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Review

Surgical management of refractory full-thickness macular holes with emphasis on autologous retinal transplantation: A narrative review

Ádám Bokor, Mariann Fodor*

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From the Contents

Abstract

Full-thickness macular holes are central defects in the neurosensory retina that result in significant visual impairment, including reduced visual acuity and central scotomas. While most cases respond well to pars plana vitrectomy combined with internal limiting membrane peeling, a subset of macular holes remains refractory to standard interventions and presents a persistent surgical challenge. Among emerging techniques, autologous neurosensory retinal transplantation has shown considerable promise, particularly in chronic or large-diameter holes where the internal limiting membrane is no longer available for use. This review offers a comprehensive overview of full-thickness macular hole pathophysiology and classification, current surgical approaches for refractory cases, and the accumulating clinical evidence supporting autologous neurosensory retinal transplantation. By conducting a narrative review of peer-reviewed studies in PubMed, anatomical and functional outcomes, procedural advantages, and associated limitations are critically examined. Additionally, recent preclinical developments, such as stem cell-derived retinal grafts, are discussed as potential future directions. Autologous neurosensory retinal transplantation represents a significant advancement in the management of refractory macular holes, while cell-based therapies may hold transformative potential for regenerative retinal surgery.

Key Words: autologous retinal transplantation; full-thickness macular hole; macular surgery; refractory macular hole; regenerative medicine; vitrectomy

Introduction

A macular hole is a full-thickness defect of the neurosensory retina located at the center of the fovea, leading to reduced visual acuity, metamorphopsia, and central scotoma—symptoms that can significantly impair a patient's quality of life.[1] The annual incidence is approximately 7.8 per 100,000 individuals, with advanced age and female sex identified as key risk factors.[2]

The current standards of care for macular holes involve pars plana vitrectomy with internal limiting membrane (ILM) peeling and intraocular gas tamponade, typically followed by prone positioning postoperatively.[3] This approach yields closure rates between 90% and 95% in idiopathic cases.[4] However, a subset of macular holes either fails to close following initial surgery or reopens after successful closure. These cases are classified as refractory macular holes. The incidence of refractory macular holes is estimated at 4%–5%,[5] with reported recurrence rates ranging from 4.8% to 9.2%, most commonly occurring within 12 to 15 months postoperatively.[6]

The management of refractory macular holes remains a significant surgical challenge. Various alternative techniques have been proposed, including the use of autologous tissue grafts. Among these, autologous neurosensory retinal transplantation (ART) has emerged as a promising option, particularly in complex cases where conventional methods are insufficient. This review outlines the surgical principles and rationale underlying ART and provides a critical summary of current clinical and experimental evidence supporting its use. Although limited in number, recent case series have demonstrated closure rates of up to 100% and meaningful visual gain following ART in chronic or large-diameter macular holes.[7]

Basic anatomy of the retina and macula

The retina is a transparent, multilayered sensory tissue with a thickness ranging from 0.10 to 0.23 mm. Its central region, the macula lutea, spans about 5.5 mm in diameter and is specialized for high-acuity vision. At the center of the macula lies the fovea, the site responsible for sharp central vision due to its high concentration of cone photoreceptors.

Histologically, the retina consists of ten distinct layers. The inner nine layers form the neuroepithelium (or neuroretina), which contains the photoreceptors, bipolar cells, and ganglion cells involved in visual signal transmission. The outermost layer is the retinal pigment epithelium, which plays a critical role in photoreceptor maintenance and metabolic support. The innermost retinal layer is the ILM, a thin, approximately 4 μm-thick basement membrane that separates the retina from the vitreous body.

Optical coherence tomography (OCT) serves as the primary imaging modality for evaluating macular anatomy. It provides high-resolution, cross-sectional, non-contact imaging that enables detailed visualization of the retinal microstructure. Retinal layers can be distinguished based on their relative optical reflectivity, allowing precise assessment of macular pathology (**Figure 1**).

Pathophysiology and classification of full-thickness macular holes

Age-related vitreous syneresis, characterized by liquefaction of the vitreous body and aggregation of collagen fibrils, contributes to a reduction in vitreous volume. This process commonly

Department of Ophthalmology and Gyula Petrányi Doctoral School of Allergy and Clinical Immunology, Faculty of Medicine, University of Debrecen, Debrecen, Hungary
***Correspondence to:** Mariann Fodor, MD, PhD, mfodor@med.unideb.hu.
https://orcid.org/0000-0002-1089-3899 (Mariann Fodor)

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culminates in posterior vitreous detachment. When posterior vitreous detachment occurs abnormally, incomplete separation of the posterior vitreous cortex from the macula exerts both anteroposterior and tangential tractional forces on the fovea. These forces can lead to vitreomacular traction and the eventual development of a full-thickness macular hole.

