Published in final edited form as:

Am J Ophthalmol. 2013 April ; 155(4): 674–680.e1. doi:10.1016/j.ajo.2012.10.017.

Risk of Endophthalmitis and Other Long-Term Complications of Trabeculectomy in the Collaborative Initial Glaucoma Treatment Study (CIGTS)

Sarwar Zahid¹, David C. Musch^{1,2}, Leslie M. Niziol¹, and Paul R. Lichter¹ on behalf of the CIGTS Study Group

¹Department of Ophthalmology and Visual Sciences, Kellogg Eye Center, 1000 Wall Street, Ann Arbor, MI 48105

²Department of Epidemiology, School of Public Health, University of Michigan, Ann Arbor, MI 48109

Abstract

Purpose—To report the risk of endophthalmitis and other long-term complications in patients randomized to trabeculectomy in the Collaborative Initial Glaucoma Treatment Study (CIGTS).

Design—A longitudinal cohort study using data collected from a multicenter, randomized clinical trial.

Methods—Long-term post-operative complications in the 300 patients randomized to trabeculectomy in CIGTS were tabulated. Kaplan-Meier analyses were used to estimate the time-related probability of blebitis, hypotony, and endophthalmitis.

Results—285 patients were included in the final trabeculectomy cohort after accounting for assignment refusal and other early events. Patients were followed for an average of 7.2 years. 163 patients (57%) received 5-fluorouracil (5-FU) intraoperatively. Of the 247 patients with at least 5 years of follow-up, 50 required further treatment for glaucoma. Cataract extraction was performed in 57 patients (20%). Forty patients (14%) required bleb revision at least once. Bleb-related complications included bleb leak (N = 15), blebitis (N = 8), and hypotony (N = 4). Three patients were noted to have endophthalmitis, although the diagnosis in two patients was presumptive. The occurrences of blebitis, hypotony, or endophthalmitis were not significantly associated with 5-FU use. The Kaplan-Meier calculated risks of blebitis and hypotony at 5 years were both 1.5%, while the risk of endophthalmitis was 1.1%.

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Corresponding author: Paul R. Lichter, M.D. University of Michigan, Kellogg Eye Center, 1000 Wall Street, Ann Arbor, MI 48105
plichter@umich.edu Phone: 734-764-6468 Fax: 734-647-0247.

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Financial Disclosures: Sarwar Zahid – None.

David C. Musch – Consultant for Glaukos Corporation and InnFocus, LLC; Board Member - Ivantis, Inc. and AqueSys, Inc.;

Supported by NIH grant EY018690.

Leslie M. Niziol – None.

Paul R. Lichter – None.

Contributions of Authors in each of these areas: design and conduct of the study (all authors); collection, management, analysis, and interpretation of the data (all authors); and preparation, review, or approval of the manuscript (all authors).

Conclusions—The potential efficacy of trabeculectomy must be weighed against the long-term risk of complications, especially endophthalmitis, when selecting treatments for patients with open-angle glaucoma. We report a low 5-year risk of endophthalmitis (1.1%) and other bleb-related complications in the trabeculectomy cohort of the CIGTS.

Introduction

Trabeculectomy is the most common penetrating surgical intervention for the treatment of open-angle glaucoma.¹ While this filtering surgical procedure has been widely utilized over the past several decades, the concern for complications of filtering surgery, especially endophthalmitis, has given rise to several non-filtering surgical procedures² that putatively carry a lower risk of endophthalmitis. Discussions around such procedures as viscocanalostomy,³ deep sclerectomy,⁴ and canaloplasty³ have emphasized the risks of endophthalmitis from standard filtering procedures as compared to non-penetrating surgery. Similarly, procedures such as mechanical goniotomy,⁵ tube shunts,^{6, 7} and intraocular shunting devices⁸ have been promoted as having lower risks for endophthalmitis since they do not produce a filtering bleb. In addition to the risk of endophthalmitis, there is a paucity of data on longer-term complications of trabeculectomy.

An earlier communication reported on the intraoperative and early postoperative complications of initial treatment with trabeculectomy in the Collaborative Initial Glaucoma Treatment Study (CIGTS),⁹ a multicenter, randomized, clinical trial which was unique in its comparison of trabeculectomy versus topical medications as initial treatment for patients with newly diagnosed open-angle glaucoma. Up to one month of post-operative follow-up revealed only transient, self-limited complications of trabeculectomy, none of which were expected to result in subsequent loss of visual acuity. With subsequent follow-up of the study patients for an average of 7.2 years and up to 11 years, we now report on the longer-term surgical complications, especially those such as endophthalmitis with major implications for visual loss.

