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Autologous Retinal Transplantation for Primary and Refractory Macular Holes and Macular Hole Retinal Detachments

The Global Consortium

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Purpose: To report the anatomic and functional outcomes of autologous retinal transplantation (ART).

Design: Multicenter, retrospective, interventional, consecutive case series.

Participants: One hundred thirty eyes of 130 patients undergoing ART for the repair of primary and refractory macular holes (MHs), as well as combined MH-rhegmatogenous retinal detachment (MH-RRD), between January 2017 and December 2019.

Methods: All patients underwent pars plana vitrectomy and ART, with surgeon modification of intraoperative variables. A large array of preoperative, intraoperative, and postoperative data was collected. Two masked reviewers graded OCT images. Multivariate statistical analysis and subgroup analysis were performed.

Main Outcome Measures: Macular hole closure rate, visual acuity (VA), external limiting membrane and ellipsoid zone (EZ) band integrity, and alignment of neurosensory layers (ANL) on OCT.

Results: One hundred thirty ART surgeries were performed by 33 vitreoretinal surgeons worldwide. Patient demographics were: mean age of 63 $\pm$ 6.3 years, 58% female, 41% White, 23% Black, 19% Asian, and 17% Latino. Preoperative VA was 1.37 $\pm$ 0.12 logarithm of the minimum angle of resolution (logMAR; Snellen equivalent, approximately 20/500), which improved significantly to 1.05 $\pm$ 0.09 logMAR (Snellen equivalent, approximately 20/225; $P < 0.001$) after surgery (mean follow-up, 8.6 $\pm$ 0.8 months). Autologous retinal transplantation was performed for primary MH repair in 27% of patients (n = 35), for refractory MH in 58% of patients (n = 76; mean number of previous surgeries, 1.6 $\pm$ 0.2), and for MH-RRD in 15% of patients (n = 19). Mean maximum MH diameter was 1470 $\pm$ 160 μm, mean minimum diameter was 840 $\pm$ 94 μm, and mean axial length was 24.6 $\pm$ 3.2 mm. Overall, 89% of MHs closed (78.5% complete; 10% small eccentric defect), with a 95% closure rate in MH-RRD (68.4% complete; 26.3% small eccentric defect). Visual acuity improved by at least 3 lines in 43% of eyes and by at least 5 lines in 29% of eyes. Reconstitution of the EZ ($P = 0.02$) and ANL ($P = 0.01$) on OCT were associated with better final VA. Five cases of ART graft dislocation (3.8%), 5 cases of postoperative retinal detachment (3.8%), and 1 case of endophthalmitis (0.77%) occurred.

Conclusions: In this global experience, patients undergoing ART for large primary and refractory MHs and MH-RRDs achieved good anatomic and functional outcomes, with low complication rates despite complex surgical pathologic features. *Ophthalmology 2021;128:672-685 © 2020 by the American Academy of Ophthalmology*

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The development of autologous retinal transplantation (ART) in 2016 as a surgical technique has unlocked new avenues for addressing challenging macular holes (MHs).[1] Since the seminal study, the technique has been performed by numerous surgeons around the world with many modifications, including combined neurosensory

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retina–retinal pigment epithelium (RPE)–choroid grafts,[2] subretinal placement of the graft,[3] and for the primary treatment of large, chronic MHs.[4] Indeed, the idea of using a graft to close an MH has expanded the surgical approach and enhanced the armamentarium of many surgeons; additional methods of grafting have been performed since, including using human amniotic membranes as an implantable graft.[5]

Whether for myopic MHs, refractory MHs, large to giant primary MHs, or combined MH-rhegmatogenous retinal detachments (MH-RRDs), the ability to close the hole with ART has made surgery possible for patients who could not be treated previously. Since the initial report of vitrectomy for MH repair in the early 1990s,[6] the surgical approach for MH repair has involved addressing tractional vectors—(1) anteroposterior traction and (2) tangential traction—whether by vitrectomy alone or by vitrectomy with membrane peeling, with internal limiting membrane (ILM) peeling, or with an ILM flap.[7–11] Other techniques, such as radial perifoveal incisions, ILM free flaps, and subretinal expansion with balanced salt solution, also have been described.[12–15] Grafting procedures, such as ART and amniotic membrane grafts, have allowed surgeons to treat MHs by way of a third mechanism: by using a scaffold to promote centripetal migration of MH edges in the case of an amniotic membrane or the addition of tissue through ART. Some surgeons also have used blood products as an adjuvant to encourage adherence of the transplant to the foveal graft site.[16–18]

A multicenter pilot study was published recently to determine whether ART is feasible in the hands of different surgeons.[19] In that study, 4 surgeons demonstrated an 87.8% MH closure rate in 41 patients with refractory MHs that had failed previous vitrectomy with ILM peeling and gas tamponade. Based on the results of that study, we were motivated to determine what the real-world global outcomes would be for cases of ART, and the ART Global Consortium was created.

Methods

An open invitation for the contribution of surgical cases of ART from any surgeon wishing to participate was announced at multiple meetings and throughout different societies and by e-mails worldwide. Surgeons were invited to contribute consecutive cases of ART for patients undergoing repair of a primary MH, a refractory (persistent or recurrent) MH, or a combined MH-RRD. Surgeons were encouraged to contribute all cases, regardless of the outcome, including a description of the intraoperative surgical technique, preoperative and postoperative deidentified data, and ancillary testing.

A standardized data collection sheet was distributed to all surgeons. Surgical cases performed between January 1, 2017, and December 31, 2019, were accepted for inclusion. This study complied with the Health Insurance Portability and Accountability Act of 1996 and adhered to the tenets of the Declaration of Helsinki. Informed consent was not required by the Institutional Review Board for this retrospective study of de-identified patient data. The Western Institutional Review Board approved this study.

All patients underwent pars plana vitrectomy and ART, with modification of intraoperative variables as desired by the surgeon. A large array of data was collected regarding surgical techniques, anatomic outcomes, and functional outcomes. Preoperative and intraoperative variables, including minimum and maximum MH diameter, axial length, lens status, retinal graft size, harvest site, tamponade agent, and intraoperative and postoperative complications, were assessed. Color fundus photography, autofluorescence, and OCT were performed at various time points using a commercially available spectral-domain OCT device (Spectralis HRA OCT [Heidelberg Engineering, Heidelberg, Germany] or Topcon SD-OCT [Topcon, Tokyo, Japan]) or a swept-source OCT device (DRI OCT Triton; Topcon). Widefield fundus photography (Optos, Marlborough, MA), OCT angiography (Carl Zeiss Meditec, Inc., Dublin, CA, or Optovue, Inc., Fremont, CA), microperimetry (MAIA; CenterVue, Padova, Italy), and multifocal electroretinography were performed when possible.

The primary outcome measured was anatomic MH closure. Secondary outcomes analyzed were numerous, and they included, but were not limited to, visual acuity (VA) at various time points, subjective patient experience, complication rates, and analysis of ancillary testing. Two masked reviewers (S.M, and N.K.) independently evaluated the OCT images and graded them using a standardized approach. The following features were assessed: (1) anatomic closure by OCT (complete vs. eccentric, whereby for these unusually large to giant holes, eccentric closure was defined on OCT by subfoveal closure of the macular hole with a small sliver of eccentric peripheral opening of less than 10% of the area of the original macular hole or at least approximately 500 μm from the foveal center), (2) reconstitution of the external limiting membrane (ELM) and ellipsoid zone (EZ) band and the timing thereof, (3) alignment of neurosensory layers (ANL; a novel finding presented herein in which the donor graft and surrounding host retina integrate in such a way as to line up layer by layer), (4) transient hyperreflectivity of the ART graft suggestive of transient hypoxia, and (5) hyperreflective foci suggestive of the presence of microglia. Additional ancillary testing, such as fluorescein angiography, OCT angiography, autofluorescence, microperimetry, and multifocal electroretinography, was reviewed, when available.

