Review Article

Taiwan J Ophthalmol 2021;11: 221-231

Access this article online

Quick Response Code:

Website:
www.e-tjo.org

DOI:
10.4103/tjo.tjo_26_20

Current management strategies for atypical macular holes

Elizabeth D. Marlow[1], Tamer H. Mahmoud[1,2]*

Abstract:

This review evaluates the current surgical management options for refractory and atypical macular holes (MH) and proposes a treatment paradigm for approaching complex cases. A review of literature was performed to deliver a thorough discussion of the epidemiology and pathophysiology of MH as well as the historic evolution of surgical management strategies. With this context established, an update on recent surgical advances for management of large, chronic, and highly myopic MH is provided. New small MH may be adequately treated with pars plana vitrectomy, while those ≥300 μm should undergo internal limiting membrane (ILM) peel. For MH ≥400 μm with risk factors for failure, primary intervention should involve creation of an ILM flap and various methods of flap creation are discussed. For very large MH ≥700 μm or in refractory cases, autologous retinal transplants and other recently proposed procedures should be considered. While typical MHs enjoy high initial surgical success rates, atypical and refractory MH require additional intraoperative and postoperative considerations to maximize surgical success and optimize vision. With many techniques at the surgeon's disposal, patient selection becomes critical to improving outcomes.

Keywords:

Autologous retinal transplant, internal limiting membrane, macular hole, vitrectomy

[1]Associated Retinal Consultants, P.C., Royal Oak, MI, USA, [2]Department of Ophthalmology, Oakland University William Beaumont School of Medicine, Rochester, MI, USA

***Address for correspondence:**
Tamer H. Mahmoud, MD, PhD. Associated Retinal Consultants, PC 3555 W Thirteen Mile Road Neuroscience Bldg, LL-20 Royal Oak, MI 48073, USA.
E-mail: tmahmoud@arcpc.net

Submission: 16-04-2020
Accepted: 11-05-2020
Published: 06-07-2020

Introduction

Macular holes (MHs) are an anatomical defect of the fovea resulting in decreased vision. The mainstay of treatment is pars plana vitrectomy (PPV) with or without internal limiting membrane (ILM) peel, which has a high success rate in small and medium MH and has been reviewed extensively. Management strategies for atypical and recurrent or persistent (i.e., refractory) MH have proliferated over the past decade, but there exists no consensus on the optimal treatment paradigm. This review discusses the surgical maneuvers currently employed in MH treatment with a focus on management of atypical or refractory holes and provides a suggested surgical approach for complex cases.

Epidemiology

MHs are an infrequent cause of decreased vision among adult populations with a higher incidence in the elderly and women. The prevalence of MH increases from 0.3% among those >55 years to 0.8% of those >75 years, with an annual incidence of 4–8.7 cases per 100,000 persons.[1-3] Women are affected 3 times more often than men, with women over age 70 having the highest incidence.

Staging and classification

The classification of MH has progressed from a biomicroscopic description to a histologic understanding of vitreoretinal interface abnormalities aided by ocular coherence tomography (OCT). Gass subclassified MH into 4 types based on slit lamp examination, only 3 of which were full thickness MHs (FTMHs). Stage 1 was described as an impending MH, appearing as a yellow spot or halo with loss of anatomic foveal depression without a posterior

How to cite this article: Marlow ED, Mahmoud TH. Current management strategies for atypical macular holes. Taiwan J Ophthalmol 2021;11:221-31.

vitreous detachment (PVD).[4,5] OCT reveals this stage as a distortion of the foveal contour or intraretinal structural changes created by vitreomacular traction (VMT) in the absence of the FTMH.[6]

Gass' description of FTMH had 3 stages: Stage 2 with small hole <400 μm; Stage 3 with a hole ≥400 μm and a progressive vitreoretinal separation often typified by a small operculum overlying the retinal defect; Stage 4 has the retinal findings of Stage 3 with a complete PVD.[4,5] The International VMT Study Group further classified hole size as small <250 μm, medium 250–400 μm, and large >400 μm based on the horizontal linear width measured at the narrowest point of the hole.[6] While these size criteria are sufficiently granular for the majority of MHs, many MH refractory to conventional management may be >400 μm and would require a revised classification scheme.

Progression from Stage 1 to FTMH is not inevitable as 50% of impending MH regress spontaneously.[2] Idiopathic MH may also be bilateral in 11.7% of cases, and a FTMH in 1 eye carries variable prognostic implications for the fellow eye depending on the status of the vitreomacular interface.[1,3] If the fellow eye has a PVD, the risk is <2% for development of MH. However, if a fellow eye's vitreous is attached, the risk of a FTMH is 15%, increasing to 50% in the presence of an impending MH.[2] High-density (24-line) radial pattern OCT scans have shown superior sensitivity in distinguishing Stage 1 and small Stage 2 holes compared to standard raster scans, which may carry prognostic and management implications.[7]

MH may be classified as primary or secondary. Idiopathic holes account for 87.1% of cases, with secondary etiologies including high myopia, trauma, macular schisis, macular telangiectasia type 2, retinal vascular disease, uveitis, and age-related macular degeneration (AMD).[3,6]

Pathogenesis

The mechanism of MH development is multifactorial, and varies based on the underlying etiology. For idiopathic MH, the posterior vitreous cortex is thought to exert both anteroposterior (AP) and tangential traction on the fovea.[8,9] When the prefoveal vitreous cortex contracts, vitreofoveal attachment may persist as perifoveal attachments release.[5,8] The importance of VMT to the evolution of the MH is evidenced by the low incidence of bilateral MH if the fellow eye has a PVD.[2]

Still, tangential traction at the fovea may contribute to MH formation in the absence of AP traction. Examination of ILM following its removal in MH repair has shown cone photoreceptors to be present on the vitreous side indicating tangential traction sufficient to evert the retina.[10] The transmission of inner retinal forces to the photoreceptors is likely conducted by Müller cells, which exist in a cone configuration around the perifovea.[8,10] While most agree that AP traction is the primary mechanism for MH formation, the degeneration of inner retinal layers at the central fovea that it provokes may make otherwise normal tangential tractional forces pathophysiologic.[9]

Retinal hydration is another theory of MH pathogenesis whereby vitreomacular separation creates small defects in the inner retina that allow liquid vitreous to accumulate in the middle and outer retinal layers and precipitate a MH.[11] This proposed mechanism has been supported in case studies using OCT.[12]

Management

There was no established treatment for FTMH until 1991 when Kelly and Wendell performed the first PPV for MH repair.[13] Prior to that time, observation was standard of care with spontaneous closure rates of 50%, 11.4%, and 3% for Gass Stage 1, Stage 2, and Stage 3, respectively.[2,14,15] The initial results following PPV showed a FTMH closer rate of 58%, and 73% of patients with anatomic closure had improvement in visual acuity (VA) of 2 lines or greater.[13] PPV has become the standard of care for FTMH, accounting for 9.8% of all PPV performed in the UK between 2002 and 2010.[16]

Peeling of the ILM at the time of PPV was introduced by Eckardt in 1997 to address the tangential traction forces on the macula,[17] and has allowed for the current single operation success rates of over 90% with significant postoperative VA improvement.[18,19] The role of ILM peeling in surgical success is greater for large MH, as those <300 μm have shown high closure rates with PPV alone.[20]

Removal of the ILM excludes any lingering residual cortical vitreous that might impair MH closure and delivers improved retina compliance.[8,21] An examination of the ILM and epiretinal tissue in eyes with refractory MH showed proliferation of cells and collagen on the residual ILM, suggesting these may create tangential traction that result in surgical failure.[22]

In support of this theory, PPV with ILM peel has a significantly lower incidence of MH recurrence compared to PPV alone.[23] ILM peeling also results in superior long-term functional improvements and no increase in complications.[24] Peeling ILM for MH is cost-effective and is now the standard of care for typical MH Stage 3 or higher without risk factors for failure.