While the lack of serious short-term complications of trabeculectomy in the CIGTS is encouraging, the risk-benefit assessment of a consideration for trabeculectomy surgery must include consideration of longer-term risks. Reported longer-term complications have included visually-significant cataracts¹⁰ with increased rates of cataract extraction post-trabeculectomy,¹¹⁻¹⁴ as well as bleb-related complications, such as hypotony, bleb leak, blebitis, and endophthalmitis.^{15, 16} More recent studies have shed greater light on long-term complications. For example, a retrospective study with at least four years of follow-up of 797 eyes of 634 patients who underwent trabeculectomy by two surgeons¹⁵ confirmed the finding of worsening lens opacity in a majority of their cohort. These same authors also report bleb leaks and infection in 4.9% (39 eyes) and 3.4% (27 eyes) of the 797 eyes, respectively, occurring later than six weeks after surgery, with a slightly higher rate and later onset of infection for limbus-based compared to fornix-based conjunctival flaps. A smaller percentage of eyes (N = 5; 0.6%) were described as exhibiting endophthalmitis.¹⁶ In 105 patients who underwent trabeculectomy with 5 years of follow-up in the Tube Versus Trabeculectomy study,¹⁷ 4.8% (5) were reported to have endophthalmitis or blebitis, with 1.9% (2) of patients exhibiting endophthalmitis. In a study comparing complication rates of trabeculectomy between patients with primary open-angle (POAG) and angle-closure glaucoma,¹⁸ 6 patients (2.9%) exhibited bleb leaks and 2 (1.0%) experienced endophthalmitis out of 208 patients with POAG. Finally, a prospective population-based study in the UK¹⁹ estimated the incidence per year of blebitis with bleb leak and endophthalmitis after trabeculectomy at 0.11% and 0.17%, respectively.

Although previous studies have improved our understanding of long-term complications of trabeculectomy, they include patients who have been on topical medications¹⁷ or have had previous surgery.^{15, 16} Further, most studies are retrospective. The CIGTS provides a unique opportunity to study the complications of trabeculectomy in previously untreated eyes, since the participants received thorough evaluation at regular follow-up intervals, and data were collected within the context of a carefully monitored clinical trial. We took advantage of this opportunity to examine the rates of longer-term complications in the trabeculectomy arm of the CIGTS study.

Methods

CIGTS was approved by the University of Michigan Institutional Review Board (IRB) as well as by the IRB at each of the 14 clinical centers. The detailed methodology of CIGTS has been described previously.^{9, 20} Briefly, the CIGTS involved 36 surgeons at 14 clinical centers and was approved by the Institutional Review Boards at each site; written informed consent was obtained from all participants. The study enrolled 607 patients with newly-diagnosed open-angle glaucoma, and randomized them to initial treatment with either a trabeculectomy or medical therapy. The first eye to be treated with either intervention was designated as the “study eye,” though if both eyes qualified for the study, the “study eye” was chosen by the treating ophthalmologist prior to randomization. Surgery for the contralateral eye was permitted 4 weeks after surgery in the study eye.

While surgeons in the CIGTS were free to perform a trabeculectomy using their own technique, all surgeons viewed a videotape illustrating the specifics of the procedure (e.g. mandating use of an iridectomy). Intraoperative and/or postoperative use of 5-fluorouracil (5-FU) was permitted in the initial trabeculectomy procedure, while use of mitomycin C (MMC) was not permitted. The operative characteristics of the trabeculectomy arm as well as peri- and 1-month post-operative complications have been reported previously [ENREF 22](#).²⁰

Protocol-dictated follow-up visits were conducted at 3 and 6 months after the treatment began and at 6-month intervals thereafter. Data on complications occurring beyond 1-month post-operatively were collected from standardized forms that were completed at these follow-up visits. The forms listed a finite number of specific complications and provided the opportunity to record unlisted complications. After tabulation of the frequencies of complications using descriptive statistics, we assessed the time to occurrence after surgery using Kaplan-Meier survival curves. All statistical analyses were conducted using SAS 9.2 software (SAS Institute, Cary, NC).

