Graefe's Archive for Clinical and Experimental Ophthalmology (2020) 258:2629–2638
https://doi.org/10.1007/s00417-020-04920-4

RETINAL DISORDERS

Macular hole closure patterns: an updated classification

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Received: 7 July 2020 / Revised: 25 August 2020 / Accepted: 2 September 2020 / Published online: 10 September 2020

Abstract

Background The classification of macular hole closure patterns (MHCPs) currently relies on time domain OCT allowing only "open" and "closed" statuses or is based on inner foveal contour shape. Both classification types give no information on retinal layer reconstitution. Novel sophisticated surgical techniques lead to previously unknown MHCPs, outdating existing classifications and urging new ones. The purpose of the present study is to introduce a new classification allowing proper description of all MHCPs resulting from newer surgeries and based on the restoration of retinal layers.

Methods Retrospective analysis of patients undergoing MH surgery with five different surgical techniques was performed. MHCPs were classified according to spectral domain optical coherence tomography (SD-OCT). Type 0: open MH (0A: flat margin, 0B: elevated, 0C: oedematous); type 1: closed MHs (1A: reconstitution all retinal layers; 1B interruption of the external layers; 1C interruption of internal layers); type 2: MH closed with autologous or heterologous filling tissue interrupting the normal foveal layered anatomy (2A: filling tissue through all layers; 2B reconstitution of normal inner retinal layers; 2C reconstitution of normal outer retinal layers; 2D H-shaped bridging of filling tissue).

Results Closure rate was 95.2% (241/253). Surgical technique and vision correlated to closure pattern ($p < 0.001$). Type 1 MHCPs had the best post-operative visual acuity (VA) compared with type 2 and type 0 ($p < 0.001$). MHCPs 1A and 1C performed better than all others. MHCP at months 1 and 3 changed in 42/254 (16.5%) and remained stable in 212/254 (83.5%). Improvement in vision was higher in eyes with shifting closure pattern (0.57 ± 0.33 vs 0.51 ± 0.48 logMAR; p 0.021).

Conclusion MHCP classification based on retinal layer restoration properly comprises post-operative anatomic morphologies. MHCPs correlate the surgical technique and post-operative visual outcomes.

Keywords Macular hole · Closure pattern · Pars plana vitrectomy · Internal limiting membrane · Human amniotic membrane · Autologous retinal transplantation · Graft · Amniotic membrane implant · Autologous retina implant

This article is part of the topical collection on *Macular Hole*

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00417-020-04920-4) contains supplementary material, which is available to authorized users.

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Key messages

- Macular hole closure patterns are currently classified according to outdated OCT technology allowing "open" or "closed" variants only or based on inner foveal contour regardless to retinal layer integrity.
- We propose a classification based on retinal layer reconstitution.
- The proposed classification allows the description of closure patterns typical of newer surgical techniques that hardly fit into previous classifications.
- There are correlations between the proposed classification based on retinal layers reconstitution and both visual acuity and surgery adopted.

Introduction

Macular hole (MH) became a curable disease when Kelly and Wendel [1] published their series showing pars plana vitrectomy (PPV) alone yielded 58% closure rate. Almost 20 years later, the surgical technique improved and anatomic success rates now exceed 90% [2], although functional improvement remains variable and sometimes unpredictable [3], as do the healing mechanisms leading to MH closure.

The introduction of internal limiting membrane (ILM) peeling, inverted ILM flaps [4–6], adjuvants, amniotic membrane [7] and autologous retinal graft [8], and injection of fluid in the macular subretinal space to favour MH edge rim approximation fluid [9] improved the anatomic success rates of all MH types; however, there are noticeable anatomical and functional distinctions possibly related to different anatomic repair methods and healing mechanisms.

The refinement of surgical technique and instrumentation [10] results in formerly unknown MH closure patterns that hardly fit into the binary, pioneering classification of Kang and colleagues. [11] based on time domain optical coherence tomography (TD-OCT) and allowing only "open" or "closed" patterns.

The aim of the present study is to introduce a spectral domain OCT (SD-OCT)–based classification encompassing the entire spectrum of macular hole closure patterns (MHCPs) that the expanded assortment of surgical techniques may generate.

Materials and methods

Three senior medical retina specialists masked to use surgical technique retrospectively reviewed SD-OCT imaging of all patients undergoing PPV [12, 13] for idiopathic, chronic, myopic, and recurrent MHs, at our respective institutions, and categorised them into homogeneous closure patterns.

For the purpose of this study, the following are definitions applied to MH categorisation:

– "Idiopathic MHs" have been defined those of documented less than 6-month duration in emmetropic patients (range in spherical equivalent between sphere + 1.75 and sphere − 3.75);
– "Chronic MHs" those with documented duration greater than 6 months in emmetropic patients (range in spherical equivalent between sphere + 1.50 and sphere − 2);
– "Myopic MHs" those with spherical equivalent more myopic than sphere − 6; all included eyes also showed the typical posterior staphyloma;
– "Recurrent MHs" have been gathered all eyes receiving previous surgery for MH.

The reconstituted integrity of an incremental proportion of restored retinal layers visible in post-operative SD-OCT images, and the possible presence of tissue filling the MH void and interrupting the retinal banded anatomy, was the main criterion instructing our classification.

