Surgeons must be aware of their outcomes in deciding how to approach DME surgically.

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The increasing incidence and prevalence of diabetes mellitus in the United States are related to the overall aging population and increasing obesity within that population. Significant health care resources have been directed toward preventive measures to manage obesity and hypertension. Ironically, the improvements in treatment for diagnosed diabetes mellitus are leading to the survival of a larger population at risk for severe diabetic ocular pathology.

The major causes of vision loss in patients with diabetes are progression to proliferative diabetic retinopathy, development of diabetic macular edema (DME), and early onset of cataract. The use of anti-VEGF medications has altered the landscape remarkably for diabetic patients and the care that ophthalmologists can provide for them. Anti-VEGF therapies have demonstrated anatomic improvement in both advanced diabetic retinopathy and DME. For many vitreoretinal specialists, use of an anti-VEGF agent is now the first line of therapy for diabetic ocular disease requiring treatment.

DME affects both visual function and anatomy, and advances in imaging with optical coherence tomography (OCT)—including spectral-domain OCT (SD-OCT), swept-source OCT, and OCT angiography—have improved our understanding of the anatomic effects of the disease. The ability to couple these advanced imaging tools with targeted intravitreal therapies employing anti-VEGF and/or steroid agents has greatly improved outcomes for patients without the need for traditional surgical intervention. At the same time, advances in surgical management, including enhanced fluidics, rapid vitrector cut rates, widefield viewing and illumination, and precise access to the retinal microarchitecture with small-gauge instrumentation, enable the consideration of surgery in eyes previously deemed inoperable.

The Diabetic Retinopathy Clinical Research Network (DRCR.net) has undertaken, and continues to undertake, large-scale clinical studies assessing our evolving treatment approaches. Further, industry continues to explore novel treatment targets and improved delivery modalities to expand our pharmacotherapeutic armamentarium.

MANAGEMENT OF DME

No consensus on management of diabetic retinopathy exists, but the best data available suggest that early screening and referral are beneficial. Encouraging systemic health is a mainstay of care for these complex patients. Particularly important are control of blood sugar levels, control of hypertension, and maintenance of renal function.

For the retina specialist, OCT imaging and indirect ophthalmoscopy are the standards for evaluation of diabetic ocular disease. In our own practice, we have
shifted to earlier treatment of DME, using SD-OCT imaging to guide anti-VEGF treatment. We use a treat-and-adjust therapy regimen, in which intravitreal therapy is adjusted based on clinical examination at the time of treatment. This approach mandates complete clinical assessment of each patient prior to intravitreal injection. In our practice, we find that the individual choice of anti-VEGF agent is less critical than the intervals between treatments.

The efficacy of vitrectomy in the management of DME has been evaluated by multiple authors. In early studies, patients had previously received multiple treatment approaches including grid/focal laser, intravitreal steroid injection, and, more recently, intravitreal anti-VEGF treatments. The use of vitrectomy for DME was an extension of early experience using surgery in a subset of patients in which DME was associated with vitreoretinal traction.1-3

Prior to the availability of OCT, determination and quantification of vitreomacular adhesion or traction was extremely difficult and required excellent macular contact lens evaluation skills. Even in the hands of an experienced clinician, recognition of the vitreomacular interface was difficult at best. Adoption of OCT enabled immediate and reproducible recognition and grading of the type and extent of DME and the status of the vitreous, epiretinal membrane (ERM), and inner limiting membrane (ILM) in these complex patients.

With the benefit of OCT, many surgeons began to use pars plana vitrectomy to improve outcomes in DME when vitreomacular traction or adhesion was present. Early interventions of this type were limited due to risk to the macula, but the risk-benefit profile has improved with advances in surgical technologies.4

The ability to visualize the ILM has had a major impact on macular surgery, most readily apparent in improvements in macular hole surgical closure rates. Reports indicate that almost 100% of small to medium macular holes can be surgically closed when ILM peeling is employed. ILM peeling also removes the scaffolding for ERM proliferation, thereby decreasing recurrence due to traction in the macula.5-7

ILM peeling is enhanced by good visualization of the ILM, allowing safe surgical removal. Visualization of the ILM is typically facilitated through the use of chromophoric dyes that bind to the ILM. In the United States, the agent most often used for staining is indocyanine green (ICG). Internationally, surgeons often use Membrane Blue-Dual (DORC International), which combines brilliant blue G and trypan blue dyes. Virtually all of these vital dye compounds have shown the potential for retinal toxicity, but we have not observed toxicity in more than 1,000 surgical cases in which we used ICG, suggesting that toxicity can be avoided when it is safely applied.

