Int Ophthalmol (2019) 39:1277–1282
https://doi.org/10.1007/s10792-018-0941-z

ORIGINAL PAPER

# Microstructural retinal regeneration after internal limiting membrane flap surgery for repair of large macular holes: a 1-year follow-up study

**Max Vieregge · Christophe Valmaggia · Hendrik P. N. Scholl · Josef Guber**

Received: 12 March 2018 / Accepted: 2 May 2018 / Published online: 9 May 2018


**Abstract**
*Purpose* To evaluate long-term change in functional and structural outcomes after successful repair of large macular holes (MH) with internal limiting membrane (ILM) flap techniques.
*Methods* Eleven consecutive patients were reviewed over a 1-year time period after the successful repair of large MH with ILM flap techniques. SD–optical coherence tomography (SD-OCT) images were taken to assess the anatomical outcome after surgery, while the best-corrected visual acuity (BCVA) was tested using Snellen charts to evaluate the functional outcome. Each patient was evaluated at 1, 6 and 12 months after surgery, respectively.
*Results* All cases achieved complete anatomical closure. All patients showed a microstructural regeneration of the retina with a decrease in ellipsoid zone defects over the 1-year follow-up. Functionally, as compared to baseline, all of the patients showed improvements in best-corrected visual acuity of 1–4 lines at the final examination after 12 months postoperatively.
*Conclusions* Long-term results show further improvement in the best-corrected visual acuity as well as further microstructural regeneration of the retina and decrease in ellipsoid zone defects over time. The exact mechanism, which promotes closure of the macular hole and reconstruction of the ellipsoid zone after internal Limiting Membrane autograft surgery, still remains unknown.

**Keywords** Ellipsoid zone · Macular hole · Internal limiting membrane flap · Inverted flap · Free flap

M. Vieregge · C. Valmaggia · J. Guber (✉)
Eye Clinic, Cantonal Hospital Sankt Gallen, Rorschacherstrasse 95, Sankt Gallen 9007, Switzerland
e-mail: josef_guber@hotmail.com

H. P. N. Scholl · J. Guber
Department of Ophthalmology, University Hospital Basel, Basel, Switzerland

## Introduction

Macular holes (MH) are full-thickness retinal defects of the fovea, which impair central vision. Even though anatomical closure following primary pars plana vitrectomy (PPV) and internal limiting membrane peel (ILM) with gas tamponade is given in 60–100% of the cases, closure rates tend to be lower in larger macular holes (> 400 µm), atrophic macular holes and macular holes associated with high myopia [1, 2]. In 2010, Michalewska et al. [3] postulated a technique for the initial surgery of large macular holes, in which a part of an incompletely peeled internal limiting membrane was placed at the base of the macular hole. Their theory was that the inverted internal limiting flap serves as a stimulus and scaffold to the proliferation of glial cells, therefore promoting macular hole closure.

Even though success rates are high after standard procedure, surgical failure still may occur. Closure is much more reluctant in refractory macular holes and rarely exceeds 50% [4–6]. The surgical technique with autologous free internal limiting membrane flaps was introduced by Morizane et al. Identically to the inverted flap technique, it is assumed that placing a peripheral graft within the hole enhances closure [7].

However, despite the high closure rate for large and refractory macular holes, some vitreoretinal surgeons are still reserved in performing these new techniques because of concerns regarding the long-term outcomes. In particular, the effect of the ILM flap on the microstructural regeneration is subject of hot debate.

This study reports the long-term results with both techniques, in which we analyse the functional, in terms of best-corrected visual acuity and anatomical outcomes, with special focus on the microstructural regeneration of the retina and the decrease in ellipsoid zone defects.

## Patients and methods

The study was performed in accordance with local clinical governance approval and as a part of departmental quality control. Research adhered to the tenets of the Declaration of Helsinki.

All patients who received inverted or free flap surgery for large macular holes (minimum diameter $> 400$ µm) and non-closing macular holes in the time period from January to September 2016, were incorporated in our study.