Results

Patients

300 of the 607 CIGTS patients were randomized to intervention with trabeculectomy. Following randomization, 10 patients changed their minds and chose not to undergo initial trabeculectomy. Eight of these patients had ALT as the first mode of intervention, while 2 patients opted for medications. Four patients had no follow-up due to either death or drop-out before or shortly after treatment, while 1 patient had only 9 months of follow-up after a several year delay in undergoing trabeculectomy, during which other treatment might have been administered. The remaining 285 patients (mean follow-up time of 7.2 years; standard deviation = 2.2 years; range = 0.7 to 10.8 years; median = 7.7 years) who received a trabeculectomy were assessed for long-term complications, which are summarized in Table 1. Of note, in 247 patients with at least 5 years of follow-up, 50 patients required further treatment for glaucoma (such as argon laser trabeculoplasty, medications, or both) secondary

to treatment failure. The most common reason for further treatment was a failure to reach the CIGTS target intraocular pressure (IOP) with trabeculectomy alone.

Antimetabolite Use

Of 285 subjects, 163 (57%) received 5-FU and 4 (1%) received mitomycin-C (a protocol violation), and the remainder (117, 41%) underwent trabeculectomy without use of an antimetabolite. One patient had missing data for antimetabolite use.

Cataract Extraction

Rates of cataract surgery in patients with trabeculectomy in CIGTS have been described previously [ENREF 13](#).¹³ Briefly, patients in the entire CIGTS cohort (N = 607) who underwent cataract extraction (N = 99) were more likely to have undergone initial treatment with trabeculectomy than with medication (P = 0.01). Further, cataract extraction was noted to occur earlier and more frequently in patients randomized to trabeculectomy when compared to the medically-managed group. The probability of cataract extraction at 5 years was significantly higher in the surgical group (19% vs. 6.5%), but the inter-group differences diminished beyond 5 years. In 285 initial trabeculectomy patients, cataract extraction was performed in 57 patients (20%).

Bleb Status and Bleb-related Complications

All 285 patients were recorded as having an observable bleb at some point during follow-up, but the number of visits with an observable bleb varied depending on length of follow-up. Bleb status and encapsulation status at 3, 5, and 7 years of follow-up are shown in Table 2. Most patients with available data at each time point exhibited an observable bleb (89.8%) and did not exhibit encapsulation (93.3%). Bleb revision was undertaken in 40 patients (14%), with six patients requiring revision twice. The estimated average time from randomization to the first bleb revision was 2.0 years (standard deviation = 2.1 years; range = 0.2 to 7.5 years; median = 1.0 years). The CIGTS reporting form did not specify what type of bleb revision was utilized.

Interval hypotony was noted in 4 patients (one of whom developed hypotony maculopathy), bleb leak in 15 patients, and blebitis in 8 patients. Patients who had interval hypotony exhibited a normal IOP at the protocol visit wherein this was noted, ranging from 15 to 20 mmHg. The occurrence of blebitis or hypotony was not statistically significantly associated with 5-FU use (P = 1.00 for both; Fisher's exact test). The Kaplan-Meier calculated risks of blebitis (Figure 1, **upper**) and hypotony (Figure 1, **middle**) at 5 years were both 1.5%.

Endophthalmitis

One patient was noted to have a definitive diagnosis of endophthalmitis. An additional two patients were noted to have interval blebitis requiring hospitalization. We are including these 2 patients as having had presumptive endophthalmitis. The Kaplan-Meier calculated risk of endophthalmitis at 5 years is 1.1% (Figure 1, **lower**). 5-FU was used intraoperatively in all 3 of these patients, though there was no statistically significant association with 5-FU use and endophthalmitis (P = 0.26; Fisher's exact test). It should be noted that these 3 patients did not necessarily exhibit signs of active infection during the protocol visits at which endophthalmitis or blebitis were noted, indicating that the episodes occurred during the interval period between follow-up protocol visits. This assumption is also supported by the lack of documented anterior chamber (AC) flare or cells at these visits on follow-up forms. Two of these patients, however, did exhibit AC flare at a subsequent follow-up visit, although none had AC cells documented at any follow-up visit.

The patient with a definitive diagnosis of endophthalmitis exhibited a significant drop in VA in the protocol visit at which this diagnosis was identified. The VA in the affected study eye dropped to 20/150 from an average of 20/63 in the 7 visits prior to the diagnosis, but recovered to 20/63 at the next visit and exhibited an average of 20/63 in 8 visits after the episode. One of the patients with blebitis requiring hospitalization did not exhibit any changes in VA around the time of presumptive endophthalmitis, and remained stable with an average VA of 20/25 during a 9-year follow-up period. The other patient exhibited a drop in VA from 20/25 to 20/50, but recovered to a VA of 20/25, though follow-up was limited to 24 months. No information was available regarding the severity of the definitive or presumptive endophthalmitis diagnoses or the treatment regimens utilized.