Risk Factors for Failure

While single surgery success for the majority of MH remains extremely high, those that are large, chronic, or associated with high myopia have a greater risk of failed initial repair. These MH require additional intraoperative and postoperative considerations to maximize surgical success and optimize vision.

Large size

Large MH size is a well-recognized risk factor for surgical failure with Stage 4 holes having lower initial closure rates compared to Stage 2 and 3, and VA results that similarly lag.[25] These trends persist for MH >400 µm, when measuring basal diameter. The Manchester Large MH Study showed that the surgical success rate for FTMH undergoing PPV with ILM peel was over 90% for holes 400–649 µm, but dropped to 76% for holes 650–1416 µm. Other studies have suggested that holes >500 µm may have initial surgical success rates of only 50%–60%.[25-27] In some cases, larger MH is associated with longer duration of symptoms, and thus chronicity, but the majority of studies have not found a consistent correlation. Consequently, large MH size is considered an independent risk factor for surgical failure.[25,28]

Chronicity

The successful repair of MH is time-sensitive. Jaycock *et al*. showed that MH undergoing PPV for surgical repair within 1 year of symptom onset was over 90% while it declined to 47.4% among those delayed beyond 1 year.[29] Even long-standing MH that achieve closure show greater variation in VA improvement, though useful vision can still be obtained.[29,30] A recent retrospective analysis by Lumi *et al*. of long-duration MH (mean 13.5 months) undergoing PPV with ILM peel showed primary success rates above 90%, though this was lower in the presence of concurrent epiretinal membrane.[31]

High myopia

High myopia, typically defined as ocular axial length (AL) of at least 26 mm or refractive error >−6.00 D is a well-established risk factor for surgical failure in MH repair.[32] It has been proposed that long AL and the presence of a posterior staphyloma may exert traction at the retinal surface and impede hole closure.[33-36] A retrospective study by Suda *et al*. showed that eyes undergoing PPV with ILM peel for MH with AL <26.0 mm had 100% initial and final surgical success rate. The success rate for MH in eyes with AL 26.0–29.9 mm was only reduced to 91.7%, but dropped to 0% for eyes with AL 30.0 mm or greater.[35] Retinoschisis of the outer retina was associated with a higher risk of initial anatomic failure. The baseline VA is often lower in highly myopic eyes and even in the event of MH closure, some studies have shown lower VA gains achieved relative to eyes without severe myopia.[32,36,37] The tempered VA improvement has been attributed to disappearance of the outer nuclear and photoreceptor layers in the foveola with associated retinal thinning noted only in myopic eyes.[36]

Surgical Strategies

While PPV with ILM peel remains the standard of care for typical MH, surgical strategies have evolved to improve outcomes for MH that are chronic, large, or associated with high myopia.

Internal limiting membrane peel width

As previously described, the introduction of ILM peeling has significantly improved surgical and functional outcomes for MH surgery. The technique was initially described as peeling a 3–4 disc diameter (DD) area of ILM around the fovea.[17] Individual practitioners show wide variation in extent of peel, with peel radii ranging from 0.5 to 3 DD, and the significance of these differences to surgical outcomes has been considered. A randomized, controlled trial conducted by Bae *et al*. in 2016 compared peel raddi of 0.75 DD versus 1.5 DD and showed that a larger ILM peel improved postoperative metamorphopsia, while both widths provided the same, high surgical success rate.[18] Other prospective studies have shown no difference in MH closure rates with 3 mm versus 5 mm peels, but have suggested that smaller peel radii might deliver greater functional gains with less nerve fiber layer disruption.[38] Though no consensus on optimal peel width exists, case reports of wide peels having success in large MH has led many surgeons to peel ILM to the arcades.[39] This is tempered by a desire to conserve ILM for flap creation in the event the MH is refractory to initial repair.

A recent study using OCT angiography (OCTA) to compare the effects of ILM peeling on the retinal vasculature, showed a lower vessel density in the deep retinal plexus where ILM was peeled compared to where it was intact.[40] Nonetheless, multifocal electroretinograms (mfERG) show no decrease in retinal sensitivity in areas of peeled ILM, and many studies support equal VA outcomes regardless of ILM peel width so long as it is sufficient to allow MH closure.[20,41]

Other techniques

Laser photocoagulation, arcuate retinotomy, radial retinal incisions, and induced MH retinal detachments (RDs) have also been used to treat refractory MH, though none have gained widespread adoption. Laser photocoagulation was first introduced by Del Priore in 1994 to promote formation of a glial plug, and success has been shown in closing MH > 400 µm with improvement in VA.[42,43] While concerns regarding creating microscotomas persist, laser remains the only nonsurgical therapeutic technique for refractory FTMH. Localized RDs under the MH, arcuate retinotomies, and radial retinal incisions are all performed in an effort to increase retinal compliance and stimulate gliosis with case reports and small retrospective studies indicating anatomic improvement.[44-47]

Internal Limiting Membrane Scaffold

For refractory MHs, the standard of care has historically been to repeat the vitrectomy and enlarge the ILM peel. Recent innovations have sought to step beyond simply the removal of structural elements that might exert traction to keep a MH open, and explore scaffolds to facilitate its closure. Glial cells on the MH surface are known to produce intermediate filaments, and material positioned over the hole may allow these to initiate tissue remodeling that promotes healing.[48,49] This is pertinent to refractory MH as well those at high risk of primary surgical failure.

Inverted internal limiting membrane flap

The inverted ILM flap technique provides a structural scaffold for MH closure while leaving a portion of the ILM attached. Initially described by Michalewska *et al*. for large Stage 4 MH, in this technique the ILM is peeled toward the MH and left attached at the MH edge before being inverted to cover the hole, leaving the retina-facing surface of the ILM directed toward the vitreous cavity.[50] In their prospective, randomized trial of patients with MH >400 μm, patients obtained a 98% closure rate with inverted ILM flap (flat-open configuration in 2%) compared to 88% achieving closure with complete ILM peel (flat-open configuration in 19%).

