after initial closure and subsequent macular hole reopening. This information would be useful to clinicians for the counseling of patients before repeated surgery and for patients to make informed decisions with regards to proceeding with further treatment.

Methods

Study Eligibility Criteria, Definitions, and Outcome Measures

All study designs were considered eligible for studies presenting outcomes of reoperation, whichever the procedure, for iFTMH that failed to close (FTC) following the primary procedure or that initially closed but later reopened (RO), with the exception of case reports and small case series including less than five cases. Only articles in English were eligible for inclusion. Studies presenting data on both FTC and RO iFTMHs were included only if separate data for these two groups were provided. Studies evaluating outcomes of non-iFTMHs (e.g., traumatic, myopic, etc) were excluded. Studies presenting data with both non-iFTMHs and iFTMHs were included only if data on the iFTMH group were provided separately. Abstracts of unpublished studies were not included.

For the purpose of this review, macular hole closure was defined as full closure of the macular hole with complete apposition of the hole margins. Flattening of

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the cuff of subretinal fluid around the hole alone was not considered hole closure if there was still a neurosensory retinal defect present. Studies in which this definition of macular hole closure was not used were excluded (e.g., the following studies; Ezra et al, Christmas et al, and Lappas et al).[19–21]

The following outcomes were determined: 1) anatomical success rate after secondary surgery, defined as complete apposition of the macular hole margins with no remaining neurosensory retinal defect; 2) postoperative BCVA and BCVA improvement comparing presecond surgery and final BCVA values; 3) any reported intraoperative and postoperative complications; and 4) any patient-reported outcomes (PROs). Outcomes were measured at 6, 12, 18, and ≥24 months (as available); a window of ±3 months was allowed for each time point. Best-corrected visual acuity values were transformed to the LogMAR scale where necessary for analysis.

Search Strategy

Systematic searches were conducted in PubMed (1946–2018) and Cochrane Library databases (1999–2018) with no date restrictions (latest search updated January 1, 2018). Two literature searches were conducted to identify studies of 1) iFTMHs that FTC following the primary procedure (FTC group) and 2) iFTMHs that initially closed but reopened thereafter (RO group).

Search terms combined the following key words

1. To identify iFTMHs that FTC after primary surgery: "Macular hole" AND "Persistent" Or "Refractory" "Macular hole surgery" and "Primary failure" "Failure of macular hole surgery" "Idiopathic full-thickness macular hole" AND "persistent," "Gas injection" and "Macular hole surgery failure," "Primary macular hole" AND "Vitrectomy" AND "Surgical failure" "Primary macular hole" AND "Reoperation" AND "Vitrectomy" "Macular hole" AND "Resurgery" "Primary macular hole" AND "Vitrectomy" AND "Reoperation" "Unclosed macular hole" AND "Reoperation" "Persistent" AND "macular hole" AND "Vitrectomy";
2. To identify iFTMHs that initially closed but reopened after primary surgery: "Reopened macular hole" "Reopened macular hole" AND "Vitrectomy" AND "Reoperation" "Primary macular hole" AND "Vitrectomy" AND "Failure" "Primary macular hole" AND "Reopen" AND "Surgery" "Reopened macular hole" AND "Reoperation" AND "Successful Repair" "Macular hole" AND "Initial closure" AND "Vitrectomy" "Primary macular hole" AND "Surgery" AND "Reoperation" "Macular hole surgery" AND "Initial success" AND "Repair" "Primary macular hole" AND "Surgery" AND "Recurrence."

Reference lists of identified studies were also reviewed; additional relevant studies identified were also included.

Selection of Studies and Data Extraction

One reviewer (N.M.) conducted searches and examined studies for eligibility, and subsequently, a second reviewer (G.A.R.) repeated the searches and consideration of eligibility; a librarian experienced with undertaking systematic searches provided guidance, training, and support to these reviewers. A third investigator (N.L.) was consulted regarding disagreements which were solved through discussion. Thus, two reviewers (G.A.R. and N.M.) independently reviewed the titles identified, and articles were classified as ineligible or potentially eligible; duplicate articles were removed. Reviewers obtained and screened abstracts of potentially eligible studies in a similar manner, classifying them as ineligible or potentially eligible. Three reviewers (G.A.R., N.M., and N.L.) obtained and reviewed full-text articles of potentially eligible studies. Full-text articles presenting studies that did not meet the inclusion criteria were excluded.

One reviewer (G.A.R. or N.M.) extracted the following data from included studies, and a second reviewer (N.L.) corroborated these data: author/year of publication, study design, number of patients receiving intervention, patient demographics (age and sex), characteristics of the iFTMHs, details of both primary and repeated surgical procedure, proportion of eyes with anatomical closure after repeated surgery and mean BCVA preoperatively and postoperatively. Information on number and type of intraoperative and postoperative complications, as well as PRO scores, where available, was also recorded at the follow-up intervals set in the outcomes section below.

We contacted the authors of two of the largest series identified (Valldeperas and Wong and Yek et al)[22,23] to enquire about the availability of IPD and their willingness to share it for the purpose of this review.

We categorized studies investigating outcomes after reintervention for iFTMHs as either those addressing iFTMH that FTC or those addressing iFTMH that RO after initial closure.

No detailed assessment of the quality of identified studies (e.g., using the Cochrane Risk of Bias Tool) was undertaken for the purpose of this review.

Data Synthesis and Analysis

Two types of data were available for synthesis: aggregate data consisting of summary statistics reported in the reviewed studies and IPD either extracted from reviewed studies or subsequently obtained from study authors. IPD was used in preference to aggregate data wherever possible, so that the influence of several covariates that varied within studies (follow-up duration and ILM peeling at first and second surgeries) on outcomes could be assessed.

Two outcomes were considered for meta-analysis: anatomical closure of iFTMHs and visual acuity. There was considerable variation in BCVA preoperatively and postoperatively among studies, and Standard Deviations (SD) for changes in BCVA were often unreported. Therefore, a binary indicator of improvement in BCVA by two or more Snellen lines or equivalent (i.e., 10 letters, 0.2 LogMAR) was used as the visual acuity outcome.

