TITLE
Visual Field Progression 8 Years after Trabeculectomy in Asian Eyes – Results from the Singapore 5-Fluorouracil Study

ANG Bryan Chin Hou[1,2]	FAMS, FRCOphth
SEEN Sophia[3,4 *]	MBBS
KUMARAN Arjunan[2,3 *]	MBBS, MRCSEd
DE LEON John Mark Sim[5]	MD
SEAH Steve Kah Leng[2]	FRCSEd
FOSTER Paul[6]	PhD, FRCSEd
GAZZARD Gus[6]	MD, FRCOphth
HTOON Hla Myint[3]	PhD
KHAW Peng Tee[6]	PhD, FRCOphth
TIN Aung[2,3]	PhD, FRCSEd
HUSAIN Rahat[2,3]	MD (Res), FRCOphth

* Authors contributed equally

1 National Healthcare Group Eye Institute, Tan Tock Seng Hospital, Singapore
2 Singapore National Eye Centre, Singapore
3 Singapore Eye Research Institute, Singapore
4 Yong Loo Lin School of Medicine, National University of Singapore, Singapore
5 East Avenue Medical Center, Quezon City, Philippines
6 The National Institute for Health Research (NIHR) Biomedical Research Centre at Moorfields Eye Hospital NHS Foundation Trust and UCL Institute of Ophthalmology, London UK

Corresponding Author:
Dr ANG Bryan Chin Hou
Department of Ophthalmology, National Healthcare Group Eye Institute
Tan Tock Seng Hospital
11 Jalan Tan Tock Seng
Singapore 308433
E-mail: Drbryanang@gmail.com

Conflict of Interest / Financial Disclosure(s): Nil

Text word count: 3000 words Abstract: 249 words
References: 35 Tables: 5 Figures: 0

Key words: Glaucoma, Trabeculectomy, Visual Field Progression, Progressor, Intraocular Pressure Fluctuation

SYNOPSIS/PRECIS
Greater post-operative IOP fluctuation, but not the use of intra-operative 5-fluorouracil, is associated with long-term visual field progression after trabeculectomy in Asian eyes.
(27 words)

ABSTRACT

Background/Aims: To study the effect of long-term intraocular pressure (IOP) fluctuation on visual field (VF) progression 8 years post-trabeculectomy in Asian eyes.

Methods: Retrospective analysis of 8-year post-trabeculectomy data from The Singapore 5-Fluorouracil (5-FU) Study. VFs were analysed using Progressor software (Medisoft, Ltd, Leeds, United Kingdom). Outcome measures included mean slope for VF per year, number of progressing points and mean slope for progressing points per year. Multivariate regression analyses were performed adjusting for age, gender, ethnicity, glaucoma type, intra-operative 5-FU, diabetes mellitus, hypertension, best pre-trabeculectomy VF mean deviation, post-trabeculectomy mean IOP, IOP reduction and IOP fluctuation (standard deviation of IOPs at 6-monthly time-points).

Results: 127 (52.3%) subjects completed 8 years follow-up with ≥5 reliable VFs and ≥8 6-monthly IOP measurements. Mean age was 61.8 ± 9.6 years. Post-operatively, mean IOP was 14.2 ± 2.8 mmHg and mean IOP fluctuation was 2.53 ± 1.20 mmHg. Higher IOP fluctuation was associated with greater mean slope for field (B=-0.071; p=0.013), number of progressing points (B=0.963; p=0.014), as well as VF progression as defined by ≥1 progressing point (OR=1.585; p=0.029). There was also a trend towards eyes with higher IOP fluctuation having ≥3 adjacent progressing points in the same hemifield (OR=1.489; p=0.055). Greater mean IOP reduction post-trabeculectomy was associated only with a lower mean slope for progressing points per year (B=-0.026; p=0.028). There was no significant effect of intra-operative 5-FU compared to placebo for all outcome measures.

Conclusion: In post-trabeculectomy Asian eyes with well-controlled IOP, higher long-term IOP fluctuation may be associated with greater VF progression.

(249 words)

INTRODUCTION

Intraocular pressure (IOP) is the primary modifiable risk factor influencing the development and progression of glaucoma, with IOP-lowering effective in reducing the progression of disease [1 2].

While minimally invasive glaucoma surgery is showing promise as a safe and effective surgical alternative [3 4], trabeculectomy has been the mainstay of glaucoma filtration surgery in the last few decades, having been shown to be able to reduce long-term glaucomatous progression [5].

Studies analyzing post-trabeculectomy outcomes with regard to long-term IOP control and VF progression [1] have yielded useful results, demonstrating likely risk factors for disease progression after surgery. However, there have been conflicting results regarding the influence of IOP fluctuation – both long and short-term – on progression [6-9]. Furthermore, post-trabeculectomy data from Asian eyes are limited, as majority of the published studies have been conducted in Caucasian populations. Asian eyes, with a greater propensity for scarring and a higher incidence of angle-closure type glaucoma, may demonstrate different surgical outcomes.