Complete ophthalmological examination was assessed with all patients. The best-corrected visual acuity (BCVA) (in decimal) was recorded, and spectral domain optical coherence tomography (SD-OCT) was performed prior to surgery as well as at 1, 6 and 12 months after surgery, respectively.

Ellipsoid zone defects were measured manually by two experienced ophthalmologists, and the best-corrected visual acuity (BCVA) was tested using a Snellen chart. Pre- and post-operative OCT measurements were taken using the same sectional images. The macular hole base diameter was noted as the baseline ellipsoid defect (Fig. 1).

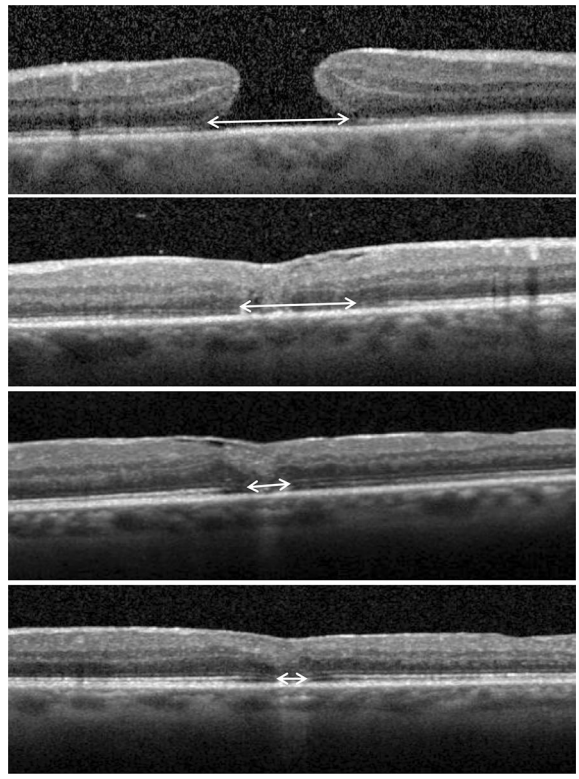

**Fig. 1** Microstructural retinal regeneration over time. Spectral domain–optical coherence tomography images showing ellipsoid zone defect decreases and microstructural retinal reconstruction over 12 months after surgery (from top to bottom: pre-operative, 1 month, 6 months and 1 year after successful surgery, arrows indicate ellipsoid zone defects)

Ellipsoid zone defect measurements and BCVA scores were analysed by calculating overall means (with standard errors) and means by method (inverted versus free ILM flap) for each time point. Data at each of the three follow-up dates were compared to pre-operative values for all patients together with Wilcoxon signed-rank tests. $p$ values were Bonferroni-adjusted for multiple testing. Data analysis was carried out with the software R, version 3.3.3 [8].

### Surgical technique

Pars plana vitrectomy (23 gauge), either using inverted flap or free flap technique, was conducted on all patients. First central and peripheral pars plana vitrectomy was performed. Secondly, dual blue was applied to stain the internal limiting membrane. Finally, 20% sulphur hexafluoride or 12%

**Table 1** Patients' characteristics at baseline

| | Inverted ILM flap $n = 8$ | Free ILM flap $n = 3$ | Total $n = 11$ |
|---|---|---|---|
| Age (mean, years) | 61 | 79 | 66 |
| Gender m:f | 3:5 | 0:3 | 3:8 |
| Mean MH smallest diameter (μm) | 512 (400–659) | 478 (432–504) | 495 (400–659) |
| Mean MH base diameter (μm, range) | 922 (662–1293) | 1038 (925–1250) | 980 (662–1293) |
| Pre-operative BCVA (decimal, range) | HM to 0.3 | CF to 0.1 | CF to 0.3 |

*MH* macular hole, *BCVA* best-corrected visual acuity, *ILM* internal limiting membrane, *HM* hand movements, *CF* counting fingers

