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RETINAL DISORDERS

360° inverted internal limiting membrane flap technique for idiopathic macular holes ≤ 250 µm, > 250 and ≤ 400 µm, and > 400 µm

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Abstract

Purpose To study the functional and morphological results of the inverted internal limiting membrane (ILM) flap technique for the treatment of idiopathic macular holes (MHs) sized ≤ 250 µm, > 250 and ≤ 400 µm, and > 400 µm.

Methods Retrospective, nonrandomized interventional study of 65 eyes with primary idiopathic MHs who underwent pars plana vitrectomy (PPV) with the inverted ILM flap technique. Closure rate, best-corrected visual acuity (BCVA), and integrity of external limiting membrane (ELM) and ellipsoid zone (EZ) were analyzed by optical coherence tomography (OCT).

Results Total closure rate was 96.9% with 100% in the ≤ 250 µm group, 100% in the > 250 and ≤ 400 µm group, and 91.7% in the > 400 µm group. Mean BCVA significantly improved after treatment: from 0.7 to 0.3 LogMAR in the ≤ 250 µm group (n = 15, p < 0.001), from 0.9 to 0.4 LogMAR in the > 250 and ≤ 400 µm group (n = 26, p < 0.001), and from 1.0 to 0.5 LogMAR in the > 400 µm group (n = 24, p < 0.001). A total of 16 patients had follow-up over 14 months: BCVA increased from 0.9 LogMAR preoperatively to 0.4 after 1 month (p < 0.00001) and to 0.3 LogMAR after 14 months (p = 0.03). A recovered ELM could be observed in 56.3% after 1 month and in 87.5% after 14 months. A recovered EZ could be observed in 18.8% after 1 month and in 68.8% after 14 months.

Conclusion The study demonstrates a high closure rate with corresponding restitution of outer retinal layers. In addition to its importance for the treatment of MHs > 400 µm, the inverted ILM flap technique also appears to be effective and safe for the treatment of MHs < 400 µm.

Trial registration: WHO: DRKS00021241

Keywords 360° inverted ILM flap technique · Cover technique · Small macular hole · Medium macular hole · Macular surgery · Closure rate · < 400 µm

Key messages

- The inverted ILM flap technique has been successfully used for the treatment of macular holes sized >400µm and myopic macular holes
- Our study shows that the inverted ILM flap technique can be effectively applied in macular holes sized ≤250µm and >250 and ≤400µm, providing high closure rates and good morphological and functional results
- At the 14-month follow-up, we found significant reintegration of the outer retinal layers and improvement in visual

Presentation at a conference The paper was presented at the at the DOG 2021 online congress (NM14-02 "Inverted ILM flap technique for idiopathic small, medium, and large macular holes") [1].

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Introduction

The term "hole at the macula" was first coined examining traumatic macular holes (MHs) in 1900 by Ogilvie [2]. Subsequently, description of idiopathic macular holes was long based on the classification of Donald Gass [3]. Since the arrival of OCT, we have the possibility to perceive this disease on a microscopic level. This led to a new classification for idiopathic MHs which is *the international vitreomacular traction study group classification of vitreomacular adhesion, traction, and macular hole* [4] and paved the way for innovative surgical techniques like the intraoperative OCT-guided macular surgery [5, 6]. However, there are efforts to update the possibly arbitrary definition of large macular holes at > 400 µm in contrast to this classification. New definitions of large macular holes are suggested at a threshold of 500 µm [7] or 630–650 µm [8], beyond which a poorer success rate is assumed.

Since Kelly and Wendel demonstrated the treatability of MHs by vitrectomy in 1991 [9], the surgical outcomes were assessed on the influence of a posterior vitreous detachment (PVD), a complete ILM removal or the application of different endotamponades. PPV with induction of a posterior vitreous detachment, peeling of the internal limiting membrane (ILM), and intravitreal gas tamponade with postoperative prone positioning became the standard therapy [10]. Closure rates of up to 100% are achieved with PPV and ILM peeling [11, 12]. Lower closure rates are seen with larger macular hole diameters and smaller holes seem to correlate with better postoperative visual acuity [10, 13].

