Macular Hole and Macular Pucker Surgery with Special Emphasis on Reoperations*

V.A.4.

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Outline

References

Keywords

Vitreous • Anomalous PVD • Vitreoschisis • Inner limiting membrane • Premacular membrane (PMM, previously ERM) • Macular hole • Macular pucker • Vitrectomy • Treatment failure • Disease recurrence • Re-Operation • Chromodissection • Inner retinal optic neuropathy

Key Concepts

1. Vitrectomy with membrane peeling for macular pucker and chromodissection for macular holes is a highly successful operation. Failures are typically due to persistent membranes related to vitreoschisis or recurrent membranes.
2. Reoperation is typically performed using inner limiting membrane peeling, typically with chromodissection and usually with good success. Rare cases of poor postoperative vision, either in primary procedures or more commonly in reoperations, are due to dissection that is too deep, injuring the retinal nerve fiber layer inducing a secondary optic neuropathy referred to as IRON (inner retinal optic neuropathy).
3. Reoperations performed later than 6 months following the initial procedure have a lower likelihood of retinal nerve fiber layer injury and IRON with a higher likelihood of good vision, probably due to an adequate enough time between the two operations for Müller cells to organize their fibrillar processes allowing the reformation of a protective tissue layer over the denuded retinal nerve fiber layer.

* The original material in this chapter was accepted for publication by Investigative Ophthalmology and Visual Science on September 8, 2014.

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I. Introduction

Recent advances in the techniques of vitrectomy with membrane peeling [See chapter V.A.2. Vitreo-maculopathy surgery], at times with chromodissection [See chapter V.A.3. Chromodissection in vitreo-retinal surgery], have greatly improved patient outcomes. There are, however, risks associated with these procedures, and on rare occasions there can be much worse vision following surgery than preoperatively. This chapter will review the current concepts of pathogenesis and surgical management of macular holes and macular pucker. Special emphasis will be placed on failed cases and reoperations.

II. Macular Hole

A. Pathogenesis of Macular Hole

There are differing theories on the mechanism of macular hole formation, though central to all of them is the idea that tractional forces by vitreous induce structural defects in the macula. Anteroposterior traction can be exerted by a firmly attached posterior vitreous cortex (PVC) [1–3], and tangential traction can be induced by a premacular membrane (PMM) [4] that consists of the PVC plus cells and additional collagen synthesized by some of these cells. Under normal conditions, the central cone of Müller cells provides structural support and binds together foveal photoreceptor cells in the fovea centralis [5]. Tractional forces exerted by the PVC can dislodge the Müller cell cone from its photoreceptor attachments [1–3]. The formation of a foveal cyst progresses to a weakening of the roof of the cystic cavity and eventually to complete dehiscence [1]. The underlying neurosensory retina, now without Müller cell support, undergoes centrifugal expansion to form a full-thickness hole [5, 6]. There is elevation of the edges at times and almost always the appearance of pericentral cystoid spaces on optical coherence tomography (OCT) imaging [7, 8], previously believed to be retinal detachment. Macular holes are also no longer considered idiopathic as they are known to be caused by vitreous [9, 10], at times associated with high myopia, status post trauma (usually blunt force), or other retinal pathologies (tears, detachments), and rarely iatrogenic after posterior segment surgery [11] [See chapter III.C. Pathology of vitreo-maculopathies]. A new classification system of vitreo-macular traction and macular holes reflects the important role of vitreous [See chapter III.D. Vitreo-macular adhesion/traction and macular holes (Pseudo, Lamellar & Full-Thickness Holes)].

B. Therapy of Macular Hole

Until the 1990s, the only macular holes that were usually treated were those with retinal detachments. Meyer-Schwickerath, in 1961, utilized a combination of scleral buckling, laser photocoagulation, and subretinal fluid drainage to flatten a macular hole retinal detachment [12]. Two decades later success was also attained without scleral buckling [13]. Early on, laser photocoagulation was attempted to treat macular holes even without retinal detachment [14–16], but this approach was never widely adopted and was subsequently abandoned when vitrectomy surgery proved to be the treatment of choice.

1. Macular Hole Surgery

In 1991 Neil Kelly and Rob Wendel published their initial experience with vitrectomy for macular hole closure [17], introducing for the first time a definitive treatment for a disease previously believed to be incurable [18]. Starting from an initial published cure rate of 58 %, the team was able to improve their success rates to 73 % after 2 years of practice [17, 19]. The initial procedure consisted of a pars plana vitrectomy with peeling of the PVC and any visible PMM to release vitreous traction that was thought to cause the macular hole. This was followed by a long-acting intraocular tamponade with prone positioning under the assumption that fluid was the cause and that this would keep the hole free of fluid, but also to allow apposition of the separated edges and provide structural bridging for fibrocellular proliferation [17, 19].

A number of randomized controlled trials have studied the natural history at different stages of macular holes. The primary aim of these studies was to determine whether observation alone would result in better outcomes compared to surgical management. The Vitrectomy for Prevention of Macular Hole (VPMH) study group looked at stage 1 macular holes and found that the benefit from a vitrectomy would likely be minimal as most do not progress to full-thickness holes. Indeed, many stage 1 holes self-resolve, particularly if smaller than 250 μm, thus making the case for conservative management [20]. The Moorfields Macular Hole Study (MMHS) studied stage 2, 3, and 4 holes and found an overall closure rate of 80.6 % in the surgical group versus 11.5 % in the observation alone group at 24 months follow-up. Additionally, eyes that underwent surgery had improved final Snellen visual acuity (6/36 to 6/18) compared to the group with observation alone, which had visual deterioration (6/36 to 6/60) [21]. The Vitrectomy for Treatment of Macular Hole Study (VMHS) investigated stage 3 and 4 holes and found a closure rate of 69 % in the surgical group versus 4 % in the observation alone group at 6 months. The final visual acuity from the surgical group was also statistically better than the observation alone group (20/115 versus 20/166 on an ETDRS chart, respectively) [22]. Thus, both the MMHS and VMHS studies showed clear benefit from surgical management of stage 3 and 4 holes [21, 22]. Furthermore, since the first published studies by Kelly and Wendel, vitreoretinal specialists have continued to refine the surgical technique resulting in closure rates that have continually increased over the years.