The Singapore 5-Fluorouracil (5-FU) Trial was a randomised, double-masked placebo-controlled clinical study conducted in 243 Asian patients with primary glaucoma randomised to receive either intra-operative 5-fluorouracil (5-FU) or placebo at the time of trabeculectomy. Both the 3- and 8-year IOP data have been previously reported [10 11].

Utilizing the Progressor software analysis (Medisoft, Ltd, Leeds, United Kingdom), this study examines VF progression 8 years after trabeculectomy in subjects from the Singapore 5-FU Trial, and retrospectively analyses the effect of long-term IOP fluctuation on various parameters and definitions of VF progression.

MATERIALS AND METHODS

The Singapore 5-FU Trial

The study methodology of the Singapore 5-FU Trial has been detailed previously [10 11] and is briefly described as follows.

Written, informed consent was obtained from all participants. The study had the approval of the Ethical Review Committee of the Singapore National Eye Centre and was carried out in accordance with the tenets of the Declaration of Helsinki. The inclusion and exclusion criteria are listed in Table 1.

Table 1. Inclusion and Exclusion Criteria for Entry into the Singapore 5-Fluorouracil Trial.

Glaucoma was defined as glaucomatous optic neuropathy (GON) in the opinion of a fellowship-trained glaucoma specialist, with an IOP>21 mmHg on at least one occasion and a reproducible VF defect (using the 24-2 SITA Standard Humphrey Field Analyzer Model 750, Zeiss Humphrey Systems, Dublin, Ca) consisting of either 2 points reduced by >5dB or 1 point reduced >10dB below age-specific threshold with no alternative explanation for VF loss. Primary angle closure glaucoma (PACG) was diagnosed if GON was present and the posterior trabecular meshwork was not visible in 270 degrees or more on non-indentation gonioscopy, with or without peripheral anterior synechiae.

Subjects underwent limbal-based trabeculectomy augmented with intraoperative 5-FU (50mg/ml for 5 minutes) or placebo, and were examined at Day 1, Weeks 1, 2 and 3, and Months 3, 6, 9, 12, 16, 20, 24, 28, 32 and 36 after surgery. After surgery, topical prednisolone acetate 1% was used at least four times a day for a minimum of three months and topical chloramphenicol 0.5% four times a day for one month. A higher dosage of steroids was used on a case-by-case basis, as determined by the attending surgeon.

The trial concluded once the last patient reached 3 years of follow-up. At that stage, the masking code was broken and the data analyzed. Patients were subsequently followed-up in glaucoma clinics outside the study protocol, with the frequency of follow-up and tests varying according to their respective clinical progress.

Study Design

Data was collected from clinical records up to 8 years after trabeculectomy. The IOP measurements taken at 6-monthly intervals during the first 3 years of the prospective Singapore 5-FU Trial when protocols were standardized were included for analysis. Thereafter, as clinical and visual field assessments were carried out at various intervals, only IOP measurements taken within 1 month of all 6-monthly time-points post-trabeculectomy were retrospectively collected for analysis. As with prior studies, standard deviations (SD) of IOP readings were used as a surrogate for IOP fluctuation [6-12]. The use of 6-monthly IOP measurements for analysis avoids the undesirable effect that numerous measurements taken within a short period of time would have had on the overall standard deviation [8]. All the VFs performed up to 8 years after were analyzed using the Progressor software, which utilizes point-wise linear regression (PLR) [13].

Outcome Measures

A progressing point was defined as a test location with a significant ($p<0.01$) regression slope. A threshold of ≥1 dB/year ($p<0.01$) of sensitivity loss was used for inner points, while a threshold of ≥2dB/year ($p<0.01$) was used for edge points. Outcome measures included the number of progressing points per subject, the mean slope for progressing points per subject per year and the mean slope for VFs per subject per year. "Overall" VF progression was defined as a VF having ≥1 progressing point, or ≥3 adjacent progressing points in the same hemifield.

Statistical Analysis

Baseline demographic data was compared between "progressors" and "non-progressors" – continuous data was analyzed using independent and paired t-tests after testing for normality, while categorical data was analyzed with chi-squared test and Fisher's Exact test. Multivariate linear and logistic regression analyses were performed, adjusting for age, gender, ethnicity, glaucoma type, use of intra-operative 5-FU, diabetes mellitus, hypertension, best pre-trabeculectomy VF mean deviation (MD), post-trabeculectomy mean IOP, post-trabeculectomy IOP reduction and IOP fluctuation. Statistical Package for Social Sciences (SPSS) version 21 (IBM Corp., Armonk, NY) was used for data analysis. Statistical significance was set at $p<0.05$.

RESULTS

243 subjects were enrolled in the original Singapore 5-FU Trial. However, 8-year post-trabeculectomy data was not available for 75 subjects (67 subjects defaulted follow-up, 6 passed away and the clinical notes of 2 subjects were not retrievable). A further 32 subjects did not have VF assessments performed up to at least 8 years after trabeculectomy. 6 subjects did not have at least 5 reliable VFs and 3 subjects did not have at least 8 IOP measurements, throughout the study period. These subjects were excluded from analysis.