In 2008, Michalewska et al. were the first to present the 360° inverted flap technique to originally achieve higher closure rates for large (Gass classification: stage 4) MHs [14]. The technique consists of peeling the perifoveal ILM and preparing a flap which is kept attached to the MH margin. The authors speculated based on their OCT findings that the ILM flap would work as a scaffold for neuronal reproliferation [15]. However, postoperative cellular recovery is not yet fully understood. Recently, it was confirmed that BCVA improvement could be strongly correlated with outer retinal layer restoration after successful inverted flap surgery [16].

Closure rates of 83–100% are achieved by the inverted flap technique in large idiopathic MHs [11, 16–26] and of 80–100% in highly myopic eyes [15, 27–29].

For small (≤ 250 µm) and medium (> 250 and ≤ 400 µm) MHs, there is a scarcity of data regarding the treatment with inverted flap. Rizzo et al. examined cases of less than 400 µm and described a closure rate of 97.3% with a BCVA increase from 0.70 preoperatively to 0.45 LogMAR postoperatively whereas an exact indication of the number of treated cases is missing [25]. Baumann et al. studied 24 cases of macular holes < 400 µm treated with inverted flap. They found no differences in postoperative BCVA and ELM or EZ restoration compared to the comparison group (conventional peeling) [30]. Da Chou et al. studied 55 cases of small and medium-sized macular holes with a semicircular, single-layer inverted flap, of which 54 cases (98%) closed [31].

We are a group of Munich-based retinal specialists with > 30 (P.H.) and > 15 (M.K.) years of expertise in vitreoretinal surgery. Since 2014, we have been using the inverted flap technique initially for the treatment of large MHs. Convinced by the results, we also started to use it for small and medium MHs. In this study, we aimed to investigate closure rate, best-corrected visual acuity, the condition of the external limiting membrane (ELM), and ellipsoid zone (EZ) for MHs ≤ 250 µm, > 250 and ≤ 400 µm, and > 400 µm.

Methods

This is a retrospective, nonrandomized, interventional study of eyes which had been treated by PPV with the inverted flap technique (cover technique) and gas (20% C_2F_6) endotamponade due to primary idiopathic MHs ≤ 250 µm, > 250 and ≤ 400 µm, and > 400 µm at the Munich-based Herzog Carl Theodor Eye Hospital between March 2015 and January 2018. The study was approved by the institutional review board (Ethik-Kommission, Bayerische Landesärztekammer) and complies with the Declaration of Helsinki. Written informed consent for participation and publication was obtained from all patients.

Exclusion criteria were refractory MH after surgical treatment, secondary or traumatic MH, age below 18 years, and the presence of other severe retinal co-pathologies. Macular drusen and pretreatment with Ocriplasmin were not considered exclusion criteria. Collected patient data consisted of age, gender, lens status, vitreous status, best-corrected visual acuity (all patients: preoperative and 1 month [median] postoperative, follow-up group: 8 and 14 months [median] postoperative), MH size (minimum diameter on horizontal optical coherence tomography [OCT] scans [Spectralis OCT, Heidelberg Engineering, Heidelberg, Germany]), MH closure rate, and postoperative status of ELM and EZ in OCT. For patients in whom both eyes met the inclusion criteria, only one eye was included in the study, which was previously selected by coin toss.

All operations were performed by two surgeons (P.H. or M.K.) using a 23-gauge system with an OS4 vitrectomy machine (Oertli, Berneck, Switzerland). After inducing a posterior vitreous detachment (if necessary) and ILM staining, a 360° perifoveal ILM flap was prepared in a circular way with end-gripping forceps and gently placed covering the MH keeping it adherent to the hole margin. The flap was prepared in the intended size, so trimming with a cutter was not necessary. ILM located peripherally to the flap was peeled within the vascular arcades. In case of lens opacity or cataract, phacoemulsification was performed at the beginning of the procedure. At the end of the operation, an intravitreal gas tamponade was applied, followed by prone positioning for 5 days.