a. Benefits and Risks of ILM Chromodissection

Inner limiting membrane (ILM) peeling was introduced and hypothesized to assist in macular hole closure by ensuring complete removal of residual posterior vitreous cortex and subclinical PMMs [23]. Vitreoschisis, a common event that occurs in diabetic eyes, but also in at least half of eyes with macular holes and macular pucker [10, 24], may give the appearance of vitreous separation while tractional forces actually persist [10, 24–26]. The removal of a potential scaffold for contractile tissue to redevelop upon and once again exert tangential traction, as well as the microtrauma induced by an ILM peel which is thought to enhance the localized fibrocellular proliferation needed for glial repair [27–29], is believed to prevent future macular hole reopening [30, 31]. Furthermore, the development of cystoid macular edema has been associated with the reopening of a macular hole, and the removal of the ILM can be prophylactic against edema formation [32, 33]. Finally, studies have shown that the duration of facedown positioning can be reduced or even eliminated in cases where an ILM peel is performed, an important consideration in patients who may have difficulty complying with a prone positioning regimen [34–37].

Mester and Kuln performed a meta-analysis of 1,654 macular holes and found that ILM peeling resulted in primary hole closure rates of 96 % versus 77 % in eyes without peeling [38]. Tognetto et al, in a multicenter retrospective study of 1,627 macular holes, found a 94 % primary closure rate in eyes undergoing an ILM peel, versus 89 % without peeling [39]. Kumagai et al. studied 877 eyes with macular hole and found a 0.39 % recurrence rate of holes after ILM peeling compared to a 7.2 % recurrence rate without peeling [40]. More recently, a number of randomized clinical trials have looked at the effects of ILM peeling on primary closure and subsequent reopening of the hole. A multicenter randomized clinical trial by Lois et al. (the FILMS group) looked at 141 eyes with stage 2 or 3 idiopathic full-thickness macular holes. The group found a significantly higher rate of primary hole closure in the ILM-peel group at 1 month follow-up (84 % vs. 48 %) and also fewer reoperations necessary at 6 months (12 % vs. 48 %) [41]. Two smaller such trials in China (49 patients) and Denmark (75 patients) found similar anatomic benefits from ILM peeling [35, 42].

While there are clear benefits to anatomical outcome in terms of improved primary closure and reduced chances for reopening, the effects on functional outcome are less well established. In a number of studies, an improvement in postoperative visual acuity has been described [38, 43–45], while in other studies, results were not statistically significant [39, 46–48]. It should be noted, however, that ILM peeling itself is a risky procedure which can result in complications such as the formation of micro-hemorrhages, defects in the retinal pigment epithelium, damage to the neurosensory retina resulting in scotomata, phototoxicity from prolonged surgical manipulation, and possible toxic effects from dyes used to assist in the procedure [49, 50], known as chromodissection [51] [See chapter V.A.3. Chromodissection in vitreoretinal surgery]. Furthermore, it has been suggested that multiple unsuccessful attempts at ILM peeling often lead to a poor functional outcome despite successful anatomic closure [52].

Because of the ILM's close proximity to the underlying neurosensory retina, inadvertent injury to the retinal nerve fiber layer (RNFL) is not uncommon [49, 52, 53]. To standardize the procedure and reduce possible trauma resulting from membrane peeling, vitals dyes have been introduced to stain the ILM for better visibility. Indocyanine green (ICG) is the most commonly utilized vital dye for chromodissection of the ILM and has been shown to decrease the amount of time it takes to remove the membrane, as well as increase the ability to perform a thorough peel. However, the use of ICG is controversial as some studies have suggested potential side effects including worsening of the functional outcome despite enhanced rates of successful anatomic closure [54, 55]. The inconsistency of literature regarding the outcomes of ICG-assisted peels is likely related to the broad range of dye concentrations and durations of application used by different surgeons [56]. Though the exact dose and duration is surgeon-specific, it is agreed that the lowest concentration for the least amount of exposure time is ideal [57].

C. Primary Failure Versus Macular Hole Reopening

One of the complications associated with macular hole surgery is primary surgical failure, an event that has decreased in frequency with the progressive refinement of surgical techniques. The only preoperative factor that has been definitively shown to be predictive of primary failure is the size of the hole, where there is an inverse relationship between size and closure rates [21]. Rarely does surgery cure macular holes greater than 400 μm in diameter. Disease chronicity may also have an impact on closure success, with primary holes of <6 months' duration being easier to successfully treat [21]. Evidence for the importance of chronicity is not strong, however, as the duration of symptoms is a notoriously subjective measure. Furthermore, based on the aforementioned MMHS and VMHS studies, it is apparent that surgery is far superior to conservative management for stages 2–4 holes. Thus, in these cases, delaying intervention may result in a poorer prognosis [21, 22].

Failure to surgically close macular holes primarily is believed to be due an inability to form a stable glial plug. The reason for this may be due to incomplete peeling of

the PVC, the presence of a subclinical PMM resulting in residual traction at the hole, or inadequate gliosis [58, 59]. Schumann et al. studied the ILM and associated PMM removed after a second operation in 16 eyes with macular holes that had failed primary surgery. Ultrastructural analysis revealed a significant amount of fibrocellular proliferation on the vitreous side of the ILM in all specimens, supporting the hypothesis that residual ILM and remnant vitreous cortex may stimulate postoperative traction and surgical failure [60].

The reopening of a macular hole is another potential complication that most often occurs within months of initial successful closure, but can even present years later [43, 58, 61–64]. Just as a PMM can cause immediate surgical failure, its presence and progression has been correlated with a significant portion of recurrent macular holes. Similar to a primary macular hole with traction from the PVC, a PMM is thought to exert tangential traction and cause foveal dehiscence [58, 59]. Cystoid macular edema is also a significant factor associated with as much as a 7-fold increase in the risk of reopening of a previously closed macular hole [33]. The development of cystoid macular edema and the associated inflammatory fibrinolysis has also been proposed as a causative agent for hole reopening [33, 61]. Finally, Kumagai et al. proposed that surgeries complicated by intraoperative retinal tears and also eyes with high degrees of myopia both may be risk factors for macular hole reopening [40, 65].

