Issue 1

CUTTING EDGE

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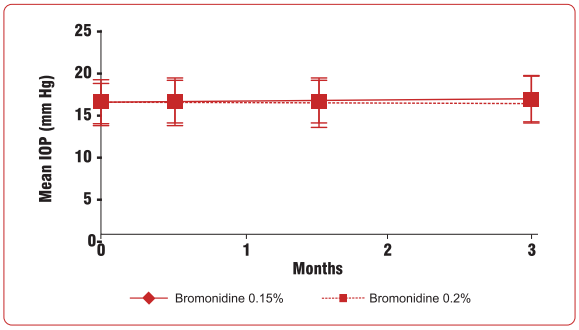

- IOP - lowering effect was maintained over the 3 month with Brimonidine 0.15% and Brimonidine 0.2%
- Lower concentration of Brimonidine in Brimonidine 0.15% may lower the incidence of allergic conjunctivitis

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1. Tom M etal, Journal of ocular pharmacology and therapeutics Volume 19, Number 1, 2003,37-44

Preserved with Polyhexamethylene biguanide • BKC - Benzalkonium Chloride • IOP - Intraocular pressure * Data on file

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CUTTING EDGE
Glaucoma

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WHAT'S NEW

Glaucoma and Oculoplasty

T. Shaarawy, A. Aref

Glaucoma Medications and its Effect on Eye Cosmesis

Glaucoma eye medications affects eye appearance and orbital fat content. These medications include both preservatives and active ingredients, that are both, independently from each other or combined, can result in a myriad of side effects.

Adverse Reactions to Preservatives Present in Glaucoma Eye Drops

Effects of preservatives have been indicated as a causative factor of ocular surface disease (OSD) associated with ophthalmic antiglaucomatous agent administration. More than 60% of patients with glaucoma have signs and symptoms of OSD.

A large number of products are available, combining in various proportions a limited number of ingredients such as glycerin, polyvinyl alcohol, propylene glycol, hydroxypropyl guar, carbomers, cellulose derivatives, and sodium hyaluronate. Most of the eyedrops contain preservatives to maintain the sterility of eye drops in multidose containers. The preservatives act in a totally unspecific manner as a detergent or by oxidative mechanisms and thereby cause damage not only to contaminating bacteria and other microorganisms but also to the cells of the ocular surface. It has also been demonstrated that they also affect the contact lenses physical properties, the trabecular meshwork, and the retina. Benzalkonium chloride (BAK) is the most commonly used preservative in ophthalmology, even though it is considered as the most toxic. New preservatives, as Purite or Polyquad have unfortunately, several toxic and inflammatory effects not less than BAK on the ocular surface.

Eye drops including glaucoma local treatment contain main therapeutic agents, along with various additives. Additive compounds may facilitate preparation, stabilize the solution/suspension, and/or increase product safety. Common additives include solubilizing agents, thickening agents, isotonizing agents, preservative agents, buffering agents, and stabilizing agents. Adverse reactions to eye treatments are caused by either the main active agent or the additive agents, particularly preservatives. A preservative is an additive agent that extends the shelf-life of a drug. Preservatives may have bacteriostatic or sterilizing properties and often accentuate product transparency. Most

T. Shaarawy (✉), A. Aref

University of Geneva, Geneva, Switzerland
e-mail: tarek.shaarawy@hcuge.ch

preservatives also act as surfactants which destabilize bacterial cell membranes. This causes destruction of the cell membrane, inhibition of cell growth, and reduction of cell adhesiveness. However, preservatives also exert these effects on normal corneal and conjunctival cells, resulting in ocular surface disorders (OSD). OSD include superficial punctate keratitis, corneal erosion, conjunctival allergy, conjunctival injection, and anterior chamber inflammation. There are many compounds which cause preservative-induced superficial punctate keratitis but benzalkonium chloride is often the cause. Thereafter, when this condition develops, switching the patient to eye drops with preservatives other than benzalkonium chloride, or eye drops without preservatives (unit dose instillation containers or membrane filter-incorporated eye drop bottles) is often beneficial. As an example, in cases where latanoprost formulations with benzalkonium chloride were changed to latanoprost formulations without preservatives, the IOP remained stable and 42.9% of patients had improvements in corneal epithelium disorders. Lopez *et al.* 2019 reported improvement of symptoms and signs of dry eye in patients who shifted from prostaglandin analogs BAK-preserved to tafluprost preservative-free with similar IOP reductions. Reducing benzalkonium chloride exposure was often sufficient to result in ocular surface improvements as in cases where the patient switched to a combination. A deleterious effect of BAK has been demonstrated both in vitro as well as in vivo. A concentration of 0.007% of BAK induces a lysis of 50% of cultured epithelial cells in less than 2 minutes. BAK exerts its damaging action mainly through a direct cytotoxic mechanism, accentuated by the cumulative effect of repeated administrations of preserved eyedrops. Alternative preservative could be used, such as polyquaternium, which is known to have less corneal toxicity, as well as less rupture of cellular junctions, when compared to BAK. Additionally, benzalkonium chloride has been reported to be involved in the appearance of macular edema after cataract surgery.

Adverse Reactions to Main Agents in Glaucoma Eye Drops

The ultimate objective of glaucoma treatments is to stop visual field defect deterioration. Intraocular pressure (IOP) reduction is the only proven treatment to prevent visual field defect progression. Eye drops, oral medications, laser therapy, and surgery have all been used to decrease IOP in glaucoma patients. Among these therapies, topical treatments are usually employed as the first choice because they are not associated with vision threatening complications that we can encounter with surgery.

Prostaglandin Analogs

Conjunctival allergy, conjunctival hyperemia, corneal epithelial disorders, and blepharitis are characteristic adverse reactions associated with prostaglandin analogs. Patients receiving these drugs might have eyelash bristling/lengthening, vellus hair, eyelid pigmentation, iris pigmentation, and deepening of the upper eyelid sulcus (DUES).

In the beginning of treatment with prostaglandin analogs, patients sometimes have intense conjunctival hyperemia, but this gradually diminishes over time. It has been shown in a meta-analyses of several systematic reviews, that conjunctival hyperemia occurred significantly less often with latanoprost than with travoprost or with bimatoprost. Conjunctival hyperemia was evaluated and graded in eyes in which latanoprost was currently being used. Medication regimens

were left unchanged or patients were switched from latanoprost to bimatoprost or travoprost. Twelve weeks later, there were no differences in conjunctival hyperemia change score for any of the three eye drops types examined. The reported incidence of conjunctival hyperemia differs between various prostaglandin analogs, occurring more often with bimatoprost use than with other prostaglandin analogs.

The incidence of eyelash lengthening/bristling may also differ between various prostaglandin analogs. In a study where only one eye was administered a prostaglandin analog, eyelash lengthening/number increase occurred 54%, 46%, 26%, and 46% more often in the eye treated with bimatoprost, travoprost, latanoprost, and tafluprost, respectively. Differences between individual drugs were not significant. In another study, eyelash changes in the lower lids were measured after administration of latanoprost only in one eye. Eyelash length was 6.95 ± 0.91 mm in the treated eye and 5.83 ± 0.76 mm in the untreated eye, a difference that was statistically significant. Gel suspensions with and without bimatoprost were also applied to each upper eyelid. After 6 weeks of daily application, the length of the longest eyelash was compared to that measured at baseline. The eyelashes in the bimatoprost group grew 2.0 ± 1.5 mm, significantly more than those in the bimatoprost-free (control) group, which only grew 1.1 ± 1.1 mm. Casson and Selva in 2005 described a patient whose trichomegaly secondary to the chronic use of latanoprost resulted in eyelash ptosis that obstructed his visual field and required a bilateral eyelid anterior lamellar transposition procedure. Eyelash length and increase in length was especially remarkable with the use of bimatoprost. Therefore, bimatoprost had been used for cosmetic reasons as an eyelash enhancer.

All prostaglandins seem to have similar effects on eyelid pigmentation. It is known that eyelid pigmentation changes caused by latanoprost resulted from markedly increased melanin levels. An increase in tyrosinase activity was thought to cause these changes because tyrosinase was involved in this melanin increase, which occurred at the RNA level. Iris pigmentation often occurs in patients, in whom iris pigments are green-brown, yellow brown, blue-brown, and/or of mixed color.

The occurrence of DUES with prostaglandin analog use was first reported with bimatoprost use in 2004 by Peplinski and Albiani Smith. They reported upper eyelid sulcus deepening and dermatochalasis involution in 3 patients who were unilaterally treated with bimatoprost. his was attributed to a possible effect of bimatoprost on Muller muscle. In another study 5 patients in whom chronic daily unilateral treatment with bimatoprost 0.03% caused upper eyelid sulcus deepening, clinically apparent relative enophthalmos, and involution of dermatochalasis. They hypothesized that preaponeurotic and deep orbital fat atrophy are responsible for the majority of these periocular changes. They documented that these adnexal changes were not evident prior to starting treatment with bimatoprost. Among patients for whom the medication could be stopped, partial or complete reversal of the clinical picture was observed in 3–6 months. Romano and colleagues in 2007 showed that bimatoprost induced smooth muscle contraction. Some patients with Prostaglandin-Associated Periorbitopathy (PAP) have inferior scleral show, which could be related to contraction of the inferior eyelid's smooth muscle retractors. In terms of atrophy, the number of a person's fat cells increases from birth until young adulthood and then remains relatively constant thereafter. Thus, it is the volume of lipid fat per cell that dictates one's physical appearance from middle age onward.

Fat metabolism is under intense regulation by hormones, mainly insulin, catecholamines, and natriuretic peptides, and paracrine factors such as cytokines, adenosine, and prostaglandins.

The FP prostanoid receptor is thought to mediate, at least in part, the pharmacologic effect of bimatoprost as evident by the lack of IOP response in FP-prostanoid receptor knockout mice. FP-receptor activation has been associated with inhibition of preadipocyte differentiation in several cell lines that are prevented from expressing adipocyte-specific genes and accumulating fat droplets. Furthermore, FP-receptor agonists have been shown to down-regulate fatty acid binding protein expression, which is important for the uptake of free fatty acids and triglyceride synthesis in adipocytes. In addition, pharmacokinetic studies indicate that eyelid specimens contain more than 2,000 times higher concentrations of bimatoprost compared with aqueous and more than 16 times higher concentrations compared with iris and ciliary body, which indicates significant periorbital absorption of the medication. Prostaglandin F2alpha can inhibit fat production. Therefore, it was thought that prostaglandin analogs reduced orbital adipose tissue mass, resulting in DUES. In a study, in which one eye was administered a prostaglandin analog and one eye was left untreated, photographs of the face were taken and DUES was evaluated using a score. The condition occurred in 60%, 50%, 24%, and 18% of patients using bimatoprost, travoprost, latanoprost, and tafluprost, respectively. The condition was noted significantly more often in patients using bimatoprost and travoprost than in patients using latanoprost and tafluprost.

Many patients find these effects disturbing, and in many cases the physician has to switch to a different class, or to consider Selective LASER trabeculoplasty (SLT) or even surgery.

Beta Blockers

Ocular adverse reactions to β-blockers include conjunctival allergies, conjunctival injection, corneal epithelium disorders, blepharitis, and ocular pemphigoid. Additionally, corneal sensitivity may be reduced because of the local anesthetic effect (membrane-stabilizing effect) of betaxolol. The subsequent reduction in reflective tearing may also lead to corneal epithelium disorders. Carteolol has intrinsic sympathomimetic activity so administration of this drug does not lead to a reduced corneal sensitivity. Therefore, carteolol administration was associated with fewer cases of corneal epithelium disorders than timolol. Timolol is available in a preservative-free formulation. Combining beta blockers with prostaglandins in fixed combinations seem to reduce hyperemia commonly associated with prostaglandins.

Alpha Agonists

Ocular adverse reactions associated with long-term sympathetic α2-receptor agonist use include conjunctival hyperemia, pupil dilation, and allergic conjunctivitis. Alphagan P(TM) has a purite preservative that breaks down into natural tear components and may be better tolerated in people who have allergic reactions to preservatives in other eye drops.

Carbonic Anhydrase Inhibitors (CAIs)

Ocular adverse reactions associated with carbonic anhydrase inhibitors include conjunctival allergy, conjunctival hyperemia, corneal epithelial disorders, blepharitis, Stevens–Johnson

syndrome, and toxic epidermal necrosis. Dorzolamide is viscous and has a fairly acidic pH (pH = 5.5–5.9), which generally causes ocular irritation. Foreign body sensation and blurred vision often occur in patients receiving brinzolamide because intraocular transitivity is slightly poor. Moreover, carbonic anhydrase naturally exists in the corneal endothelium, and caution is needed in patients with corneal endothelial disorders.

Rho Khinase Inhibitors

Netarsudil is a new class of glaucoma drug that increase the drainage of intraocular fluid. It is prescribed once-daily at night in the form of an ophthalmic solution 0.02% (Rhopressa) and is approved for lowering elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension. It is a Rho kinase (ROCK) inhibitor that lowers IOP primarily by increasing trabecular outflow. The most frequent adverse events were ocular: conjunctival hyperemia, conjunctival hemorrhage, and cornea verticillata. Conjunctival hyperemia is an extension of the pharmacology of ROCK inhibitors, which cause vasodilation of blood vessels by inducing relaxation of vascular smooth muscle. In most part, the hyperemia was mild, transient, and self-resolving. Conjunctival hemorrhage was similarly relatively mild and self-resolving, and typically described as small petechial hemorrhages. Cornea verticillata was typically scored as mild with no associated decrease in visual function.

Combined Medications

Combination can offer an alternative for patients who need more than one type of medication. In addition to the convenience of using one eye drop bottle instead of two, there is decreased exposure to preservatives. There may also be a financial advantage. Some types are also available in generic form and also as a preservative-free formulation. Side effects of combined medications may include any of the side effects of the drug types they contain.

Oculoplastic Effects of Glaucoma Surgeries

Ptosis

Ptosis have been reported as a complication following glaucoma surgery that can lead to cosmetic and functional defects. Its incidence tends to be around 10.7–12% in trabeculectomy without mitomycin C (MMC) and 19% with MMC 6 months after surgery. The incidence of ptosis following trabeculectomy was not influenced by the type of conjunctival flap, combined surgery, or previous intraocular surgery. Some of the proposed mechanisms behind the cause of ptosis after surgery include lid edema from locally administered anesthetic, initial myotoxic effects, and the compression of the upper eyelid against the orbital bones from the eyelid speculum reducing blood flow to the levator muscle contributing to the edema. Another theory is that the use of a lid speculum, stiffness of the lid speculum, and a smaller palpebral fissures may play a greater role.

In general, ptosis that arises after ophthalmic surgeries are associated with myogenic or neurogenic factors due to anesthetic effects, mechanical factors due to edema or hematoma of the eyelid, or aponeurotic factors due to traction on the aponeurosis of the levator palpebrae muscle separating it from the tarsal plate. Specially in trabeculectomy where adequate exposure is mandatory, manipulations are often necessary to obtain an adequate surgical field, which may partially account for the incidence of ptosis. In addition, the use of antimetabolites, postoperative globe massage or needling, chronic stimulation of the eyelid by the filtering bleb, and other factors may also contribute to the high incidence of ptosis. Unfortunately, in glaucoma patients with visual field defect, the additional visual field impairment due to ptosis will further decrease the quality of vision. Ptosis have been reported to occur in 22.5% in patients with shunting procedures, a higher percentage compared with filtering surgery. The potential cause of increased ptosis in patients with shunting surgery could be due to the need for increased exposure required during shunting surgery to place a glaucoma drainage device 8–10 mm posterior to the limbus. The need for increased exposure possibly resulted in more pressure on the levator palpebrae aponeurosis by the lid speculum compared with the fornix-based filtering surgery.

Eyelid Retraction After Glaucoma Surgeries

Upper eyelid retraction as a complication after trabeculectomy have been reported in several studies. Mechanical, chemical, and myogenic mechanisms have been suggested. The mechanical hindrance from a diffuse, large superior bleb is supported by the fact that the retracted eye lids assumes the contours of the bleb. Putterman and Urist advocated that sympathetic stimulation of Muller muscle from chemical substances in the aqueous humor would cause eyelid retraction. This argument was further supported by a widened palpebral fissure in affected eyes, the use of a sympathetic antagonist such as guanethidine to reduce lid retraction, and increased sensitivity to phenylephrine. Awwad and colleagues in 2004 suggested that lid retraction was due to a myogenic mechanism of Muller muscle fibrosis.

Medical and surgical options on both filtering bleb and eyelid can be used to treat eyelid retraction in patients with glaucoma. Botulinum toxin injections to induce ptosis to neutralize the lid retraction in cases of sight-threatening bleb exposure are used. Alternatively, retro septal injection of Hyaluronic acid gel in the affected upper eyelid skin fold to restore the normal upper eyelid position can be used. In term of surgical procedures weakening of the upper eyelid retractors can be performed. These include lengthening or excision of either or both the levator and Muller muscle through an anterior or posterior approach. Both anterior and posterior-approach techniques, carry the risk of possible disruption of the conjunctival filtering bleb. A conjunctiva-sparing recessions of levator and Muller muscle in patients with glaucoma filtering blebs minimizing the risks of bleb injury have been also described. Some manipulation procedures that reduce the height of the bleb may help in treatment of lid retraction. Bleb compression sutures, posterior bleb needling, and cautery-induced scleral fibrosis alter the geometry of the bleb, thus decreasing the superior forces that cause lid retraction.

Glaucoma Draining Implants

Glaucoma drainage implants (GDIs) have been an effective therapeutic option in the management of refractory glaucoma. The complications associated with GDIs, however, include hypotony, choroidal effusion, corneal decompensation, cataract, endophthalmitis, diplopia, and migration of the implant. Transconjunctival tube erosion is an infrequent but well-known complication of GDIs surgery. It is estimated that 2–7% of patients undergoing GDIs procedure develop melting of the overlying scleral or pericardial patch with erosion of the tube through the conjunctiva. Possible causes of conjunctival erosion include mechanical abrasion of the conjunctiva by the lid, excessive conjunctival tension over the tube, tube malposition, or lack of a smooth and tapered surface between the patch graft and the host along with poor ocular lubrication. Various methods such as a conjunctival advancement, a conjunctival patch graft, an amniotic membrane patch graft or an interpolated conjunctival pedicle flap have been described to cover the exposed tube. If the tube exposure is accompanied by the infectious inflammatory signs which do not respond to antibiotics, the tube and the valve plate should be removed to help stop the propagation of the infectious process and prevent the subsequent development of endophthalmitis.

Glaucoma drainage devices allow outflow of aqueous humor from a tube inserted into the anterior chamber to the subtenon space around the ocular equatorial area. The body connected to the rear outlet of the tube prevents closure of the tube outlet by surrounding tissue and forms a large retention area beneath the bleb, which is helpful in long-term IOP control. The most common cause of IOP elevation after GDI implantation is the formation of an encapsulated bleb due to excessive fibrosis around the body of the GDI during the wound-healing process.

A case of Bleb incarceration following Ahmed valve surgery have been reported. The patient had a large superotemporal filtering bleb following Ahmed valve surgery for uncontrolled glaucoma. While instilling her glaucoma medication, she retracted her eyelids sufficiently to pull the upper lid over her filtering bleb where it became entrapped causing a similar presentation to globe luxation. Traditional methods of repositioning the globe were unsuccessful. Bleb needling was ultimately required to return the globe to a normal position.

Suggested Readings

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XEN Gel Stent Open Conjunctiva Technique: A Practical Approach Paper

Joseph F. Panarelli, David B. Yan, Brian Francis, E. Randy Craven

Abstract

The Xen Gel Stent lowers intraocular pressure by shunting aqueous humor to the subconjunctival space. While published studies include both open conjunctiva and closed conjunctiva approaches, most publications feature a closed conjunctiva, ab interno approach. While this approach is widely used, other approaches may be preferred for some patients. This paper provides details on surgical steps and tips for enhancing outcomes for an open conjunctiva technique for the implantation of the Xen Gel Stent, as well as reasoning as to when this approach should be used.

Key Summary Points
The XEN Gel Stent lowers intraocular pressure by shunting aqueous humor to the subconjunctival space.
Published studies include both open conjunctiva and closed conjunctiva approaches to implantation.
While the popularity of micro-invasive glaucoma surgery has favored the adaption of a closed conjunctiva approach, some surgeons have found great benefit in an open conjunctiva approach.
This paper provides details on surgical steps of an open conjunctiva implantation of the gel stent and tips for enhancing outcomes.

Keywords: Glaucoma; Glaucoma surgery, Ophthalmology, Surgical technique, XEN Gel Stent

Introduction

The Xen Gel Stent (Allergan) is a surgical implant designed to lower intraocular pressure (IOP) via the creation of a subconjunctival filtration pathway for aqueous humor. The device's length

J. F. Panarelli (✉)
NYU Langone Health Center, New York, NY, USA
e-mail: joepanarelli@gmail.com

D. B. Yan
University Eye Clinic, Toronto, ON, Canada

B. Francis
Doheny Eye Institute, UCLA Orange County, Fountain Valley, CA, USA

E. R. Craven
Wilmer Eye Institute, Bethesda, MD, USA

(6 mm) and luminal diameter (45 μm) provide sufficient resistance to help control outflow and prevent hypotony in the early postoperative period. Multiple studies have shown that the device has an excellent safety profile and comparable efficacy to trabeculectomy and other subconjunctival drainage devices [1, 2].

Grover and colleagues reported 12-month efficacy and safety results in eyes with refractory glaucoma implanting the Xen via an ab interno approach, after opening and dissecting the conjunctiva to apply sponges soaked with mitomycin C (MMC) (0.2 mg/ml for 2 min) [1]. In contrast, the majority of published studies report a Xen implantation method without conjunctival dissection and an ab interno approach [3-5]. However, many glaucoma surgeons find that there remains a benefit to an open conjunctiva approach both for implantation and revision, as it may allow for better and more consistent results in patients where a closed conjunctiva approach may not be ideal due to ocular tissue or anatomical considerations.