In the 10 patients with endophthalmitis or blebitis (2 patients had endophthalmitis only, 7 patients had blebitis only, and 1 patient had both endophthalmitis and blebitis), there was no statistically significant association between time to endophthalmitis/blebitis and intraoperative 5-FU use ($P = 0.32$; log-rank test from a Kaplan-Meier survival analysis).

Other Complications

Anterior chamber reformation was performed in 7 patients. Four patients exhibited corneal dellen and 3 were noted to have iritis. One patient each exhibited hyphema, aqueous misdirection, keratoconjunctivitis, scleritis/episcleritis, choroidal detachment, posterior vitreous detachment (PVD) with vitreomacular traction, and ptosis surgery. Twenty-four patients had at least one emergency room visit for an ophthalmologic reason, though the specific reasons for these visits were not indicated on the follow-up forms.

Discussion

For surgical approaches to treating open-angle glaucoma with the potential for infectious complications, an adequate assessment of risks and benefits is critical. There is a theoretically reduced risk of infection in non-penetrating glaucoma surgery, given the lack of complete ocular penetration when compared to conventional trabeculectomy. Reported infectious complications in non-penetrating glaucoma surgery have been limited to isolated reports of fungal²¹ and bacterial keratitis [ENREF 24](#),²² and blebitis [ENREF 25](#).²³ We were able to find only one reported case in the literature of endophthalmitis occurring in a patient after undergoing non-penetrating surgery [ENREF 24](#).²⁴

Head-to-head comparisons between non-penetrating glaucoma surgery and conventional trabeculectomy so far have been limited by small sample sizes and limited follow-up, though many have suggested better IOP-lowering efficacy in conventional trabeculectomy [ENREF 27](#).²⁵ A more recent meta-analysis²⁶ of trials comparing trabeculectomy and non-penetrating glaucoma surgery also suggests superior efficacy with conventional trabeculectomy, especially with respect to IOP reduction, although non-penetrating surgery exhibited less complications. However, the authors do not specify which complications occurred less frequently in non-penetrating surgery. CIGTS^{27, 28} has also reported effective IOP control and less visual field deterioration in patients with advanced field loss initially treated with trabeculectomy as compared to initial medical therapy. Another recent study reported significantly reduced success rates at two years of ab interno trabeculectomy--i.e. Trabectome--(22.4%) compared to conventional trabeculectomy (76.1%).²⁹ Although overall post-operative complications were higher in the trabeculectomy group, most of those "complications" were expected and self-limited sequelae of surgery. Endophthalmitis did not occur in either arm of the study. Our data do not indicate that trabeculectomy is a dangerous procedure and its success rate in CIGTS weighed against its risks would seem to support its use in patients whose glaucoma is in need of surgical IOP reduction.

In the context of potentially differing rates of efficacy between trabeculectomy and non-penetrating glaucoma surgery (as well as other treatments), an understanding of the risk of long-term complications is crucial. As stated earlier, studies of the long-term complications of trabeculectomy have thus far been limited by the fact that most have been retrospective and relatively short-term, involving patients who have previously been on topical medications¹⁷ or have had prior surgical intervention.^{15, 16, 30} In some studies, blebitis and endophthalmitis are categorized and reported together, despite blebitis being a distinct diagnosis and a pathogenic precursor to endophthalmitis. Previous head-to-head trials comparing trabeculectomy against non-penetrating glaucoma surgery have also included patients with uncontrolled glaucoma refractory to medical therapy and their limited follow-up precludes a proper assessment of long-term risks. Topical medical therapy has been shown to alter conjunctival and Tenon's capsule histology, especially with respect to inflammation,^{32, 33} and may affect the outcome of trabeculectomy.^{34, 35} It is also possible that previous conjunctival changes may alter the risk of postoperative endophthalmitis.

Given that many patients who underwent trabeculectomy in CIGTS had greater than 7 years of follow-up, our report contributes valuable information to the literature regarding long-term complication rates of trabeculectomy in previously untreated eyes. Cataract extraction in CIGTS has been reported previously¹³ and was more frequent in patients who had undergone initial trabeculectomy compared to those patients who were initially treated with medications at 5 years of follow-up. Importantly, bleb-related complications such as bleb leak, hypotony and blebitis were low.

