2015

Surgical outcomes of recurrent macular hole

https://hdl.handle.net/2144/16129

Boston University
BOSTON UNIVERSITY
SCHOOL OF MEDICINE

Thesis

SURGICAL OUTCOMES OF RECURRENT MACULAR HOLE

by

ARYA SHARIFZADEH

B.A., Boston University, 2013

Submitted in partial fulfillment of the requirements for the degree of Master of Science 2015
DEDICATION

I would like to dedicate this project to the wonderful patients whose unrelenting energy, spirit, and kind words of inspiration put a smile on my face each and every day.

Thank you all, and best wishes.
ACKNOWLEDGMENTS

I would like to give thanks to my primary thesis advisor at the Longwood Medical Eye Center of Beth Israel Deaconess Medical Center, Dr. Jorge G. Arroyo, for offering me the opportunity to experience first-hand all the best of ophthalmology, both in practice and in research. Dr. Arroyo has been an extraordinary mentor and truly a pedagogue in every sense of the word. It’s been nothing short of an honor and privilege to learn under his distinguished guidance, supervision, and care. Secondly, to Gina Yu, the most phenomenal research coordinator and helping-hand one could ever ask for. Her positivity, hard work, and drive have been truly contagious. Thank you.
SURGICAL OUTCOMES OF RECURRENT MACULAR HOLE
ARYA SHARIFZADEH

ABSTRACT

Idiopathic macular hole is a disease of the eye with unknown cause, but a pathology that, over the course of several decades of investigation by clinicians and researchers alike, has become readily treatable with surgical intervention at a very high rate of successful repair. The current study presents a retrospective case series exploring surgical outcomes for treatment of recurrent macular holes. The study additionally provides a window into the past, present, and future of macular holes across all clinical considerations, and importantly performs a supplementary statistical meta analysis of reoperation success rates in the relevant field of published data— the first of its kind. The introductory background of the present study establishes a natural history of idiopathic macular holes in clinical discovery, classification, and management. The study’s case series data specifically focuses on the phenomenon of macular hole recurrence, offering surgical outcome measures of patients undergoing primary and secondary repair operations in a single-center, single-surgeon design. The findings of the retrospective series support the hypothesis that macular hole reoperation does achieve successful anatomical closure in a majority of cases. A meta analysis performed on the current field of published clinical research pertaining to recurrent macular holes established cumulative success rates across a variety of surgical conditions. The present study’s findings were then compared to the corresponding measures across the landscape of recurrent macular hole literature, to help inform a niche of clinical research that continues
to be an area of investigation and discovery. In presenting a cohesive, synthesized narrative of recurrent macular holes, the study provides a foundation wherein ongoing collaborative efforts in the field can continue to build upon a blueprint currently set in place, and work towards finding a cause behind an otherwise idiopathic disease.
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>TITLE</td>
<td>i</td>
</tr>
<tr>
<td>COPYRIGHT PAGE</td>
<td>ii</td>
</tr>
<tr>
<td>READER APPROVAL PAGE</td>
<td>iii</td>
</tr>
<tr>
<td>DEDICATION</td>
<td>iv</td>
</tr>
<tr>
<td>ACKNOWLEDGMENTS</td>
<td>v</td>
</tr>
<tr>
<td>ABSTRACT</td>
<td>vi</td>
</tr>
<tr>
<td>TABLE OF CONTENTS</td>
<td>viii</td>
</tr>
<tr>
<td>LIST OF TABLES</td>
<td>x</td>
</tr>
<tr>
<td>LIST OF FIGURES</td>
<td>xi</td>
</tr>
<tr>
<td>LIST OF ABBREVIATIONS</td>
<td>xii</td>
</tr>
<tr>
<td>INTRODUCTION</td>
<td>1</td>
</tr>
<tr>
<td>Anatomic Considerations</td>
<td>1</td>
</tr>
<tr>
<td>Historical Background</td>
<td>4</td>
</tr>
<tr>
<td>Clinical Classification: Stages of Idiopathic Macular Hole</td>
<td>8</td>
</tr>
<tr>
<td>Surgical Interventions and Management</td>
<td>12</td>
</tr>
<tr>
<td>Surgical Technique</td>
<td>13</td>
</tr>
<tr>
<td>Considerations of Intraocular Tamponade</td>
<td>15</td>
</tr>
<tr>
<td>Internal Limiting Membrane Removal</td>
<td>16</td>
</tr>
</tbody>
</table>
Adjunctive Additives ........................................................................................................... 18
Complications of Vitrectomy ............................................................................................... 18
Treatment of Recurrent Macular Hole .................................................................................. 19
Aims and Objectives ............................................................................................................. 23

METHODS .................................................................................................................................. 24

Diagnosis and Background ..................................................................................................... 24
Surgical Procedure .................................................................................................................. 26
Outcome Measures ................................................................................................................ 28

RESULTS ..................................................................................................................................... 29

DISCUSSION .............................................................................................................................. 35

REFERENCES ............................................................................................................................ 40

CURRICULUM VITAE ................................................................................................................ 43
# List of Tables

<table>
<thead>
<tr>
<th>Table</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Macular Hole Diagnoses &amp; Primary Surgery Outcomes</td>
<td>29</td>
</tr>
<tr>
<td>2</td>
<td>Secondary Surgery Outcomes</td>
<td>30</td>
</tr>
<tr>
<td>3</td>
<td>Postoperative Outcomes &amp; Visual Acuity</td>
<td>31</td>
</tr>
<tr>
<td>4</td>
<td>Meta Analysis of Macular Hole Reoperations</td>
<td>33</td>
</tr>
</tbody>
</table>
# LIST OF FIGURES

<table>
<thead>
<tr>
<th>Figure</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Structure of the eye and ocular barriers</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>Cells and layers of the retina</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>The fundus of the eye</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>Development of idiopathic macular hole</td>
<td>5</td>
</tr>
<tr>
<td>5</td>
<td>Representation of macular hole formation</td>
<td>7</td>
</tr>
<tr>
<td>6</td>
<td>Optical Coherence tomography of macular hole</td>
<td>8</td>
</tr>
<tr>
<td>7</td>
<td>Idiopathic macular hole formation in different stages</td>
<td>11</td>
</tr>
<tr>
<td>8</td>
<td>Original Surgical Technique</td>
<td>14</td>
</tr>
<tr>
<td>9</td>
<td>Intraoperative internal limiting membrane removal</td>
<td>17</td>
</tr>
<tr>
<td>10</td>
<td>Preoperative and postoperative OCT</td>
<td>21</td>
</tr>
</tbody>
</table>
LIST OF ABBREVIATIONS

FTMH .......................................................... Full-thickness macular hole
ILM ........................................................ Internal limiting membrane
ICG ........................................................ Indocyanine green
MH ........................................................ Macular hole
OCT ......................................................... Optical coherence tomography
PPV ......................................................... Pars plana vitrectomy
VMT ......................................................... Vitreomacular traction disorder
INTRODUCTION

Anatomic considerations

The eye is among the most complex and intricate organs of the human body, responsible for the functionality of mankind’s ever-precious sense of sight. Three distinct layers inside the human eye are traditionally delineated anatomically. The outermost region, part of which acts to refract and transmit light, is made up of the cornea and sclera. The eye’s pigmented middle layer, which serves to provide nutrients, regulate light passage, and control overall power and shape of the crystalline lens, consists of the choroid, iris, and ciliary body. Lastly, an inner light-capturing and neural processing region is defined as the neurosensory retina. There exist three additional transparent structures surrounded by these aforementioned ocular layers, and they are defined as the aqueous, vitreous, and lens of the eye respectively (1).

