ARTICLE ORIGINAL

Idiopathic large macular holes: management and review of literature

Les trous maculaires larges idiopathiques : traitement et revue de la littérature

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Key-words
idiopathic macular hole, surgery, large

Abstract

Introduction. The closure rate of large or wide idiopathic macular holes (MH) varied between 50 and 70%. The inverted flap (IF) technique is a potential procedure that would considerably improve postoperative anatomical and functional surgery success rate. The aim of our study was to evaluate the efficacy of the IF technique for the management of large idiopathic MH.
Methods. Prospective, interventional, descriptive and evaluative study interesting 40 eyes operated on for large MH, randomized into 3 groups according to the variant of the IF technique: classic, temporal and without manipulation, with a minimum postoperative follow-up of 6 months. Postoperative functional and anatomical outcomes were searched for the entire population and within each group. A value of p <0.05 was considered as statically significant.
Results. Preoperatively, the mean visual acuity (VA) was 1 LogMAR; the mean MH size was 689.59 ± 153.13 µm. The classic, temporal and without manipulation IF groups had 13, 13 and 14 eyes respectively. Postoperatively, the closure rate was 84.61%, 100% and 92.8% respectively. At six months postoperatively, significant VA improvement was observed in 70% of the eyes (p<0.001); the visual gain in the classic, temporal and without manipulation IF group was 0.47, 0.34 and 0.34 LogMAR respectively (p=0.66, 0.182 and 0.182, respectively). The outer limiting membrane and ellipsoid zone were regenerated in 38% and 32.4% of the eyes. The three variants were comparable in terms of MH closure (p=0.222) and final visual gain (p=0.66). Significant predictors of no-closure of the MH were: a diameter > 900 µm (p=0.015) and a duration of visual decline > 13 months (p= 0.02).
Conclusion. The IF technique significantly improves the closure rate of large MH with excellent functional results. The three variants are comparable and guarantee the same postoperative results.

Mots-clés
trou maculaire idiopathique, chirurgie, trou maculaire large

Résumé

Introduction. Le taux de fermeture des trous maculaires (TM) larges idiopathiques variait entre 50 et 70 %. La technique du lambeau inversé est une procédure potentielle qui a considérablement amélioré les résultats post opératoires aussi bien sur le plan anatomique que fonctionnel.
Le but de notre étude était d'évaluer l'efficacité de cette technique dans la prise en charge des TM larges idiopathiques.
Méthodes. Etude prospective, interventionnelle, descriptive et évaluative intéressant 40 yeux opérés pour des TM larges, randomisés en 3 groupes selon la variante de cette technique : lambeau inversé 'classique', 'temporal' et 'sans manipulation', avec un suivi postopératoire minimum de 6 mois. Les résultats fonctionnels et anatomiques postopératoires ont été recherchés pour l'ensemble de la population et au sein de chaque groupe. Une valeur de p <0,05 a été considérée comme statiquement significative.
Résultats. En préopératoire, la meilleure acuité visuelle (AV) moyenne corrigée était de 1 LogMAR ; la taille moyenne du TM était de 689,59 ± 153,13 µm. 13 patients ont été opérés par la technique du lambeau inversé classique, 13 autres patients par la technique du lambeau temporal et 14 patients ont été opérés par la méthode sans manipulation. En postopératoire, le taux de fermeture était de 84,61 %, 100 % et 92,8 % respectivement. Six mois après l'opération, une amélioration significative de l'AV a été observée dans 70 % des yeux (p<0,001) ; le gain visuel dans le groupe lambeau inversé 'classique', 'temporal' et 'sans manipulation' était de 0,47, 0,34 et 0,34 LogMAR respectivement (p=0,66, 0,182 et 0,182, respectivement). La membrane limitante externe et la zone ellipsoïde ont été régénérées dans 38 % et 32,4 % des yeux. Les trois variantes étaient comparables en termes de fermeture du TM (p = 0,222) et de gain visuel final (p = 0,66). Les prédicteurs significatifs de non-fermeture du TM étaient : un diamètre > 900 µm (p=0,015) et une durée de baisse visuelle > 13 mois (p= 0,02).
Conclusion. La technique du lambeau inversé améliore significativement le taux de fermeture des TM larges avec d'excellents résultats fonctionnels. Les trois variantes sont comparables et garantissent les mêmes résultats postopératoires.