Patients with incomplete charts, follow-up less than 3 months, and/or incomplete or suboptimal OCT imaging were excluded. All post-operative OCT images were characterised according to the classification reported in Fig. 1 and Table 1 at months 1 and 3 post-operatively.

Follow-up was limited to 3 months after surgery as the main purpose is to describe closure pattern, not visual prognosis.

The proposed MHCP classification is based on the following principles (Figs. 1 and 2):

– Type 0 are unsuccessful, "open" MHs with bare retinal pigmented epithelium (RPE) exposed to the vitreous chamber. Those have been further classified according to whether the centremost rim of photoreceptors is adherent to the RPE (0A) or elevated (0B) or oedematous (0C).
– Type 1 are closed MHs with some reconstitution of the banded anatomy, either throughout all retinal layers (1A)

Table 1 Macular hole type and choice of tamponade of sample population

	Number	Percentage
MH type		
Idiopathic	62	24.5
Myopic	74	29.2
Recurrent	96	37.9
Chronic	21	8.3
Total	253	100.0
Tamponade choice		
Air	37	14.6
SF6	93	36.8
C3F8	64	25.3
SiO	55	21.7
PFCL	4	1.6
Total	253	100.0

or with residual interruption of the external (1B) or internal (1C) layers. For the purpose of this classification, we defined "outer retina" the ellipsoid zone, the external limiting membrane, the outer nuclear, and the outer plexiform layers which marked the boundary with the "inner retina" comprising the remainder of retinal layers.

– Type 2 are formally closed MHs, meaning there is no bare RPE exposed to the vitreous chamber and there is tissue filling the MH void (ILM, human amniotic membrane or autologous retina), interrupting the foveal anatomy. Type 2 pattern has been further divided according to whether interposed "filling" tissue plugs the foveolar dehiscence throughout all layers (2A); there is a reconstitution of normal inner retinal layers (2B) or outer retinal layers (2C). The rare persistence of a bridging filling tissue in the "H-shaped" has been defined as pattern 2D.

Visual acuities were analysed (1) related to the described closure patterns; (2) by clustering all subgroups of types 0, 1, and 2; and (3) by clustering subgroups according to retinal layer integrity restoration as follows: restored outer retinal layer group including closure patterns 1A, 1C, and 2C (Figs. 1 and 2), restored inner retinal layer group including patterns 1B and 2B, "alien tissue" interposition group included patterns 2A and 2D. Open MHs were all clustered as type 0 patterns.

The following surgical techniques were used at surgeons' discretion: (1) PPV with ILM peeling alone, (2) ILM flap over or (3) within the MH, (4) human amniotic membrane implants, (5) autologous retinal transplant.

Statistical analysis

Analysis of variance with post hoc Bonferroni correction (for 3 or more groups) was used for continuous variables while nominal and ordinal variables statistics used contingency tables with lambda statistics, Pearson' chi-square, and Pearson correlation. In all cases (except when post hoc Bonferroni correction applies), p values less than 0.05 have been considered statistically significant.

Results

Retrospective chart review yielded 274 eyes belonging to 274 patients referred to the respective tertiary referral centres where the authors work. After excluding those with incomplete charts or insufficient image quality, the study comprised 253 eyes belonging to 253 patients.

The type of MH on presentation and choice of tamponade are reported in Table 1 while types of surgery are reported in

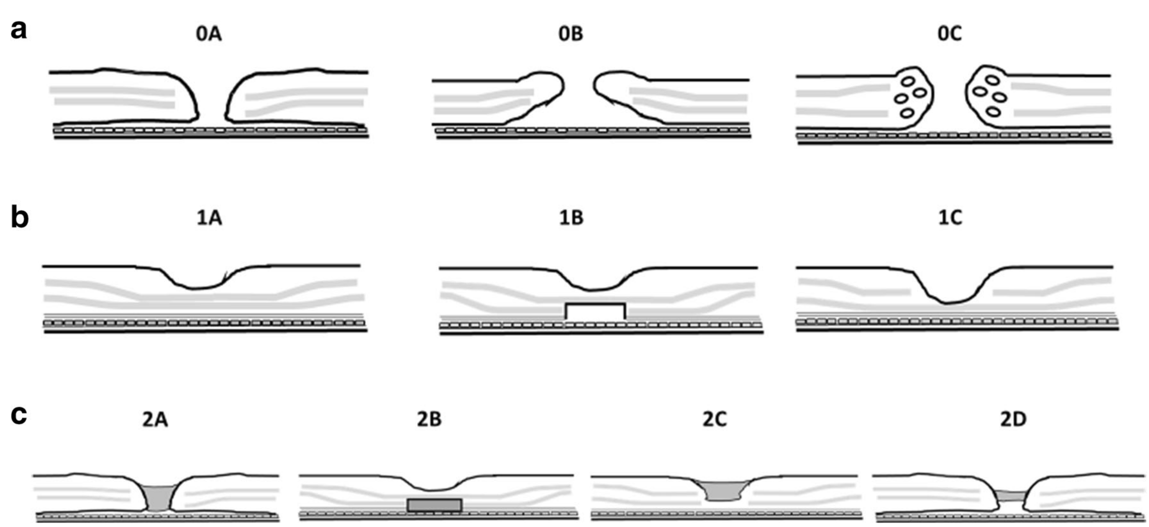

Fig. 1 Schematic drawing of macular hole closure patterns. **a** Type 0 patterns. **b** Type 1 patterns. **c** Type 2 patterns. The schematic grey lines within the retina represent the outer and inner plexiform layers. Note that the outer plexiform layer represents the chosen boundary between "outer" and "inner" retina. See text for patterns description