Since the Xen Gel Stent was launched in 2017, one fortuitous feature has been the ability to adapt the surgical implantation procedure to the demands of the individual patient. The authors of this paper are Xen experts who continue to implant the stent by opening the conjunctiva and then using either an ab interno or an ab externo approach to place it. Table 1 provides a brief comparison of the two surgical techniques, their advantages and their disadvantages. This paper will provide details on their surgical steps for this approach, as well as tips for enhancing outcomes. This article does not contain any studies with human participants or animals performed by any of the authors.

Advantages of an Open Conjunctiva, Ab Interno Placement

Two benefits to the open conjunctiva approach are the ability to work with patients with conjunctival scarring and the ability to better control placement of the stent.

In a closed conjunctiva approach, the Xen Gel Stent applicator needle needs to be positioned just beneath the conjunctiva for optimal implant placement. This requires a healthy and mobile conjunctiva to be tented up for delivery of the implant in the subconjunctival space, and usually means that patients who have conjunctival scarring in the target area (from previous incisional glaucoma surgery) should be excluded to avoid perforation. With an open conjunctiva approach, an area of scarring can be easily avoided.

In addition, the open conjunctiva approach allows the surgeon to dissect or move the Tenon's capsule away, choose the exact location for placement, and then easily make small adjustments. The microstent can be pulled out or pushed further into the anterior chamber to ensure that it is positioned properly in the anterior chamber and sub-Tenon's space.

Ensuring ideal positioning of the distal end of the stent by placing it beneath Tenon's layer and conjunctiva can improve the predictability of results, as well as create a more diffuse and posteriorly directed bleb. Placing the device beneath the Tenon's layer can also help prevent the device erosion through the conjunctiva. In the pivotal study by Grover and colleagues [1], no erosions were seen with the open conjunctiva approach.

Open Conjunctiva, Ab Interno Placement Technique

Some authors (JP) prefer to start the procedure with a retrobulbar block so that the patient remains comfortable and still during the procedure, but the procedure can also be carried out under topical anesthesia, sub-conjunctiva, or sub-Tenon's injection of Lidocaine (with epinephrine). A corneal traction suture can be placed to help rotate the eye downward (Fig. 1). A 3- to 4-mm superior conjunctival peritomy is made at the 12 o'clock position to create a conjunctival flap (fornix-based) (Fig. 2). Vannas scissors (Sklars) can be used to make a small opening in the conjunctiva; dissection is continued posteriorly until Tenon's is incised at the point of insertion. A good-sized pocket is dissected with blunt Westcott scissors (Fig. 3), and cautery is used as needed to control any bleeding.

Once the dissection is complete, a paracentesis, as well as a 2-mm clear, corneal wound are made, and the anterior chamber is filled with a cohesive viscoelastic. The needle of the injector is inserted through the main incision and advanced across the anterior chamber toward the targeted quadrant and into the angle. The needle enters the trabecular meshwork and is pushed through the sclera, exiting 2 mm posterior to the limbus with the needle's beveled tip oriented upward. A second instrument (cyclodialysis spatula, Vera hook, etc.) can be inserted into the paracentesis to help stabilize the eye during this step. After the needle exits the sclera, any torsion or counterforce

Table 1: Comparison of Xen implantation techniques.

	Ab interno open conjunctiva	Ab externo open conjunctiva
Technique	1. Corneal traction suture is optional 2. Conjunctival peritomy and dissection are performed 3. Main and side port incisions (clear cornea) are made—AC is filled with cohesive OVD 4. The injector is inserted through the main incision, across anterior chamber towards the target area 5. The needle enters the trabecular meshwork and is advanced through the sclera exiting 2 mm posterior to limbus using counter traction 6. The stent is deployed and adjusted as needed 7. Flow is confirmed after removing OVD and priming the bleb 8. Tenon's layer and conjunctiva are sutured closed	1. Corneal traction suture may be placed in the superior cornea 2. Conjunctival peritomy and dissection are performed 3. Side port is optional—only needed if using OVD 4. The injector is placed in sclera 2–2.5 mm from the limbus; using the traction suture for counter traction 5. The needle is advanced through sclera until visible in AC 6. The stent is deployed and adjusted as needed 7. Flow of aqueous is confirmed by visualizing beading at the distal end of the stent 8. Tenon's layer and conjunctiva are sutured closed
Advantages	1. Better control of placement of stent in the angle 2. Can be easily combined with phacoemulsification	1. Expands the targeted area of implantation to the supero-temporal quadrant 2. Can be performed without corneal incisions or viscoelastic use 3. Easiest transition for glaucoma surgeons 4. Safer in phakic eyes
Disadvantages	1. Requires maneuvers in the AC 2. Can be challenging in eyes with corneal opacification	1. Entry into AC cannot be performed under gonioscopic guidance

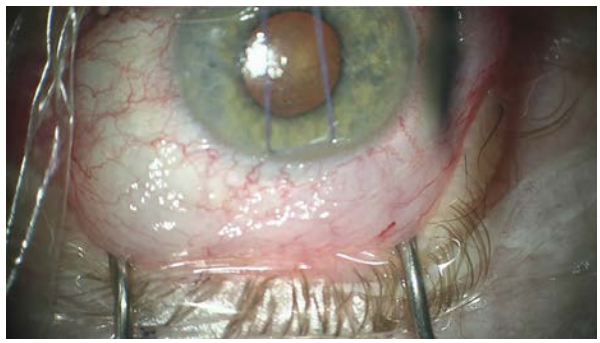


Fig. 1: Corneal traction suture place for counter traction. (image courtesy of Joseph F. Panarelli, MD)

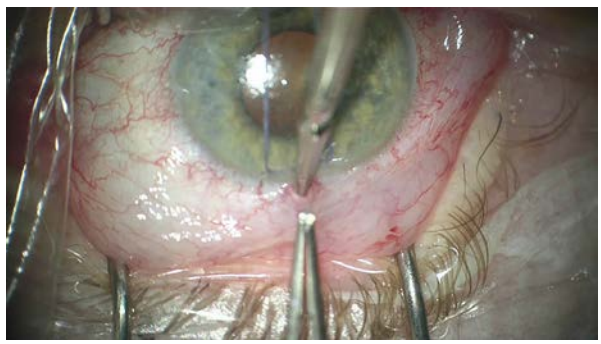


Fig. 2: Conjunctival peritomy at 12 o'clock with Vannas scissors. (image courtesy of Joseph F. Panarelli, MD)

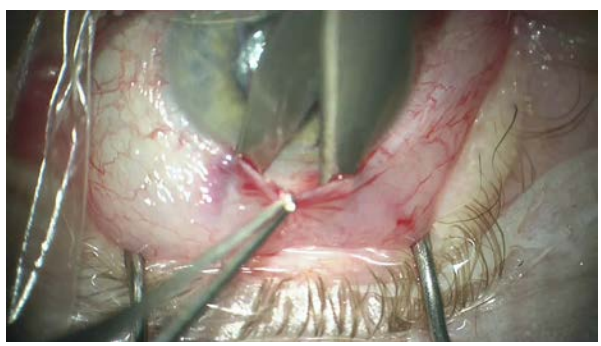


Fig. 3: Blunt dissection to ensure good size pocket. (image courtesy of Joseph F. Panarelli, MD)

should be released to assume a natural position of the eye prior to delivering the stent, which is then deployed by moving forward the blue slider of the injector. An ideally implanted stent should be visible 2–3 mm outside the sclera with 1 mm in the anterior chamber. Stent position in the angle can be verified with a gonioscopy lens. The open peritomy and direct visualization of the external tip of the Xen Gel Stent (Fig. 4) allow the surgeon to easily make micro-adjustments. Tying forceps can be used to pull the stent out or push it into the anterior chamber to ensure that it is properly positioned (Fig. 5).

The next step is to check for flow through the stent. After the viscoelastic has been removed from the anterior chamber, a Weck-cel (BVI Medical) can be used to touch the distal end of the device to make sure there is some slow percolation of fluid (Fig. 6).

If no fluid is detected, the device can be primed by back-flushing the device with balanced salt solution (BSS) in a 25-gauge cannula. The conjunctiva and Tenon's layers are then brought up over the device (Fig. 7) and closed in a watertight fashion (Fig. 8). This can be carried out with two winged sutures, or a short running closure on one side, along with two horizontal mattress stitches to close the limbal incision. The corneal incisions should be hydrated with BSS and a bleb should form (priming the bleb). A Seidel test can be performed to ensure there is no conjunctival or corneal incision leakage.

Patients can be injected with a bolus of corticosteroid at the completion of the case followed by topical corticosteroids at home. Patients are typically kept on steroids four times a day for 1 month, two times a day for the second month, and then tapered over the third month.

Ensuring ideal positioning of the distal end of the Xen Gel Stent beneath Tenon's layer has resulted in more predictable surgical outcomes for the authors and less need for post-operative manipulation such as needling. Blebs also tend to be more diffuse and posteriorly directed.

Advantages of an Open Conjunctiva, Ab Externo Placement

There are unique benefits to an ab externo placement of the Xen Gel Stent, which have led many surgeons to include this technique to their surgical armamentarium. The first benefit is to expand the targeted area of implantation. When the stent is placed ab interno, it is typically left in the superonasal quadrant as it is difficult to pivot the injector in the main incision and move further temporal. An ab externo approach provides easy accessibility to the entire superior quadrant. The ab externo technique is especially advantageous in patients who have had previous trabeculectomy in the superior or superonasal areas, as the Xen Gel Stent can be placed much further from pre-existing scar tissue than with an ab interno approach.

A second benefit to an ab externo approach is that it avoids maneuvers inside the anterior chamber and obviates the need for corneal incisions and the use of viscoelastic. Absence of maneuvers inside the anterior chamber may eliminate reported and potential complications, such as corneal wound leaks, retained viscoelastic and consequent IOP spikes, lens or endothelial cell touch, among others [1]. In phakic eyes, the ab externo approach essentially eliminates the risk of inadvertent damage to the lens capsule. This benefit is especially important in phakic patients

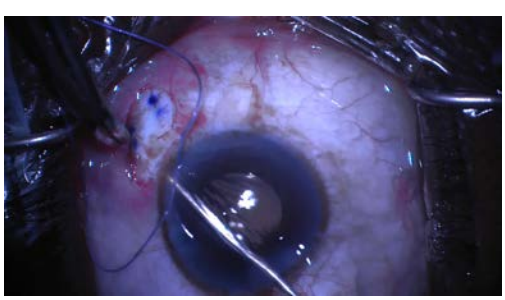


Fig. 4: Direct visualization of the stent during deployment. (image courtesy of Joseph F. Panarelli, MD)

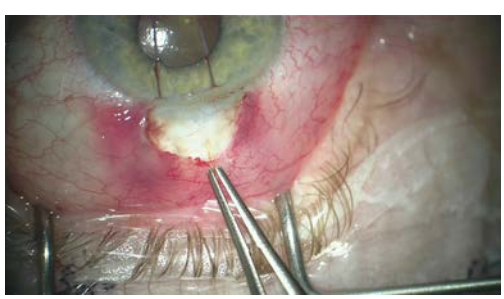


Fig. 5: Tying forceps used make micro-adjustments of the implant, ensuring 1-2-3 placement. (image courtesy of Joseph F. Panarelli, MD)

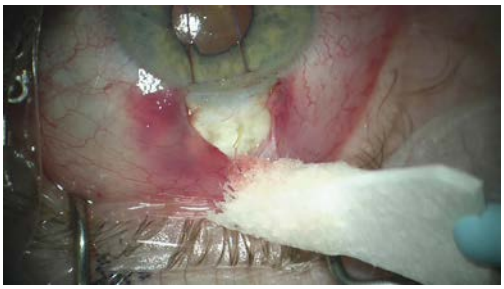


Fig. 6: Direct outflow check through the stent. (image courtesy of Joseph F. Panarelli, MD)

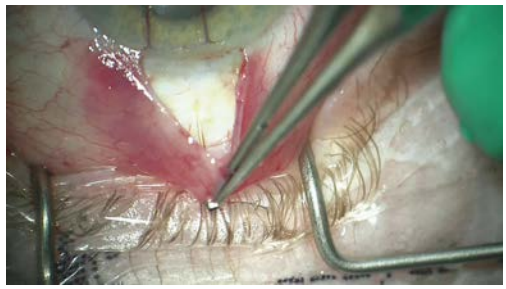
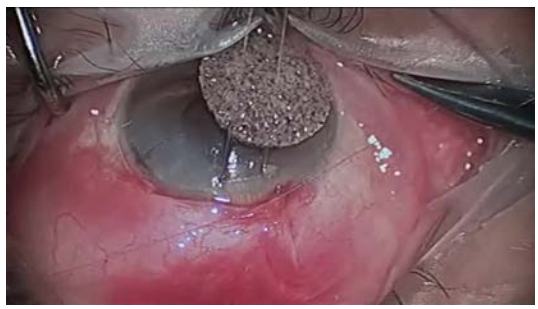


Fig. 7: Conjunctiva and Tenon brought over the implant for closure. (image courtesy of Joseph F. Panarelli, MD)

Fig. 8: Conjunctival closure. (image courtesy of Brian Francis, MD)



with significant lens rise and a shallow chamber where concomitant phacoemulsification may not be indicated.

Third, the ab externo technique may be the easiest transition technique for glaucoma surgeons new to the use of the Xen Gel Stent, as it most closely utilizes existing surgical skills and does not involve any new angle-surgery skills. Opening and closing of the conjunctiva is similar to trabeculectomy, and the insertion technique with the Xen injector needle is very similar to the creation of a needle track for the insertion of tube shunts.

Finally, as mentioned above, the open conjunctiva approach allows the surgeon to dissect or move the Tenon's capsule away and to easily make micro-adjustments of the stent by grasping it directly. The stent can be pulled out or pushed further into the anterior chamber to ensure that it is positioned properly.

Open Conjunctiva, Ab Externo Placement Technique

A 7.0 Vicryl (polyglactin 910; Johnson & Johnson Vision) traction suture may be placed in the superior cornea to rotate the eye looking down. A peritomy (around 2 mm for RC and 1 clock hour for DY), ideally at 12 o'clock, followed by a blunt dissection to break the adhesions between the conjunctiva and the Tenon's at the limbus, is more than sufficient to allow for delivery of the device (Fig. 9).

As with trabeculectomy, the vessels can be cauterized, if desired. Next, a Tenon's incision is made to enter sub-Tenon's space and expose the bare sclera (Fig. 10).

An optional tenectomy can be performed in cases of significant Tenon's thickening due to race, inflammation, scarring from previous surgery or other risk factors (Fig. 11). Performing a limited tenectomy may decrease the risk of stent obstruction/early failure. However, this may potentially lead to a higher risk of erosion through the conjunctiva. The Xen injector is then placed bevel up in the sclera, 2.0–2.5 mm from the limbus (Fig. 12); the original traction suture can be released and used for counter traction as the applicator needle is advanced through the sclera.

Advance the needle superficially until the tip is at the surgical limbus. The needle is then tilted downwards by about 30° and advanced until it enters the anterior chamber. The most common problems encountered during the delivery process are amputation of the stent or pulling the stent back out of the anterior chamber due to the tendency of the needle to flick upwards. These can be avoided by rotating the injector needle 90° or beveling down prior to deploying the stent and ensuring there is no upwards or side pressure on the injector. One option to avoid any issues when deploying the stent is to pull the injector back slightly (the sleeve of the injector should be about 1 mm from the scleral needle entry point) prior to pushing the blue slider forward. There is no need for forward pressure for the needle to stay in place within the scleral tunnel unlike with an ab interno delivery approach.

Once the stent is fully released, the flow of aqueous can be confirmed. As this technique does not create an entry into the anterior chamber, the anterior chamber remains very stable without the use of viscoelastic. At this point, a slow but steady flow of aqueous through the device can usually be visible. If no flow is seen, it is often due to peri-tubular flow. One of the authors (D.Y.) uses a pre-placed 10.0 nylon encircling suture (before the injector enters the sclera) approximately 1 mm posterior to the limbus to reduce peri-tubular filtration and the risk of early hypotony (Fig. 13). The Xen injector is then placed bevel up 1 mm posterior to the pre-placed scleral suture (Fig. 14). Beading of aqueous will frequently start as soon as an encircling suture is tied (Fig. 15) in these cases.

Once flow has been confirmed, the length and position of the Xen Gel Stent can be adjusted with tying forceps so that it is 1 mm in the anterior chamber (Fig. 16).

If the tip of the Xen Gel Stent is lifting off the wall of the sclera, it may be advantageous to secure the tip of the stent back against the scleral wall with a 10.0 nylon suture. This will reduce the risk of conjunctival erosion, especially in patients where a tenectomy was necessary.

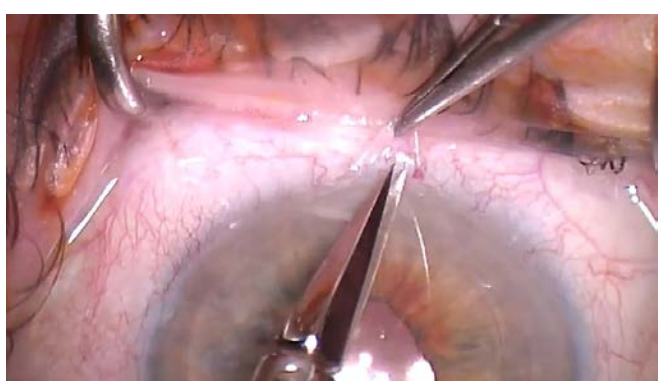


Fig. 9: An approximately 2-mm peritomy is created, and Vanass scissors are used to open the conjunctiva. (image courtesy of Randy Craven, MD)

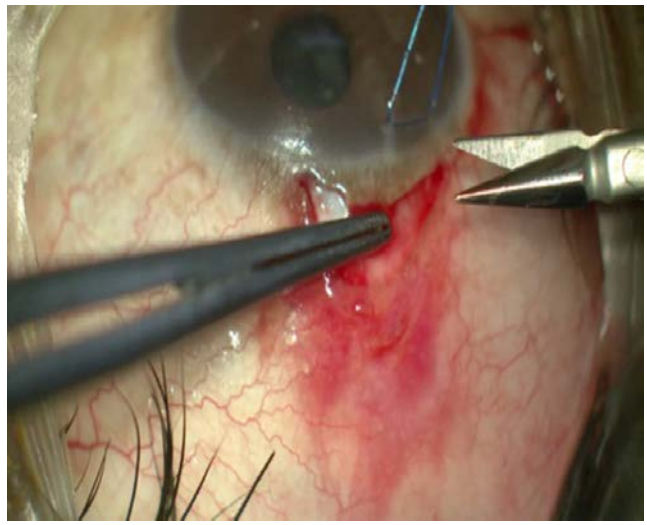


Fig. 10: Tenon's incision is made at the limbus to enter the sub-Tenon's space and expose the bare sclera. (Image courtesy of David Yan, MD)

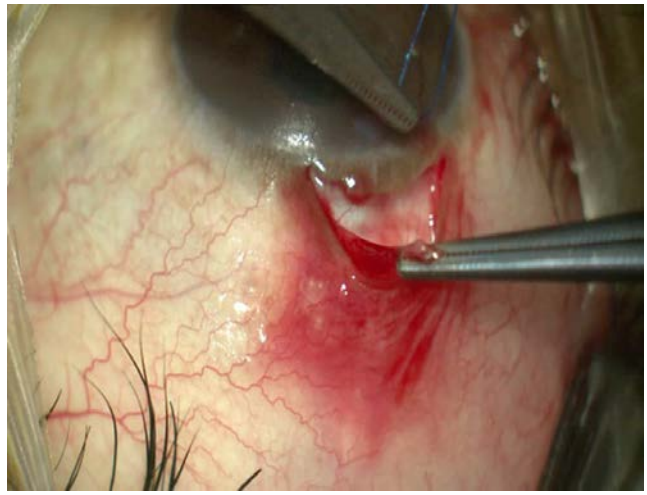


Fig. 11: Tenectomy may be performed in cases of significant Tenon's presence. (image courtesy of David Yan, MD)

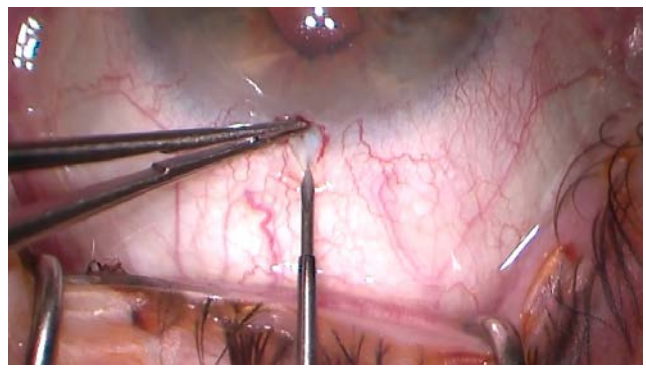


Fig. 12: Enter the eye 2–2.5 mm from the limbus. (image courtesy of Randy Craven, MD)

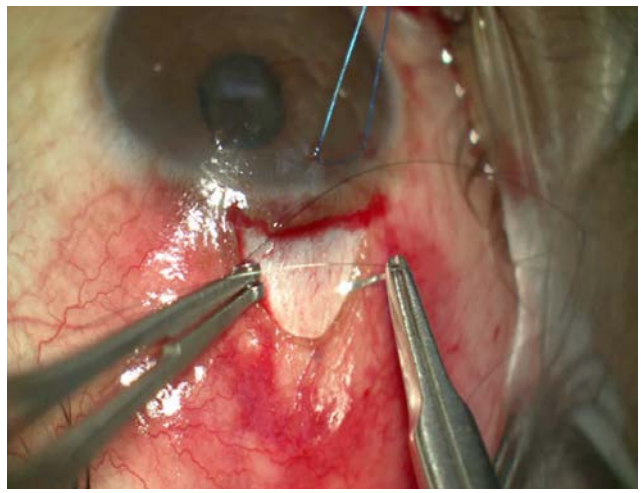


Fig. 13: A 10.0 nylon encircling suture is pre-placed ~ 1.0 mm posterior to the limbus to reduce peri-tubular filtration. (image courtesy of David Yan, MD)

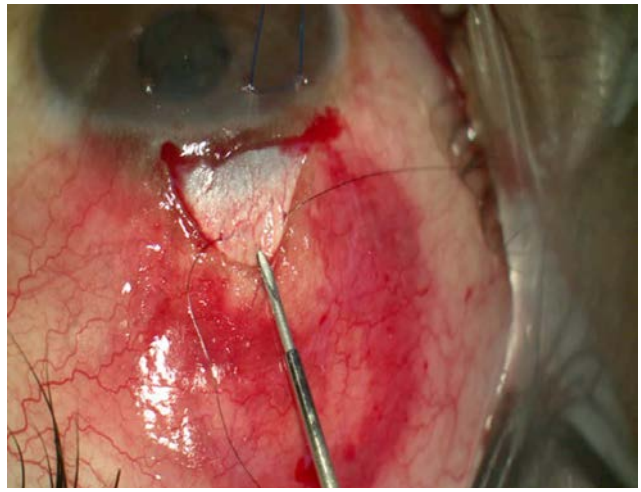


Fig. 14: Injector is then placed bevel up ~ 1 mm posterior to the pre-placed scleral suture. (image courtesy of David Yan, MD)

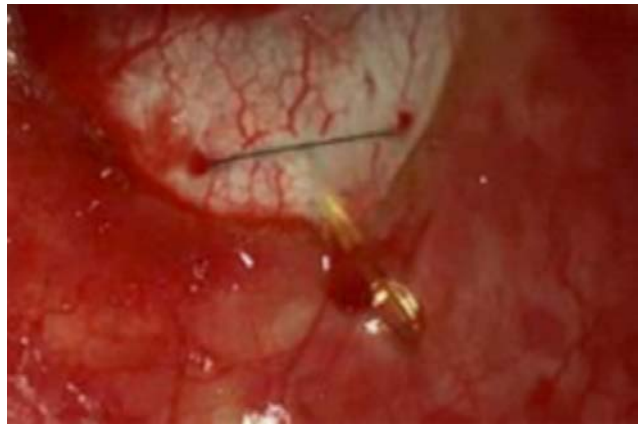


Fig. 15: Note beading of aqueous at distal end of the Xen Gel Stent after 10.0 nylon suture has been tied tight. (image courtesy of David Yan, MD)

The Tenon's layer and conjunctiva are then pulled anteriorly and closed (in two steps or both layers at once) with Vicryl sutures (Fig. 17) or 10-0 Nylon, creating a watertight closure with two wings or a running suture technique, as per surgeon preference. Care should be taken when pulling the conjunctiva forward to avoid dragging the Xen into the anterior chamber. Ideal placement with this technique is the Xen Gel Stent tip to be either directly under the conjunctiva (when generous tenectomy is performed) or tucked inferior underneath Tenon's capsule.