For statistical analysis, the software *Excel (Microsoft®)* and the online-based software *socscistatistics.com* were used. Continuous variables were displayed as statistical mean or median. The *t*-test was used to compare continuous variables with normal distribution. Comparisons between categorical variables were made using the chi-squared test for nominal data. Logistic regression was calculated for nominally scaled or ordinally scaled dependent variables. A significance level of $p = 0.05$ was defined.

Results

We included 65 eyes of 65 patients (42 women and 23 men) in the study. Mean age was 68.7 years. All eyes were treated by 23 gauge PPV and the 360° inverted flap technique (cover technique). A total of 19 eyes (29.2%) had been pseudophakic at the first consultation. Preoperative BCVA did not vary significantly between the pseudophakic ($n = 19$, mean BCVA 0.8 LogMAR) and phakic ($n = 46$, mean BCVA 0.9 LogMAR) groups ($p = 0.16$). In 42 cases, combined phacoemulsification and IOL implantation were performed. Thus, 61 eyes were pseudophakic and four phakic postoperatively. Two eyes had been pretreated unsuccessfully with ocriplasmin. Three eyes (4.6%) had macular drusen.

The average MH size (minimum horizontal diameter) was 356 µm. The smallest diameter among the examined cases was 69 µm, the largest 709 µm. There were 15 MHs ≤ 250 µm including 14 with vitreomacular traction (VMT) and one without VMT, 26 MHs > 250 and ≤ 400 µm including 19 with VMT and seven without VMT, and 24 MHs > 400 µm including 18 with and 6 without VMT according to *the International Vitreomacular Study Group classification of vitreomacular adhesion, traction, and macular hole* [4] (Fig. 1).

Of the 65 eyes examined, 14 (21.5%) already had a posterior vitreous detachment at the time of surgery and 51 (78.5%) had a posterior vitreous detachment induced by vitrectomy. In six cases, intraoperative exocryocoagulation or endolaser was needed to treat peripheral retinal breaks or degenerations.

The overall closure rate was 96.9% (63/65eyes). Closure rate was 100% (15/15 eyes) in the ≤ 250 µm group, 100% (26/26 eyes) in the > 250 and ≤ 400 µm group, and 91.7% (22/24 eyes) in the > 400 µm group. The difference between the results of the > 400 µm group and each of the ≤ 250 µm and the > 250 and ≤ 400 µm group was statistically significant regarding closure rates ($p < 0.001$).

Mean BCVA improved from 0.7 LogMAR preoperatively to 0.3 LogMAR postoperatively in the ≤ 250 µm group ($n = 15$, $p < 0.001$, average 1.96 months after surgery), from 0.9 LogMAR preoperatively to 0.4 LogMAR postoperatively in the > 250 and ≤ 400 µm group ($n = 26$, $p < 0.001$, average 1.8 months after surgery), and from 1.0 LogMAR preoperatively to 0.5 LogMAR postoperatively in the > 400 µm group ($n = 24$, $p < 0.001$, average 1.95 months after surgery). In all eyes ($n = 65$, $p < 0.001$, average 1.89 months after surgery), mean BCVA improved from 0.9 LogMAR preoperatively to 0.4 LogMAR postoperatively (Table 1).

Postoperative BCVA varied significantly between the ≤ 250 µm group and the > 250 and ≤ 400 µm group ($p = 0.04$), as well as between the > 250 and ≤ 400 µm group and the > 400 µm group ($p = 0.03$).

In eyes with postoperatively (median 1 month) regenerated EZ ($n = 21$), mean BCVA (0.3 LogMAR) was significantly better than in eyes with interrupted EZ ($n = 44$), which reached a mean BCVA of 0.4 LogMAR ($p = 0.001$).