Introduction

The management of large idiopathic macular holes (MH) (diameter > 400 µm) has always been a matter of debate. Simple peeling of the internal limiting membrane (ILM) has been shown to be successful in small and medium-sized MH (<400 µm) with closure rates of up to 100% and significant improvement in visual acuity. However, in large MH, the results were disappointing with a closure rate of only 40% [1]. The advent of the inverted flap (IF) technique with Michalewska in 2010 has improved the prognosis of large macular holes (MH). According to foreign series, this technique has an anatomical success rate of over 90% and a significant visual gain in the treatment of large MH [1]. In their first comparative interventional study, Michalewska and al [2] reported a 98% anatomic success rate with the classic inverted flap technique with a significant improvement in visual acuity. However, there may be some limitations regarding the inverted flap technique variants such as deterioration of visual acuity, as well as pigmentary epithelium atrophy and the high number of DONFLs associated with the classic technique. The two other variants, the temporal and the free flap inverted flap techniques, were invented in order

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to limit the flap manipulations on the macular hole and the flap itself. The aim of this study is to evaluate the anatomical and functional results after large MH surgery using the inverted flap technique; to compare the efficacy of variants of the IF technique and to determine prognosis factors for functional and anatomical recovery based on OCT-SD data.

Methods

The study was conducted in accordance with the Declaration of Helsinki. We undertook a prospective, interventional, descriptive and comparative study of patients with large idiopathic macular hole (> 400 µm) in the department A; at Hedi Raies Institute of Ophthalmology of Tunis. This study was conducted over a 20-month period, between January 2019 and august 2020, and involved a series of 40 eyes of 38 consecutive patients managed, operated on, and followed in our department. Patients were recruited in a single-blind randomization. No patient had a history of amblyopia or macular pathology previously affecting visual acuity. All patients included in the study had undergone a complete ophthalmologic and tomographic examination with the Heidelberg Spectralis Spectral Domain OCT, before and after eye surgery, with a minimum postoperative follow-up of 6 months. The performing and interpretation of SD-OCT sections were done by the same operator.

Surgical technique

Surgery was performed by the same retinal surgeon using the same instrumentations. We performed a pars plana 23-gauge vitrectomy. Peeling was performed under a high magnification lens, using a 23G ILM forceps. We used Brilliant Blue G (BBG or ILM blue) to stain the ILM. Non expansive sulfur hexafluoride (SF6) tamponade was performed in all patients at the end of surgery.

The ILM was peeled using the following operative techniques:

The "classic inverted flap technique" During this procedure the BBG-stained the internal limiting membrane. Then, the ILM was grasped with the ILM forceps in the superior temporal of the macular hole. Peeling of the ILM flap was performed for approximately 2 papillary diameters (PD) of radius around the macular hole (maculorhexis), while maintaining a 360-degree attachment to the MH edges. Next, we inverted the first part of the ILM flap with the cutter so that the vitreous side of the ILM was deposed on the MH, and then the second part of the flap was applied over the other one **(Figure 1).**

The" temporal inverted flap technique"
The maculorhexis is primed temporally like the classic technique. A temporal flap of ILM is peeled off with a radius of 2 PD. There is no manipulation of the inter maculo-papillary retina in this technique**.** Finally, the ILM temporal flap is inverted over the MH before the fluid-air exchange **(Figure 2).**

The "inverted flap without manipulation technique"
The difference between this technique and the classic one is the absence of manipulation of the ILM flap after maculorhexis. The fluid-air exchange is performed while the ILM flaps are directed towards the vitreous cavity and not deposed over the MH **(Figure 3).**

Results

Our series included 40 eyes of 38 consecutive patients with a large idiopathic macular hole. The sex ratio was 2/3 with a female predominance (60%). The mean age was 64 years with a standard deviation of 8.42. The mean duration of evolution of the delayed MH in our study was 7 ± 4.4 months. Bilateral involvement was recorded in 6 patients (15%).