Figure 1: Structure of the eye and ocular barriers. Figure taken from Willoughby et al., 2008 (1).
Retinal tissue, lining the eye’s innermost surface around the vitreous cavity, can further be divided into a neural retina and retinal pigment epithelium. The latter of these layers is formed by a cuboidal epithelial monolayer, and acts to maintain the function of photoreceptors, overall retinal adhesion, as well as vitamin A storage and metabolism. Within the neural retina, six major classes of neurons (photoreceptors, bipolar cells, horizontal cells, amacrine cells, ganglion cells, Müllerian glia) are arranged in parallel layers and serve to both capture and process light signals (1).

Figure 2: Cells and layers of the retina. Figure taken from Willoughby et al., 2008 (1).
The macula is a small (5 mm diameter) portion of the retina in which roughly half of the human eye’s cones (photoreceptors responsible for color vision) are found to be concentrated (1). At the macula’s center there lies an excavation (1500 µm diameter) called the fovea. While this particular area of the retina is responsible for sharp central vision and acuity, it is importantly defined clinically by annular light reflexes off of an internal limiting membrane (ILM) of Müller cells composed of type IV collagen (1, 2). The vitreous cortex, consisting of densely packed type II collagen fibrils, is attached to the retina by varying location-dependent degrees such that overall vitreoretinal adherence is strongest at the fovea, the site where the retina’s ILM is at its thinnest (2).

**Figure 3:** The funds of the eye. Macula, fovea, and the optic disc. Figure taken from Willoughby et al., 2008 (1).
**Historical Background**

The ocular condition now identified clinically as macular hole (MH) presented ophthalmologists with challenges and bewilderment for decades before the medical community collectively reached a formal classification. Throughout the 1970s and 1980s, a number of retrospective clinical studies were carried out with aims of better interpreting the signs and symptoms that accompanied macular hole progression (refs for these studies). Early investigations pointed to central foveal depressions, the result of macular thinning, as one of several potential precursors to hole formation (3). Investigators at the time additionally hypothesized on possible links between macular hole formation and ocular pathologies including retinal pigment epithelium disease, systemic vascular disorders, and macular cyst degeneration, among others (2, 3). As very few patients ever observed palpable symptom onset during the condition’s earliest stages, opportunities to clinically observe the initial development and evolution of a macular hole were extremely limited.

The first definitive breakthrough in the clinical exploration of macular holes came by way of two 1988 American Medical Association publications by Dr. Donald M Gass, who has since been widely recognized as the “Father of Macular Disease”, and his colleague Dr. Robert N. Johnson (2, 4). Gass presented evidence for a condition he gave the denomination *idiopathic macular hole*, a pathological result of focal shrinkage of the vitreous cortex in the area of the fovea (4). Rather than solely retrospectively reviewing his pool of 250 patients with confirmed fully developed idiopathic macular holes, Gass critically identified photographs of 15 patients from a twenty-year period (between 1966
and 1986) whom he believed were representative of early stage “prehole” cases (4). As a result of observing patients across a spectrum of macular hole evolution, Gass was able to provide clinical illustrations of early idiopathic macular hole developmental characteristics, a thorough hypothesizing of disease pathogenesis, and clinical opinion regarding the potential feasibility for surgical intervention.

Figure 4: Development of idiopathic macular hole. A single patient across there different stages of pathogenesis (Left: December 1968, Center: January 1969, Right: February 1969). Taken from Gass 1988 (4).

Preliminarily, Gass classified a detectable state of impending hole formation, which he termed more broadly as “stage 1 lesion”, to be the first clinical step in pathogenesis. This initial stage was found markable by the development of a yellow spot or ring (left panel of Figure 4) in the center of the fovea, loss of foveal depression, and absence of any separation by the vitreous from the foveal retina (4). Gass also observed the potential for some patients in this initial stage to undergo sudden vitreous separation
without hole formation, although the vast majority of cases did present a progression of disease pathogenesis without any spontaneous amelioration of conditions.

In parallel with these foundational clinical findings, Gass and Johnson later completed a secondary review of 158 eyes in which idiopathic macular holes were either evolving or completely formed (5). The observations that followed lent credence to the hypothesis that idiopathic macular holes develop as the result of perifoveal vitreous cortex contraction. Histopathologic studies following the publication of the Gass hypothesis of macular hole formation went on to confirm tangential vitreous cortex traction as the principal mechanism underlying disease pathogenesis (2).

The advent of Optical coherent tomography (OCT) as a diagnostic imaging technique in ophthalmology functioned to further add detail to macular hole classification. The high-resolution, 2-dimensional cross sectional images of the retina have become paramount in both making a diagnosis and assigning corresponding staging to macular holes (2). Gaudric et al (6) presented an invaluable study using OCT-generated data to conclusively illustrate a schematic of hole formation wherein posterior hyaloid detachment, beginning around the macula, functions along with the action of anteroposterior forces (due to the hyaloid remaining adherent to the foveolar center) to result in an intraretinal split. This initial pathological development progresses and evolves into the creation of a cystic space, which consequently generates a disruption of the outer retinal layer and an opening of the foveal floor (6). This sequence of events critically provided a definitive characterization of each step in the clinical progression from vitreofoveal traction of full-thickness macular hole (FTMH) formation.
Figure 5: Representation of macular hole formation. Taken from Gaudric et al., 1999 (6).
**Figure 6:** Optical Coherence topography of macular hole. Full-thickness with separation of the posterior vitreous from the fovea. Taken from Huang et al., 2011 (7).

**Clinical Classification: Stages of Idiopathic Macular Hole**

As initially described by Gass, macular hole formation typically evolves throughout a period of weeks to months over the course of four distinct stages (4). The original Gass definitions of each respective stage have undergone some degree of revision, but remain largely consistent with their earliest versions. The stages of formation and descriptive characteristics that follow are informed by the American Academy of Ophthalmology’s Preferred Practice Pattern Guidelines, a current standard in clinical diagnosis of idiopathic macular holes (8).

*Stage 1 (Impending Macular Holes):*

Important in clinical classification of macular hole stages is the lack of a retinal defect in stages defined as 1-A and 1-B. For this reason, both subdivisions of stage 1 macular holes are more generally referred to as “impending” (8). In stage 1-A, there is a
characteristic loss of foveal depression and the appearance of a foveal spot sized 100 - 200 µm in diameter. This primary characteristic is critical in differentiating 1-A from 1-B impending holes, as stage 1-B is defined by the formation of a yellow ring 200 - 250 µm in diameter. In stage 1-A impending macular hole, there is an observed localized shallow detachment of the perifoveal vitreous cortex while still remaining adherent to the foveola, and, in some cases, a horizontal splitting at the fovea (a pseudocyst) that corresponds to the aforementioned yellow spot. By contrast, in stage 1-B impending macular hole there is a posterior extension of the pseudocyst that occurs with disruption of the outer retinal layer, while the retinal roof remains intact by the retina’s persisting adherence to the posterior hyaloid (8). Both 1-A and 1-B feature visual acuity ranges from 20/25 to 20/80, and neither stage is accompanied by a recommendation for surgical intervention (8).

Stage 2: Stage 2 macular holes are classified as small full-thickness (<400 µm diameter) retinal defects. As is the case in stage 1-A and 1-B, overall acuity remains in the 20/25 to 20/80 ranges, however distorting visual symptoms such as metamorphosia (straight lines appearing as wavy) are often observed. It should additionally be noted that in neither stage 1 nor stage 2 macular holes are epiretinal membranes commonly present.