In 50 (76.9%) of all ($n = 65$) cases, a continuous ELM could be observed on average 1.89 months (1 month median) postoperatively. The mean hole size of these cases was 330 µm. In 15 cases (23.1%), the ELM showed an

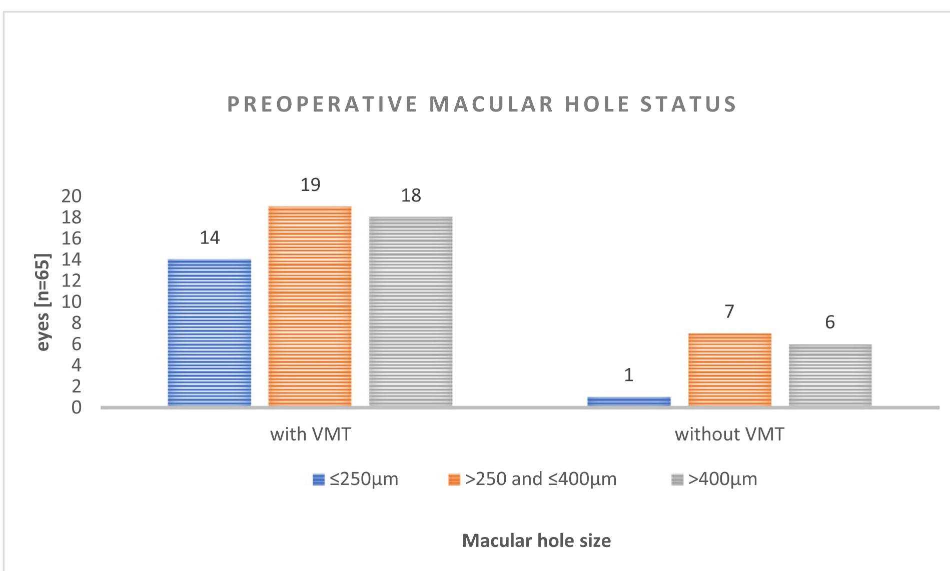


Fig. 1 Preoperative macular hole status according to minimum horizontal diameter (size) and presence of vitreomacular traction (VMT): ≤ 250 µm group ($n = 15$), > 250 and ≤ 400 µm group ($n = 26$), and > 400 µm group ($n = 24$) among 65 eyes of 65 patients

Table 1 Preoperative and postoperative BCVA of the subgroups according to macular hole size and all eyes, *p*-value of visual acuity increase and time of BCVA measurement in the respective group

	BCVA [LogMAR]		*p*	Ø months after surgery
	Preoperative	Postoperative		
≤250 µm group (*n*=15)	0.7	0.3	<0.001	1.96
>250 and ≤400 µm group (*n*=26)	0.9	0.4	<0.001	1.8
>400 µm group (*n*=24)	1.0	0.5	<0.001	1.95
All eyes (*n*=65)	0.9	0.4	<0.001	1.89

interruption. Among them, there were two persistent MHs in which the ELM was completely absent in the hole area. The average hole size of these 15 cases was 443 µm. The difference between the groups with postoperative continuous and interrupted (including missing) ELM was statistically significant with respect to the hole size ($p=0.002$).

In 21 (32.3%) of all cases, a continuous EZ was detectable on average 1.89 months (1 month median) postoperatively. The mean hole size of these cases was 296 µm. In 44 cases (67.7%), there were interruptions of the EZ. Among them, there were two persistent MHs. The mean hole size of these cases was 385 µm. The difference between the groups with postoperative continuous and interrupted (including missing) EZ was statistically significant regarding the hole size ($p=0.006$).

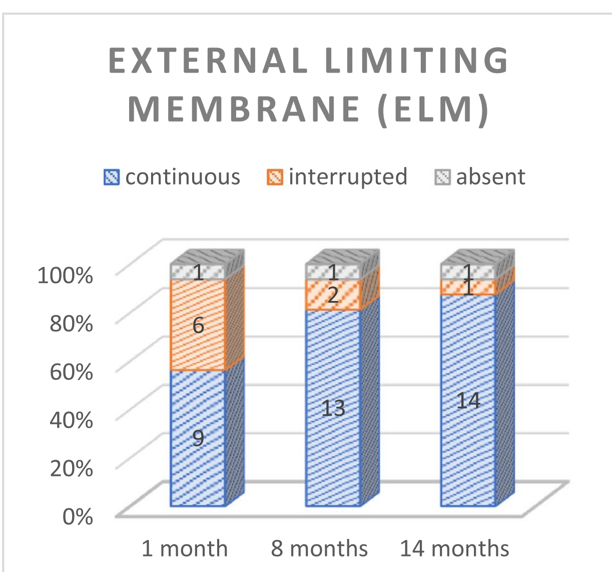
All cases of interrupted ELM ($n=16$) had an interruption of the EZ simultaneously.