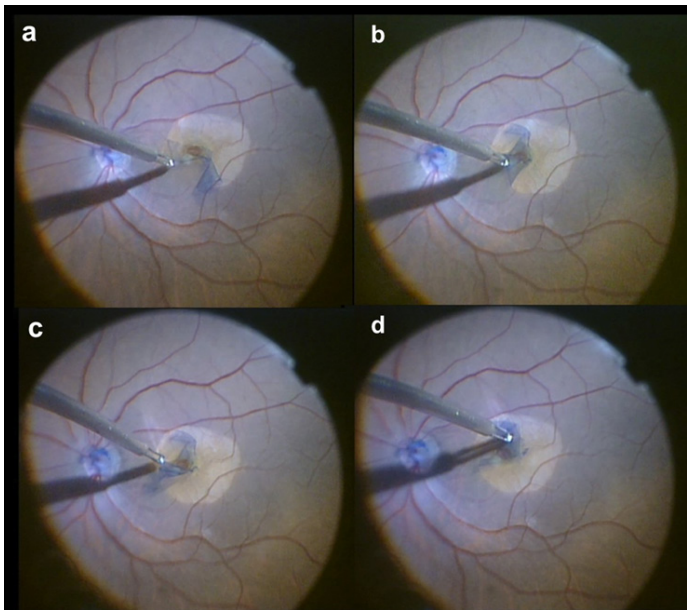
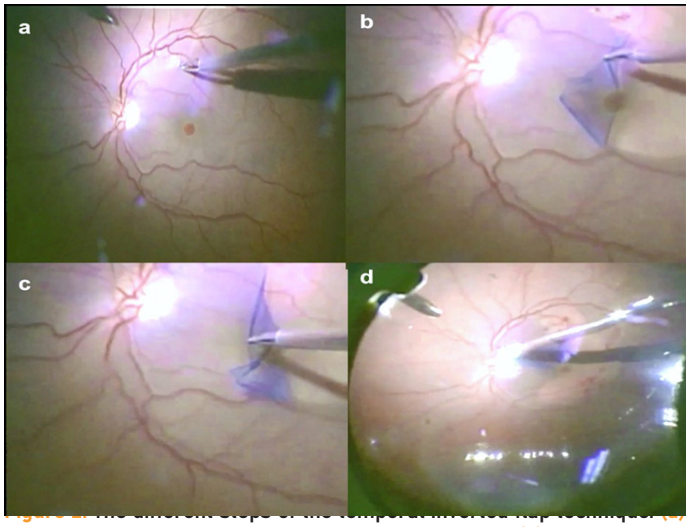


Figure 1. The different steps of the classic inverted flap technique (a) Peeling and inversion of the first internal limiting membrane flap; (b) Peeling of the second flap (c,d). Inversion of the second flap over the first flap

Clinically, all patients had decreased visual acuity; 43% had metamorphopsia and 45% complained of central scotoma. The mean macular hole size was 692.59 ± 147.207 µm with a mean maximum size of 1436.06 ± 200.246 µm. All our patients have been operated using the inverted flap technique: the classic one in 13 eyes (32%), without manipulation in 14 eyes (36%) and the temporal flap technique in 13 eyes (32%).



Initiation of maculorhexis after retinal blue staining; (b) Peeling of the temporal internal limiting membrane flap; (c:) Inversion of the flap on the inter maculo-papillary retina; (d) Fluid-air exchange before gas injection.

After complete resorption of SF6, with average duration of tamponade of 3 weeks, we recorded a closure rate of 93% of the MH (37 eyes). This rate was 85% in the classic inverted flap technique group, 100% in the temporal inverted flap technique group and 93% in the without manipulation group **(Table I)**. At 6 months postoperatively, 18 eyes (49%) had "U" shaped foveolar closure, 14 eyes (38%) had "V" shaped foveolar closure, and 5 eyes (13%) had "W" shaped foveolar closure with better visual recovery in the "U" foveolar closure group **(Figure 4)**. Functionally, we observed a decrease in the rate of metamorphopsia and central