In total, 127 (52.3%) subjects successfully completed 8 years follow-up with ≥5 reliable VFs and ≥8 IOP assessments. The mean age of subjects at the time of surgery was 61.8 ± 9.6 years old. The

majority (n=82, 64.6%) were male and of Chinese ethnicity (n=102, 80.3%). 65 (51.2%) eyes suffered from primary open-angle glaucoma (POAG) and 59 (46.5%) from PACG. 66 (52.0%) eyes received 5-FU while 61 (48.0%) eyes received placebo. 29 (22.8%) subjects had diabetes and 36 (28.3%) had hypertension at the time of surgery. The mean IOP over the 8-year post-operative period was 14.2 ± 2.8 (range: 6.4 to 21.0) mmHg. The mean IOP fluctuation was 2.53 ± 1.20 mmHg.

When VF progression was defined as the presence of ≥3 adjacent progressing points in the same hemifield, there was a statistically significant difference in age (p=0.025) and the presence of hypertension (p=0.015) between groups, with the progressor group having a higher mean age and a greater proportion of subjects with hypertension. In addition, progressors demonstrated a higher mean IOP fluctuation compared to non-progressors (p=0.048). These results are detailed in Table 2a.

Table 2a. Patient Demographics and Post-Operative characteristics - Progressors vs Non-Progressors (progression defined by ≥3 or more adjacent progressing points in the same hemifield).

With a less stringent criteria for VF overall progression, defined as the presence of ≥1 progressing point, a greater proportion of subjects in the progressor group being found to have diabetes (p=0.025). These results are detailed in Table 2b.

Table 2b. Patient Demographics and Post-Operative characteristics - Progressors vs Non-Progressors (progression defined by ≥1 progressing point).

Parameters for VF progression were analyzed. The mean slope for field was -0.15 ± 0.35 dB/year and the mean number of progressing points was 2.31 ± 4.74. After trabeculectomy, majority of eyes (n=67, 57.8%) did not have any progressing points. However, a quarter of eyes continued to have ≥3 progressing points (n=32, 25.2%). The mean slope for progressing points was -1.74 ± 0.46 dB/year. When the most stringent definition of VF progression (≥3 adjacent progressing points in the same hemifield) was applied, the VFs of 25 (19.7%) eyes were still deemed to have progressed. These results are detailed in Table 3.

Table 3: Visual Field Progression Outcomes for all 127 Subjects.

Multivariate analyses demonstrated a significant association between greater IOP fluctuation and most VF progression parameters and criteria for progression, including slope for field (B=-0.071; 95% CI -0.126 to -0.015; p=0.013), total number of progressing points (B=0.963; 95% CI 0.198 to 1.727; p=0.014), VFs with ≥1 progressing points (OR=1.585; 95% CI 1.049 to 2.393; p=0.029). There was a trend towards eyes with higher IOP fluctuation having ≥3 adjacent progressing points in the same hemifield (OR=1.489; 95% CI 0.992 to 2.235; p=0.055). Greater mean IOP reduction post-trabeculectomy was associated only with a lower mean slope for progressing points per year (B=-0.026; p=0.028). Male gender was associated with greater slope for field (B=-0.153; 95% CI -0.297, -0.008; p=0.038) while there was a trend towards older subjects having a greater number of progressing points (B=0.056; 95% CI -0.002, 0.190, p=0.056). Subjects with diabetes were more likely to have ≥1 progressing point (OR=3.825, 95% CI 1.298 to 11.271, p=0.015). These results are detailed in Table 4a and 4b.

Table 4a. Multivariate Linear Analyses with Slope for Field, Number of Progressing Points and Slope for Progressing Points as Dependent Variables.

Table 4b. Multivariate Logistic Analyses with VF Progression defined by ≥1 progressing point and ≥3 adjacent progressing points in the same hemifield as Dependent Variables.

Given our findings that post-trabeculectomy IOP fluctuation was the IOP parameter most consistently associated with VF progression, demographics and post-operative characteristics were compared between eyes with an IOP SD of ≥ 3 mmHg with eyes with an IOP SD of <3 mmHg.

Table 5. Patient Demographics and Post-Operative Characteristics – Eyes with IOP SD ≥ 3 mmHg vs Eyes with IOP SD <3 mmHg.

Eyes which had intra-operative 5-FU did not appear to have different outcomes from eyes which had received the placebo, in the analysis for the slope for field (B=0.045; 95% CI -0.085, 0.174; p=0.495), number of progressing points (B=-0.767; 95% CI -2.531, 0.996, p=0.391) and slope for progressing points (B=0.00, 95% CI -0.325, 0.324; p=0.998).

DISCUSSION

The Progressor software performs a univariate linear regression at each VF point and allows for both event- and trend-based analyses. It demonstrates better inter- and intra-observer agreement compared to standard perimeter output [13 14]. PLR has been shown to be superior in detecting VF progression compared to utilizing the MD – which lacks specificity in assessing glaucomatous change [15]. To improve the sensitivity and specificity of progression detection, we included only subjects with ≥5 reliable VFs for analysis, similar to the inclusion criteria used in other studies [15].