Search Strategy

A targeted literature search was performed using the PubMed database to identify English-language peer-reviewed articles relevant to refractory macular holes. The search strategy incorporated combinations of keywords such as "refractory macular hole," "autotransplantation," "retinal transplantation," and related terms. Studies were selected based on their relevance to the topic and their contribution to current clinical or preclinical understanding. Emphasis was placed on original research articles, systematic reviews, and meta-analyses, with a preference for high-impact publications from the past 10 years.

Inclusion criteria:

1.Reported original clinical or preclinical data on the management of refractory macular holes
2.Focused specifically on surgical interventions such as ART
3.Published within the past ten years
4.Available in full-text and written in English

Exclusion criteria:

1.Case reports with fewer than three patients
2.Conference abstracts or non-peer-reviewed sources
3.Articles not primarily focused on refractory macular holes or related surgical innovations
4.Duplicate publications across databases
Priority was given to original studies, systematic reviews, and meta-analyses that contributed significantly to the current understanding of clinical or experimental approaches in this field.

Discussion

The clinical classification of macular holes was first proposed by Gass in 1994, based primarily on biomicroscopic observations and the presumed pathogenesis of hole formation.[8] With advances in imaging, the International Vitreomacular Traction Study Group later introduced an OCT-based classification system, defining macular holes with a minimum linear diameter greater than 400 µm as "large."[9]

More recently, in 2023, the CLOSE study group refined this classification to provide a more granular stratification based on minimum linear diameter:

• Large: 400–550 µm

• X-Large: 550–800 µm

• XX-Large: ≥ 800 µm (**Figure 2**)

This classification emphasizes the importance of macular hole size in surgical outcomes and helps guide treatment selection.[10]

Vitreoretinal surgery and current surgical approaches for refractory macular holes

Vitreoretinal surgery comprises a range of advanced microsurgical techniques used to manage disorders involving the vitreous body, retina, and macula. The most frequently performed procedure is pars plana vitrectomy, which entails the removal of the vitreous gel to treat various retinal pathologies, including vitreous hemorrhage, retinal detachment, intraocular foreign bodies, endophthalmitis, lens dislocation, retinopathy of prematurity, and vitreoretinal interface disorders such as full-thickness macular holes.

The procedure begins with the creation of at least three sclerotomy ports in the pars plana, allowing access for surgical instruments, including the vitrector, endoilluminator, infusion cannula for intraocular pressure regulation, and micro-forceps or scissors for membrane dissection. In complex cases, particularly in retinal detachment surgery, intraoperative tamponade agents such as perfluorocarbon liquids (PFCL) (e.g., perfluorodecalin) may be used to stabilize the posterior retina and assist in subretinal fluid displacement. These agents must be meticulously removed by the end of the procedure due to their potential for long-term retinal toxicity.

Vital dyes are often employed to enhance visualization of transparent intraocular structures such as the vitreous cortex, ILM, and epiretinal membranes. Upon completion of vitrectomy, the vitreous cavity is typically filled with either balanced salt solution or an endotamponade agent, such as intraocular gas (air, sulfur hexafluoride [SF_6], hexafluoroethane [C_2F_6], octafluoropropane [C_3F_8]) or silicone oil, selected according to the specific pathology and desired tamponade duration. Modern vitreoretinal procedures are routinely performed under high-resolution operating microscopes, with many now integrated with intraoperative OCT for real-time imaging of retinal architecture.

Refractory macular holes

Figure 2 presents a significant surgical challenge and may result from factors such as large hole size, chronicity, high myopia, ocular trauma, or inflammatory eye disease. Surgical failure may also be attributed to incomplete release of vitreomacular traction, inadequate ILM peeling, insufficient endotamponade, or suboptimal postoperative positioning and compliance.[11] Large cohort analyses have shown that baseline factors such as hole diameter and symptom duration are strong predictors of anatomical and visual outcomes, even with advanced techniques.[12] A recent individual participant meta-analysis confirmed that longer symptom duration significantly reduces anatomical and functional outcomes in macular hole surgery, emphasising early intervention.[13]

A variety of surgical modifications and adjunctive strategies have been proposed to address refractory macular holes, which often demonstrate limited response to standard interventions.