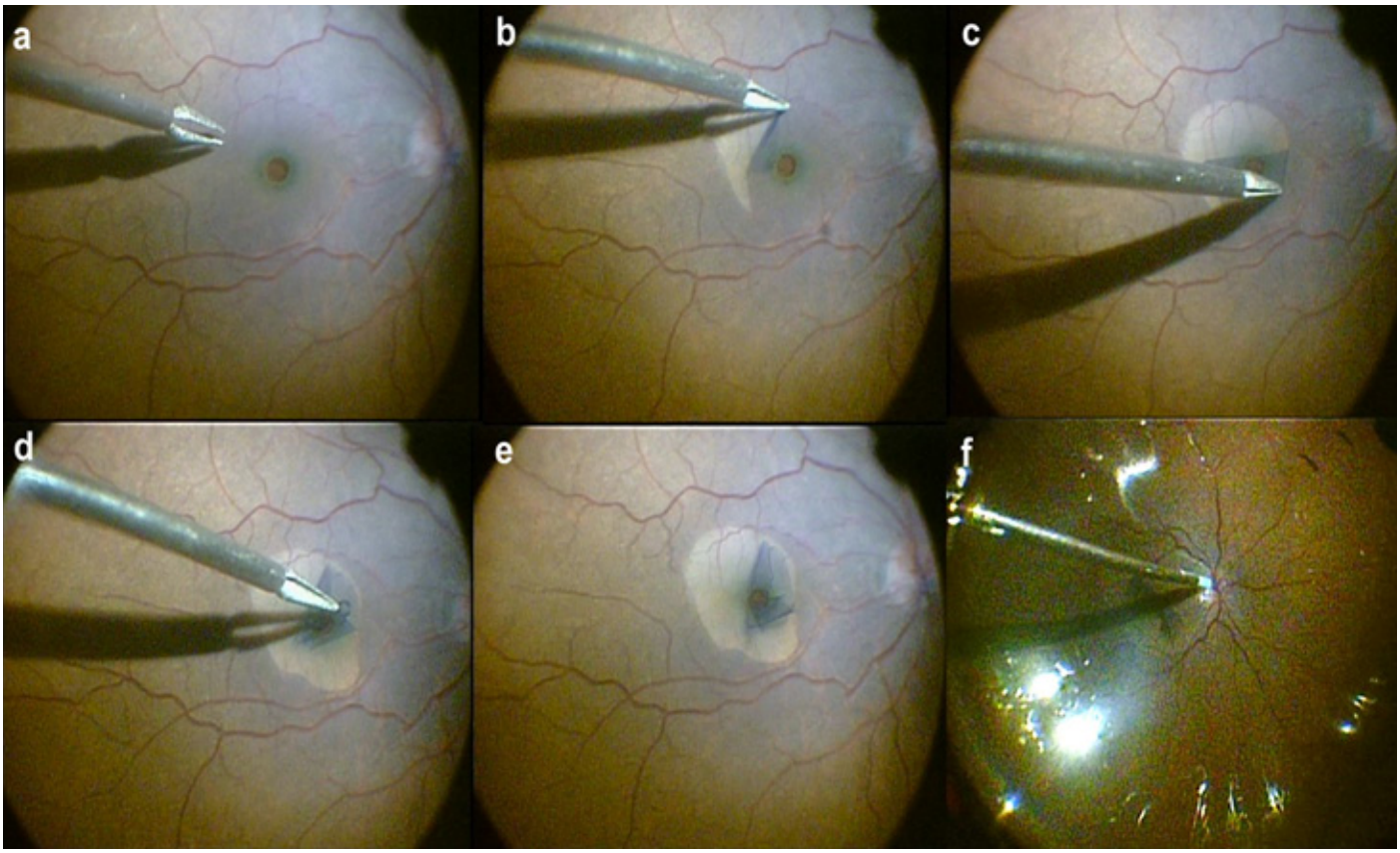


Figure 3. The different steps of the inverted flap technique without manipulation (a) Initiation of maculorhexis in the temporal area; (b,c) Peeling of the first internal limiting membrane flap; (d,e) Peeling of the second internal limiting flap without inversion; (f)Fluid-air exchange.

Table I. Macular hole closure rates according to surgical technique

	Closure of the macular hole		Non-closure of the macular hole	
Surgical technique	**number**	**percentage**	**Number**	**Percentage**
Classic inverted flap	11	85	2	15
Temporal inverted flap	13	100	0	0
Inverted flap without manipulation (free flap)	13	93	1	7

scotoma (10% and 18% respectively) with an improvement in visual acuity (VA) in 26 eyes (70%). The mean best corrected visual acuity (BCVA) was 3/10 Snellen (0.52 LogMAR) in 30% of patients, 6/10 Snellen (0.22 LogMAR) in 22% and 4/10 Snellen (0.4 LogMAR) in 12% of eyes. **Table II** summarizes the visual acuity and visual gain at 6 months post-operatively according to the surgical technique. At 6 months postoperatively, the regeneration of the external limiting membrane was observed in 38% with ad-integrum restitution of the ellipsoid zone in 32% of eyes. Concerning the dissociated optic nerve fiber layer (DONFL), we observed a decrease in their number at 3 and 6 months postoperatively. Indeed, six months after surgery, DONFLs disappeared in 20% of eyes. On the other hand, we found that the greatest number of DONFLs was diagnosed in patients operated by the inverted flap technique without manipulation **(Figures 5, 6).**

Comparing the classic inverted flap technique to the inverted flap technique without manipulation, we concluded that these two techniques were statistically comparable in terms of MH closure (p=0.222) and visual gain (p=0.66). Similarly, the classic inverted flap technique was statistically comparable to the temporal one in both of MH closure and visual gain (p=0.5 and p=0.189 respectively). After multivariate analysis of the different actual factors impacting MH closure and visual gain, we found that the only prognosis factor influencing anatomic closure was the evolution of MH, and this when comparing the classic technique to the IF technique without manipulation (p=0.044), and to the temporal flap technique (p=0.037) **(Tables III, IV).**