Peri-operative/Adjunctive Use of Antifibrotic Agents

Most cases of failure following glaucoma filtering surgeries are related to the proliferation of fibroblasts, synthesis of extracellular matrix, and subsequent development of subconjunctival fibrosis [6]. Research has been carried out to investigate the potential for excising Tenon's capsule [7, 8], placing valve implants above Tenon's [9], and locating filtering blebs under Tenon's [10]. However, it seems that the most important element to a successful glaucoma filtering surgery is the use of antimetabolites [1, 11, 12].

As the Xen Gel Stent procedure results in a subconjunctival filtration bleb, the use of MMC or 5 fluorouracil to control subconjunctival and episcleral fibrosis is becoming the standard of care. Initial studies of the Xen Gel Stent, without the use of an antifibrotic agent, resulted in failure rates of between 50% and 80% [1, 13]. Failure rates in single digits have been published in trials that included use of the MMC with the Xen Gel Stent procedure [2, 14, 15].

The authors employ antifibrotic agents according to the characteristics of the specific patient and their preferences. We present here four perioperative approaches employed by these authors.

Option 1 Prior to starting the peritomy, MMC may be injected (0.4 mg/ml × 0.1 ml) approximately 10 mm posterior to the limbus, followed by use of a Weck-cel at the limbus to limit anterior spread of MMC. If a lower concentration of MMC is desired, it may be mixed with the Lidocaine. Due to the diffuse and posteriorly directed bleb, some authors (J.P.) feel comfortable injecting a higher concentration of MMC (60–80 mcg) at the beginning of the procedure (Figs. 18, 19).

Option 2 MMC-soaked sponges may be placed posteriorly underneath Tenon's after both the conjunctiva and Tenon's have been dissected.

Option 3 MMC can be applied with a cannula into the dissected subconjunctiva space ~ 4 mm posterior to the distal end of the Xen Gel Stent (~ 8 mm posterior to the limbus) after the stent has been placed (Fig. 20). A small amount of balanced salt solution can be used to diffuse the MMC and create a larger bleb.

Option 4 MMC may be injected subconjunctivally at the end of the case after the conjunctiva has been closed. Since the Xen Gel Stent is already in place, it is desirable to repressurize the anterior chamber with BSS to ensure there is no ingress of MMC into the anterior chamber.

Applying MMC after conjunctival dissection has the advantage of minimizing hydration of the Tenon's, preserving the natural tissue architecture and ease of dissection.

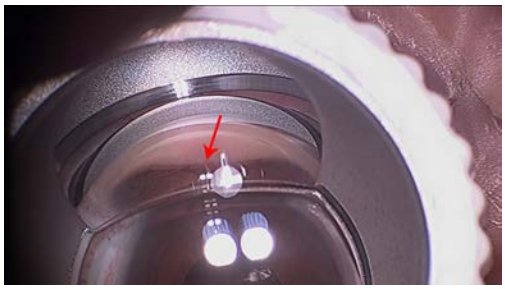


Fig. 16: The length and position of the Xen Gel Stent can be checked with gonioscopy prior to closing the conjunctiva. (image courtesy of Brian Francis, MD)

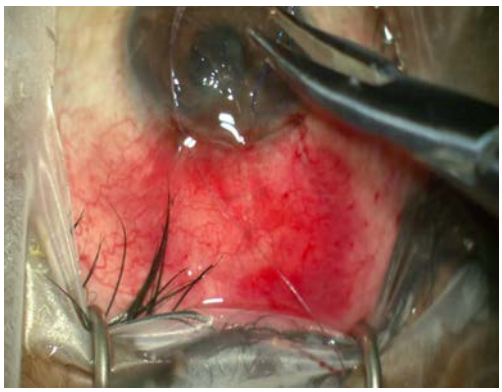
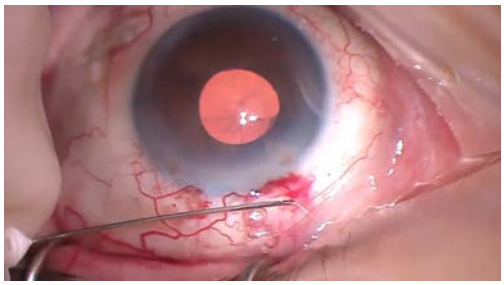


Fig. 17: Conjunctival closure. (image courtesy of David Yan, MD)



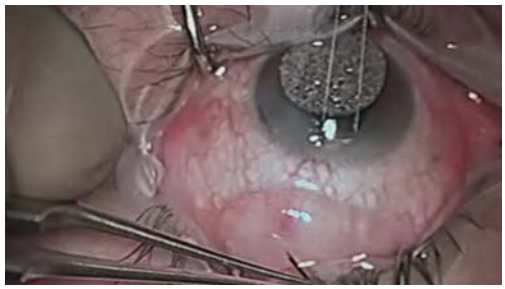


Fig. 18: MMC is injected > 10 mm from the limbus prior to conjunctival opening and stent implantation. (image courtesy of Brian Francis, MD)

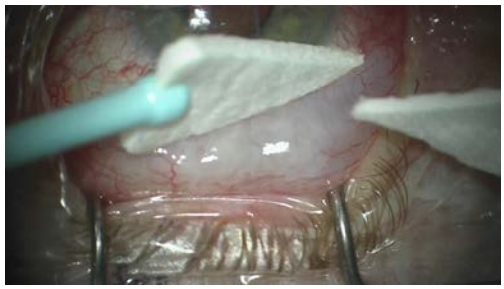


Fig. 19: Weck-cel placed at the limbus to limit anterior spread of MMC and kept posteriorly. (image courtesy of Joseph F. Panarelli, MD)

Fig. 20: MMC is injected > 8 mm from the limbus after conjunctival dissection and stent implantation. (image courtesy of Randy Craven, MD)

Open Conjunctiva Revision of Xen Gel Stent

A Xen Gel Stent surgery that has failed can be addressed via needling or by open conjunctiva revision. One of the authors (D.Y.) usually performs needling in cases where there is a focal bleb with a "ring of steel" limiting the bleb size; it should have a good conjunctiva that is mobile, not inflamed or vascularized outside of the ring. Many surgeons (B.F.) have transitioned to proceed directly to an open conjunctiva revision as the success rate seems to be higher with longer lasting effect.

Open revision can be performed in any case of Xen failure due to fibrosis, encapsulation when medical management or needling was not successful (clinically seen as a focal encapsulated bleb or a sleeve of tissue seen surrounding the distal tip of the implant) or in the presence of a curled and not freely mobile distal tip, indicating that it is embedded in Tenons tissue. Prior to surgery, confirm that the proximal end of the implant in the anterior chamber is in good position and not blocked with iris tissue.

Surgical Technique

1. If a subconjunctival injection of MMC is preferred, start with a dose of MMC between 40 and 80 μg in the area surrounding the distal tip of the failed implant. An alternative is applying MMC via sponges once the tissue is opened.
2. A conjunctival peritomy is made at the limbus, keeping Tenon's insertion intact.
3. A blunt posterior dissection is carried out to separate Tenon's from the conjunctiva.
4. Careful dissection of the capsule or tissue surrounding the implant with Vannas scissors is performed to uncover the Xen Gel Stent. If the implant is damaged during this step, a new implant can be placed via ab externo approach.
5. If the Tenon's layer is thickened and fibrotic, perform a limited removal of the tissue in the filtration zone.
6. At this point, flow through the device should be confirmed. If there is no apparent outflow from the Xen Gel Stent, it may be unblocked by inserting the stent tip inside a 27G cannula mounted on a 3-ml syringe and flushing the stent with BSS into the anterior chamber.
7. If MMC is applied via sponges, it should be done at this time.
8. BSS is used to wash out MMC. The cannula can be inserted more posteriorly to provide posterior tissue dissection to facilitate a larger and more posterior filtration zone.
9. The conjunctiva is closed using the surgeon's preferred technique. Two wing sutures with 8.0 Vicryl on a BV needle with the knots buried is preferred by most of the authors of this paper. If needed, add a central mattress suture at the limbus.

The key takeaway points are (1) reapplication of MMC, (2) freeing up Tenon's adhesions, (3) creating a space between Tenon's and sclera for the distal tip of the implant (rather than in the subconjunctival space), and (4) ensuring integrity and function of the implant (a new implant can be placed if needed).

One of the authors (B.F.) anecdotally found the success rate to be approximately 70–80%. Based on the high success rate in his hands, an open conjunctiva revision is his go-to procedure after Xen Gel Stent failure. Traditional filtration glaucoma surgery is recommended if this approach fails.

Discussion

A retrospective cohort study was conducted by Yan *et al.* [16] on 45 consecutive patients with previous glaucoma surgery and conjunctival scarring who underwent ab externo, open conjunctiva

Xen Gel Stent implantation. At 12 months after Xen placement, 71% of patients had an IOP less than 18 mmHg or an IOP reduction greater than 20% on no medications, while 96% of patients met the same IOP criteria with IOP lowering medications. Patients with conjunctival scarring from previous surgery are generally poor candidates for Xen Gel Stent implantation by a closed conjunctiva, ab interno approach, and a tube shunt is more commonly utilized after the first glaucoma surgery has failed. The results of this retrospective study are encouraging for expanding the scope of usage for the Xen Gel Stent to more challenging cases by adopting an open conjunctiva, ab externo technique. One author (J.P.) reports that, in patients implanted with the Xen Gel Stent using an open conjunctiva, ab externo approach, less than 5% of his patients require a needling procedure, and the remaining authors concur that their needling rates have plummeted (unpublished data). None of the authors of this paper have seen any erosions with this technique to date, likely because the implant is deeper in the tissue, leaving a protective layer of Tenon's above the distal end of the tip. Based on personal clinical experience, some authors (B.F.) prefer the open conjunctiva, ab externo approach in patients that have a lower target IOP of around 10–12 mmHg. While a comparative study has not been carried out, the clinical experience of the authors has led them to believe that an open conjunctiva approach allows for a lower IOP compared to a closed conjunctiva approach.

Opening the conjunctiva with a small incision provides many advantages. First, it allows for direct anatomical confirmation of stent placement and the possibility of placement in the superotemporal conjunctiva. Second, it allows for clear separation of the Tenon's insertion from the episclera and a nice posterior "pocket" where the Xen Gel Stent can be placed to achieve a posterior bleb and avoids the stent getting tangled in the Tenon's. In addition, it provides the option to perform a tenectomy if the tissues are found to be scarred or thickened upon initial dissection. Third, this approach allows anti-metabolites to be injected near the distal tip of the Xen Gel Stent under the conjunctiva or applied with sponges, based on surgeon preference.

Conclusion

The benefits of the ab externo technique include easier visualization of the angle in patients with a very shallow chamber, with severe corneal opacity, or with extremely deep-set eyes and open access to cauterize bleeding in cases with increased hyperemia. Additionally, it allows surgeons to limit the trauma secondary to intraocular surgery (corneal incisions, anterior chamber manipulation, etc.) The ab interno technique, on the other hand, lends itself to use with cataract surgery. Hence, proficiency with both approaches helps the surgeon customize gel stent surgery to the needs of the individual patient and greatly expands the scope of utilization of the Xen Gel Stent to patients with a wide variety of challenges.

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Compliance with Ethics Guidelines: This article does not contain any studies with human participants or animals performed by any of the authors.

Data Availability: Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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CLINICAL VIGNETTE

Intraocular Lens Placement in the Setting of Glaucoma

Emily M. Zepeda, Brenda L. Bohnsack

Glaucoma in the Setting of Aphakia

The most common clinical scenarios in which glaucoma complicates aphakia are glaucoma following cataract surgery and uveitic glaucoma. Intraocular pressure (IOP) management must take precedence as substantial vision loss due to glaucoma negates the importance of intraocular lens (IOL) placement for visual rehabilitation. In both glaucoma following cataract surgery and uveitic glaucoma, topical antihypertensive medications are the first-line treatment for increased intraocular pressures [1, 2]. In eyes refractory to medications, the choice of traditional surgical options including goniotomy, trabeculotomy, trabeculectomy, glaucoma drainage devices, and cycloablation (transscleral and endoscopic) is dependent on factors such as angle configuration, corneal clarity, eye size, and previous eye surgeries [3-11]. Glaucoma surgery that is required to obtain IOP control should be done prior to secondary IOL placement.

Evidence of good IOP control includes serial pressure measurements, reversal of optic nerve cupping, resolution of corneal edema, and stabilization of corneal diameter and axial length. While axial lengths measured via A-scan ultrasound or optical biometry systems (i.e., Lenstar®, IOL-Master®) are most accurate, they may not be plausible in-clinic options for young children. In this case, stabilization of the refraction may be an acceptable substitute. For the purpose of IOL selection, it is important to note that in glaucomatous eyes with buphthalmos, rapid intraocular pressure control obtained through glaucoma surgery often causes a sudden decrease in axial length followed by a slower re-expansion of the globe. The final length may fall between the immediate postoperative and the maximum buphthalmic eye lengths [12, 13]. Thus, selecting a lens based on a buphthalmic measurement can result in a hyperopic shift, while not waiting until axial length stabilization following glaucoma surgery may cause a more myopic end refraction [14, 15].

E. M. Zepeda
Department of Ophthalmology, Dean McGee Eye Institute, University of Oklahoma, Oklahoma City, OK, USA

B. L. Bohnsack (✉)
Department of Ophthalmology and Visual Sciences, Kellogg Eye Center, University of Michigan, Ann Arbor, MI, USA
e-mail: brendabo@med.umich.edu

Intraocular Lens Placement in Glaucoma Following Cataract Surgery

Following congenital cataract extraction, it is well-known that the newly rendered aphakic eye is at high risk for developing glaucoma, with an incidence ranging from 15% to 50% [16, 17]. In these patients, elevated IOP is often observed within the first few years after surgery but can occur years later, highlighting the importance of diligent, lifelong surveillance.

The majority of cases of glaucoma following cataract surgery have an open-angle configuration and arise directly because of the aphakic status [16-19]. In these cases, the angle typically has a normal appearance both prior to and following cataract surgery making it unclear as to the pathogenesis of this form of glaucoma [20, 21]. Since the most notable risk factor is age at the time of cataract surgery, with infants under the age of 2 months having the highest rate of glaucoma, the mechanistic theories revolve around the lens, mechanically (tension from the lens on the ciliary body) and/or molecularly (secreted factors), being required for angle and aqueous outflow channel development [16, 19, 22]. Additional theories suggest that post-surgical inflammation or vitreous factors released after breaking the anterior hyaloid damage the aqueous channels [23]. In these cases, antihypertensive medication is the first-line treatment; however, up to 50% of eyes require glaucoma surgery for IOP control [24, 25]. Angle surgery (goniotomy or trabeculotomy) is typically the primary glaucoma surgery and has a 50–70% success rate [26-30]. If angle surgery fails to control IOP, many patients will have placement of a glaucoma drainage device [31, 32]. In eyes that are aphakic, placement of the tube in the pars plana with a concurrent vitrectomy should be considered. This is especially true if a secondary IOL will be implanted in the future [33-35]. Additional patients may undergo trabeculectomy, although filtering surgeries with adjunctive anti-fibrotics have become less popular in the pediatric population due to the lifelong risk of endophthalmitis [36, 37]. Another option is cyclophotocoagulation, which can be successfully used to control IOP either alone or in conjunction with glaucoma drainage devices [38].

In some cases of glaucoma following cataract surgery, there is a narrow-angle or a closed-angle configuration. In these eyes, there are often preexisting pathologic states such as microphthalmia and/or microcornea [16, 18]. Elevated IOP may develop early during childhood due to the congenital anatomically shallow anterior chambers. In addition, glaucoma may be diagnosed in late childhood to adulthood due to further crowding of the anterior chamber from the Soemmering ring, which gradually increases in diameter due to proliferation of the lens epithelial cells and cortical fibers within the posterior and anterior capsules [39-41]. In these situations, angle surgery often fails, and glaucoma drainage device implantation is typically used to obtain IOP control [33]. However, given the shallow anterior chamber, the safest place for the tube is posteriorly placed within the pars plana.

Case 1

The patient is a 9-year-old girl with a history of congenital cataracts with microphthalmia of both eyes. She underwent cataract extraction of the right eye at 6 weeks of age and the left eye at 7 weeks of age. Her vision was corrected with contact lenses, which she tolerated well. She was diagnosed with glaucoma following cataract surgery in both eyes at 7 years of age and underwent combined

180-degree trabeculotomy with trabeculectomy at 8 years of age. However, her intraocular pressure in her right eye remained uncontrolled, and she was referred for further treatment.

At the time of presentation, the patient's best-corrected visual acuity with +20.0 SilSoft® contact lenses was 20/40 in the right eye and 20/25 in the left eye. The intraocular pressures by Goldmann tonometry were 30 mmHg in the right eye and 17 mmHg in the left eye on timolol, dorzolamide, brimonidine, and latanoprost in both eyes. Slit lamp examination showed that both corneas were thin and clear (Fig.1a). The right cornea was 9 mm in diameter, and the left cornea was 10 mm in diameter. The anterior chambers were shallow with approximately 2.5 mm depth centrally and 0.5 mm depth peripherally. Both eyes were aphakic and had Soemmering rings. Fundoscopic examination showed a dysplastic optic nerve with a cup to disc ratio of 0.8 in the right eye. The left eye had a cup to disc ratio of 0.1. The macula, vessels, and retinal periphery of both eyes were normal.

For glaucoma control, the patient underwent pars plana placement of a Baerveldt® 350 glaucoma drainage device with concurrent vitrectomy in the right eye at 9 years of age. This was followed by pars plana placement of a Baerveldt® 350 glaucoma drainage device with concurrent pars plana vitrectomy in the left eye at 10 years of age.

At 12 years of age, the patient desired placement of IOLs. At that time, her best-corrected visual acuity was 20/20 in each eye. Slit lamp examination showed blebs over the superotemporal Baerveldt plates in both eyes. Intraocular pressures by Goldmann applanation tonometry were 15 mmHg in both eyes on no glaucoma medications. The right optic nerve showed reversal of cupping with a color cup to disc ratio of 0.3 (Fig. 1b). Axial lengths measured 20.4 mm in the right eye and 19.73 mm in the left eye, and keratometry was 42.39 × 44.64 @ 98 in the right eye and 44.57 × 45.82 @ 94 in the left eye. The patient underwent serial placement of a three-piece acrylic lens in the sulcus in both eyes.

At final follow-up at 14 years of age, the patient's uncorrected visual acuity was 20/20 in each eye. Her intraocular pressures by Goldmann applanation tonometry were 16 mmHg in the right eye and 15 mmHg in the left eye on no glaucoma medications. She had superotemporal blebs over the Baerveldt plates, thin and clear corneas, shallow anterior chambers, and sulcus IOLs in both eyes. The optic nerves were stable in appearance (Fig.1b) as was retinal nerve fiber layer thickness and visual field testing (Fig. 1c) compared to before IOL placement.

Comment

Placement of a secondary IOL in an eye with glaucoma following cataract surgery requires IOP control and recognition of the angle and anterior chamber anatomy. Special consideration should be given to the anatomical features of the aphakic eye with glaucoma when deciding whether to place the lens in the sulcus or the capsular bag [42, 43].