Inverted flap for large macular hole

The advantages of an inverted ILM flap over conventional ILM peel for large MH has been confirmed by multiple comparative studies, with inverted ILM flaps achieving both higher surgical success rates and improved VA outcomes.[51,52] The difference in outcomes between conventional ILM peel and inverted ILM flaps is greatest with increasing MH size. Retrospective comparison of primary closure rates for conventional ILM peel versus inverted ILM flap in holes 400–550 μm was 95.2% and 100%, respectively. Among holes >550 μm, the closure rates for conventional peel declined to 88.4% compared to 100% for the inverted ILM, though this difference was not statistically significant.[53] A prospective randomized controlled trial (RCT) of large FTMH between 600–1500 μm showed that conventional ILM peel had a primary closure success rate of 70% while inverted ILM flap was 90%.[54] Even extremely large MH >1000 μm have shown 100% primary closure with inverted ILM flap technique.[55] A meta-analysis of MH >400 μm including 4 RCT and 4 retrospective studies showed that the rate of MH closure was significantly higher with inverted ILM flap compared to peel, and also offered superior short-term VA recovery.[56]

The improved VA outcomes are correlated with higher rates of external limiting membrane and ellipsoid zone recovery and gliosis rates for eyes receiving inverted ILM flaps.[52,57,58] Beyond morphologic outcomes, microperimetry shows improved retinal sensitivity following closure with inverted ILM flap in eyes with MH > 400 μm, though degree of recovery is limited by pre-operative retinal sensitivity.[59]

Inverted flap for myopic macular hole

Inverted ILM flaps have also shown superiority for myopic MH, offering greater advantages for eyes with higher AL. A large retrospective review of 620 eyes undergoing MH repair with inverted ILM flap versus ILM peel showed that primary closure success rate was significantly higher at 88.4% for AL >26 mm using inverted ILM flaps than the 38.9% for AL >26 mm in the conventional ILM peel group.[60] One comparative study showed that among 14 eyes with AL >30 mm, primary closure was achieved only in 37.5% of those who underwent ILM peel while primary closure rate was 100% with inverted ILM flap.[61] A larger study conducted by Mete *et al*. in 70 eyes comparing complete ILM removal versus inverted ILM flap showed a primary surgical failure rate of 39% and 3%, respectively; this corresponded to a 22 time higher probability of anatomic success with the inverted ILM flap technique, regardless of MH diameter.[62] The few studies that have failed to show statistically significant difference in outcomes between ILM peeling and inverted ILM flaps for myopic MH have been small with potentially insufficient power to support the superiority of a particular technique.[63,64]

Given the concurrence of RD with MH in highly myopic eyes, the inverted ILM flap has also shown superior success rates for retinal reattachment and MH closure in several retrospective and meta-analysis studies.[65-70] One large meta-analysis looking at MH-associated RDs (MHRD) showed that while conventional ILM peel and inverted flaps offer equivalent outcomes for retinal reattachment rate and best corrected VA (BCVA), the MH closure rate was significantly higher with inverted ILM flap.[71]

Inverted flap technique and adjuvants

When applying inverted ILM flaps, various configurations of ILM hinge placement and flap positioning with or without layering of the ILM in the MH have been explored, and many techniques appear to offer similar functional and anatomic improvement.[72-74] Although loss of the ILM flap is less likely when it retains a connection to the retinal surface, effectively positioning the inverted flap over the MH still poses challenges.

Indeed, primary surgical failure following an inverted ILM flap is typically due to the flap returning to its original position instead of covering the MH.[75]

Adjuvants such as perfluoro-n-octane (PFO), blood clots, and viscoelastic have been used to facilitate inverted ILM flap positioning. In particular, autologous gluconated blood has been used in combination with inverted ILM flaps to serve as a macular plug, and one study showed initial surgical success in all patients with MH >500 µm without the need for gas tamponade or postoperative positioning.[76] MHRD in highly myopic eyes can be particularly challenging, and autologous blood in combination with inverted ILM flaps is effective, with reports of single surgery success of 96% and VA improvement.[77]

However, further technique refinements have suggested ILM flap manipulation and the use of adjuvants for flap positioning may be unnecessary. Peeling the ILM from the temporal macula allows the suction applied over the optic nerve during the fluid-air exchange to reliably position the flap over the MH.[78]

In summary, inverted ILM flaps allow for improved anatomic and functional outcomes in large and myopic MH and should be considered as part of the initial surgical approach for cases at high risk of primary surgical failure.

Noninverted Internal Limiting Membrane Flaps

Retracting *d*oor

The inflexibility of the taut ILM contributes tangential traction leading to MH formation, and in the context of high AL or posterior staphyloma may resist AP traction to provoke retinoschisis and RD.[79,80] The retracting door ILM flap technique developed by Finn and Mahmoud in 2019 involves creating an ILM flap on the nasal side of the MH with a temporal hinge in highly myopic eyes.[80] On the basis of relieving tangential traction, the myopic contour of the globe allows temporal retraction of the ILM flap from its initial position to cover the MH [Figure 1].[81] In addition, a study by Akahori *et al*. used OCTA to observe changes in retinal vasculature orientation relative to the fovea and optic disc following PPV with ILM peel for idiopathic MH and showed nasal displacement of the macula over an 8 weeks postoperative period.[82] The nasal migration of the macula combined with the temporal retraction of the ILM flap allows MH coverage with ILM and facilitates MH closure. Unlike the inverted ILM flap, the retracting door allows complete relief of the traction around the myopic MH. The retracting door technique avoids any deleterious effects of ILM removal on the inner retinal architecture and preserves ILM for use in future surgeries if needed.[83]

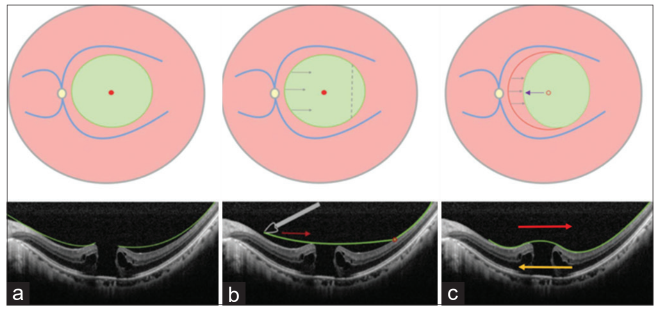

Figure 1: Technique for ILM retracting door. Upper animation shows an en-face depiction of OCT appearance. (a) Preoperatively, highly myopic patients have taught ILM (green). (b) Intraoperatively, the ILM is peeled nasal to temporal over the hole with a temporal hinge remaining. Red arrow depicts direction of ILM peel. (c) Postoperatively, ILM is relaxed and lays over the macular hole. Nasal retina is denuded as previously taut ILM retracts temporally. Purple arrow in animation highlights nasal movement of macula with tangential traction released. Red arrow reflects direction of ILM flap displacement and yellow arrow indicates nasal migration of macula following ILM peel. Figure and legend adapted from Finn A, Mahmoud TH. The ILM retracting door for myopic macular holes. Retina 2017. ILM: Internal limiting membrane, OCT: Ocular coherence tomography

Free flap

MHs refractory to initial surgery with PPV and ILM peel that undergo a second surgery with enlargement of the ILM peel width have success rates ranging from 46% to 61%.[84,85] In comparison, transplantation of an autologous free ILM flap for refractory MH has shown the potential to achieve anatomical success rates over 90%.[86] A recent retrospective review of recurrent idiopathic MH compared the effectiveness of performing a free autologous ILM flap versus enlarging the area of ILM peel on repeat surgery and showed a success rate of 93.3% with ILM free flap compared to 64.2% of controls with greater improvement in VA at 3 months in the autologous ILM flap group compared to the controls.[87] The use of multiple free ILM flaps and ILM free flaps layered over inverted flaps have also been shown to facilitate retinal reattachment and MH closure in MHRD with superior anatomic outcomes compared to ILM peeling.[88,89]