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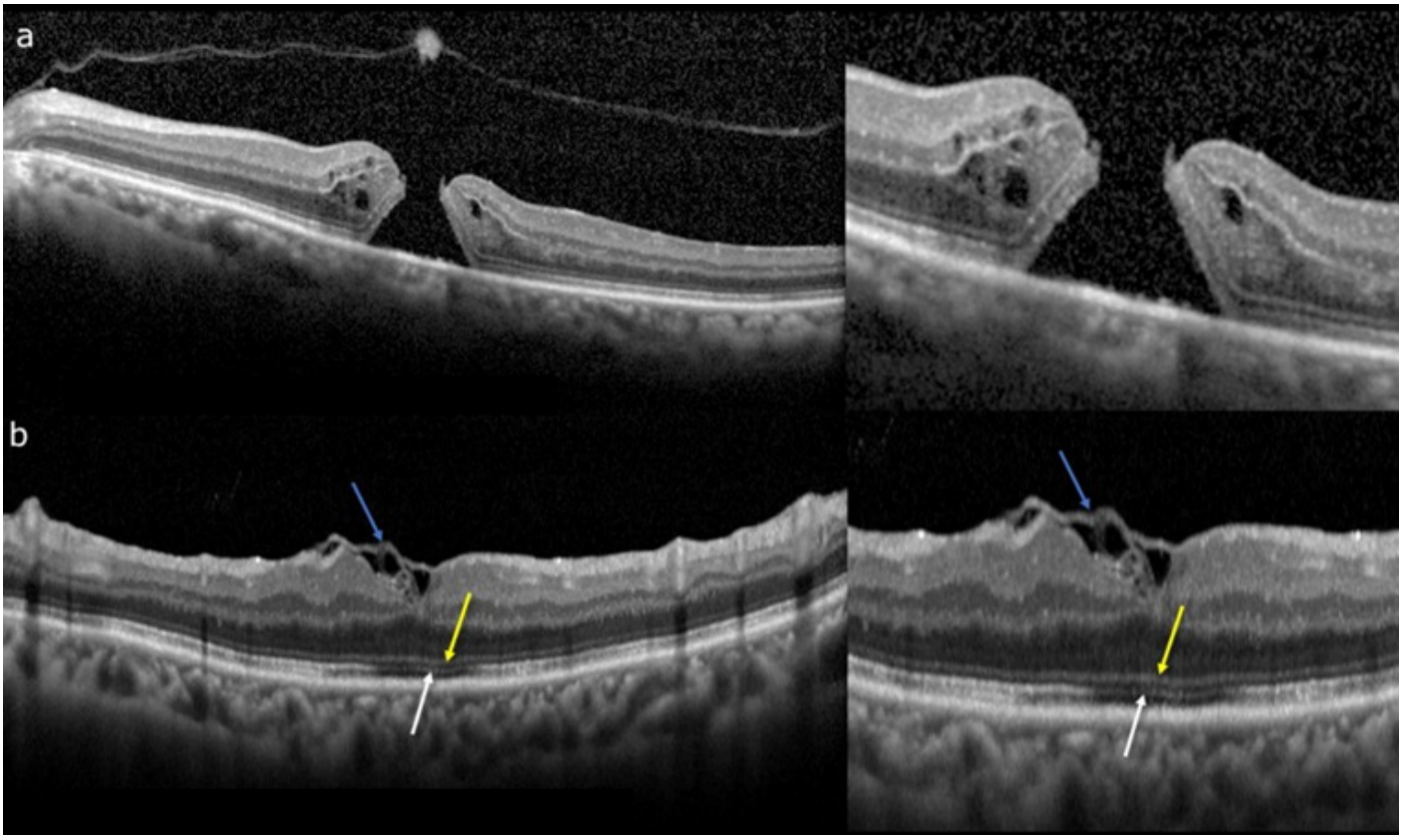

Figure 4. Tomographic illustration of complete postoperative regeneration of the different neuroretinal layers after surgery (a) Preoperative SD-OCT showing a 520 µm full thickness idiopathic macular hole with best corrected visual acuity (BCVA) of 1 LogMAR; (b) SD-OCT at 6 months postoperatively showing closure of the macular hole with regeneration of the outer limiting membrane (yellow arrow) and the IS/OS line (white arrow), the flap is still visible on the surface (blue arrow) over a "U" shaped closure, the BVCA was up to 0.52 LogMAR (the same visual acuity as at 3 months but with disappearance of the metamorphopsias and central scotoma).

Table II. Distribution of the best-corrected visual acuity by surgical technique.

Tomographic parameters	Preoperative BCVA (LogMAR)	Postoperative BCVA (LogMAR)	Visual gain (LogMAR)	P
Classic inverted flap	0.95 ± 1	0.48 ± 0.63	0.47	
Inverted flap without manipulation	1.03 ± 1.69	0.69 ± 1	0.34	0.016
Temporal inverted flap	0.92 ± 1	0.58 ± 0.69	0.34	

flap technique (p=0.037) **(Table III).** Furthermore, we calculated the MH diameter at which the risk of non-closure was maximal through the study of the ROC curve and we found that a diameter greater than 900 µm was correlated with a risk of non-closure greater than 97.3%, with a very good predictive value (p=0.015) **(Figure 7)**. Similarly, we calculated the duration of evolution from which the risk of non-closure was maximal, and we found that a duration more than 13 months was correlated with a risk of non-closure higher than 87% with a good predictive value (p=0.02) **(Figure 8).**