In 16 patients (mean MH diameter: 317 µm), follow-up over a period of 14 months was possible. BCVA was 0.9 LogMAR preoperatively, 0.4 LogMAR after 1 month ($p<0.00001$), 0.3 LogMAR after 8 months ($p=0.03$), and 0.3 LogMAR after 14 months ($p=0.42$). In the follow-up group, a recovered ELM could be observed in 56.3% (9/16 eyes) after 1 month, in 81.3% (13/16 eyes) after 8 months ($p=0.04$), and in 87.5% (14/16 eyes) after 14 months ($p=0.33$). A recovered EZ could be observed in 18.8% (3/16 eyes) after 1 month, in 50% (8/16 eyes) after 8 months ($p=0.02$), and in 68.8% (11/16 eyes) after 14 months ($p=0.08$) (Fig. 2).

In the group of continuous ELM ($n=50$), mean BCVA was 0.3 LogMAR 1 month (median) postoperatively. This was significantly better ($p=0.003$) than in the group of interrupted ELM ($n=13$, 0.5 LogMAR). In the group of absent ELM ($n=2$), postoperative BCVA was 0.8 LogMAR (Fig. 3).

In the group of continuous EZ ($n=21$), mean BCVA was 0.3 LogMAR 1 month (median) postoperatively. This was significantly better ($p=0.015$) than in the group of interrupted EZ ($n=42$, 0.4 LogMAR). In the group of absent EZ ($n=2$), postoperative BCVA was 0.8 LogMAR (Fig. 3).

A binary logistic regression analysis to predict the state of ELM and EZ as continuous or interrupted was performed with the following variables: age at time of surgery, gender (male/female), and presence of posterior vitreous



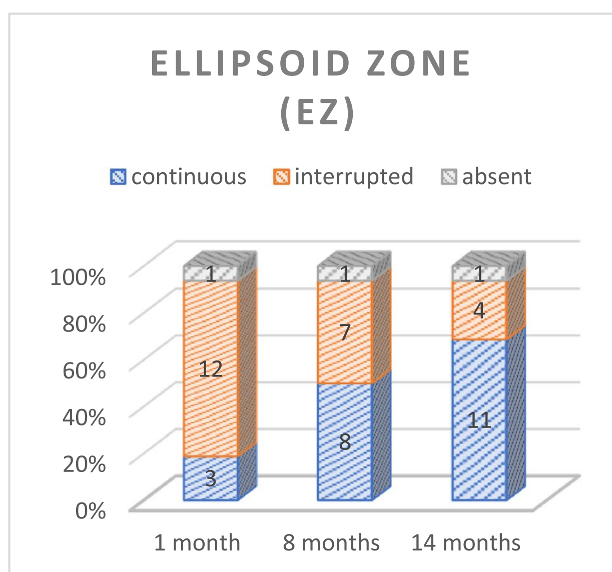


Fig. 2 Status of the external limiting membrane (left) and the ellipsoid zone (right) as continuous/interrupted/absent in a follow-up group of 16 eyes 1 month, 8 months, and 14 months (median) postoperatively