Multivariate statistical analysis was performed. Subgroup analysis was performed for primary MHs, refractory (recurrent plus persistent) MHs, and combined MH-RRDs. Statistical analysis was performed using SPSS software version 26 (SPSS, Inc., Chicago, IL). Recorded VA measurements, including Early Treatment of Diabetic Retinopathy Study and Snellen VA, were converted to logarithm of the minimum angle of resolution (logMAR) VA. Counting fingers and hand movements were defined as 0.01 (Snellen equivalent, 20/2000; 2.0 logMAR) and 0.001 (Snellen equivalent, 20/20000; 3.0 logMAR), respectively. Visual improvement was defined as an increase of at least 0.3 logMAR, and decline was defined as a decrease of at least 0.3 logMAR (equivalent to 15 Early Treatment of Diabetic Retinopathy Study letters). Descriptive statistics were computed. Two-tailed paired *t* tests were utilized. *P* values of less than 0.05 were considered statistically significant. Multivariate analysis of variance was performed. The variables were assessed for normality first by Levine's test of equality and were found to be approximately normally distributed. A post hoc Tukey test was selected for further analysis.

Results

Case Selection and Patient Demographics

Thirty-three surgeons from around the world contributed their cases. One hundred thirty consecutive surgeries were performed on 130 eyes of 130 unique patients (Table 1). All cases reported by surgeons were analyzed, and those included primary MHs (n = 35 [27%]), refractory MHs (n = 76 [58%]), and combined MH-RRDs (n = 19 [15%]; of which 68.4% [13/19] had undergone previous vitrectomy and 63.2% [12/19] had undergone previous ILM peeling). The mean patient age was 63 ± 6.3 years and 58% of patients were women. The racial and ethnic backgrounds of the patients were diverse: 41% were White, 23% were Black, 19% were Asian, and 17% were Latino.

Surgical Technique

Three-port 23- or 25-gauge pars plana vitrectomy (Constellation [Alcon, Fort Worth, TX], EVA [DORC International, Zuidland, The Netherlands], or Stellaris Elite [Bausch & Lomb, Inc., Rochester, NY]) was performed with retrobulbar or peribulbar anesthesia using monitored anesthesia care or under general anesthesia. Most procedures were performed unimanually with either the pneumatic scissors (Alcon or DORC) or the vitrector in one hand and the light pipe in the other. A 25-gauge chandelier illuminator (Alcon) was used to facilitate bimanual maneuvers when necessary. Brilliant Blue (Doubledyne, Alfaintes, Italy), indocyanine green dye solution (25 mg indocyanine green in 20 ml 5% dextrose plus water solution), or ILM Blue (DORC) was delivered to the retinal surface around the MH to confirm the status of the ILM. The surgical techniques and instrumentation were left to the discretion of the individual surgeon.

As previously described, a neurosensory or combined retina and choroid graft was selected, with some surgeons choosing a donor site between the arcades and the equator (posterior) and others choosing a site peripheral to the equator (anterior). Surgeons chose to harvest from various sectors: superonasal, superior, superotemporal, temporal, inferotemporal, inferior, inferonasal, and nasal. The size of the graft was at the discretion of the surgeon and was recorded as a multiple of the optic disc (e.g., 1 disc diameter, 2 disc diameters, etc.). Barrier endolaser treatment was delivered in multiple rows around the graft harvest site, as well as endodiathermy to cauterize blood vessels at the edges of the graft site in most cases. The graft itself was harvested from healthy retinal tissue within the barrier zone of the endolaser so that the edges of the graft were not affected by laser or diathermy.

Most surgeons performed the transfer of the ART graft to the MH under perfluoro-n-octane (PFO; Perfluoron [Alcon]) for stability. The edge of the graft was held, if required, using end-grasping forceps (e.g., Alcon 23-gauge or 25-gauge Max Grip or ILM forceps). The graft was cut using vertical or curved scissors (Alcon 23-gauge or 25-gauge Revolution DSP vertical or curved scissors or 23-gauge pneumatic scissors) or the vitrector. The graft then was transferred to its intended site, at the MH, with some surgeons leaving it preretinally or at the level of the retina and others tucking it subretinally. Some surgeons chose to leave PFO as a short-term tamponade, whereas others performed a fluid−air exchange and then delivered either silicone oil (SO) or diluted gas (sulfur hexafluoride or perfluoropropane) as the tamponade agent; other surgeons performed a direct PFO-to-SO exchange. All sclerotomies either were closed with a single interrupted suture or were noted to be self-sealing after external tamponade. The patients were positioned face down after surgery for 3 to 7 days, depending on surgeon preference (in the case of gas or SO), except when PFO was used as tamponade, in which case patients were positioned supine. The timing of SO or PFO removal was at the discretion of the surgeon.

Intraoperative Surgical Variables

Ninety percent of transplants were taken from neurosensory retina alone, whereas 10% were harvested deeper to include neurosensory retina, RPE, and choroid. Grafts were harvested from the following locations: 45% superiorly, 17% inferonasally, 11% superotemporally, 8% inferiorly, 8% superonasally, 7% temporally, and 4% inferotemporally. The graft was harvested posterior to the equator in 84% of cases and anterior to the equator in 16% of cases. The graft was positioned preretinally or in the same plane as the host retina in 81% of cases, and it was tucked subretinally in 19% of cases. Some surgeons aimed to oversize the ART donor graft relative to the MH (40%), whereas others aimed to fit it edge to edge with the host tissue (60%); during surgery, grafts measured up to 1 disc diameter in 70% of cases, 1 to 2 disc diameters in 29% of cases, and 2 to 3 disc diameters in 1% of cases.

Seventy-two percent of surgeries were performed with 23-gauge vitrectomy and 28% were performed with 25-gauge vitrectomy. Perfluoro-n-octane was used during almost every case to assist with harvesting and delivering the transplant. The final tamponade agent used at the end of the case was SO in 60% of cases, PFO in 20% of cases, and gas in 20% of cases. In cases where intraoperative exchange of tamponade agent was performed, a PFO-to-air exchange followed by delivery of SO or gas was performed in 72% of cases; a direct PFO-to-SO exchange was performed in the other 28% of cases (Videos 1 and 2, available at www.aaojournal.org).

Intraoperative complications were rare. Three cases of intraoperative graft slippage (2.3%), 2 cases of undersized graft (1.5%), 1 case of subfoveal RPE damage (0.8%), and 4 cases of intraoperative bleeding (3.1%) occurred.

Anatomic Outcomes for Primary and Refractory Macular Holes

Thirty-five ART surgeries were performed for primary MHs (27% of cases; Table 2). Most patients were phakic (77%). Mean maximum MH diameter was 1480 ± 297 μm, and the mean minimum MH diameter was 882 ± 176 μm. The mean axial length was 23.1 ± 4.9 mm, and the mean spherical equivalent was −0.95 ± 0.20 diopters (D). An 85.7% MH closure rate after ART surgery was observed; 97% of anatomic closures were complete, compared with 3% of closures being eccentric. One case of graft dislocation (2.9%) and 1 case of postoperative proliferative vitreoretinopathy (2.9%) occurred. Of phakic patients, 11% underwent cataract extraction with intraocular lens placement during the study period.

