Review

Current Approaches in the Management of Complicated Macular Holes

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Abstract

Kelly and Wendel reported the first successful intervention for idiopathic full-thickness macular holes in 1991. Since then, pars plana vitrectomy and internal limiting membrane peeling have become the standard treatment approach, with >90% hole closure rates. However, the results were not satisfactory in cases of complicated macular holes, including large, recurrent, refractory, and myopic macular holes. To date, several surgical approaches, including the inverted internal limiting membrane flap technique, autologous retinal transplantation, the human amniotic membrane plug, and the autologous Tenon's capsule plug, have been described by various authors to improve the anatomical and functional outcomes of challenging cases. Although these techniques have significantly increased hole closure rates, each technique has its own strengths and weaknesses. Currently, there is no consensus among vitreoretinal surgeons on a single ideal technique for treating challenging macular holes. In this review, the inventors of each innovative surgical technique will discuss the indications, pros and cons, complications, and anticipated future applications.

Keywords: Amniotic membrane, autologous retinal graft, inverted internal limiting membrane flap, macular hole, Tenon's capsule

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Introduction

Following Kelly and Wendel's first successful macular hole (MH) surgery in 1991, advancements in technology and the development of new techniques over the past 30 years have enabled closure rates of over 90% to be achieved in standard cases. However, in complex MHs, such as large, myopic, refractory, or traumatic cases, anatomical closure rates achieved with traditional approaches remain lower, and these cases continue to present a challenge. This review will address six surgical techniques currently used in the treatment of complicated MHs, all of which have high reported success rates. The advantages and disadvantages of each technique, key surgical points, and complications will be discussed.

1. Inverted Internal Limiting Membrane Flap

Small idiopathic MHs often respond favorably to pars plana vitrectomy (PPV), regardless of positioning or internal limiting membrane (ILM) peeling. Larger, myopic, chronic MHs, or MHs secondary to other diseases—particularly those associated with proliferative diabetic retinopathy, age-related macular degeneration (AMD), trauma, or uveitis—have historically exhibited lower closure rates and poorer functional outcomes.[1,2] The advent of the inverted ILM flap technique, introduced by Michalewska et al.[3], has dramatically changed this landscape, virtually eliminating type 2 closure patterns (flat margins of the hole and bare retinal pigment epithelium [RPE]) and achieving closure in the vast majority of complicated cases regardless of hole size or chronicity.

The standard surgical procedure for the inverted ILM flap technique typically begins with a core vitrectomy (without indentation of the periphery), followed by staining of the ILM with MembraneBlue-Dual (DORC, Zuidland, the Netherlands) to enhance visualization of the vitreous, epiretinal membranes (ERM), and ILM. In the classical approach, circumferential ILM peeling was performed to create multiple flaps, which were then trimmed and carefully placed over the MH, taking care to avoid inserting the flap into the MH itself (flower technique).[3] This distinction is important because placement of the ILM inside the hole has been associated with less favorable restoration of retinal microarchitecture, particularly the external limiting membrane (ELM) and ellipsoid zone (EZ), both critical to photoreceptor function and therefore to vision.[3,4] However, the classical approach has been abandoned, and Michalewska et al.[5] currently perform the temporal inverted ILM flap technique. The ILM is only peeled on the temporal side of the fovea and positioned on top of the MH. In some cases, viscoelastics are used for better stabilization. The procedure is completed with air tamponade, and patients are instructed to maintain prone positioning for three days to facilitate proper anatomical closure. Long-acting gases are not usually required for MH repair.[5]

The mechanism underlying the success of the inverted ILM flap technique appears to involve both mechanical and biological factors. The ILM acts as a basement membrane for Müller cells, which proliferate and migrate along the scaffold provided by the inverted flap. This cellular activity facilitates centripetal contraction, leading to gradual closure of the MH and subsequent restoration of the ELM and EZ layers.[3,4] Animal models have confirmed Müller cell activation and migration along the ILM scaffold,[6] while *in vitro* experiments have shown that the adult retina retains some degree of regenerative potential when supported by this substrate.[7] Thus, the inverted ILM flap technique not only provides a physical barrier but also promotes cellular processes essential for both anatomical and functional recovery.

Clinical outcomes with the inverted ILM flap technique have consistently demonstrated its superiority over traditional ILM peeling across diverse and challenging scenarios (Table 1).[3,8,9] In large and chronic MHs, randomized studies have reported closure rates of 98% with the inverted ILM flap technique compared to 88% with standard peeling, with type 2 closures effectively eliminated in the inverted ILM flap technique group.[3] Primary closure was observed in 95-96% of large idiopathic MHs using both classical and superior flap techniques, with comparable improvements in best-corrected visual acuity (BCVA) at six months postoperatively.[10]

In highly myopic MHs with or without retinal detachment (RD), the inverted ILM flap technique has yielded particularly striking results. Comparative studies by different authors confirm that the clinical advantage of the inverted ILM flap technique is even more pronounced in these cases than in large MHs. Mete et al.[11] demonstrated a 22-fold higher likelihood of anatomical closure with the inverted ILM flap technique compared to conventional peeling, while Rizzo et al.[9] reported closure rates of 88.4% versus only 38.9% with peeling alone in high myopia. Importantly, functional outcomes are superior when the ILM flap is positioned over the MH rather than tucked into it, further emphasizing the role of the flap as a scaffold for retinal repair rather than a mere physical plug (Table 2).[9,11,12,13,14]

Proliferative diabetic retinopathy-associated MHs present a unique surgical challenge due to their often markedly high base-to-minimum diameter ratio (approximately 10:1), which resembles that of MHs in high myopia. Furthermore, these cases may involve the coexistence of tractional RD. Michalewska and Nawrocki[15] observed that the inverted ILM flap technique achieves closure beginning at the inner retina, followed by gradual reattachment of the outer retinal layers over several weeks to months, offering a level of success not previously attainable with standard techniques (Figure 1).

Table 1. Summary of clinical outcomes with the inverted ILM flap technique compared to ILM peeling in MH repair

Author, year[ref]	ILM peeling % closed	Visual acuity	Inverted flap % closed	Visual acuity
Michalewska et al., 2010[3]	88% (19% type 2)	0.17 Snellen	98%	0.28 Snellen
Kannan et al., 2018[8]	75%	0.69 logMAR	89.3%	0.48 logMAR
Rizzo et al., 2018[9]	78.75%	0.77 logMAR	91.93%	0.74 logMAR

MH: Full-thickness macular hole, ILM: Internal limiting membrane, logMAR: Logarithm of the minimum angle of resolution

Table 2. Summary of clinical outcomes with the inverted ILM flap technique compared to ILM peeling for the repair of highly myopic MHs				
Author, year[ref]	**ILM peeling % closed**	**Visual acuity (logMAR)**	**Inverted flap % closed**	**Visual acuity (logMAR)**
Mete et al., 2017[11]	61%	0.58	94%	0.39
Chen and Yang, 2016[12]	35%	1.17	100%	1.32
Baba et al., 2017[13]	36%	0.75	80%	1.0
Matsumura et al., 2016[14]	33%	1.56	90%	1.1
Rizzo et al., 2018[9]	38.9%	N/A	88.4%	N/A

MH: Full-thickness macular hole, ILM: Internal limiting membrane, logMAR: Logarithm of the minimum angle of resolution, N/A: Not reported

Similarly, the inverted ILM flap technique is also indicated for AMD-related MHs, whether occurring in the context of dry or neovascular AMD (Figure 2). This approach has been shown to achieve both anatomical closure and clinically meaningful improvements in vision, including in cases where MHs developed during ongoing anti-VEGF therapy.[16,17] Interestingly, in dry AMD, disappearance of drusen was observed in some cases. This might be due to phagocytosis of the drusenoid material. In neovascular AMD, it is of high importance to continue anti-VEGF treatment if vitrectomy is delayed for any reason. Shortly after vitrectomy and MH closure, the anti-VEGF treatment should be resumed. The authors did not observe a change in injection intervals in the operated cases.

Secondary MHs resulting from uveitis, trauma, Coats disease, or retinitis pigmentosa have likewise been successfully managed with the inverted ILM flap technique, with high closure rates and substantial visual gains documented across multiple case series.[18,19] In those cases, a longer regeneration time might be expected when compared to idiopathic MHs. However, the technique cannot be applied in refractory cases where the ILM has been completely removed in prior surgeries. In such cases, other surgical techniques are advised.