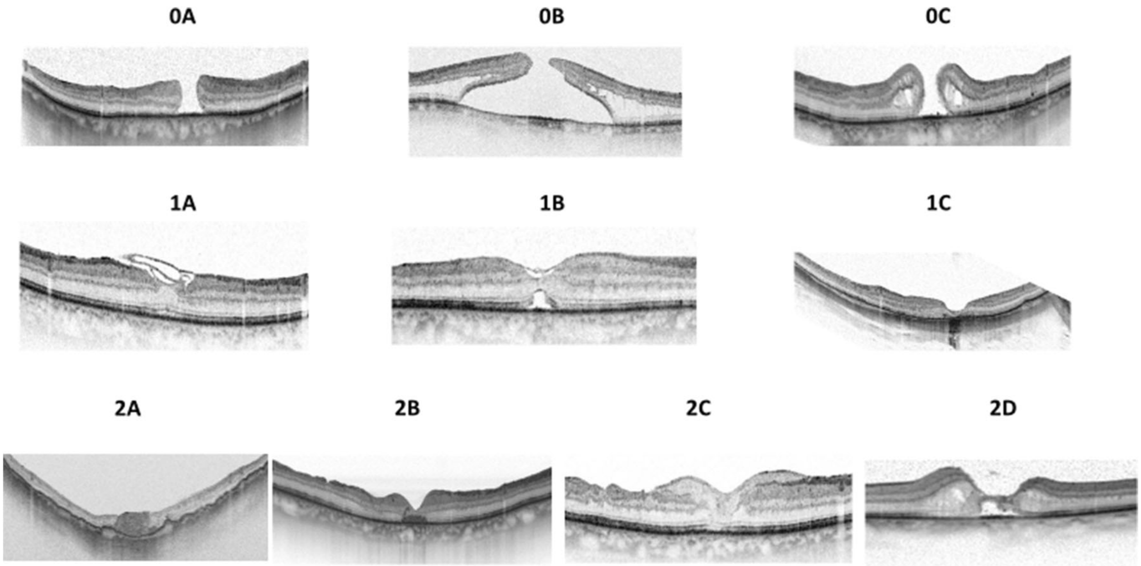

Fig. 2 OCT images of typical closure patterns as in Fig. 1 schematic drawing

Table 2: autologous retinal transplantation, ILM peeling and ILM inverted flap placed over the MH were the surgical techniques preferred by involved surgeons. Average pre-operative size was 475 ± 184 microns.

Overall closure rate at 3 months, regardless of closure pattern was 95.2% (241/253). Closure pattern types at months 1 and 3 post-operatively are reported in Table 3. The type of surgery significantly influenced closure pattern ($p < 0.001$). There was no correlation between choice of tamponade and neither closure rate nor healing pattern.

Closure patterns observed at month 1 and month 3 post-operatively and stratified according to surgery type are reported in Table 4 and graphically in Figs. 3 and 4, respectively.

Surgery type 1 (ILM peeling *tout court*) resulted only in type 1 closures unless if it failed while surgery types 2 and 3 (ILM flap over or within the MH) resulted in any closure type. The use of grafted tissues in surgery types 4 (human amniotic membrane) and 5 (autologous retina), on the other hand, invariably resulted in closure patterns 2 if successful (Figs. 3 and 4).

In 42/254 (16.5%) eyes, the macular hole closure pattern at month 3 changed compared with month 1 post-operatively, and remained the same in the remaining 211/253 (83.5%; Table 5). Mean best-corrected visual acuity (BCVA) at month 1 post-operatively was similar between the 2 abovementioned groups. At month 3, BCVA was significantly better in eyes whose closure pattern had changed compared with 1-month post-operatively (0.57 ± 0.33 vs 0.51 ± 0.48 logMAR; p 0.021) showing as well a statistically significant higher visual acuity improvement in those eyes (− 0.19 ± 0.29 vs − 0.08 ± 0.21 logMAR; $p = 0.018$, Table 5).

The most frequent change in MH closure pattern was 1B becoming 1A (12/42 eyes; 28.6%) followed by 2A becoming 2C (8/42 eyes; 19.1%, Table 6). Macular hole closure patterns 0A, 0C, 1A, and 1C never changed between month 1 and month 3 follow-up visits.