ILM appears to provide a mechanical scaffold for proliferating Müller cells that produce growth factors such as neurotrophic and basic fibroblasts growth factors to promote MH closure.[48,49] Despite the anatomic improvement, microstructural analysis of fovea following ILM flap transplantation have shown that the ILM can create prolonged proliferation of the glial tissue in the fovea with fibrosis and depigmentation.[90,91] Consequently, even when anatomic closure is achieved, VA tends to improve in only about 80% of cases[86,92]

Moreover, a free ILM flap is challenging to position and stabilize over the MH. It requires controlled intraocular fluidics and a careful fluid-air exchange to prevent flap displacement or accidental extrusion. Compounding the technical difficulties of this task is the sometimes poor view of the flap's location, even with vital dye staining. Although intraoperative OCT may confirm flap position, its availability remains limited for most surgeons. Perfluoro-n-octane or viscoelastic-assisted free ILM flap technique has been adopted as a means to position and stabilize the flap over the MH, and allows the majority of the fluid-air exchange to be performed without disruption to the flap.[86,93,94] Alternatively, the free ILM flap may be tucked into the edge of the hole to anchor it, though this carries risk of increased trauma to the underlying RPE and photoreceptors.[95] Ultimately, depending on the size of the initial ILM peel and the facility with which ILM is harvested, it can be difficult to obtain a single sheet of ILM adequate to cover the MH.

Pedicle flap

When performing repeat surgery on an eye that initially underwent conventional ILM peel, creating a pedicle flap in which an ILM flap is transposed to cover the FTMH may allow the same advantages as the free and inverted ILM flaps.[96-98] A retrospective series of 12 eyes undergoing noninverted pedicle flap for MH >400 μm showed closure rates over 90% with significant improvement in VA and macular sensitivity on mfERG.[99] However, the pedicle flap has not been widely adopted, and in our experience with its application in refractory holes, the flap tends to retract over time with reopening of the MH.

Scaffold Tissue Alternatives

Lens capsule

While the pedicle flap and ILM free flap may be used in cases of primary surgical failure after conventional ILM peel, sufficient portions of ILM may at times be difficult to collect from the mid-periphery. Lens capsule, either autologous or from the fellow eye, combined with autologous blood has shown success in closing large MH with an average basal diameter >1400 μm.[100] The use of lens capsule in MHRD has also shown the capacity to seal the MH with the capsular fragment and allows retinal reattachment.[101,102] This technique is often performed with anterior lens capsule which is more rigid and can potentially be maneuvered into retinal breaks without necessitating the use of PFO for stability.[101] Careful harvesting of anterior lens capsule with scissors and forceps mitigates the risk of destabilizing the intraocular lens. Considering the technique's initial positive results, lens capsule grafts are a promising therapeutic option, though it may have more limited applicability in countries where combined phacovitrectomy is uncommon.

Amniotic membrane

The application of human amniotic membrane (hAM) grafts into the subretinal space was first introduced in 2019, showing successful closure of recurrent and myopic MHs.[103] In the initial technique described by Rizzo *et al*. chandelier illumination was used to allow bimanual manipulation of a hAM graft that was inserted into the subretinal space underlying the MH under PFO. Position of the graft was confirmed by intraoperative OCT, and endotamponade with 20% sulfur hexafluoride (SF6) was applied. In this prospective study, all 8 patients with MH showed neurosensory retina overfilling the hAM plug and closure at 1 week. VA continued to improve up to 6 months postoperatively, and there were no serious adverse events of graft rejection out to 1 year. Human AM grafts were used in a series of 16 eyes with recurrent myopic MH with AL >30 mm achieving >90% MH closure after initial repair.[104] One case required repeat surgery for graft displacement after the endotamponade had absorbed, which resulted in MH closure. The same technique has shown similar efficacy in managing myopic MHRD.[105] In cases of MHRD, endotamponade was either octafluoropropane (C3F8) or SO, though no difference in outcomes between these tamponade groups has been noted.[106] In one case report, hAM was also effective in closing a chronic traumatic MH that had been present for >25 years with improvement in postoperative BCVA.[107]

Autologous retinal transplants

An alternative to creating a scaffold to facilitate primary apposition of the MH edges is to place retinal tissue from the mid-periphery into the MH where it can potentially function. The initial description of this technique by Grewal and Mahmoud in 2016 involved harvesting neurosensory retina from a donor site superior to the superotemporal arcade and transposing it under PFO to cover a 1100 μm MH refractory to closure after multiple prior surgeries in an eye with 15.00 D myopia.[108] In this case, VA recovered to 20/80 at postoperative month 3 with improved retinal sensitivity on microperimetry.

A tamponade agent is required to keep the graft in good position while it is anchored to the adjacent retinal tissue by glial cell proliferation. The use of autologous blood clots in combination with autologous retinal transplant (ART) was initially reported in 2018 with 4 of 6 eyes achieving closure.[109] In a subsequent case series of 10 patients with refractory large MH who underwent ART, an adhesive agent such as whole blood or Viscoat was used to stabilize the retinal free flap prior to silicone oil (SO) tamponade.[110] MH closure was achieved in 90% of cases with significant improvement in postoperative VA at 1 year.

Autologous retinal grafts have also been utilized in MHRD by positioning the flap either subfoveally or preretinally.[111-113] A multicenter, retrospective case series followed 41 patients with large refractory

FTMH (range 621–2600 μm) who had undergone prior PPV with ILM peel and subsequently underwent ART with either gas, SO, or short-term PFO tamponade. In this series, complete anatomic closure was observed in 88% of eyes and VA improved in 52.3% of eyes that achieved closure, with 37% improving 3 or more lines. Postoperative complications included 1 RD and 1 vitreous hemorrhage.[113] The global ART study is being finalized and data from more than 34 international surgeons is forthcoming.

The ultimate visual recovery following ART depends on the integration of the donor retina into the surrounding macular tissue. Many hypotheses have been entertained about how ART works and include, but are not limited to, growth factors, ectopic and adaptive synaptogenesis, Müller cells acting as stem cells for photoreceptors, material transfer, and cell migration. Choroid-RPE grafts showed the capacity to reperfuse on OCTA in a series of 18 patients with advanced exudative AMD.[114] A recent study by Tabandeh *et al*. revealed a similar capacity for transplanted neurosensory retinal tissue to vascularize. Two patients with giant MH (>2000 μm) who underwent ART showed MH closure with graft integration on OCT, and perfused superficial inner retinal blood vessels on OCTA 6 weeks postoperatively. Fluorescein angiography also confirmed retinal graft perfusion.[115] Transplantation of RPE-choroidal and neurosensory retinal free grafts in eyes with advanced fibrosis and atrophy associated with AMD with and without MH showed the capacity to integrate into the surrounding retina in a majority of patients and improved vision in 44%.[116] Among those cases with improved vision, microperimetry indicated fixation and retinal sensitivity over the choroidal free graft.

Tamponades and Positioning

A discussion of endotamponades available for use in MH surgery is beyond the scope of this review article. In general, the more complex the surgery or refractory the MH, the longer the endotamponade employed. In the majority of routine MH surgery, air or SF6 is used. For refractory, large, or myopic MH, SF6 or C3F8 are more commonly employed. In the case of hAM graft or ART, C3F8, SO, or short-term PFO (typically 2 weeks) have all been employed with success.