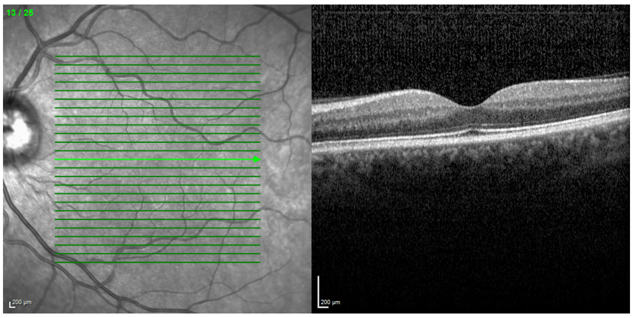

Figure 1 | **Optical coherence tomography (OCT) scan of a healthy macula demonstrating a broad vitreomacular adhesion.**
The left panel shows an en face infrared image of the macula acquired with a Heidelberg Spectralis OCT device, where the green lines indicate the locations of the cross-sectional scans. The right panel presents one of these scans, demonstrating a normal foveal contour and intact outer retinal layers. The outer retinal layers, including the ellipsoid zone, are intact and well delineated. Unpublished data.

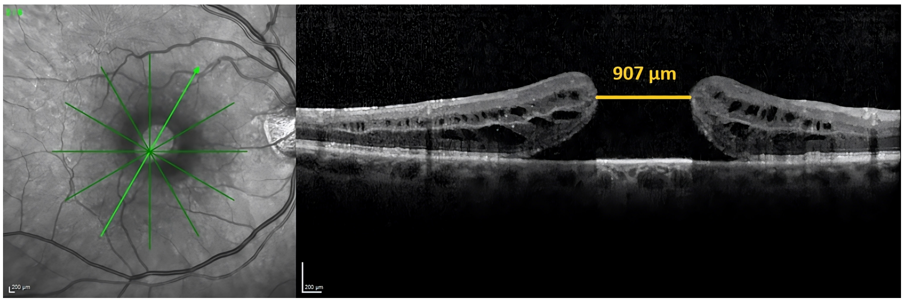

Figure 2 | **Preoperative optical coherence tomography images of a refractory full-thickness macular hole measuring 907 µm in minimum linear diameter.**
The green lines in the en face image (left) represent the location of the radial scan lines. The yellow line and annotation indicate the minimal linear diameter of the hole (right). Extensive perifoveal cystoid changes are evident, consistent with chronicity and a poor prognosis using conventional surgical techniques. Unpublished data.

These include advanced techniques such as ART,[14] repeat fluid–gas exchange,[15] radial relaxing retinotomy,[16] macular hydrodissection,[17] and the viscostretch technique.[18] A recent narrative review has categorized ART alongside novel adjunctive strategies such as capsular flaps and viscostretch, highlighting its growing acceptance in complex macular hole management.[19] Extended ILM peeling beyond the vascular arcades[20] and subretinal workingILM transplantation[21] have also been introduced to improve anatomic closure rates.

Adjunctive measures involve the use of tamponade agents such as silicone oil or heavy silicone oil,[22] as well as biologic adjuvants, including whole blood and autologous plasma concentrate,[23] which may enhance tissue adherence and wound healing. Various tissue grafts have been utilized, including autologous ILM,[24] anterior or posterior lens capsule,[25] and human amniotic membrane (**Figures 3** and **4**),[26] each offering unique structural and biological properties for foveal reconstruction.

In addition, preclinical studies have demonstrated the potential of human pluripotent stem cell-derived retinal organoids for repairing macular holes in non-human primate models,[27] highlighting a promising future direction for regenerative therapies in complex retinal pathologies.

Despite the range of available techniques, many yield inconsistent or suboptimal outcomes, particularly in cases of large or chronic macular holes. Approaches such as repeat fluid–gas exchange or extended ILM peeling may improve closure rates but often lack the necessary structural support to promote durable foveal reconstruction. Techniques involving mechanical mobilization, such as macular hydrodissection or the viscostretch technique, aim to increase tissue pliability but carry the risk of collateral damage to adjacent retinal layers.