A complication associated with pars plana vitrectomy is the development and/or progression of cataracts, occurring in up to 76 % of cases at 2 years post vitrectomy [66–70]. Although cataracts themselves are not a serious problem, the subsequent removal of cataracts after macular hole surgery has been associated with hole reopening, usually within 6 months of cataract extraction [33, 61, 63]. The hypothesis for this relates both the risk of developing cystoid macular edema and the risk of PMM formation after cataract surgery due to the same underlying cause – postoperative inflammatory mediators that break down the blood-retinal barrier. To avoid these complications, some retinal surgeons have elected to proceed with a combined macular hole surgery with phacoemulsification. These combined surgeries have been shown to be effective and safe without increased risks of adverse events [71–73]. Another factor that has been implicated in the reformation of macular holes is Nd:YAG laser capsulotomy for treatment of posterior capsular opacification. The mechanism of action is thought to be related to perifoveal vitreous contraction associated with the laser pulse [74], but is more likely due to biochemical changes in the vitreous following capsulotomy after cataract surgery [75, 76]. Indeed, YAG capsulotomy has been shown to be associated with nearly a doubling in the incidence of PVD [77], due most likely to the same biochemical changes [78] [See chapters II.C. Vitreous aging and PVD; III.B. Anomalous PVD and Vitreoschisis].

III. Macular Pucker

A. Pathogenesis of Macular Pucker

Premacular membranes are avascular, fibrocellular membranes that develop anterior to the ILM [79, 80]. The literature refers to these membranes as “epiretinal”; however, this term is inappropriate because “epi” refers to a location next to or beside the retina. Thus, the term “epiretinal” could refer to a subretinal as well as preretinal location. In macular pucker, the pathologic membrane location is in front of the retina; thus, the prefix “pre” is more accurate than “epi.” Furthermore, since this membrane forms primarily in front of the macula, or at least is only relevant to vision in front of the macula, the term “premacular membrane” is a more precise term than “epiretinal membrane.” The former term will be used here and elsewhere.

Histopathological studies have shown a number of different cell types to be associated with PMMs depending on the etiology, including glial cells, retinal pigment epithelial cells, myofibroblasts, and macrophages [81–84]. When the proliferation occurs in the region of the macula, it can cause tangential traction and wrinkling of the underlying neurosensory retina, resulting in macular pucker and visual distortion [85–88]. The development of PMM can be primary, i.e., the result of anomalous PVD with vitreoschisis, or secondary, i.e., associated with a number of retinal diseases including retinal breaks, retinal detachment, retinal vascular diseases, diabetic retinopathy, inflammatory conditions, and others [89]. Anomalous PVD with vitreoschisis may indeed be an important mechanism in many of these conditions [See chapter III.B. Anomalous PVD and vitreoschisis].

In the setting of anomalous PVD, vitreoschisis produces a split between the anterior and posterior portions of the PVC, leaving the outermost (posterior) layer attached to the macula [9, 25]. If the vitreoschisis split occurs anterior to the level of hyalocytes (approximately 50–75 μm anterior to the ILM), the hyalocytes embedded in the outer layer can elicit monocyte migration from the circulation and/or undergo transdifferentiation into myofibroblasts as well as secrete collagen, a key component of PMM [90] [See chapter III.J. Cell Proliferation at vitreo-retinal interface in PVR and related disorders]. Based on the anomalous PVD theory proposed by Sebag, if vitreoschisis occurs at a level resulting in hyalocytes that remain attached to the macula, then there is considerable risk of contractile PMM formation and the development of macular pucker [9, 25] [See chapter III.F. Vitreous in the pathobiology of macular pucker].

B. Macular Pucker Surgery

The standard cure for macular pucker is surgical removal of the offending PMM, thus releasing the tangential traction, resulting in resolution of metamorphopsia in most cases

and, less frequently, visual acuity improvement. Prognostic factors associated with a better postoperative visual acuity include a better preoperative visual acuity, better preoperative photoreceptor integrity documented on OCT, and a shorter duration of symptoms [91–93]. Indeed, a number of studies have shown that earlier surgery results in better results postoperatively, perhaps due to a reduced duration of neurosensory disruption [94–96]. Studies employing coronal plane *en face* OCT/SLO imaging identified that there can be as many as 4 centers of retinal contraction in an eye with macular pucker [10, 97]. Cases with 3 or 4 centers had a higher incidence of retinal cysts and more macular thickening than cases with 1 or 2 centers of retinal contraction. Thus, it may be that eyes with more than 2 centers of retinal contraction should undergo surgery sooner.

Surgery involves vitrectomy followed by peeling of the PMM with or without the additional peeling of the ILM. Several studies have shown that PMM removal will concurrently result in unintentional ILM removal. However, the rates of inadvertent ILM stripping vary widely between studies, ranging from 27 to 77 % depending on surgical technique and use of chromodissection [98–102]. Ducournau and Ducournau found that cleavage planes between the ILM and the underlying retina could be easily induced in primary (post-anomalous PVD with vitreoschisis) PMMs, but that the ILM was more difficult to peel in secondary cases of PMM [103]. Thus, in cases of secondary PMM, more aggressive dissection may be required if the intention is to remove the ILM in addition to the PMM. There is some controversy in the literature, however, regarding postoperative visual acuity after ILM peeling in macular pucker surgery. Early papers described poor functional outcomes associated with ILM peeling [84, 104]; however, a considerable body of evidence has since been published that shows no adverse effects from ILM removal in PMM surgery, and indeed a number of studies demonstrate improved visual acuity with ILM removal [101, 105–108]. It is unclear why there is such a discrepancy between early reports and more recent literature on postoperative functional outcomes related to ILM removal, but it is at least partly due to improved surgical techniques, instrumentation, and development of vital dyes that can assist in tissue visualization [See chapter V.A.3. Chromodissection in vitreo-retinal surgery].