Reoperations following failure of the inverted ILM flap technique occur in only about 4-5% of cases. These interventions can be performed using either flap repositioning techniques or by creating a new flap, often employing the temporal inverted approach for its technical simplicity and tissue-sparing advantages.[20] Michalewska and Nawrocki[20] proved that the choice of tamponade during the second intervention does not play a statistically significant role in the results. However, silicone oil should be advised in patients with failure associated with positioning problems. Final vision after repeated surgery is usually worse when compared with the primary success.

From a practical standpoint, several key principles have emerged to optimize surgical success with the inverted ILM flap technique. It is recommended to place the ILM flap over the MH rather than inside it to promote physiological retinal healing and reduce the risk of delayed microstructural recovery.[21] Intraoperative stabilization with viscoelastic agents can be employed. Although originally conceived for large and chronic defects, the inverted ILM flap technique can also be applied to smaller MHs to minimize the risk of surgical failure. In particular, repeated surgery with the available ILM is considerably simpler when compared to other techniques and is associated with superior functional outcomes.

In conclusion, the inverted ILM flap technique and its various modifications have fundamentally transformed the surgical management of complicated MHs. By combining mechanical support with biological stimulation of retinal repair, this technique achieves high closure rates, facilitates restoration of retinal microarchitecture, and delivers meaningful visual improvement across a wide spectrum of challenging clinical scenarios. Technique selection should be individualized based on MH characteristics, comorbidities, and the patient's ability to comply with postoperative positioning. However, both classical and modified approaches have proven to be safe, effective, and widely adaptable in modern vitreoretinal surgery.

2. Autologous Retinal Transplant

The conventional surgical approach to MH repair, consisting of PPV, elevation of the posterior hyaloid, ILM peeling, and gas tamponade, yields primary closure rates of over 90% for simple MH.[1,22,23] Conversely, complex MHs, such as myopic MH[24] and primary, refractory, and/or chronic MH with a minimum linear diameter (MLD) ≥535 µm (i.e., CLOSE study group classification of X-large, XX-large, or giant), have poorer closure rates with an isolated conventional approach and may benefit from adjunctive techniques to facilitate MH closure.[1,24] One such technique is autologous retinal transplantation (ART), which was first described for refractory myopic MH closure in 2016.[24] As originally described, the method consists of a bimanual approach with chandelier illumination to harvest a full-thickness neurosensory retinal graft approximately two disc-diameters in size from the midperipheral retina, reposition the graft over the macula in its correct orientation, instill perfluorocarbon liquid (PFCL) over the graft to flatten its edges and ensure it lies flat over the MH, and perform a PFCL-to-silicone oil exchange.

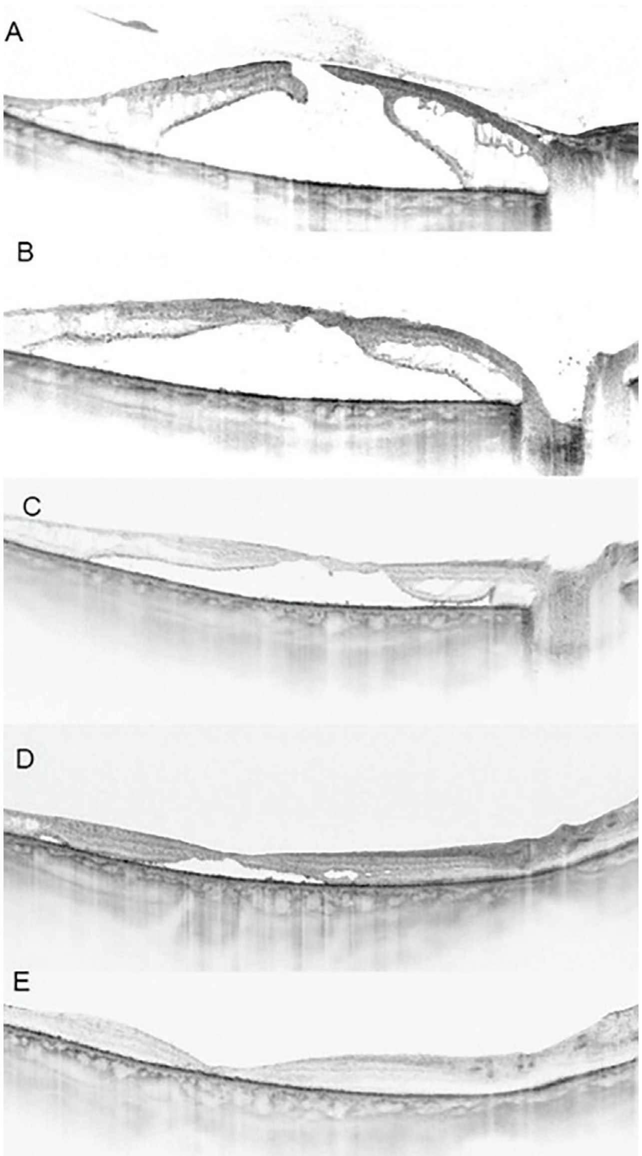

Figure 1. A 68-year-old male patient with proliferative diabetic retinopathy presented with a full-thickness macular hole (MH) associated with foveal detachment. The posterior vitreous remained attached. The minimum diameter was 589 µm and the base diameter was 5485 µm (A; visual acuity 20/1000 [1.7 logMAR]). One week after surgery, the MH was closed but subretinal fluid was still visible (B; visual acuity 20/320 [1.2 logMAR]). One month after surgery, the MH remained closed while the subretinal fluid persisted (C; visual acuity 20/320 [1.2 logMAR]). Six months after surgery, the amount of subretinal fluid had decreased (D; visual acuity 20/320 [1.2 logMAR]). Nine months after surgery, retinal thinning was visible at the fovea (E; visual acuity 20/500 [1.4 logMAR]) (*Source: Archive of Michalewska et al.*)

logMAR: Logarithm of the minimum angle of resolution

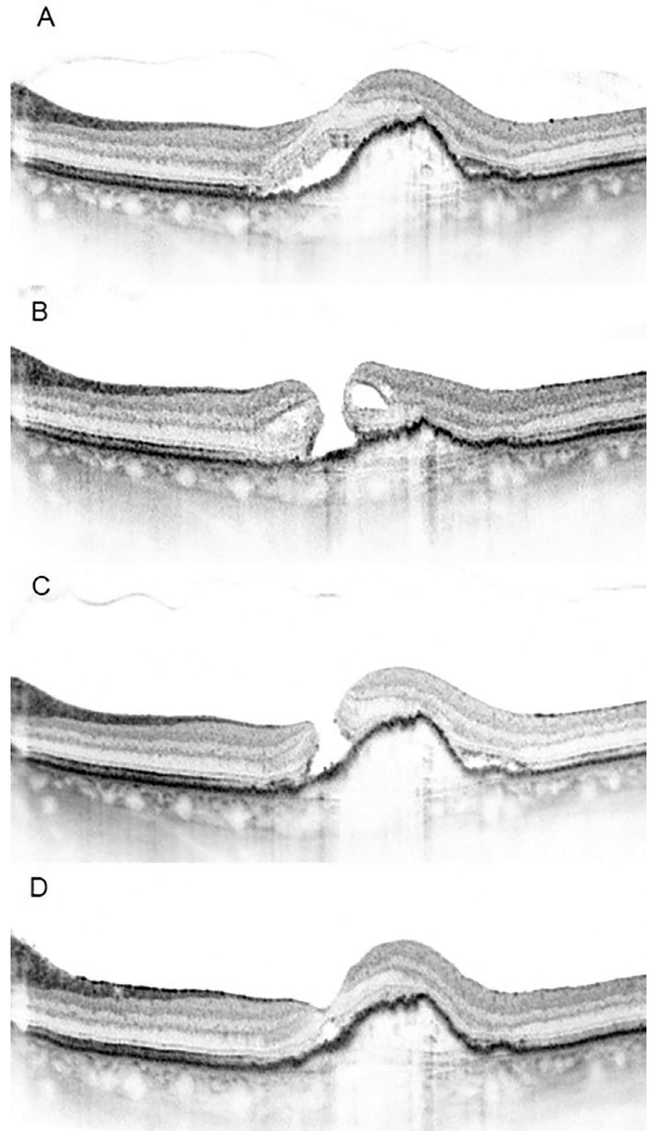

Figure 2. Spectral-domain optical coherence tomography (SD-OCT) confirmed the presence of a neovascular membrane with subretinal fluid (A). SD-OCT revealed a full-thickness macular hole (MH) and visible type 1 neovascular age-related macular degeneration with persistent subretinal fluid (B). SD-OCT image of the closed MH one week after vitrectomy with the temporal inverted ILM flap technique (C). SD-OCT one year after surgery (D). Aflibercept injections were administered using a treat-and-extend regimen during the entire postoperative follow-up period (*Source: Archive of Michalewska et al.*)

ILM: Internal limiting membrane

Since its introduction, many variations of the technique have been described, including ILM peeling over the donor site, differing endotamponade types and graft harvest sites, and combination with other adjunctive techniques such as macular hydrodissection or human amniotic membrane (hAM) graft.[1,25,26] There is no consensus in the literature on optimal modifications of the technique. The preferred approach includes harvesting a graft from the superior midperipheral retina that is approximately 25% larger than the MH to account for shrinkage of the graft after integration, followed by endotamponade with perfluoro-n-octane (PFO; Perfluoron; Alcon, Dallas, TX, USA) for approximately two weeks. The benefits of PFO tamponade may include theoretically superior retinal oxygenation and an anecdotally reduced risk of graft dislocation.[27] We generally default to a unimanual approach and consider bimanual surgery on a case-by-case basis, such as for the repair of MH with concomitant RD. We recommend supine positioning for one day, followed by the avoidance of face-down positioning. Two weeks after MH repair with ART, the graft is inspected intraoperatively, and the decision for air versus gas endotamponade is made based on how secure the graft's position appears.