Secondary IOLs are typically placed within the sulcus, using the Soemmering ring as a scaffold [44]. However, in the setting of glaucoma, placement of the IOL within the sulcus may further impede outflow through the trabecular meshwork especially in eyes with shallow anterior chambers due to microphthalmia or microcornea. Furthermore, in eyes that have previously undergone angle surgery, gonioscopy should be done prior to IOL placement to evaluate patency of the cleft

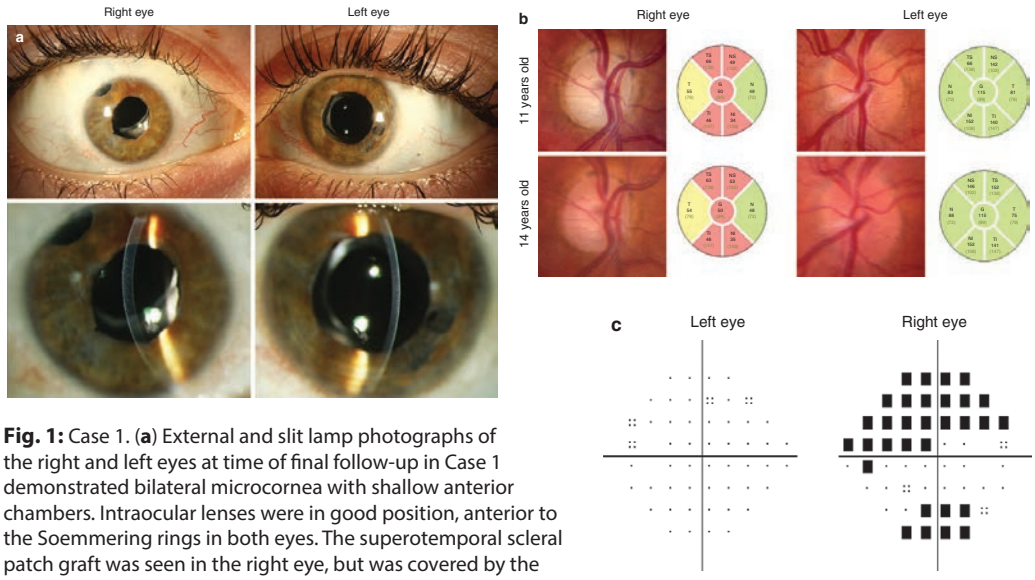

Fig. 1: Case 1. (**a**) External and slit lamp photographs of the right and left eyes at time of final follow-up in Case 1 demonstrated bilateral microcornea with shallow anterior chambers. Intraocular lenses were in good position, anterior to the Soemmering rings in both eyes. The superotemporal scleral patch graft was seen in the right eye, but was covered by the upper lid in the left eye. The tubes in both eyes were in the pars plana and thus not evident in the photographs. (**b**) Optic nerve photographs and optical coherence testing prior to intraocular lens placement (11 years of age) and at final follow-up (14 years of age) showed no glaucomatous progression. (**c**) Humphrey visual field testing demonstrated a superior arcuate and an early inferior arcuate defect in the right eye that correlated with the retinal nerve fiber layer thickness. Visual field in the left eye was full.

and the amount of space within the peripheral anterior chamber. Another consideration for the surgeon is that commercially available one-piece acrylic lenses (Alcon® SA60AT) come in powers up to 40 diopters; the three-piece acrylic lenses (Alcon® MA60AC) only have a maximum power of 30 diopters. Especially in small, microphthalmic eyes, placement of a high-power one-piece lens within the capsule allows for greater accuracy in achieving the target refraction.

In order to minimize anterior chamber crowding, maintain patency of the angle, and place the IOL within the capsule, the Soemmering ring needs to be opened and debulked [43]. In this procedure, a 4–5-clock-hour peritomy is created. A 3 mm scleral tunnel is centered within the incision, and a stab incision at the limbus is made on each side of the tunnel. An anterior chamber maintainer is placed through one of the stab incisions. A MVR blade, placed through the other stab incision, is used to separate the anterior and posterior capsules where they are fused centrally. Care should be taken to open the ring 360 degrees for maximal removal of lens material. The vitrector is then used to remove the proliferated cortical fibers and lens epithelial cells within the capsule. Dense Soemmering rings with hardened, calcified cortical fibers may not be easily removed with the vitrector. Viscoelastic can be injected into the anterior chamber, and the calcified fibers can be prolapsed out of the capsule in the anterior chamber. The scleral tunnel is then opened with a keratome, and the calcified fibers can be removed "extracapsular" style through the scleral tunnel. Following removal of the remnant lens fibers, the anterior and posterior capsules are inspected. If there is adequate support, then the IOL can be carefully placed within the capsule.

If the posterior capsule does not have enough support, the entire IOL can be placed in the sulcus, or only the haptics can be placed in the sulcus with optic capture. A third option for older teenagers (>16 years of age) and adults is complete removal of the Soemmering ring and capsule and placement of a scleral-fixated IOL.

In microphthalmic eyes with glaucoma, if the aqueous outflow is not dependent on the angle, a secondary lens can be placed in the sulcus without debulking the Soemmering ring as described in the case above. In this example, the patient's intraocular pressures were controlled by glaucoma drainage devices allowing the lenses to be placed in the sulcus and the Soemmering ring left intact. It is important to note that in both eyes the tube portion of the glaucoma drainage device was preemptively placed in the pars plana in a combined procedure with a vitrectomy [33]. Posterior placement of the tube serves two purposes: (1) long-term prevention of corneal decompensation in a shallow anterior chamber and (2) better positioning of the tube for later placement of a secondary IOL [33, 34, 45]. In aphakic eyes with glaucoma drainage devices previously placed within the anterior chamber, consideration should be given to moving the tube to the pars plana either in conjunction with or prior to placement of a secondary IOL. The disadvantage to posterior placement of glaucoma drainage devices is the need for concurrent vitrectomy. Coordination of surgery between retina and glaucoma specialists can be difficult but decreases the need for multiple surgeries and improves communication to ensure adequate vitreous removal in the area of the tube. The increased risk of retinal detachment due to vitrectomy is low and outweighs the risk of corneal decompensation, especially in eyes with crowded anterior chambers [33-35, 45]. With pre-planning and appropriate tube placement, Case 1 demonstrates how sulcus placement of a secondary IOL achieves excellent uncorrected visual acuity and maintenance of intraocular pressure control.

Thus, when placing an IOL in an eye with glaucoma following cataract surgery, attention should be paid to the size of the anterior chamber and the previous glaucoma surgeries. Care must be taken to prevent exacerbation of intraocular pressures in eyes that are prone for glaucoma due to the aphakic status and inherent ocular anatomy.

Intraocular Lens Placement in Uveitic Glaucoma

Uveitis causes significant visual impairment as chronic inflammation leads to cataracts, glaucoma, band keratopathy, synechiae, and macular edema [46-48]. Treatment focuses on suppression of inflammation in order to prevent long-term damage first with local and systemic steroids and second with systemic steroid-sparing therapy. However, both the inflammation and steroids contribute to cataract formation and increased intraocular pressures [49, 50]. The removal of uveitic cataracts should only be undertaken after preoperative inflammation control has been achieved. In general, there should be at least 3 months without uveitic activity prior to cataract extraction. However, whether an IOL can be placed in uveitis remains unsettled. Although many surgeons now elect to place standard acrylic IOLs, there remains a possibility that the IOL could exacerbate the inflammation inciting further complications. Thus, it is an acceptable practice to leave the eye aphakic, especially in situations of tenuous uveitis control [51-53].

Increased IOP in uveitis is due to multiple mechanisms. Uveitic debris collects within the trabecular meshwork and angle leading to decreased aqueous humor outflow [54-56]. In this

situation, a membrane is often removed during angle surgery, rendering goniotomy and trabeculotomy highly successful [3, 4, 5, 6]. Chronic inflammation also causes synechiae formation and a closed-angle configuration. In some cases, goniosynechiolysis may be employed to reopen the angle, but in others, either glaucoma drainage device implantation or trabeculectomy is a better option to obtain IOP control [57-66]. It is also important to remember that local steroids needed for inflammation control can raise eye pressure [67-69]. Aggressive use of systemic steroid-sparing therapy in order to taper off of local steroids may be required. Regardless of the mechanism, control of the uveitis is paramount for treating the glaucoma. Any consideration of IOL implantation should occur only following both inflammation and IOP control.

Case 2

The patient is a 20-year-old woman with a history of idiopathic uveitis diagnosed at 4 years of age. Her uveitis was controlled with topical steroids, and she did not require steroid-sparing therapy. She was successfully tapered off of topical steroids at 15 years of age without uveitis recurrence. The patient underwent cataract extraction without IOL placement in both eyes at 5 years of age, and glaucoma was diagnosed at 8 years of age. At 11 years of age, the right eye underwent a trabeculectomy with mitomycin C, which was complicated by a postoperative suprachoroidal hemorrhage. She then underwent two goniotomies of the left eye at 16 and 18 years of age. Her intraocular pressures in her left eye remained uncontrolled, and she was referred for further treatment.

At the time of presentation, the patient's best-corrected visual acuity was 20/100 in the right eye and 20/40 in the left eye. Her aphakic correction was +10.75 in the right eye and +10.00 in the left eye. The intraocular pressures by Goldmann applanation tonometry were 8 mmHg in the right eye and 20 mmHg in the left eye. The patient was on timolol, dorzolamide, brimonidine, and bimatoprost in the left eye and oral acetazolamide. Slit lamp examination showed an avascular, thin, and cystic bleb at the superonasal limbus in the right eye. Both corneas were thin and clear. The anterior chambers were deep and quiet. The eyes were aphakic with synechiae between the iris and the Soemmering ring. Fundoscopic examination showed pale optic nerves with a cup to disc ratio of 0.95 in both eyes. The macula in the right eye lacked a foveal light reflex. The macula, vessels, and retinal periphery of the left eye were normal.

For the increased IOP in the left eye, the patient underwent pars plana placement of a Baerveldt® 350 glaucoma drainage device with concurrent vitrectomy. Following surgery, the patient's intraocular pressure in the left eye ranged from 6 to 10 mmHg off of all glaucoma medications.

At 25 years of age, the patient desired placement of IOLs. Her visual acuity had remained stable. Slit lamp examination showed a stable trabeculectomy bleb superonasally in the right eye and a large bleb over the superotemporal Baerveldt® plate in the left eye. Intraocular pressures by Goldmann applanation tonometry were 12 mmHg in the right eye and 7 mmHg in the left eye on no glaucoma medications. Axial lengths measured 23.6 mm in the right eye and 23.4 mm in the left eye, and keratometry was 42.15 × 44.91 @ 38 in the right eye and 42.74 × 44.40 @ 87 in the left eye. The patient desired a mild myopic target. In the right eye, the Soemmering ring was opened and debulked, and a three-piece acrylic lens was placed in the capsular bag. In addition, a subconjunctival injection of

mitomycin C (0.2 mg/ml) was administered posterior to the trabeculectomy bleb, and the bleb was needled to remove surrounding Tenon's encapsulation. In the left eye, the Soemmering ring was opened and debulked, and a three-piece acrylic lens was placed in the capsule.

At final follow-up at 27 years of age, the patient's best-corrected visual acuity was 20/125 in the right eye and 20/40 in the left eye. Her refraction was −2.00 in the right eye and −3.50+1.50 × 105 in the left eye. Intraocular pressures by Goldmann applanation tonometry were 10 mmHg in the right eye and 8 mmHg in the left eye off of all glaucoma medications. Slit lamp examination showed a diffuse, mildly elevated trabeculectomy bleb at the superonasal limbus of the right eye and an elevated bleb over the Baerveldt® plate superotemporally in the left eye. The corneas were clear, and the anterior chambers were deep with no evidence of uveitis. In both eyes, the IOLs were in good position within the capsules (Fig. 2a). The optic nerves, retinal nerve fiber layer thicknesses (Fig. 2b), and visual fields were stable (Fig. 2c).

Comment

Placement of a secondary IOL in an eye with uveitic glaucoma requires inflammation and IOP control. Unlike cataract surgery, which has to be done to improve vision, secondary IOL implantation is elective and should only be pursued if the uveitis has become quiescent [70]. In pediatric cases of uveitis, this typically occurs after puberty and is established when the patient has been successfully tapered off of all steroid and steroid-sparing therapies. Even though the uveitis has been inactive, the patient should be treated with oral steroids for 3–5 days prior to and following surgery to suppress the anticipated higher inflammatory response.

There are additional considerations in uveitic eyes that have undergone glaucoma surgery. Similar to eyes with glaucoma following cataract surgery, in eyes that have undergone angle surgery for uveitic glaucoma, attention should be paid to maintaining the open-angle configuration and cleft patency [3-6]. This includes placement of the IOL within the capsule and treatment with oral and topical steroids to minimize the postoperative inflammation and synechiae formation. The surgeon should be aware that the robust postoperative inflammatory response can result in hypotony, bleb flattening, and subsequent bleb failure. In eyes that have previously undergone trabeculectomy, the incisions for the IOL placement should be placed temporally to avoid injury to the superior bleb. Case 2 illustrated how a subconjunctival injection of mitomycin C posterior to the existing bleb and removal of Tenon's encapsulation tissue are important in preventing postoperative bleb failure. The bleb should be monitored carefully, and additional subconjunctival anti-fibrotic injections and bleb revisions may be needed to salvage flow through the trabeculectomy and maintain bleb morphology [71, 72]. As stated, in eyes with glaucoma drainage devices, the ideal position for the tube is within the pars plana as placement of the IOL will not interfere with tube function. A previously placed tube within the anterior chamber may be moved posteriorly concurrent with vitrectomy and IOL placement [33]. Although less important in uveitis compared to microphthalmia, posterior placement of the tube prevents corneal decompensation [33-35]. Thus, in uveitic glaucoma, IOLs should be placed within the capsule to prevent reactivation of inflammation. Additional procedures may be required in eyes, which have had glaucoma surgery, especially trabeculectomies and glaucoma drainage devices.

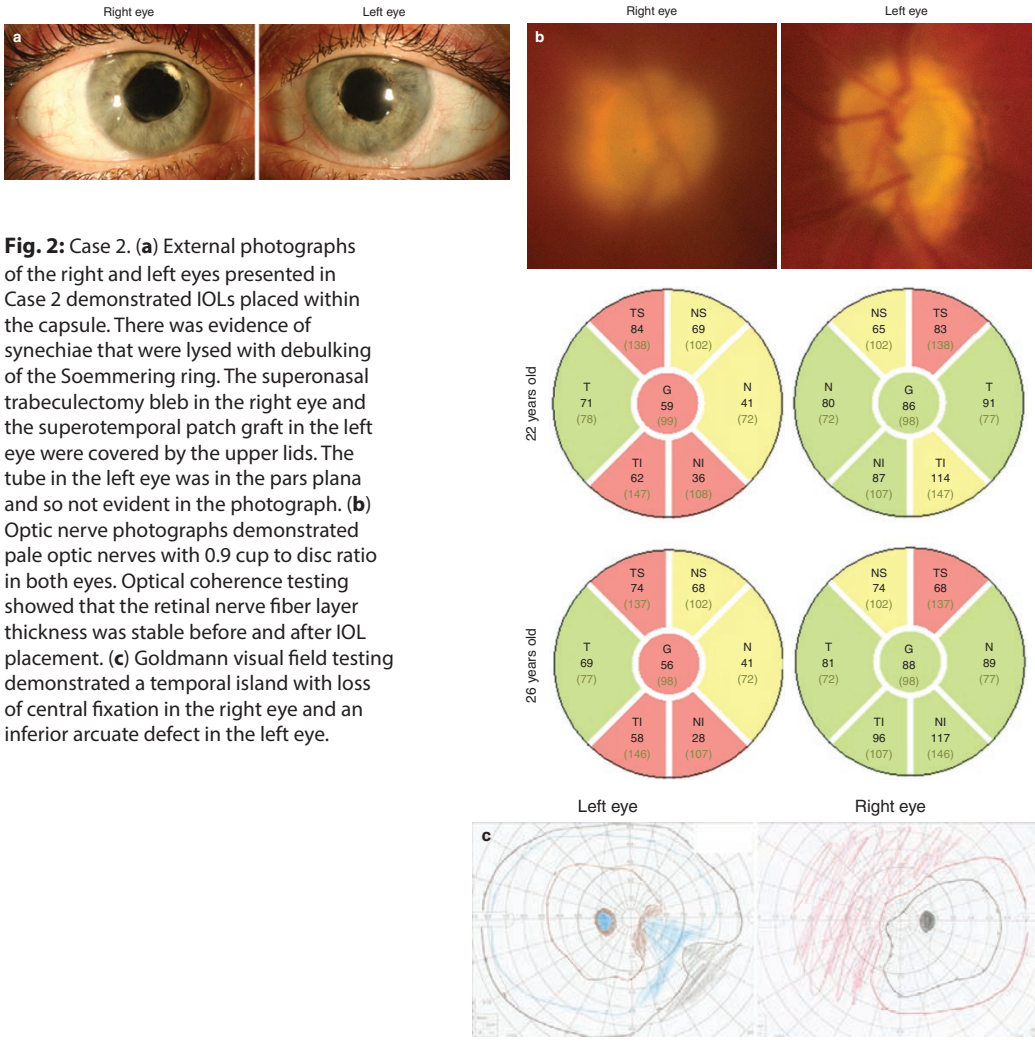

Fig. 2: Case 2. (**a**) External photographs of the right and left eyes presented in Case 2 demonstrated IOLs placed within the capsule. There was evidence of synechiae that were lysed with debulking of the Soemmering ring. The superonasal trabeculectomy bleb in the right eye and the superotemporal patch graft in the left eye were covered by the upper lids. The tube in the left eye was in the pars plana and so not evident in the photograph. (**b**) Optic nerve photographs demonstrated pale optic nerves with 0.9 cup to disc ratio in both eyes. Optical coherence testing showed that the retinal nerve fiber layer thickness was stable before and after IOL placement. (**c**) Goldmann visual field testing demonstrated a temporal island with loss of central fixation in the right eye and an inferior arcuate defect in the left eye.

Intraocular lenses can be safely placed in the setting of glaucoma, but attention needs to be paid to a number of special considerations. The intraocular pressure must be well-controlled prior to IOL placement; this is for preserving vision as well as for accurate lens calculations in young children. In eyes with glaucoma following cataract surgery, the angle and size of the anterior chamber should be evaluated. In uveitic glaucoma, the IOL is ideally placed within the capsule to prevent reactivation of the inflammation. In both of these clinical scenarios, prior glaucoma surgeries may dictate the safest location for the incision for IOL placement, and additional procedures may be required to maintain pressure control. While the goal of lens placement is to improve visual function without contacts or glasses, it is essential that intraocular pressure control not be compromised.

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OCT and Glaucoma: Case Review

Sasan Moghimi, Mona SafiZadeh, Andrew Camp, Robert N. Weinreb

Early diagnosis of glaucoma is essential to prevent significant visual impairment. Patients have already lost 25 to 40% of their retinal ganglion cells before they demonstrate visual field changes. However, structural changes usually precede functional visual field loss. Structural diagnostic modalities can detect glaucoma in earlier stages before irreversible functional damage has occurred. Optical coherence tomography (OCT) is the most promising technique for early detection of glaucomatous damage to the optic nerve head (ONH) and retinal nerve fiber layer (RNFL). In this chapter we present glaucoma cases in different stages of the disease and reviews role of OCT in diagnosis and monitoring of these cases.

Case 1- Glaucoma (Perimetric and Preperimetric)

RNFL OCT can detect glaucomatous change earlier than visual fields. This patient presented to clinic with an IOP of 24 mmHg OD and 22 mmHg OS. She has a superior visual defect in the right eye and normal visual field in left eye. Superior and inferior RNFL thinning in right eye and inferior RNFL thinning in the left eye can be seen in the Spectralis RNFL Report (Fig. 1a). The Minimum Rim Width Analysis Report also depicts areas of rim thinning in the superior and inferior regions bilaterally (Fig. 1b). The patient was diagnosed with perimetric glaucoma in the right eye and preperimetiric glaucoma in the left eye. Medication was started for both eyes.