Table 2 Type of surgery, overall numerosity, and percentage. *ILM*, internal limiting membrane; *MH*, macular hole

Type	Technique	Number	Percentage
1	ILM peeling	60	23.72
2	ILM inverted flap over MH	72	28.46
3	ILM inverted flap within MH	20	7.91
4	Amniotic membrane patch	25	9.88
5	Autologous retinal transplant	76	30.04
Total		253	100.00

Table 3 Type of macular hole closure pattern at 1 month and 3 months post-operatively

	1 month		3 months	
	Number	Percentage	Number	Percentage
0A	1	0.40	1	0.40
0B	7	2.77	8	3.16
0C	4	1.58	6	2.37
1°	60	23.72	73	28.85
1B	33	13.04	22	8.70
1C	6	2.37	8	3.16
2°	70	27.67	60	23.72
2B	32	12.65	29	11.46
2C	33	13.04	41	16.21
2D	7	2.77	5	1.98
Total	253	100.00	253	100.00

Table 4 Macular hole closure pattern at 1 month and 3 months post-operatively stratified for type of surgery: (1) PPV with ILM peeling alone, (2) ILM flap over or (3) within the MH, (4) amniotic membrane implant, (5) autologous retinal implant. See also Figs. 3 and 4

Surgery type	Macular hole closure pattern																					
	0A		0B		0C		1A		1B		1C		2A		2B		2C		2D		Total	
At 1 or 3 months	1 M	3 M	1 M	3 M	1 M	3 M	1 M	3 M	1 M	3 M	1 M	3 M	1 M	3 M	1 M	3 M	1 M	3 M	1 M	3 M	1 M	3 M
1	0	0	1	0	3	4	36	41	16	10	4	5	0	0	0	0	0	0	0	0	60	60
2	1	1	1	0	0	1	22	30	16	11	2	3	19	12	6	3	6	3	2	9	72	72
3	0	0	0	0	1	1	2	2	1	2	0	0	8	3	0	0	0	0	8	12	20	20
4	0	0	0	1	0	0	0	0	0	0	0	0	1	1	24	23	24	23	0	0	25	25
5	0	0	5	7	0	0	0	0	0	0	0	0	42	44	2	3	2	3	23	20	76	76
Total	1	1	7	8	4	6	60	73	33	23	6	8	70	60	32	29	32	29	33	41	253	253

Best-corrected visual acuity of all closure patterns significantly differed ($p < 0.001$) and is reported in Fig. 5: pattern closures 1A and 1C performed significantly better than all others. Similarly, all type 1 clustered reached better visual acuities than type 2 and type 0 ($p < 0.001$; Fig. 6); Bonferroni correction shows all differences are statistically significant (type 0 vs type 2 $p = 0.039$; all others $p < 0.001$).

The analysis of retinal layer integrity (Fig. 7 and Table 7) showed that restoration of outer layers yielded a significantly better post-operative BCVA, as expected. Visual acuity in case of outer retinal layer restoration was 0.63 ± 0.26 logMAR at 1 month and 0.35 ± 0.21 logMAR at 3 months vs 0.82 ± 0.27 and 0.68 ± 0.24 logMAR, respectively ($p < 0.001$ in all cases). There was no significant difference in BCVA for inner retinal reconstitution achieved by grafted tissue (types 4 and 5) than by ILM peel or flap (types 1, 2, and 3).

Discussion

Soon after vitrectomy became the standard of care for MHs, OCT imaging has been largely utilised to clarify the details of pre- and post-operative macular anatomy, in an effort to understand the healing mechanisms and inform prognosis.

In 1999, Imai and colleagues [14] described U-, V-, and W-shaped post-operative foveal contours in a descending order of anatomical restoration, relying exclusively on the inner retinal profile mostly due to the limited resolution of available OCT technology. They found a significant correlation between pre-operative condition and visual prognosis. Later on, Kang and colleagues [10] proposed a classification based on the absence (type 1; 61.3% of closed MHs) or presence (type 2; 38.7% of closed MHs) of a foveal neurosensory retinal defect, significantly associated to both initial MH diameter and final visual acuity.

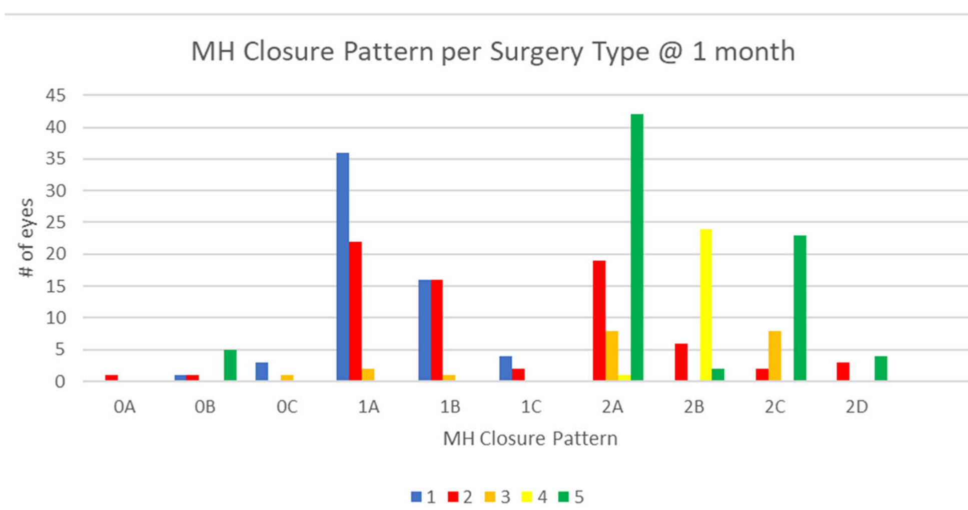

Fig. 3 Bar chart of macular hole closure pattern stratified per surgery type at 1-month post-surgery. Colour coding indicates type of surgery: (1) PPV with ILM peeling alone, (2) ILM flap over or (3) within the MH, (4) amniotic membrane implant, (5) autologous retinal implant