Indications for ART as an adjunct in MH repair surgery are evolving and include, but are not limited to: primary, refractory, and/or chronic MH that is XX-large (XXL; 800 µm < MLD ≤1000 µm) or giant (MLD > 1000 µm) according to CLOSE study group classification; primary and refractory myopic MH; refractory macular telangiectasia MH; and MH with concomitant RD.[1,24,28,29,30]

Importantly, transverse measurements such as MLD should be adjusted for axial length (e.g., via linear scaling).[31] The use of ART as an adjunctive procedure is less favorable when ischemic, neovascular, or inflammatory retinal diseases are present and when there is insufficient tissue for a viable retinal transplant, such as in the setting of diffuse chorioretinal scarring.[32] There is no consensus regarding the most appropriate adjunctive technique (ART, hAM, or macular hydrodissection) for XXL and giant MH repair. The CLOSE study group performed a pooled analysis and found significant improvement in BCVA after giant MH repair with ART but not with hAM or macular hydrodissection. However, these findings should be interpreted with caution due to the asymmetric and small sample sizes of cohorts after stratifying by both treatment and MH size.[1]

Anatomical success rates with ART are generally high.[32,33,34] The Multicenter International Collaborative Study Group investigated the outcomes of ART for refractory MH and found an approximately 90% closure rate.[32] The Global Consortium included 130 eyes from 33 surgeons and found anatomical closure with ART in 85.7% of primary MH cases, 88% of refractory MH cases, and 95% of MHs with concomitant RD. Visual acuity significantly improved after ART in each of these subgroups, with 43% gaining 3 lines, 29% gaining more than 5 lines, and 12% reaching 20/50 or better, simulating macular function from a peripheral retinal graft.[33] Similarly, a recent meta-analysis of large MHs treated with ART found a closure rate of 91% for primary MH, 93% for refractory MH, and 88% for MH with concomitant RD. Postoperative visual acuity improved after ART in each of these groups as well.[34] A subanalysis of hyperopic patients in the refractory MH group found successful closure in 98% of patients. The first case of ART for a high myopic MH showed visual acuity improvement to 20/80. Ten years later, it improved even further to 20/50, indicating the importance of long-term follow-up.[24]

ART is generally well tolerated with a low risk of complications.[33] In addition to the general complications of vitrectomy (e.g., endophthalmitis and RD) and anesthesia, complications specific to adjunct ART procedures include dislocation of the ART graft and subretinal PFCL. These occurred in 3.8% and 1.5% of cases, respectively, in the Global Consortium Study[33] and can easily be prevented and treated.[35]

Although the exact mechanism of how ART improves the outcomes of complex MH repair surgery is not entirely understood, it is theorized that benefits are derived from its plugging the MH, providing a scaffold for glial tissue proliferation or migration, and integrating into the donor site with some reconstitution of more physiological retinal morphology.[24,32] Indeed, imaging studies evaluating postoperative morphological changes have shown that some patients demonstrate alignment and integration of the host and donor retinal layers, as well as EZ reconstitution (Figure 3).[33] EZ reconstitution after ART was found to be a positive prognostic factor for final surgical outcomes.[33,34,35,36] Progressive increased vascularization of the graft has also been observed in some MH cases during the postoperative period.[33,34,35,36,37]

The introduction of adjunctive techniques for MH repair, such as ART, has enabled the successful treatment of many cases that were previously deemed inoperable. Indeed, these advancements have shifted the paradigm of MH treatment. Further study, refinement, and development of these adjunctive approaches would be prudent.

3. Human Amniotic Membrane

The hAM is derived from the innermost layer of the placenta and exhibits distinctive biological properties that render it a suitable scaffold for retinal repair. The membrane demonstrates antifibrotic properties by downregulating transforming growth factor-β signaling and exerts anti-inflammatory effects via the expression of interleukin-1

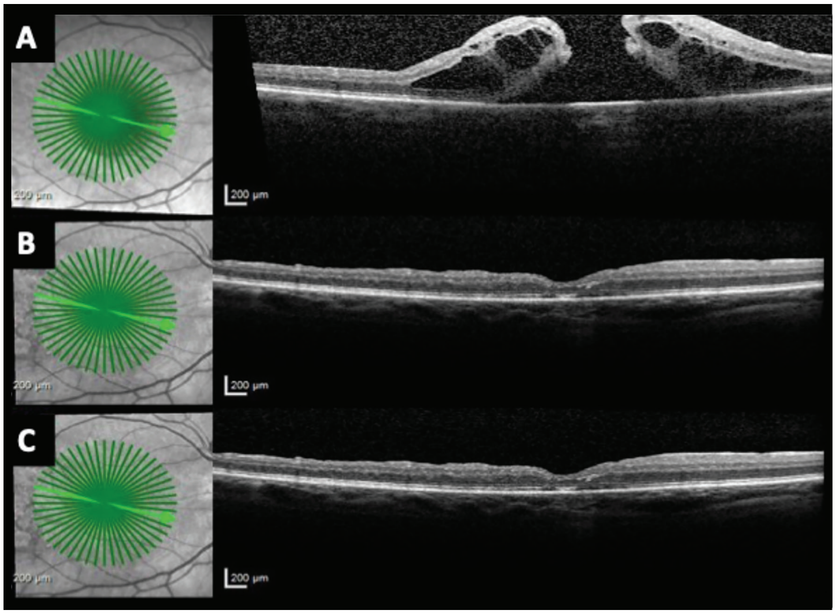

Figure 3. Refractory macular hole (A; visual acuity 20/400) after a failed wide internal limiting membrane peeling, treated with an autologous retinal transplant. Gradual improvement in visual acuity at postoperative month 12 (B; visual acuity 20/60) and month 30 (C; visual acuity 20/25) with alignment of the neurosensory layers, recovery of the ellipsoid zone, and foveal depression (*Source: Archive of Mahmoud et al.*)

receptor antagonist. It also contains growth factors such as epidermal growth factor and basic fibroblast growth factor, which promote tissue repair.[38,39,40,41] It is crucial to emphasize that hAM has low immunogenicity, as it does not express HLA antigens.

Rizzo et al.[42] first reported the use of hAM for recurrent MHs in vitreoretinal surgery. Since then, its applications have broadened considerably, with the ReMaHo study group identifying hAM as an optimal treatment for large MHs.[43]

Preparation Method

Cryopreservation and lyophilization (freeze-drying) are the two primary methods of preparation. Cryopreserving hAM in -80 °C glycerol preserves its structural integrity and most biological factors. Cryopreserved grafts are attached to carrier paper, which allows trimming of the grafts to the optimal size without the need for rehydration. Lyophilized hAM is freeze-dried, which results in a dehydrated membrane that is stored at room temperature and rehydrated prior to subsequent use. While this preparation offers storage and transportation benefits and increases mechanical strength, biological activity may be reduced.[42,43] According to a recent meta-analysis, cryopreserved hAM may provide superior results in the enhancement of visual acuity and anatomical closure, as the cryopreservation procedure more effectively preserves bioactive factors.[42,43,44]

Surgical Technique

Current approaches to MH treatment include four main surgical techniques that employ hAM grafts. Subretinal MH plugging has become the technique of choice among retinal specialists for refractory MHs.[45] This intricate procedure requires advanced surgical expertise to accurately place the hAM graft beneath the neurosensory retina. The subretinal placement of the hAM may be achieved through localized RD, manipulation of the MH borders, or utilization of a pre-existing detachment to position the graft beneath the neurosensory retina, ensuring contact with the RPE.[46]

The application of epiretinal patches has achieved growing popularity due to its technical simplicity and consistent clinical results.[44,47] This approach represents a significant change in surgical theory, as surgeons recognize that simplified approaches can yield excellent therapeutic outcomes.