Biological scaffolds, including ILM flaps and anterior or posterior lens capsule grafts, can provide physical support for hole closure; however, they lack retinal specificity and do not possess intrinsic regenerative capacity. In contrast, ART offers several theoretical and demonstrated advantages, including native structural integration, potential for cellular survival and synaptic connectivity, and the provision of neurotrophic support to the surrounding retinal tissue.[24] These properties position ART as a promising strategy for anatomically and functionally challenging macular hole cases. Among these, updated management strategies also include subretinal fluid injection to temporarily detach the retina and facilitate closure prior to ART.[28]

Autologous retinal transplantation

ART was first successfully reported by Grewal and Mahmoud in 2016 in a highly myopic eye with foveoschisis and a refractory macular hole.[14] The technique involves harvesting a full-thickness neurosensory retinal graft—typically from the mid-periphery—and transplanting it into the macular hole under PFCL. Graft placement may be epiretinal or subretinal, with subretinal positioning associated with improved tissue integration and enhanced photoreceptor survival.[29] The donor site is photocoagulated to prevent retinal detachment (**Figure 5**), and the procedure is concluded with fluid–gas or silicone oil exchange. A temporary PFCL tamponade may be used intraoperatively to stabilize the graft. Multicenter experience has confirmed that ART can consistently achieve anatomical closure and favorable functional outcomes even in eyes with prior failed vitrectomy.[30]

Compared with ILM flaps or lens capsule grafts, ART offers several advantages: the transplanted tissue is thicker, structurally more robust, and easier to manipulate, with a lower tendency for dislocation. The graft serves a dual role as both mechanical scaffold and biological plug. Importantly, transplanted Müller cells within the graft may act as retinal progenitors, potentially contributing to photoreceptor regeneration and functional visual recovery.[31]

Morphologically, the graft has demonstrated the capacity to integrate with adjacent host retina and support the reconstitution of outer retinal layers, including the ellipsoid zone and external limiting membrane (**Figure 6**). Restoration of these layers has been correlated with improvements in visual acuity, particularly in eyes achieving ellipsoid zone continuity.[32] A 2024 meta-analysis of 19 studies

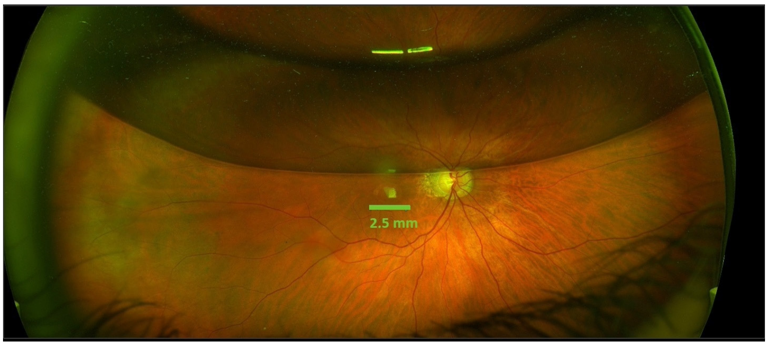

Figure 3 | **Ultra-widefield fundus image following amniotic membrane transplantation.**
The graft is visible covering the area of the macular hole, with a residual intraocular gas bubble in the superior vitreous cavity. A 2.5 mm green scale bar below the graft provides a spatial reference; it does not correspond to the graft size. Unpublished data.

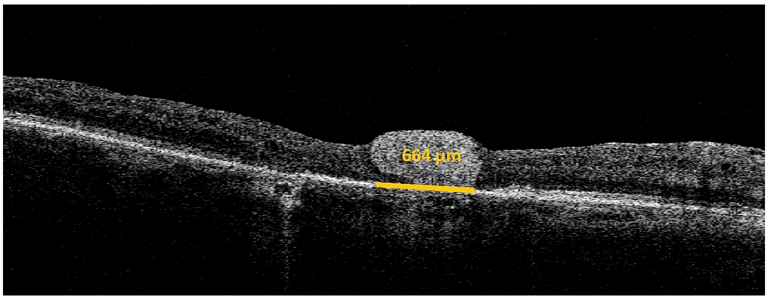

Figure 4 | **Postoperative optical coherence tomography image following amniotic membrane transplantation for a refractory macular hole.**
The yellow line and annotation indicate the horizontal width of the amniotic membrane graft (664 μm). The dome-shaped graft occupies the foveal defect but lacks structural integration with the adjacent retinal tissue, reflecting a limitation of non-retinal graft materials. Unpublished data.

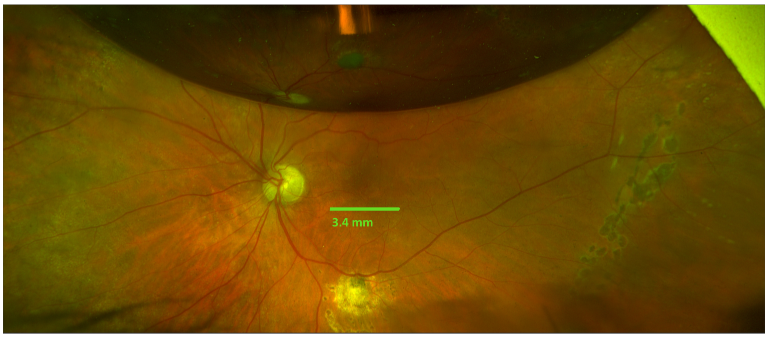

Figure 5 | **Ultra-widefield fundus photograph following autologous retinal transplantation.**
A residual intravitreal gas bubble is visible in the superior vitreous cavity. The retinal graft harvest site is evident in the inferior quadrant, surrounded by laser photocoagulation marks. Additional laser scars are noted in the temporal periphery. A green 3.4 mm scale bar near the optic disc serves as a spatial reference and does not represent the size of the graft. Unpublished data.