C. Primary Failure Versus Macular Pucker Recurrence

Immediate postsurgical failure to resolve metamorphopsia or improve visual acuity after macular pucker surgery is thought to relate to incomplete removal of the PMM, whereas delayed recurrence of symptoms is thought to be due to true disease recurrence. Incomplete removal is most likely due to the lamellar anatomy of the PVC [See chapter II.E. Vitreo-retinal interface and ILM], which can split during surgery to peel the PMM and relieve the pucker, essentially *intraoperative vitreoschisis*. In this case, membranes are often transparent or semi-transparent [31, 109, 110]. If the PMM forms directly on the ILM and is tightly apposed to it, then it is more likely for both to be peeled together in a single dissection. However, if vitreoschisis occurs, surgical dissection may remove the PMM and inner (anterior) portions of the PVC, while sparing the ILM and residual cortical vitreous and cells. This is even more likely in the setting of an incomplete ILM peel [9, 25, 111]. Fortunately, this issue is currently not as common owing to the use vitals dyes during chromodissection [31, 102, 107, 112]. Furthermore, intraoperative OCT will likely be very useful in mitigating these circumstances [113, 114].

True recurrence, which in our experience only occurs about 10 % of the time, can develop after complete removal of the PMM as a result of cell (primarily glial) migration via breaks in the ILM that were induced during membrane peel surgery and subsequent proliferation of these cells on the anterior surface of the macula [102, 115]. In this regard, the issue of ILM peeling is important because the ILM can serve as a scaffold for the proliferation of another PMM. When the PMM is removed without attempts to further dissect the ILM, rates of recurrence have been reported to be as high as 56 % [101, 106, 115], although it is not known whether these studies distinguished between persistent and recurrent disease, as described above. However, when combined PMM and ILM removal is pursued, recurrence is observed to be less than 9 % [101, 106, 115], more consistent with our experience. The higher incidence of recurrence when PMM removal is performed in isolation may be due to a number of factors. One big risk is that residual ILM provides a scaffold for the re-proliferation of a PMM [100]. Haritoglou et al. found that there was a layer of collagen between the ILM and PMM which helps explain the high rate of PMM recurrence when ILM peeling is not undertaken [116]. Other studies found that recurrent PMMs had a higher frequency of myofibroblasts, supporting the theory that re-proliferation is an important mechanism for pucker recurrence [117]. Gandorfer et al. showed that residual ILM left on the macula contained cells that expressed alpha-smooth muscle actin and were capable of exerting continued tangential traction [100]. Park et al. showed that reformation of an PMM occurs directly on residual ILM [106]. Thus, by completely removing the ILM, one can eliminate a number of potential sources for treatment failure and/or disease recurrence. Complete ILM removal, however, places the patient at risk for inner retinal optic neuropathy (IRON; see below).

Shimada et al. [107] studied the effects of different types of staining and peeling patterns and its effect on PMM and ILM removal. They found that peeling without staining resulted in a high percentage (78 %) of residual ILM due to an unclear PMM-ILM border. They noted that without chromodissection, not only was it difficult to remove the PMM completely, but the ILM was left intact in the majority of

cases. When staining with Brilliant Blue G dye, they noted that a single episode of staining with a single episode of peeling resulted in reduced rates of residual ILM (39 %). Furthermore, they noted that restaining the peeled zone with a second course of Brilliant Blue G dye and re-peeling to ensure thorough removal of residual ILM helped to further reduce recurrence rates of PMM. Beyond studying the effects of staining, the group also demonstrated that grade 3 PMM cases had a much higher rate of total ILM remaining after a single peel attempt, indicating that the thicker the PMM, the more aggressive the initial peel may need to be [107] [See chapter V.A.3. Chromodissection in vitreoretinal surgery].

The ILM is a multi-laminar structure [See chapter II.E. Vitreo-retinal interface and ILM]. Removal of the innermost layer(s) during ILM peeling is effective because it assures removal of all vitreous and pathologic cellular membranes attached to the anterior surface of the ILM. ILM peeling is safe because the posterior layers, which are adjacent to the RNFL and firmly adherent to the inner segment of Müller cells, are likely left undisturbed. In cases where there is no split in the ILM and full-thickness ILM peeling is performed, there is damage to the inner retina, at times severely affecting vision. This is especially true during reoperations when much of the inner ILM was removed at the first procedure.

IV. Retreatment of Persistent/Recurrent Disease

A. Retreatment Strategies

1. Macular Hole Reoperations

The approach to re-treating a macular hole largely depends on what was already performed during the primary surgery. If clinically apparent cystoid macular edema exists, then its resolution should be sought nonsurgically. If a PMM was missed during the initial procedure or formed postoperatively, then it should be removed. If an ILM peel was not performed initially, then ILM peel should be performed during reoperation to ensure that all traction is released and no future PMMs develop [31, 39, 114, 118]. However, the vast majority of failed surgeries and reopened macular holes do not have any obvious features that can be resolved with revised surgery [61]. To address this, different techniques have been described with varying degrees of success. Some surgeons have restained the macula to ensure that the ILM was adequately removed and subsequently pursue a further expansion of the original dissection [119]. Studies have also looked at the efficacy of an increased duration of tamponade using gases and oils. Heavy silicone oils, in particular, have gained popularity as an internal tamponade agent that can be used in noncompliant macular hole patients as it does not require patient positioning [120, 121].