Moreover, the hAM plug without subretinal placement is a technique that successfully positions the graft within the macular defect while minimizing extensive manipulation of the retina.[48,49,50] Despite its potential advantages, this intermediate approach seems to be decreasing in clinical practice.

The dual-layer technique represents a significant advancement in the field of MH surgery.[51,52] This innovative method integrates principles from established approaches by employing two distinct hAM grafts in a stratified configuration (Figure 4). Preliminary findings from early-adopting surgeons indicate significant therapeutic potential.

Primary and Recurrent Macular Holes

Rizzo et al.[42] conducted a pioneering study that achieved 100% anatomical success with subretinal implantation in 8 eyes with recurrent MH. The results showed that mean visual acuity improved from 1.48 logarithm of the minimum angle of resolution (logMAR) preoperatively to 0.48 logMAR at six months. Caporossi et al.[53] conducted a prospective trial in 36 eyes with recurrent MHs, achieving a 100% closure rate and improved visual acuity in 91.6% of the participants. Similarly, Bamberger et al.[54] achieved a 91% closure rate using hAM plugs for chronic or persistent MHs in two Canadian tertiary care centers. Ferreira et al.[55] conducted a retrospective, multicentric, interventional study on large and refractory MHs in 19 eyes. Following a single intervention, 100% closure was achieved over a mean follow-up period of 9±3.87 months, with a postoperative BCVA of approximately 20/200 and with a median visual improvement of three lines.

Furthermore, the ReMaHo study group examined 116 eyes, including 19 (16%) undergoing primary repair and 97 (84%) refractory cases, and found that MHs over 680 µm in diameter demonstrated higher closure rates with hAM compared to autologous ILM free flap transplantation, establishing its superiority for closing large MHs.[45] Other recent studies have explored innovative approaches, including split-thickness thin amniotic membrane grafts and autologous blood clot-assisted lyophilized hAM, with encouraging long-term outcomes.[56,57]

Finally, a recent extensive meta-analysis of 8 studies encompassing 103 eyes with recurrent MH demonstrated visual acuity improvement in 66% of cases, a 94% MH closure rate, and a 6% hAM graft dislocation rate.[44,45] Cryopreserved hAM grafts have shown exceptional outcomes, achieving 99% closure rates and a mere 3% dislocation rate.[42] Regarding tamponade selection, sulfur hexafluoride (SF_6) gas was predominantly preferred, followed by air, silicone oil, and perfluoropropane (C_3F_8) gas.[46,60]

Myopic Macular Holes

MHs related to high myopia and posterior staphyloma present distinct challenges due to altered architecture and increased tractional forces. Caporossi et al.[53] achieved a 100% closure rate with hAM in severely myopic eyes with an axial length of 30 mm or greater. The same group demonstrated success in recurrent high myopic MHs associated with RD treated with hAM. Qiao et al.[59] evaluated 17 eyes with high myopic MHs associated with RD after unsuccessful initial surgery, successfully achieving closure and reattachment in all cases. Visual acuity increased in 88.24% of eyes, with only 1 eye (5.89%) requiring an adjustment of the hAM graft.

Innovative surgical techniques have been developed for myopic MHs. Iannetta et al.[47] reported epiretinal positioning of hAM for primary MH accompanied by RD in a patient with high myopia, in contrast to the more common subretinal placement. Fan et al.[60] introduced an innovative method utilizing biological ultrathin amniotic membrane flaps (<10 µm thick) for refractory MHs, providing adequate support while reducing visual impairment.

However, challenges specific to myopic eyes have been recognized. Tsai et al.[61] reported parafoveal atrophy in 40% of eyes with extremely myopic MHs after hAM graft transplantation. However, this finding did not significantly impact visual outcomes in the majority of cases.

Pediatric and Syndromic Cases

The hAM is also applicable in pediatric populations and syndromic conditions. Abdullah et al.[51] described a sandwich-type double-layer amniotic membrane graft approach for the treatment of myopic MH-associated RD in a pediatric patient with Knobloch syndrome.

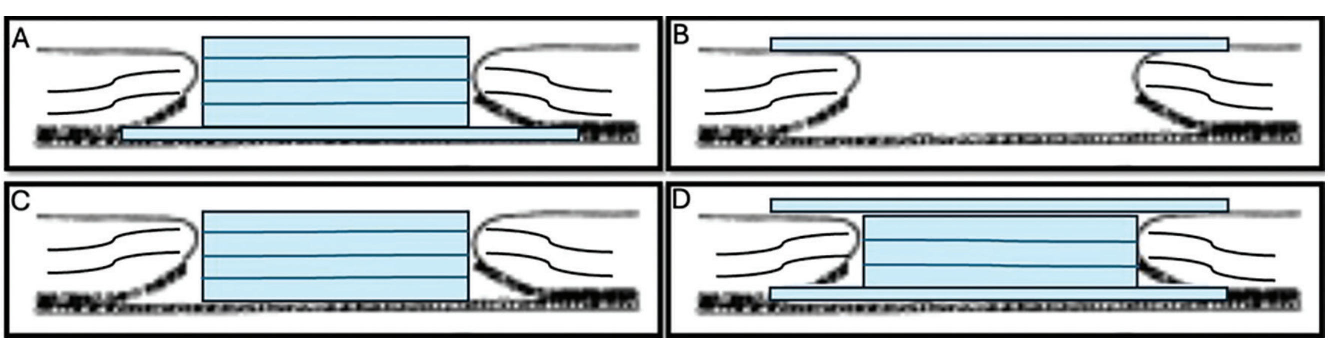

Figure 4. Schematic illustration of the human amniotic membrane (hAM) placement techniques with cross-sectional representation. A) hAM plug with subretinal placement; B) Epiretinal patch technique; C) hAM plug without subretinal placement; D) Double-layer technique (*Source: Archive of Rizzo et al.*)

Complications and Safety

Despite promising outcomes, potential complications include intraoperative difficulties in membrane handling and positioning, especially with cryopreserved hAM due to its flexibility and tendency to fold. Dislocation and contracture are other significant surgical complications. However, cryopreserved grafts exhibit these complications at a favorable 3% rate, in contrast to a troubling 26% rate associated with dehydrated preparations.[42] The difference indicates that cryopreservation more effectively preserves the structural integrity of hAM, thereby significantly decreasing the risk of postoperative graft instability and contracture, which can contribute to surgical failure.[42]

Postoperative displacement of the hAM has been reported in 3-7% of cases with epiretinal placement, appearing less common with subretinal placement, where the membrane is more securely positioned between the retina and RPE.[43,62,63,64] Other reported complications include peripheral retinal tears occurring postoperatively, suprachoroidal hemorrhage, and localized RPE atrophy.[54,65,66] As mentioned above, complications specific to myopia include parafoveal atrophy and graft contraction leading to secondary detachment.[61]

Clinical and *in vitro* safety assessments of epiretinal amniotic membrane conducted by Hillenmayer et al.[46] yielded positive findings concerning the biocompatibility of intravitreal hAM, with no evidence of cellular immunological rejection. Similarly, overall safety data for subretinally implanted hAM reveals no reported immunological or inflammatory rejection, nor any major complications such as RD or endophthalmitis.

Future Directions and Outcomes

Current evidence demonstrates that hAM grafts offer consistent anatomical benefits, with closure rates typically exceeding 90%. Advanced multimodal diagnostic imaging including spectral-domain optical coherence tomography (OCT), OCT-angiography, microperimetry, and adaptive optics reveals tissue growth, layer formation, and signs of remodeling at both the retinal capillary plexus and cellular levels. These findings suggest an ongoing biological integration that may continue to improve functional outcomes over time.

The development of scaffold-based approaches offers tailored solutions to achieve better anatomic and functional outcomes in eyes with large or complicated MHs. While anatomical success is consistently achievable, functional improvement remains variable and depends on multiple factors, including the chronicity of the hole, baseline macular architecture, and surgical technique. The development of innovative techniques such as ultrathin grafts, combined approaches, and temporary placement methods, as described by various authors, continues to expand the therapeutic potential of hAM in MH surgery.[57,67,68]

Future research should focus on standardizing techniques, conducting randomized controlled trials, and establishing definitive guidelines for optimal patient selection and surgical approaches.