The criteria used for progression of individual VF points and for overall VF progression has varied in literature. We defined progression as ≥1 dB/year loss of sensitivity at a significance of $p<0.01$. This particular threshold has been demonstrated to be ten times faster than expected age-normal decay [16] and has been used previously [17-19] – although a minority of studies have also employed lower thresholds [20]. This study also employed stricter criteria for edge points [17 18]. Criteria used to decide "overall" VF progression has differed more widely – some studies have used a threshold of only ≥1 progressing point [18], while others have considered the contiguity and location of points [19]. Our study applied 2 definitions in our analysis – we utilized the definition of ≥1 progressing point, as well as ≥3 adjacent progressing points in the same hemifield, as criteria for overall VF progression.

Our results suggest that eyes with higher long-term IOP fluctuation may have greater VF progression. This observation appears to hold true across multiple VF progression outcome measures, including the mean slope for field, number of progressing points, as well as in overall VF progression (defined by both definitions of ≥1 progressing point, and ≥3 adjacent progressing points in the same hemifield).

The association between long-term IOP fluctuation and glaucomatous progression has been a subject of debate. Our correlation was found in a subject population which had undergone filtering surgery and had a reasonable post-operative mean IOP of approximately 14mmHg. Previous studies finding an association between IOP fluctuation and VF progression appear to also have been conducted in eyes with at least moderately-advanced disease with a low mean IOP, or which had undergone IOP-lowering surgical intervention. Hong et al [6] analyzed data from long-term studies on post-trabeculectomy POAG and PACG eyes with IOPs <18 mmHg, also utilizing PLR VF analysis. They demonstrated that eyes with a lower IOP fluctuation of SD<2 had better preservation of the VFs compared to eyes with an IOP fluctuation of SD>2. There was no difference in the mean IOPs of both groups. Fukuchi et al [21] demonstrated that IOP fluctuation and range were associated with more rapid progression among NTG eyes, but not in OAG eyes. The AGIS, utilizing PLR and defining progression as worsening of >1 test location within a Glaucoma Hemifield Test cluster,

showed that IOP fluctuation remained a risk factor for progression in eyes with and without previous cataract extraction [9]. However, in a post-hoc analysis of AGIS data, examining only IOP measurements after surgical intervention, Caprioli et al [22] showed that greater long-term IOP fluctuation (SD>3) was associated with VF progression, and had a greater influence on VF progression in patients with a low mean IOP. On the basis of these findings by Caprioli et al, we used a threshold IOP SD of 3 mmHg to define "higher" fluctuation, in comparing the demographics and characteristics between eyes with higher IOP fluctuation and eyes with lower IOP fluctuation, in Table 5. The CIGTS [23] demonstrated that maximum IOP, SD and range were associated with a worse VF in medically-treated eyes with newly-diagnosed OAG. In another study on NTG eyes, long-term IOP fluctuation which was time-adjusted (adjusted for diurnal IOP variation with a preferred time) was associated with progression [24].

Conversely, studies which included eyes with early (or no) glaucoma and which received modest (or no) treatment did not demonstrate any significant correlation between long-term IOP fluctuation and progression. These include the EMGT [5], Glaucoma Progression Study [16], Diagnostic Innovations in Glaucoma Study (in their analysis on OHT subjects) [12], OHTS [25] and European Glaucoma Prevention Study [26]. Fogagnolol et al [27] could not find any difference in IOP fluctuation between POAG subjects who progressed and those who did not. Among some of these studies, it was instead the mean IOP which appeared to be associated with greater progression [7 12], with the association between fluctuation and progression demonstrated in eyes with higher mean IOPs but not in eyes with lower mean IOPs. Differences in methodology may explain differences in findings among studies. The EMGT analyzed IOP measurements only up to the point of progression. In contrast, the AGIS included in their analysis post-progression IOP measurements, which, likely to be lowered, may have resulted in an apparent "increase" in overall IOP fluctuation. Furthermore, the possible inherent correlation between various IOP parameters (mean IOP, SD, peak IOP, IOP range) [12 27] makes it difficult discern their individual effects on glaucomatous progression. In our study, multivariate analyses did not show a consistent association between post-trabeculectomy mean IOPs and the amount of IOP reduction with the outcome measures of VF progression. Only a greater mean post-trabeculectomy IOP reduction appeared to be associated with a lesser slope for progressing points.

A number of postulations may explain the correlation between IOP fluctuation and glaucomatous progression. Firstly, large IOP fluctuations may reflect a lack of steady state, reflecting disruptions in homeostatic mechanisms. Secondly, large fluctuations sometimes also involve periodic but significant IOP peaks, which reflect another, although likely correlated [12 28], parameter which has been shown to influence VF progression [28]. These mechanisms may have a greater influence on disease progression when the mean IOP is low.