For the FTC group, an initial analysis was conducted to determine whether either outcome was associated with follow-up duration or whether ILM peeling was conducted at either or both surgeries. Meta-regressions were conducted using IPD alone because it provides greater statistical power to detect patient-level associations. This was particularly relevant for follow-up duration as mean values demonstrated considerable variation within studies (Table 1). These models revealed no statistically significant associations between visual acuity or anatomical hole closure and any of the following covariates: follow-up duration, ILM peeling at first surgery, ILM peeling at second surgery (data not shown, available on request). Therefore, simple intercept only models were selected for the main analysis. For the meta-analysis, measurements at the point at which they were reported (e.g., 6, 12 months, etc.) were used. Follow-up time was not included in any of the final meta-analysis models (given the lack of evidence of associations in the aggregate or individual-level data between follow-up time and either of the outcomes of interest, as explained above).

Meta-analysis was conducted for each outcome combining both aggregate data and IPD. Summary statistics were calculated for each study reporting IPD, and all studies were included in a single model. Heterogeneity among studies was calculated using the I^2 statistic. Where there was evidence of high heterogeneity, a random-effects model was fitted; where heterogeneity was low, a fixed-effects model was used. Meta-analysis was performed using the *metafor* package in R version 3.4.[24]

Results

Literature Search

A total of 1,023 study titles were identified across both literature searches (Figure 1) (715 titles in the FTC group and 310 titles in the RO group; 2 titles were identified in both of literature searches and referred to 2 studies that presented data for both FTC and RO groups separately), and 977 titles (677 titles in FTC and 300 titles in RO) were excluded as duplicates or not relevant to the search criteria. Forty-six abstracts were retrieved as potentially eligible; eight abstracts were excluded as not meeting inclusion criteria. Two further articles from the group where iFTMH failed to close were identified through the reference lists when full articles were reviewed and one additional article was forwarded by the author just before its publication after presentation of some of the current work at a meeting. Thus, a total of 41 full-text articles (35 in FTC and 8 in RO, with 2 articles presenting data for both FTC and RO groups) were reviewed. Thirteen full-text articles (9 FTC and 4 RO) were excluded for the following reasons: case report of <5 cases; definition of FTMH closure did not meet criteria; results for FTC and RO groups not distinct; diagnosis other than iFTMHs; and not second FTMH procedure. Twenty-eight articles were eligible and included, dating from 1993 to 2017. Twenty-six studies were included in the FTC group, and four studies were included in the RO group (Figure 1). As stated above, two studies (Rao et al and Valldeperas and Wong) provided separate data for both the FTC group and RO groups and were included in both groups.[22,25]

In the FTC group, there was one randomized controlled trial[26] and one pilot study,[27] both of which were prospective and 24 case series, 3 of which were prospective and 21 retrospective (Table 1). The RO group consisted of four studies all of which were retrospective case series (Table 2).

The populations of included studies had an overall predominance of women versus men (313 vs. 149), with mean ages ranging from 60 to 75 years (weighted mean 68 years).

Outcomes: Failed to Close Group

Macular hole closure. Data on anatomical outcomes after repeat surgery to repair iFTMHs which FTC after the primary surgery were collected from 26 identified studies and included 520 eyes. Meta-analysis was conducted combining aggregate data (13 studies, 331 eyes)[22,25,26,28–37] and IPD (13 studies, 189 eyes).[23,27,38–48] There was moderate heterogeneity among studies (I^2 = 54.9), and so, a random-effects meta-analysis was used to estimate the proportion of patients with anatomical closure following a second surgical procedure. The pooled estimated proportion of macular holes that closed after repeat surgery in FTC eyes was 0.78 (95% CI 0.71–0.84, Figure 2).

The proportion of eyes with anatomical closure after repeated surgery ranged from 44% to 100% (weighted mean 75%, 389 of 520 eyes, 26 studies) (Table 1).

Table 1. Characteristics, Surgical Techniques and Outcome Measures for Studies Included in the FTC Group

Author/Year	Study design	Mean FTMH (μm)/Stage 3 and 4 (%)	No. of Second Surgery Eyes (Female/Male)*	ILM Peel at Initial Surgery	ILM Peel at Second Surgery	Tamponade Agent	Further Adjuvant	Posturing Days (Position)	Complications, n (%)
Ie et al (1993)[27]	Pro. series	NA/80	10 (NA)	No	No	C_3F_8	TGF-β	14 (p)	Cat prog: 9 (90)§, Cat sx: 4 (40)§
Johnson et al (1997)[44]	Retro. series	NA/70	23 (16/7)	No	No	C_3F_8	None	7–10 (p)	Cat prog: 10 (53)§, Cat sx: 5 (26)§, IOP rise: 1 (4)
Ikuno et al (1998)[41]	Retro. series	610 μm/100	11 (3/9)	No	No	SF_6	Laser	14 (p)	Cat prog: 5/6§
Imai et al (2005)[42]	Retro. series	NA/100	5 (3/2)	Yes	No	C_3F_8	None	7 (p)	IOP rise: 1 (20)
Hillenkamp et al (2007)[40]	Retro. series	560 μm/NA	28 (20/8)	Yes	No (ILM check)	SF_6 (54%) SO (43%) none (4%)	Auto plt (79%) blood (3%)	NA	RD: 3 (11)
Valldeperas and Wong (2008)[22]	Retro. series	NA	51 (37/14)	Yes (in 4%)	Yes (in 55%)	C_3F_8 (90%) SO (10%)	Auto plt (98%)	10–14 (p)	Cat sx: 30 (79)§
Saeed et al (2008)[47]	Retro. series	NA/100	5 (NA)	Yes	Yes (ILM extend)	Heavy SO	None	(s)	NA
Iwase et al (2008)[43]	Retro. series	NA/100	7 (5/2)	Yes	No	SF_6	None	1–11 (p)	IOP rise: 3 (43)
Rizzo et al (2009)[28]	Retro. series	560 μm/NA	23 (14/9)	Yes	No (ILM check)	Heavy SO	None	1 (s)	Cat sx: 2 (100)§, IOP rise: 3 (13)
D'Souza et al (2011)[29]	Retro. series	NA	21 (NA)	Yes	Yes (ILM extend)	C_3F_8	Auto serum (19%)	7 (p)	IOP rise: 17 (81)
Hejsek et al (2013)[30]	Retro. series	NA/100	6 (5/1)	Yes (in 83%)	Yes (ILM extend)	C_3F_8	None	7 (p)	NA
Rao et al (2013)[25]	Retro. series	NA/100	29 (NA)	Yes	No	C_3F_8 (78%) SF_6 (22%)	None	7 (p)	NA
Moisseiev et al (2013)[37]	Retro. series	801 μm/90	29 (21/8)	Yes (in 86%)	Yes (in 90%)	C_3F_8 SF_6	None	7 (p)	Cat sx: 3 (50)§ IOP rise: 1 (3)
Dimopolous et al (2016)[31]	Retro. series	494 μm/NA	27 (17/10)	Yes	No	Gas	Auto plt (100%)	NA	NA
Cillino et al (2016)[26]	RCT	711 μm/NA	21 (13/8)	Yes	No (ILM check)	C_3F_8 (48%) SO (52%)	None	3 (p) gas, 1 (s) SO.	IOP rise: 5 (24)
Pires et al (2016)[46]	Pro. series	655 μm/NA	12 (10/2)	Yes	No (ILM check)	C_3F_8	ILM autograft	Avoid s	None
Dai et al (2016)[39]	Pro. series	811 μm/NA	7 (5/2)	Yes	No	C_3F_8	ILM autograft	7 (p)	None
Chen et al (2016)[38]	Retro. series	805 μm/NA	9 (4/5)	Yes	No	C_3F_8 (56%) SF_6 (44%)	Lens capsule autograft	7–14 (p)	NA