Seventy-six ART surgeries were performed for refractory MHs (58% of cases; Table 3). Most patients were pseudophakic (57%). Mean maximum MH diameter was 1440 ± 210 μm, and the mean minimum MH diameter was

Table 1. Demographic and Preoperative Characteristics for Patients Undergoing Autologous Retinal Transplantation for Repair of Primary Macular Holes, Refractory Macular Holes, and Combined Macular Hole—Rhegmatogenous Retinal Detachments

Characteristic	Data
No. of patients	130
Age (yrs), mean ± SD	62.9 ± 6.3
Gender, no. (%)	
Female	58.5
Male	41.5
Race, no. (%)	
White	41.6
Black	22.8
Asian	18.8
Latino	16.8
MH diameter (μm), mean ± SD	
Maximum	1470 ± 165
Minimum	837 ± 94
Mean spherical equivalent (D), mean ± SD	−3.4 ± 0.4
Mean axial length (mm), mean ± SD	24.6 ± 3.2
Pseudophakic, no. (%)	49.2

D = diopters; SD = standard deviation.

796 ± 117 μm. The mean axial length was 24.8 ± 4.6 mm, and the mean spherical equivalent was −2.4 ± 0.40 D. An 88% MH closure rate after ART surgery was observed; 89% of anatomic closures were complete, compared to 11% of closures being eccentric. Three cases of graft dislocation (4.0%), 1 case of postoperative retinal detachment (1.3%), 1 case of endophthalmitis (1.3%), 2 cases of subfoveal RPE damage (2.7%), and 5 cases of subretinal or vitreous hemorrhage (6.6%) occurred. Of phakic patients, 12% underwent cataract extraction with intraocular lens placement during the study period.

Visual Acuity Outcomes for Primary and Refractory Macular Holes

In the primary MH group, preoperative mean VA was 1.090 ± 0.184 logMAR (Snellen equivalent, 20/246), which improved significantly to 0.838 ± 0.142 logMAR (Snellen equivalent, 20/138; $P = 0.003$) after surgery (mean follow-up, 8.5 ± 1.4 months; Table 2). Thirty-seven percent of patients achieved a 3-line gain in VA and 17% gained at least 5 lines of VA.

In the refractory MH group, preoperative mean VA was 1.258 ± 0.144 logMAR (Snellen equivalent, approximately 20/362), which improved significantly to 1.063 ± 0.123 (Snellen equivalent, approximately 20/231; $P = 0.002$) after surgery (mean follow-up, 8.6 ± 1.0 months; Table 3). Thirty-seven percent of patients achieved a 3-line gain in VA and 25% gained at least 5 lines of VA.

OCT Analysis of Postoperative Anatomic Outcomes for Primary Macular Holes

In the primary MH group, 24 cases with MH closure had OCTs of sufficient quality and follow-up for anatomic analysis. Two masked reviewers (S.M. and N.K.) independently reviewed the images and graded them using a standardized approach. Thirteen cases demonstrated reconstitution of the ELM (54%) at a mean of 2 ± 0.72 months (Fig 1). Twelve cases conveyed reconstitution of the EZ band (50%) at a mean of 5.8 ± 1.5 months. Four cases demonstrated ANL (17%; Fig 2), a novel OCT finding in which the layers between the donor graft and host retina appear to align (e.g., inner plexiform to inner plexiform, outer plexiform to outer plexiform, etc.).

Table 2. Anatomic and Functional Outcomes for Patients with Primary Macular Holes Undergoing Autologous Retinal Transplantation

Outcome	Data
No. of patients (%)	35 (26.9)
Age (yrs), mean ± SD	57.8 ± 11.3
Gender (%)	
Female	51.4
Male	48.6
Race (%)	
White	11.6
Black	19.2
Asian	42.3
Latino	26.9
MH diameter (μm), mean ± SD	
Maximum	1480 ± 297
Minimum	882 ± 176
Spherical equivalent (D), mean ± SD	−0.9 ± 0.2
Axial length (mm), mean ± SD	23.1 ± 4.9
Pseudophakic (%)	22.9
Final follow-up (mos), mean ± SD	8.486 ± 1.434
VA (logMAR), mean ± SD	
Preoperative	1.090 ± 0.184
Approximate Snellen equivalent	20/470
Final postoperative	0.838 ± 0.142
Approximate Snellen equivalent	20/149
P value	0.0028*
Gained VA (%)	
≥3 lines	37.1
≥5 lines	17.1
Macular hole closed, no. (%)	30 (85.7)
Complete	29 (96.7)
Eccentric	1 (3.3)
No. with acceptable quality follow-up OCT for analysis	24
Reconstitution of ELM, no. (%)	13 (54.2)
Reconstitution of EZ band, no. (%)	12 (50.0)
Alignment of neurosensory layers, no. (%)	4 (16.7)
Hyperreflective foci (e.g., microglia) , no. (%)	18 (75.0)
Transient graft hyperreflectivity, no. (%)	8 (33.3)
Graft dislocation, no. (%)	1 (2.9)
Retinal detachment, no. (%)	0 (0.0)
Subretinal PFO, no. (%)	0 (0.0)
Endophthalmitis, no. (%)	0 (0.0)
High IOP requiring treatment, no. (%)	2 (5.7)

D = diopters; ELM = external limiting membrane; EZ = ellipsoid zone; IOP = intraocular pressure; logMAR = logarithm of the minimum angle of resolution; MH = macular hole; PFO = perfluorocarbon liquid; SD = standard deviation; VA = visual acuity.

OCT Analysis of Postoperative Anatomic Outcomes for Refractory Macular Holes

In the refractory MH group, 39 cases of MH closure had OCTs of sufficient quality and follow-up for anatomic analysis (Table 3). Twenty-six cases demonstrated

Table 3. Anatomic and Functional Outcomes for Patients with Refractory Macular Holes Undergoing Autologous Retinal Transplantation

Outcome	Data
No. of patients (%)	76 (58.5)
Age (yrs), mean ± SD	66.9 ± 8.9
Gender (%)	
Female	65.3
Male	34.7
Race (%)	
White	48.2
Black	21.4
Asian	14.3
Latino	16.1
MH diameter (μm), mean ± SD	
Maximum	1440 ± 210
Minimum	796 ± 117
Spherical equivalent (D), mean ± SD	−2.4 ± 0.4
Axial length (mm), mean ± SD	24.8 ± 4.6
Pseudophakic (%)	56.6
No. of previous PPV or ILM peel procedures, mean ± SD	1.7 ± 0.2
Final follow-up (mos), mean ± SD	8.6 ± 1.0
VA (logMAR), mean ± SD	
Before surgery	1.258 ± 0.144
Approximate Snellen equivalent	20/362
Final after surgery	1.063 ± 0.123
Approximate Snellen equivalent	20/231
P = 0.0019*	
Gained VA (%)	
≥3 lines	36.8
≥5 lines	25.0
Macular holes closed, no. (%)	67 (88.2)
Complete	60 (89.6)
Eccentric	7 (10.4)
Postoperative, masked OCT analysis	
No. with acceptable quality follow-up OCT for analysis	39
Reconstitution of ELM, no. (%)	26 (66.7)
Reconstitution of EZ band, no. (%)	26 (66.7)
Alignment of neurosensory layers, no. (%)	8 (20.5)
Hyperreflective foci (e.g., microglia), no. (%)	19 (48.7)
Transient graft hyperreflectivity, no. (%)	15 (38.5)
Graft dislocation, no. (%)	3 (3.9)
Retinal detachment, no. (%)	1 (1.3)
Subretinal PFO, no. (%)	0 (0.0)
Endophthalmitis, no. (%)	1 (1.3)*
High IOP requiring treatment, no. (%)	2 (2.6)

D = diopters; ELM = external limiting membrane; EZ = ellipsoid zone; ILM = internal limiting membrane; IOP = intraocular pressure; logMAR = logarithm of the minimum angle of resolution; MH = macular hole; PFO = perfluorocarbon liquid; PPV = pars plana vitrectomy; SD = standard deviation; VA = visual acuity.
*One case of possible endophthalmitis was treated with intravitreal tap and injection of antibiotics; the culture results were negative.

reconstitution of the ELM (67%) at a mean of 2.5 ± 0.60 months. Twenty-six cases conveyed reconstitution of the EZ band (67%) at a mean of 3.2 ± 0.46 months. Eight cases demonstrated ANL (21%).