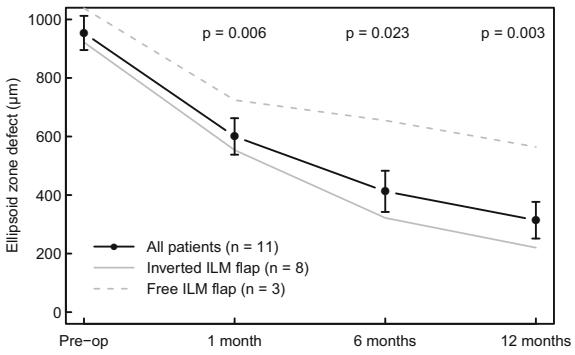


**Fig. 2** Changes in ellipsoid zone defect size through time. Black lines show means (± SE) of all patients at each visit, and grey lines show means by method (inverted versus free ILM flap). *p* values for the difference between pre-operative values and each of the three follow-up times were obtained using Wilcoxon signed-rank tests with Bonferroni adjustment for multiple testing. ILM = internal limiting membrane

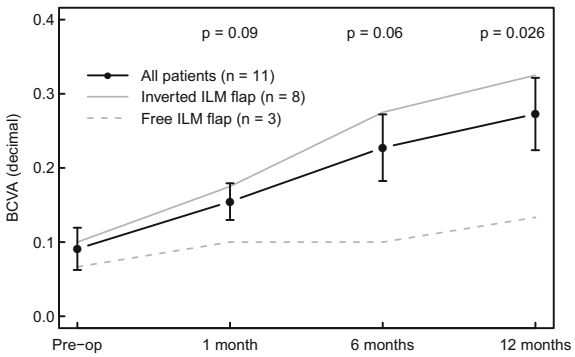


**Fig. 3** Changes in BCVA scores through time. Black lines show means (± SE) of all patients at each visit, and grey lines show means by method (inverted versus free ILM flap). *p* values for the difference between pre-operative values and each of the three follow-up times were obtained using Wilcoxon signed-rank tests with Bonferroni adjustment for multiple testing. BCVA = best-corrected visual acuity (in decimal), ILM = internal limiting membrane

perfluoropropane tamponade was injected, and patients were instructed to hold a face-down posture for approximately 5 days [9].

*Inverted internal limiting membrane flap*

The internal limiting membrane flap was prepared in a circular pattern, approximately 1.5–2 disk diameters surrounding the macular hole using a 23G forceps. The innermost part was left attached at the rim of the macular hole. Thereafter, the inverted flap was placed gently into the hole. Finally, the operation was completed with a fluid–air exchange [9].

*Free internal limiting membrane flap*

After applying dual blue dye, the internal limiting membrane was shown to be absent in the macular area. At the edge of the previous peeling, near the vascular arcades, an internal limiting membrane graft of approximately one disc diameter was created. A small amount of viscoelastic solution was applied within the macular hole in order to prevent the graft from dislocating. The graft was then placed within the macular hole. At the end of surgery fluid–air exchange was performed [9].

## Results

Altogether, 11 patients were incorporated in this study. The inverted internal limiting membrane flap technique, for large macular holes, consisted of eight patients and three patients were part of the free internal limiting membrane flap technique for non-closing macular holes. All cases showed complete anatomical closure. Combined surgery with phacoemulsification

was conducted on three patients, while the rest of the patients were already pseudophakic.

Pre-operatively the smallest mean macular hole diameter in the inverted flap group was 511.5 µm (range 400–659 µm), compared to a mean of 478 µm (range 423–504 µm) in the free flap group. The mean pre-operative macular hole base defect in the inverted flap group was 922 µm (range 662–1293 µm) and 1038 µm (range 925–1250 µm) in the free flap group, respectively. The pre-operative best-corrected visual acuity ranged from hand movements to 0.3 in the inverted flap group and from counting fingers to 0.1 in the free flap group. Patients' characteristics at baseline are summarized in Table 1.