Our study revealed that diabetes mellitus was more prevalent among subjects with ≥1 VF progression point. Diabetes may be associated with retinal ganglion cell death in glaucomatous eyes [29]. In post-trabeculectomy eyes, diabetes has been shown to be associated with increased IOP as well as VF progression. The AGIS observed a higher prevalence of diabetes in patients with higher IOPs [1] which was attributed to their possibly-reduced response to IOP-lowering treatments. Diabetes was also a risk factor for sustained VF deterioration [11]. Law SK et al [30] demonstrated that diabetic POAG patients had poorer long-term IOP control and surgical survival rates. This association between diabetes and poor trabeculectomy outcomes also appears to extend to NTG eyes [31]. The poorer surgical outcomes in diabetic eyes may be explained by the increased risk of scarring and bleb encapsulation [32]. However, in our study, it is acknowledged that the low threshold of ≥1 progressing point may not be sensitive enough to draw a definitive conclusion regarding the association between diabetes and VF progression. Furthermore, this association was lost when the criteria

of ≥3 adjacent progressing points in the same hemifield was applied. We did not collect data regarding diabetic retinopathy and laser treatment, which may have influenced results – retinopathy has been shown to further influence post-trabeculectomy IOPs, compared to the presence of diabetes alone [32].

Our multivariate analysis suggests that male gender may be associated with greater slope for field but not with other outcome measures. The association between gender and glaucomatous progression has not been consistently demonstrated [1]. However, de Moraes, et al, in a review of treated glaucoma patients from the Glaucoma Progression Study, showed that male gender was a risk factor for glaucomatous progression in patients with a lower mean IOP of <15.32 mmHg [10]. Notably, our study population also had a low mean IOP of 14.18 mmHg and demonstrated a similar association.

There was no difference in VF outcomes between eyes which had intra-operative 5-FU compared to placebo. 5-FU has been well-established to reduce post-trabeculectomy scarring and better surgical outcomes [33 34]. However, the efficacy of any surgical technique or augmentation is likely to be ultimately still mediated by the post-operative IOP [6], which remains the target of intervention after trabeculectomy. Previous results from the Singapore 5-FU Trial showed that while indeed there was no difference in IOPs between both the 5-FU and placebo groups, there was a trend toward eyes in the 5-FU group using fewer pressure-lowering medications 8 years after trabeculectomy [11].

There are limitations to this study. Firstly, its retrospective design is less favorable when investigating risk factors for disease progression. However, retrospective cohort studies may be better representative of real-life outcomes, compared to controlled RCTs. This study also has a considerably large sample size with a substantial follow-up period, particularly for a study on trabeculectomy outcomes in this population. Secondly, after the first 3 years of the 5-FU study, management protocols were not standardized. This heterogeneity may reduce the strength of results and conclusions. Thirdly, the authors acknowledge that mitomycin-C, not 5-FU, is the anti-metabolite of choice today. However, this study was not primarily designed to study the effect of 5-FU, but instead to examine long-term trabeculectomy outcomes. Fourthly, our study does not account for the influence of cataract surgery. Of note, however, the AGIS demonstrated that IOP fluctuation remained a risk factor for VF progression in eyes both with, and without previous cataract extraction [1]. Fifthly, our study utilized only single IOP measurements. We acknowledge that diurnal variation in IOPs may influence progression [24]. Glaucomatous eyes have greater diurnal IOP fluctuations than controls, and greater fluctuations may result in even greater disease progression [35]. Finally, our study did not collect medication data, which we acknowledge may better contextualize our findings.

Hence, in post-trabeculectomy Asian eyes with a low mean IOP, increased long-term IOP fluctuation may be associated with greater long-term VF progression up to 8 years after surgery. This finding was independent of other variables, including the use of intra-operative 5-FU.

Authorship statement

The following are members of the study team: Bryan Ang, Sophia Seen, Arjunan Kumaran, John Mark, Steve Seah Kah Leng, Paul Foster, Gus Gazzard, Htoon Hla Myint, Khaw Peng Tee, Aung Tin and Rahat Husain.

Contributorship statement

BA designed the study, performed the analyses and drafted and revised the paper. SS drafted and revised the paper. AK performed the analyses and drafted and revised the paper. JM monitored data collection. SSKL designed the data collection tools and monitored data collection. PF designed the

data collection tools and monitored data collection. GG designed the data collection tools and monitored data collection. HHM wrote the statistical plan and performed the analyses. KPT designed the data collection tools and monitored data collection. AT designed the data collection tools, monitored data collection and drafted and revised the paper. RH designed the data collection tools, monitored data collection and drafted and revised the paper.

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TABLES

Table 1. Inclusion and Exclusion Criteria for Entry into the Singapore 5-Fluorouracil Trial.

Inclusion Criteria

1. A measured IOP ≥ 21 mmHg on ≥ 1 visit before the time of listing for surgery.
2. Ability to complete a Humphrey 24-2 visual field test with <20% false positives, <33% false negatives, and <20% fixation losses and the presence of 2 locations >5 dB less than normal or 1 location > 10 dB less than normal, with 2 results giving mean defect within 2 dB.
3. The presence of a focal or diffuse area of optic disc rim loss, as shown by reduction of optic rim thickness to less than one tenth of disc diameter at any time on the disc.