Stage 3: Stage 3 macular holes are defined as clinically full-thickness macular holes equal to or larger than 400 µm in diameter. It is in this stage where the posterior hyaloid is largely separated from the macula, with possible persisting attachment at the optic disc or peripheral regions. Additionally, stage 3 holes feature an operculum (flap) present on the posterior hyaloid over the hole, which is detectable clinically by means of OCT imaging. In some cases, stage 3 holes can also feature a cuff of subretinal fluid with
intraretinal edema, or even the occasional appearance of drusen-like yellowish deposits in the base of the hole. Often times in patients with long-standing cases of stage 3 macular hole, there is a rim of hyper- or hypo-pigmentation of the RPE at the junction between detached and normal-appearing retina. Visual acuity ranges tend to fall between 20/100 and 20/400, and epiretinal membranes may be present at this stage (8).

Stage 4: Stage 4 full-thickness holes are larger in size than their stage 3 predecessors, and are characterized by a complete posterior vitreous detachment (PVD) and the presence of a Weiss ring, clinically signified by a condensed, thickened posterior surface of the vitreous that pulls away from the optic disc. (4, 8). Cuffs of subretinal fluid are usually present at this stage, and epiretinal membranes are also found to occur more frequently. Visual acuity tends to decrease more profoundly into the 20/100 to 20/400 range.

As it stands today, clinical data would suggest that roughly 50% of stage 1-A or 1-B impending holes progress to a full-thickness macular hole. When disease progression continues beyond stage 2, patients experience significant vision loss and debilitation without treatment. Additionally, the gradual increasing of macular hole enlargement can often lead to the development of epiretinal membranes, a pathologic puckering of the macula that often creates further visual impairments and poorer overall prognoses (2, 4, 5, 8).
**Figure 7:** Idiopathic macular hole formation in different stages. Taken from Lam et al., 1999 (2).

Idiopathic macular holes can be associated to some degree with changes in the human eye as a result of aging. Natural, age-related changes to the degree of vitreoretinal adherence in the eye could potentially result in the onset of macular holes in even the healthiest of patients. Epidemiological findings of one case-control study found that over 50% of idiopathic macular holes were found in individuals aged 65 to 74 years old, with
only 3% prevalence in those under the age of 55 (8). Incidence rates of idiopathic macular holes are significantly higher in women than men (8).

Patients who present with a macular hole in the clinic typically experience blurred central vision, in addition to the aforementioned symptoms of metamorphosia. In asymptomatic patients, holes are often noticed during routine eye examinations — informed both by physicians’ observations during ophthalmoscopy and OCT image analysis. In making a differential diagnosis, clinicians are sure to distinguish macular hole from other forms of ocular disease that may mimic its symptoms, ranging from lamellar holes (partial thickness macular holes whose symptoms do not typically progress or require surgical intervention), to foveal cysts and epiretinal membranes. (2). The use of Watzke-Allen slit beam testing is a traditional method of clinical examination that may be helpful in confirming macular hole diagnoses made by OCT. Both fluorescein angiography and scanning laser ophthalmoscopy are additional auxiliary eye center tests that can prove useful in making a differential diagnosis in the most difficult of presentations (2).

Surgical Interventions and Management

As is the case with many pathologies of the eye, early detection and diagnosis is associated with better success in management and intervention. In some patients presenting with stage 1-A or early 1-B lesions there is the chance for spontaneous resolution of symptoms in the eye following vitreofoveal separation without treatment, wherein the appearance of the fovea consequently returns to normal or appears as a reddish spot (8). As only about 50% of impending macular holes progress to full-
thickness macular holes, in those cases with spontaneous vitreous detachment there is typically a rapid improvement and amelioration of visual symptoms. For this reason, the recommended management for stage 1-A and 1-B macular hole is close observation, with regular follow-ups every 2 to 4 months in the absence of new symptom onset. As macular holes progress to stage 2 and beyond, their enlargement is accompanied by progressive vision loss and increased chances of epiretinal membrane development. However, some case series have interestingly observed spontaneous resolution with hole closure and foveal contour restoration to occur in a very small minority, 2-3%, of full-thickness macular holes (8). In order to halt further disease progression and loss of central visual function, macular holes categorized or stage 2 or later are recommended to undergo vitreous surgery (2, 4, 5, 8).

**Surgical Technique**

The current clinical standard of surgery in treatment of full-thickness macular holes is that of pars plana vitrectomy (PPV) operation. The principal anatomic goal underlying a PPV procedure is to separate the posterior cortical hyaloid from the retinal surface with a careful surgical technique. Upon successful completion of this primary objective, procedures conclude with the creation of a retinal tamponade to achieve anatomic macular hole closure (2,8). Several different agents can be employed to carry out this intraocular liquid exchange, with options for agents ranging from the use of air alone to sulfur hexafluoride (SF6), perfluoropropane (C3F8), or silicone oil.

The clinical utility of pars plana vitrectomy in treatment of full-thickness macular holes was first demonstrated by Dr.’s Neil E. Kelly and Robert T. Wendel in a landmark
1991 publication (9). Their pragmatic clinical approach offered major contributions to clinical management of a condition previously considered untreatable. Operating on a series of 52 patients with full-thickness (stage 3 or 4) macular holes, Kelly and Wendel carried out a procedure consisting of PPV, removal of adherent cortical vitreous, stripping of epiretinal membranes, and a total SF6 fluid-gas exchange. This pilot study established detailed protocol on the various instruments used in surgery, as well as preoperative and postoperative observations for each patient. Importantly, their series also offered specific techniques for aspiration during vitreous detachment, and a method for usage of silicone tip extrusion needles in identification and removal of adherent posterior cortical hyaloid (9).

**Figure 8:** Original surgical technique. Sweeping silicone-tipped extrusion needle over the retinal surface to identify adherent cortical vitreous (the so-called “fish-strike” sign) Taken from Kelly and Wendel, 1991 (9). Kelly and Wendel were able to successfully perform their procedure and reattach detached macula in 30 (58%) of the eyes they operated on (9), and, of particular value to
clinicians, laid a cornerstone upon which all future surgical intervention mechanisms in
the treatment of macular holes could be built.

Since the preliminary introduction of the Kelly and Wendel protocols in macular
hole surgery, both the modification of medical instruments and gradual refinement of
technique for tissue removal have rendered the success rate of postoperative hole
flattening to be now nearly 90% efficient. The following considerations are currently part
of standard preoperative treatment plans for clinicians and their patients in surgical
management of idiopathic macular holes.

Considerations of Intraocular Tamponade:

While the medical community has yet to reach a definitive consensus on the
single best choice of tamponade agent in vitreous surgery, there are many factors that
impact physicians’ selections when carrying out macular hole treatment procedures.
Among the gasses, SF6 has a lifetime of 2 to 4 weeks, while C3F8 remains present over
the course of 1 to 3 months. Critical to the selection of these long-acting gasses in
intraocular tamponade is managing steadfast patient compliance to a recommended 1 to 2
week regimen of facedown positioning (2, 3, 8). While the use of these gasses has been
very successful in achieving postoperative hole closure in patients who practice strict
adherence to the head positioning guidelines, usually inevitable cataract formation results
in a generally slower visual recovery period (2). In patients who are unable or unwilling
to comply with the facedown positioning practices of gas tamponade, silicone oil has
emerged as an alternative consideration. Although the silicone tamponade force is less
than that of intraocular gas, patients can typically return to near normal day-to-day
activities much sooner than those receiving SF6 or C3F8. However, a disadvantage in silicone oil tamponade is the need for a second oil-removal procedure when the initial postoperative period completes, and thus, a greater total expense of treatment. Independent of time considerations in recovery, some investigators have found better overall anatomic and visual outcomes with gas tamponade as compared to silicone oil, and yet other case series have observed a higher rate of spontaneous macular hole reopening (8).