Methods have also been described that attempt to enhance glial proliferation, which is thought to help bridge the hole and promote healing [27–29]. These include the use of adjuvants such as autologous platelets [122], autologous serum [123], transforming growth factor beta [124], as well as disruption of the underlying retinal pigment epithelium via photocoagulation [125]. These techniques, however, have not been studied in-depth and lack sufficient clinical evidence to be routinely recommended. There are also sporadic reports of spontaneous closure of macular holes (both primary and recurrent) that have been described in literature, though the incidence is very low [11, 126–131] and usually limited to small holes. These events are thought to be related to the self-resolution of an underlying inciting factor: resorption of cystoid macular edema [131], relief of vitreous traction [129], or the growth of a therapeutic PMM in a direction that relieves tension [124, 127, 128]. However, unless the macular hole is small (<250 μm), the chance for spontaneous resolution is low [20].

One prominent hypothesis of why macular holes close after surgery is that fibrocellular proliferation occurs, bridging the two separated retinal edges [27–29]. Indeed, there are scattered case reports of macular holes spontaneously closing, with the only evidence being the presence of a PMM that formed over the hole. However, the presence of a PMM has, more often than not, been the culprit underlying the formation or reformation of macular holes [28–31, 132–135], owing to its influence on cell organization into a therapeutic membrane. Indeed, histopathological analyses of PMMs associated with reformed macular holes have shown haphazard proliferation of fibrous astrocytes and Müller cells [60].

Hillenkamp et al. found that after a failed primary closure, a repeat surgery would be more likely to close if the hole had a cuff of elevation (claimed to be due to subretinal fluid) on OCT. The rationale is that the closure of a macular hole requires the displaced retinal tissue to reoccupy the fovea, and thus having a separation of the retinal tissue off of the underlying retinal pigment epithelium may facilitate the centripetal transition [136]. Interestingly, the hole size prior to repeat surgery was found not to be associated with either functional or anatomic success, unlike in cases of primary macular hole surgery.

2. Macular Pucker Reoperations

Much like reoperations for macular holes, retreatment for persistent/recurrent macular pucker depends largely on what was already performed during the first surgery. If the most likely cause for the persistence/recurrence of symptoms (reduced visual acuity, metamorphopsia) is incomplete removal of the PMM, then enhancement of PMM visualization can be performed with a number of staining methods during chromodissection, including ICG, trypan blue, triamcinolone acetonide, and Brilliant Blue G [98, 102, 103, 111]. If the ILM was not peeled initially, or if there was possibly inadequate ILM peeling, then staining for improved

visualization can be performed and further ILM removal attempted [98, 102, 103, 108, 111]. Finally, in cases where both adequate PMM and ILM peeling have been performed in the region of the macula, it has been suggested that further ILM removal toward the edges of the vascular arcades may be an option [106].

B. Inner Retinal Optic Neuropathy (IRON)

Abrupt optic neuropathy following any type of eye surgery is a well-known phenomenon that is often due to anterior ischemic optic neuropathy (AION) [137, 138]. In this setting, the patient usually describes the sudden onset of a scotoma that occurs hours, days or even weeks after cataract surgery. The ophthalmologist will note significant loss of visual acuity, an afferent pupillary defect (APD), and a visual field defect that is often altitudinal. The optic disc often appears hyperemic and edematous and then progresses, in about 2 months, to optic atrophy.

In contradistinction, inner retinal optic neuropathy (IRON) seems to occur specifically after vitrectomy with membrane peeling. As described, the patient notes a dark patch in the center of their vision hours or days after surgery. And, as in AION, there is an APD. However, unlike in AION, the visual field loss in IRON does not respect the horizontal raphe (it is not altitudinal). Furthermore, there is no disc edema. But like AION, there will be optic atrophy in about 2 months. The optic atrophy of IRON is more likely to be confined to the temporal aspects of the optic disc. In both AION and IRON, the condition is static with little likelihood of progression or resolution. Unfortunately, in both cases, there is no effective treatment [139].

C. Timing of Reoperations

Nakamura et al. looked at the effects of ILM peeling on the vitreoretinal interface. In their study, 10 monkey eyes underwent pars plana vitrectomy with ILM peeling assisted by ICG chromodissection. Eyes were enucleated at 3, 6, and 12 months post vitrectomy to evaluate the process of healing and regeneration. It was noted that 3 months following surgery there were regions of the retina where ILM peeling had been performed which had evidence of Müller cell fragmentation and exposed areas of the RNFL. At the 6- and 12-month time points, reactive gliosis from the remaining Müller cells formed a mesh-like network that expanded across the originally denuded surface. There was no evidence of complete ILM regeneration even at the 12-month time point [27].

Pan et al. studied the timing of repeat surgeries in 10 patients and found that patients who underwent reoperation at least 6 months after the primary surgery ($n=6$) had better functional outcomes [140] (Figure V.A.4-1). Reoperating too soon (<6 months) after an initial surgery was associated with poor visual results (postoperative decimal visual acuity = 0.13 ± 0.19; equivalent to 20/800). On the other hand, waiting ≥6 months before reoperation was associated with excellent functional outcomes (postoperative decimal visual acuity = 0.45 ± 0.24 (equivalent to 20/50); $P=0.03$). The proposed explanation was that peeling of the ILM causes a significant amount of trauma to the underlying Müller cell foot processes that form the outer layers of the ILM. If a repeat peel was performed too soon (<6 months out from the primary), there would be a much greater chance to injure the underlying RNFL and neurosensory retina as the Müller cells would not have had enough time to reform a protective layer. This hypothesis was confirmed by studying OCT measurements of RNFL thickness and histopathological features of the inner retina in cases of membrane peel surgery.

RNFL thickness measurements were obtained after repeat operation in the study patients (Figure V.A.4-2). In the <6 month group, the average thickness and standard deviation of the temporal, inferior, superior, and nasal quadrants were 53.75 ± 8.42 µm, 80.50 ± 10.38 µm, 86.75 ± 27.20 µm, and 74.50 ± 8.06 µm, respectively, with an overall peripapillary thickness of 73.75 ± 7.41 µm. In the ≥6 month group, the measurements were 72.60 ± 13.26 µm, 87.80 ± 19.15 µm, 103.60 ± 7.02 µm, and 85.20 ± 24.69 µm, respectively, with an overall peripapillary thickness of 87.00 ± 14.95 µm. This difference in the temporal quadrant between groups was statistically significant ($P=0.04$). However, no such difference was detected in the inferior, superior, nasal, or overall thickness measurements.