Endophthalmitis was found in 3 of 285 patients (1.1% Kaplan-Meier calculated risk at 9 years) who underwent initial trabeculectomy in CIGTS, which is comparable to rates previously reported in the literature. ENREF 15^{15-19, 31, 32} However, two of those three patients were reported as having had a bleb leak with blebitis requiring hospitalization, and did not exhibit a dramatic reduction in VA. Therefore, it is possible that we are overstating our rate of endophthalmitis per se by presuming that the blebitis patients who were hospitalized, in fact, have endophthalmitis. We feel that this is an appropriate assignment of a diagnosis of endophthalmitis since we prefer to err on the side of over-reporting such a vision-threatening complication. It is important to note that none of these three patients exhibited active signs of infection during the protocol follow-up visits at which this diagnosis was noted, indicating that the endophthalmitis occurred during the interval between follow-up visits. All 3 of these patients had received intraoperative 5-FU, which was allowed in the protocol.

A high proportion of patients, at as late as 84-months of follow-up, exhibited an observable bleb. Presence of a bleb is likely an indicator of which patients are at greatest risk for endophthalmitis. At the 84-month follow-up visit, 141 patients can be considered to have been at risk for developing blebitis or endophthalmitis. Given that 8 patients were reported as having had blebitis and only three (or fewer) endophthalmitis, it seems reasonable to conclude that the risk of endophthalmitis in the CIGTS initial surgery cohort was at most 1.1% (Kaplan-Meier calculated risk).

An important consideration in endophthalmitis risk is the use of antimetabolite agents intraoperatively to reduce postoperative scarring. Studies in the past have reported complications such as hypotony³³ and endophthalmitis^{34, 35} with use of MMC. Others report an overall increased risk of endophthalmitis with antimetabolite use³⁶ with similar rates between MMC and 5-FU ENREF 40.³⁷ More recent studies have reported that the most common complication with intraoperative antimetabolites is bleb leak¹² ENREF 12 (especially with MMC), with similar rates of endophthalmitis between MMC and 5-FU.^{12, 41} In our cohort, none of the patients with bleb-related complications or

endophthalmitis were given MMC, though a majority of those with blebitis or bleb leak and all three patients with endophthalmitis were given 5-FU. Occurrence of these complications was not statistically associated with 5-FU use. Importantly, however, the lack of a significant association with infrequent complications cannot rule out an association given substantial limitations of power to assess such relationships in our outcome data.

There are several limitations of our study. First, while a limited number of specific complications were listed on follow-up forms, endophthalmitis, blebitis and bleb leak were not listed, thus leaving it up to the investigator to hand-write those complications in a section of the form provided for that purpose. While we assumed that the clinical centers' principal investigators would have written in major complications if they were not specified in the follow-up form, there is no way to be certain that they did so. Thus, there is a possibility that some complications may not have been reported. Second, there is a lack of data on the treatments utilized for blebitis and endophthalmitis. Thus, for patients with blebitis and those with interval endophthalmitis who exhibited good recovery to pre-infection VA, we are assuming that the conditions were self-limited or adequately treated. Despite these limitations, we believe that our findings are an adequate reflection of long-term complications of primary trabeculectomy in previously untreated eyes.

Acknowledgments

Funding/Support: CIGTS was supported by the National Institutes of Health grants EY09100, EY09140, EY09141, EY09142, EY09143, EY09144, EY09145, EY09148, EY09149, EY09150, EY09639. An unrestricted grant from Allergan, Inc. allowed for the collection of an additional two years of data.

We would like to specially thank Brittany Benson (University of Michigan Medical School) for her assistance in data collection.

Appendix: CIGTS Study Group

Members of the CIGTS Study Group are listed in the Appendix to Musch DC et al. Ophthalmology 1999;106:653– 662.

Biography

Sarwar Zahid is a fourth year medical student at the University of Michigan Medical School. Given his immense interest in ophthalmology, he pursued a one-year research fellowship with the retinal dystrophy team at the Kellogg Eye Center. His long-term career goal is to further build on his research training in order to become an excellent clinical and academic ophthalmologist.