(*continued on next page*)

Table 1. (*Continued*)

Author/Year	Study design	Mean FTMH (μm)/Stage 3 and 4 (%)	No. of Second Surgery Eyes (Female/Male)*	ILM Peel at Initial Surgery	ILM Peel at Second Surgery	Tamponade Agent	Further Adjuvant	Posturing Days (Position)	Complications, n (%)
Szigiato et al (2016)[48]	Retro. series	699 μm/NA	8 (5/3)	Yes	No (ILM check)	C_3F_8	Induced macular RD	7 (p)	None
Hagiwara et al (2017)[32]	Retro. series	814 μm/NA	9 (5/4)	Yes	Yes (ILM extend)	SF_6 (89%) air (11%)	None	NA	NA
Purtskhvan-dize et al (2017)[33]	Retro. series	470 μm/NA	74 (NA)	Yes	No	C_2F_6	Auto plt (81%) whole blood (19%)	2–3 (p)	RD: 1 (1)
Modi et al (2017)[34]	Retro. series	NA	9 (NA)	Yes	No	C_3F_8 (44%) SF_6 (56%)	None	(p)	NA
Patel et al (2017)[35]	Retro. series	809 μm/NA	25 (17/8)	Yes	No	C_3F_8	None	7 (p)	NA
Ozdek et al (2017)[45]	Retro. series	512 μm/NA	11 (7/4)	Yes	No (ILM check)	C_3F_8 (64%) SF_6 (36%)	ILM autograft	4–7 (p)	NA
Gurelik et al (2017)[36]	Retro. eries	NA	7 (NA)	Yes	No (ILM check)	SF_6	Induced macular RD	7 (p)	None
Yek et al (2018)[23]	Retro. Series	470 μm/NA	53 (31/22)	Yes (in 94%)	Yes (in 75%)	C_3F_8 (71%) SF_6 (23%) C_2F_6 (6%)	None	(p)	Cat sx: 10 (100)§
Total Weighted mean			520 (297/144)						

Author/Year	Inter-Surgical Time (Months)†	Anat. Closure, n (%)	Mean BCVA Presecond Sx ± (SD)‡	Mean BCVA Postsecond Sx ± (SD)‡	Mean Improvment after Second Sx‡	≥2 Lines Gain in BCVA%	Follow-up (Months) Mean (Range)	6	12	18	≥24
Ie et al (1993)[27]	9.3	10 (100)	1.19 (0.30)	0.82 (0.29)	0.37	70%	11 (8–16)				
Johnson et al (1997)[44]	0.9	17 (74)	1.09 (0.27)	0.63 (0.41)	0.46	35%	13 (3–30)				
Ikuno et al (1998)[41]	1.2	8 (73)	0.92 (0.25)	0.59 (0.26)	0.33	36%	10 (3–15)				
Imai et al (2005)[42]	0.3	5 (100)	0.94 (0.13)	0.41 (0.27)	0.53	100%	13 (9–18)				
Hillenkamp et al (2007)[40]	2.5	19 (68)	1.10 (0.33)	1.04 (0.42)	0.06	36%	15 (6–36				
Valldeperas and Wong (2008)[22]	NA	39 (76)	1.00	0.78	0.22	29%	12				
Saeed et al (2008)[47]	2.5	3 (60)	0.91 (0.35)	0.61 (0.31)	0.30	40%	6				
Iwase et al (2008)[43]	0.3	7 (100)	0.84 (0.23)	0.38 (0.27)	0.46	86%	6				
Rizzo et al (2009)[28]	NA	20 (87)	1.14	0.61	0.53	NA	12				
D'Souza et al (2011)[29]	NA	11 (52)	1.40	1.18	0.22	10%	12				
Hejsek et al (2013)[30]	7.8	6 (100)	NA	0.48¶	NA	NA	10 (7–13)				

(*continued on next page*)

Table 1. *(Continued)*

Author/Year	Inter-Surgical Time (Months)†	Anat. Closure, n (%)	Mean BCVA Presecond Sx ± (SD)‡	Mean BCVA Postsecond Sx ± (SD)‡	Mean Improvment after Second Sx‡	≥2 Lines Gain in BCVA%	Follow-up (Months)				
							Mean (Range)	6	12	18	≥24
Rao et al (2013)[25]	2.7	18 (62)	NA	NA	NA	NA	28				
Moisseiev et al (2013)[37]	4.1	20 (69)	1.10 (0.31)	0.83 (0.40)	0.27	62%	13 (4–49)				
Dimopolous et al (2016)[31]	NA	21 (78)	1.00 (0.33)	0.74 (0.36)	0.26	NA	6				
Cillino et al (2016)[26]	2.5	12 (57)	1.04	0.67	0.37	NA	12				
Pires et al (2016)[46]	NA	11 (92)	1.27 (0.49)	0.88 (0.33)	0.39	67%	12				
Dai et al (2016)[39]	NA	7 (100)	1.20 (0.27)	1.00 (0.18)	0.20	43%	12				
Chen et al (2016)[38]	34.6	6 (67)	1.28 (0.39)	0.97 (0.34)	0.31	67%	≥3				
Szigiato et al (2016)[48]	9.6	8 (100)	1.52 (0.37)	1.10 (0.39)	0.42	63%	7				
Hagiwara et al (2017)[32]	0.6	9 (100)	NA	0.28¶	NA	89%	17 (6–36)				
Purtskhvan-dize et al (2017)[33]	3.0	52 (70)	1.00	0.60	0.40	NA	58				
Modi et al (2017)[34]	NA	4 (44)	NA	NA	NA	NA	NA				
Patel et al (2017)[35]	4.8	16 (64)	1.00	0.85 (0.34)	0.15	NA	2				
Ozdek et al (2017)[45]	4.6	10 (91)	0.97 (0.46)	0.41 (0.28)	0.56	82%	8				
Gurelik et al (2017)[36]	NA	7 (100)	NA	NA	NA	NA	7				
Yek et al (2018)[23]	1.9 (median)	43 (81)	1.00	0.78	0.22	NA	24				
Total		356									
Weighted mean	4.2	74.8%	1.07	0.76	0.31	41%	20.1				