**Internal Limiting Membrane Removal**

Another factor that has presented potentially valuable clinical utility is the introduction of ILM peeling during conventional vitreous surgery for macular hole. The ILM is thought to act as a physiological scaffold for both cellular proliferation and contractile tissue element attachment — both factors capable of producing significant vitreomacular traction (8). Thus, the theory behind this surgical modification is that increasing the flexibility of the retina around a macular hole by ILM removal could potentially allow for easier anatomic hole closure (8). ILM removal can be achieved by the use of special instruments, and requires surgeons to perform a precise technique of peeling over a transparent, unicellular, non-elastic basement membrane (10). The difficulty in successful execution of this procedure is two-fold: both poor visibility of ILM to the naked eye, as well as the risk of damage to the retina in cases of inappropriate removal, render this surgical technique as one requiring extreme vigilance by physicians in their practice and perfection of its method. The most promising development aiding clinicians’ ability to successfully carry out this peeling technique arrived at the
introduction of an indocyanine green dye (ICG), shown to successfully stain collagen fibrils, proteoglycans, Muller cell plasma membranes, and basement membrane of the ILM to optimize visualization during macular hole surgery (10). Since the advent of ICG staining in ILM removal, trypan blue, brilliant blue, and other dyes have also emerged as possible choices for ILM staining in macular hole surgeries. While several studies have put forth evidence to support significant enhancement of anatomical closure rates in procedures utilizing the technique as compared to primary surgeries without peeling (2), technique optimization will likely require further testing by large randomized trials comparing outcomes across the various ILM peeling conditions.

**Figure 9:** Intraoperative internal limiting membrane removal. View of an eye with idiopathic macular hole during internal limiting membrane removal. Beginning of continuous curvilinear peel (L) completion of membrane peel (R). Indocyanine green stained flap is clearly visualized. Taken from Kadonosono et al., 2000 (10).
**Adjunctive Additives**

Surgeons seeking to improve success of macular hole surgeries and bypass the need for epiretinal membrane peeling have in the past incorporated the use of different tissue adhesives in addition to traditional surgical procedures (2). The idea behind these additives is that the chemical stimulation of fibroglial proliferation can aid in achieving macular hole closure. Transforming growth factor-β is an adjuvant which has been explored across a few different case series to date. In coupling the use of this growth factor to pars plana vitrectomy and gas tamponade, there was evidence presented of elevated closure rates in some macular hole operation series, but additional randomized placebo-controlled trials failing to find any statistical differences in adjuvant-receiving patients have rendered techniques incorporating additives in macular hole surgery as inconclusive and a continued area of investigation (2).

**Complications of Vitrectomy**

A large majority of phakic eyes are observed to develop cataracts following vitrectomy surgery in macular hole repair. Several study series have found the rate of visually significant development to be somewhere around in 80% in the first few years after a pars plana vitrectomy (8). Considering these markedly high rates of cataract formation, many surgeons advocate a combining of macular hole surgery with a phacoemulsification and intraocular lens placement. In essence a prophylactic measure, this combining of procedures totally eliminates the need for a second operation that so often is necessitated for by cataract development in treatment of macular hole (11). Additionally, intraoperative retinal tears and postoperative retinal detachments are
possible complications accompanying and vitrectomy including macular hole repair, although both present low rates of occurrence. In addition, it should be noted that patients who have undergone gas bubble tamponade must completely avoid air travel in the postoperative recovery period, as ascension to higher altitudes could result in gas expansion, an increase in intraocular pressure, and consequential development of damage to the optic nerve (8).

Interestingly, recent clinical research work on vitreomacular traction syndrome (VMT), which occurs when tugging caused by strong retinal adherence of the posterior vitreous results in morphological changes to the macula, has explored the potential efficacy of intravitreal expansile C3F8 injection treatments alone, a technique known as pneumatic vitreolysis, in patients that presented VMT with or without concurrent macular holes (11). The results of the study notably found pneumatic vitreolysis to achieve higher rates of VMT resolution and hole closure as compared to other treatment standards in a retrospective case series and meta analysis, providing a potentially valuable clinical foundation for approaching certain VMT-associated early-stage macular hole presentations with a lower rate of complication in treatment (11).

**Treatment of Recurrent Macular Holes**

While major improvements since the Kelly and Wendel introduction of surgery in treatment of macular hole have made intervention largely effective, there exists the reality that not all patients undergo these procedures successfully. Studies across the last five years of literature concerning surgical outcomes for macular hole treatment report closure rates in primary operations to be in the range of 90% (8). While the median of
postoperative visual acuity for macular holes successfully sealed in a first surgery is approximately 20/40, studies find less favorable acuity outcomes in holes failing to seal after primary surgery (8).

Anatomic closure can be defined clinically as a flattening and reattachment at the hole’s rim that extends along the entire circumference of the macular hole (13). By OCT imaging analysis, the nature of sealed macular holes can further be classified with regards to postoperative continuity of foveal tissue above the retinal pigment epithelial layer, and the presence or absence of any defects or interruptions of the neurosensory retina (13).

Several factors have been retrospectively hypothesized as potential causes at the root of postoperative failure in macular hole surgery. From a strictly physical, dexterity-based perspective, the actual precision of technique during PPV procedures to ensure complete peeling of the cortical vitreous is paramount. Anatomically, surgical failure or re-opening of idiopathic macular holes could be related to insufficient stability of the glial plug at the hole’s center. While there have been some investigations into the possible effect of patient non-compliance with postoperative posture and head-positioning requirements, it is difficult to gather such subjective data empirically.
An important distinction in analysis of macular holes requiring treatment beyond primary surgery is the delineation between closed and unclosed groups. In instances where PPV and gas exchange treatment yield anatomic closure of macular holes that re-open some period of time after surgery, the cases are classified as reopened holes. By contrast, clinical presentations in which primary surgery fails to establish any postoperative anatomic closure are described as unclosed holes. Notably, a single-center retrospective cases series that took place over ten years at the United Kingdom’s Royal Liverpool Hospital (14) compiled data on 532 patients undergoing pars plana vitrectomy.

Figure 10: Preoperative (A) and postoperative (B) OCT. Representing successful macular hole closure resulting in a normal foveal contour. Kang et al., 2003 (13).
for idiopathic full-thickness macular hole, with successful closure accomplished in 460 eyes (86%). The study established outcome rates in the 72 patients who underwent a second operation, specifically categorized by unclosed versus reopened cases (14). The results of the series illustrated that patients undergoing secondary surgery for macular holes had successful overall outcomes in a majority of cases, both among unclosed and reopened eyes. The study importantly provided comparative data to support the utility of secondary surgery for macular hole in achieving anatomic closure and improvement to visual acuity across groups.

The predictive value of OCT in retreatment of macular holes is also emerging as a highly significant area for further clinical investigation in retreatment of macular holes. A 2007 publication by Hillenkamp et al. (15) presented evidence concerning hole configuration as a strong prognostic indicator of anatomical closure in retreatment of full-thickness macular holes. In particular, the study characterized holes associated with a cuff of subretinal fluid at their margin as having significantly increased likeliness to achieve anatomic closure in reoperation following failed primary surgeries. The interventional case series documented patients with idiopathic full-thickness macular holes that had undergone standard PPV, ICG-assisted ILM peeling, and gas tamponade. In defining a mechanism for this finding, the group hypothesized that as macular hole closure depends on the centripetal movement of retinal tissue to occupy the foveal region, those cases with identifiable cuffs of subretinal fluid achieve a higher rate of facilitated closure as the result of an absence of adhesion between the macular hole margin and underlying retinal pigment epithelium. (15).
Aims and Objectives