Positioning for MH surgery is varied among providers who may instruct face-down durations of none to 2 weeks with refractory or unusual MH typically being prescribed longer positioning. Various small studies have presented conflicting results about the importance of face-down positioning for MH repair.[117-119] However, both RCT and meta-analyses show that while there was no difference in surgical outcomes when face-down positioning was utilized versus no positioning for MH <400 μm, positioning does provide an advantage if MH >400 μm.[120,121] One advantage of short-term PFO is relative ease of supine positioning in the immediate postoperative period.

Patient Selection

With the many techniques available, the key question becomes patient selection. The chart below shows our current preference of surgical options according to presentation. As more studies become available about newer procedures, selection and preferences may change and choices will also be influenced by surgeons' own experiences [Figure 2].

For recent small Stage 2 MH without ERM, PPV alone may be sufficient.

For MH <400 μm or <300 μm with ERM, PPV with ILM peel is preferred.

For MH >400 μm or that are chronic, inverted ILM flap is appropriate. In the presence of moderate or greater myopia, retracting door flap is our choice. For highly myopic eyes with a deep staphyloma conferring the added difficulty of customizing a perfect flap, the use of any type of ILM flap that can cover the hole is sufficient.

For holes >700 μm, primary ART.

For refractory holes where ILM has been peeled or failed ILM flap, one can consider a free ILM flap or inverted ILM flap for holes where some ILM is left close

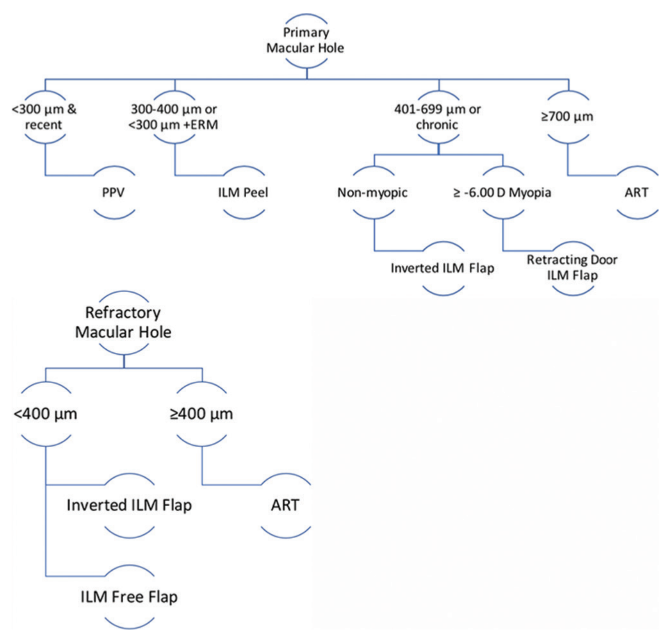

Figure 2: Surgical management preferences for primary and refractory macular holes. All measurements indicate minimum linear diameter

to the hole, and if size is <400 μm. If ILM is unable to be harvested, lens capsule, ART, or hAM grafts may be considered. For refractory holes ≥400 μm, ART is our preference.

Financial support and sponsorship

Nil.

Conflicts of interest

The authors declare that there are no conflicts of interests of this paper.

References

1. McCannel CA, Ensminger JL, Diehl NN, Hodge DN. Population-based incidence of macular holes. Ophthalmology 2009;116:1366-9.
2. la Cour M, Friis J. Macular holes: Classification, epidemiology, natural history and treatment. Acta Ophthalmol Scand 2002;80:579-87.
3. Darian-Smith E, Howie AR, Allen PL, Vote BJ. Tasmanian macular hole study: Whole population-based incidence of full thickness macular hole. Clin Exp Ophthalmol 2016;44:812-6.
4. Gass JD. Idiopathic senile macular hole: Its early stages and pathogenesis. 1988. Retina 2003;23:629-39.
5. Johnson RN, Gass JD. Idiopathic macular holes. Observations, stages of formation, and implications for surgical intervention. Ophthalmology 1988;95:917-24.
6. Duker JS, Kaiser PK, Binder S, de Smet MD, Gaudric A, Reichel E, *et al*. The international vitreomacular traction study group classification of vitreomacular adhesion, traction, and macular hole. Ophthalmology 2013;120:2611-9.
7. Schneider EW, Todorich B, Kelly MP, Mahmoud TH. Effect of optical coherence tomography scan pattern and density on the detection of full-thickness macular holes. Am J Ophthalmol 2014;157:978-84.
8. Bainbridge J, Herbert E, Gregor Z. Macular holes: Vitreoretinal relationships and surgical approaches. Eye (Lond) 2008;22:1301-9.
9. Smiddy WE, Flynn HW Jr. Pathogenesis of macular holes and therapeutic implications. Am J Ophthalmol 2004;137:525-37.
10. Grinton ME, Sandinha MT, Steel DH. Photoreceptor outer segment on internal limiting membrane after macular hole surgery: Implications for pathogenesis. Case Rep Ophthalmol 2015;6:339-44.
11. Tornambe PE. Macular hole genesis: The hydration theory. Retina 2003;23:421-4.
12. Gentile RC, Landa G, Pons ME, Eliott D, Rosen RB. Macular hole formation, progression, and surgical repair: Case series of serial optical coherence tomography and time lapse morphing video study. BMC Ophthalmol 2010;10:24.
13. Kelly NE, Wendel RT. Vitreous surgery for idiopathic macular holes. Results of a pilot study. Arch Ophthalmol 1991;109:654-9.
14. Sugiyama A, Imasawa M, Chiba T, Iijima H. Reappraisal of spontaneous closure rate of idiopathic full-thickness macular holes. Open Ophthalmol J 2012;6:73-4.
15. Tadayoni R, Massin P, Haouchine B, Cohen D, Erginay A, Gaudric A. Spontaneous resolution of small stage 3 and 4 full-thickness macular holes viewed by optical coherence tomography. Retina 2001;21:186-9.
16. Jackson TL, Donachie PH, Sparrow JM, Johnston RL. United Kingdom national ophthalmology database study of vitreoretinal surgery: Report 1; case mix, complications, and cataract. Eye (Lond) 2013;27:644-51.
17. Eckardt C, Eckardt U, Groos S, Luciano L, Reale E. Removal of the internal limiting membrane in macular holes. Clinical and morphological findings. Ophthalmologe 1997;94:545-51.
18. Bae K, Kang SW, Kim JH, Kim SJ, Kim JM, Yoon JM. Extent of internal limiting membrane peeling and its impact on macular hole surgery outcomes: A randomized trial. Am J Ophthalmol 2016;169:179-88.
19. Jackson TL, Donachie PHJ, Sparrow JM, Johnston RL. United Kingdom national ophthalmology database study of vitreoretinal surgery: Report 2, macular hole. Ophthalmology 2013;120:629-34.
20. Brooks HL Jr. Macular hole surgery with and without internal limiting membrane peeling. Ophthalmology 2000;107:1939-48.
21. Wollensak G, Spoerl E, Grosse G, Wirbelauer C. Biomechanical significance of the human internal limiting lamina. Retina 2006;26:965-8.
22. Schumann RG, Rohleder M, Schaumberger MM, Haritoglou C, Kampik A, Gandorfer A. Idiopathic macular holes: Ultrastructural aspects of surgical failure. Retina 2008;28:340-9.
23. Rahimy E, McCannel CA. Impact of internal limiting membrane peeling on macular hole reopening: A systematic review and meta-analysis. Retina 2016;36:679-87.
24. Spiteri Cornish K, Lois N, Scott NW, Burr J, Cook J, Boachie C, *et al*. Vitrectomy with internal limiting membrane peeling versus no peeling for idiopathic full-thickness macular hole. Ophthalmology 2014;121:649-55.
25. Williamson TH, Lee E. Idiopathic macular hole: Analysis of visual outcomes and the use of indocyanine green or brilliant blue for internal limiting membrane peel. Graefes Arch Clin Exp Ophthalmol 2014;252:395-400.
26. Susini A, Gastaud P. Macular holes that should not be operated. J Fr Ophtalmol 2008;31:214-20.
27. Michalewska Z, Michalewski J, Cisiecki S, Adelman R, Nawrocki J. Correlation between foveal structure and visual outcome following macular hole surgery: A spectral optical coherence tomography study. Graefes Arch Clin Exp Ophthalmol 2008;246:823-30.
28. Ullrich S, Haritoglou C, Gass C, Schaumberger M, Ulbig MW, Kampik A. Macular hole size as a prognostic factor in macular hole surgery. Br J Ophthalmol 2002;86:390-3.
29. Jaycock PD, Bunce C, Xing W, Thomas D, Poon W, Gazzard G, *et al*. Outcomes of macular hole surgery: Implications for surgical management and clinical governance. Eye (Lond) 2005;19:879-84.
30. Willis AW, Garcia-Cosio JF. Macular hole surgery. Comparison of longstanding versus recent macular holes. Ophthalmology 1996;103:1811-4.
31. Lumi X, Mahnic M, Petrovski BÉ, Petrovski G. Outcomes of vitrectomy for long-duration macular hole. J Clin Med 2020;9:444.
32. Wu TT, Kung YH. Comparison of anatomical and visual outcomes of macular hole surgery in patients with high myopia vs. non-high myopia: A case-control study using optical coherence tomography. Graefes Arch Clin Exp Ophthalmol 2012;250:327-31.
33. Alkabes M, Pichi F, Nucci P, Massaro D, Dutra Medeiros M, Corcostegui B, *et al*. Anatomical and visual outcomes in high myopic macular hole (HM-MH) without retinal detachment: A review. Graefes Arch Clin Exp Ophthalmol 2014;252:191-9.
34. Alkabes M, Padilla L, Salinas C, Nucci P, Vitale L, Pichi F, *et al*. Assessment of OCT measurements as prognostic factors in myopic macular hole surgery without foveoschisis. Graefes Arch Clin Exp Ophthalmol 2013;251:2521-7.
35. Suda K, Hangai M, Yoshimura N. Axial length and outcomes of macular hole surgery assessed by spectral-domain optical coherence tomography. Am J Ophthalmol 2011;151:118-270.
36. Qu J, Zhao M, Jiang Y, Li X. Vitrectomy outcomes in eyes with high myopic macular hole without retinal detachment. Retina 2012;32:275-80.
37. Sulkes DJ, Smiddy WE, Flynn HW, Feuer W. Outcomes of macular