S. Moghimi (✉), A. Camp · R.N. Weinreb
Department of Ophthalmology, Hamilton Glaucoma Center, Shiley Eye Institute,
University of California, San Diego,
CA, USA
e-mail: sasanimii@yahoo.com

M. SafiZadeh
Tehran University of Medical Sciences,
Tehran, Iran

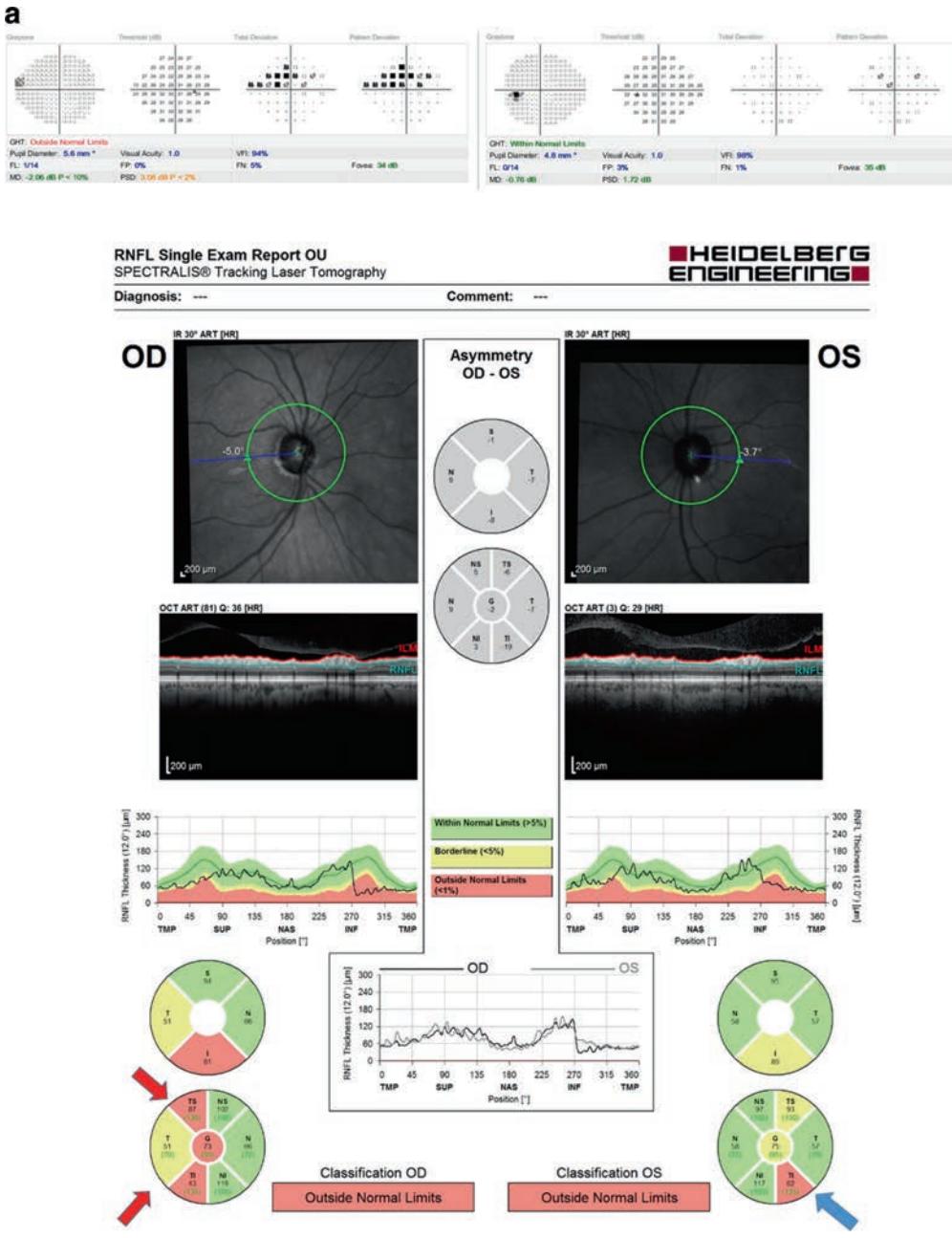


Fig. 1: a The Spectralis OCT single exam report demonstrates superior and inferior RNFL thinning in the right eye (red arrows) and inferior RNFL thinning in the left eye (blue arrow). The average RNFL is 75 µm and is flagged as 'borderline' in the left eye, which had a full visual field. **b** The Minimum Rim Width analysis demonstrates that the MRW parameter is borderline in the inferotemporal sector and supranasal sector of the left eye (blue arrows). However, the average MRW is still 'within normal limit'. In the right eye, the inferotemporal sectors are thinned and flagged as 'outside normal limit' (red arrow).

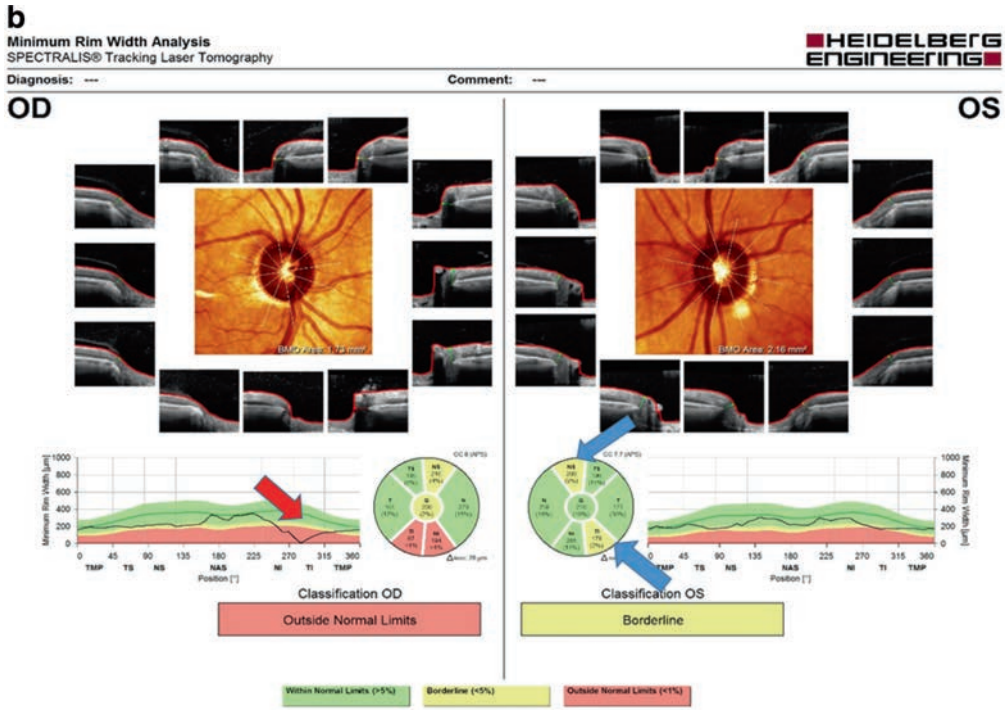


Fig. 1: (continued).

Case 2- Early Glaucoma with Central VF Damage

A 42-year-old woman was referred for glaucoma evaluation based on family history and elevated intraocular pressure. The IOP of her right eye was 23 mmHg and the left eye was 21 mmHg. She has a record of maximum IOP of 26 mmHg OU. Central corneal thickness is 525 µm OU. The optic nerve head showed a large cup-to-disc ratio but otherwise healthy-appearing disc (Fig. 2a). The 24–2 Visual fields are normal (Fig. 2a). The Cirrus ONH and RNFL OU Analysis report shows thinning in the supratemporal region of both eyes, left greater than right (Fig. 2b). The Ganglion Cell OU Analysis Report demonstrates ganglion cell Inner plexiform layer (GCIPL) thinning in the superior macula of the left eye (Fig. 2c). A 10–2 visual field was performed to better elucidate macular loss and an inferior arcuate was seen in the left eye (Fig. 2d). A prostaglandin analogue was started for the patient OU.

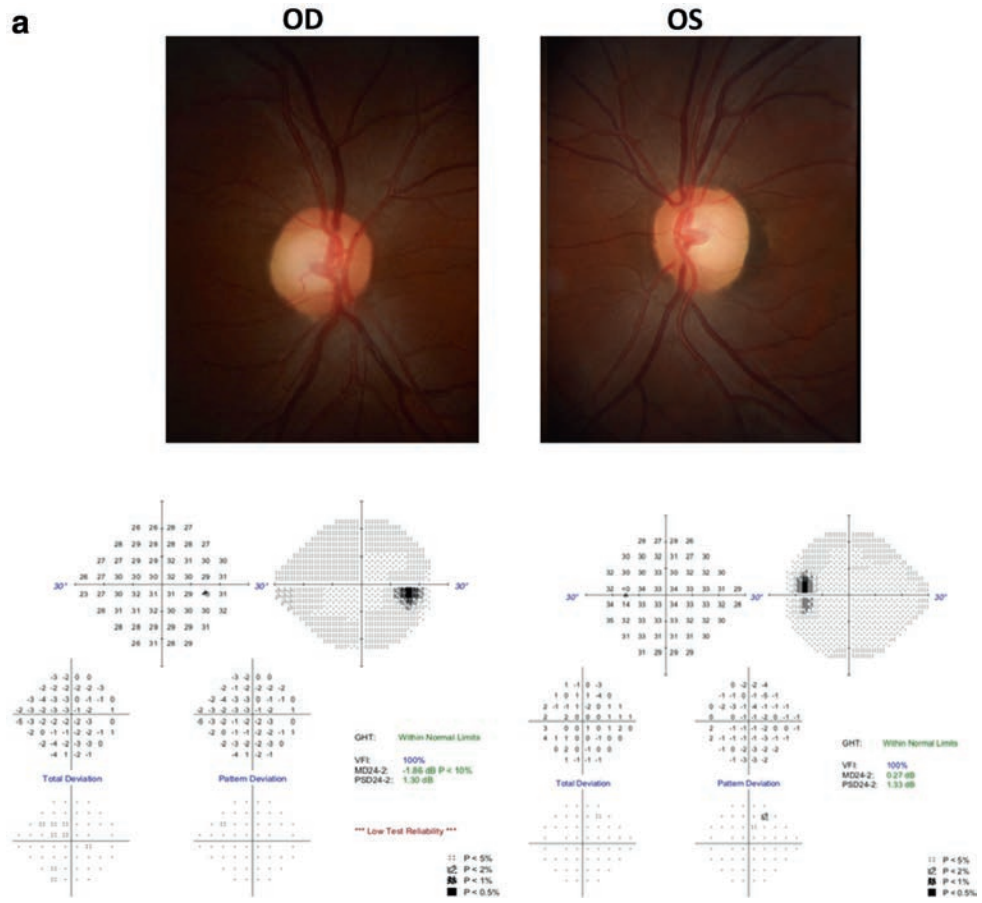


Fig. 2: a Optic nerve head shows a large cup-to-disc ratio but otherwise healthy-appearing disc. The 24–2 visual fields are normal in both eyes. **b** Cirrus HD-OCT shows an area of supratemporal RNFL thinning in both eyes (upper red arrows). Note that this thinning can be observed in both the Deviation map and RNFL Clock hours (red arrows). The RNFL profile is fairly symmetric and normal. Tabular data shows normal global RNFL OU. However, the ONH data (cup volume and average c/d ratio) is outside normal limit. **c** Cirrus Ganglion Cell OU report- an area of GCIPL thinning in the left eye can be seen in both the Thickness and Deviation map. The degree of thinning is abnormal in the superior sector and borderline in the supratemporal sectors. **d** An inferior arcuate defect is observed in the 10–2 visual field of the left eye (red arrow).

Raphe Sign

Various types of optic neuropathy, including compressive optic neuropathy and ischemic optic neuropathy, can affect the macula and GCIPL. However, in glaucoma, the inferotemporal region is frequently affected first. The temporal raphe sign is an important sign for distinguishing glaucoma from other neuropathies. The temporal raphe sign is positive if there is a horizontal straight line longer than one-half of the inner-to-outer-annulus length on the macular GCIPL thickness map (Fig. 3).

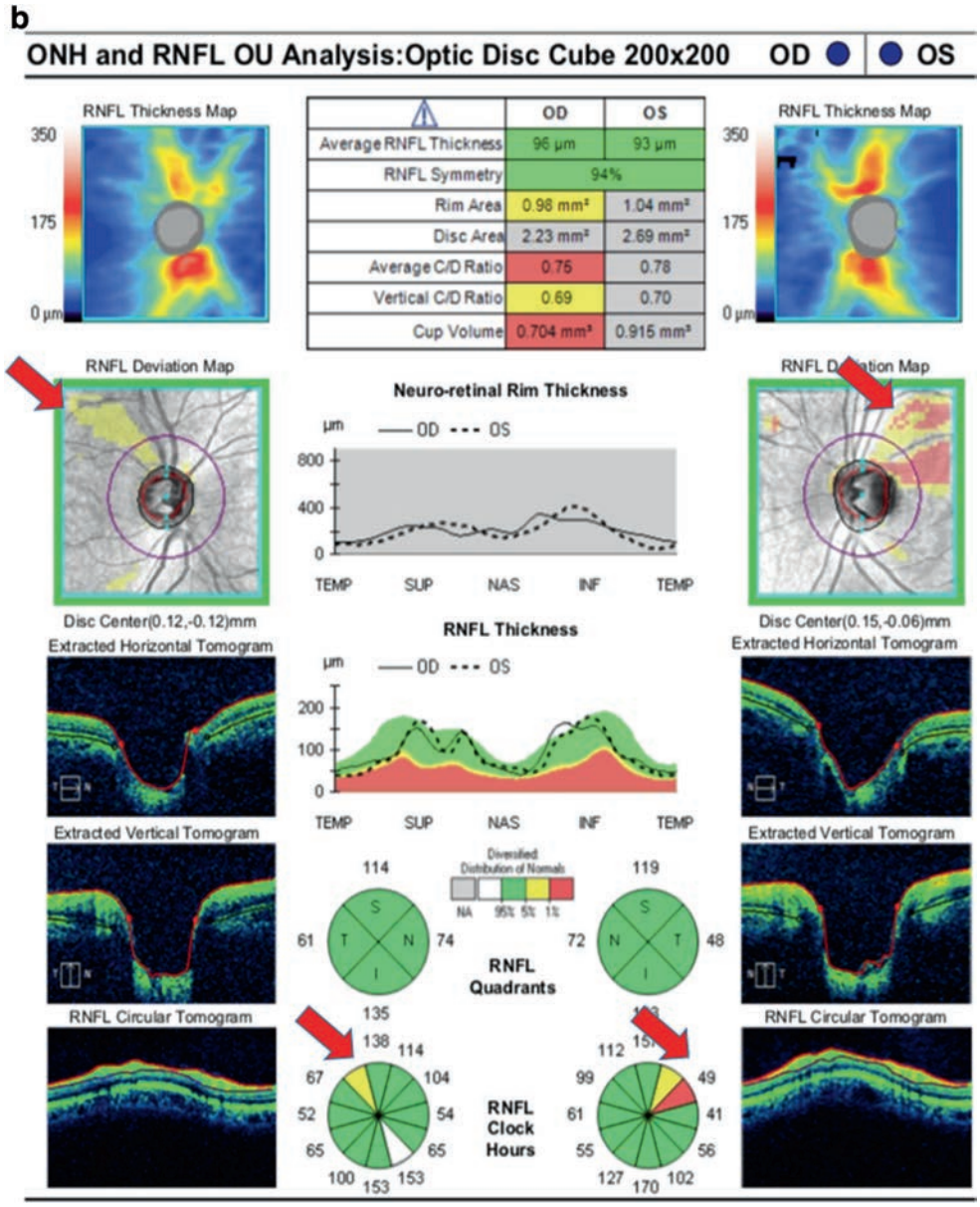


Fig. 2: (continued).

The temporal RNFL, the origins of which strictly respect the horizontal raphe, enters into the supratemporal and inferotemporal aspects of the optic disc. Glaucomatous structural damage and functional loss corresponding to the anatomic arrangement of the RNFL are often asymmetric across the horizontal meridian, especially in the early stages, leading to the temporal raphe sign on the GCIPL OCT thickness map [1].

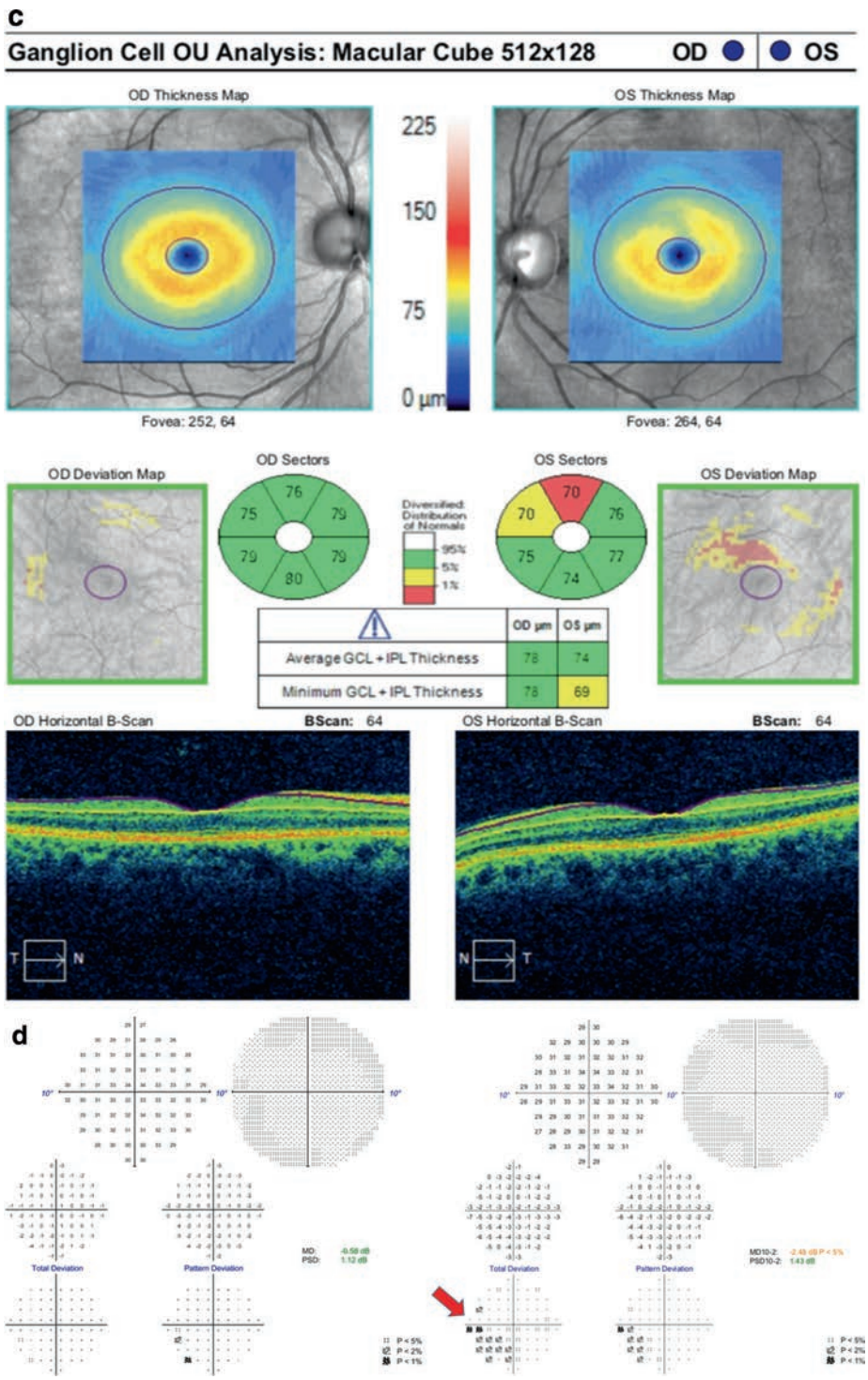


Fig. 2: (continued).

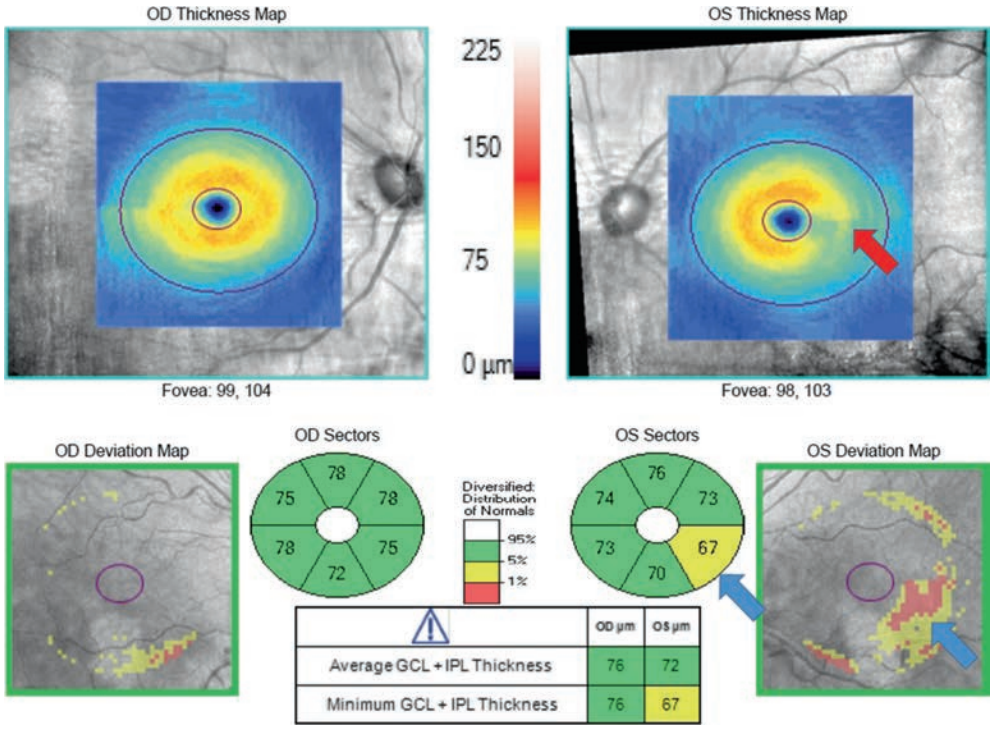
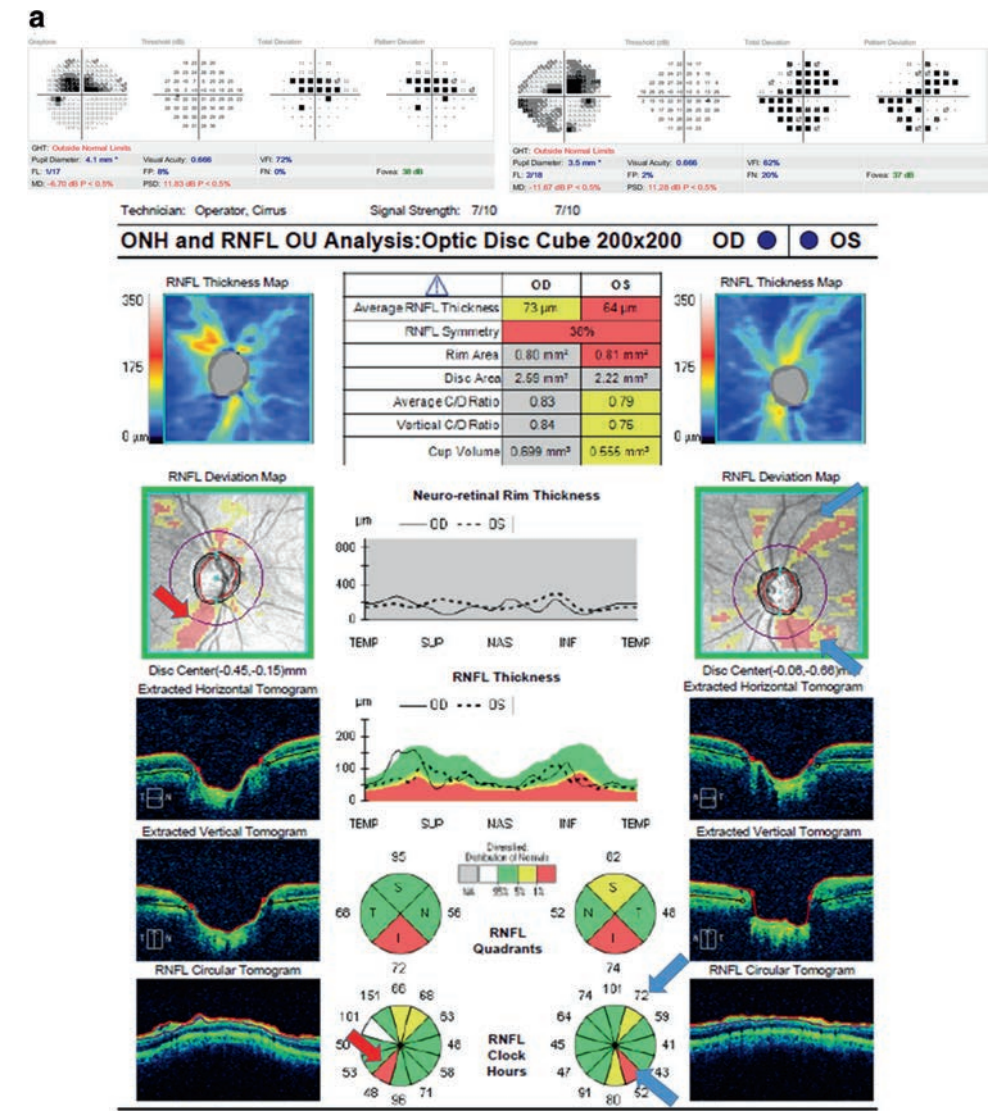


Fig. 3: Raphe sign. The GCIPL analysis demonstrates inferotemporal thinning in the left eye with a raphe sign on the thickness map (red arrow). The macula GCIPL thickness is shaped more like a snail, as opposed to the typical donut appearance. Inferotemporal thinning can also be seen in the deviation map and sectoral analysis (blue arrows). In the right eye the GCIPL looks normal.