Partial microstructural regeneration of the retina with a decrease in ellipsoid zone defects, demonstrated on SD–optical coherence tomography, was observed in all cases 1 month after surgery and continued to improve in all patients throughout 12 months (Fig. 2). In all 11 patients, ellipsoid zone defects decreased statistically significant at all three follow-ups ($p < 0.05$). After 12 months, the mean ellipsoid defect in the inverted flap group was 220 µm (range 0–381 µm) and 564 µm (range 561–668 µm) in the free flap group, respectively.

Functionally, as compared to baseline, most of the patients in both groups showed a statistically significant improvement in best-corrected visual acuity of 1 to 4 lines by the final follow-up after 12 months ($p < 0.05$), (Fig. 3). The best-corrected visual acuity ranged from 0.08 to 0.5 in the inverted flap group and 0.1–0.2 in the free flap group at the final follow-up, respectively.

## Discussion

There are only a few options concerning surgical repair for large or refractory macular holes. In 2010, Michalewska et al. [3] were first to apply the inverted flap technique for large macular holes. Free flaps for non-closing macular holes were then first used by Morizane et al. [7]. Both techniques are easily applied with minimal extra effort.

Anatomical closure resulted in 100% in both groups, respectively [9]. However, long-term data are missing, and therefore, we conducted a long-term follow-up study to furthermore analyse the progression of the functional and anatomical outcomes over a 12-month time span. Functional recovery following

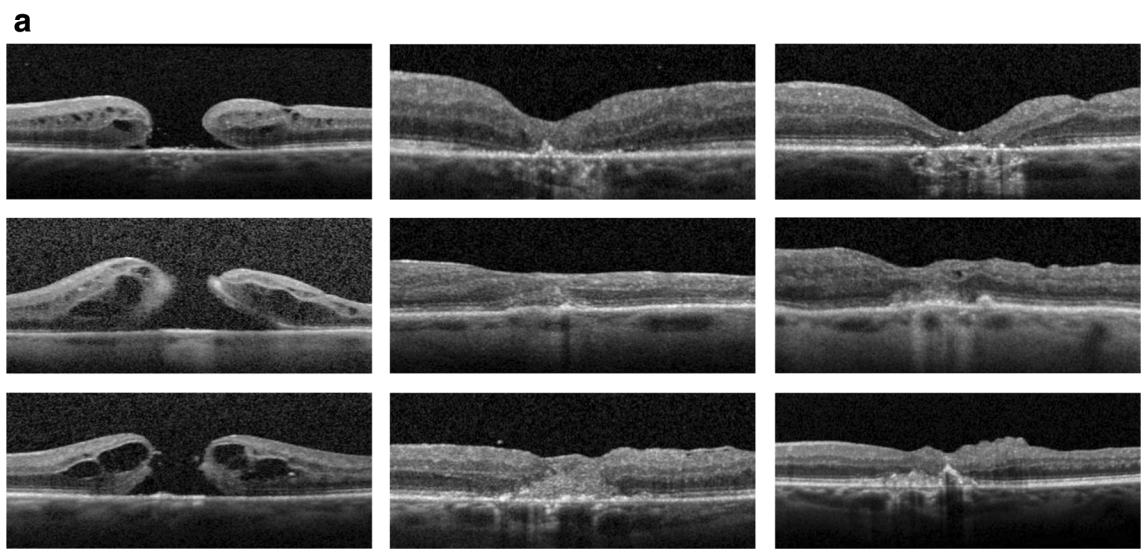


**Fig. 4** **a** Microstructural retinal regeneration after ILM free flap surgery. Spectral domain optical coherence tomography images showing ellipsoid zone defect decreases and microstructural retinal reconstruction over 12 months after surgery (from left to right: pre-operative, 1 month and 1 year after successful surgery, from top to bottom: patients one to three). **b** Microstructural retinal regeneration after ILM inverted flap surgery. Spectral domain optical coherence tomography images showing ellipsoid zone defect decreases and microstructural retinal reconstruction over 12 months after surgery (from left to right: pre-operative, 1 month and 1 year after successful surgery, from top to bottom: patients one to eight)