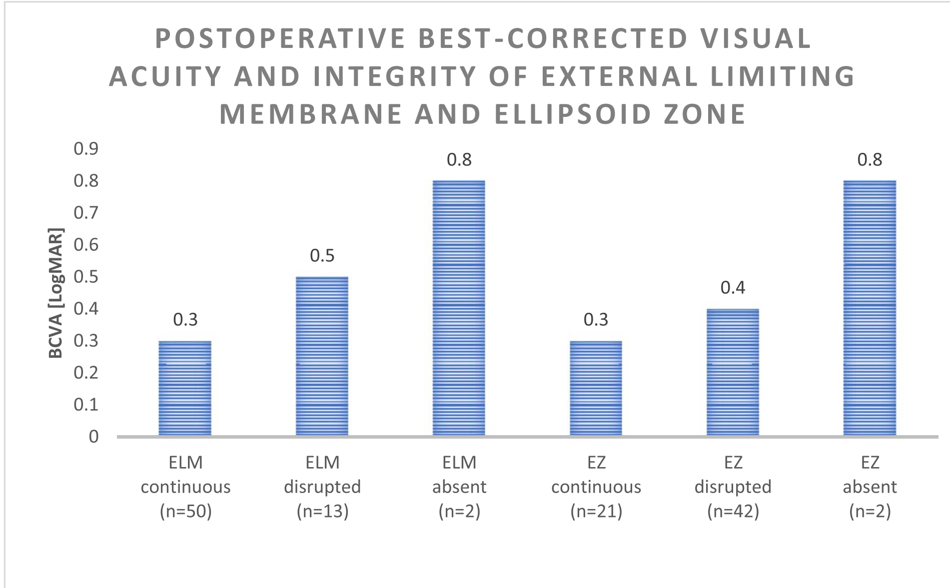


Fig. 3 Mean postoperative BCVA [LogMAR] in the groups of continuous, disrupted, and absent external limiting membrane (ELM) and ellipsoid zone (EZ)

detachment at time of surgery, none of which proved relevant in this context.

Discussion

With the inverted flap technique, closure rates of 83–100% are achieved in idiopathic MHs > 400 µm [11, 16–26]. However, only limited data is available so far on the treatment of small- and medium-sized MHs with the inverted flap technique.

The overall closure rate in this study was 96.9% with 100% in the ≤ 250 µm group, 100% in the > 250 and ≤ 400 µm group, and 91.7% in the > 400 µm group. Mean BCVA significantly increased after treatment: from 0.7 to 0.3 LogMAR in the ≤ 250 µm group, from 0.9 to 0.4 LogMAR in the > 250 and ≤ 400 µm group, and from 1.0 to 0.5 LogMAR in the > 400 µm group. In 76.9% of all eyes examined, a continuous ELM could be observed postoperatively. In 23.1%, the ELM showed an interruption. Continuous EZ was present postoperatively in 32.3% of all cases, whereas 67.7% showed an interruption of the EZ.

Follow-up was completed in 16 patients over 14 months: BCVA improved from 0.9 LogMAR preoperatively to 0.4 at 1 month and to 0.3 at 14 months. A recovered ELM could be observed in 56.3% after 1 month and in 87.5% after 14 months. A recovered EZ could be observed in 18.8% after 1 month and in 68.8% after 14 months.

Postoperative ELM integrity represents a key prognostic factor for photoreceptor layer recovery and thus for positive visual outcome after MH surgery [32, 33]. At the cellular level, an intact ELM corresponds to the junctional zone including cell membranes and zonulae adherentes between photoreceptor inner segments and glia, especially Müller cells [32, 34]. Regenerated ELM is thought to form the basis for photoreceptor migration, leading to regeneration of the photoreceptor layer. It would also be imaginable that contractile properties of the ILM [35] cause the flap to contribute to a sphincter-like centripetal movement of the macular hole margins. This process eventually results in macular hole closure [34] (Fig. 4). Subsequently, a reintegration of ELM and EZ characterizes the morphological restitution. In this regard, the inverted flap does not appear to have any detrimental effects. We found no case of regenerated EZ without regenerated ELM. This finding is consistent with the results of previous studies [32, 36].

Iwasaki et al. investigated the effects of the inverted flap on structures of the outer retina, in particular the ELM and EZ. The postoperative recovery rate was significantly lower and the postoperative recovery period of the ELM was significantly longer in the inverted group than in the ILM peeling group. Postoperative visual acuity was worse in the inverted group than in the ILM peeling group. These negative effects were attributed to the inverted flap technique [11]. In contrast, in our study postoperative ELM recovery was high at 76.9%. Among these, the average hole size was 330 µm. This difference could be explained by the fact that in the study of Iwasaki et al., the MH diameter was higher in the inverted flap group (655 µm) than in the peeling group (551 µm). In addition, variability in the surgical technique could play a role: Iwasaki et al. used both cover ($n = 6$) and fill ($n = 8$) technique, partly with ocular viscoelastic device as an adjunct. There were, with a relatively small number of cases, four different surgeons performing the operations which could have led to variability in flap construction.