Outcomes for Combined Macular Hole–Rhegmatogenous Retinal Detachments

Nineteen ART surgeries were performed for combined MH-RRDs (15% of cases; Table 4). Most patients were pseudophakic (68%). Mean maximum MH diameter was 1630 ± 576 μm, and the mean minimum MH diameter was 932 ± 330 μm. The mean axial length was 28.0 ± 9.3 mm, and the mean spherical equivalent was −10.3 ± 2.9 D. A 95% MH closure rate was observed after ART surgery; 72% of anatomic closures were complete, compared with 28% that were eccentric closures. A 79% retinal reattachment rate was observed with a single surgery; in 66.7% of these cases, the final tamponade agent (SO, PFO, gas) had been removed or resolved by the date of study closure. One case of graft dislocation (5.3%), 4 cases of postoperative retinal detachment (21%) resulting from proliferative vitreoretinopathy, and 2 cases of subretinal PFO (11%) occurred. The preoperative mean VA was 2.316 ± 0.531 logMAR (approximately hand movements), which improved significantly to 1.403 ± 0.322 logMAR (Snellen equivalent, 20/500; $P < 0.001$) after surgery (mean follow-up, 8.9 ± 2.0 months). Seventy-four percent of patients achieved a 3-line gain of VA and 68% gained at least 5 lines of VA. Of phakic patients, 17% underwent cataract extraction with intraocular lens placement during the study period.

OCT Analysis of Postoperative Anatomic Outcomes for Combined Macular Hole–Rhegmatogenous Retinal Detachments

In the combined MH-RRD group, 17 cases of MH closure had OCTs of sufficient quality and follow-up for anatomic analysis (Table 4). Five cases demonstrated reconstitution of the ELM (29%) at a mean of 1.9 ± 0.60 months. Four cases conveyed reconstitution of the EZ band (24%) at a mean of 1.5 ± 0.29 months, and the reconstitution was partial in 3 of those 4 cases. One case demonstrated ANL (5.9%).

Multivariate Analysis of Factors Affecting Macular Hole Closure Rates

Multivariate analysis showed no statistically significant association between any preoperative patient characteristics and the rate of MH closure (Table 5). Likewise, no statistically significant association was found between any intraoperative surgical variables and the rate of MH closure (Table 5).

Multivariate Analysis of Factors Affecting Final Visual Acuity

Multivariate analysis demonstrated a statistically significant association between better preoperative VA ($P < 0.001$) and better final VA after surgery and an association between MH closure ($P < 0.001$) and better final VA after surgery (Table 5). Also, a statistically significant association was found between preoperative diagnosis and final VA after surgery ($P = 0.026$; primary MH final VA, 0.838 ± 0.142 logMAR; refractory MH final VA, 1.063 ± 0.123 logMAR; MH-RRD final VA, 1.403 ± 0.322 logMAR); patients with MHs and no retinal detachment, whether primary or refractory, were more likely to have better final VA than patients with MH-RRDs (Table 5). Nevertheless, patients with MH-RRD were more likely to

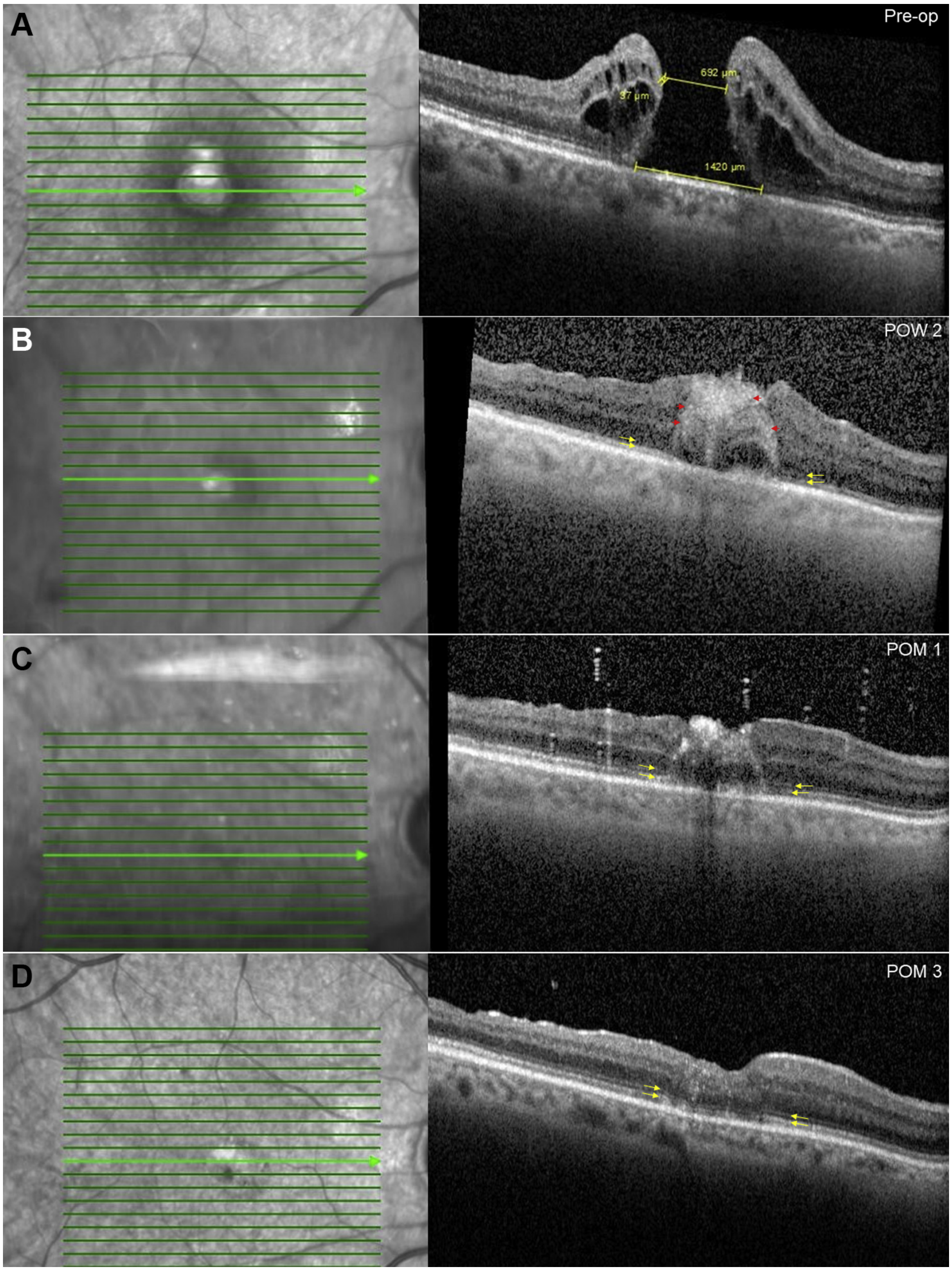

Figure 1. OCT findings after autologous retinal transplantation (ART). **A**, OCT scan obtained before surgery showing a macular hole with minimum diameter of 692 μm and maximum diameter of 1420 μm. **B**, OCT obtained at postoperative week 2 after ART showing early integration of the graft and partial reconstitution of the external limiting membrane (ELM) and ellipsoid zone (EZ) band (yellow arrows). Multiple hyperreflective foci within the graft suggest microglia are present (red arrows). **C**, OCT scan obtained at postoperative month 1 showing further reconstitution of the ELM and EZ band and a decrease in the hyperreflective foci. **D**, OCT scan obtained at postoperative month 3 showing complete reconstitution of the ELM and EZ band.

gain 3 lines of VA or more, as well as 5 lines of VA or more, compared with either of the other MH groups (compare Tables 2–4). No statistically significant associations were found between any other preoperative patient characteristics or any intraoperative surgical variables and final VA (Table 5).