4. Autologous Tenon's Capsule Plug

Tenon's capsule is a thin, elastic fibrovascular tissue that envelops the eyeball from the optic nerve to the corneal limbus, creating a nest in which the globe can move freely. This connective tissue membrane is firmly attached to the episcleral tissue approximately 1.5 mm behind the limbus, attaches to the fascial sheaths of the extraocular muscles, and finally joins the meningeal sheath of the optic nerve.[69,70]

Tenon's capsule is divided into anterior and posterior portions at the point of insertion of the recti muscles.[69] The anterior part of the capsule consists of collagen, smooth muscle, and elastic fibers and is firmly attached to the underlying episclera.[71,72] As the rectus muscle sheath is an extension of Tenon's capsule, it is assumed that the anterior capsule develops during the early stages of embryonic development, before the rectus muscles reach their insertion points.[73] The posterior part of Tenon's capsule, in contrast, forms during later stages of development and is simply composed of a condensation of collagen fibers.[74] Therefore, the anterior and posterior portions of Tenon's capsule appear to have different origins. The anterior part of the capsule contains corneal epithelial stem cells located within the limbus to maintain healthy epithelial turnover and preserve epithelial integrity.[75,76]

As a connective tissue matrix containing stem cells, Tenon's capsule is suggested to improve wound healing. Successful results have been reported for the management of several ocular pathologies, including penetrating eye injuries, phaco burns, exposure of glaucoma drainage device tubes, and limbal or scleral ischemia due to chemical injuries.[77,78,79,80] Based on these studies, Yilmaz et al.[81] introduced the autologous Tenon's capsule plug technique for the treatment of giant (>1000 µm) and refractory MHs in 2024. The authors suggested that this novel technique can provide a simple, cost-effective, repeatable, and readily available surgical solution for the treatment of complicated MHs.

Surgical Technique

Illumination with a disposable Eckardt Twinlight Chandelier (DORC, Zuidland, the Netherlands) is used to enable bimanual surgery. For giant MHs, following core vitrectomy and removal of the posterior hyaloid, the ILM is stained and peeled for approximately 3 disc diameters around the fovea using ILM forceps. In previously vitrectomized, recurrent MH cases, the procedure begins directly with obtaining the Tenon's capsule plug. The graft is harvested from the lower temporal quadrant of the operated eye due to its easily accessible location and safe distance from the rectus muscles.

To facilitate the separation of Tenon's capsule from the conjunctiva, approximately 0.3-0.4 mL of balanced salt solution is injected into the subconjunctival space. The conjunctiva is then incised using conjunctival scissors (McPherson-Westcott conjunctival scissors), and a small piece (measuring approximately 2 × 2 mm) of the underlying Tenon's capsule is carefully harvested. The tissue is delivered into the vitreous cavity using serrated microforceps. The plug size is reduced to approximately 1 disc diameter using microscissors and microforceps in the anterior vitreous cavity. Subsequently, a drop of PFCL is instilled onto the MH to facilitate manipulation, and the Tenon's capsule plug is gently placed over the hole under the PFCL. Owing to the adhesive nature of Tenon's capsule, it readily adheres to the defect.

A 360-degree peripheral retinal examination is performed with scleral indentation. Prophylactic endolaser photocoagulation is applied if needed. A fluid-air exchange is then performed, the PFCL drop is aspirated, and an 8% C_3F_8 gas tamponade is administered. To ensure graft stabilization in the early postoperative period, a small drop (0.05-0.1 mL) of viscoelastic (Viscoat; Alcon Laboratories, Fort Worth, TX, USA) can be injected over the autologous Tenon's plug. Patients are instructed to remain in a prone position for one week after surgery.

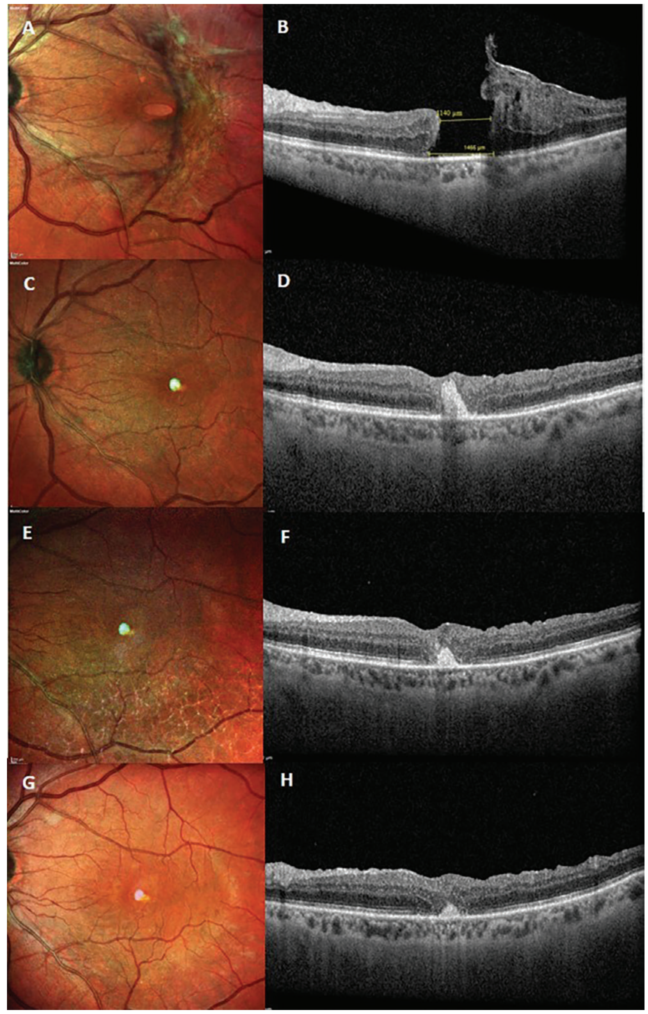

Figure 5. A 69-year-old female presented with an irregular, giant macular hole and a dense, tractional epiretinal membrane (ERM) temporal to the fovea (A). The minimum and base hole diameters were 1154 µm and 1403 µm, respectively (B). The patient underwent 23-gauge pars plana vitrectomy and membranectomy. As a considerable amount of ILM was simultaneously removed during the ERM peeling, it was not possible to create an ILM flap. Therefore, the autologous Tenon's capsule plug technique was performed. Five weeks after the surgery, the hole was closed and the Tenon plug was stable under the retina (C, D). Gradual shrinkage of the Tenon plug and simultaneous regeneration of the retinal layers was observed at 3 months (E, F) and 6 months (G, H) after the surgery (*Source: Archive of Yılmaz et al.*)

ILM: Internal limiting membrane

Results

In their initial description of the autologous Tenon's capsule plug technique for giant and refractory MHs, Yilmaz et al.[81] reported the outcomes of 3 cases (2 refractory, 1 giant). Successful closure and visual acuity improvement was achieved in all cases (Figure 5). In addition, a significant improvement in microperimetric fixation stability was achieved in all three patients. Only one of the patients who could not maintain prone positioning in the early postoperative period required a second surgery due to dislocation of the Tenon's plug into the vitreous cavity. This patient underwent a repeat autologous Tenon's capsule plug, including placing a freshly harvested Tenon's plug in the hole, fluid–air exchange, and an 8% C_3F_8 gas tamponade injection. One month after the second surgery, the hole was completely closed.

In all cases, the Tenon's capsule plug gradually reduced in size during the postoperative period, becoming nearly invisible on OCT within 6 to 12 months. Simultaneously, microstructural regeneration of the retina at the edges of the plug was observed. This behavior pattern of Tenon's capsule resembles that of the hAM plug. No serious complications, including endophthalmitis, RD, proliferative vitreoretinopathy, or secondary choroidal neovascularization, occurred in any of the patients during follow-up.

The authors concluded that the autologous Tenon's capsule plug may be a good alternative for treating complex MHs in clinical settings where access to amniotic membrane is not possible. The advantages of this novel technique can be summarized as follows:

1. Autologous nature and lack of immunogenicity.
2. High accessibility and repeatability: The tissue is easily accessible, and a new graft can readily be obtained if the initial attempt is unsuccessful.
3. Technical simplicity: The surgical technique has a flat learning curve and is relatively easy to apply.
4. Tissue-sparing approach: As no tissue is harvested from any layer of the retina (e.g., ILM or autologous retinal graft), it causes no additional damage or complications.
5. Cost-effective: There is no additional cost beyond that of standard vitrectomy.

However, despite these encouraging results, it is important to acknowledge that the data represent preliminary results characterized by limited clinical evidence.