hole surgery in severely myopic eyes: A case-control study. Am J Ophthalmol 2000;130:335-9.
38. Modi A, Giridhar A, Gopalakrishnan M. Comparative analysis of outcomes with variable diameter internal limiting membrane peeling in surgery for idiopathic macular hole repair. Retina 2017;37:265-73.
39. Al Sabti K, Kumar N, Azad RV. Extended internal limiting membrane peeling in the management of unusually large macular holes. Ophthalmic Surg Lasers Imaging 2009;40:185-7.
40. Michalewska Z, Nawrocki J. Swept-source optical coherence tomography angiography reveals internal limiting membrane peeling alters deep retinal vasculature. Retina 2018;38 Suppl 1:S154-60.
41. Horiguchi M, Tanikawa A, Mizuguchi T, Tanaka H, Sugimoto M, Shimada Y. The effect of an inverted internal limiting membrane flap on retinal function after macular hole surgery. Ophthalmol Retina 2017;1:421-7.
42. Del Priore LV, Kaplan HJ, Bonham RD. Laser photocoagulation and fluid-gas exchange for recurrent macular hole. Retina 1994;14:381-2.
43. Cho HY, Kim YT, Kang SW. Laser photocoagulation as adjuvant therapy to surgery for large macular holes. Korean J Ophthalmol 2006;20:93-8.
44. Reis R, Ferreira N, Meireles A. Management of stage IV macular holes: When standard surgery fails. Case Rep Ophthalmol 2012;3:240-50.
45. Shah AA, Thomas BJ, Yonekawa Y, Capone A Jr. Radial retinal incisions for complex pediatric traumatic macular holes. Retina 2016;36:211-5.
46. Charles S, Randolph JC, Neekhra A, Salisbury CD, Littlejohn N, Calzada JI. Arcuate retinotomy for the repair of large macular holes. Ophthalmic Surg Lasers Imaging Retina 2013;44:69-72.
47. Szigiato AA, Gilani F, Walsh MK, Mandelcorn ED, Muni RH. Induction of macular detachment for the treatment of persistent or recurrent idiopathic macular holes. Retina 2016;36:1694-8.
48. Kase S, Saito W, Mori S, Saito M, Ando R, Dong Z, *et al*. Clinical and histological evaluation of large macular hole surgery using the inverted internal limiting membrane flap technique. Clin Ophthalmol 2017;11:9-14.
49. Shiode Y, Morizane Y, Matoba R, Hirano M, Doi S, Toshima S, *et al*. The role of inverted internal limiting membrane flap in macular hole closure. Invest Ophthalmol Vis Sci 2017;58:4847-55.
50. Michalewska Z, Michalewski J, Adelman RA, Nawrocki J. Inverted internal limiting membrane flap technique for large macular holes. Ophthalmology 2010;117:2018-25.
51. Baumann C, Kaye S, Iannetta D, Sultan Z, Dwivedi R, Pearce I. Effect of inverted internal limiting membrane flap on closure rate, postoperative visual acuity, and restoration of outer retinal layers in primary idiopathic macular hole surgery. Retina 2019;10.1097/IAE.0000000000002707. doi:10.1097/IAE.0000000000002707.
52. Hu XT, Pan QT, Zheng JW, Zhang ZD. Foveal microstructure and visual outcomes of myopic macular hole surgery with or without the inverted internal limiting membrane flap technique. Br J Ophthalmol 2019;103:1495-502.
53. Yamashita T, Sakamoto T, Terasaki H, Iwasaki M, Ogushi Y, Okamoto F, *et al*. Best surgical technique and outcomes for large macular holes: Retrospective multicentre study in Japan. Acta Ophthalmol 2018;96:e904-10.
54. 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.
55. Shakya K, Pokharel RP, Malla OK. A short term anatomical and visual outcomes of large idiopathic macular holes surgery following inverted internal limiting membrane flap technique. Nepal J Ophthalmol 2019;11:29-32.
56. Shen Y, Lin X, Zhang L, Wu M. Comparative efficacy evaluation of inverted internal limiting membrane flap technique and internal limiting membrane peeling in large macular holes: A systematic review and meta-analysis. BMC Ophthalmol 2020;20:14.
57. Mete M, Alfano A, Maggio E, Guerriero M, Pertile G. Inverted ILM Flap for the Treatment of Myopic Macular Holes: Healing Processes and Morphological Changes in Comparison with Complete ILM Removal. J Ophthalmol 2019;2019:1314989.
58. Ramtohul P, Parrat E, Denis D, Lorenzi U. Inverted internal limiting membrane flap technique versus complete internal limiting membrane peeling in large macular hole surgery: A comparative study. BMC Ophthalmol 2020;20:11.
59. Sborgia G, Niro A, Sborgia A, Albano V, Tritto T, Sborgia L, *et al*. Inverted internal limiting membrane-flap technique for large macular hole: A microperimetric study. Int J Retina Vitreous 2019;5:44.
60. 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:S73-8.
61. Wu TT, Kung YH, Chang CY, Chang SP. Surgical outcomes in eyes with extremely high myopia for macular hole without retinal detachment. Retina 2018;38:2051-5.
62. Mete M, Alfano A, Guerriero M, Prigione G, Sartore M, Polito A, *et al*. Inverted internal limiting membrane flap technique versus complete internal limiting membrane removal in myopic macular hole surgery: A Comparative Study. Retina 2017;37:1923-30.
63. Peralta Iturburu F, Garcia-Arumi C, Bové Alvarez M, Garcia-Arumi J. Comparison of anatomical and visual outcomes between idiopathic and myopic macular holes using the internal limiting membrane or inverted internal limiting membrane flap technique. J Ophthalmol 2019;2019:6723824.
64. Bové Álvarez M, Sabaté S, Gómez-Resa M, García-Arumí J. Anatomical and visual outcomes of inverted internal limiting membrane flap technique versus internal limiting membrane peeling in myopic macular hole without retinal detachment: A preliminary retrospective study. Retina 2019;2019:6723824. doi:10.1155/2019/6723824.
65. Kuriyama S, Hayashi H, Jingami Y, Kuramoto N, Akita J, Matsumoto M. Efficacy of inverted internal limiting membrane flap technique for the treatment of macular hole in high myopia. Am J Ophthalmol 2013;156:125-310.
66. Kinoshita T, Onoda Y, Maeno T. Long-term surgical outcomes of the inverted internal limiting membrane flap technique in highly myopic macular hole retinal detachment. Graefes Arch Clin Exp Ophthalmol 2017;255:1101-6.
67. Ho TC, Ho A, Chen MS. Vitrectomy with a modified temporal inverted limiting membrane flap to reconstruct the foveolar architecture for macular hole retinal detachment in highly myopic eyes. Acta Ophthalmol 2018;96:e46-53.
68. Yuan J, Zhang LL, Lu YJ, Han MY, Yu AH, Cai XJ. Vitrectomy with internal limiting membrane peeling versus inverted internal limiting membrane flap technique for macular hole-induced retinal detachment: A systematic review of literature and meta-analysis. BMC Ophthalmol 2017;17:219.
69. Chen SN, Yang CM. Inverted internal limiting membrane insertion for macular hole–associated retinal detachment in high Myopia. Am J Ophthalmol 2016;166:211.
70. Chen SN. Large semicircular inverted internal limiting membrane flap in the treatment of macular hole in high myopia. Graefes Arch Clin Exp Ophthalmol 2017;255:2337-45.
71. Xu Q, Luan J. Vitrectomy with inverted internal limiting membrane flap versus internal limiting membrane peeling for macular hole retinal detachment in high myopia: A systematic review of literature and meta-analysis. Eye (Lond) 2019;33:1626-34.
72. Rossi T, Gelso A, Costagliola C, Trillo C, Costa A, Gesualdo C, *et al*. Macular hole closure patterns associated with different internal limiting membrane flap techniques. Graefes Arch Clin