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Figure 1. Risk of Blebitis, Hypotony, and Long-Term Endophthalmitis in the Collaborative Initial Glaucoma Treatment Study (CIGTS) Initial Trabeculectomy Cohort

Kaplan-Meier analysis was used to calculate the probability of blebitis, hypotony and endophthalmitis during 5 years of follow-up. Based on 8 documented cases, the probability of blebitis (upper) during 5 years of follow-up was 0.015. The probability of hypotony (middle) based on 4 documented cases was 0.015; one of these patients was noted to exhibit hypotony maculopathy. Finally, three patients in the CIGTS initial trabeculectomy cohort were noted as having endophthalmitis, resulting in a 5-year Kaplan-Meier probability of endophthalmitis of 0.011 (lower). As described in the text, the diagnoses in two of these patients were presumed based on requirement of hospitalization, though the route of antibiotic administration is unclear. Excluding these two patients, the 5-year probability of endophthalmitis is 0.004.

Table 1

Long-Term Complications in the Collaborative Initial Glaucoma Treatment Study (CIGTS) Initial Trabeculectomy Cohort.

CIGTS Trabeculectomy	# Patients (%)^a
Originally Randomized to Trabeculectomy	300
Final Trabeculectomy Cohort	285 (95%)
Trabeculectomy Only Cohort at 5 years (after excluding patients requiring further treatment including argon laser trabeculoplasty, medications, or repeat trabeculectomy)	197 (79.8%)
Antimetabolite Use	
None	117 (41.0%)
5-fluorouracil (5-FU)	163 (57.2%)
Mitomycin C (MMC)	4 (1.4%)
<u>Long-Term Complications</u>	
Cataract Extraction	57 (20%)
Bleb Revision	40 (14.0%)
Capsulotomy	7 (2.5%)
Anterior Chamber Reformation	7 (2.5%)
Bleb-related Complications	27 (9.5%)
Bleb Leak	15 (5.3%)
Blebitis	8 (2.8%)
Hypotony	4 (1.4%)
Endophthalmitis	3 (1.1%) ^b
Keratoconjunctivitis	1 (0.4%)
Scleritis/Episcleritis	1 (0.4%)
Corneal Dellen	4 (1.4%)
Choroidal Detachment	1 (0.4%)
PVD ^c w/ Vitreomacular Traction	1 (0.4%)
Aqueous Misdirection	1 (0.4%)
Iritis	3 (1.1%)
Ptosis Surgery	1 (0.4%)
Hyphema	1 (0.4%)
Ophthalmologic Emergency Room Visits	24 (8.4%)

^aPercentages are based on the total number of patients in the final trabeculectomy cohort (N = 285), except for the Final Trabeculectomy Cohort, where the denominator was set as the total number of patients initially randomized to trabeculectomy (N = 300). Percentage for the Trabeculectomy Only Cohort at 5 years is based on 247 patients remaining at 5 years.

^bIncludes 2 patients noted to have had interval bleb leak with blebitis requiring hospitalization

^cPVD = posterior vitreous detachment

Table 2

Bleb Status and Encapsulation Status at 3, 5, and 7 Years of Follow-up in the Collaborative Initial Glaucoma Treatment Study (CIGTS) Initial Trabeculectomy Cohort.

Bleb Status	# Patients (%)^a
At 3 Years Follow-Up	
Patients with Bleb Data at 36-Month Visit	243
Observable Bleb at 36-Month Visit	227 (93.4%)
At 5 Years Follow-Up	
Patients with Bleb Data at 60-Month Visit	222
Observable Bleb at 60-Month Visit	202 (91.0%)
At 7 Years Follow-Up	
Patients with Bleb Data at 84-Month Visit	157
Observable Bleb at 84-Month Visit	141 (89.8%)
<u>Encapsulation Status</u>	
At 3 Years Follow-Up	240
No encapsulation	224 (93.3%)
Untreated encapsulation	10 (4.2%)
Encapsulation, treated w/ medications	0 (0.0%)
Encapsulation, treated w/ surgery	5 (2.1%)
Encapsulation, treated w/ surgery and medications	1 (0.4%)
At 5 Years Follow-Up	218
No encapsulation	208 (95.4%)
Untreated encapsulation	6 (2.8%)
Encapsulation, treated w/ medications	1 (0.5%)
Encapsulation, treated w/ surgery	3 (1.4%)
At 7 Years Follow-Up	152
No encapsulation	145 (95.4%)
Untreated encapsulation	4 (2.6%)
Encapsulation, treated w/ medications	1 (0.7%)
Encapsulation, treated w/ surgery	2 (1.3%)

^aPercentages are based on the total number of patients with available data at the 3-, 5-, and 7-year visits in the trabeculectomy cohort.