*Some eyes have been excluded from numbers published in studies as they were not FTC eyes, second surgery eyes or iFTMHs.
†Time in months between initial and secondary surgery.
‡LogMAR BCVA.
§Phakic eyes only.
¶Final BCVA value not included in calculation of median as no preop BCVA value available.
Auto Plt, autologous platelet; Auto serum, autologous serum; (p), prone; (s), supine; Cat prog, cataract progression; Cat Sx, cataract surgery; ILM check, ILM status checked but no further peeling performed; NA, not available; Pro, prospective; Retro, retrospective; RCT, randomized controlled trial; RD, retinal detachment; TFG-β, transforming growth factor-beta.

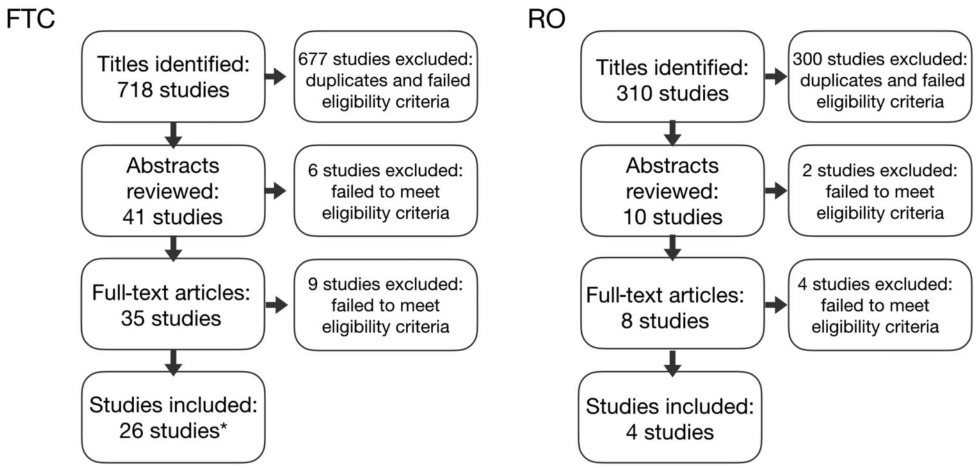

Fig. 1. Flow diagram of studies identified on iFTMHs that FTC after the primary surgical procedure (FTC, left) and those that initially closed which later reopened (RO, right). *Two studies identified through reference lists of included studies, one study identified after presentation of the systematic review at the Fernie Vitreoretinal Meeting, Fernie, Canada, January 26, 2017, and following discussion with the author.

Anatomical closure at a mean follow-up of 6 months ranged from 60% to 100% (weighted mean 84%, 62/74 eyes; 7 studies),[31,36,38,43,45,47,48] at 12 months ranged from 52% to 100% (weighted mean 76%, 166/219 eyes; 12 studies),[22,26–30,37,39,41,42,44,46] at 18 months, mean follow-up ranged from of 68% to 100% (weighted mean 76%, 28/37 eyes; 2 studies),[32,40] and at ≥24 months, mean follow-up (range 24–58 months) mean iFTMH closure ranged from 62% to 81% (weighted mean 72%, 113/156 eyes; 3 studies).[23,25,33]

Best-corrected visual acuity. Data on BCVA were provided in 23 studies (475 eyes) of the FTC group; however, there was considerable variation among studies in BCVA both before and after surgery, indicating heterogeneity in terms of measured outcomes among studies and patient characteristics. Most studies reported the mean and SD of BCVA measurements before and after the second surgery along with the mean change in BCVA. However, the SD of the change in BCVA was frequently not reported; so, it was not possible to use change in BCVA as the outcome of a meta-analysis (meta-analysis requires measures of both central tendency and dispersion for each study). Therefore, it was decided to use the categorical variable "improvement in BCVA by two Snellen lines" (or 10 letters, 0.2 LogMAR) as the outcome for meta-analysis as this measure was reported or could be derived for a greater number of studies. Data on improvement in BCVA by 2 Snellen lines were available from 17 studies, and meta-analysis was conducted combining aggregate data (4 studies, 110 eyes) and IPD (13 studies, 189 eyes). Due to high heterogeneity among studies ($I^2 = 64.3\%$), a random-effects model was fitted. The pooled estimate of the proportion of patients with a ≥2 Snellen line improvement in BCVA was 0.58 (CI 0.45–0.71) (approx. 6/24 Snellen equivalent) (Figure 3). Of the 189 eyes for which IPD was available, visual acuity of 6/12 Snellen equivalent or better was achieved in 15% (28 eyes, 13 studies) (Table 1).

Mean BCVA from each study before the secondary surgical procedure ranged from 1.52 to 0.84 logMAR (weighted mean 1.07 [approx. 6/72 Snellen equivalent]; 460 eyes); while postoperative mean BCVA ranged from 1.18 to 0.28 logMAR (weighted mean 0.76 [approx. 6/36 Snellen equivalent]; 460 eyes). Best-corrected visual acuity before the second surgery was not provided by 2 studies[30,32] who instead provided mean BCVA before the first surgery and after the second procedure.