Case 3- Moderate Glaucoma with Raphe Sign

A 79-year old glaucoma patient was followed for 7 years in the clinic. The RNFL report showed superior wedge defects OU and an inferior wedge defect OS. The GCIPL analysis demonstrates inferotemporal thinning OU with a typical raphe sign. GCIPL thinning is suggestive of damage close to the fixation point, which can affect the quality of life more profoundly (Fig. 4a). A 10–2 visual field showed an arcuate scotoma close to fixation which was consistent with the GCIPL analysis (Fig. 4b).



	OD	OS
Average RNFL Thickness	73 µm	64 µm
RNFL Symmetry	30%	
Rim Area	0.80 mm²	0.81 mm²
Disc Area	2.59 mm²	2.22 mm²
Average C/D Ratio	0.83	0.79
Vertical C/D Ratio	0.84	0.76
Cup Volume	0.699 mm³	0.555 mm³

Fig. 4: a Cirrus HD-OCT RNFL report demonstrating the inferior wedge defects in the right eye (red arrow) and superior and inferior wedge defects in the left eye (blue arrows). **b** The GCIPL analysis demonstrates inferotemporal thinning OU with a typical raphe sign on the thickness map of both eyes. The superior arcuate defect in both eyes is consistent with the loss demonstrated on GCIPL.

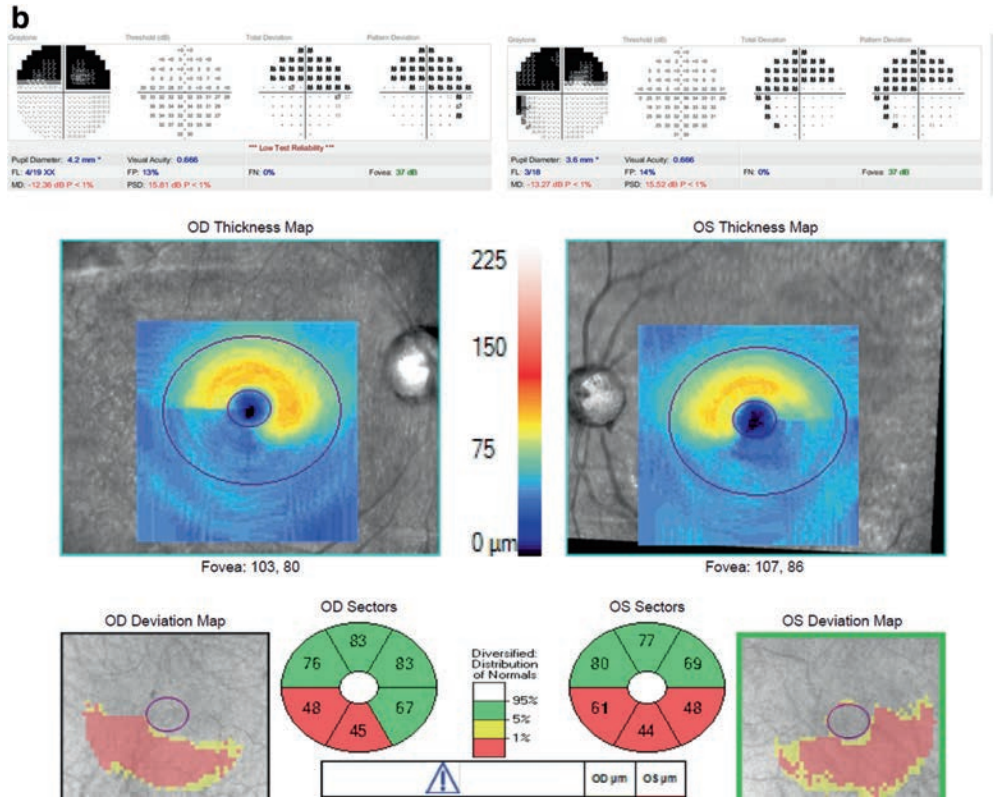


Fig. 4: (continued).

Case 4- Glaucoma Affecting the Central Field

A 79-year old female is followed in the glaucoma clinic with a diagnosis of normal tension glaucoma. Her visual field shows a paracentral scotomas in the right eye and is normal in the left eye. OCT shows inferior RNFL wedge defects in the inferotemporal region of both eyes (Fig. 5a). Significant asymmetrical inferior thinning in macula can be seen in both eyes, right eye more than left (Fig. 5b).

Case 5- Preperimetric Glaucoma with Abnormal OCT

OCT can detect glaucoma before any change in visual field. A 73-year woman with normal IOP is referred to glaucoma clinic for evaluation of a glaucomatous optic disc (Fig. 6a). Significant thinning is more prominent for ONH rim, and there is an inferotemporal wedge defect in RNFL. However, the 24–2 visual field is normal. Macular GCIPL does not show significant thinning. The patient has preperimetric glaucoma and ocular hypotensive therapy has been started. Cirrus HD-OCT GPA analysis showed no progression in her eyes over 3 years (Fig. 6b and c).

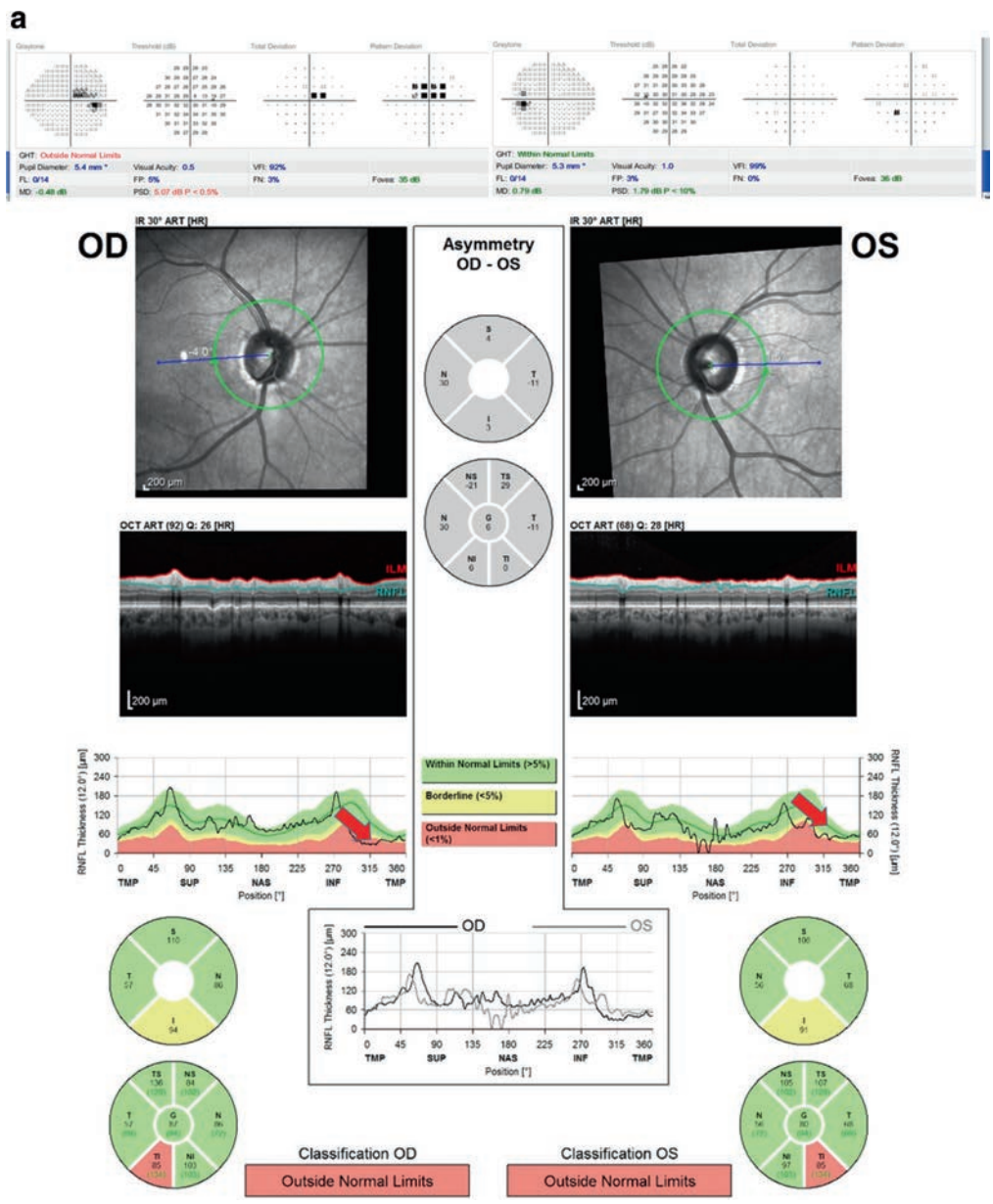


Fig. 5: a Spectralis RNFL report with good quality (Q = 26 and 28 in right eye and left eye, respectively) shows RNFL thinning in the inferotemporal region in both eyes. The RNFL thickness profile should be checked carefully as sometimes the narrow thinning of RNFL might not be flagged in the pie chart (red arrow). 24–2 visual field shows a superior paracentral scotoma in the right eye and is normal in the left eye. **b** Posterior pole Asymmetry Analysis Report shows arcuate thinning in the inferior macula in both eyes (red arrow). The Hemisphere Asymmetry map also demonstrates areas of significant thinning in the inferior hemisphere compared to superior hemisphere (blue arrow). This is also confirmed by the values shown in the Average Thickness Chart (orange arrow).

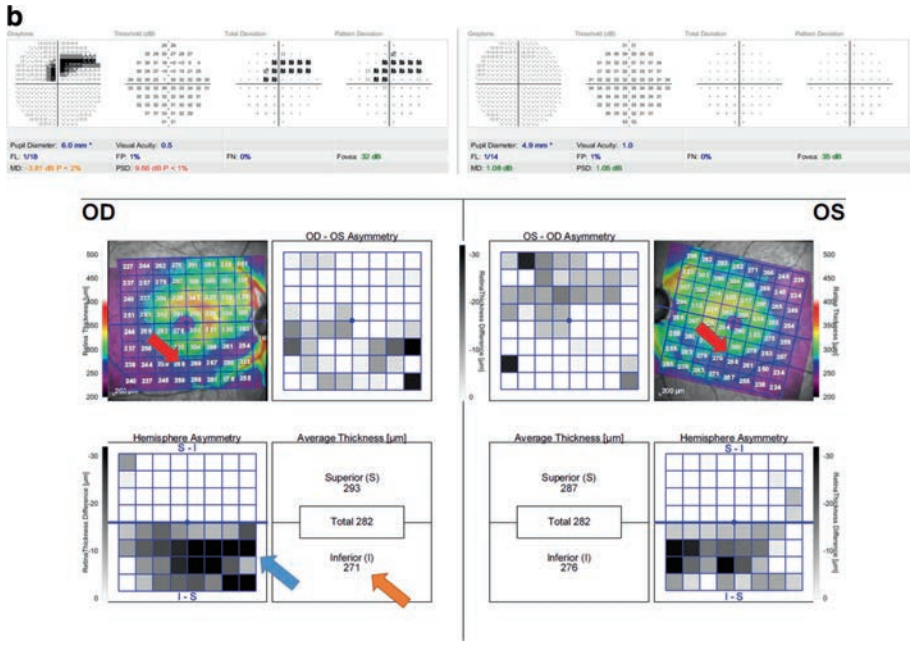
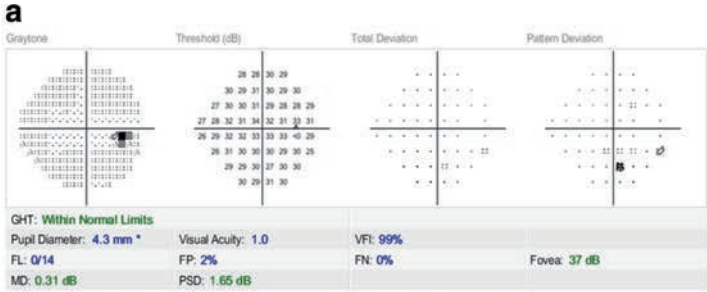


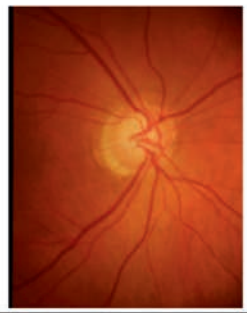
Fig. 5: (continued).

Case 6- Moderate Glaucoma (Structure–Function Relationship)

GCIPL can detect changes in structure prior to RNFL. An 82-year male glaucoma patient is followed in glaucoma clinic. He has an inferior arcuate defect OD and biarcuate defects OS (Fig. 7a). He has significant RNFL thinning in the supratemporal region OU. The GCIPL report showed superior thinning in the right eye and thinning in both hemispheres in the left eye. There is a good anatomical structure–function relationship between superior RNFL and GCIPL thinning and inferior visual defects in right eye. In the left eye the GCIPL detects inferior and superior macular thinning that is consistent with the biarcuate defect (Fig. 7b). However, the RNFL does not demonstrate inferior thinning expected with the biarcuate defect. In this case GCIPL showed earlier structural loss than RNFL.

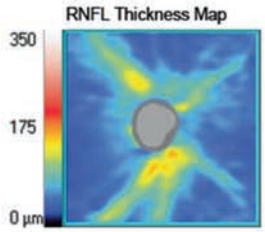
a



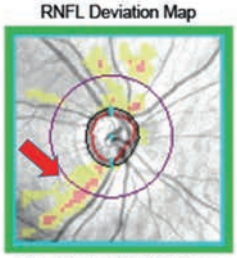


Technician: Operator, Cirrus Signal Strength: 9/10

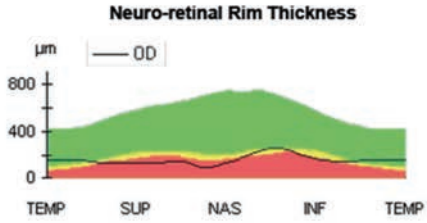
ONH and RNFL OU Analysis:Optic Disc Cube 200x200 OD ● | ○ OS

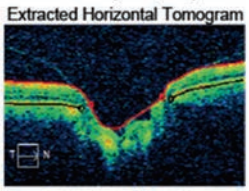


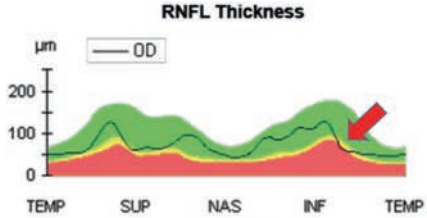
	OD	OS
Average RNFL Thickness	75 µm	X
RNFL Symmetry	X	
Rim Area	0.70 mm²	X
Disc Area	1.92 mm²	X
Average C/D Ratio	0.80	X
Vertical C/D Ratio	0.84	X
Cup Volume	0.513 mm³	X

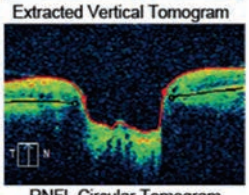


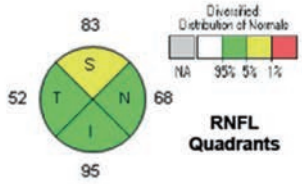
Disc Center(-0.24,0.12)mm

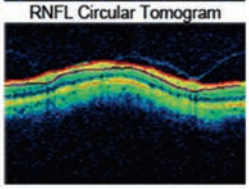


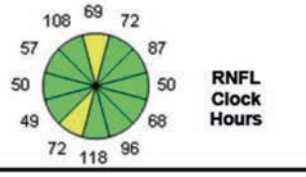












◀ **Fig.** 6: **a** Cirrus HD-OCT ONH and RNFL OU report. The most useful parameters for differentiating normal and glaucomatous patients are: vertical thickness of neuroretinal rim, overall area of rim, vertical C/D ratio, average RNFL thickness, RNFL thickness in lower temporal zone and in the lower quadrant. Although average RNFL thickness is normal, deviation map shows significant thinning of the RNFL in inferotemporal region (red arrows). **b** PanoMap Analysis Report displays the information from ONH, and macula in one printout. ONH parameters are affected more than RNFL thickness parameters. GCIPL and macula thickness is pretty normal in this preperimetric case. **c** Cirrus HD-OCT GPA, right eye (2011–2014). No significant change has been shown in RNFL thickness map progression Analysis and trend analysis. In the summary analysis box, check boxes are not checked for RNFL thickness map progression, RNFL thickness profile progression, average RNFL thickness progression, and Average cup-to-disc ratio progression.