The goal of the current investigation was to retrospectively analyze outcomes of macular hole reoperations among a series of patients in a single treatment center. The case series comprised of patients who underwent both primary and secondary pars plana vitrectomy procedures for full-thickness macular holes, which either reopened after initially-successful primary repairs or remained unclosed postoperatively and thus required revision surgery. The objective in gathering this data was firstly to provide potentially useful clinical insights as to success rates for recurrent macular hole surgeries as performed by a single vitreoretinal surgeon over the course of a decade of macular hole repairs. Moreover, the current study aimed to supplement its case series data by placing the primary outcome measure of successful anatomic macular hole closure following secondary surgery in both the historical context of macular hole surgery, and the current medical research niche of macular hole reoperation. The latter was achieved by conducting a meta analysis of relevant clinical publications with inclusion criteria centering around surgical technique in macular hole operations, and determining cumulative statistical calculations with literature deemed to fall within the study’s parameters.
METHODS

For the purposes of performing a retrospective clinical case study, a total of 13 eyes (12 total patients) were selected from archived medical records at the Beth Israel Deaconess Medical Center in Boston, Massachusetts. These cases represented those which underwent two separate surgical treatments following a diagnosis of full thickness macular hole between 2004 and 2013. The surgeries performed were standard 3-point pars plana vitrectomy procedures, with or without internal limiting membrane peeling, with or without epiretinal membrane peeling, and tamponade with C3F8, SF6, or silicone oil. Following primary surgeries, holes were classified in follow-up as either anatomically closed or unclosed (persistent). In the 13 cases currently presented, secondary operations were carried out following reopening or persistence of macular hole under the same standard surgical conditions, with revision vitrectomies again supplemented by optional ILM peeling, ERM peeling, and C3F8, SF6, gas or silicone oil tamponade.

Diagnosis and Background

Before beginning any course of surgical intervention, patients were given preliminary background on macular holes following an ophthalmoscopic and OCT-informed diagnosis by an eye center retina specialist. Patients were provided with information on the idiopathic nature of macular holes, their increased occurrence rate among women, and a typical age range for onset (between 50 and 70 years). The physician then engaged in a broad discussion of treatment options with their patients, weighing the benefits of continued observation versus pars plana vitrectomy, membrane
peeling, and intraocular gas or silicone oil tamponade. The patients were informed as to a generally accepted 90% closure rate for full-thickness macular holes after one surgery.

In cases for which patients decided to proceed with surgical intervention, the physician then proceeded on to present options for tamponade. The first choice of intraocular tamponade, long-acting gas bubbles (SF6 or C3F8), were discussed in the context of their mechanism and accompanying head-position regiments. Patients were given instruction as to a strict regiment that required 2-week commitment after surgery, and which called for maintenance of face down positioning during 45 minutes of every hour, while awake, on their sides at night. The instructed facedown regiment was since shortened to 1 week once routine ILM peeling was introduced into macular hole repair operations. In patients who were unable or unwilling to adhere to these requirements (or who had to travel by air within 1-3 months after surgery), silicone oil was chosen for tamponade, with understanding that a brief, 15 minute removal surgery would have to take place anywhere between 8 to 12 weeks after the primary operation.

Lastly, patients were given a detailed account of risks associated with vitrectomy for macular hole repair. The physician informed patients that 10% of cases do not close with surgery or reopen after successful macular hole closure, and that in these instances additional surgery to close the macular hole is typically performed. Patients were told there exists a 1 in 1,000 risk of bleeding and infection, as with any intraocular procedures, that can lead to rare complications resulting in total loss of vision. Moreover, the physician discussed a 1 in 100 risk for development of retinal tears or retinal detachments, which can typically be corrected at the time of surgery, but in rare cases can
require an additional surgical repair. In patients who were still phakic at the time of surgery, the physician recommended the combining of cataract extraction and intraocular lens placement with vitrectomy, due to the elevated rates of visually significant cataract formation postoperatively in macular hole treatment.

After the indications, risks, benefits, and alternatives were thoroughly presented and deliberated upon, patients signed consent forms and were scheduled for operation as soon as was possible. Additionally, patients were instructed to remain in a fasting state after midnight the day before surgery, and to take any necessary medications with just a sip of water in the morning.

**Surgical Procedure**

Inside the operating room, EKG, O2, and blood pressure monitors were put in place and monitored throughout the case. The operative eye was then prepared and draped by typical ophthalmic protocol, and a wire lid speculum was placed to keep the lids apart. Next, a retrobulbar infusion of a 50:50 mixture of 2% lidocaine and 0.75% marcaine with epinephrine was given behind the operative eye to produce suitable anesthesia and akinesia. Sclerotomies were then carefully made 3.5 mm posterior to the limbus in the superonasal, superotemporal, and inferotemporal quadrants. A 4 mm infusion cannula was inserted into the inferotemporal sclerotomy. The tip of the infusion cannula was inspected to ensure that it was in the vitreous cavity prior to turning on the infusion. Triamcinolone acetonide (Kenalog) was then used to stain the vitreous gel for visualization. In the case that posterior hyaloid remained attached, the retinal surgeon elevated the hyaloid using the soft-tip aspirating cannula and vitreous cutter in order to
create a posterior vitreous detachment. Once this was done, peripheral vitrectomy could be performed 360 degrees around. Internal limiting membrane staining was accomplished by use of ICG dye in the large majority of cases. ICG dye was applied twice for a total of 2 minutes, and followed by ILM forcep peeling of the internal limiting membrane 360 degrees around the macular hole. In the instance of epiretinal membrane association with the ILM, dissection was adjusted and carried out accordingly. In the case of impact hemorrhage associated with any portion of the vitrectomy, notes were made as to the details and measures were taken to stabilize conditions during and after surgery.

Surgeons then performed a complete 360-degree scleral depressed examination to ensure no evidence of retinal tear or detachment. At this stage, patients underwent tamponade by either complete fluid-air exchange or silicone oil tamponade. Infusions of 50 cc of 20% or 25% SF6 or C3F8 gas were performed and pressures were ensured to be normal. In the case of silicone oil tamponade, patients received either 1,000 or 5,000 centistokes. After sclerotomies were closed and found to be-water tight, a subconjunctival injection of Kefzol and dexamethasone was given. Operative eyes were patched with 1 drop of 0.25% scopolamine, Bacitracin ointment, and a soft eye pad with hard eye shield. Due to the delicate intraocular manipulations involved the procedure, fully-trained ophthalmologists were required in all operations to assist with surgery. Patients had patches removed on postoperative day one, and given instruction for proper use of topical drops.

For all secondary operations, the standard preoperative discussions and indications were again presented to patients. In these cases of recurrent full thickness
macular holes, whether reopened or unclosed, the physician informed patients that the loss of central vision and corresponding visual symptoms would likely remain at the current level if untreated with reoperation, and some degree of peripheral vision could be salvaged in those instances. Revision vitrectomies were performed under the same monitored anesthesia controls as used previously.

**Outcome Measures**

The main outcome measure of this study was anatomical closure of macular hole as observed by ophthalmoscopic examination and supplementary OCT image analysis by the vitreoretinal specialist in clinic. When available, visual acuity measures both pre- and postoperatively were gathered for patients across primary and secondary surgeries. Time duration between macular hole diagnosis and primary operation was informed by medical record assessment notes made during eye center visits. Surgeon operative notes were consulted for details as to the specific conditions surrounding each individual procedure.
RESULTS

The following results reflect the collected data from a case series of 13 recurrent macular hole patients, organized by the respective outcomes of primary and secondary surgery, as well as background information on gender, age, and stage classification.