Tissues removed from 6 eyes at the time of reoperation were processed for immunohistochemistry with antibodies targeting neurofilament, a component of the RNFL. This allowed for unmistakable identification of neurosensory retinal in the tissue removed. In the early intervention group (<6 months), positive neurofilament staining was present in 2/2 (100 %) specimens (Figures V.A.4-3 and V.A.4-4). Transmission EM confirmed the presence of cellular debris (Figure V.A.4-5), ostensibly fragments of the RNFL. Postoperative vision in each subject was very poor. In the late (≥6 months) reoperation group, there was no evidence of neurofilament staining in 4/4 (100 %) of specimens (Figures V.A.4-3 and V.A.4-4). Postoperative vision was good in all cases. These findings suggest that in cases of reoperation, the risk of iatrogenic RNFL damage is heightened if the second operation is performed too soon (in this study before 6 months) after the first operation. The aforementioned experimental data suggest that this unfortunate consequence occurs when there has been too little time for reformation of a Müller cell barrier and the inner retinal surface is still exposed. During reoperation on an eye that has not reformed this "protective" barrier, membrane peeling, especially with chromodissection, risks damaging the RNFL, as found in this study. To reduce the risk of IRON following reoperation, a minimum duration of 6 months should be allowed between consecutive membrane peel operations.

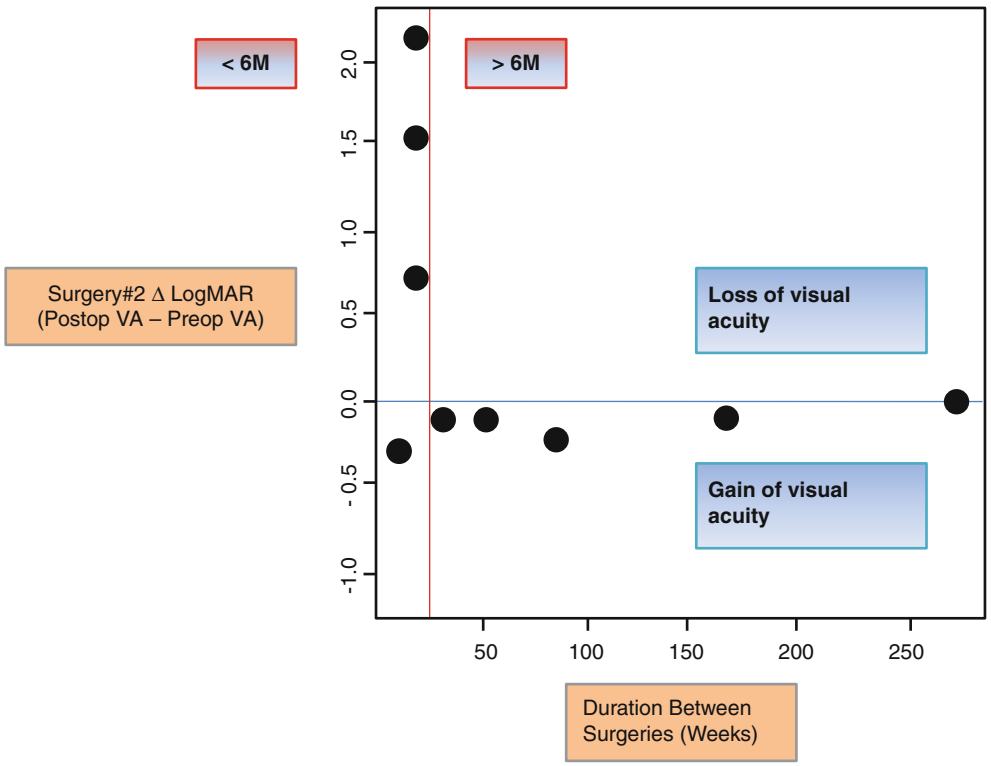

Figure V.A.4-1 Graphic presentation of visual acuity change after a repeat operation for macular hole/macular pucker. The *x*-axis represents the duration of time that elapsed between the first and the second surgeries, in weeks. The *vertical line* represents the 6-month demarcation. The *y*-axis represents the change in visual acuity (represented in LogMAR format) after the second surgery, calculated using the second surgery postoperative visual acuity minus the associated preoperative visual acuity. The *horizontal line* demarcates loss of visual acuity (*above the line*), gain of visual acuity (*below the line*), and no change in visual acuity (*on the line*). It is notable that 3 of the 4 patients who received repeat surgeries before 6 months had elapsed between surgeries had worsening of visual acuity. In contrast, patients who received a repeat surgery after 6 months had elapsed between surgeries either had improved or stable visual acuities