For the studies where preoperative BCVA was reported (n = 16), the mean improvement from pre-second surgery to final postoperative BCVA ranged from 0.06 to 0.56 (weighted mean 0.31, approx. 6/12 Snellen equivalent) LogMAR (460 eyes). Best-corrected visual acuity gain by ≥2 Snellen lines was presented in 17 of 26 studies (246 eyes) with a range of 10% to 100% (weighted mean 41%) achieving this improvement (Table 1). Rizzo et al and Yek et al used a three Snellen line improvement and found 83% (19 of 23 eyes) and 22% (11 of 53 eyes) achieving at least three Snellen lines of BCVA improvement respectively.[23,28]

Best-corrected visual acuity at 6 months postop was reported in 6 studies; preop and 6-month mean BCVA ranged from 1.52 to 0.84 and 1.10 to 0.38 LogMAR, respectively (weighted mean 0.97–0.65, approx. 6/60–6/24 Snellen equivalent; 67 eyes).[31,38,43,45,47,48] Best-corrected visual acuity at 12 months postop was reported in 12 studies; preop and 12-month mean BCVA ranged from 1.40 to 0.94 and 1.18 to 0.41 LogMAR, respectively (weighted mean 1.11–0.78, approx. 6/75–6/36 Snellen equivalent; 213 eyes).[22,26–30,37,39,41,42,44,46] Mean BCVA at 18-month follow-up was recorded by Hillenkamp et al[40] preop and postop at 1.10 and 1.04 LogMAR (6/75–6/60). At ≥24-month

Table 2. Characteristics, Surgical Techniques, and Outcome Measures for Studies Included in the (RO) group

Author/Year	Study Design	FTMH Reopening Incidence, n (%)	Event Before Reopening, n (%)	Time From Initial Surgery to Reopening (Months)	No. of Second Surgery Eyes, n (Male/Female)	ILM Peel at Initial Surgery	ILM Peel at Second Surgery
Paques et al (2000)[50]	Pro. series	10/109 (9.2)	Cat sx: 7 (78)	14.9	8 (NA)	No	No
Valldeperas and Wong (2008)[22]	Retro. series	21/481 (4.4)	Cat sx: 0–2 (0–10)	13.5	21 (16/5)	Yes (in 12%)	Y (in 57%)
Rao et al (2013)[25]	Retro. series	7/530 (1.3%)	NA	2–6	7 (NA)	Yes	No
Abbey et al (2017)[49]	Retro. series	13/392 (3.3)	Cat sx: 5 (38)	28	13 (NA)	Yes	No
Total		51/1,512 (3.4)	1		49		
Weighted average							

Author/Year	Tamponade Agent	Additional Adjuvant	Complications, n (%)	Anat. Closure, n (%)	Mean BCVA Presecond Sx*	Mean BCVA Postsecond Sx*	Mean Improve after Second Sx*	≥2 Lines Gain in BCVA %	Follow-up (Months) Mean (Range)	6	12	18	≥24
Paques et al (2000)[50]	Gas (not specified)	Auto plts	NA	5 (62)	NA	NA	NA	NA	27 (24–58)				
Valldeperas and Wong (2008)[22]	C_3F_8	Auto plts	Cat sx: 16 (84)† ret tear: 2 (10)	20 (95)	0.85	0.50	−0.35	76%	12				
Rao et al (2013)[25]	C_3F_8 (78%) SF_6 (22%)	None	RD: 2 (6) IOP rise: 3 (8) (not separate FTC vs. RO)	4 (57)	NA	NA	NA	NA	28				
Abbey et al (2017)[49]	C_3F_8 (92%) SF_6 (8%)	None	Retinal tear: 1 (8)	10 (77)	0.88	0.78	−0.10	NA	118 (19–258)				
Total				39									
Weighted average				79.6%	0.86	0.61	0.25		44.9				

Time in months between initial surgery and reopening of macular hole.
*LogMAR BCVA.
†Phakic eyes.
Auto Plts, autologous platelets; Cat sx, cataract surgery; n, number; NA, not available; Pro, prospective; Retro, retrospective; RD, retinal detachment; Ret tear, retinal tear; Sx, surgery.