**Table 1: Macular Hole Diagnoses & Primary Surgery Outcomes**

<table>
<thead>
<tr>
<th>Case #</th>
<th>Age</th>
<th>Sex</th>
<th>Diagnosis to Surgery Duration</th>
<th>Macular Hole Stage</th>
<th>Tamponade</th>
<th>ILM Peel?</th>
<th>Macular Hole Status Postop #1</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>67</td>
<td>F</td>
<td>1 month</td>
<td>2</td>
<td>C3F8 gas</td>
<td>No</td>
<td>Closed</td>
</tr>
<tr>
<td>2</td>
<td>71</td>
<td>F</td>
<td>1 month</td>
<td>3</td>
<td>SF6 gas</td>
<td>Yes</td>
<td>Closed</td>
</tr>
<tr>
<td>3</td>
<td>69</td>
<td>F</td>
<td>1 month</td>
<td>2</td>
<td>C3F8 gas</td>
<td>No</td>
<td>Closed</td>
</tr>
<tr>
<td>4</td>
<td>59</td>
<td>F</td>
<td>2 weeks</td>
<td>2</td>
<td>C3F8 gas</td>
<td>Yes</td>
<td>Closed</td>
</tr>
<tr>
<td>5</td>
<td>68</td>
<td>F</td>
<td>1 month</td>
<td>2</td>
<td>Silicone oil</td>
<td>Yes</td>
<td>Closed</td>
</tr>
<tr>
<td>6</td>
<td>82</td>
<td>F</td>
<td>5 months</td>
<td>2</td>
<td>SF6 gas</td>
<td>Yes</td>
<td>Unclosed</td>
</tr>
<tr>
<td>7</td>
<td>55</td>
<td>M</td>
<td>1 month</td>
<td>3</td>
<td>Silicone oil</td>
<td>Yes</td>
<td>Closed</td>
</tr>
<tr>
<td>8</td>
<td>60</td>
<td>F</td>
<td>2 weeks</td>
<td>3</td>
<td>Silicone oil</td>
<td>Yes</td>
<td>Closed</td>
</tr>
<tr>
<td>9</td>
<td>62</td>
<td>F</td>
<td>1 month</td>
<td>3</td>
<td>Silicone oil</td>
<td>No</td>
<td>Closed</td>
</tr>
<tr>
<td>10</td>
<td>63</td>
<td>F</td>
<td>1 month</td>
<td>3</td>
<td>Silicone oil</td>
<td>Yes</td>
<td>Closed</td>
</tr>
<tr>
<td>11</td>
<td>61</td>
<td>F</td>
<td>1 month</td>
<td>3</td>
<td>C3F8 gas</td>
<td>No</td>
<td>Closed</td>
</tr>
<tr>
<td>12</td>
<td>78</td>
<td>M</td>
<td>2 month</td>
<td>3</td>
<td>C3F8 gas</td>
<td>No</td>
<td>Unclosed</td>
</tr>
<tr>
<td>13</td>
<td>71</td>
<td>F</td>
<td>1 month</td>
<td>3</td>
<td>SF6 gas</td>
<td>Yes</td>
<td>Closed</td>
</tr>
</tbody>
</table>

The series sample consisted of 10 female and 2 male patients, as Cases 9 and 10 represent two separate macular hole recurrences in either eye of a single subject, one year apart respectively. The average age of cases at the time of primary operation was 67 years. Of the 13 total macular hole cases presented, 5 were classified as stage 2 full-thickness macular holes, and 8 were classified as stage 3 full-thickness macular holes.
The average duration of time between clinical diagnosis of macular hole by retina specialist and primary operation was 1.3 months, although it should be noted that Case 6 describes an outlier data point of 5 month’s delay before surgical intervention. Of the primary macular hole repair operations, 11 of 13 resulted in initial macular hole closure (84.6%), while 2 of 13 persisted as unclosed macular holes (15.5%). 8 of 13 cases underwent ILM peeling during primary surgery. Cases 4, 7, and 13 underwent epiretinal membrane dissection during primary operation and all achieved primary hole closure.

**Table 2: Secondary Surgery Outcomes**

<table>
<thead>
<tr>
<th>Case #</th>
<th>Age</th>
<th>Sex</th>
<th>Recurrent Macular Hole Type</th>
<th>Reoperation Tamponade</th>
<th>Reoperation ILM Peel?</th>
<th>Macular Hole Status Postop #2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>67</td>
<td>F</td>
<td>Reopened</td>
<td>Silicone oil</td>
<td>Yes</td>
<td>Closed</td>
</tr>
<tr>
<td>2</td>
<td>71</td>
<td>F</td>
<td>Reopened</td>
<td>C3F8 gas</td>
<td>Yes</td>
<td>Closed</td>
</tr>
<tr>
<td>3</td>
<td>69</td>
<td>F</td>
<td>Reopened</td>
<td>Silicone oil</td>
<td>Yes</td>
<td>Closed</td>
</tr>
<tr>
<td>4</td>
<td>59</td>
<td>F</td>
<td>Reopened</td>
<td>SF6 gas</td>
<td>No</td>
<td>Closed</td>
</tr>
<tr>
<td>5</td>
<td>68</td>
<td>F</td>
<td>Reopened</td>
<td>SF6 gas</td>
<td>Yes</td>
<td>Closed</td>
</tr>
<tr>
<td>6</td>
<td>82</td>
<td>F</td>
<td>Unclosed</td>
<td>Silicone oil</td>
<td>Yes</td>
<td>Unclosed</td>
</tr>
<tr>
<td>7</td>
<td>55</td>
<td>M</td>
<td>Reopened</td>
<td>Silicone oil</td>
<td>Yes</td>
<td>Unclosed</td>
</tr>
<tr>
<td>8</td>
<td>60</td>
<td>F</td>
<td>Reopened</td>
<td>Silicone oil</td>
<td>Yes</td>
<td>Closed</td>
</tr>
<tr>
<td>9</td>
<td>62</td>
<td>F</td>
<td>Reopened</td>
<td>Silicone oil</td>
<td>No</td>
<td>Closed</td>
</tr>
<tr>
<td>10</td>
<td>63</td>
<td>F</td>
<td>Reopened</td>
<td>Silicone oil</td>
<td>Yes</td>
<td>Unclosed</td>
</tr>
<tr>
<td>11</td>
<td>61</td>
<td>F</td>
<td>Reopened</td>
<td>Silicone oil</td>
<td>Yes</td>
<td>Closed</td>
</tr>
<tr>
<td>12</td>
<td>78</td>
<td>M</td>
<td>Unclosed</td>
<td>Silicone oil</td>
<td>Yes</td>
<td>Closed</td>
</tr>
<tr>
<td>13</td>
<td>71</td>
<td>F</td>
<td>Reopened</td>
<td>Silicone oil</td>
<td>Yes</td>
<td>Closed</td>
</tr>
</tbody>
</table>
Of the 13 total macular hole reoperations, 10 resulted in anatomical closure (76.9%). Nine of 11 reopened macular holes achieved anatomical closure (81.8%) and 1 of the 2 unclosed holes were successfully closed after secondary surgery (50%). 11 of 13 total reoperations underwent ILM peeling, and in instances where ILM peeling was performed in primary operation, the peeling area was increased during secondary repair. Cases 1, 9, and 12 underwent epiretinal membrane dissection during reoperation, with all achieving successful hole closure.