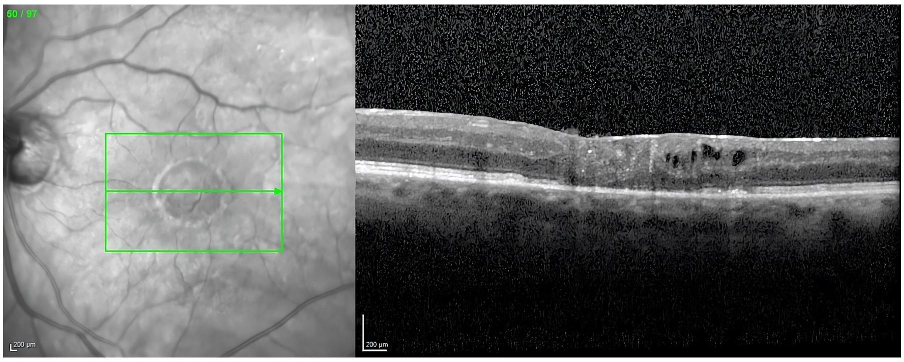

Figure 6 | Postoperative optical coherence tomography image following autologous retinal transplantation for a refractory macular hole.
On the left panel, on the en face image, the green rectangle indicates the location of the cross-sectional scan. On the right panel, the outer retinal bands, including the ellipsoid zone, appear reconstituted, suggesting successful structural integration of the graft with the host retina. Unpublished data.

involving 322 eyes reported an overall anatomical closure rate of 94% and a mean improvement in logarithm of the minimum angle of resolution visual acuity of 0.45.[6] Notably, according to the CLOSE study, ART was the only technique that resulted in significant visual improvement in macular holes larger than 800 μm, underscoring its value in managing the most challenging cases.[9]

The overall complication rate associated with ART is relatively low, estimated at approximately 15%, with graft dislocation being the most frequently reported adverse event.[6] Additional complications may include subretinal retention of PFCL, intraoperative retinal hemorrhage, iatrogenic retinal detachment, transient or sustained elevation of intraocular pressure, choroidal detachment, and, less commonly, choroidal neovascular membrane formation. Postoperative sequelae such as macular edema and epiretinal membrane development have also been observed. Common ART-specific complications—including graft displacement, PFCL retention, and donor-site hemorrhage—have been systematically described, underscoring the need for intraoperative vigilance and post-operative correction strategies.[33] Despite these risks, most complications are manageable with timely intervention and do not significantly compromise anatomical success or visual outcomes.

Limitations

While autologous retinal transplantation shows considerable promise, several limitations remain. Harvesting donor tissue from the peripheral retina may result in localized visual field defects, particularly in the inferior field. The procedure is technically demanding, requiring advanced microsurgical skill, and carries intraoperative risks, including retinal hemorrhage, iatrogenic retinal detachment, and graft dislocation. Furthermore, although anatomical integration is often achieved, the extent of functional synaptic connectivity between the graft and host retina remains uncertain. Long-term outcomes, standardized surgical protocols, and optimal patient selection criteria continue to be areas of ongoing investigation.

Conclusion and Future Perspectives

ART represents a significant advancement in the surgical management of refractory full-thickness macular holes, particularly in cases where the ILM is absent or previous interventions have failed. It may also be considered as a primary surgical option for chronic macular holes ≥ 600 μm, where traditional techniques are less likely to yield functional improvement. Favorable anatomical closure rates and visual acuity gains reported in recent studies support its broader clinical adoption in carefully selected cases.

While the focus of this review is on ART, recent preclinical studies have explored stem cell-based retinal therapies as a potential future direction. In particular, human pluripotent stem cell–derived retinal sheets have demonstrated promising results in non-human primate models of macular hole, showing anatomical closure and improved visual function without the need for autologous tissue grafts. However, these approaches remain at an early experimental stage, and full synaptic integration has not yet been conclusively demonstrated. We include this emerging line of research briefly, as it may complement surgical methods like ART in the long term.

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