5. Retracting Door Internal Limiting Membrane Flap

The ILM retracting door was first described by Finn and Mahmoud[82] in 2017 for the treatment of myopic MHs. This technique involves creating a nasal ILM flap, extending it temporally over the fovea and the MH, leaving the temporal edge of the flap as a hinge, then draping the flap back over the hole. The retracting door flap offers the advantages of the temporal inverted ILM flap and provides a scaffold for Müller cell proliferation. The ILM remains partially intact, which is beneficial if reoperation is required. Moreover, as the original position of the ILM is preserved, there is no risk of flap reversal, which is one of the most significant postoperative complications associated with the temporal inverted ILM flap. It is also technically less complicated and less dependent on early postoperative head positioning.

Later, in 2022, Marlow et al.[83] reported the use of the retracting door ILM flap for larger MHs with concurrent ERM. As the tangential traction exerted by the ERM contributes to MH development, its removal is a primary objective during surgery. However, due to the tight adhesions between the ERM and the ILM, the ILM is usually partially or completely removed when the ERM is peeled away. This eliminates the ILM flap option, which is known to improve surgical success in challenging MHs. In such scenarios, a combined ERM and ILM retracting door flap technique may offer a relatively simple and successful method for hole closure. Despite these advantages, there are still only a limited number of reports in the literature regarding this method, and they are largely restricted to case series.

6. Lens Capsule Transplant

Lens capsule transplantation to manage refractory or persistent MHs was first described by Chen and Yang[84] in 2016. The technique demonstrated high success rates in closing large, complex MHs.

Lens capsule transplantation is a promising option for refractory MHs where extensive ILM removal has been performed during the initial surgery, making the use of an ILM flap impossible. This technique involves harvesting a piece of the anterior or posterior lens capsule and placing it into the hole to help facilitate closure. It has been hypothesized that the lens capsule might behave like a basement membrane and provide a vitreous-free environment, similar to an ILM flap, for optimal glial proliferation and MH closure.

In 2022, Peng et al.[85] reported the use of lens capsule transplantation as the primary treatment for the management of large MHs. An autologous capsule flap was used in more than half of the patients, while an allogeneic capsule flap was used in the others. In addition, whole blood was used in some cases to enhance flap stability. The authors stated that all of the MHs were closed successfully. Studies in the literature show that this technique offers promising results and increases the MH closure rate, particularly in refractory cases.[86,87]

Conclusion

The aims of MH surgery are to eliminate or reduce the forces causing the defect, provide scaffolding to join the edges of the hole together, and thereby achieve anatomical closure and improve vision. As not all MHs arise from the same pathophysiology, there is no single ideal technique for managing all complex cases. Substantial evidence supports the inverted ILM flap as the primary treatment for large and myopic MHs. However, in cases of refractory MH where the ILM flap technique cannot be performed, as well as for XXL MHs (exceeding 800-1000 µm), various autologous or allogeneic tissue grafts may be considered, such as autologous retinal transplants, hAM, lens capsule transplants, and Tenon's capsule plugs (Figure 6). The choice of graft tissue depends on numerous factors, including the surgeon's experience, the technical and logistical capabilities of the operating room, and the specific clinical characteristics of the patient.

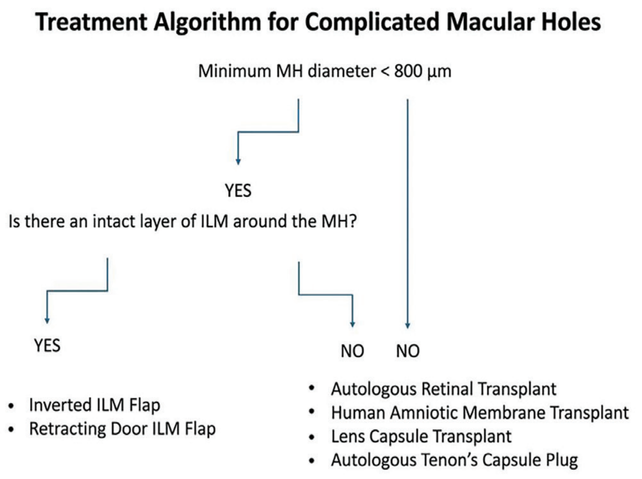

Figure 6. Treatment algorithm for complicated macular hole cases
MH: Macular hole, ILM: Internal limiting membrane

Declarations

Authorship Contributions

Surgical and Medical Practices: R.A., Z.A.N., S.R., S.Y., T.H.M., Concept: R.A., A.M.Y., Design: R.A., A.M.Y., Data Collection or Processing: Z.A.N., S.R., S.Y., E.A., F.G., A.L., T.H.M., Analysis or Interpretation: R.A., A.M.Y., Z.A.N., S.R., S.Y., E.A., T.H.M., Literature Search: A.M.Y., Z.A.N., S.R., E.A., F.G., A.L., T.H.M., Writing: A.M.Y., Z.A.N., S.R., F.G., A.L., T.H.M.

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References

1. Rezende FA, Ferreira BG, Rampakakis E, Steel DH, Koss MJ, Nawrocka ZA, Bacherini D, Rodrigues EB, Meyer CH, Caporossi T, Mahmoud TH, Rizzo S, Johnson MW, Duker JS. Surgical classification for large macular hole: based on different surgical techniques results: the CLOSE study group. Int J Retina Vitreous. 2023;9:4.
2. Duker JS, Kaiser PK, Binder S, de Smet MD, Gaudric A, Reichel E, Sadda SR, Sebag J, Spaide RF, Stalmans P. The International Vitreomacular Traction Study Group classification of vitreomacular adhesion, traction, and macular hole. Ophthalmology. 2013;120:2611-2619.
3. Michalewska Z, Michalewski J, Adelman RA, Nawrocki J. Inverted internal limiting membrane flap technique for large macular holes. Ophthalmology. 2010;117:2018-2025.
4. Bonińska K, Nawrocki J, Michalewska Z. Mechanism of "Flap closure" after the inverted internal limiting membrane flap technique. Retina. 2018;38:2184-2189.
5. Michalewska Z, Michalewski J, Dulczewska-Cichecka K, Adelman RA, Nawrocki J. Temporal inverted internal limiting membrane flap technique versus classic inverted internal limiting membrane flap technique: a comparative study. Retina. 2015;35:1844-1850.
6. Shiode Y, Morizane Y, Matoba R, Hirano M, Doi S, Toshima S, Takahashi K, Araki R, Kanzaki Y, Hosogi M, Yonezawa T, Yoshida A, Shiraga F. The role of inverted internal limiting membrane flap in macular hole closure. Invest Ophthalmol Vis Sci. 2017;58:4847-4855.
7. Thomas AS, Mahmoud TH. Subretinal transplantation of an autologous retinal free flap for chronic retinal detachment with proliferative vitreoretinopathy with and without macular hole. Retina. 2018;38(Suppl 1):121-124.
8. Kannan NB, Kohli P, Parida H, Adenuga OO, Ramasamy K. Comparative study of inverted internal limiting membrane (ILM) flap and ILM peeling technique in large macular holes: a randomized-control trial. BMC Ophthalmol. 2018;18:177.
9. Rizzo S, Tartaro R, Barca F, Caporossi T, Bacherini D, Giansanti F. Internal limiting membrane peeling versus inverted flap technique for treatment of full-thickness macular holes: a comparative study in a large series of patients. Retina. 2018;38(Suppl 1):73-78.
10. Tiryaki Demir S, Kol G, Dedeli FK, Karapapak M, Özal E. Comparison of outcomes between the classical and superior inverted internal limiting membrane flap techniques in idiopathic large macular hole surgery. Retina. 2025;45:1945-1950.
11. Mete M, Alfano A, Guerriero M, Prigione G, Sartore M, Polito A, Pertile G. Inverted internal limiting membrane flap technique versus complete internal limiting membrane removal in myopic macular hole surgery: a comparative study. Retina. 2017;37:1923-1930.
12. Chen SN, Yang CM. Inverted internal limiting membrane insertion for macular hole-associated retinal detachment in high myopia. Am J Ophthalmol. 2016;162:99-106.e1.
13. Baba R, Wakabayashi Y, Umazume K, Ishikawa T, Yagi H, Muramatsu D, Goto H. Efficacy of the inverted internal limiting membrane flap technique with vitrectomy for retinal detachment associated with myopic macular holes. Retina. 2017;37:466-471.
14. Matsumura T, Takamura Y, Tomomatsu T, Arimura S, Gozawa M, Kobori A, Inatani M. Comparison of the inverted internal limiting membrane flap technique and the internal limiting membrane peeling for macular hole with retinal detachment. PLoS One. 2016;11:e0165068.
15. Michalewska Z, Nawrocki J. Fovea morphology after vitrectomy in eyes with full-thickness macular hole coexisting with diabetic retinopathy. J Vitreoretin Dis. 2021;5:53-59.
16. Nawrocka ZA, Nawrocka Z, Nawrocki J. Vitrectomy for full thickness macular hole developed during the course of anti-VEGF treatment of type 1 neovascular AMD. Eur J Ophthalmol. 2022;32:NP5-NP8.
17. Michalewska Z, Nawrocki J. Vitrectomy with the inverted internal limiting membrane flap technique in eyes with full-thickness macular hole and dry age-related macular degeneration. Eur J Ophthalmol. 2021;31:1320-1325.
18. Abou Shousha MA. Inverted internal limiting membrane flap for large traumatic macular holes. Medicine (Baltimore). 2016;95:e2523.
19. Kanda K, Nakashima H, Emi K. Macular pucker formation after inverted internal limiting membrane flap technique: two case reports. Am J Ophthalmol Case Rep. 2022;25:101282.
20. Michalewska Z, Nawrocki J. Repeat surgery in failed primary vitrectomy for macular holes operated with the inverted ILM flap technique. Ophthalmic Surg Lasers Imaging Retina. 2018;49:611-618.
21. Tao M, Wang G, Gou Y, Zhang M. Comparative study of conventional inverted ILM flap covering and ILM flap filling technique in idiopathic macular hole treatment: a meta-analysis and systematic review. J Ophthalmol. 2022;2022:4922616.