Exp Ophthalmol 2017;255:1073-8.
73. Ghassemi F, Khojasteh H, Khodabande A, Dalvin LA, Mazloumi M, Riazi-Esfahani H, *et al*. Comparison of three different techniques of inverted internal limiting membrane flap in treatment of large idiopathic full-thickness macular hole. Clin Ophthalmol 2019;13:2599-606.
74. 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;35:1844-50.
75. 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;49:611-8.
76. Chakrabarti M, Benjamin P, Chakrabarti K, Chakrabarti A. Closing macular holes with "macular plug" without gas tamponade and postoperative posturing. Retina 2017;37:451-9.
77. Lai CC, Chen YP, Wang NK, Chuang LH, Liu L, Chen KJ, *et al*. Vitrectomy with internal limiting membrane repositioning and autologous blood for macular hole retinal detachment in highly myopic eyes. Ophthalmology 2015;122:1889-98.
78. Casini G, Mura M, Figus M, Loiudice P, Peiretti E, De Cillà S, *et al*. Inverted internal limiting membrane flap technique for macular hole surgery without extra manipulation of the flap. Retina 2017;37:2138-44.
79. Ikuno Y, Sayanagi K, Ohji M, Kamei M, Gomi F, Harino S, *et al*. Vitrectomy and internal limiting membrane peeling for myopic foveoschisis. Am J Ophthalmol 2004;137:719-24.
80. Finn AP, Mahmoud TH. Internal limiting membrane retracting door for myopic macular holes. Retina 2019;39 Suppl 1:S92-4.
81. Kubo S, Inoue M, Mahmoud TH, Kato Y, Hirakata A. Intraoperative optical coherence tomographic imaging during internal limiting membrane retracting-door technique for macular hole. J VitreoRetinal Dis 2018;2:379-83.
82. Akahori T, Iwase T, Yamamoto K, Ra E, Kawano K, Ito Y, *et al*. Macular displacement after vitrectomy in eyes with idiopathic macular hole determined by optical coherence tomography angiography. Am J Ophthalmol 2018;189:111-21.
83. Ito Y, Terasaki H, Takahashi A, Yamakoshi T, Kondo M, Nakamura M. Dissociated optic nerve fiber layer appearance after internal limiting membrane peeling for idiopathic macular holes. Ophthalmology 2005;112:1415-20.
84. D'Souza MJ, Chaudhary V, Devenyi R, Kertes PJ, Lam WC. Re-operation of idiopathic full-thickness macular holes after initial surgery with internal limiting membrane peel. Br J Ophthalmol 2011;95:1564-7.
85. Che X, He F, Lu L, Zhu D, Xu X, Song X, *et al*. Evaluation of secondary surgery to enlarge the peeling of the internal limiting membrane following the failed surgery of idiopathic macular holes. Exp Ther Med 2014;7:742-6.
86. Morizane Y, Shiraga F, Kimura S, Hosokawa M, Shiode Y, Kawata T, *et al*. Autologous transplantation of the internal limiting membrane for refractory macular holes. Am J Ophthalmol 2014;157:861-90.
87. Rossi T, Trillo C, Ripandelli G. Autologous internal limiting membrane transplant for recurrent idiopathic macular holes [published online ahead of print, 2020 Feb 11]. Eur J Ophthalmol. 2020;1120672120906391. doi: 10.1177/1120672120906391.
88. Chen SN, Hsieh YT, Yang CM. Multiple free internal limiting membrane flap insertion in the treatment of macular hole-associated retinal detachment in high myopia. Ophthalmologica 2018;240:143-9.
89. Chen SN, Yang CM. Double Internal Limiting Membrane Insertion for Macular Hole-Associated Retinal Detachment. J Ophthalmol. 2017;2017:3236516. doi:10.1155/2017/3236516.
90. Pires J, Nadal J, Gomes NL. Internal limiting membrane translocation for refractory macular holes. Br J Ophthalmol 2017;101:377-82.
91. Ra H, Lee WK. Contralateral autologous internal limiting membrane transplantation for closure of a refractory macular hole: Surgical technique. Ophthalmic Surg Lasers Imaging Retina 2018;49:e75-7.
92. De Novelli FJ, Preti RC, Ribeiro Monteiro ML, Pelayes DE, Junqueira Nóbrega M, Takahashi WY. Autologous internal limiting membrane fragment transplantation for large, chronic, and refractory macular holes. Ophthalmic Res 2015;55:45-52.
93. Park SW, Pak KY, Park KH, Kim KH, Byon IS, Lee JE. Perfluoro-n-octane assisted free internal limiting membrane flap technique for recurrent macular hole. Retina 2015;35:2652-6.
94. Ozdek S, Baskaran P, Karabas L, Neves PP. A modified perfluoro-n-octane-assisted autologous internal limiting membrane transplant for failed macular hole reintervention: A case series. Ophthalmic Surg Lasers Imaging Retina 2017;48:416-20.
95. Fung NS, Mak AK, Yiu R, Wong IY, Lam WC. Treatment of large, chronic and persistent macular hole with internal limiting membrane transposition and tuck technique. Int J Retina Vitreous 2020;6:3.
96. Leisser C, Hirnschall N, Döller B, Varsits R, Ullrich M, Kefer K, *et al*. Internal limiting membrane flap transposition for surgical repair of macular holes in primary surgery and in persistent macular holes. Eur J Ophthalmol 2018;28:225-8.
97. Gekka T, Watanabe A, Ohkuma Y, Arai K, Watanabe T, Tsuzuki A, *et al*. Pedicle internal limiting membrane transposition flap technique for refractory macular hole. Ophthalmic Surg Lasers Imaging Retina 2015;46:1045-6.
98. Wang LP, Sun WT, Lei CL, Deng J. Clinical outcomes with large macular holes using the tiled transplantation internal limiting membrane pedicle flap technique. Int J Ophthalmol 2019;12:246-51.
99. Hu Z, Ye X, Lv X, Liang K, Zhang W, Chen X, *et al*. Non-inverted pedicle internal limiting membrane transposition for large macular holes. Eye (Lond) 2018;32:1512-8.
100. Peng J, Chen C, Jin H, Zhang H, Zhao P. Autologous lens capsular flap transplantation combined with autologous blood application in the management of refractory macular hole. Retina 2018;38:2177-83.
101. Chen YC, Yang CM, Chen SN. Lens capsular flap in the management of posterior retinal hole associated retinal detachment in high myopic eyes with previous internal limiting membrane peeling: 3 case reports. Medicine (Baltimore) 2019;98:e16422.
102. Chen SN, Yang CM. Lens capsular flap transplantation in the management of refractory macular hole from multiple etiologies. Retina 2016;36:163-70.
103. Rizzo S, Caporossi T, Tartaro R, Finocchio L, Franco F, Barca F, *et al*. A human amniotic membrane plug to promote retinal breaks repair and recurrent macular hole closure. Retina 2019;39 Suppl 1:S95-103.
104. 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 [published online ahead of print, 2019 Dec 20]. Retina. 2019;10.1097/IAE.0000000000002699. doi:10.1097/IAE.0000000000002699.
105. Moharram HM, Moustafa MT, Mortada HA, Abdelkader MF. Use of epimacular amniotic membrane graft in cases of recurrent retinal detachment due to failure of myopic macular hole closure. Ophthalmic Surg Lasers Imaging Retina 2020;51:101-8.
106. Caporossi T, De Angelis L, Pacini B, Tartaro R, Finocchio L, Barca F, *et al*. A human Amniotic Membrane plug to manage high myopic macular hole associated with retinal detachment. Acta Ophthalmol 2020;98:e252-6.