Discussion

In our study we used and compared three different techniques: the classic inverted flap technique that has been considered un til nowadays, according to the literature, as the reference technique for the treatment of large idiopathic MH (13 patients), the temporal inverted flap technique (13 patients) and the inverted flap without manipulation (14 patients). In their first comparative interventional study, Michalewska and al [2] reported a 98% anatomic success rate with the inverted flap technique versus 88% with the single peel technique of the ILM. Rizzo and al [3] reported an anatomical success rate of 95.6% in the inverted flap group (300 eyes) compared to 78.6% in the single peel ILM group (320 eyes). However, there may be some limitations regarding the inverted flap technique. The most reported complications in the literature were a detachment of the inverted flap during fluid-air exchange [2], deterioration of visual acuity reported by Deshpande and al [4] and Hirano and al [5] as well as pigmentary epithelium (PE) atrophy and especially the high number of DONFLs associated with this technique [6]. To deal with these complications,
Shin and al [7], in 2014, presented a modified technique that used perfluoro-n-octane (PFO) to stabilize the inverted flap on the macular hole.
On the other hand, in 2015, Michalewska Z and al introduced the variant of the inverted flap technique, the temporal inverted flap , which removes the ILM only from the temporal side of the hole, and demonstrated that the closure rate and functional improvement with this variant for large MHs did not differ from that of the conventional technique [8].
In 2016, Andrew and al [9] described a modified technique that involves inserting the ILM into the macular hole and using a viscoelastic cap to improve flap retention in the hole.
In 2017, Casini and al [10] introduced another modified technique to perform an inverted flap without manipulating the ILM flap in order to reduce the risk of PE damage. In our study, we found, regardless of surgical techniques, a significant improvement in visual acuity in 26 eyes (70%) at 6 months postoperatively (p<0.001). These results are in agreement with the results of the systematic review published by Chufeng Gu and al in 2017 [11], who found that