**Table 3: Postoperative Outcomes & Visual Acuity**

<table>
<thead>
<tr>
<th>Case #</th>
<th>Recurrent Macular Hole Type</th>
<th>Macular Hole Status Postop #2</th>
<th>Visual Acuity Pre-Primary Operation</th>
<th>BCVA Post-Reoperation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Reopened</td>
<td>Closed</td>
<td>20/200</td>
<td>20/200</td>
</tr>
<tr>
<td>2</td>
<td>Reopened</td>
<td>Closed</td>
<td>CF</td>
<td>20/80</td>
</tr>
<tr>
<td>3</td>
<td>Reopened</td>
<td>Closed</td>
<td>20/60</td>
<td>20/30</td>
</tr>
<tr>
<td>4</td>
<td>Reopened</td>
<td>Closed</td>
<td>20/50</td>
<td>20/25</td>
</tr>
<tr>
<td>5</td>
<td>Reopened</td>
<td>Closed</td>
<td>20/200</td>
<td>20/40</td>
</tr>
<tr>
<td>6</td>
<td>Unclosed</td>
<td>Unclosed</td>
<td>CF</td>
<td>CF</td>
</tr>
<tr>
<td>7</td>
<td>Reopened</td>
<td>Unclosed</td>
<td>20/80</td>
<td>20/200</td>
</tr>
<tr>
<td>8</td>
<td>Reopened</td>
<td>Closed</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>Reopened</td>
<td>Closed</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>Reopened</td>
<td>Unclosed</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>11</td>
<td>Reopened</td>
<td>Closed</td>
<td>20/60</td>
<td>20/200</td>
</tr>
<tr>
<td>12</td>
<td>Unclosed</td>
<td>Closed</td>
<td>CF</td>
<td>20/200</td>
</tr>
<tr>
<td>13</td>
<td>Reopened</td>
<td>Closed</td>
<td>20/200</td>
<td>20/40</td>
</tr>
</tbody>
</table>

Table 3 presents all 13 cases of reoperation classified by recurrent macular hole type (Reopened vs. Unclosed) and corresponding visual acuity data where available (at
time of primary operation vs. best recorded visual acuity after secondary operation). 8 of the 10 cases for which visual acuity data was available presented post-secondary operation visions at either the same level as or improved from acuity measured at the time of primary surgery (80%). Measures reported as “CF” refer to a “Count Fingers” visual acuity. In instances where vision is worse than 20/400, patients are asked to count the number of fingers on a hand at distances typically between 3 and 6 feet away during examination.

In order to better understand the results of the current study within the landscape of clinical research on macular hole reoperation, a meta analysis was performed using 10 different publications found to meet a predefined set of parameters. The inclusion criteria for these papers required that patients presented full-thickness macular holes deemed to have failed primary surgical repair— either due to a failure to close the macular hole or the reopening of a previously closed macular hole. In addition, primary and secondary surgeries were required to consist of 3-port pars plana vitrectomies, with or without ILM peeling, with or without ERM peeling and tamponade of C3F8, SF6, or silicone oil.
Table 4: Meta Analysis of Macular Hole Reoperations (14-23)

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Combined</th>
<th>Unclosed</th>
<th>Reopened</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Success</td>
<td>Total</td>
<td>Success</td>
</tr>
<tr>
<td>Heisek</td>
<td>2013</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Smiddy</td>
<td>1996</td>
<td>41</td>
<td>48</td>
<td>Unknown</td>
</tr>
<tr>
<td>D’Souza</td>
<td>2011</td>
<td>14</td>
<td>30</td>
<td>11</td>
</tr>
<tr>
<td>Hillenkamp</td>
<td>2007</td>
<td>19</td>
<td>28</td>
<td>19</td>
</tr>
<tr>
<td>Valdeperas</td>
<td>2008</td>
<td>60</td>
<td>72</td>
<td>39</td>
</tr>
<tr>
<td>Ezra</td>
<td>1997</td>
<td>37</td>
<td>46</td>
<td>37</td>
</tr>
<tr>
<td>Ile</td>
<td>1993</td>
<td>12</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>Christmas</td>
<td>1998</td>
<td>10</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Paques</td>
<td>2000</td>
<td>8</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Smiddy</td>
<td>1993</td>
<td>11</td>
<td>15</td>
<td>unknown</td>
</tr>
</tbody>
</table>

The cumulative results of this meta analysis found the successful secondary surgery rate among all 10 case series to be 79% (218 of 276 total reoperations). The success rate of secondary operations for macular holes unclosed after primary operation was 75% (122 of 162 “unclosed” reoperations). The success rate of secondary operations for macular holes which reopened after initially achieving a postoperative anatomical closure was found to be 91% (42 of 46 total “reopened” reoperations). It should be noted that a much larger sample size underwent reoperation with macular holes unclosed after primary surgery as compared to the “reopened” group (162 vs. 46 total cases).
DISCUSSION

The data presented in the current retrospective case series falls in line with much of the current scientific literature on recurrent macular hole surgery. Although the success rate of primary macular hole operation across all surgeries is widely accepted as quite high (90%) (8), recurrence of holes by reopening or persistence still remains a complication in clinical intervention and management of this ocular condition worthy of investigation. The combined success rate of reoperation, between both reopened and unclosed recurrent macular hole groups, was found to be 76.9% in the current series as compared to 79% in meta analysis. While a majority of surgeries for recurrent macular holes in the meta analysis were found to be performed in unclosed cases, only two such cases were represented in the current series, with successful closure achieved in one of the reoperations (50%). In the single case (#6) representing a recurrent macular unclosed after both primary and secondary surgeries, a significantly lengthy duration of 5 months passed between the time of in-clinic macular hole diagnosis and date of primary operation. This delay in initial operation could undoubtedly have played a role in the inability to achieve surgical macular hole closure in either repair procedure. As a whole, the combined outcome measure results of the current series provide evidence to confirm the benefit of secondary surgery in treatment of recurrent macular hole. While more cases of unclosed persistent holes will need to be compiled before any cross-group conclusions can be drawn, a high percentage of reoperations achieved successful macular hole closure, the majority of which were accompanied by the maintenance of pre-surgery visual acuity levels, or improvements from baseline.
In compiling the selected publications for meta analysis, each presents valuable information relating to various surgical considerations important to the treatment of macular holes. Notably, the previously discussed Liverpool Hospital case series by Valldeperas and Wong (14) found patients with full thickness macular holes unclosed after primary surgery to have lower reoperation closure rates, and poorer overall postoperative visual acuity outcomes, as compared to reopened holes. While the Valldeperas series achieved closure of macular holes in 100% (21 of 21) of reopened cases, it should be noted that the use of autologous platelet concentrate as adjuvant in surgery without a corresponding control group makes it difficult to extrapolate a definitive conclusion behind the observed results. Moreover, the case series presented a total of 72 patients that underwent secondary surgery for macular hole repair, of which a large majority consisted of unclosed macular holes as compared to reopened cases (51 of 72, 70% of total reoperations). Coupled with the fact that several surgeons performed repair operations over the given study period, this elevated rate of anatomically unclosed macular holes following primary surgery should be paid heed to and considered before drawing any conclusions across the two experimental groups.

By general consensus, rates for secondary surgeries in reopened holes were indeed found to be higher than those for unclosed cases in cumulative meta analysis of published literature (91% closure of reopened holes vs. 75% closure of unclosed hopes), though there exists disparity in the number of represented cases per group. However, there is undoubtedly a need within the medical community to produce larger-scale case
series data comparing surgical outcomes between the two types of recurrent macular hole groups before success rates can be considered definitive.

In Ezra et al.’s 1997 series (19), eyes that had previously undergone macular hole surgery and remained unclosed were retreated with secondary surgery and C3F8 gas tamponade. Anatomical closure was achieved in 80% of the previously unclosed cases, over half of which underwent rigorous epiretinal membrane dissection (membranectomy) as part of reoperation. By comparison, one case in the current series (#12) presented an unclosed macular hole that underwent secondary surgery with dissection of a notably thick epiretinal membrane, and did successfully achieve anatomical closure.