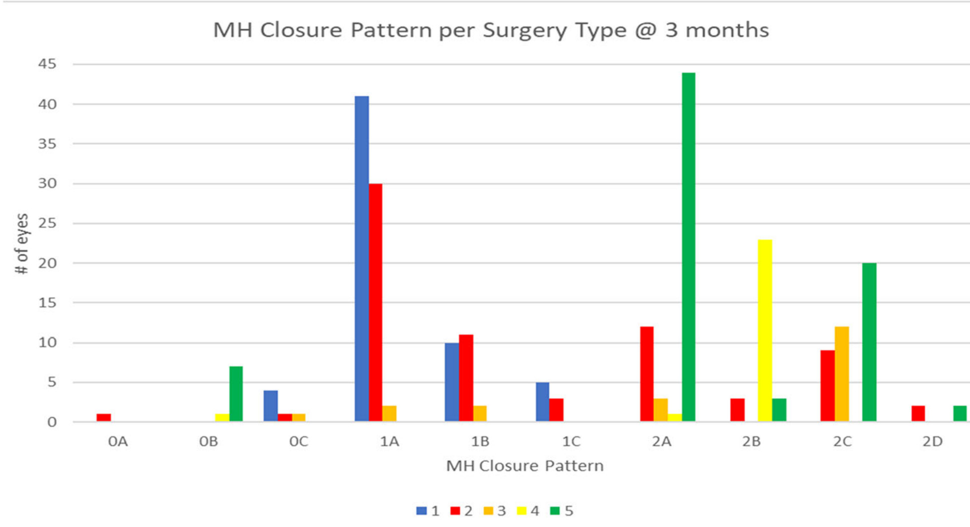

Fig. 4 Bar chart of macular hole closure pattern stratified per surgery type at 3-month post-surgery. Colour coding indicates type of surgery: (1) PPV with ILM peeling alone, (2) ILM flap over or (3) within the MH, (4) amniotic membrane implant, (5) autologous retinal implant

Michalewska et al. in 2008 [15] reappraised the issue, proposing four types of MH closure patterns: U-shaped, V-shaped, irregular, and flat/open. Retinal layer defects were also described in their work but foveal contour remained the hallmark of their classification.

The recent introduction of newer surgical techniques [2, 4–6, 9] has led to previously unknown MHCPs, raising in our opinion the need for an updated classification. The "binary" concept introduced by Kang and colleagues ("open" or "closed") could not comprehensively describe surgical results anymore; for instance, the presence of heterologous tissue within the MH bed poses the question of whether this should be regarded as a closure in the absence of local neurosensory retina at the fovea.

Our classification takes into consideration the extension, type, and location of anatomic restoration defined as the incremental integrity of foveal retinal layers in an effort to conjugate anatomy and function. It also accounts for the presence of "filling" tissue, either grafted or autologous and proved capable of adequately classifying all 243 eyes included in the study.

Unlike previous classifications, we defined "MH closure" a condition where no bare RPE is exposed to the vitreous chamber and there is tissue continuity over the RPE, either normal-looking retina with its reconstituted anatomy (type 1; Figs. 1 and 2) or by autologous or heterologous tissue (type 2), regardless of foveal contour and MH edge rim status. Conversely, we defined as "non-closures" (type 0) all cases where there was bare RPE exposed to the vitreous chamber even if MH rim was flat.

Surgical therapy significantly correlated to closure pattern ($p < 0.05$; Figs. 3 and 4): PPV with ILM peeling alone invariably lead to type 1 closures (or failed); ILM flap covering the MH gave rise to all described closure patterns while the use of autologous or heterologous tissue only resulted in type 2 closures.

It should be notated that PPV without any ILM peeling is still a viable option; however, no such patients have been included in this series as none of the involved surgeons perform it. Closure patterns demonstrated stability within the 3-month time frame of our study: only 16.5% changed between the month 1 and month 3 follow-up visits (Table 3), mostly 1B becoming 1A (Fig. 8a, b) and 2A becoming 2C (Table 6). The subgroup of patients with an evolving closure pattern between 1 and 3 months significantly improved their vision compared with the remaining 83.5% (Table 5). These shifting patterns represent consecutive steps of the healing process and offer a different glimpse of the healing process for each used technique: when peeling alone was performed (surgery type 1) or the ILM was placed over the MH rim (surgery type 2) inner

Table 5 Mean BCVA at 1 month and 3 months in eyes of patients whose macular hole closure pattern changed and did not change

	Number (%)	BCVA 1 month (logMAR)	BCVA 3 months (logMAR)	BCVA change (logMAR)
Pattern change	42 (16.5%)	0.79 ± 0.47	0.71 ± 0.48	− 0.08 ± 0.21
No pattern change	211 (83.5%)	0.76 ± 0.47	0.57 ± 0.33	− 0.19 ± 0.29
p value	-	0.722	0.021	0.018