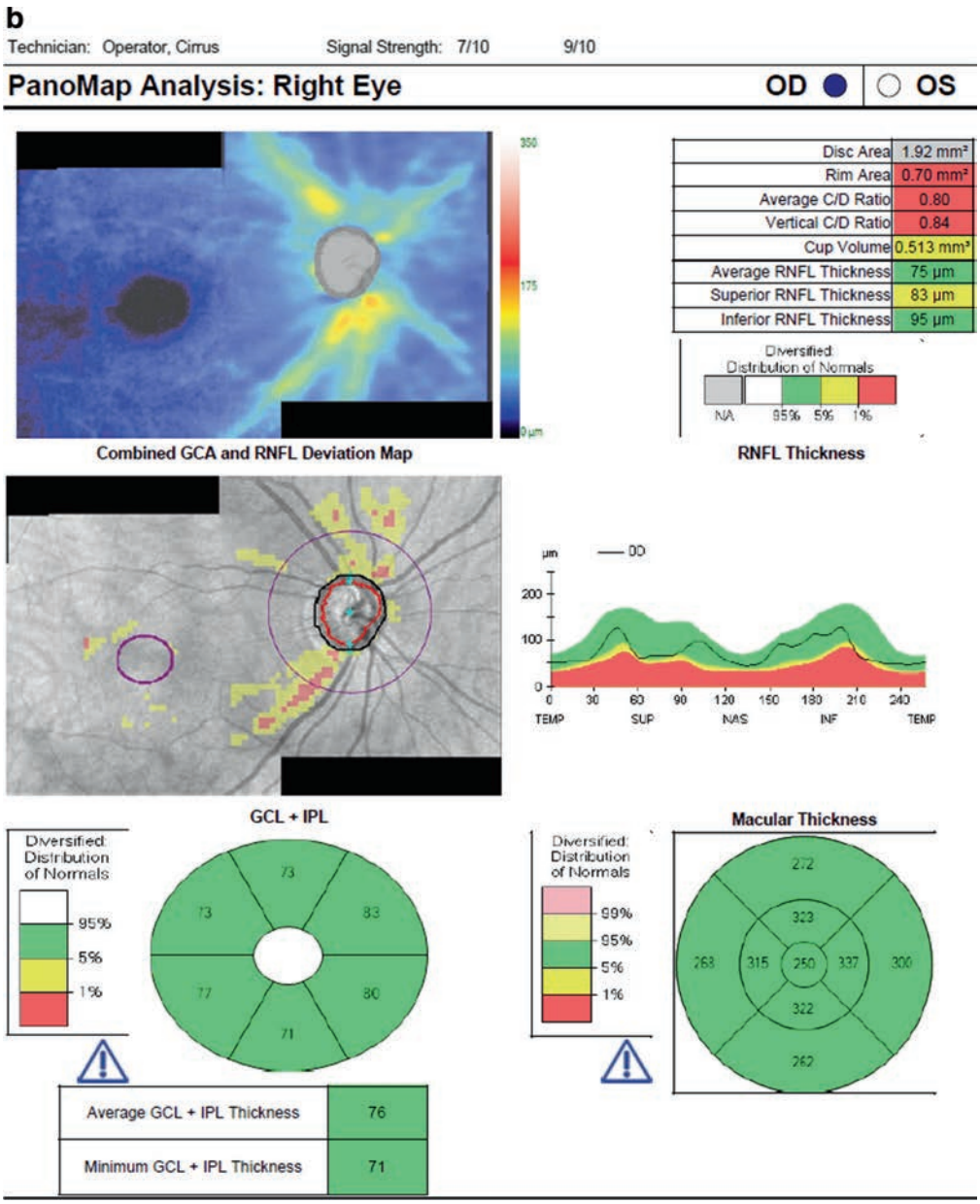
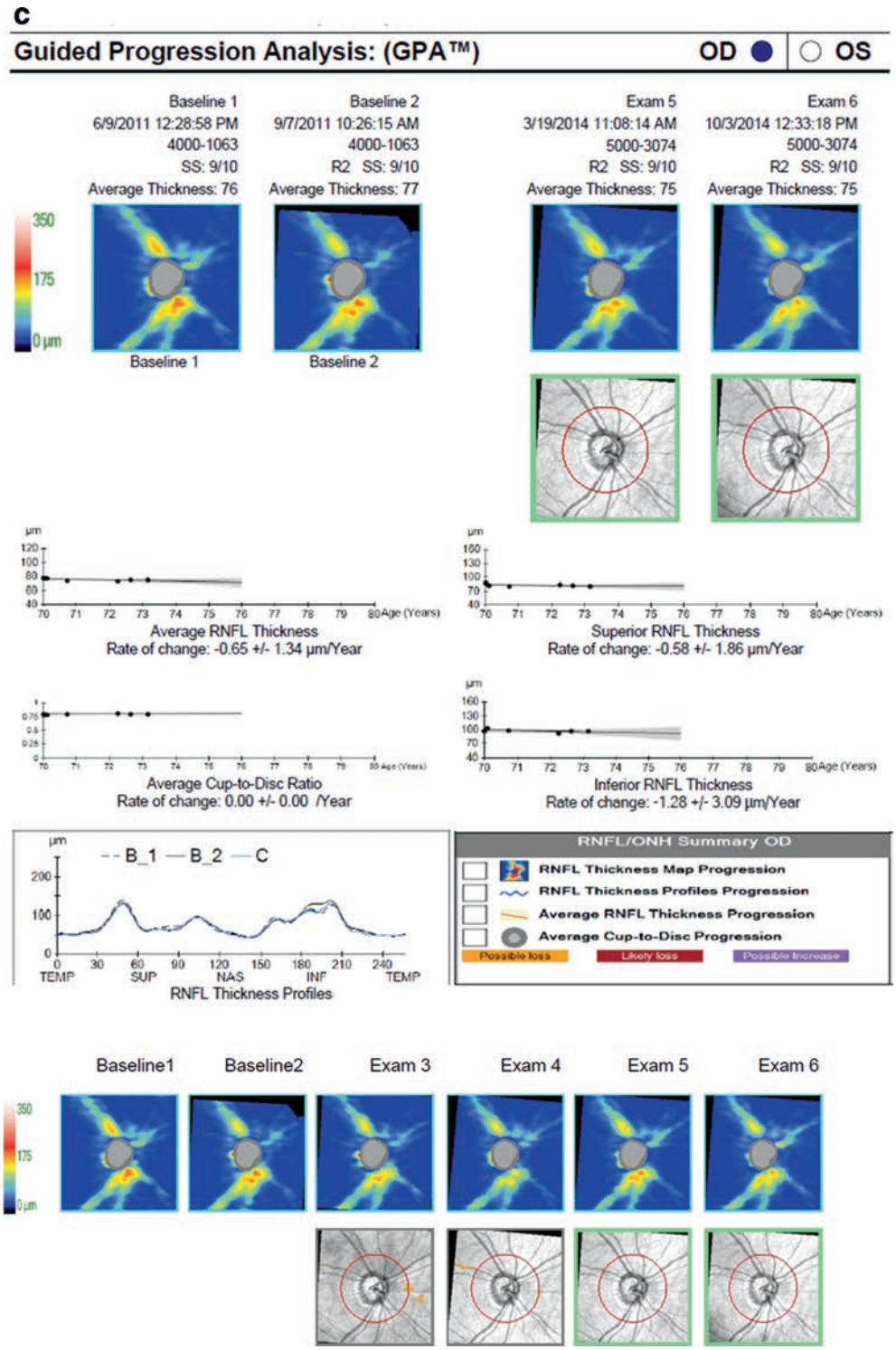


Fig. 6: (continued).



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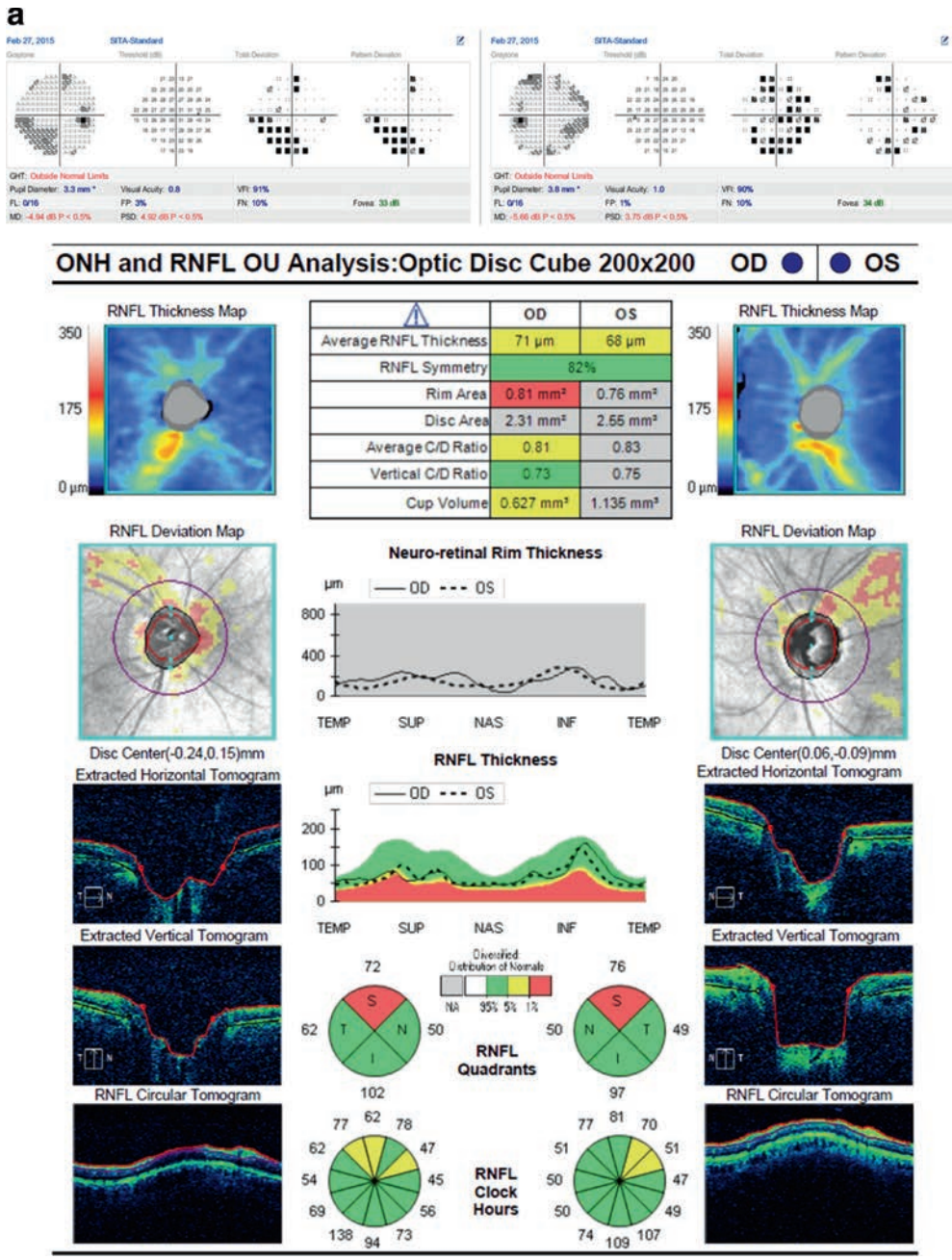


	OD	OS
Average RNFL Thickness	71 µm	68 µm
RNFL Symmetry	82%	
Rim Area	0.81 mm²	0.76 mm²
Disc Area	2.31 mm²	2.55 mm²
Average C/D Ratio	0.81	0.83
Vertical C/D Ratio	0.73	0.75
Cup Volume	0.627 mm³	1.135 mm³

Fig. 7: a ONH and RNFL OU report shows a wedge-shaped RNFL defect in the supratemporal quadrant of the both eyes. The TSNIT profile, RNFL quadrant and clock hour graphs are abnormal in both eyes. The 24–2 visual field shows an inferior arcuate scotoma in the right eye and inferior and superior arcuate scotoma in the left eye. **b** Cirrus-HD OCT Ganglion Cell Analysis. A large area of GCIPL damage is evident in the inferotemporal and supratemporal regions of the left macula confirmed by abnormal sectors in average GCIPL thickness. In the right eye, although the GCIPL thinning can be detected in the superior sector, an area of increased thickness [focal hot area temporal to macula (red arrow), white sectors in pie chart (blue arrow)] can also be seen. The right eye has a parafoveal telangiectasia, and the macula scans are not reliable for glaucoma monitoring due to retinal edema in this eye.

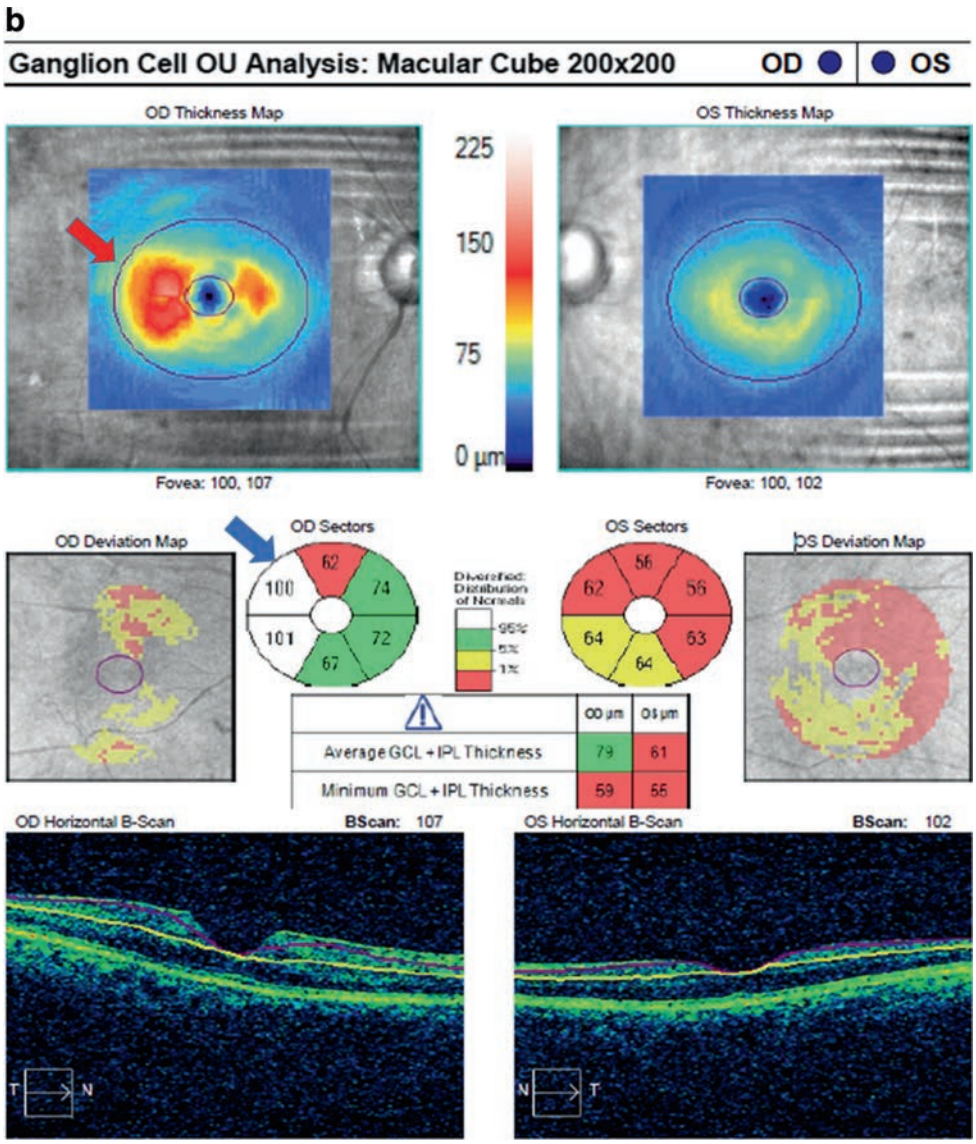


Fig. 7: (continued).

Floor Effect

Some evidence exists that in advanced disease SDOCT measurements are not useful for measuring tissue thickness because of the presence of a floor effect, after which no more thinning is observable. This floor effect, possibly owing to the presence of residual tissue (eg, glial cells, blood vessels or failure of tissue segmentation algorithms (ie, an artifactual floor)), is thought to be a

serious problem for monitoring structural changes in eyes with advanced glaucoma [6]. It is often challenging to detect any observable change with optical imaging even though the patient with advanced disease may be progressing. The RNFL thickness values almost never decrease to less than 30 μm, and in most of the devices 50 μm is considered the floor of RNFL thickness.

Monitoring of disease in eyes with advanced glaucoma must rely on standard automated perimetry or other visual function tests. A longitudinal study [2] found that GCLIPL thickness was the least likely SDOCT parameter to reach the floor across most of the image area at baseline, suggesting that this parameter could be the most useful parameter for detecting change in advanced glaucoma. Recently, we demonstrated OCTA-measured vessel density parameters are promising tools for monitoring progression in late-stage glaucoma (particularly when VF MD is worse than -14 dB) because they do not have a detectable measurement floor [3].

Case 7- Advanced Glaucoma

A 44-year old female is monitored in clinic due to glaucoma. She has had trabeculectomy on both eyes, with IOP ranging from 15 to 18 mmHg OU. Although the OCT shows extensive thinning OU, there was no change in RNFL thickness over 4 years (Fig. 8a). Meanwhile, 24–2 demonstrates deterioration in both the superior hemifield and inferior hemifield of both eyes. The lack of RNFL progression is due to the floor effect (Fig. 8b).

RNFL Asymmetry

Inter-eye RNFL asymmetry is an early sign of glaucoma. 95% of normal eyes showed an asymmetry in mean inter-eye average RNFL thickness of 9 to 17 μm. The inter-eye difference of RNFL thickness for global average followed by superior and inferior were shown to be greatest among SDOCT machines in glaucomatous patients. The average inter-eye asymmetry of the mean RNFL thickness for global average is 6.60 times greater in open angle glaucoma than normal eyes by SDOCT (Spectralis; Heidelberg Engineering). Inter-eye average RNFL thickness asymmetry is the best differentiator between normal and glaucoma subjects. Difference of inter-eye average RNFL thicknesses greater than 6 μm is suggestive of glaucoma.

Case 8- Preperimetric Glaucoma

A 52-year-old woman with a diagnosis of ocular hypertension was referred to our clinic. The IOP of her right eye was 26 and left eye was 25 mmHg. There was minimal disc excavation in either eye. Central corneal thickness was 524 and 526 μm in right eye and left eye, respectively. Visual fields were normal and the OCT printout sectors were all in the green zones. However, the average RNFL was 9 μm thinner in the right eye (Fig. 9). Due to RNFL asymmetry and thinned corneas an anti-glaucoma medication was started.

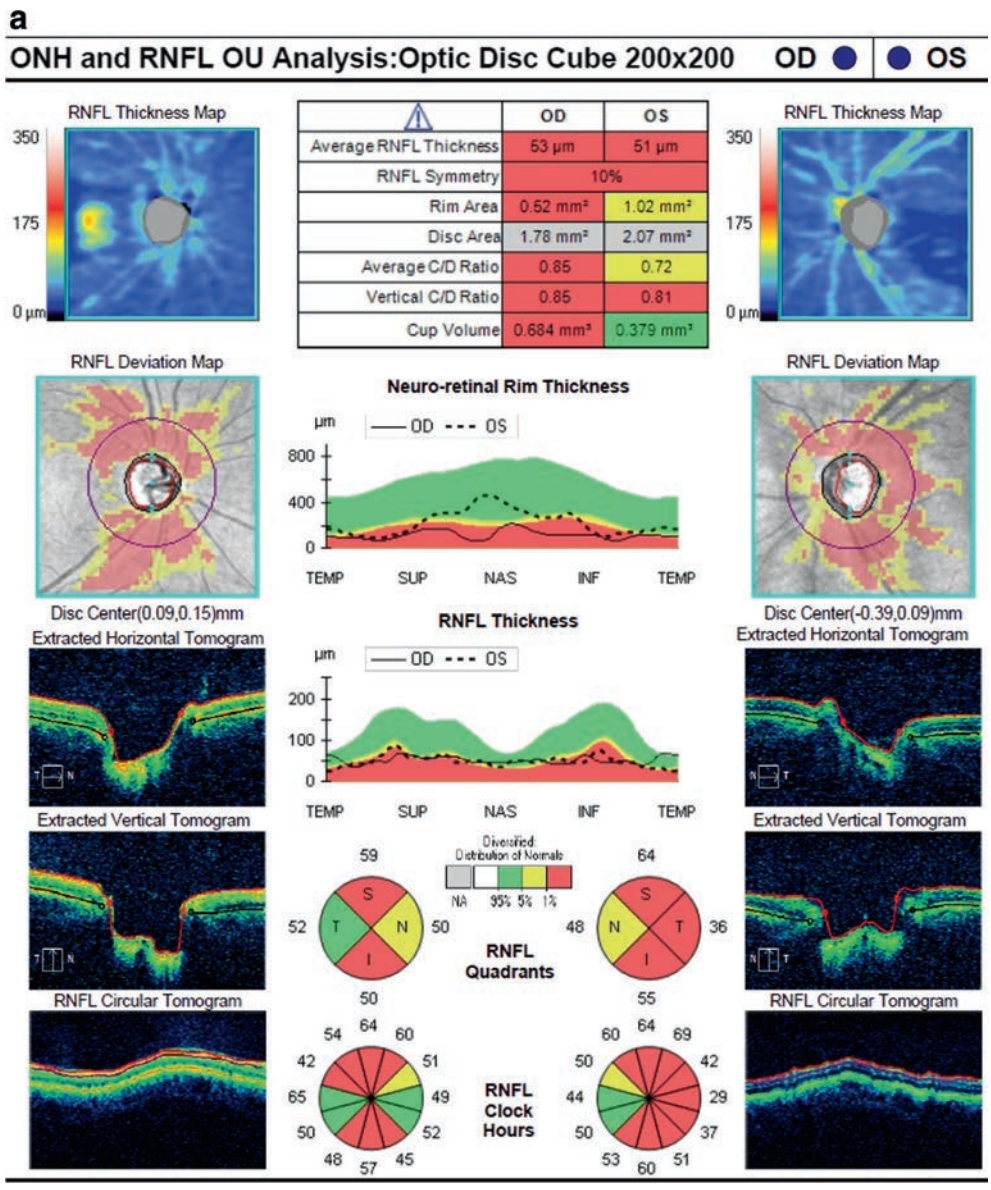


Fig. 8: a Cirrus HD-OCT report demonstrates that ONH and RNFL parameters are severely altered in both eyes. ONH morphological parameters are all pathological and average RNFL thickness of the right and left eye are 53 µm and 51 µm, respectively. However, certain areas (nasal and temporal sectors) show RNFL thickness within normal limits. The thickness maps are diffusely blue due to thinning. **b** Guided Progression Analysis of the right eye shows stable glaucoma without any significant change in the thickness map or RNFL thickness profile. The RNFL trends are also stable in the superior and inferior hemispheres. The visual field demonstrates functional damage, showing decrease of MD from –8.12 to –10.39 dB, and expansion of the inferior arcuate scotoma and development of a new scotoma superiorly. This is the end stage of the disease where functional damage outweighs OCT evidence of structural damage.

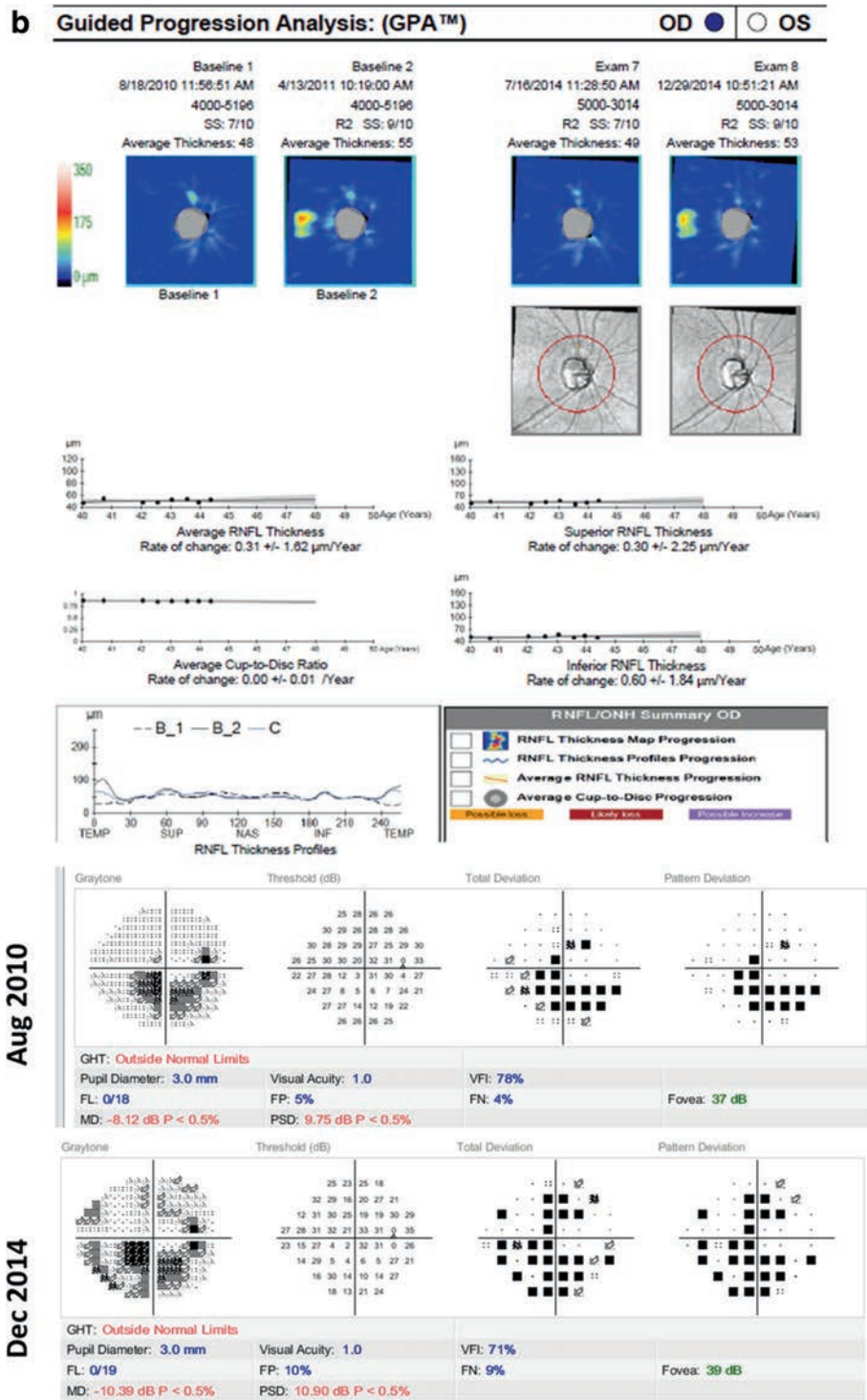


Fig. 8: (continued).

