Five-year Follow-up of the Fluorouracil Filtering Surgery Study

THE FLUOROURACIL FILTERING SURGERY STUDY GROUP*

• PURPOSE: To determine the efficacy and safety of subconjunctival 5-fluorouracil injections after trabeculectomy in patients with poor prognoses, to determine risk factors for surgical failure, and to examine the relationship of intraocular pressure and visual function.

• METHODS: In this multicenter clinical trial, 213 patients with previous cataract surgery or previous failed filtering surgery were randomly assigned to receive either trabeculectomy alone or trabeculectomy with postoperative subconjunctival 5-fluorouracil injections. Measurements of intraocular pressure, visual acuity, and visual fields were performed throughout the five years, with the clinician masked to the treatment group. Failure was defined as a reoperation to control intraocular pressure or an intraocular pressure greater than 21 mm Hg at or after the first-year examination.

• RESULTS: Fifty-four (51%) of the 105 eyes in the 5-fluorouracil group and 80 (74%) of the 108 eyes in the standard filtering surgery group were classified as failures ($P < .001$, Mantel-Cox survival analysis). Risk factors for failure include high intraocular pressure, a short time interval after the last procedure involving a conjunctival incision, the number of procedures with conjunctival incisions, and Hispanic ethnicity. Patients in both treatment groups with controlled intraocular pressures were more likely to maintain visual acuity. Patients in the 5-fluorouracil group had a higher risk of late-onset bleb leaks (9%, nine of 105) than those in the standard filtering surgery group (2%, two of 108) ($P = .032$, Fisher's exact test).

• CONCLUSIONS: We recommend the use of subconjunctival 5-fluorouracil after trabeculectomy in eyes after previous cataract surgery or unsuccessful filtering surgery, but caution against its routine use in patients with good prognoses.

TO DETERMINE THE LONG-TERM SAFETY AND EFFICACY of postoperative subconjunctivally injected 5-fluorouracil in eyes with uncontrolled glaucoma and poor prognoses for filtering surgery (specifically, aphakic and pseudophakic eyes, and phakic eyes after failed filtering surgery), we recruited patients into a multicenter, randomized clinical trial, the Fluorouracil Filtering Surgery Study. The baseline patient characteristics, risk factors, outcome by prospectively defined intraocular pressure levels and reoperation rates, and adverse events in the 5-fluorouracil group and in the standard filtering surgery group during the first postoperative year and the first three postoperative years were described in previous publications.[1,2] In the present study, we provide the five-year follow-up data on these patients.

PATIENTS AND METHODS

PATIENT RECRUITMENT BEGAN IN SEPTEMBER 1985 AND follow-up continued through December 1993. The following seven centers participated: University of Miami, University of Florida, University of Illinois, Washington University, Lorain Community Hospital

Accepted for publication Oct. 10, 1995.

The Fluorouracil Filtering Surgery Study was supported by the Department of Health and Human Services, Public Health Service grants EY10900, EY05473, and EY05480 (University of Miami), EY05604 (University of Florida), EY06806 (University of Southern California), EY05446 (University of Illinois), EY08612 (University of Iowa), EY05436 (Washington University), and EY06500 (Lorain Community Hospital). *Members of the Fluorouracil Filtering Surgery Study Group are listed at the end of the article.

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(Ohio), University of Southern California, and University of Iowa. The institutional review board at each center approved the human research study protocol before initiating recruitment. The trial was monitored by a Safety and Data Monitoring Committee.

Efforts were made to recruit all eligible patients with uncontrolled glaucoma (intraocular pressure greater than 21 mm Hg), who had undergone cataract extraction or who had undergone at least one unsuccessful filtering procedure in a phakic eye. Specific inclusion and exclusion criteria were previously published.[1,2] Patients who had previously received 5-fluorouracil systemically, or in the study eye, were excluded. All eligible patients had uncontrolled intraocular pressures while taking maximally tolerated medical therapy. Only one eye of each patient was included in the study.

Measurements of intraocular pressure in eyes with normal corneal thickness were performed with certified Goldmann applanation tonometers by ophthalmologists who were masked to the treatment status. In eyes with corneal scarring or thickening, calibrated pneumotonometers and Schiotz tonometers were used. Information regarding visual acuity, visual field, and ocular surgery was sought from all nonstudy ophthalmologists who had examined the patients within the five-year follow-up period.