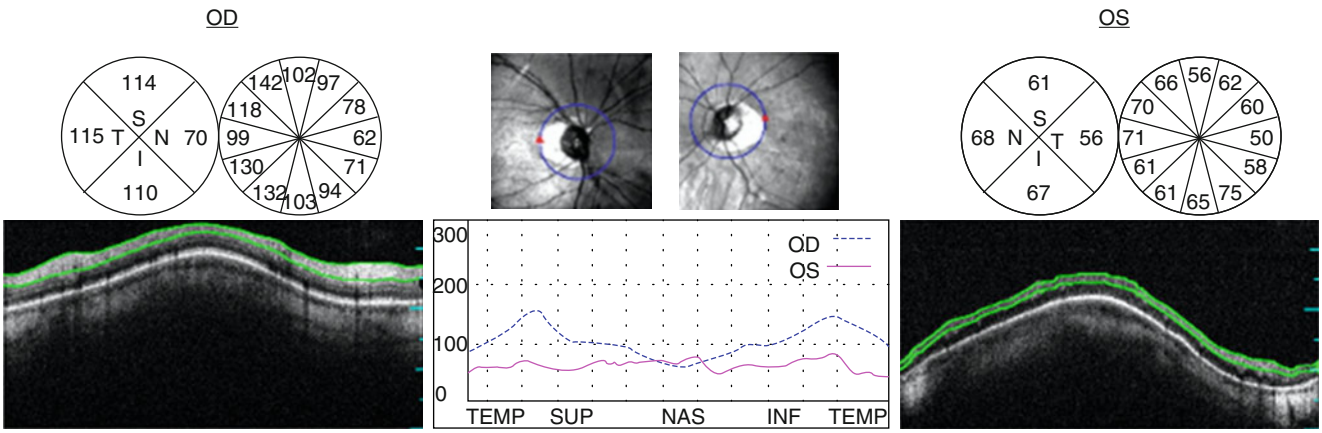

Figure V.A.4-2 Retinal nerve fiber thickness measured by optical coherence tomography demonstrates thinning in the superior, inferior, and temporal quadrants of the eye affected (*OS*) with inner retinal optic neuropathy (IRON) following membrane peeling with chromodissection during reoperation for macular pucker. Nasal fibers remain unaffected as the membrane peel is performed temporal to the optic nerve OD right eye, OS left eye

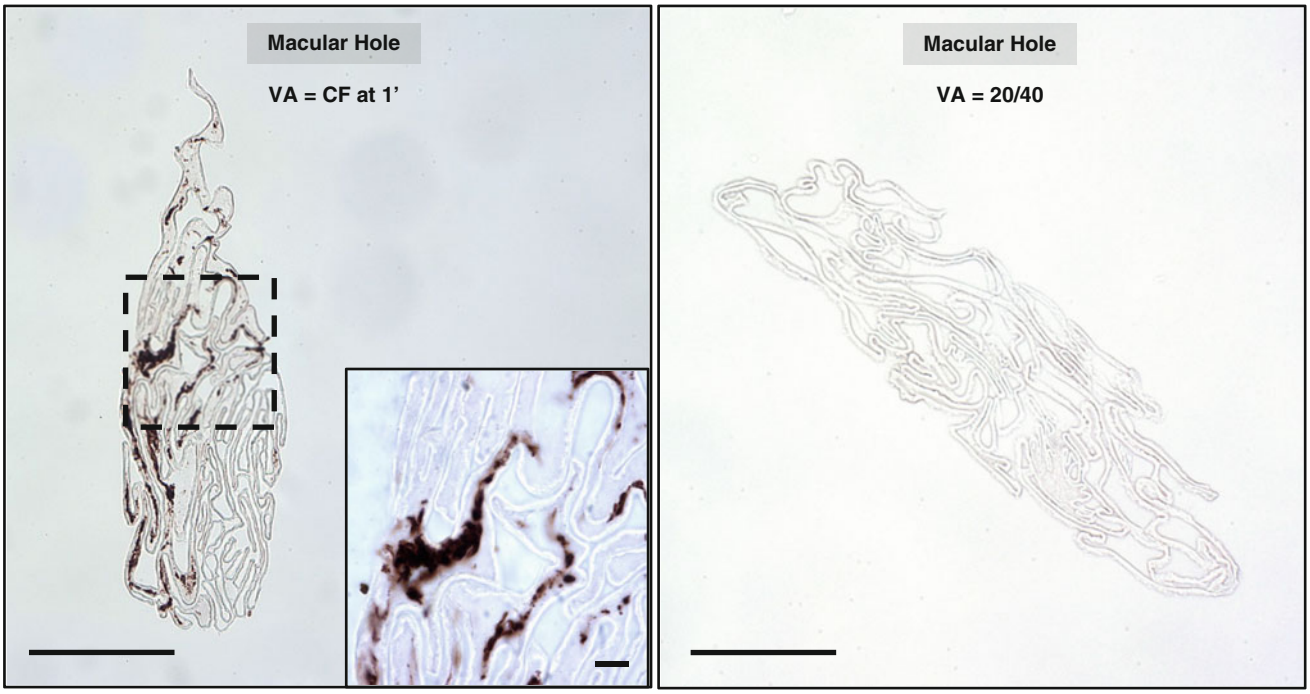

Figure V.A.4-3 Surgical specimens obtained from patients with macular hole. Specimens were processed for immunohistochemistry targeting neurofilament, a component of the retinal nerve fiber layer. *Brown staining* is indicative of neurosensory retina that was removed with the surgical specimen. Image on the left is from a patient who received a repeat operation <6 months after the first, while the image on the right is from a patient who received a repeat operation >6 after the first operation. Postoperative vision was far better in the latter case (*right image*). *VA* visual acuity, *CF* count fingers. Large scale bar = 50 μm; small scale bar = 5 μm