Table 6 Macular hole closure pattern change between 1 and 3 months post-operatively. Note 1B and 2A accounted for more than half changes

		MH Closure Pattern at 3 months										Total
		0A	0B	0C	1A	1B	1C	2A	2B	2C	2D	
MH Closure Pattern at 1 month	0A											0
	0B			2								2
	0C											0
	1A											0
	1B				12		1				1	14
	1C											0
	2A					2			1	8	2	13
	2B	1						1		3		5
	2C		1					2				3
	2D		1		1	1	1		1			5
	Total	1	2	2	13	3	2	3	2	11	3	42

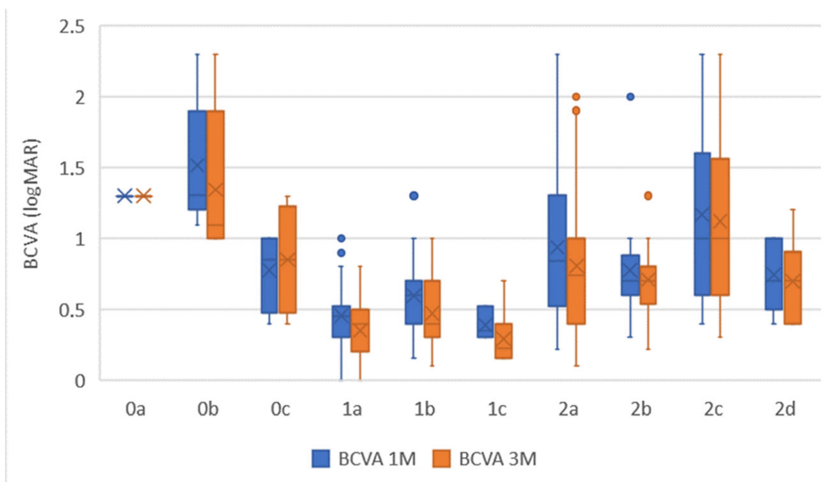

Fig. 5 Box and whisker plot of best-corrected visual acuity at 1 month and 3 months per macular hole closure pattern type

layer repair before outer layers (Fig. 8a, b), a picture previously described as "foveolar lucency" and associated to a higher MH closure rate and tamponade choice [16–18].

Healing mechanisms induced (or favoured) by grafted tissue interposition seem to behave differently: after plugging the MH throughout all layers during surgery (2A pattern;

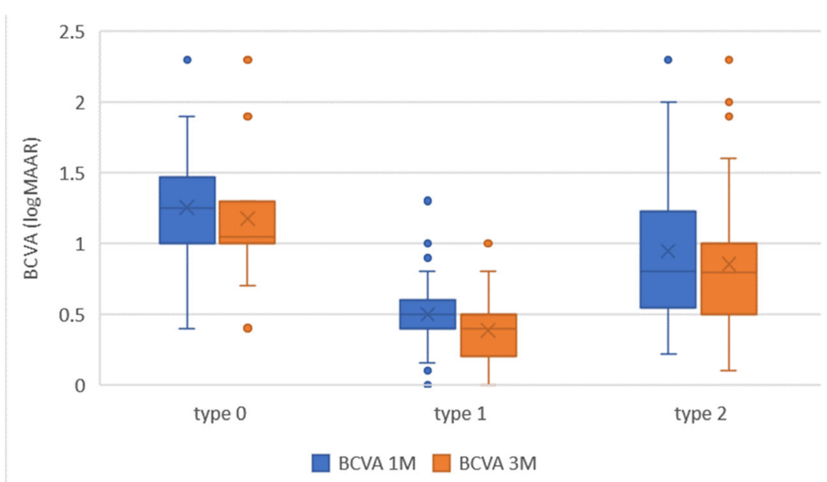

Fig. 6 Box and whisker plot of best-corrected visual acuity at 1 month and 3 months when macular hole closure pattern types are clustered together: all types 0, 1, and 2. Type 1 has a BCVA significantly better than types 2 and 0 ($p < 0.001$)

Table 7 Best-corrected visual acuity at 1 month and 3 months when considering retinal layer integrity reconstitution. *P* values of ANOVA with post hoc Bonferroni test are reported for each group vs all others. Significant values ($p < 0.05$) are presented in italic

	1 month					3 months				
	BCVA 1 month (logMAR)	Outer layers (*p*)	Inner layers (*p*)	Grafted tissue (*p*)	Open MH (*p*)	BCVA 3 months (logMAR)	Outer layers (*p*)	Inner layers (*p*)	Grafted tissue (*p*)	Open MH (*p*)
Outer layers	0.69 ± 0.53	-	1	*0.005*	*0.001*	0.60 ± 0.54	-	1	*0.021*	*0.001*
Inner layers	0.69 ± 0.28	1	-	*0.014*	*0.001*	0.59 ± 0.25	1	-	*0.028*	*0.001*
Grafted tissue	0.92 ± 0.45	*0.005*	*0.014*	-	0.119	0.80 ± 0.41	*0.021*	*0.028*	-	*0.037*
Open MH	1.25 ± 0.50	*0.001*	*0.001*	0.119	-	1.17 ± 0.50	*0.001*	*0.001*	*0.037*	-