Exclusion Criteria

1. Anterior segment neovascularization.
2. Any intraocular epithelial ingrowth.
3. Retinal or optic nerve neovascularization.
4. Aphakia.
5. Previous glaucoma filtering surgery.
6. Uveitis.
7. Previous acute angle closure glaucoma.
8. Any previous intraocular surgery.
9. Inability or unwillingness to give informed consent.
10. Inability or unwillingness to return for postoperative follow-up as prescribed in the trial regimen.
11. Unwillingness to accept randomization.
12. Patient ≤35 years of age.
13. Any previous anticancer treatment.
14. Any other disease causing visual field loss or likely to cause visual field loss over the next 3 years (e.g., diabetic retinopathy, pituitary disease, stroke).
15. Pregnancy or female of childbearing age who may be pregnant at the time of treatment. A pregnancy test should be performed on all women of childbearing age to rule out pregnancy.
16. Cataract that is deemed significant enough to require surgery during the course of the trial or that makes field testing or optic disc recording by either photography unreliable or not technically possible.
17. Patients receiving systemic anticoagulant treatment.
18. Any medical treatment likely to prevent the patient regularly attending for the next 3 years.
19. Previous conjunctival surgery at proposed site of surgery.
20. Previous squint surgery.

dB = decibel; IOP = intraocular pressure

Table 2a. Patient Demographics and Post-Operative Characteristics - Progressors vs Non-Progressors (progression defined by ≥3 or more adjacent progressing points in the same hemifield).

		VF Progression		
Characteristic	Total	No	Yes	p-value
Eyes (%)		102 (80.3)	25 (19.7)	
Age (yr)				
Mean ± SD	61.83 ± 9.553	61.03 ± 9.63	65.12 ± 8.68	0.025
Range	37, 79	37, 79	46, 75	
Gender				
Female (%)	45 (35.4)	38 (37.3)	7 (28.0)	0.386
Male (%)	82 (64.6)	64 (62.7)	18 (72.0)	
Ethnicity				
Chinese (%)	102 (80.3)	83 (81.4)	19 (76.0)	0.341
Malay (%)	12 (9.4)	10 (9.8)	2 (8.0)	
Indian (%)	10 (7.9)	6 (5.9)	4 (16.0)	
Others (%)	3 (2.4)	3 (2.9)	0 (0)	
Glaucoma Type				
OAG (%)				
POAG (%)	65 (51.2)	49 (48.0)	16 (64.0)	0.456
PXF (%)	2 (1.6)	2 (2.0)	0 (0.0)	
PDS (%)	1 (0.8)	1 (1.0)	0 (0.0)	
PACG (%)	59 (46.5)	50 (49.0)	9 (36.0)	
Treatment Group				
5-FU (%)	66 (52.0)	45 (44.1)	16 (64.0)	0.075
Placebo (%)	61 (48.0)	57 (55.9)	9 (36.0)	
Diabetes Mellitus				
No (%)	98 (77.2)	81 (79.4)	17 (68.0)	0.223

Yes (%)	29 (22.8)	21 (20.6)	8 (32.0)	
Hypertension				
No (%)	91 (71.7)	78 (76.5)	13 (52)	0.015
Yes (%)	36 (28.3)	24 (23.5)	12 (48)	
Best Pre-Trabeculectomy VF MD (dB)				
Mean ± SD	-13.82 ± 8.89	-13.58 ± 9.11	-14.82 ± 8.01	0.413
Range	-30.87, -1.40	-30.87, -1.40	-28.64, - 4.10	
Mean IOP Fluctuation (SD of IOP readings) (dB)				
Mean ± SD	2.53 ± 1.20	2.40 ± 1.03	3.08 ± 1.62	0.048
Range	0.93, 7.18	0.93, 6.40	1.36, 7.18	
Mean IOP (mmHg)				
Mean ± SD	14.18 ± 2.78	14.06 ± 2.69	14.64 ± 3.13	0.354
Range	6.35, 20.96	6.35, 19.21	9.12, 20.96	
Mean IOP Reduction Post-Trabeculectomy (mmHg)				
Mean ± SD	-9.87 ± 6.51	-9.99 ± 6.39	-9.44 ± 7.12	0.710
Range	-36.94, -0.29	-36.42, -0.29	-36.94, -2.04	

Table 2b. Patient Demographics and Post-Operative Characteristics - Progressors vs Non-Progressors (progression defined by ≥1 progressing point).

		VF Progression		
Characteristic	Total	No	Yes	p-value
Eyes (%)		67 (52.8)	60 (47.2)	
Age (yr)				
Mean ± SD	61.83 ± 9.553	61.10 ± 9.97	62.65 ± 9.08	0.299
Range	37, 79	37, 79	42, 75	
Gender				
Female (%)	45 (35.4)	28 (41.8)	17 (28.3)	0.113
Male (%)	82 (64.6)	39 (58.2)	43 (71.7)	
Ethnicity				
Chinese (%)	102 (80.3)	54 (80.6)	48 (80.0)	1.00
Malay (%)	12 (9.4)	6 (9.0)	6 (10.0)	
Indian (%)	10 (7.9)	5 (7.5)	5 (8.3)	
Others (%)	3 (2.4)	2 (3.0)	1 (1.7)	
Glaucoma Type				
OAG (%)				
POAG (%)	65 (51.2)	29 (43.3)	36 (60.0)	0.083
PXF (%)	2 (1.6)	2 (3.0)	0 (0.0)	
PDS (%)	1 (0.8)	1 (1.5)	0 (0.0)	
PACG (%)	59 (46.5)	35 (52.2)	24 (40.0)	
Treatment Group				
5-FU (%)	66 (52.0)	39 (58.2)	27 (45.0)	0.137
Placebo (%)	61 (48.0)	28 (41.8)	33 (55.0)	