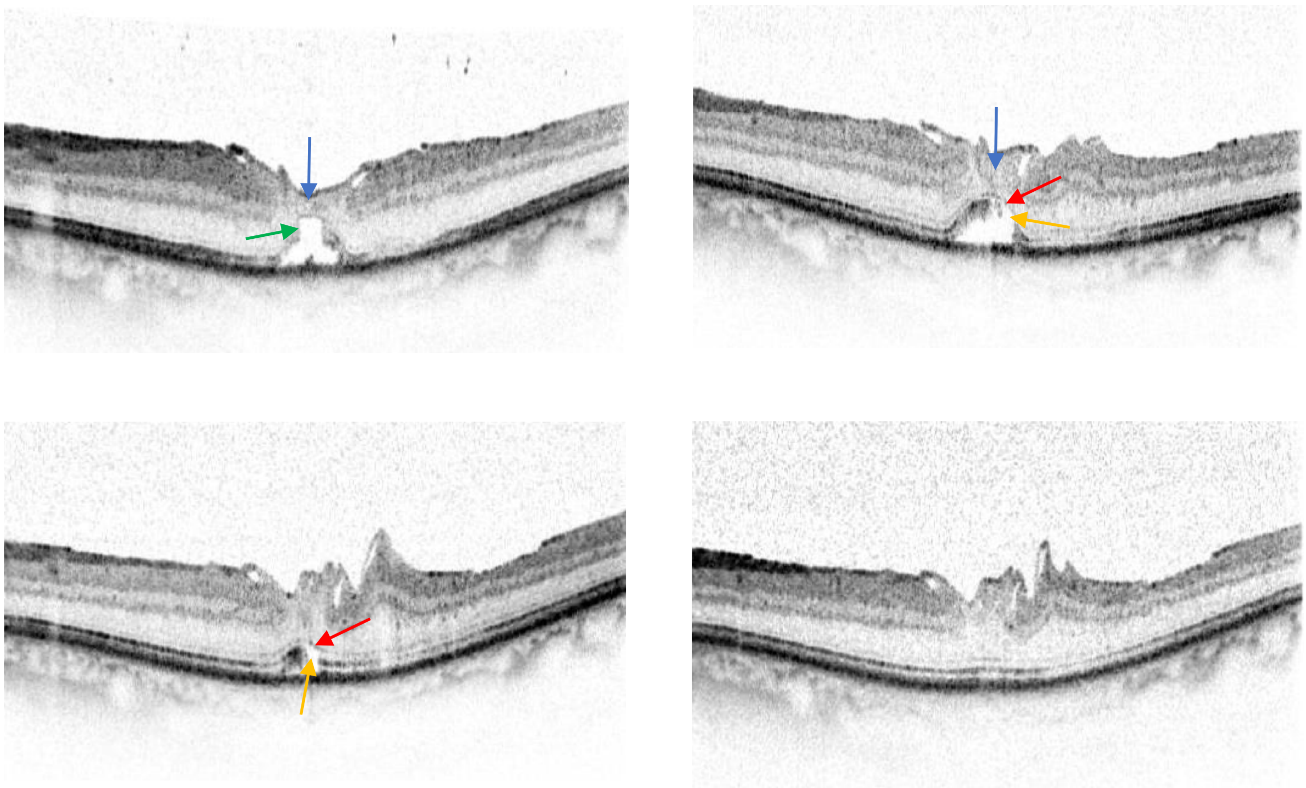


Fig. 4 Morphology of MH closure over 14 months. *Top left:* Bridge-like closure configuration/subfoveal space. Two weeks postoperatively, thin tissue bridge (blue arrow), ELM and EZ interrupted (green arrow). *Top right:* 2 months postoperatively, firmer tissue bridge (blue arrow), continuous ELM (red arrow), interrupted EZ (yellow arrow). *Bottom left:* 7 months postoperatively, reduction of the subfoveal space, continuous ELM (red arrow), interrupted EZ (yellow arrow). *Bottom right:* 14 months postoperatively: complete resolution of the subfoveal space and regeneration of the outer retinal layers