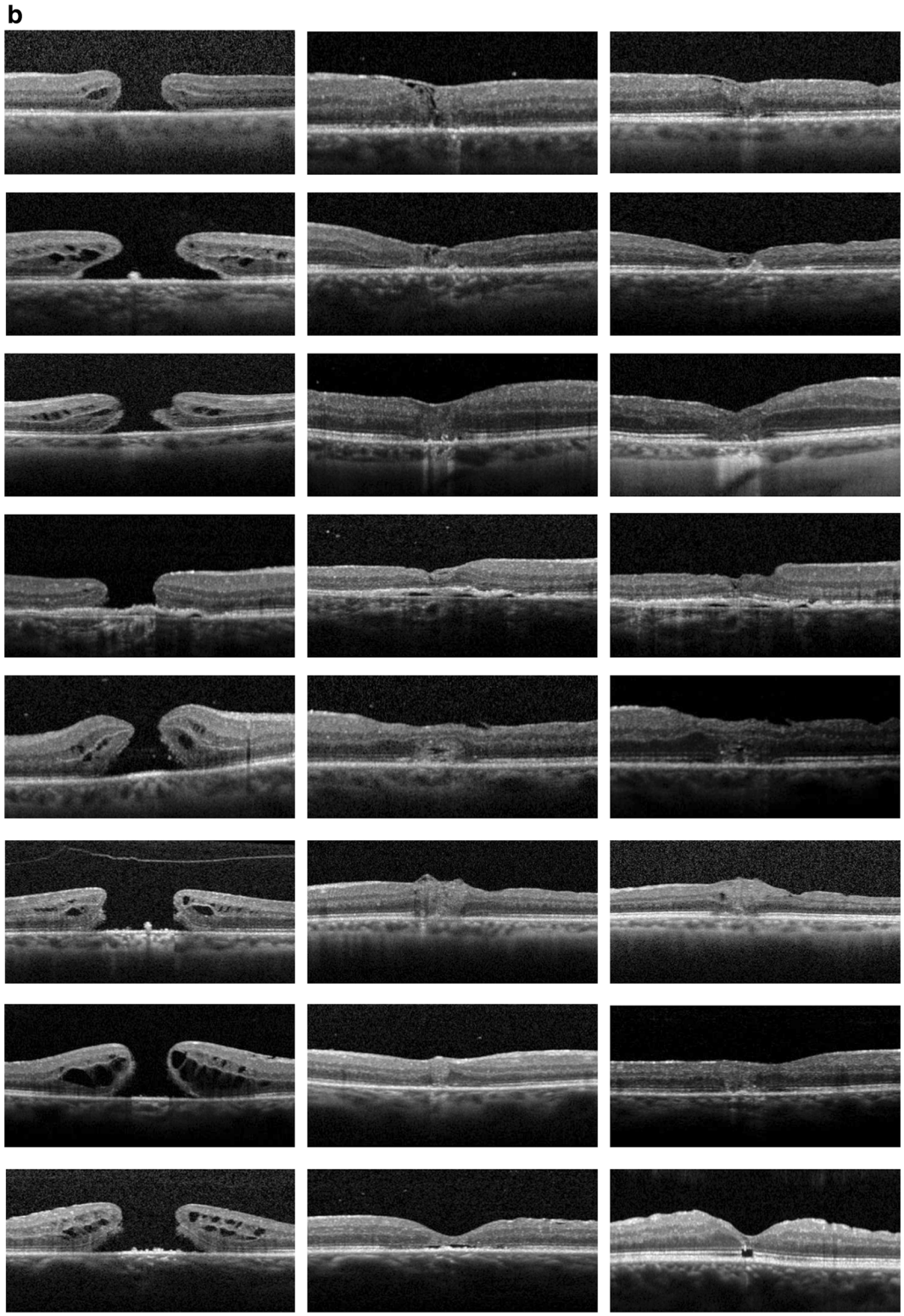


**Fig. 4** continued

standard procedure takes time and is continuous for up to 2 years [10].