For anatomic outcomes of MH closure based on OCT findings, patients with reconstitution of the EZ band achieved a significantly better final VA ($P = 0.02$), as did those with ANL ($P = 0.01$). No significant association was found between final VA and any other anatomic variable (Table 5).

The Effect of Tamponade Agent on Outcomes for All Cases

In 78 cases, SO was used for tamponade (60%), compared with 26 cases with PFO (20%), compared with 26 cases with gas (20%). No significant difference was found between

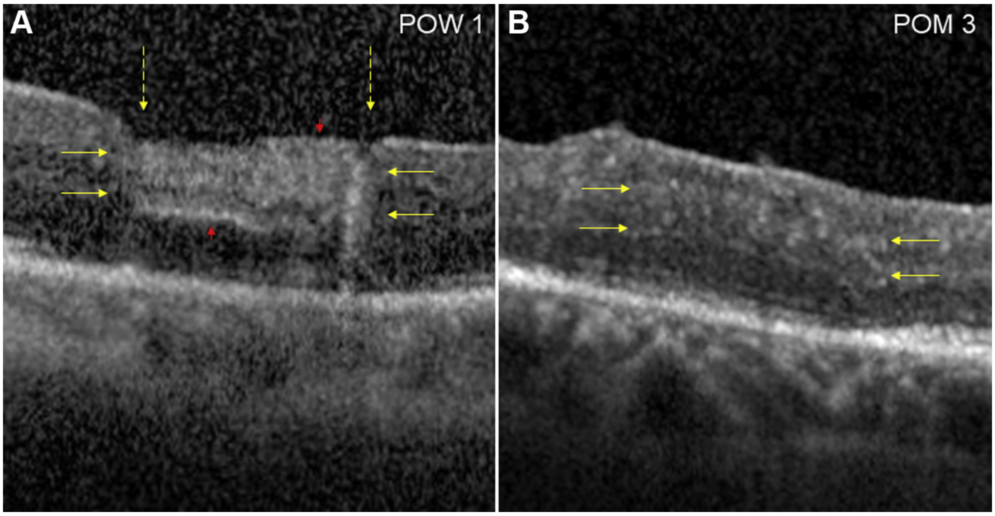

Figure 2. Integration of the transplanted autologous donor graft into the host tissue. **A**, OCT scan obtained at postoperative week 1 showing early integration of the transplant, with vertical striation lines noted between the donor graft and host tissue (dotted yellow arrows). The plexiform layers appear to align with plexiform layers, nuclear layers with nuclear layers, and so forth (solid yellow arrows). Also, hyperreflectivity is noted within the graft. **B**, OCT scan obtained at postoperative month 3 showing resolution of the vertical striation lines and seemingly continued alignment of the neurosensory layers between donor and host tissue. In cases where apparent alignment between donor and host was observed, a novel OCT finding of alignment of neurosensory layers was reported.

tamponade agent and MH closure rate ($P = 0.939$), nor for the presence of transient postoperative hyperreflectivity suggestive of graft hypoxia ($P = 0.357$). Nor was a significant difference found for tamponade agent and final VA ($P = 0.10$) or change in VA from before surgery to final VA assessment ($P = 0.071$), although a trend toward better VA was found in cases with PFO tamponade (final VA, 1.03 ± 0.20 logMAR; change in VA, −0.17 ± 0.03 logMAR) compared with cases with SO tamponade (final VA, 1.13 ± 0.13 logMAR; change in VA, −0.38 ± 0.04 logMAR). A trend toward better final VA was found in cases with gas tamponade (final VA, 0.84 ± 0.17 logMAR; change in VA, −0.27 ± 0.05 logMAR), compared with those with both PFO and SO. However, when adjusting for preoperative diagnosis and preoperative VA, no significant difference was found in final VA or change in VA for any tamponade agent. Given the small number of cases, varying preoperative diagnoses, and confounding variables, a larger study would be needed to further assess the effect of intraoperative tamponade agent on outcomes.

Subgroup Analysis for Patients with a Final Visual Acuity of 20/50 or Better

Twelve percent (n = 15) of patients achieved a final VA of 20/50 or better. Mean age was 65.3 ± 20.7 years, 53% (n = 8) were women, 50% were Black, 30% were Asian, and 20% were White. Preoperative diagnosis was primary MH for 33.3% of patients (n = 5) and refractory MH (with a mean number of previous surgeries of 1.4 ± 0.4) for 66.7% of patients (n = 12). No cases of combined MH-RRD were noted in this subgroup. Mean maximum MH diameter was 1650 ± 520 μm and mean minimum MH diameter was 816 ± 258 μm. Mean spherical equivalent was −0.83 ± 0.29 D, and mean axial length was 22.3 ± 7.4 mm. Sixty percent of patients were phakic. Preoperative mean VA was 0.848 ± 0.219 logMAR (Snellen equivalent, 20/140), and it improved significantly to 0.308 ± 0.079 logMAR (Snellen equivalent, 20/40; $P < 0.001$). Mean follow-up was 9.3 ± 2.4 months.

Neurosensory retina was harvested in 86% of these cases, compared with both retina and choroid in 14% of cases. The graft was taken from posterior to the equator in 80% of cases compared with anterior to the equator in 20% of cases. The location of the harvest site was inferonasal in 62%, superonasal in 25%, and superotemporal in 13%. Sixty-seven percent of grafts were sized to position edge to edge with the perifoveal host border, whereas 33% of grafts were sized to overlap with the perifoveal host border. Sixty percent of grafts were placed preretinally or at the level of the retina compared with 40% being placed subretinally. Gas was used as a tamponade in 54% of cases, compared with SO in 31% and PFO in 15%. In cases with SO tamponade, a fluid-to-air-to-SO exchange was performed in 60% of cases, compared with a direct PFO-to-SO exchange in 40%.

On analysis of OCT images, 80% of cases showed reconstitution of the ELM, 67% of cases showed complete reconstitution of the EZ band, and 7% of cases showed partial reconstitution of the EZ band. Alignment of neurosensory layers occurred in 44% of these cases. Microperimetry was available for 3 cases in this subgroup and showed improved fixation at the graft with a mean response of 11.3 ± 6.5 dB. Given the small subset of data, definitive conclusions regarding microperimetry could not be drawn.