Fig. 7 Box and whisker plot of best-corrected visual acuity (BCVA) at 1 month and 3 months. Patients have been clustered into groups according to retinal layer integrity: restored outer retinal layer group included closure patterns 1A, 1C, and 2C; restored inner retinal layer group comprised patterns 1B and 2B; grafted tissue interposition group encompassed patterns 2A and 2D. Open MHs were 0A, 0B, and 0C patterns

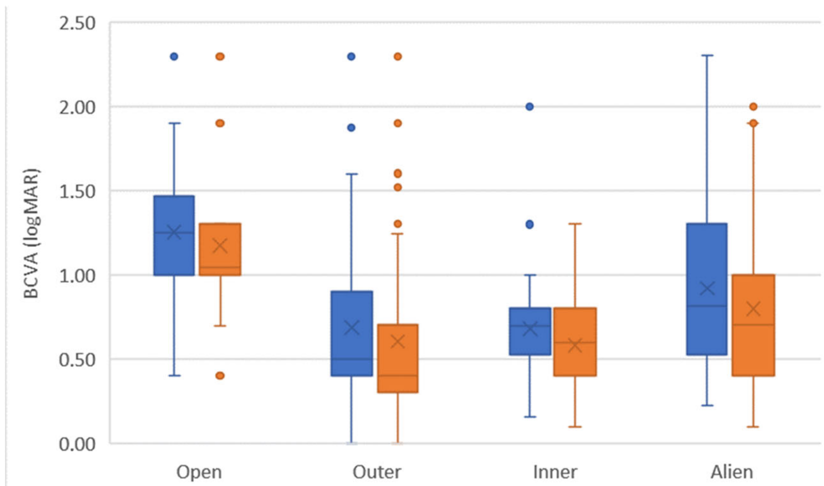

Fig. 9a, b), the outer retina reconstitutes (2C pattern), possibly thanks to the shifting of glial tissue enhanced by tissue guidance or due to growth factors pooling or to both [5].

Autologous retinal transplant may also show interesting closure pattern modifications that can be still adequately described by our classification: the immediate post-op type 2a presentation (Fig. 10a) becomes fainter at 3 months (Fig. 10) and completely disappears by 19 months (Fig. 10c; type 1b) leaving only a small ellipsoid zone defect and some lucency in the outer retina.

Closure patterns showed significantly different visual recovery, even more so when types 0, 1, and 2 were clustered together: types 1 (A, B, and C together) achieved a better vision than types 2 (A, B, C, and together; $p < 0.001$) who saw better than types 0 (A, B, and C together; p = 0.039; Fig. 6).

Visual acuity significantly correlated to retinal integrity when closure types were clustered on the basis of retinal layer repair (Table 7): closure types sharing outer layer restoration (1A, 1C, 2C) showed a significantly better BCVA at month 1 and month 3 than those with inner retinal layer restoration

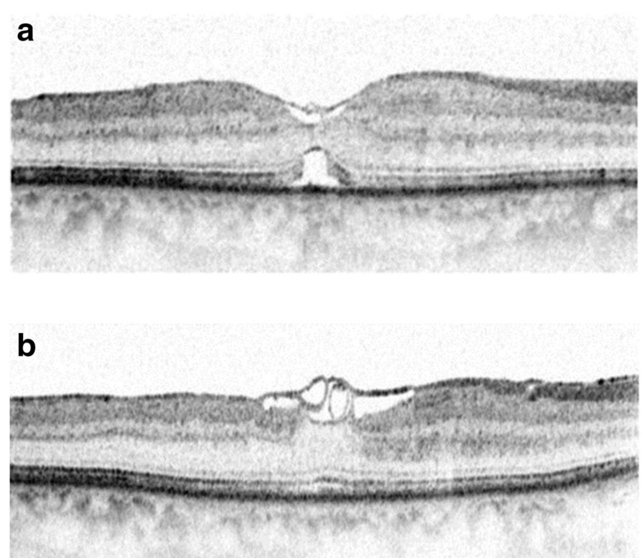

Fig. 8 Type 2 surgery patient (ILM flap positioned over the MH) showing type 1B closure pattern 1 month after surgery (**a**) and type 1A at the 3-month visit (**b**)

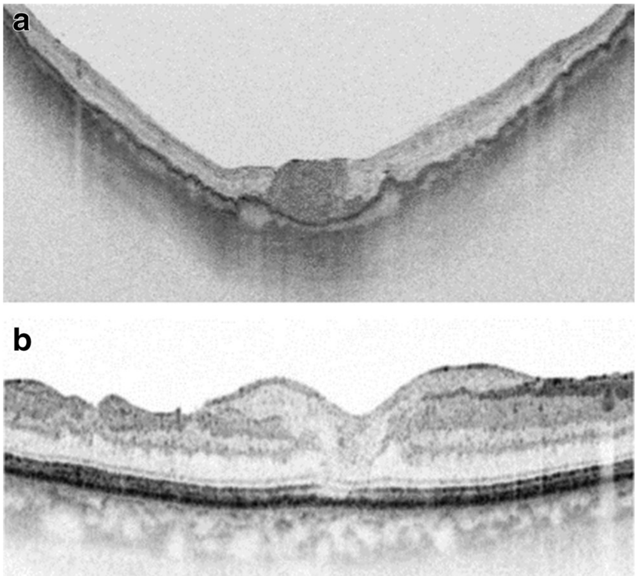

Fig. 9 Type 4 surgery patient (human amniotic membrane implant) showing type 2a closure 1 month after surgery (**a**) and type 2C 2 months later (**b**)