BEST PRACTICES FOR SURGERY

Before injecting the ILM staining dye, we typically complete the PPV, elevate the hyaloid membrane, remove obvious ERMs, and lower the intraocular pressure to 5 mm Hg. Then we gently drop the ICG, first at the nerve and then moving to the macula while avoiding the foveal center. We then rapidly remove the dye to achieve minimal staining. We typically remove the ICG within 30 seconds, using active cutting on the vitrector, until we have a good view of the retina, and then with active suction over the optic nerve head.

Lastly, we peel the ILM with a focus on achieving an atraumatic approach. We employ either a pinch-release-peel approach with ILM forceps or initiate the ILM peel with a Finesse Flex Loop scraper (Alcon/Grieshaber) and then use the ILM forceps. We recently reported on using the cutter to
remove the ILM, but we employ this rarely, typically in cases in which the ILM elevates easily and peels perfectly.

**PLATFORM IMPROVEMENTS**

Although staining of the ILM is the most important recent surgical advance in ILM removal, improvements in technology have also had significant impacts on the ease and safety of this surgical technique. Over the past decade, manufacturers have improved viewing options (widefield contact and noncontact systems), illumination (enhanced light sources, better endoillumination probes, directional probes, and chandelier systems), vitreoretinal cutting (faster cut rates, better port designs, dual-drive cutters), and fluidics, and have introduced valved trocar entry systems.

For our practice, these advances are manifested in our approach to microincisional vitrectomy surgery (MIVS). The availability of MIVS has shifted our surgical window, allowing patients to be operated on earlier in their disease processes while also lowering complication rates (fewer iatrogenic retinal tears, less intraoperative bleeding, less intraoperative hypotony, and lower sclerotomy site compromise). We also execute fewer instrument changes because of the versatility of the instruments.

**EARLIER SURGERY**

The aforementioned shift in the therapeutic window means that surgery becomes a viable option in more patients with visually compromising macular pathology. Earlier surgical intervention has been shown to achieve better visual outcomes for patients. Much of surgery depends on the assessment of the risk-to-benefit ratio. Everything that shifts the curve by lowering risk enables more intervention to improve benefit.

Many surgeons are now operating on macular pathology
in patients with visual acuities better than 20/40, and some are even operating in eyes with traditional visual acuity measurement of 20/20 but with severe visual compromise as perceived by the patient (metamorphopsia, contrast sensitivity compromise, severe floaters). Our service has not moved to operating on 20/20 eyes, but we do appreciate that this is only possible when the chances of intraoperative and postoperative surgical complications are remote.

**Clinical Experience**

With the advances outlined above—advanced imaging with OCT, enhanced surgical instrumentation, and superb visualization of the ILM with staining—we have shifted our practice to consider ILM staining in virtually all cases with complex macular pathology. MIVS surgery using valved trocars with either 23-, 25-, or 27-gauge instrumentation is ideal when employed with advanced high-speed cutting (10,000 cpm), contact widefield viewing, ICG staining, and removal of the ILM with forceps peeling.

At the inaugural Retina World Congress, we presented the results of an institutional review board–approved retrospective series of 89 eyes of 76 patients undergoing this surgical approach for DME deemed unresponsive to pharmacotherapy in the Miami Ocular Oncology and Retina surgical service. Mean patient age was 64 years, mean entry visual acuity was 20/400, and mean duration of macular edema was 11 months. All patients had received intravitreal pharmacotherapy with bevacizumab (Avastin, Genentech) and/or triamcinolone acetonide injectable suspension (Triesence, Alcon) prior to surgery.

At a mean follow-up of 30 months, visual acuity had improved to 20/50, and 62% of patients experienced a 3 line or greater improvement in visual acuity. Postsurgical follow-up was critical, as 47 of the 76 patients (62%) developed recurrent retinal edema that was responsive to intravitreal pharmacotherapy. No patients in the series developed endophthalmitis, hypotony, or retinal detachment within the follow-up window.