22. Eckardt C, Eckardt U, Groos S, Luciano L, Reale E. Entfernung der Membrana limitans interna bei Makulalöchern. Klinische und morphologische Befunde [Removal of the internal limiting membrane in macular holes. Clinical and morphological findings]. Ophthalmologe. 1997;94:545-551.

23. Mester V, Kuhn F. Internal limiting membrane removal in the management of full-thickness macular holes. Am J Ophthalmol. 2000;129:769-777.

24. Grewal DS, Mahmoud TH. Autologous neurosensory retinal free flap for closure of refractory myopic macular holes. JAMA Ophthalmol. 2016;134:229-230.

25. Ashraf H, Haghpanah S, Nowroozzadeh MH. Modified autologous neurosensory retinal transplantation and bevacizumab injection in primary extra-large chronic macular holes. Am J Ophthalmol Case Rep. 2025;38:102269.

26. Tauqeer Z, Park J, Mahmoud TH. Combined amniotic membrane graft and autologous retinal transplant for repair of refractory chronic myopic macular holes. Retin Cases Brief Rep. 2025;19:434-438.

27. Wilson CA, Berkowitz BA, Srebro R. Perfluorinated organic liquid as an intraocular oxygen reservoir for the ischemic retina. Invest Ophthalmol Vis Sci. 1995;36:131-141.

28. Tanaka S, Inoue M, Inoue T, Yamakawa T, Uchio E, Grewal DS, Mahmoud TH, Kadonosono K. Autologous retinal transplantation as a primary treatment for large chronic macular holes. Retina. 2020;40:1938-1945.

29. Park JG, Adrean SD, Begaj T, Capone A Jr, Charles S, Chen SN, Chou HD, Cohen MN, Corona ST, Faia LJ, Garg SJ, Garretson BR, Gregori NZ, Haller JA, Houghton OM, Hsu J, Jo J, Kaiser RS, Lai CC, Mahgoub MM, Mansoor M, Matoba R, Morizane Y, Nehemy MB, Raphaelian PV, Regillo CD, Ruby AJ, Runner MM, Sneed SR, Sohn EH, Spirn MJ, Vander JF, Wakabayashi T, Wolfe JD, Wykoff CC, Yonekawa Y, Yoon YH, Mahmoud TH. Surgical management of full-thickness macular holes in macular telangiectasia type 2: a global multicenter study. Ophthalmology. 2024;131:66-77.

30. Karabaş L, Seyyar SA, Tokuç EÖ. Management of retinal detachment with a coexistent macular hole: submacular placement of retinal autograft through a macular hole. Retina. 2023;43:2199-2203.

31. Scoles D, Mahmoud TH. Inaccurate measurements confound the study of myopic macular hole. Ophthalmol Retina. 2022;6:95-96.

32. Grewal DS, Charles S, Parolini B, Kadonosono K, Mahmoud TH. Autologous retinal transplant for refractory macular holes: multicenter international collaborative study group. Ophthalmology. 2019;126:1399-1408.

33. Moysidis SN, Koulisis N, Adrean SD, Charles S, Chetty N, Chhablani JK, Cortes JC, Embabi SN, Gordon C, Gregori NZ, Habib A, Hamza H, Hassaan H, Hassan TS, Houghton O, Kadonosono K, Kusaka S, La Mantia A, Lai CC, Lumi X, Maeno T, Mahgoub MM, Mohamed El Baha S, Morales-Cantón V, Nowara M, Okonkwo ON, Parolini B, Rezende FA, Rogalinska I, Rojas S, Steel DH, Stopa M, Wu AL, Yamada K, Yamada M, Mahmoud TH. Autologous retinal transplantation for primary and refractory macular holes and macular hole retinal detachments: the Global Consortium. Ophthalmology. 2021;128:672-685.

34. Hanai M, Amaral DC, Jacometti R, Aguiar EHC, Gomes FC, Cyrino LG, Alves MR, Monteiro MLR, Fuganti RM, Casella AMB, Louzada RN. Large macular hole and autologous retinal transplantation: a systematic review and meta-analysis. Int J Retina Vitreous. 2024;10:56.

35. Shields RA, Mahmoud TH. Management of autologus retinal transplant complications: a case series. Retina. 2023;43:2030-2033.

36. Kitahata S, Inoue T, Nagura K, Nakamura K, Tanaka S, Maruyama-Inoue M, Kadonosono K. Retinal morphologic features in patients with large macular holes treated by autologous neurosensory retinal transplantation. Ophthalmol Retina. 2023;7:406-412.

37. Tabandeh H. Vascularization and reperfusion of autologous retinal transplant for giant macular holes. JAMA Ophthalmol. 2020;138:305-309.

38. Hao Y, Ma DH, Hwang DG, Kim WS, Zhang F. Identification of antiangiogenic and antiinflammatory proteins in human amniotic membrane. Cornea. 2000;19:348-352.

39. He H, Li W, Chen SY, Zhang S, Chen YT, Hayashida Y, Zhu YT, Tseng SC. Suppression of activation and induction of apoptosis in RAW264.7 cells by amniotic membrane extract. Invest Ophthalmol Vis Sci. 2008;49:4468-4475.

40. Lee SB, Li DQ, Tan DT, Meller DC, Tseng SC. Suppression of TGF-beta signaling in both normal conjunctival fibroblasts and pterygial body fibroblasts by amniotic membrane. Curr Eye Res. 2000;20:325-334.

41. Kubo M, Sonoda Y, Muramatsu R, Usui M. Immunogenicity of human amniotic membrane in experimental xenotransplantation. Invest Ophthalmol Vis Sci. 2001;42:1539-1546.

42. Rizzo S, Caporossi T, Tartaro R, Finocchio L, Franco F, Barca F, Giansanti F. A human amniotic membrane plug to promote retinal breaks repair and recurrent macular hole closure. Retina. 2019;39(Suppl 1):95-103.

43. Lorenzi U, Mehech J, Caporossi T, Romano MR, De Fazio R, Parrat E, Matonti F, Mora P; ReMaHo Study Group. A retrospective, multicenter study on the management of macular holes without residual internal limiting membrane: the refractory macular hole (ReMaHo) study. Graefes Arch Clin Exp Ophthalmol. 2022;260:3837-3845.

44. Zhang H, Li Y, Chen G, Han F, Jiang W. Human amniotic membrane graft for refractory macular hole: a single-arm meta-analysis and systematic review. J Fr Ophtalmol. 2023;46:276-286.

45. Carlà MM, Giannuzzi F, Hu L, Rizzo C, Crincoli E, Catania F, Gambini G, Caporossi T, Mateo C, Rizzo S. The human amniotic membrane in vitreoretinal surgery: applications, outcomes and limitations. Surv Ophthalmol. 2026;71:14-24.

46. Hillenmayer A, Wertheimer CM, Gerhard MJ, Priglinger SG, Ohlmann A, Wolf A. Epiretinal amniotic membrane in complicated retinal detachment: a clinical and in vitro safety assessment. Ophthalmol Ther. 2023;12:1635-1648.