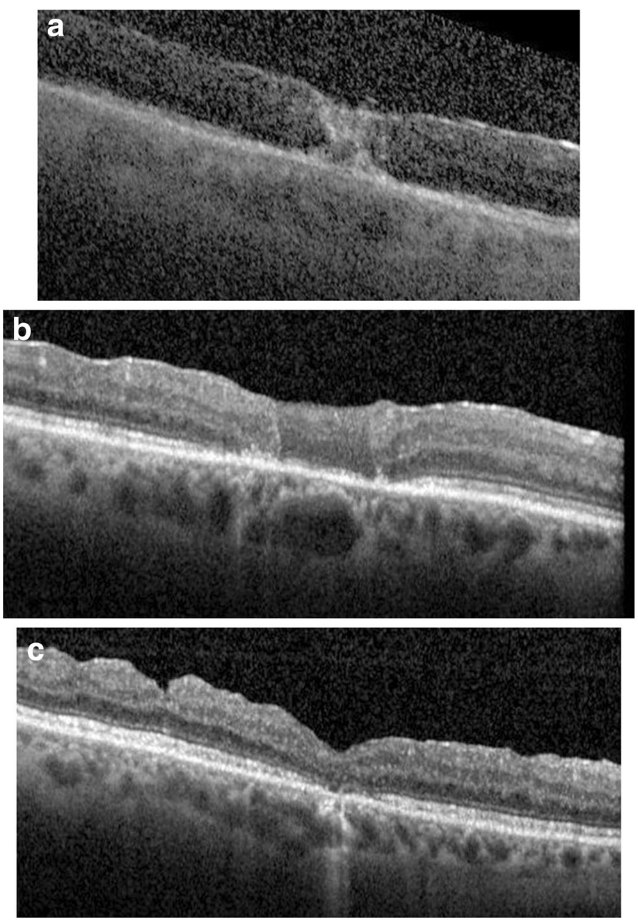

Fig. 10 Type 5 surgery patient (autologous retinal transplantation) showing type 2A closure pattern at week 1 (**a**) fainting but still present at month 3 and evolving into pattern 1B at 11 months when there is alteration of the ellipsoid zone and good restoration of the inner retinal layers

(types 1B, 2B) who saw significantly better than open MHs (0A, 0B, 0C) ($p < 0.001$; Fig. 7). The interposition of grafted tissue resulted in significantly better visual acuity than open MHs but worse than the final visual acuity reached by outer or inner retina restoration.

It is important to highlight that the present study aims at proposing an OCT classification of MH closure patterns and is therefore neither intended nor powered to assess surgical outcome, visual acuity, and/or compare different techniques. There are obviously multiple biases: patients' initial condition, type of macular hole (primary vs recurrent), aetiology, surgeon's preferences, experience, and judgement. All involved surgeons work in tertiary referral centres receiving difficult cases, and this adds a selection bias explaining why type 3, 4, and 5 surgeries, reserved to the most difficult cases, were so numerous. For this reason, the sample population included in the study does not represent an unbiased sample of primary MHs but may offer the chance of seeing a wider range of healing patterns.

The patients' initial condition likely informs the final outcome: such an analysis is beyond the scope of the present manuscript and requires further study.

On the other hand, those biases marginally affect the purpose of deploying and testing a MHCP classification and indeed allowed a broad case load and a significant diversity of surgical techniques giving the opportunity of classifying the largest possible spectrum of closure patterns and outcomes.

As novel surgical techniques lead to novel morphology of macular hole closure and wound healing, reclassification of terminology is needed. A morphology-based MHCP classification system should account for the type of surgery, the closure pattern, and stability and should provide insight in changes over time. While there may be an association between MHCPs and visual prognosis, our study was not powered to detect differences between surgical techniques; further studies using this classification system could assess long-term outcomes between groups.

Compared with previous classifications, this one takes advantage of improved retinal layer visualisation by higher resolution SD-OCT and enhances our insight and understanding of healing mechanisms. It may also provide a prognostic value.

The standardisation of terminology accounting for new surgical techniques and the adoption of a univocal classification could improve the assessment of post-operative anatomic and functional outcomes.

Acknowledgements The authors would like to thank the Fondazione Roma for support.

Author contributions T. Rossi: manuscript writing and design study. D. Bacherini: data search, proof reading, and design study. T. Caporossi: data search and manuscript writing. S. Telani, N. Koujlisis, and T. Mahmoud: manuscript writing and proof reading. D. Iannetta, S. Rizzo, and G. Ripandelli: data search and proof reading. S. Moysidis: data search

Compliance with ethical standards

Present research complies with the guidelines for human studies and was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. IRB approval was obtained, and informed consent was obtained by patients involved in the study.

Conflict of interest The authors declare that they have no conflict of interest.

Disclaimer All authors certify that they have no affiliations with or involvement in any organisation or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licencing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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