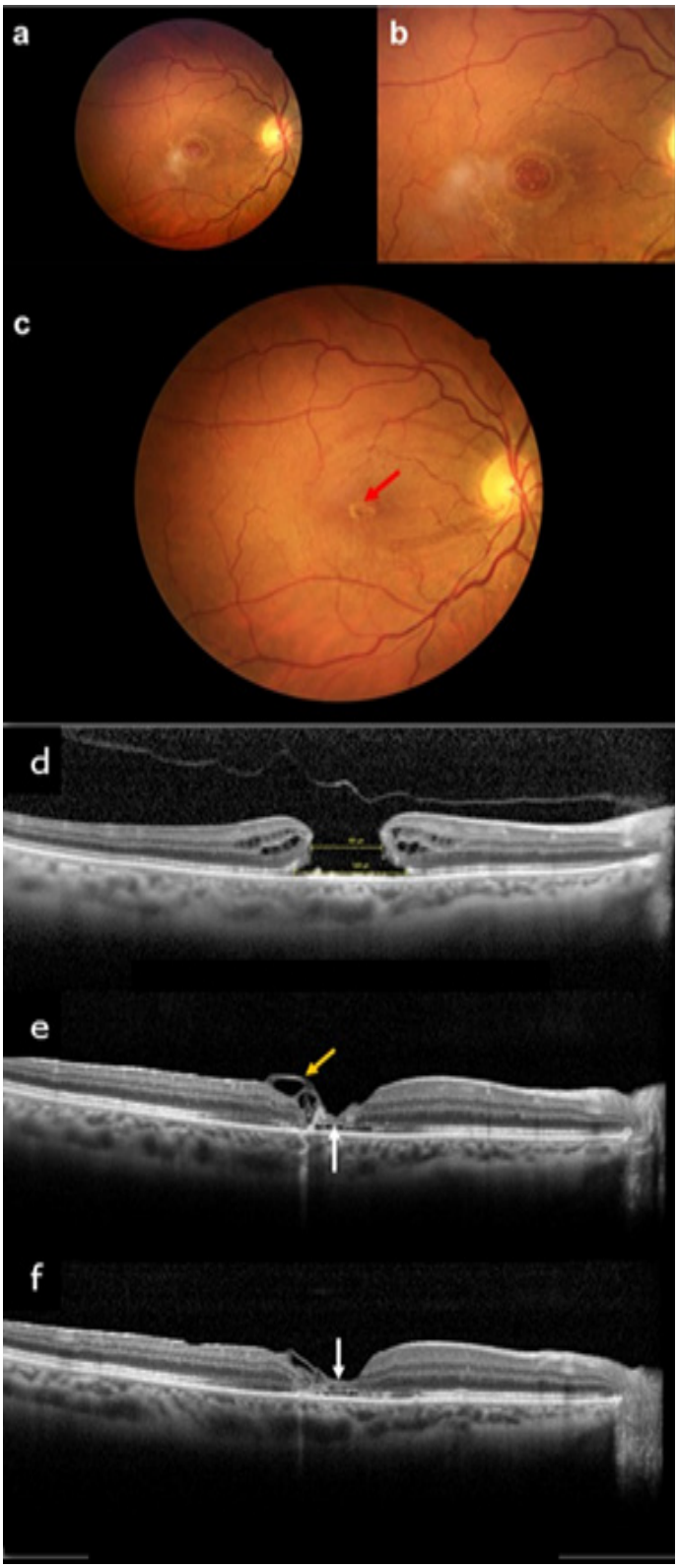

Figure 5. **Pre-and postoperative retinography and tomographic appearance of a large idiopathic macular hole operated by the temporal inverted flap technique (a,b) Preoperative retinography (b) high magnification) in a 62-year-old woman showing a full thickness macular hole (TM) evolving for 10 months exposing the pigment epithelium with lifting of the TM edges; (c) Retinography at 1 month post-op showing closure of the hole (red arrow); (d) Pre-operative OCT-SD showing a large macular hole of 721 µm; best corrected visual acuity (BCVA) at distance at 2 LogMAR with absolute central scotoma; (e) OCT-SD at 1 month post-op: closure of the macular hole with formation of the inner retinal bridge connecting the 2 edges of the macular hole (white arrow), the outer neuroretina is not yet developed. The temporal flap is clearly visible (yellow arrow). The BCVA was 1.4 LogMAR with a decrease in the size of the central scotoma; (f) OCT-SD at 3 months post-op: healing of the U-shaped foveal contour and regeneration of the outer limiting membrane without IS/OS line (white arrow) with a BCVA at 1.1 LogMAR and complete disappearance of the central scotoma.**

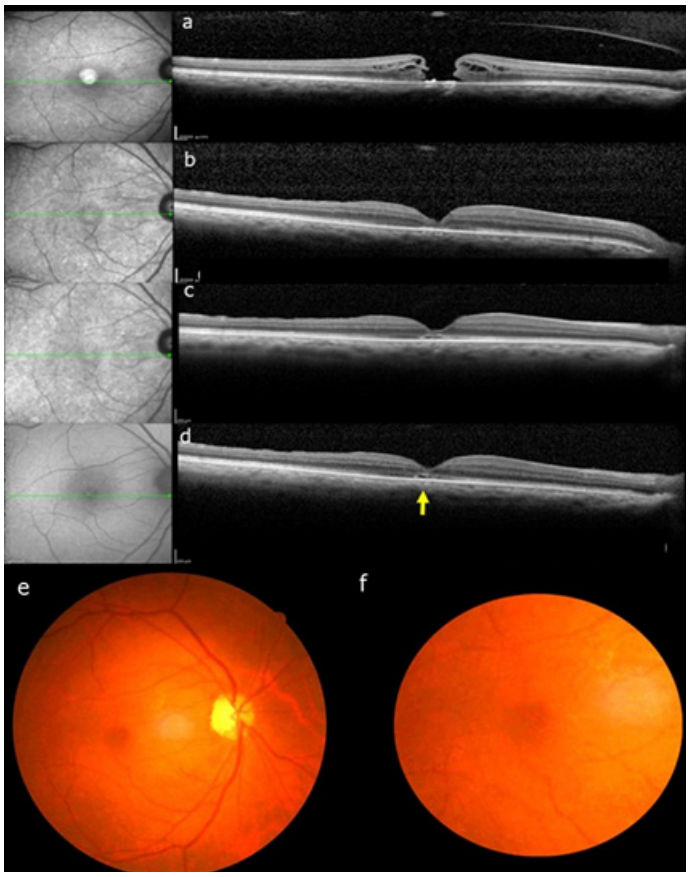

Figure 6. **Illustration of the closure of an idiopathic macular hole operated by the inverted flap technique without manipulation (a) Preoperative SD-OCT of a 57 year old woman showing a large macular hole of 800 µm diameter evolving for 4 months with a best corrected visual acuity (BCVA) of 1.7 LogMAR associated with a central scotoma; (b) SD-OCT at 1 month postoperatively: closure of the macular hole with complete regeneration of the inner retina; the BCVA was up to 1.2 LogMAR with complete disappearance of the central scotoma; (c) SD-OCT at 3 months postoperatively: healing of the U-shaped foveal contour and regeneration of the outer limiting membrane without regeneration of the IS/OS line, the BCVA was at 1 LogMAR; (d) SD-OCT 6 months postoperatively: definitive healing of the macular hole with "U" shaped foveal contour without regeneration of the IS/OS line (yellow arrow), the BCVA was at 1 LogMAR; (e,f) Retinography of the right eye at 3 months after surgery showing closure of the macular hole with a normal foveal reflection (f).**