D’Souza et al. (18) presented the largest case series on macular hole reoperation within a patient population whose ILM was routinely peeled in primary surgical procedures (18). While an 88% success rate was observed in primary operation, reoperation rendered decreased anatomical closure rates of 46.7% among a large majority of macular holes unclosed after primary surgery. The paper hypothesized that reoperation is less likely to succeed once ILMs have been peeled, and found that secondary surgeries with enlargement of ILM peeling areas, in both reopened (4 total) and unclosed groups (21 total), were not associated with significantly better outcome measures. In the 11 secondary operations of the current series for which ILM peeling was performed, 7 cases underwent ILM peel in primary operation and had the peeling area enlarged in reoperation, and 4 cases underwent ILM peel for the first time. Successful closure was achieved in 8 of 11 cases (72.5%). Worth noting in the De Souza et al.’s study design was that retrospective data collection was carried out using medical records belonging to three
different surgeons. In analyzing an operation which critically relies on the most delicate of intraocular manipulations, variables associated with a particular’s surgeon’s technique and dexterity can have a potentially confounding effect in regards to the variable of ILM peeling when unaccounted for across a sample. Hejsek et al (16) presented a series of 6 cases in which primary PPV procedures were supplemented by ILM peeling in an area of 2-3 disc diameters. All cases were unclosed after first surgery, and underwent a second operation with enlargement of ILM peeling area, and a special surgical technique to loosen the edges of macular holes manually by silicone brush. In the limited sample size of cases presented, 100% anatomical closure was observed following reoperation. This unusually high closure rate was attributed by the authors to be a result of the manual loosening of the elevated rigid macular hole edges, and the potential utility of this surgical technique could undoubtedly be explored in greater detail across larger sample sizes.

A limitation of current investigatory studies on macular hole retreatment is the retrospective nature of medical records, spanning across time periods with varying degrees of technological availability to vitreoretinal specialists in clinic. Factors such as macular hole diameter and the presence or absence of subretinal fluid cuffs at the base of macular holes are now readily measurable through OCT analysis, and could certainly prove valuable as electronic databases grow in hospitals across all institutions. In order to make definitive progress in improving success rate for patients with recurrent macular holes, there is a need for greater collaborative efforts between the medical community at large. As in all realms of medical intervention and management, there exists a degree of
useful debate and discussion between clinicians over current treatment modalities and any potential improvements to technique. In the specific context of recurrent macular hole surgery, questions regarding surgical considerations such as ILM peeling and postoperative head-positioning requirements following intraocular gas tamponade are areas that could benefit from collaboration to produce standardized practice patterns. More generally, future research in the area of macular holes should undoubtedly continue the multiple decades-long effort to find some type of root behind this otherwise “idiopathic” development of disease. Perhaps attempts to explore potential associative causes of macular hole could venture into previously uncharted waters, bridging laboratory sciences and clinical research to produce novel, unique, and outside-the-box investigatory study designs. In the process of drafting the current cases series, one such idea emerged as a possible next step in continuing research on macular holes. Considering an idiopathic macular hole occurrence rate among women found to be as high as a 72% majority in one case-control study, with over 50% of cases occurring in individuals 65 years of age and older, there could be otherwise unexplored factors such as physiological gender-specific aging patterns among women as compared to men. Could the presence of estrogen and progesterone receptors in the retina predispose postmenopausal women to macular hole development? Could the gradual decreases in hormone levels result in atrophy of cells and breakdown of adhesion at the fovea? Could the application of hormonal treatment in early macular holes result in cellular regeneration and prevention of vitreofoveal separation? There is much room for future work within the landscape of ophthalmologic research, and the current case series seeks
to offer outcome data from a single-center, single-surgeon set of recurrent macular hole operations to be put in context both historically, with background origins of disease diagnosis and treatment, and comparatively, by meta analysis across the relevant publications of the present day clinical research realm.
REFERENCES


CURRICULUM VITAE

ARYA SHARIFZADEH

1991

246 Grove Street

Westwood, MA 02090

Education

- Boston University School of Medicine: September 2013 – Current
  Division of Graduate Medical Sciences, Master of Science, Medical Sciences

- Boston University: September 2009 – May 2013
  College of Arts and Sciences, Bachelor of Arts in Psychology, Pre-Medicine

  Activities and Societies: Global Brigades, Persian Student’s Association, BU Public Health Brigades (Secretary 2012, Vice President 2013), Iranian American Medical Association (IAMA), University Dean’s List (2010, 2011, 2012)


  Activities and Societies: National Honors Society, Class Officer (Vice President), WHS Student Council (President), WHS Student Representative to MA Board of Education, Varsity Tennis (Captain), Mock Trials (Officer), National Latin Exam Gold Medalist (2006, 2007, 2008), Excellence in Latin Studies (2009)

Experience

- Massachusetts General Hospital Vaccine and Immunotherapy Center: 2014 – Current

  Graduate researcher role as a member of the Poznansky Laboratory research team, with project work assessing the novel isoform-specific roles of CXCL12 chemokine in tumor metastasis and growth in both ovarian cancer and mesothelioma models.
Beth Israel and Deaconess Medical Center: 2014 – Current

Clinical researcher working on projects exploring the various surgical outcomes and considerations in recurrent macular hole repair operations. Duties also include working independently during full clinical hours performing visual acuity and eye exam work-ups on patients, optical coherence tomography scans, dilating and anesthetizing patient’s eyes before examinations, and assisting surgeons during intravitreal injections. Additional experience in performing patient examinations using indirect ophthalmoscopy and laser photocoagulation procedure observation.


Began work on a research project studying antimicrobial effects of an Aqueous O-Zone solution in surface sanitation and overall antibiotic efficacy. General experiences included plate-preparation, bacterial swabs, incubation, treatment-measures, data analysis, and adherence to sanitary laboratory practices.

Global Brigades of Boston University: September 2010 – May 2013

Served as Vice President of university’s public health service organization chapter, organizing student-led missions abroad to implement sustainable holistic health projects in underdeveloped countries, alongside Medical and Dental brigades. Partook in two such missions as an undergraduate chapter leader:

- *El Cantón*, Honduras – January 2012 – 7-day mission, focus on oral health & sanitation in a mountainous community of sustenance coffee farmers in rural Honduras. Provided free community-wide public health clinics, working in collaboration with Honduran government & military

- *Embera Puru* Tribe, Panama – January 2013 - First ever student-led Public Health Brigade to Panama. Worked with an indigenous tribe of along the Colombian border Volunteer work and health-practice education clinics aimed at stopping preventable illness among region’s inhabitants & were supplemented by the distribution of free healthcare materials U.S.

Fulbright Summer Institute Student Ambassador: May – August 2010

Worked as the lead student ambassador for a summer-long European-exchange program, operating on a grant from the Fulbright Scholar commission, responsible for organizing an intensive summer term of classes and community service. Experience included presenting at U.S. State Department in Washington, D.C. on the benefits of student-led foreign exchange for the international community.
- **Iranian American Medical Association (IAMA) 2011 – Current**
  
  Organization of physicians and health science students hosting monthly symposiums on topics in relevant fields. Members participate in lectures, discussions, debates, and mentoring.

- **Caritas Norwood Hospital Volunteer 2007 - 2009**
  
  Volunteer work at a local hospital, working with patients pre- and post-surgery in preparation, recoveries, and discharge. Direct patient interaction, including monitoring and transport. Worked alongside the hospital’s Day Surgery and Recovery team.

**Skills**

- **Laboratory research protocols**
  
  Diverse experience in a wide range of experiments: PCR amplification, DNA ligation, bacterial transformations, tissue culture harvest, lentiviral transfection, Western Blot assays, data collection, laboratory reports, and literature reviews.

- **Multimedia editing, web page design, statistical analysis**
  
  Currently serving as operating Web Administrator for AdvancingCures.org. Experiences include site design on WordPress platform, and managing a blog. Operational skills in Microsoft Excel, PowerPoint, IBM SPSS, FinalCut Pro.

- **Linguistics**
  
  Native fluency in English and Persian. High-level of conversant fluency in Spanish, regularly used clinically for direct patient care without interpreters.