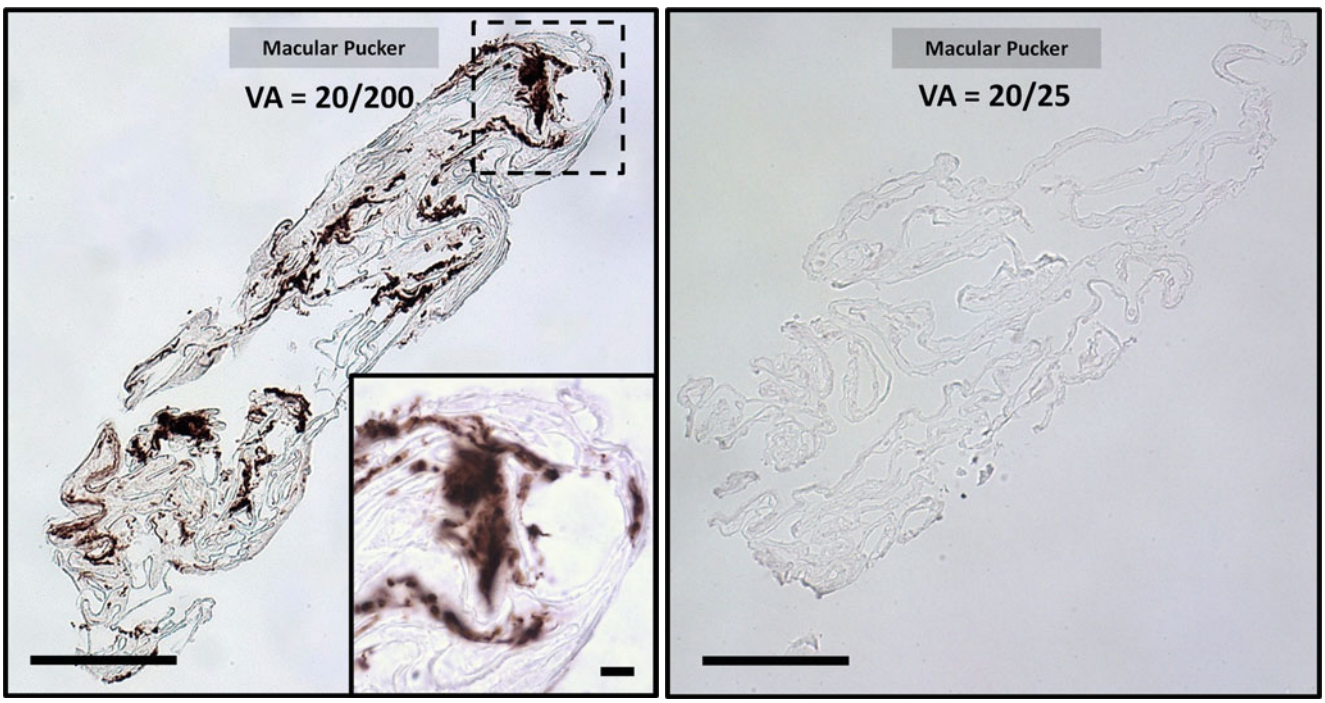

Figure V.A.4-4 Surgical specimens obtained from patients with macular pucker. Specimens were processed for immunohistochemistry targeting neurofilament, a component of the retinal nerve fiber layer. *Brown staining* is indicative of neurosensory retina that was removed with the surgical specimen. Image on the left is from a patient who underwent a repeat operation< 6 months after the first, while the image on the right is from a patient who underwent reoperation >6 after the first surgery. Postoperative vision was far better in the latter case (*right image*). *VA* visual acuity. Large scale bar = 50 μm; small scale bar = 5 μm

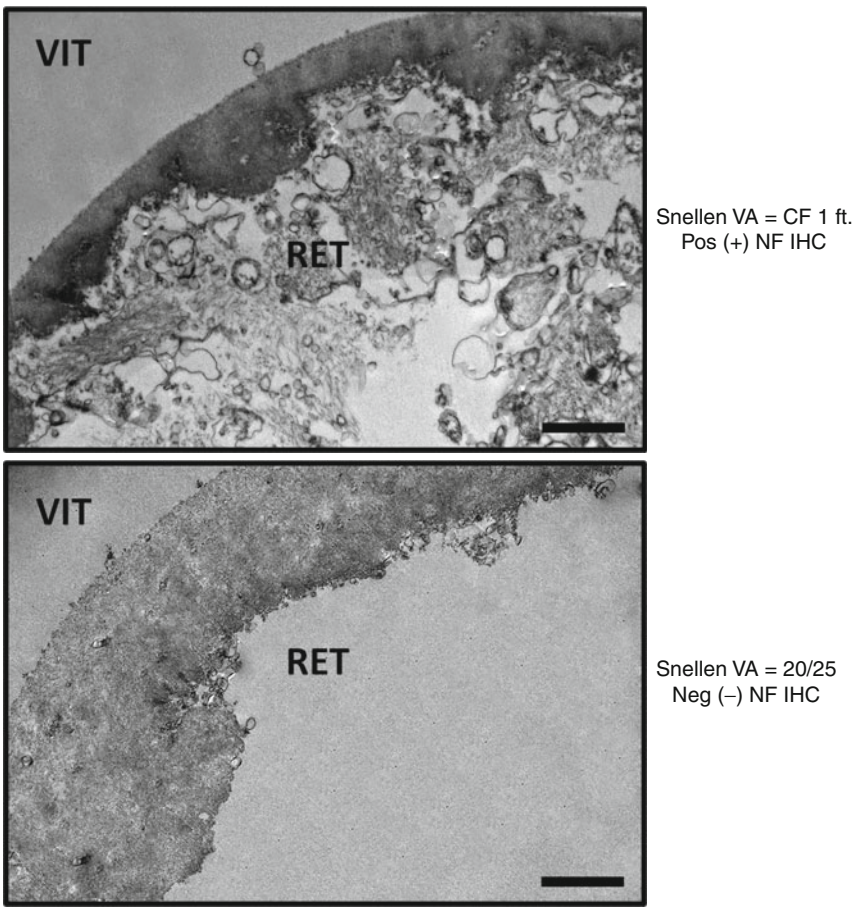

Figure V.A.4-5 Ultrastructural analysis of tissues taken from patients who had repeat surgeries for macular hole. The *upper image* is taken from a patient who underwent reoperation <6 months after the primary surgery, whereas the *lower image* is taken from a patient who underwent reoperation >6 months after the first surgery. The upper image shows a significant amount of cellular tissue adherent to the retinal aspect of the inner limiting membrane, ostensibly fragments of the retinal nerve fiber layer. *VIT* vitreous, *RET* retina, *CF* count fingers, *Pos* positive, *Neg* negative, *NF* neurofilament, *IHC* immunohistochemistry. Scale bar = 2 μm

Abbreviations

AION	Anterior ischemic optic neuropathy
APD	Afferent pupillary defect
ICG	Indocyanine green
ILM	Inner limiting membrane
IRON	Inner retinal optic neuropathy
MMHS	Moorfields Macular Hole Study
OCT	Optical coherence tomography
PMM	Premacular Membrane (previously referred to as epiretinal membrane, or ERM)
PVC	Posterior vitreous cortex
RNFL	Retinal nerve fiber layer
VMHS	Vitrectomy for treatment of macular hole study
VPMH	Vitrectomy for Prevention of Macular Hole

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