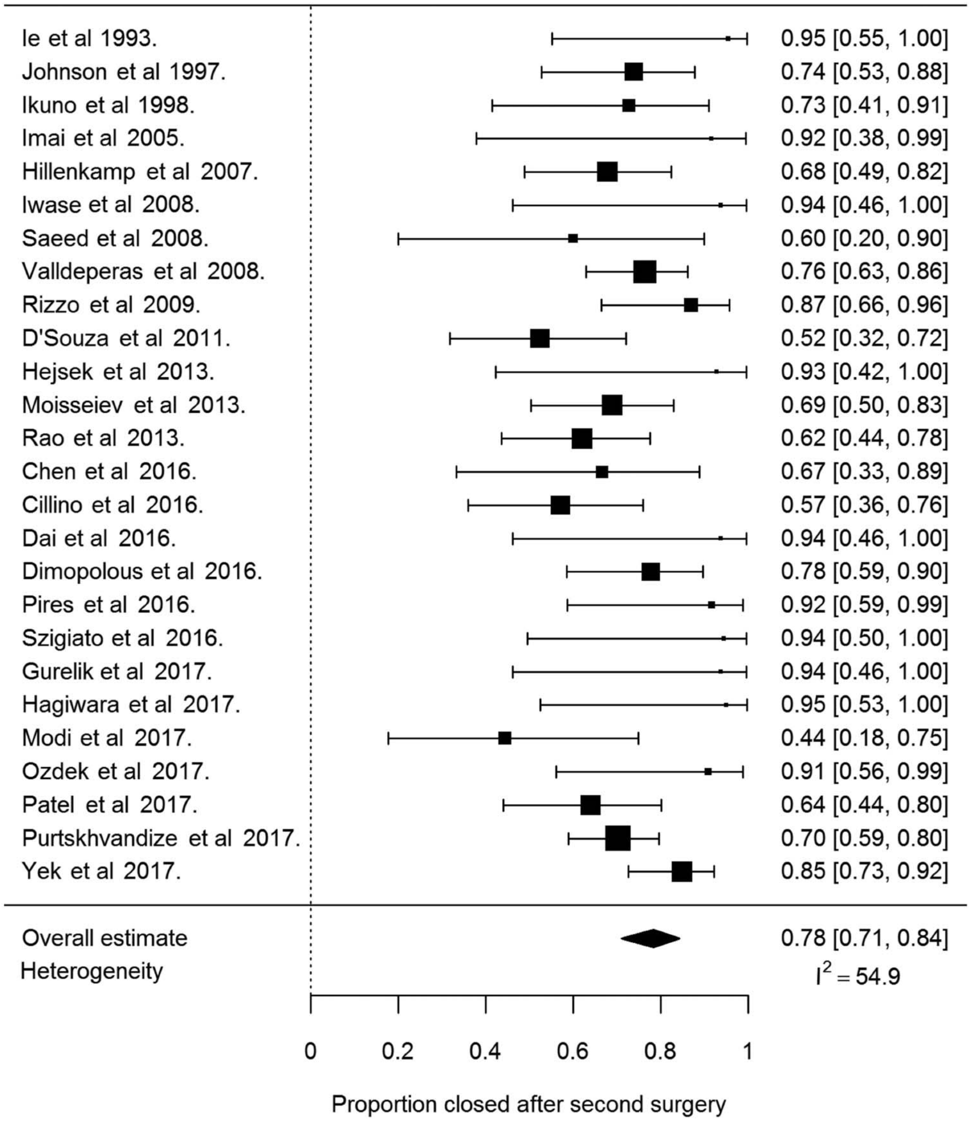

Fig. 2. Proportion of iFTMHs that closed after repeated surgery. Estimates and 95% CIs for 26 studies along with overall estimate from meta-analysis and I^2 measure of among study heterogeneity. Point size is proportional to weighting of individual studies in the meta-analysis.

follow-up, preop and postop mean BCVA was reported in 2 studies and ranged from 1.26 to 1.00 and 0.78 to 0.60 LogMAR, respectively (weighted mean 1.11–0.68, approx. 6/75–6/30 Snellen equivalent; 127 eyes).[23,33]

Surgical techniques. All surgical techniques used in identified studies have been summarized in Table 1. Of all eyes included in the review, ILM peeling was undertaken at the primary surgery in 419 of 520 eyes (81%) (23 of 26 studies, 2005–2017).

During the second surgery, 101 eyes (7 studies) underwent further ILM peeling (note that in Valldeperas and Wong,[22] Hejsek et al,[30] Moisseiev et al,[37] and Yek et al,[23] the ILM peeling was performed for the first time in 96, 17, 14, and 6% of eyes, respectively, during second surgery). Fluid–gas exchange alone was performed as a secondary procedure in 108 eyes.[25,34,35,42–44] Autologous ILM graft transplants were used in 30 eyes (3 studies),[39,45,46] and one study[38] used lens capsule transplantation (9 eyes). Additional techniques described were as follows: autologous blood products, used in 183 eyes; transforming growth factor-beta-2, used in 10 eyes; laser photocoagulation, used in 11 eyes; and an induced macular detachment in 15 eyes (Table 1).

The endotamponade agents used included air in 1 eye (0.2%), C_3F_8 in 250 eyes (48%), C_2F_6 in 77 eyes (15%), SF_6 in 79 eyes (15%), and silicone oil (SO) in 56 eyes (11%); in 57 eyes, the type of tamponade used was not specified.

Complications. Data on complications were recorded in 17 studies (Table 1).

Progression of cataract was reported in 3 studies (35 phakic eyes),[27,41,44] with a weighted mean of

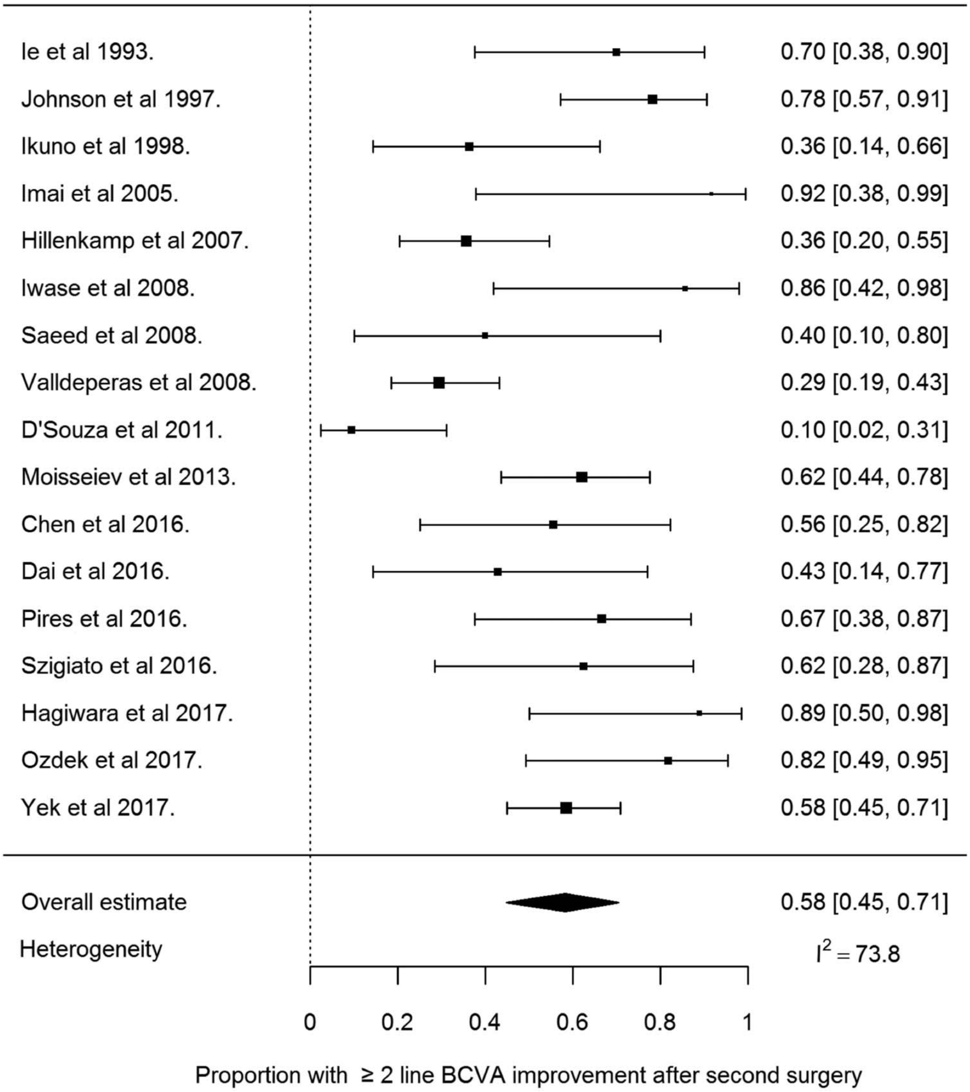

Fig. 3. Proportion of iFTMHs exhibiting a ≥2 Snellen line gain in BCVA after repeated surgery. Estimates and 95% CIs for 17 studies along with overall estimate from meta-analysis and I^2 measure of among study heterogeneity. Point size is proportional to weighting of individual studies in the meta-analysis.