In our studies, we have not only observed the anatomical closure of the macular holes, but also the positive long-term outcomes of best-corrected visual acuity and continuous regeneration of all retinal layers especially of the ellipsoid zone after using internal limiting membrane flap techniques (Fig. 4a, b).

As postulated by Wong and Steel, the specific mechanism that promotes closure by autografts is still not clearly defined [11]. Michalewska and collaborators have implied that the flaps may serve as a Müller cell source, which are situated upon the graft surface. Possibly, the grafts also serve as a scaffold for both Müller cell proliferation and migration [3]. Morizane et al., and other authors, have speculated that signals from Müller cells, located on the graft, may also enhance closure as well as photoreceptor restoration [7, 12–14]. It still also remains unclear how the ellipsoid zone is able to regenerate over time.

In order to better understand these mechanisms further histological studies are required.

**Acknowledgements** Dr. sc. Nat. Sabine Güsewell is acknowledged for statistical analysis.

**Compliance with ethical standards**

**Conflict of interest** No conflicting relationship exists for any author.

## References

1. Lim LS, Ng WY, Wong D et al (2015) Prognostic factor analysis of vitrectomy for myopic foveoschisis. Br J Ophthalmol 99(12):1639–1643
2. Seike C, Kusaka S, Sakagami K et al (1997) Reopening of macular holes in highly myopic eyes with retinal detachments. Retina. 17(1):2–6
3. Michalewska Z, Michalewski J, Dulczewska-Cichecka K et al (2014) Inverted internal limiting membrane flap technique for surgical repair of myopic macular holes. Retina 34(4):664–669
4. Hillenkamp J, Kraus J, Framme C et al (2007) Retreatment of full-thickness macular hole: predictive value of optical coherence tomography. Br J Ophthalmol 91(11):1445–1449
5. Valldeperas X, Wong D (2008) Is it worth reoperating on macular holes? Ophthalmology 115(1):158–163
6. D'Souza MJ, Chaudhary V, Devenyi R et al (2011) Re-operation of idiopathic full-thickness macular holes after initial surgery with internal limiting membrane peel. Br J Ophthalmol 95(11):1564–1567
7. Morizane Y, Shiraga F, Kimura S et al (2014) Autologous transplantation of the internal limiting membrane for refractory macular holes. Am J Ophthalmol 157(4):861–869
8. R Core Team (2017) R: A Language and Environment for Statistical Computing. https://www.R-project.org
9. Guber J, Lang C, Valmaggia C et al (2017) Internal limiting membrane flap techniques for repair of large macula holes: a short-term follow-up of anatomical and functional outcomes. Klin Monbl Augenheilkd 234(4):493–496
10. Kang SW, Lim JW, Chung SE et al (2010) Outer foveolar defect after surgery for idiopathic macular hole. Am J Ophthalmol 150(4):551–557
11. Wong D, Steel DH (2016) Free ILM patch transplantation for recalcitrant macular holes; should we save some internal limiting membrane for later? Graefes Arch Clin Exp Ophthalmol 254(11):2093–2094
12. Funata M, Wendel RT, de la Cruz Z, Green WR (1992) Clinicopathologic study of bilateral macular holes treated with pars plana vitrectomy and gas tamponade. Retina 12:289–298
13. Madreperla SA, Geiger GL, Funata M, de la Cruz Z, Green WR (1994) Clinicopathologic correlation of a macular hole treated by cortical vitreous peeling and gas tamponade. Ophthalmology 101:682–686
14. Oh J, Yang SM, Choi YM, Kim SW, Huh K (2013) Glial proliferation after vitrectomy for a macular hole: a spectral domain optical coherence tomography study. Graefes Arch Clin Exp Ophthalmol 251:477–484