Multivariate analysis revealed that patients with VA of 20/50 or better were more likely to have a preoperative diagnosis of primary or refractory MH than of combined MH+RRD ($P = 0.008$). No statistically significant association was found for any other preoperative characteristic. Patients with VA of 20/50 or better were more likely to have

Table 4. Anatomic and Functional Outcomes for Patients with Combined Macular Hole–Rhegmatogenous Retinal Detachments Undergoing Autologous Retinal Transplantation

Outcome	Data
No. of patients (%)	19 (14.6)
Age (yrs), mean ± SD	58.2 ± 13.4
Gender (%)	
Female	47.4
Male	52.6
Race (%)	
White	63.2
Black	31.6
Asian	0.0
Latino	5.3
MH diameter (μm), mean ± SD	
Maximum	1630 ± 576
Minimum	933 ± 330
Spherical equivalent (D), mean ± SD	−10.3 ± 2.9
Axial length (mm), mean ± SD	28.0 ± 9.3
Pseudophakic (%)	68.4%
No. of previous PPV procedures, mean ± SD	1.5 ± 1.4
Final follow-up (mos), mean ± SD	8.9 ± 2.0
VA (logMAR), mean ± SD	
Before surgery	2.316 ± 0.531
Snellen equivalent	HM
Final after surgery	1.403 ± 0.322
Snellen equivalent	20/506
$P < 0.001$*	
Gained VA (%)	
≥3 lines	73.7
≥5 lines	68.4
Macular holes closed, no. (%)	18 (94.7)
Complete	13 (72.2)
Eccentric	5 (27.8)
No. with acceptable quality follow-up OCT for analysis	17
Reconstitution of ELM, no. (%)	5 (29.4)
Reconstitution of EZ band, no. (%)	4 (23.5)
Alignment of neurosensory layers, no. (%)	1 (5.9)
Hyperreflective foci (e.g., microglia), no. (%)	10 (58.8)
Transient graft hyperreflectivity, no. (%)	9 (52.9)
Graft dislocation, no. (%)	1 (5.3)
Retinal detachment, no. (%)	4 (21.1)
Subretinal PFO, no. (%)	2 (10.5)
Endophthalmitis, no. (%)	0 (0.0)
High IOP requiring treatment, no. (%)	1 (5.3)

D = diopters; ELM = external limiting membrane; EZ = ellipsoid zone; IOP = intraocular pressure; logMAR = logarithm of the minimum angle of resolution; MH = macular hole; PFO = perfluorocarbon liquid; PPV = pars plana vitrectomy; SD = standard deviation; VA = visual acuity.

grafts harvested posterior rather than anterior to the equator ($P = 0.007$). No statistically significant association was found for any other intraoperative surgical variable. Complete reconstitution of the EZ band ($P = 0.039$) and ANL ($P = 0.022$) on OCT were found to be associated with better final VA. All of the cases in this subgroup showed closure of the MH (100%).

Ancillary Testing after Autologous Retinal Transplantation

OCT angiography was performed for 11 cases. Because of the small number, the varying devices used, and the nonstandardized approach in image collection, quantitative analysis could not be performed. Qualitatively, there appeared to be some limited, secondary vascularization into the region of the graft in both the superficial and deep capillary plexus (Fig 3). In the superficial capillary plexus, a pattern of tangential secondary growth of vessels to anastomose with other vessels circumferential to the graft

Table 5. The Effect of Preoperative Characteristics and Intraoperative Surgical Variables on Anatomic and Functional Outcomes

	P Value	
	Macular Hole Closure	*Final Visual Acuity*
Preoperative characteristics		
Age	0.87	0.55
Gender	0.90	0.36
Race	0.54	0.46
Diagnosis*	0.33	**0.026**
MH diameter		
Maximum	0.95	0.24
Minimum	0.80	0.52
Previous ILM peel	0.93	0.66
Previous no. of PPV surgeries	0.53	0.45
Mean spherical equivalent	0.38	0.24
Mean axial length	0.61	0.19
Lens status	0.72	0.67
Preoperative VA	0.27	**<0.001**
Intraoperative variables		
PPV gauge	0.70	0.64
Type of graft†	0.68	0.97
Harvest octant‡	0.98	0.63
Harvest site§	0.81	0.49
Size of graft	0.77	0.12
Graft placement‖	0.52	0.13
Graft fit¶	0.54	0.96
Tamponade agent#	0.94	0.10
Tamponade exchange**	0.53	0.18
Postoperative OCT findings		
Macular hole closure	—	**<0.001**
Reconstitution of ELM	—	0.15
Reconstitution of EZ band	—	**0.02**
Alignment of neurosensory layers	—	**0.01**
Hyperreflective foci (microglia)	—	0.3
Transient graft hyperreflectivity	—	0.63

ELM = external limiting membrane; EZ = ellipsoid zone; ILM = internal limiting membrane; MH = macular hole; PPV = pars plana vitrectomy; VA = visual acuity; — = statistical analysis was not performed because those anatomic findings do not have an effect on macular hole closure. Boldface indicates statistical significance.

*Compares primary MHs, refractory MHs, and combined MHs-rhegmatogenous retinal detachments.

†Compares neurosensory retina to neurosensory retina with retinal pigment epithelium and choroid.

‡Compares graft locations of superonasal, superior, superotemporal, temporal, inferotemporal, inferior, inferonasal, and nasal.

§Compares posterior with anterior to the equator.

‖Compares preretinal or at the level of the retina with subretinal positioning.

¶Compares edge to edge with preretinal.

#Compares silicon oil with perfluorocarbon liquid with gas.

**Tamponade exchange compares direct perfluorocarbon liquid to silicon oil exchange, perfluorocarbon liquid with air to silicon oil, and perfluorocarbon liquid with air to gas.