Of note, every patient undergoing ILM peeling received intravitreal triamcinolone acetonide at the conclusion of the surgical procedure. The intraoperative placement of a therapeutic dose of steroid significantly benefited the rapidity of resolution of retinal edema, both preexisting and potentially surgically induced.

**Algorithm**

The results in this series are supported by similar data from multiple centers using ILM peeling during MIVS for complications of diabetes requiring surgical intervention. Nonetheless, MIVS management is not our first line of therapy.

Our algorithm for DME management begins with encouraging early referral. Referred patients undergo vitreoretinal assessment with OCT, targeted treatment of DME with an intravitreal anti-VEGF agent, and short-term follow-up for assessment of treatment response. At follow-up, we re-treat with anti-VEGF agent if improvement is documented or transition to intravitreal triamcinolone acetonide if worsening of DME is noted. Again we reassess at short-interval follow-up, and we consider surgical intervention with MIVS in the face of vitreomacular interface abnormalities or short-course retreatment with intravitreal pharmacotherapy. On follow-up, if the DME is nonresponsive, we then offer the patient MIVS intervention after a discussion of risks, benefits, and expected outcomes. If the patient has visually significant early or more advanced cataract, we offer combined anterior-posterior surgery with small incision phacoemulsification.
and intraocular lens implantation along with MIVS, achieving more rapid anatomic and visual recovery and eliminating the necessary second surgical management of the cataract without significantly increasing surgical complications.9

This approach, like virtually all defined surgical approaches in vitreoretinal management, is not without controversy. For this approach to be effective, the individual surgeon must be aware of his or her own outcomes. This information is easily attainable in the era of electronic health records, and it enables the surgeon to evaluate indications and outcomes within his or her own surgical practice.

The historical controversies are well-known and, in most cases, incorrect. The myths include the following:

- Vitrectomy does not work for nontractional DME;
- ILM peeling is not necessary;
- ILM staining is not necessary;
- ICG toxicity is significant;
- Intravitreal steroid is not effective for DME;
- Intravitreal steroid will cause glaucoma requiring surgical intervention; and
- Intravitreal gas tamponade is necessary for DME management.

One concern that has been discussed often is surgical management in the face of large central cystic DME. Historically, surgery has avoided membrane peeling or ILM peeling in these areas. Recent data from eyes with extensive schisis or cystic myopic macular degeneration has suggested the exact opposite strategy, whereby, during surgical intervention, the release of both ERM and ILM with intravitreal gas tamponade has been able to markedly restore the anatomy. These data, and our personal surgical experience, suggest that peeling ILM in the face of large cystic DME does not increase the incidence of full-thickness macular hole. In these complex cases, atraumatic removal of the ILM coupled with intravitreal gas tamponade yields excellent anatomic and visual function.

**CLINICAL PEARLS**

In the series described above, and from further surgical experience, it is our opinion that OCT-guided DME therapy achieves the best anatomic and visual outcomes when the following conditions are observed:

- MIVS is employed early after intravitreal pharmacotherapy has been deemed unsuccessful;
- MIVS includes the use of valved trocars;
- ILM peeling is critical to surgical success;
- ILM peeling should be performed with staining;
- ILM staining time should be minimized, but staining is not associated with clinically significant toxicity;
- Atraumatic ILM removal is enhanced with use of ILM forces, with or without induction using the Flex Loop;
- Intraoperative placement of intravitreal triamcinolone acetonide is effective against postsurgical edema;
- Intraoperative triamcinolone acetonide is not associated with complex secondary glaucoma;
- Intravitreal gas tamponade is not routinely necessary and should be employed only when there is concern of a full thickness macular hole or retinal tear.

These clinical pearls address our response to much of the controversy surrounding surgical management of DME.

Clinical experience varies, and individual surgeons must adjust their indications and surgical approaches to maximize outcomes for their patients. Historically, this subset of patients with progressive DME has been difficult to manage, and this condition was often associated with early, severe visual compromise. Advances in imaging, surgical technologies, adjunctive intravitreal pharmacologics, and surgical instrumentation are helping us to bring long-term visual stability to our patients with sight-threatening disease.10-12

Vitreoretinal surgeons can expect to see an increasing population at risk for diabetic ocular disease. We will likely find ourselves employing treatment strategies that incorporate MIVS earlier in our patients who do not respond to nonsurgical treatment of DME.