47. Iannetta D, Chhablani J, Valsecchi N, Mesiani M, de Smet MD, Fontana L. Epiretinal implant of human amniotic membrane to treat highly myopic macular hole retinal detachments: a novel surgical technique. Eur J Ophthalmol. 2024;34:304-309.

48. Caporossi T, Pacini B, De Angelis L, Rizzo S. Amniotic membrane plug to promote chronicpost-traumatic macular hole closure. Ophthalmic Surg Lasers Imaging Retina. 2019;51:50-52.

49. Saad SM, Rizvi SF, Tufail Khan MA, Mehmood SA, Abbasi S, Hassan Khan MT. Outcome of recurrent macular hole closure with amniotic membrane plug. J Ayub Med Coll Abbottabad. 2021;33:179-182.

50. Khaqan HA, Sahyoun JY, Haider MA, Buksh HM. Amniotic membrane graft for the treatment of large refractory macular hole. Retina. 2022;42:1479-1483.

51. Abdullah OO, Özdemir Zeydanlı E, Özdek Ş. A sandwich-type double-layer amniotic membrane graft for repairing myopic macular hole-related retinal detachment in a child with Knobloch syndrome. Turk J Ophthalmol. 2025;55:57-60.

52. Hayakawa Y, Inada T. Amniotic membrane coverage for intractable large macular holes: a first report with Japanese patients. J Clin Med. 2025;14:3708.

53. Caporossi T, Pacini B, De Angelis L, Barca F, Peiretti E, Rizzo S. Human amniotic membrane to close recurrent, high myopic macular holes in pathologic myopia with axial length of ≥30 mm. Retina. 2020;40:1946-1954.

54. Bamberger MD, Felfeli T, Politis M, Mandelcorn ED, Galic IJ, Chen JC. Human amniotic membrane plug for chronic or persistent macular holes. Ophthalmol Retina. 2022;6:431-433.

55. Ferreira MA, Maia A, Machado AJ, Ferreira REA, Hagemann LF, Júnior PHER, Rezende FA. Human amniotic membrane for the treatment of large and refractory macular holes: a retrospective, multicentric, interventional study. Int J Retina Vitreous. 2021;7:38.

56. Chen H, Lin W, Tang Y, Wei Y. The long-term follow-up of autologous blood clot-assisted lyophilized human amniotic membrane covering treatment unclosed macular hole. Retina. 2023;43:1340-1347.

57. Trivedi V, You Q, Me R, Lee PSY, Le K, Tran D, Lin X. Temporary amniotic membrane graft placement for treatment of refractory macular holes. Retin Cases Brief Rep. 2026;20:39-42.

58. Caporossi T, Tartaro R, Finocchio L, Pacini B, De Angelis L, Bacherini D, Rizzo S. Human amniotic membrane to treat macular holes that failed to close, sulfur hexafluoride endotamponade versus air endotamponade: a prospective comparative study. Retina. 2021;41:735-743.

59. Qiao G, Zhang XJ, Tang ZY, Zou QX, He CM, Lei XM, Zhao L, Quan Y, Yang HQ, Cao K, Dong WJ. Amniotic membrane for covering high myopic macular hole associated with retinal detachment following failed primary surgery. Int J Ophthalmol. 2022;15:760-765.

60. Fan Y, Wang J, Lei J, Ji J, Xie P, Hu Z. Biological ultrathin amniotic membrane flap to close refractory macular holes associated with high myopia. Graefes Arch Clin Exp Ophthalmol. 2024;262:3519-3530.

61. Tsai DC, Huang YH, Chen SJ. Parafoveal atrophy after human amniotic membrane graft for macular hole in patients with high myopia. Br J Ophthalmol. 2021;105:1002-1010.

62. Huang YH, Tsai DC, Wang LC, Chen SJ. Comparison between cryopreserved and dehydrated human amniotic membrane graft in treating challenging cases with macular hole and macular hole retinal detachment. J Ophthalmol. 2020;2020:9157518.

63. Gutierrez-Benitez L, Biarge G, Asaad M, Delas B. Human amniotic membrane plug to treat failed and highly myopic macular holes. Our experience. Arch Soc Esp Oftalmol (Engl Ed). 2025;100:213-218.

64. Garcin T. Epiretinal scroll of lyophilized amniotic membrane used to close a large, long-standing, idiopathic, full-thickness macular hole. J Fr Ophtalmol. 2022;45:142-143.

65. Lipková B, Rosocha J, Maurská A. Report on amniotic membrane for surgery of persistent macular hole. Cesk Slov Oftalmol. 2022;78:130-137.

66. Lin W, Chen H, Tang Y, Lin X, Wei Y. Pretreated lyophilized human amniotic membrane graft covering for retinal detachment with posterior retinal breaks above chorioretinal atrophy in pathologic myopia. Retina. 2024;44:974-981.

67. Trivedi V, You Q, Lee PSY, Im J, Tran DV, Me R, Benenati B, Gregory A, Le K, Lin X. Efficacy of split-thickness thin amniotic membrane graft for closure of refractory or large macular holes. Retina. 2025;45:833-838.

68. Patel H, Swiatek K, Rivera-Zengotita M, Chen J. Human amniotic membrane graft removal and histopathologic evaluation following closure of a full thickness macular hole. Am J Ophthalmol Case Rep. 2025;37:102239.

69. Dutton JJ. Atlas of clinical and surgical orbital anatomy. 3rd ed. Philadelphia: Elsevier; 2024.

70. Snell RS, Lemp MA. Clinical anatomy of the eye. 2nd ed. Oxford: Blackwell Science; 1998.

71. Doxanas MT, Anderson RL. Clinical orbital anatomy. Baltimore: Williams & Wilkins; 1984.

72. Whitnall SE. The anatomy of the human orbit and accessory organs of vision. J Am Med Assoc. 1933;100:362-363.

73. Jones LT. A new concept of the orbital fascia and rectus muscle sheaths and its surgical implications. Trans Am Acad Ophthalmol Otolaryngol. 1968;72:755-764.

74. Roth A, Mühlendyck H, De Gottrau P. La fonction de la capsule de Tenon revisitée [The function of Tenon's capsule revisited]. J Fr Ophtalmol. 2002;25:968-976.

75. Tsang SH. Stem cell biology and regenerative medicine in ophthalmology. Springer New York; 2013.

76. Notara M, Alatza A, Gilfillan J, Harris AR, Levis HJ, Schrader S, Vernon A, Daniels JT. In sickness and in health: corneal epithelial stem cell biology, pathology and therapy. Exp Eye Res. 2010;90:188-195.

77. Yi QY, Wang SS, Gui Q, Chen LS, Li WD. Autologous tenon capsule packing to treat posterior exit wound of penetrating injury: a case report. World J Clin Cases. 2021;9:5211-5216.

78. Sharma S, Kate A, Donthineni PR, Basu S, Shanbhag SS. The role of Tenonplasty in the management of limbal and scleral ischemia due to acute ocular chemical burns. Indian J Ophthalmol. 2022;70:3203-3212.

79. Mansour HA, Mansour AM. Autologous tenon plug and patch in phacoburn. BMJ Case Rep. 2021;14:e238970.

80. Wagdy FM. Tenon capsule grafting versus autologous scleral graft in Ahmed glaucoma valve surgery. J Ophthalmol. 2020;2020:1248023.

81. Yilmaz S, Mavi Yildiz A, Avci R. A novel surgical technique for giant and refractory macular holes: autologous tenon capsule plug. Retin Cases Brief Rep. 2025;19:439-446.

82. Finn AP, Mahmoud TH. Internal limiting membrane retracting door for myopic macular holes. Retina. 2019;39(Suppl 1):92-94.

83. Marlow ED, Bakhsh SR, Reddy DN, Farley ND, Williams GA, Mahmoud TH. Combined epiretinal and internal limiting membrane retracting door flaps for large macular holes associated with epiretinal membranes. Graefes Arch Clin Exp Ophthalmol. 2022;260:2433-2436.

84. Chen SN, Yang CM. Lens capsular flap transplantation in the management of refractory macular hole from multiple etiologies. Retina. 2016;36:163-170.

85. Peng J, Chen C, Zhang L, Huang Y, Zhang H, Zheng Y, Ren J, Zou Y, Zhang X, Zhao P. Lens capsular flap transplantation as primary treatment for closure of large macular holes. Retina. 2022;42:306-312.

86. Cisiecki S, Bonińska K, Bednarski M. Autologous lens capsule flap transplantation for persistent macular holes. J Ophthalmol. 2021;2021:8148792.

87. Li D, Ye Q, Li C. Auto-transplantation of the anterior lens capsule and blood for a recurrent large macular hole. Int J Ophthalmol. 2020;13:1839-1840.