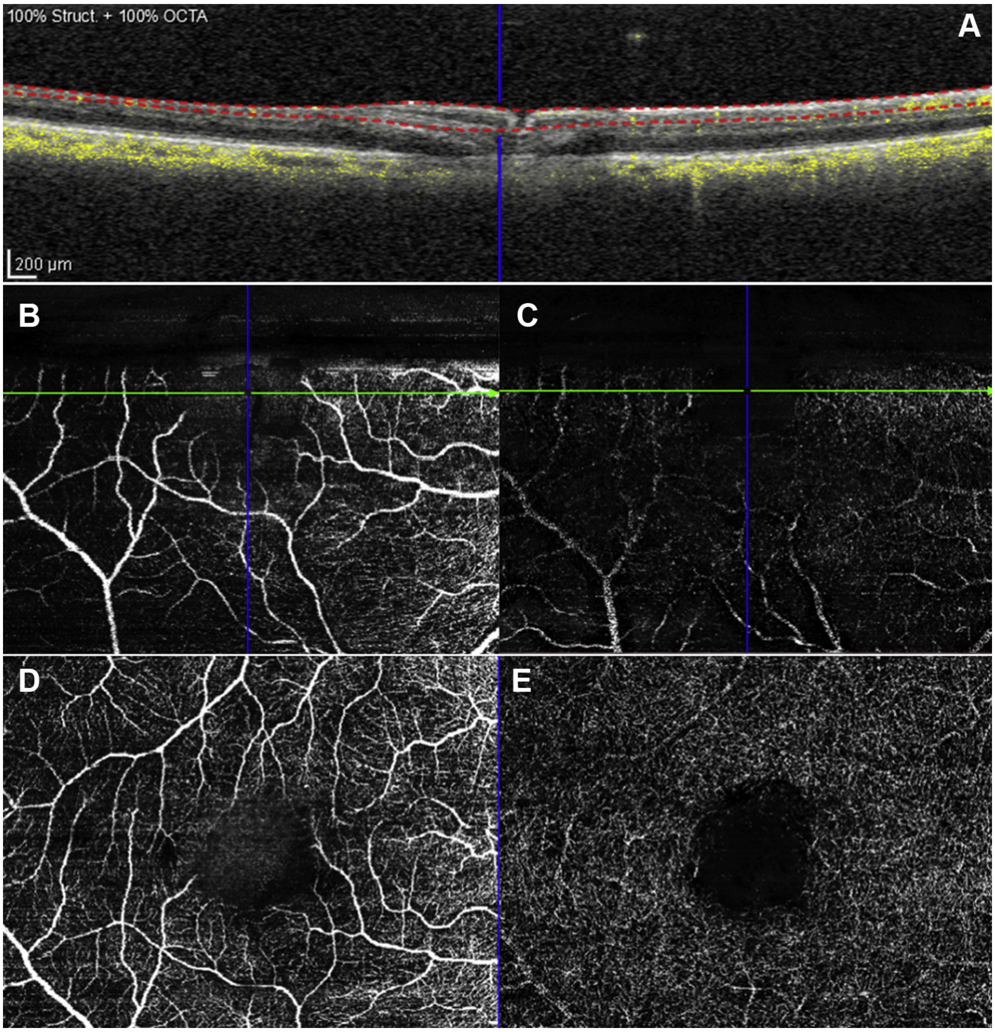

Figure 3. OCT angiography changes after autologous retinal transplantation. **A**, Structural B-scan showing integration of the autologous retinal transplant graft at postoperative week 1. **B**, En face OCT angiography image of the superficial vascular plexus (SVP) showing hyporeflectivity and absence of vessels centrally within the area of the graft, whereas the preoperative host vessels elsewhere in the macula are intact. **C**, The same postoperative week 1 findings are also noted within the deep vascular plexus (DVP), with absence of vascularity immediately surrounding the graft. **D**, OCT angiography scan obtained at postoperative month 2 showing increased density of small arterioles, venules, and capillary networks in the vicinity immediately around the graft within the SVP. **E**, OCT angiography scan obtained at postoperative month 2 also showing increased density of vessels noted within the DVP. This suggests secondary vascularization and vascular remodeling that occurs around the transplant over time.

was noted in some cases. Vessel growth tended to be limited, and often erratic, with large avascular patches noted on long-term follow-up. The subset of images was too small to draw definitive conclusions about post-transplantation secondary vascularization.

Microperimetry, which was performed in 12 cases, showed a mild increase in fixation corresponding to the ART graft. The mean response was 6.7 $\pm$ 1.9 dB. Given the small subset of data, definitive conclusions regarding microperimetry could not be drawn. Multifocal electroretinography was performed in 3 cases. Multifocal electroretinography showed slow but measurable B-wave amplitudes in the region corresponding to the ART graft. Given the small data set, definitive conclusions could not be drawn.

Discussion

Surgical techniques for the repair of MHs have undergone a stepwise evolution since the initial reports of vitrectomy and gas tamponade in the early 1990s.[6,20] The initial reports were met with widespread skepticism and debate as to efficacy; some wondered whether vitrectomy should be the method of choice for addressing MHs.[21,22] The field has come a long way since that time.

Vitrectomy, intraocular gas tamponade, and face-down positioning have shown good efficacy for closing smaller MHs, although persistent MHs and late reopening (recurrence) of closed holes have been reported.[23] The initial technique was useful for addressing one of the most important mechanisms of typical MH formation: anteroposterior traction. Tangential traction also may have been treated in some cases with residual adherent cortical vitreous or with an epiretinal membrane noted on biomicroscopy if peeled during surgery. After the development of OCT, the technique subsequently was taken a step further by introducing peeling of the ILM, which enhanced the possibility of closing larger holes and addressed tangential traction.[9] The advent of the inverted ILM flap has further enhanced our surgical armamentarium for addressing large and myopic MHs.[11] Additional surgical modifications to this technique have included the use of viscoelastic, blood, or PFO as an adjuvant.[24,25]

The emergence in 2019 of human amniotic membrane grafts for the treatment of refractory MHs, as well as MH-RRDs, similar to autologous retinal transplantation (introduced in 2016), has unlocked the potential for treating previously untreatable pathology by way of grafting.[5,26–29] Early anatomic and functional results of human amniotic membrane transplantation for patients with refractory MH and MH-RRD are encouraging. Larger series and global collaborations will continue to inform our experience with the technique. It is difficult to draw comparisons between the surgical techniques for MH closure from the various publications, given the small size of the studies, diverse variability in the pathologic features, including MH diameter and axial length, significant variation in surgical techniques, and lack of randomization. A large randomized controlled clinical trial could offer further insights.

The advent of ART has generated new and interesting clinical questions. How does the graft survive from the metabolic standpoint? How does a piece of peripheral retina respond functionally when translocated to the posterior pole? What happens anatomically at the graft donor–host border? How does the graft integrate?

In primary MH cases, 33% showed transient hyperreflectivity of the ART graft on OCT, compared with 39% in refractory MH cases and 53% in combined MH-RRD cases, suggestive of transient hypoxia of the graft. This hyperreflectivity was seen predominantly in the first postoperative week and was resolved in all cases by approximately postoperative month 1 without thinning of the graft in most cases. OCT angiography was performed in 11 cases, and in that small subset of patients, the qualitative suggestion of limited, secondary vascularization into the graft was observed. The pattern of blood vessel growth often was tangential, with new vessels anastomosing with old vessels circumferentially around the graft, but this growth usually was limited and erratic, with large avascular patches (Fig 3). The graft likely depends on diffusion of oxygen from the choroid, adjacent retina, and vitreous cavity for its survival in the early postoperative period. The postoperative angiogenesis noted herein was similar to that in previously published work showing partial vascular reperfusion of the transplanted retina within 6 weeks that further vascularizes by 3 months after surgery; small areas of vascular leakage were noted, suggestive of fine retinal neovascularization at the graft–host junction.[30] Taken together, vascular patterns at the graft–host junction after ART suggest that an angiogenic stimulus promotes late vascularization of the transplant.

Silicone oil partially blocks the transfer of oxygen between the retina and the anterior chamber after vitrectomy.[31,32] It then may reduce oxygen diffusion to the transplant, which may be facilitated better under PFO.[33] In 78 cases, SO was used for tamponade, compared with 26 cases in which PFO was used and 26 cases in which gas was used. Subanalysis showed that no significant difference was found between tamponade agent and MH closure rate ($P = 0.939$), presence of transient postoperative hyperreflectivity ($P = 0.357$), final VA ($P = 0.10$), or change in VA from before surgery to the final assessment ($P = 0.071$). Future studies with hyperspectral imaging at various postoperative time points could help us to understand oxygenation and perfusion patterns of the transplant in the setting of various tamponade agents, given the better theoretical diffusion of oxygen through perfluorocarbon liquids relative to SO and gas tamponades.

A multivariate analysis revealed no statistically significant difference for any of the surgeon-modified intraoperative variables and final anatomic outcome or final VA (Table 5). Nor were differences found in outcomes between surgeons. This suggests that this technique can be performed successfully by surgeons around the world, with modification of the previously mentioned intraoperative variables, to address previously untreatable MHs. However, this does not exclude that a specific peripheral retinal location in a specific patient, in a specific eye, may be the best source for an autologous transplant. In the subgroup with better final VA of 20/50 or better, 87% of grafts were from a nasal location (combined superonasal and inferonasal). However, after adjusting for other confounding variables, location of the graft was not associated significantly with better outcomes. Further studies, guided by advanced imaging such as adaptive optics and hyperspectral imaging, may help to answer some of these questions and guide us to the ideal location in a given eye.

A technique for transplanting combined neurosensory retina and RPE plus choroid for the treatment of advanced fibrosis resulting from age-related macular degeneration with or without concomitant MH showed positive functional and anatomic outcomes.[2] Within the present study, no difference was found in outcomes for neurosensory graft versus combined neurosensory, RPE, and choroid graft, but the sample size was likely too small truly to detect a difference. It may show, however, that the combined procedure, which is a more complex surgery, is tolerated with reasonable outcomes for patients with advanced pathologic features.

A number of interesting postoperative findings were noted on OCT relative to the anatomic features of the ART graft. Across all cases, a 55.0% rate of reconstitution of the ELM at 2.28 ± 0.42 months, a 52.5% rate of reconstitution of the EZ band at 3.52 ± 0.47 months, and a 16.3% rate of ANL, a novel OCT finding, were noted. In cases with ANL, the layers between the donor graft and host retina appear to line up anatomically (e.g., inner plexiform to inner plexiform, outer plexiform to outer plexiform, etc.). A vertical striation or dividing line between the graft and host tissue was noted in the first postoperative week in many cases, and it resolved typically by the first or second postoperative month, as the graft integrated with the host retina. Reconstitution of the EZ band ($P = 0.02$) and ANL ($P = 0.01$) on OCT were found to be associated with better final VA and may serve as important prognostic postoperative biomarkers.