107. 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;51:50-2.
108. Grewal DS, Mahmoud TH. Autologous neurosensory retinal free flap for closure of refractory myopic macular holes. JAMA Ophthalmol 2016;134:229-30.
109. Wu AL, Chuang LH, Wang NK, Chen KJ, Liu L, Yeung L, *et al*. Refractory macular hole repaired by autologous retinal graft and blood clot. BMC Ophthalmol 2018;18:213.
110. Chang YC, Liu PK, Kao TE, *et al*. Management Of Refractory Large Macular Hole With Autologous Neurosensory Retinal Free Flap Transplantation [published online ahead of print, 2019 Dec 23]. Retina. 2019;10.1097/IAE.0000000000002734. doi:10.1097/IAE.0000000000002734.
111. 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:S121-4.
112. Chen SN, Yang CM. Perfluorocarbon liquid-assisted neurosensory retinal free flap for complicated macular hole coexisting with retinal detachment. Ophthalmologica 2019;242:222-33.
113. Grewal DS, Charles S, Parolini B, Kadonosono K, Mahmoud TH. Autologous retinal transplant for refractory macular holes: Multicenter international collaborative study group. Ophthalmology 2019;126:1399-408.
114. Veckeneer M, Augustinus C, Feron E, Schauwvlieghe PP, Ruys J, Cosemans I, *et al*. OCT angiography documented reperfusion of translocated autologous full thickness RPE-choroid graft for complicated neovascular age-related macular degeneration. Eye (Lond) 2017;31:1274-83.
115. Tabandeh H. Vascularization and reperfusion of autologous retinal transplant for giant macular holes. JAMA Ophthalmol 2020;138:305-9.
116. Parolini B, Grewal DS, Pinackatt SJ, Baldi A, Di Salvatore A, Besozzi G, *et al*. Combined autologous transplantation of neurosensory retina, retinal pigment epithelium, and choroid free grafts. Retina. 2018;38 Suppl 1:S12-22.
117. Lange CA, Membrey L, Ahmad N, Wickham L, Maclaren RE, Solebo L, *et al*. Pilot randomised controlled trial of face-down positioning following macular hole surgery. Eye 2012;26:272-7.
118. Elborgy ES, Starr MR, Kotowski JG, Chehade JE, Iezzi R. No face-down positioning surgery for the repair of chronic idiopathic macular holes. Retina 2020;40:282-9.
119. Alberti M, la Cour M. Nonsupine positioning in macular hole surgery. Retina 2016;36:2072-9.
120. Hu Z, Xie P, Ding Y, Zheng X, Yuan D, Liu Q. Face-down or no face-down posturing following macular hole surgery: A meta-analysis. Acta Ophthalmol 2016;94:326-33.
121. Guillaubey A, Malvitte L, Lafontaine PO, Jay N, Hubert I, Bron A, *et al*. Comparison of face-down and seated position after idiopathic macular hole surgery: A randomized clinical trial. Am J Ophthalmol 2008;146:128-34.