the improvement in VA in patients operated on by the inverted flap technique was up to 95%. Michalewska and al, in their two series published in 2010 and 2015 [2,8], found a statistically significant improvement in postoperative visual acuity in 100% of cases with the two surgical techniques, namely the classic inverted flap and the temporal inverted flap. Regardless of operative technique and MH size, our study in addition to the literature review concluded that preoperative visual acuity was the main predictor of surgical success. Indeed, better preoperative visual acuity was associated with higher rate of visual gain and anatomic closure [12-16]. On the other hand, the short evolution time is also a crucial factor for achieving both better visual results and anatomical closure of the MH [16]. Gupta and al [17] showed through a multivariate regression analysis that age, preoperative visual acuity and hole size were the only significant predictors of visual success in terms of operated wide MH. In conclusion, the last decade has seen big surgical advances in the treatment of large idiopathic macular holes (> 400 µm). These new techniques have allowed a spectacular improvement in the anatomical and functional prognosis of large macular holes but also a great solutions to propose for the management of chronic, post-traumatic, refractory macular holes and macular holes of high myopia. Choosing which variant of the inverted flap technique to use, remains for the retinal surgeon and will depend mainly on his surgical skills.

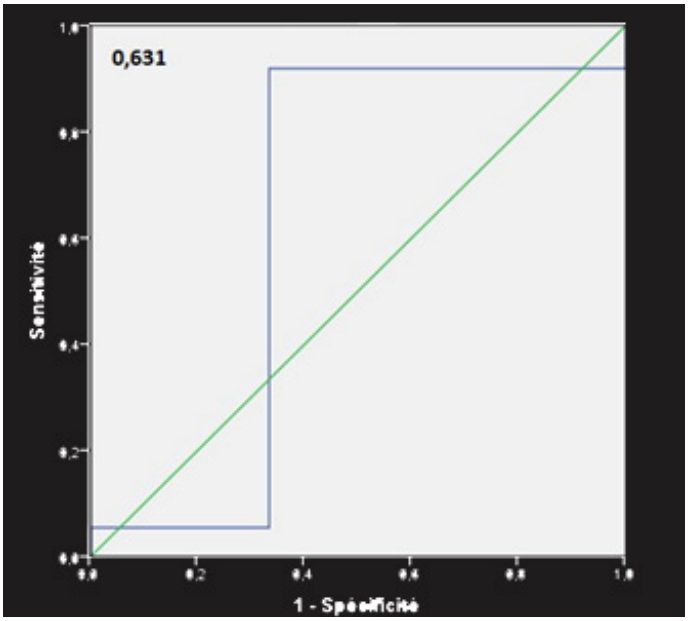

Figure 7. ROC curve for macular hole diameter

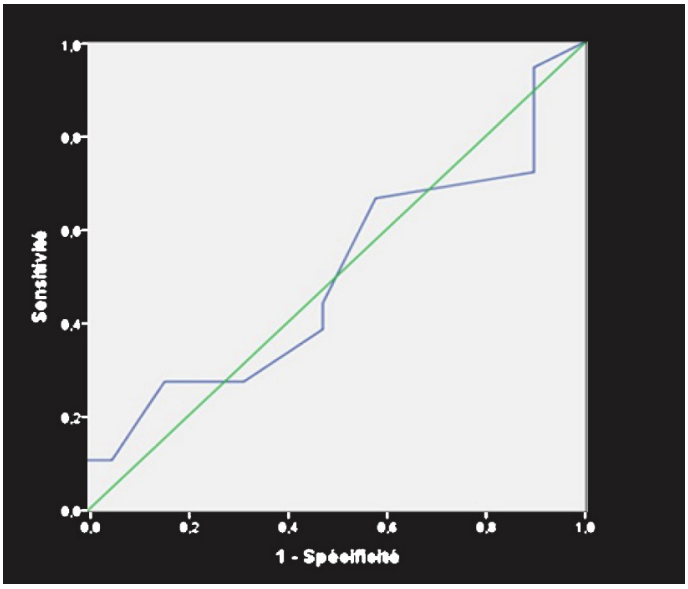

Figure 8. ROC curve for macular hole evolution time

Table III. Correlations between macular hole closure and prognosis factors in the classic inverted flap group versus the inverted flap technique without manipulation (P1) or the temporal inverted flap technique (P2): multivariate analysis.

Prognosis factor	P1	P2
Age	0.087	0.087
Sex	0.465	0.465
Macular hole evolution time	0.040	0.040
Diameter of the macular hole	0.849	0.849

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