Among 63 eyes treated with the inverted flap technique, Baumann et al. (2020) found a completely regenerated EZ in 13% and a partially regenerated EZ in 56% after 3 months. The ELM showed complete recovery in 52% and partial recovery in 30%. From this group, 25 eyes could be followed for 12 months with significant visual improvement. After 12 months, complete EZ integrity was found in 60% of the ILM peeling group and 64% of the ILM flap group; complete ELM integrity was found in 90% of the ILM peeling group and 80% of the ILM flap group. In the ILM flap group, EZ recovery tended to be slower, but not significantly. It might be noteworthy that the mean hole size in the ILM flap group was larger (560 µm) than in the ILM peeling group (504 µm) [16]. The work of Baumann et al. and the results of our study demonstrate that time plays an essential role in both morphological and functional restitution: Integrity of ELM and EZ and visual acuity improved over time.

Concerns that large MHs have worse functional and morphological outcomes after therapy with the inverted flap than with ILM peeling seem unlikely according to recent study results. Bleidißel et al. used a radial rosette-shaped inverted flap (five radially arranged sectional flaps attached to the MH margin) covering the MH. It would be conceivable that the radial rosette-shaped construction could favor an inward turn of the flap by avoiding centrifugal unfolding forces. They found a closure rate of 100% in 55 patients with an average MH diameter of 517 µm and showed the technique to have good morphological and functional short-term and long-term results [13].

The importance of surgical details such as cover vs. fill and radial rosette-shaped technique or the use of viscoelastic device for flap adherence is probably hard to clarify, since there is not always a standardized protocol for flap preparation in the recent literature. Moreover, positional changes or unfolding of the inverted flap could occur intraoperatively during fluid-air exchange or postoperatively making an exact assignment to the cover or fill technique difficult. In our study, a standardized protocol with the cover technique was used. No ocular viscoelastic device for flap manipulation was applied.

A meta-analysis of four randomized controlled trials of the inverted flap concluded that the inverted ILM flap technique had advantages over conventional ILM peeling in idiopathic large MHs in terms of better morphologic and functional outcomes and assigns high efficacy to the method [37].

Certainly, the question of whether the use of the inverted flap technique is necessary for small and medium MHs should be discussed in the light of closure rates of up to 100% with complete ILM peeling [11, 12].

However, why not treat small and medium MHs with inverted flap if the closure rates are as good as with complete peeling? Rizzo et al. achieved a closure rate of 97.3% in MHs < 400 µm using the inverted flap technique [25]. Da Chou et al. found that in MHs < 400 µm, there was less gliosis in the closure process and faster restitution of outer retinal layers in the inverted flap group compared to the peeling group. They used a semicircular single-layer inverted flap [31].

Our study shows that in small and medium macular holes, the inverted flap technique can achieve closure rates equal to those achieved with complete ILM peeling. In addition, the inverted flap technique does not appear to negatively affect hole closure. We consider the encouraging findings of our study and those of Baumann et al. [30] as evidence for good morphological and functional long-term results of the 360° inverted flap in cover technique in small and medium MHs. However, further studies with standard ILM peeling as a comparison group would be necessary to better evaluate functional and morphological outcomes.

Limitations in this study include the retrospective nature, which lacks a standardized follow-up protocol. In addition, we did not have a control group that could have provided reference data by vitrectomy with complete ILM peeling. A strength of our study is on the other hand the relatively large number of participants, a standardized surgical protocol and the long follow-up period of up to 14 months.

Author contribution All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Gregor Kastl and Michael Janusz Koss. The first draft of the manuscript was written by Gregor Kastl and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Declarations

Ethics approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the Helsinki Declaration. Registration number from the local institutional review board (Ethik-Kommission, Bayerische Landesärztekammer): 17061. World Health Organization (WHO) trial number: DRKS00021241.

Consent to participate and consent to publish The patients gave their written informed consent to participate in the study and to the publication of their data.

Conflict of interest The authors declare no competing interests.

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