Autologous retinal transplantation led to anatomic and functional improvement in the treatment of primary and refractory MHs, as well as combined MH-RRDs. These results suggest that a vitreoretinal surgeon may consider grafting techniques for large, primary MHs or if an MH failed to close by traction-relieving techniques, such as vitrectomy, ILM peeling, or ILM flaps with gas tamponade. In this study, 25% of patients with refractory MHs (all of whom had undergone ILM peeling previously) gained 5 lines or more of VA. Thus, patients have a meaningful opportunity for a better functional outcome if ART or grafting surgery is performed, as evidenced by the visual gains in the refractory MH group.

One limitation of this study is that we did not have sufficient data available on the chronicity of the MHs in this series. Such data could help determine if there are differential outcomes based on the timing of MH repair. This also may explain, in part, the similar outcomes between primary and refractory MHs. If cases in the primary MH group were chronic, functional outcomes may have had a reduced opportunity for visual gains. Furthermore, most patients in this group were phakic, compared with most in the refractory MH group being pseudophakic; no difference was found in the rate of cataract surgery between the two groups during the study period.

In the MH-RRD group, a 95% MH closure rate was achieved. Part of the VA gains in the MH-RRD group are the result of the reattachment of the retina and not necessarily of MH closure. Importantly, the presence of MH in many of these cases is also the cause of the retinal detachment, and thus achieving closure is important for reattachment of the retina. A 79% rate of retinal attachment occurred in the MH-RRD group with a single surgery. By the date the study was closed, in 66.7% of these cases, the final tamponade agent (SO, PFO, gas) had been removed or resolved.

Additionally, 12% of patients in this study reached 20/50 VA or better. This merits further exploration as to the role and potential of peripheral retina in acquiring macular resolution, which then could be a sign of hope for other macular diseases. Indeed, neural stem and progenitor cells have been detected in the vicinity of the peripheral retina in humans. Those may become activated in response to injury and detachment with proliferative vitreoretinopathy.[3,34–36] Some of those cells could have been included in autologous retinal graft tissue and might have helped to achieve better visual outcomes. Additionally, in animal models in which cones were absent, rod photoreceptors formed functional ectopic synapses to cone bipolar cells.[37] Whether rod photoreceptors from peripheral grafts could behave similarly remains to be determined. Rod photoreceptor transplantation in a pig model restored glucose transport in the subretinal space and helped to regenerate cone synthesis and electrophysiologic function.[38] Furthermore, rod photoreceptor transplantation can reactivate and support dormant cone inner and outer segments at the edges of the MH, reversing end-stage dormancy and restoring visual function.[38] Restoration of the structure of those cones and potential migration into the graft may be reflected in the reconstitution of the EZ and ANL, and it may explain some of the functional gains. Indeed, EZ band reconstitution after MH surgery previously was found to be associated significantly with better postoperative vision.[39,40]

We also believe that anatomic closure can be achieved in close to 100% of large, chronic, and unusual MHs. This technique was relatively new at the time of surgery for a number of surgeons worldwide, and outcomes may improve with experience. Because subretinal placement of the graft did not differ from preretinal positioning, and because PFO can help to secure the graft in place, additional manipulation of the graft to tuck its edge under the MH edge may be unnecessary. Positioning the graft in the same plane as the surrounding tissue may give it the best opportunity to form edge-to-edge connections and to stimulate ANL. Cases with ANL, although not easily achieved, resulted in better functional outcomes. Even if slight movement of the graft occurs and is detected by OCT after surgery, the graft can be readjusted at the time of PFO removal at 2 weeks. Also, ANL may explain partially the resolution of the central scotoma in patients undergoing ART, and connection with surrounding ganglion cells may increase the receptive field, changing a positive scotoma into a negative one.

Interestingly, a high rate (75%) of discrete, round, hyperreflective foci were noted in the graft in the early postoperative period; similar findings have been reported previously to be microglia in nonhuman primates, playing a role in the wound healing and immunologic response of the retina.[41] A larger study, as well as ex vivo or postmortem immunohistopathologic studies, could shed further light on this finding. The presence of these hyperreflective foci did not seem to affect anatomic or functional outcomes in this study.

Another important consideration from the present study regards the nomenclature of MHs. The classic nomenclature defines a large MH as having a diameter of 400 μm. The average MH in this study was 1170 ± 70 μm. The advent of grafting procedures to complement traction-relieving techniques for closing MHs has allowed surgeons the opportunity to close MHs that previously were thought to be too large to be addressed adequately with surgery and with functional improvement. In some ways, grafting surgery has created a need for an update to the classification system for MHs to address this appreciably larger subset. At what MH diameter would a grafting technique be a better first choice over a traction-relieving technique?

Although data regarding microperimetry (n = 12) and multifocal electroretinography (n = 3) were limited, the results were interesting. The mean response of the ART graft on microperimetry was 6.7 ± 1.9 dB. Cases with multifocal electroretinography showed slow but measurable B-wave amplitudes in the ART graft. Further study with a larger array of data is needed.

Limitations of this study include its retrospective design, with ancillary tests available in some cases and not others, the lack of comprehensive data regarding the chronicity of MH duration or changes in vision for all cases, the lack of a control or comparative group, and the variability of surgical techniques among surgeons. To understand better the efficacy, safety, and cost of ART relative to other surgical techniques of MH closure (e.g., vitrectomy with ILM peel or flap, amniotic membrane graft, etc.), an international, multicenter, randomized, single-masked, prospective clinical trial could be designed, including standardized ancillary testing with OCT, OCT angiography, autofluorescence, microperimetry, multifocal electroretinography, and adaptive optics at prespecified time points. Postmortem histopathologic analysis and ex vivo studies in nonhuman primate eyes or porcine eyes could help us to understand better the OCT finding of ANL and its significance.

In conclusion, 130 ART surgeries were performed by 33 vitreoretinal surgeons globally for patients with complex pathologic features. Patients achieved anatomic and functional improvement with low complication rates. Patients came from diverse backgrounds representative of a truly global project. This group of patients had MHs that were several times larger than the lower limit of large based on the traditional classification of 400 μm. Importantly, 43% of patients experienced a 3-line gain in VA, 29% of patients gained at least 5 lines of vision, with an 89% MH closure rate (78.5% complete, 10% small eccentric defect) and a 95% closure rate in MH-RRD (68.4% complete, 26.3% small eccentric defect). Twelve percent of patients achieved 20/50 vision or better, suggesting excellent graft function. We are hopeful that this global study will stimulate further research on ART and will provide guidance in the surgical management of complex MHs.

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Abbreviations and Acronyms:

ANL = alignment of neurosensory layer; **ART** = autologous retinal transplantation; **D** = diopters; **ELM** = external limiting membrane; **EZ** = ellipsoid zone; **logMAR** = logarithm of the minimum angle of resolution; **MH** = macular hole; **MH+RRD** = macular hole plus rhegmatogenous retinal detachment; **PFO** = perfluoro-n-octane; **RPE** = retinal pigment epithelium; **SO** = silicone oil; **VA** = visual acuity.

Keywords:

Anteroposterior and tangential traction, Autologous retinal transplantation of neurosensory graft, Donor, Graft integration, High myopia, Host, Internal limiting membrane peel and flap, Macular hole, OCT, OCT angiography, Pathologic myopia, Rhegmatogenous retinal detachment.

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