69% (at a median follow-up of 12 months). Cataract extraction was reported in 6 studies,[22,23,28,37,44] with a weighted mean of 59%. At a median follow-up of 13 months, retinal detachment was reported in 2 studies and occurred in 4 of 380 eyes (1.5%).[33,40] Transient intraocular pressure (IOP)-related complications were reported in 14 of 400 eyes (3.5%) (Table 1).

Two studies[25,29] did not differentiate second surgery complications between FTC and RO groups. Rao et al[25] reported cataract extraction in 34 phakic eyes (94%), retinal detachments in 2 eyes (6%), and IOP complications in three eyes (8%). D'Souza et al[29] report IOP complications in 17 eyes (68%).

Patient-reported outcomes. No studies provided information on PROs after repeated surgery for FTC iFTMH.

Outcomes: Reopened Group

Proportion of eyes with anatomical closure of macular hole. Meta-analysis was performed on the aggregate data sets of the 4 studies, 49 eyes[22,25,49,50] in the RO group. There was low to moderate heterogeneity among the studies (I^2 = 42.8), and a fixed-effects meta-analysis model was used to estimate a pooled effect size of iFTMH anatomical closure following a second surgical procedure of 0.80 (CI 0.66–0.89) (Figure 4).

The proportion of eye with iFTMH reopening following the primary vitreoretinal procedure ranged from 1.3% to 9.2%, occurring in 51 of 1,512 eyes (weighted mean 3.4%). Of these iFHTMs, outcomes following a second surgical procedure were presented for 49 eyes. Anatomical closure after the second surgery ranged from 57% to 95% (weighted mean 80%, 39 eyes) (Table 2).

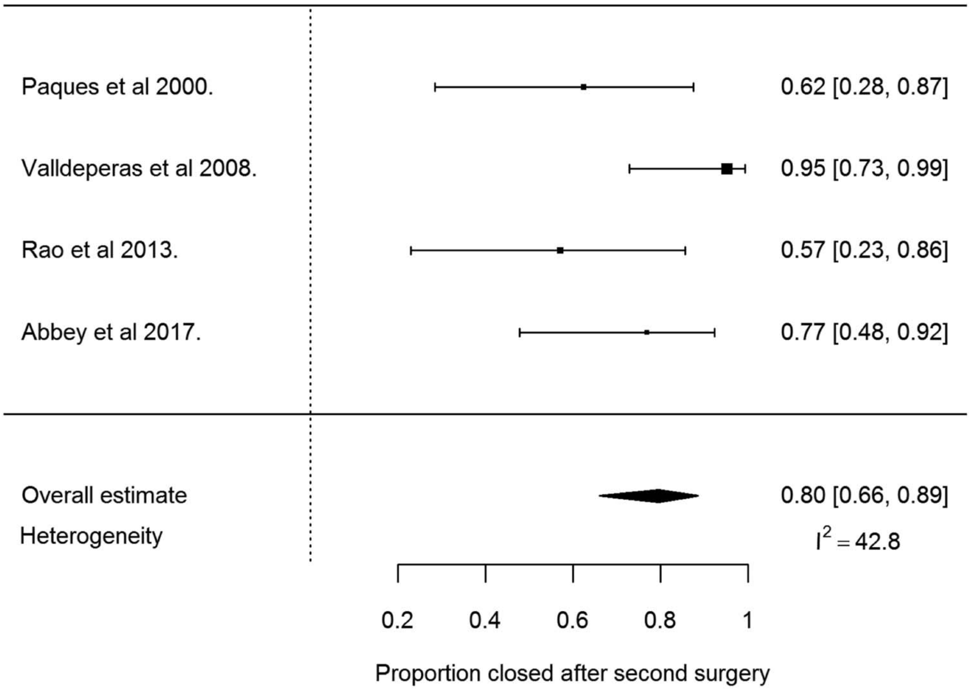

Fig. 4. Proportion of iFTMHs that closed and then RO after initial surgery that subsequently closed after repeated surgery. Estimates and 95% CIs for four studies along with overall estimate from meta-analysis and I^2 measure of among study heterogeneity. Point size is proportional to weighting of individual studies in the meta-analysis.

Best-corrected visual acuity. Data on BCVA were available in 2 studies (34 eyes).[22,49] Meta-analysis of ≥2-line Snellen improvement following a secondary procedure was not possible in the RO group as only Valldeperas and Wong[22] provided data on this outcome.

Mean BCVA before a second procedure ranged from 0.88 to 0.85 logMAR (weighted mean 0.86 [approx. 6/45 Snellen equivalent]), and postoperative ranged from 0.78 to 0.50 logMAR (weighted mean 0.61 [approx. 6/24 Snellen equivalent]) in Abbey et al and Valldeperas and Wong, respectively.[22,49] The mean improvement from preoperative to postoperative levels ranged from 0.1 to 0.35 LogMAR (weighted mean 0.25, approx. 6/10 Snellen equivalent). Only Valldeperas and Wong[22] included data on gain of ≥2 Snellen line BCVA which occurred in 76% (16/20 eyes) at 12 months. Mean BCVA preop and at 6 months and 12 months postop as recorded by Valldeperas and Wong was 0.85, 0.48, and 0.50 LogMAR, respectively (approx. 6/45, 6/18, and 6/19 Snellen equivalent, respectively).[22,50] No study recorded BCVA at 18 months; however, Abbey et al presented preop BCVA and at ≥24-month follow-up with values of 0.88 preop and 0.78 LogMAR, respectively (approx. 6/45 and 6/36, Snellen equivalent, respectively).[49]

Surgical techniques. Paques et al (8 eyes) did not undertake any ILM peeling at either initial or secondary vitrectomy. An initial pars plana vitrectomy plus ILM peeling was performed by Rao et al and Abbey et al in all eyes (20 eyes), whereas Valldeperas and Wong performed only a limited number of ILM peels (2 eyes, 12%) (Table 2). During the secondary procedure, Valldeperas and Wong performed ILM peeling on 12 eyes (57%), whereas Abbey et al "stained and attempted" further ILM peel (13 eyes). Rao et al performed fluid–gas exchange only without further vitrectomy (7 eyes). Autologous platelets were used as adjuvant in Valldeperas and Wong (Table 2).