Visual acuity was determined by trained personnel who used a standardized refraction protocol with Diabetic Retinopathy Vitrectomy Study charts and standardized illumination.[3] Visual acuity scores were converted to logMAR equivalents for the purpose of data analysis, where the logMAR score is minus the logarithm of the visual fraction, that is, the numerator of visual acuity divided by the denominator of visual acuity.[4] For example, a visual acuity of 20/20 is a logMAR score of 0; 20/40 is 0.3; 20/200 is 1.0; 2/200 is 2.0. Visual acuity too poor to be measured on the Diabetic Retinopathy Vitrectomy Study charts, such as hand motions, light perception, and no light perception, were assigned logMAR values of 2.3, 3.0, and 4.0, respectively. This scale is similar to one used by Scott and associates.[5] Thus, a decrease in visual acuity from 20/20 to 20/40 or a decrease from 2/200 to hand motions would appear as an increase of 0.3 on the logMAR scale.

The visual field data collected in the Fluorouracil Filtering Surgery Study were heterogeneous and consisted primarily of visual fields recorded by the 30-2 program of the Humphrey automated perimeter with a size III stimulus. Fewer fields were obtained by program 32 of the Octopus instrument, especially in the first two years of the study. Conventional, manual kinetic perimetry with the Goldmann instrument was performed when adequate determinations could not be conducted by one of the automated techniques. In all patients, the appropriate spectacle correction for the perimeter bowl size was used. A method of estimating the extent of visual field damage, which would be comparable for all of the various forms of examination, was needed.

One of us (W. M. Hart, Jr.) devised a scoring technique analogous to the ergoperimetric map of Esterman and associates.[6-9] The scale quantified the extent of visual field damage by using a total dynamic range of 16 steps from a normal visual field (visual field damage score of zero) to one of no useful visual function (visual field damage score of 16). For baseline visual fields, which were performed with an automated perimeter, the Pearson correlation coefficient of this score with the mean sensitivity was $r = -.895$ ($P < .001$). The dynamic range of the human visual field approximates 2.5 to 3.0 log units, depending on age, when averaged over the central 30 degrees of eccentricity. The standard size test objects for automated perimetry match the size III test object of the Goldmann perimeter. This relatively large test object at maximal luminance represents a suprathreshold stimulus value that is close to a measure of minimal useful visual function. Therefore, any quadrant of the visual field in which the size III test object at maximal luminance was not visible within 30 degrees of fixation was assigned a damage score of 4. Goldmann size I test objects have stimulus values one log unit below those for the size III, and test objects of size I attenuated to I_2 are an additional 0.5 log unit less in stimulus value. The various methods of perimetry used in the Fluorouracil Filtering Surgery Study all assess central 30-degree visual field sensitivity.

Each quadrant of the central 30 degrees of the visual field was further subdivided into two radial sectors of 45 degrees each, and each sector was further divided into an inner half and an outer half. Each quadrant with its four sections was given a score between 0 and 4, depending on visual field performance in each section. For each of the 16 regions, a

score of 1 denoted complete loss of perception for a size III test object; a score of 0.5 was assigned to an individual region when a generalized 50% reduction in sensitivity was demonstrated. Scores for quadrants were rounded to whole numbers. Estimates of the degree of loss in a given region were based on the numeric values for threshold sensitivity. Sections with scores of 0.5 usually occurred in pairs. When fractional sections were not paired, fractional scores were rounded down. All visual fields were assigned a score, with this system, by one of us (W. M. Hart, Jr.), who was masked to treatment assignment and outcome.

At each clinical center, either the principal ophthalmologist or an associate ophthalmologist operated on all eyes. A trabeculectomy was performed in all eyes under a limbal-based conjunctival flap. If no serious complications were noted and the conjunctival wound was watertight, patients were randomly assigned either to the standard filtering surgery group (trabeculectomy without 5-fluorouracil) or to the 5-fluorouracil group (trabeculectomy with 5-fluorouracil).

Eyes in the 5-fluorouracil group received 5.0-mg (0.5-ml) injections of 5-fluorouracil solution 180 degrees from the operative site twice daily on postoperative days 1 through 7 and once daily on postoperative days 8 through 14, unless serious postoperative complications, such as wound leakage, were observed. Eyes assigned to the standard filtering surgery group received no 5-fluorouracil but were examined once a day during postoperative days 1 through 14. Eyes in both groups received frequent topical corticosteroids and 1% atropine sulfate in the immediate postoperative period.

Patients in the standard filtering surgery group were not given placebo injections. Intraocular pressures were measured by an ophthalmologist masked to treatment status at each center at six months, one year, 18 months, two years, three years, four years, five years, and before reoperation for intraocular pressure control in both treatment groups. Patients whose glaucoma could not be controlled underwent either reoperation with or without 5-fluorouracil, or another procedure, such as drainage implant surgery or cyclodestruction, to decrease intraocular pressure. The choice of procedure for reoperation was determined by the operating physician. Patients initially assigned to the standard filtering surgery group were given the option of receiving postoperative subconjunctival 5-fluorouracil injections. The treatment analyses were performed on the patients' original random assignments. Subsequent surgery to decrease intraocular pressure was occasionally performed by nonstudy ophthalmologists at the discretion of the patients.