Diabetes Mellitus				
No (%)	98 (77.2)	57 (85.1)	41 (68.3)	0.025
Yes (%)	29 (22.8)	10 (14.9)	19 (31.7)	
Hypertension				
No (%)	91 (71.7)	51 (76.1)	40 (66.7)	0.238
Yes (%)	36 (28.3)	16 (23.9)	20 (33.3)	
Best Pre-Trabeculectomy VF MD (dB)				
Mean ± SD	-13.82 ± 8.89	-12.73 ± 9.21	-15.03 ± 8.43	0.413
Range	-30.87, -1.40	-30.87, -1.40	-28.64, -2.58	
Mean IOP Fluctuation (SD of IOP readings) (dB)				
Mean ± SD	2.53 ± 1.20	2.29 ± 0.82	2.81 ± 1.47	0.094
Range	0.93, 7.18	0.93, 4.65	1.20, 7.18	
Mean IOP (mmHg)				
Mean ± SD	14.18 ± 2.78	14.08 ± 2.86	14.27 ± 2.71	0.693
Range	6.35, 20.96	6.35, 19.21	9.12, 20.96	
Mean IOP Reduction Post-Trabeculectomy (mmHg)				
Mean ± SD	-9.87 ± 6.51	-9.98 ± 6.30	-9.77 ± 6.80	0.860
Range	-36.94, -0.29	-36.42, -0.29	-36.94, -2.04	

Table 3: Visual Field Progression Outcomes for all 127 Subjects.

Slope for Field	
Mean (SD), dB/year	-0.15 ± 0.35
No. of Progressing Points	
Mean (SD)	2.31 ± 4.74
Eyes without Progressing Points	67 (57.8%)
Eyes with VF Progression defined as:	
≥1 progressing point	60 (47.2%)
≥2 progressing points	38 (29.9%)
≥3 progressing points	32 (25.2%)
≥2 progressing points, adjacent in the same hemifield	35 (27.6%)
≥3 progressing points, adjacent in the same hemifield	25 (19.7%)
Slope for Progressing Points	
Mean (SD), dB/year	-1.74 ± 0.46

Table 4a. Multivariate Linear Regression Analyses with Slope for Field, Number of Progressing Points and Slope for Progressing Points as Dependent Variables.

	Dependent variable								
	Slope for field			Number of progressing points			Slope for progressing points		
	B	95% CI	p-value	B	95% CI	p-value	B	95% CI	p-value
Age (at time of surgery)	-0.002	-0.009, 0.006	0.673	0.094	-0.002, 0.190	0.056	0.001	-0.015, 0.017	0.880
Male (referenced to Female)	-0.153	-0.297, -0.008	0.038	0.982	-0.978, 2.943	0.323	0.129	-0.190, 0.447	0.420
Ethnicity (referenced to Chinese)									
Malay	-0.001	-0.222, 0.221	0.995	-0.607	-3.636, 2.423	0.692	-0.281	-0.788, 0.227	0.271
Indian	-0.040	-0.273, 0.193	0.734	1.447	-1.748, 4.642	0.371	-0.037	-0.527, 0.453	0.880
Others	0.177	-0.232, 0.585	0.393	-0962	6.564, 4.640	0.734	0.033	-1.012, 1.078	0.949
PACG (referenced to POAG)	0.006	-0.137, 0.150	0.933	-0.911	-2.848, 1.026	0.353	-0.196	-0.510, 0.118	0.215
5-FU (referenced to Placebo)	0.045	-0.085, 0.174	0.495	-0.767	-2.531, 0.966	0.391	-0.028	-0.312, 0.256	0.843
IOP Fluctuation (SD of IOP readings)	-0.071	-0.126, -0.015	0.013	0.963	0.198, 1.727	0.014	-0.010	-0.112, 0.092	0.846
Mean IOP, per mmHg more	0.010	-0.016, 0.037	0.439	-0.136	-0.497, 0.225	0.457	0.019	-0.046, 0.084	0.560

Pre-trabeculectomy Best VF MD, per dB better	-0.003	-0.011, 0.005	0.485	0.033	-0.076, 0.142	0.550	0.005	-0.012, 0.023	0.544
IOP reduction, per mmHg reduced	-0.004	-0.014, 0.007	0.471	0.015	-0.128, 0.157	0.839	-0.026	-0.048, -0.003	0.028
Comorbidities (referenced to no comorbidity)									
Hypertension	-0.017	-0.161, 0.126	0.811	-369	-2.336, 1.598	0.711	-0.039	-0.324, 0.246	0.786
Diabetes Mellitus	-0.146	-0.310, 0.018	0.081	0.313	-1.936, 2.563	0.783	0.000	-0.325, 0.324	0.998

CI = confidence interval; PACG = primary angle closure glaucoma; POAG = primary open-angle glaucoma; 5-FU = 5-fluorouracil; IOP = intraocular pressure; VF = visual field; MD = mean deviation; dB = decibel

Table 4b. Multivariate Logistic Regression Analyses with VF Progression defined by ≥1 progressing point and ≥3 adjacent progressing points in the same hemifield as Dependent Variables.