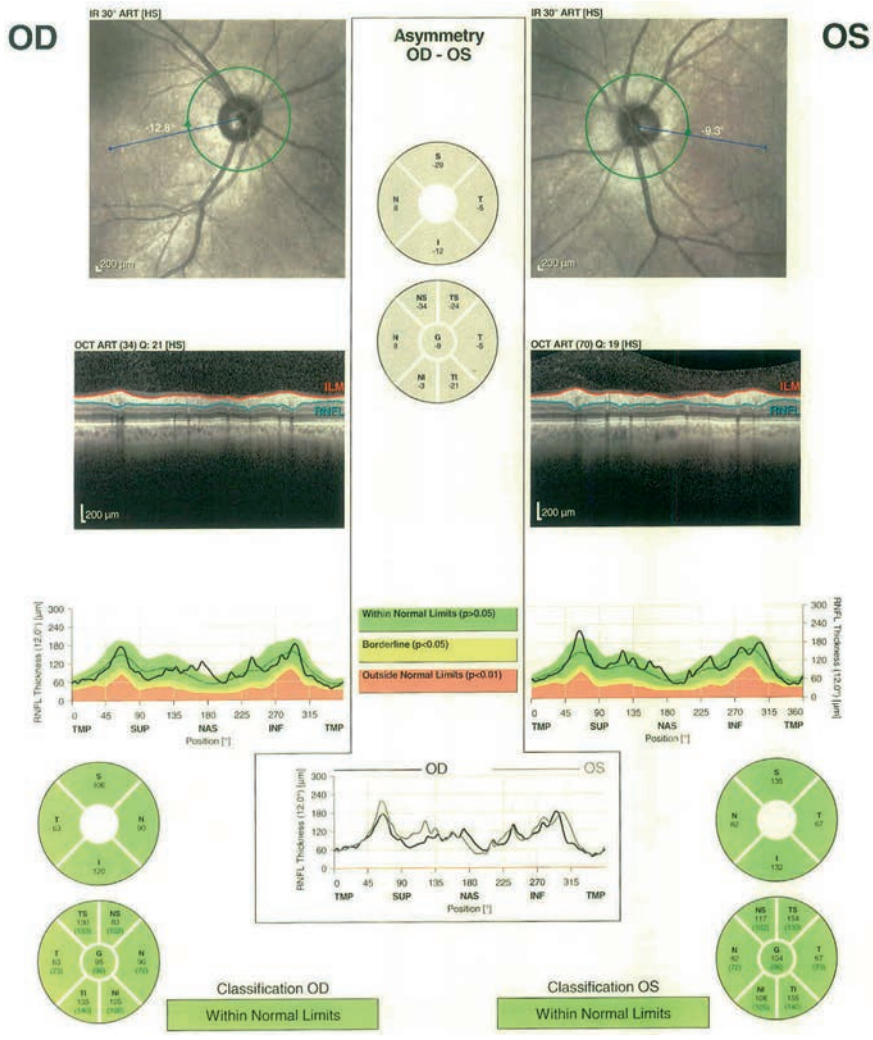


Fig. 9: Spectralis SDOCT retinal nerve fiber layer printout. The printout is for a 52-year-old woman with ocular hypertension. Average RNFL is 95 µm in the right eye and 104 µm in the left eye with an inter-eye global RNFL thickness difference of –9 µm. Although global average thickness is within normal limits (green), the asymmetry of 9 µm is an early sign of glaucomatous damage and early treatment is beneficial. This is an example of 'Green Disease'.

Case 9- Physiologic Cup

A 44-year old patient was referred to glaucoma clinic due to suspicious cupping. IOP is 16 mmHg OU. Optic cup-to-disc ratio was 0.7 in right eye and 0.8 in the left eye, with no obvious RNFL wedge defect. Visual field was normal in both eyes. RNFL thickness from Spectralis OCT report was also normal (Fig. 10). A diagnosis of familial high cup-to-disc ratio was made and confirmed by examination of his brother and his son.

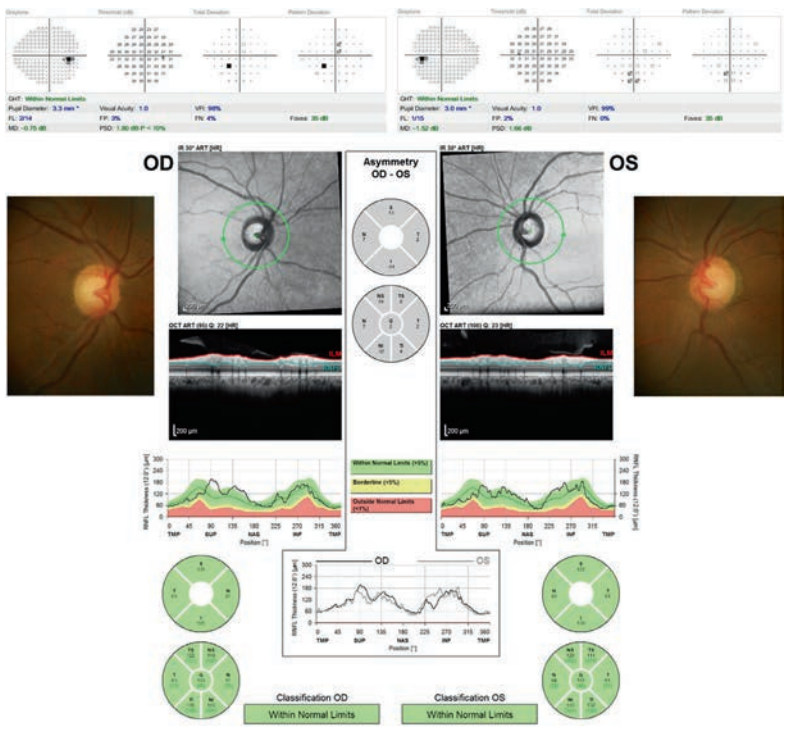


Fig. 10 Spectralis RNFL single report demonstrating normal RNFL profile and average thickness of 100 and 103 µm in right eye and left eye respectively. No obvious wedge defect is observed. Optic cup-to-disc ratio was 0.7 in right eye and 0.8 in the left eye. The visual field is full in both eyes.

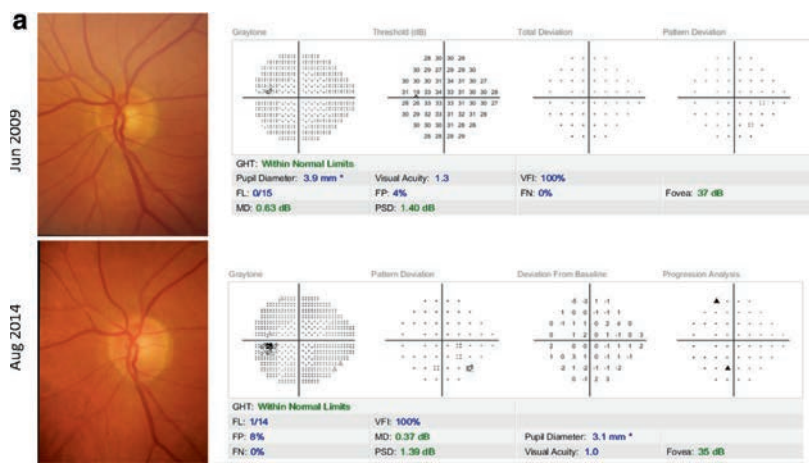


Fig. 11 **a** Optic disc photograph and visual field of the patient in 2009 and 2014. No significant change was found in disc and 24–2. **b** Cirrus HD-OCT GPA, Left eye (2009–2014). (a) RNFL thickness map progression analysis shows significant RNFL thinning in the inferior and superior quadrants (yellow arrow). The GPA marked these areas as "likely loss" and a red checkmark is present in the summary box because the thinning is present in consecutive scans. RNFL thickness profile progression plot also shows RNFL thinning in the superior quadrant and areas with significant progression are displayed in red. The trend analysis based RNFL thickness plots detected statistically significant progression as shown in the summary box. The rate of progression is fastest in the superior quadrant (red arrow). Average cup-to-disc ratio progression is also statistically significant. Repeatable changes in both the superior and inferior quadrants on the change maps can be observed after exam 5 which are flagged with red color (blue arrow).

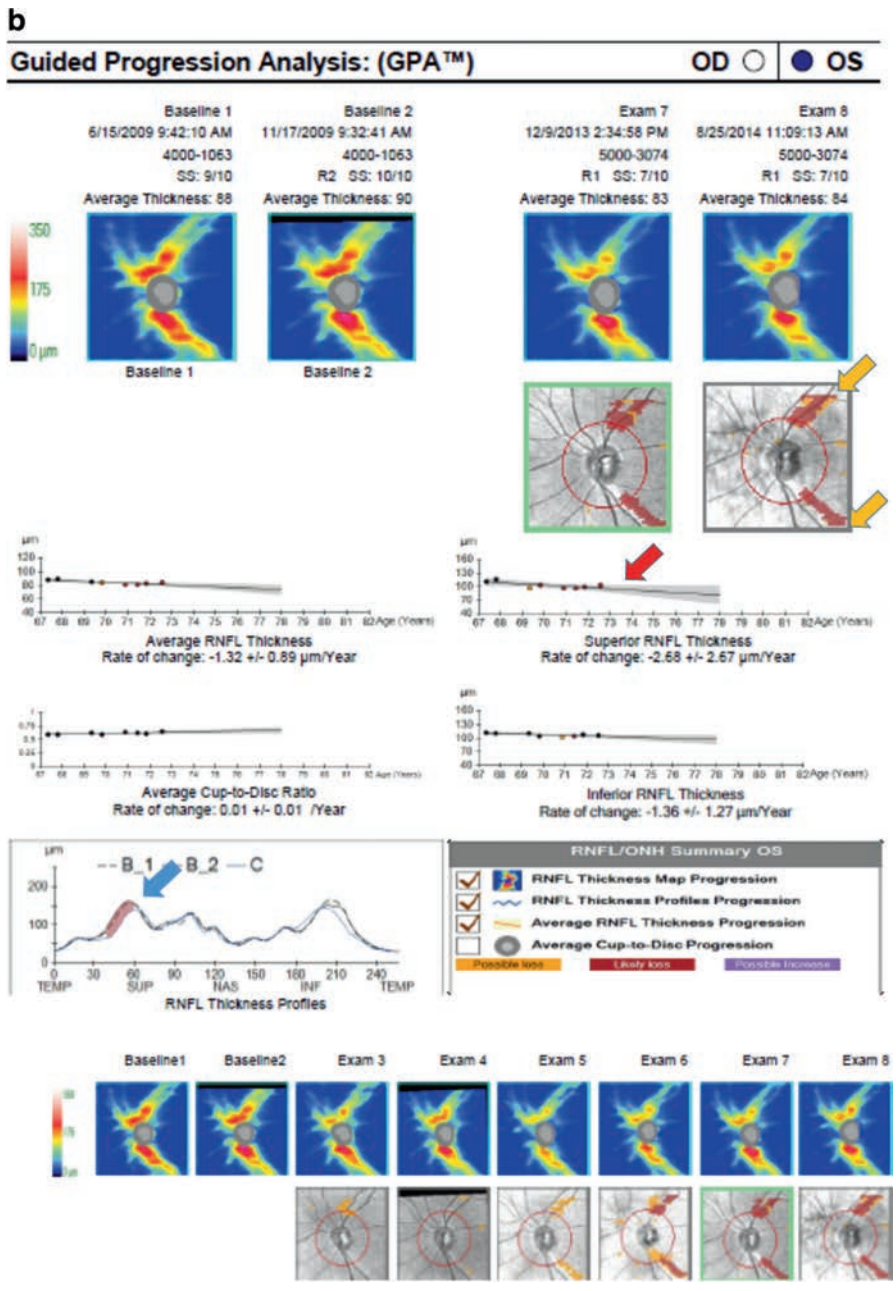


Fig. 11: (continued).

Case 10- Glaucoma Progression in Early Glaucoma

A 67-year old was first seen in 2009. Her IOP in the right eye was 24 mmHg in 2009 and she was started on prostaglandin analogue drops. The IOP ranged between 18 and 21 mmHg during follow-up without any findings of optic nerve head progression on funduscopy. Multiple abnormal points on the visual field developed on the event tracker in 2014 but the GPA report did not show progression. Meanwhile, the **OCT GPA Report** showed significant progression in OCT (Fig. 11a). A fixed combination of a carbonic anhydrases inhibitor and beta blocker was added, which lowered the IOP to 14 mmHg (Fig. 11b).

Case 11- Early Glaucoma, no Progression

A 59-year old woman was referred to glaucoma clinic with an IOP of 23 mmHg in the left eye. Central corneal thickness was 535 µm. Optic disc was suspicious with an area of rim thinning inferiorly. The visual field showed inferior nasal step in the left eye. Anti-glaucoma medication was started. The patient was followed every 6 month with Cirrus HD-OCT and no significant change was found on VF or OCT during follow-up (Fig. 12a and b).

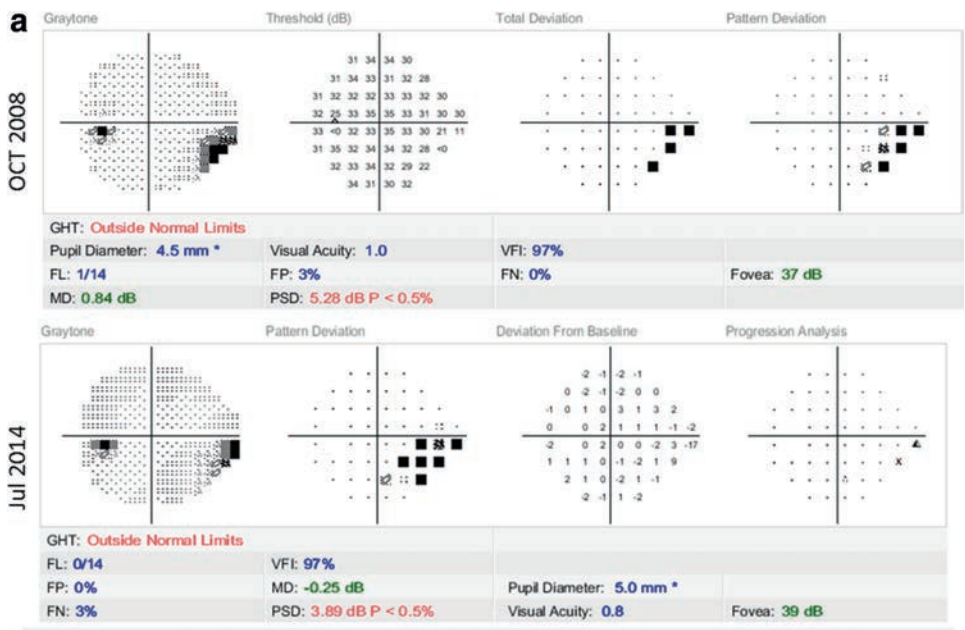
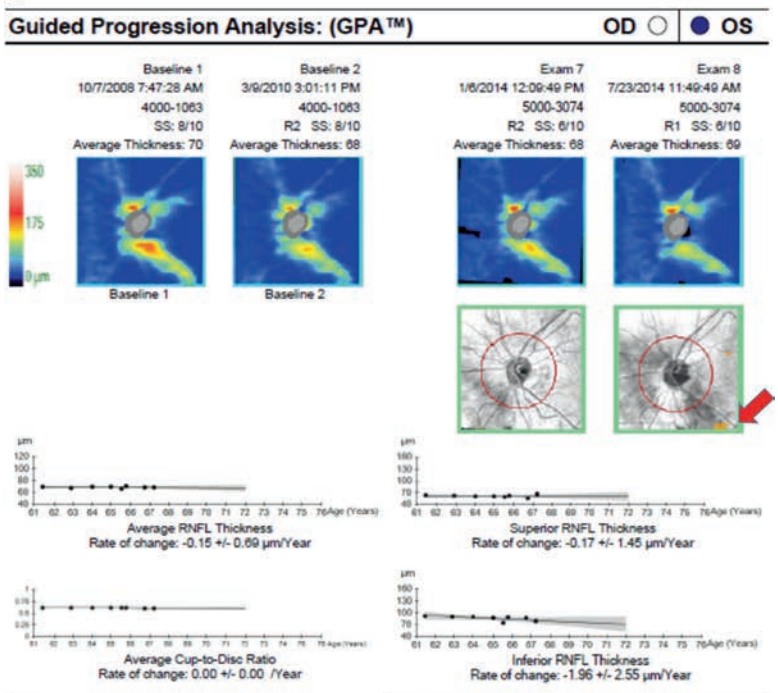


Fig. 12: a Visual field shows inferior nasal step in the left eye. No significant change was found in the VF GPA analysis on 2014. **b** Cirrus HD-OCT's GPA (2008–2014) shows stabilized thickness, and no likely loss in change map, RNFL thickness profile progression plot, trend analysis. The average RNFL thickness is stable around 70 µm. RNFL thickness map is flagged as probable progression but the change map does not show a characteristic wedge shape defect (red arrow). This is probably artifactual due to an artifact of the image in the periphery of the image.

b



RNFL and ONH Summary Parameters

		Exam Date/Time	Serial Number	Registration Method	SS	Avg RNFL Thickness (µm)	Inf Quadrant RNFL (µm)	Sup Quadrant RNFL (µm)	Rim Area (mm²)	Average Cup-to-Disc Ratio	Vertical Cup-to-Disc Ratio	Cup Volume (mm³)
Baseline 1:	1	10/7/2008 7:47:28 AM	4000-1063		8/10	70	92	64	0.78	0.62	0.62	0.135
Baseline 2:	2	3/9/2010 3:01:11 PM	4000-1063	R2	8/10	68	91	63	0.81	0.61	0.59	0.131
	3	4/22/2011 2:37:34 PM	4000-1063	R2	7/10	70	91	61	0.82	0.61	0.60	0.141
	4	4/9/2012 12:54:54 PM	4000-1063	R2	7/10	69	88	61	0.76	0.62	0.61	0.141
	5	10/25/2012 12:28:01 PM	4000-1063	R2	7/10	66	75	60	0.83	0.61	0.61	0.139
	6	1/25/2013 1:15:42 PM	4000-1063	R2	8/10	70	89	63	0.80	0.62	0.63	0.136
	7	1/6/2014 12:09:49 PM	5000-3074	R2	6/10	68	87	57	0.83	0.60	0.60	0.131
Current:	8	7/23/2014 11:49:49 AM	5000-3074	R1	6/10	69	79	67	0.80	0.60	0.63	0.124

Fig. 12: (continued).

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In Primary Open Angle Glaucoma &
Ocular Hypertension

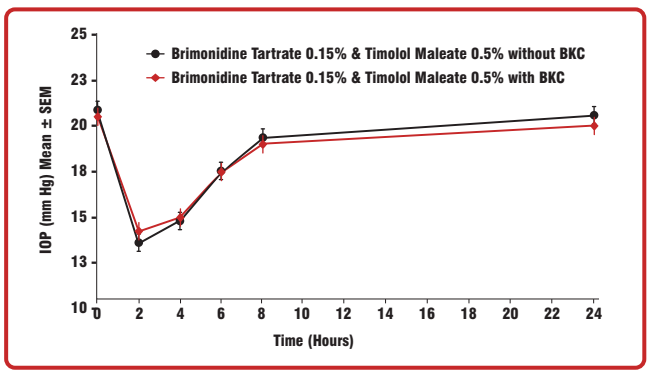
℞

BRIMOLOL

Brimonidine Tartrate 0.15% + Timolol Maleate 0.5%

Combined power, Greater benefits

BKC free BTFC offers comparable IOP lowering to BKC preserved BTFC[1*]



- Single ocular instillation of BTFC without BKC showed statistically significant IOP reduction at 6 hrs. compared with baseline mean IOP value
- Maximum reduction in IOP observed at 2 hrs. following single instillation:
  - BTFC without BKC was 35.8%
  - BTFC with BKC was 32%

“The efficacy of Brimonidine Tartrate 0.15% & Timolol Maleate 0.5% preserved with PHMB was comparable to reference item Brimolol® (BKC preserved)[1]”

1. Thavkar A et al. Int J Basic Clin Pharmacol. 2020 Jul;9(7):1050-1054 • BTFC - Brimonidine Timolol Fixed Combination *Efficacy study in NZW rabbits
• BKC - Benzalkonium Chloride • PHMB - Polyhexamethylene biguanide • IOP - Intraocular Pressure • SEM: Standard Error of Mean