Complications. In the RO group, Valldeperas and Wong[22] reported cataract surgery after second surgery in 16 of 19 phakic (84%) eyes at 12-month follow-up. Valldeperas and Wong and Abbey et al reported retinal breaks/tears in 2 eyes (10%) and 1 eye (8%), respectively.[22,49]

Patient-reported outcomes. No studies provided information on PROs.

Discussion

Meta-analysis of probability of iFTMH anatomical closure following a second surgical procedure generated a pooled estimate of 78% (CI 71–84%) in the FTC group and 80% (CI 66–89%) in the RO group. Meta-analysis of the probability of gain in BCVA by ≥2 Snellen lines was only possible in the FTC group; this generated a pooled estimate of 58% (45–71%), with 15% of eyes achieving visual acuity of 6/12 or better at the last recorded follow-up. Based on these data, reoperation for iFTMH seems to be justified; available evidence, however, should be discussed with patients before surgery to ensure they have realistic expectations to what can be achieved following a repeated procedure. No data were provided on PROs in any of the identified studies. Thus, it is difficult to determine whether or not the benefits of further surgery were relevant to patients. It would seem important in future studies to take this into consideration and include health-related and visual-related quality-of-life testing as outcome measures.

The proportion of patients with an improvement of ≥2 Snellen lines was significantly higher in the single study reporting this outcome in the RO group (i.e., 76%, Valldeperas and Wong[22]) than our pooled estimate across the FTC group (58%). Valldeperas and Wong and Rao et al provided a comparison between FTC and RO in their series.[22,25] Valldeperas and Wong stated that differences between the two groups (RO and FTC) were not statistically significant before the second intervention; anatomical success (95 vs. 76%, $P = 0.012$) and 6-month BCVA (0.48 vs. 0.92 LogMAR [6.18 vs. 6/50]) were significantly better in the RO group when compared with the FTC group, although statistically significant differences in BCVA at 12 months were no longer present (0.50 vs. 0.78 LogMAR [6.19 vs. 6/36]).[22] Rao et al[25] did not attempt a statistical comparison between these groups but reported anatomical success rates that were similar between the two groups (57 vs. 62%); unfortunately, visual acuity data were not presented separately.

At primary macular hole surgery, an increased period before the surgical repair[51–53] and a larger pre-op macular hole size[54,55] have been associated with worse outcomes both in terms of anatomical closure and postop BCVA. It has been suggested that an increased time between first and second surgeries may contribute to poorer visual and anatomical outcomes.[29,35,37] In addition, increased size of the iFTMH may also negatively impact surgical outcomes[33,37]. These findings, however, were not consistent across all reviewed studies,[40] and as noted by Yek et al,[23] it is difficult to assess these variables in studies with small sample sizes.

There was variation among studies in the surgical maneuvers undertaken at the repeated procedure (listed in Tables 1 and 2), including the postop endotamponade agent used, the use of autologous blood products, grafting with autologous ILM or lens capsule, and macular detachment. The large variation in surgical techniques and small study sizes made it impossible to determine which ones may have contributed most to the success of the second surgery. There were multiple postoperative tamponade agents used among the studies we reviewed; however, Cillino et al[26] (FTC group) compared C_2F_6 gas with SO in a randomized clinical trial. The SO group achieved greater anatomical closure and BCVA at 12 months. It was, however, not stated whether the ILM had been peeled at the time of the primary surgery or whether ILM peel was performed or extended during repeated surgery. Silicone oil also requires an additional surgical procedure for its removal with the potential of complications such as retinal detachment and unexplained visual loss can occur after removal of SO.[40]

Recently described maneuvers included the use of an autologous ILM flaps or free grafts, which are suggested to provide a scaffold for glial cell proliferation and macular hole closure.[56] Inverted ILM flap can be successful in closing large iFTMHs[57]; however, at a secondary procedure, a free ILM graft may be required, as an ILM peel will have been previously undertaken in most cases; free ILM grafts are more challenging given the possibility of them to dislodge at the time of fluid–air exchange.[58] Anatomical closure after ILM grafting was reported in 3 studies and ranged from 91% to 100% (28 eyes); functional improvement, however, varied.[39,45,46] Alternatively, grafting with lens capsule has also been described with possible greater ease of manipulation intrasurgically. During repeated iFTHM surgery, this technique closed 67% of cases (6 of 9 eyes).[38]

This study has several limitations. Thus, most studies identified were retrospective, and many were relatively small case series. This fact limits the quality of the primary evidence identified to the lower end of the evidence hierarchy and allows for the potential entry of biases through, for example, case selection, lack of masking, attrition bias (incomplete reporting of outcome data), and reporting bias (selective reporting), among others. A further limitation of this review was the heterogeneity of studies included with multiple surgical techniques used, making it impossible to determine what may be the best surgical approach to treat FTC or RO iFTMH. On this regard, this systematic review highlights the need for high-quality studies especially those investigating the relative effectiveness of the different surgical techniques used in the repair of iFTMH that FTC or RO. Available data, however, suggest repeated macular hole surgery is beneficial in terms of anatomical closure and functional improvement. The strengths of this review include the systematic identification of studies, standardized data extraction, and the meta-analysis on anatomical and functional outcomes undertaken in the FTC group and on anatomical outcomes in the RO group, providing useful information for the counseling of patients before repeated surgery.

Conclusion

Our review and meta-analysis indicate that just more than half of the patients undergoing a second surgery for FTC iFTMH are likely to experience visual acuity improvement of ≥2 Snellen lines after a second surgery, with a small risk of complications. Only a small proportion of these (15%), however, may achieve very good vision (≥6/12). We found weak evidence that visual success may be higher in the RO group. Repeated surgery is likely to lead to anatomical closure of the iFTMH in a high proportion of patients with FTC and RO iFTMHs (estimated at 78 and 80%, respectively). This information is useful for the counseling of patients before surgery.

Key words: failed primary procedure, failure to close, failed surgery, idiopathic full-thickness macular hole, internal limiting membrane, ILM flap, ILM peeling, redo surgery, reoperation, reopening, vitreoretinal surgery.

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