	Dependent variable					
	≥1 progressing point			≥3 progressing points, adjacent in the same hemifield		
	OR	95% CI	p-value	OR	95% CI	p-value
Age (at time of surgery)	1.010	0.966, 1.057	0.660	1.060	0.988, 1.138	0.106
Male (referenced to Female)	0.492	0.197, 1.226	0.128	0.520	0.155, 1.747	0.290
Ethnicity (referenced to Chinese)						
Malay	0.740	0.187, 2.935	0.669	0.305	0.029, 3.253	0.325
Indian	0.738	0.163, 3.341	0.694	2.319	0.486, 11.055	0.291
Others	0.506	0.039, 6.567	0.602	0.000	0.000	0.999
PACG (referenced to POAG)	0.532	0.216, 1.312	0.170	0.543	0.168, 1.751	0.306
5-FU (referenced to Placebo)	0.619	0.272, 1.408	0.252	0.440	0.148, 1.304	0.139
IOP Fluctuation (SD of IOP readings)	1.585	1.049, 2.393	0.029	1.489	0.992, 2.235	0.055
Mean IOP, per mmHg more	0.932	0.785, 1.107	0.424	0.993	0.786, 1.253	0.950
Pre-trabeculectomy Best VF MD, per dB better	0.965	0.916, 1.016	0.173	0.998	0.934, 1.066	0.946
IOP reduction, per mmHg reduced	0.972	0.907, 1.041	0.411	0.957	0.873, 1.049	0.347
Comorbidities (referenced to no comorbidity)						
Hypertension	1.053	0.426, 2.604	0.910	2.436	0.803, 7.390	0.116

Diabetes Mellitus	3.825	1.298, 11.271	0.015	1.158	0.321, 4.177	0.822

OR = odds ratio; CI = confidence interval; PACG = primary angle closure glaucoma; POAG = primary open-angle glaucoma; 5-FU = 5-fluorouracil; IOP = intraocular pressure; VF = visual field; MD = mean deviation; dB = decibel

Table 5. Patient Demographics and Post-Operative Characteristics – Eyes with IOP SD ≥ 3 mmHg vs Eyes with IOP SD <3 mmHg.

		IOP SD (mmHg)		
Characteristic	Total	≥ 3	<3	p-value
Eyes (%)		30 (23.6)	97 (76.4)	
Age (yr)				
Mean ± SD	61.83 ± 9.553	60.77 ± 9.57	62.16 ± 9.58	0.486
Range	37, 79	40,75	37,79	
Gender				
Female (%)	45 (35.4)	12 (40.0)	33 (34.0)	0.550
Male (%)	82 (64.6)	18 (60.0)	64 (66.0)	
Ethnicity				
Chinese (%)	102 (80.3)	23 (76.7)	79 (81.4)	0.807
Malay (%)	12 (9.4)	3 (10)	9 (9.3)	
Indian (%)	10 (7.9)	3 (10)	7 (7.2)	
Others (%)	3 (2.4)	1 (3.3)	2 (2.1)	
Glaucoma Type				
OAG (%)				
POAG (%)	65 (51.2)	14 (46.7)	51 (52.6)	0.115

PXF (%)	2 (1.6)	2 (6.6)	0 (0.0)	
PDS (%)	1 (0.8)	0 (0.0)	1 (1.0)	
PACG (%)	59 (46.5)	14 (46.7)	45 (46.4)	
Treatment Group				
5-FU (%)	66 (52.0)	11 (36.7)	55 (56.7)	0.055
Placebo (%)	61 (48.0)	19 (63.3)	42 (43.3)	
Diabetes Mellitus				
No (%)	98 (77.2)	25 (83.3)	73 (75.3)	0.357
Yes (%)	29 (22.8)	5 (16.7)	24 (24.7)	
Hypertension				
No (%)	91 (71.7)	22 (73.3)	69 (71.1)	0.815
Yes (%)	36 (28.3)	8 (26.7)	28 (28.9)	
Best Pre-Trabeculectomy VF MD (dB)				
Mean ± SD	-13.82 ± 8.89	-14.28 ± 8.08	-13.68 ± 9.17	0.749
Range	-30.87, -1.40	-28.64, -3.56	-30.87, - 1.40	
Mean IOP Fluctuation (SD of IOP readings) (dB)				
Mean ± SD	2.53 ± 1.20	4.25 ± 1.21	2.00 ± 0.47	<0.001
Range	0.93, 7.18	3.00,7.18	0.93, 2.99	
Mean IOP (mmHg)				
Mean ± SD	14.18 ± 2.78	15.57 ± 2.86	13.74 ± 2.62	0.001
Range	6.36, 20.96	10.62,20.96	6.36,19.20	
Mean IOP Reduction Post-Trabeculectomy (mmHg)				
Mean ± SD	-9.87 ± 6.51	-10.36 ± 7.46	-9.73 ± 6.23	0.645
Range	-36.94, -0.29	-36.94, -0.79	-36.43, -0.29	