Treatment failure was defined as (1) the patient had a reoperation performed to decrease intraocular pressure before the five-year examination or (2) the patient had an intraocular pressure greater than 21 mm Hg with or without medication at or after the one-year postoperative examination, that is, at the one-year, 18-month, two-year, three-year, four-year, or five-year examination. For survival analyses, the time to failure was defined either as the time from trabeculectomy to reoperation for the purpose of decreasing intraocular pressure, or as the time from the trabeculectomy to the first study examination at or after one year, when intraocular pressure was greater than 21 mm Hg. For these analyses, treatment failure was also defined as reoperation for intraocular pressure control and time to failure was defined as the time from trabeculectomy to reoperation.

We also used visual acuity and visual fields as outcome measures. The logMAR change in visual acuity from the preoperative examination to a postoperative examination was defined as an outcome variable in some analyses. The change in visual field damage score was used as another outcome measure.

The primary outcome event, reoperation, was defined as further surgery to control intraocular pressure performed before the five-year examination, or intraocular pressure greater than 21 mm Hg with or without medication at any examination on or before the five-year examination. The five-year examination interval extended to 66 months postoperatively. The time to failure of trabeculectomy was compared in the two treatment groups by using Kaplan-Meier survival analysis and the log-rank test.

Variables considered as possible risk factors for trabeculectomy failure included treatment and study stratum (aphakic or phakic with previous failed filter), clinic, gender, race, ethnicity, eye color, intraocular pressure at qualifying examination, visual acuity at qualifying examination, age at entry into the study, number of previous ocular procedures with conjunctival incisions, time elapsed since most recent ocular procedure with a conjunctival incision, location of

trabeculectomy (superior or inferior), scarring status at trabeculectomy site, diabetes, and type of glaucoma. The risk factors were assessed for statistical significance with the Kaplan-Meier survival analysis log-rank test, stratified by treatment group.

Multivariate analysis was carried out with the Cox proportional hazards regression model by using backward stepwise elimination (the P value for removal of a variable was set at .05). Results are given for the following two outcomes: (1) time to reoperation and (2) time to reoperation or time when intraocular pressure was greater than 21 mm Hg at or after the one-year examination. Models were checked for the influence of extreme points, and, when appropriate, transformations of variables were used.

Minor differences between these results and the results reported in the one-year and three-year follow-up[1,2] may be noted. Visual acuity and intraocular pressure measurements were obtained from nonstudy ophthalmologists, when possible, if a patient missed a study examination. Three patients, two in the 5-fluorouracil group and one in the standard group, who were originally classified as reoperations for intraocular pressure control, were reclassified to having undergone other ocular surgery, because these procedures were revisions to the trabeculectomy caused by wound leaks and low intraocular pressure. The Safety and Data Monitoring Committee made these recommendations for data assessment, which did not affect the study conclusions.

RESULTS

FIFTY-FOUR (51%) OF THE 105 EYES IN THE 5-FLUOROURACIL group and 80 (74%) of the 108 eyes in the standard filtering surgery group were classified as failures, which is defined by reoperation for control of intraocular pressure or an intraocular pressure greater than 21 mm Hg at or after the first-year examination ($P < .001$, Mantel-Cox survival analysis). At five years, the cumulative success rates were 48% in the 5-fluorouracil group and 21% in the standard group ($P < .001$, survival analysis log-rank test) (Table 1 and Fig. 1), where failure is defined as reoperation for intraocular pressure control or intraocular pressure greater than 21 mm Hg at or after the one-year examination. The five-year cumulative success rate for the eyes with a history of cataract extraction in the 5-fluorouracil group was 48%, and for the standard filtering surgery group, 23% ($P < .001$ survival analysis, log-rank test). The five-year cumulative success rate for phakic eyes with a history of failed filtering surgery in the 5-fluorouracil group was 47%, and for the standard filtering surgery group, 17% ($P = .009$, survival analysis log-rank test). Failure rates based on reoperation for intraocular pressure control during the first five postoperative years were also calculated. The results of both analyses were similar (Table 2 and Fig. 2).

To determine the necessity of postoperative glaucoma medication for intraocular pressure control after

TABLE 1

CUMULATIVE PROPORTION (STANDARD ERROR) OF PATIENTS WITHOUT REOPERATION OR INTRAOCULAR PRESSURE FAILURE

	5-FLUOROURACIL GROUP			STANDARD FILTERING SURGERY GROUP		
FOLLOW-UP (YRS)	PREVIOUS CATARACT EXTRACTION (N=81)	PREVIOUS FAILED FILTER (N=24)	TOTAL (N=105)	PREVIOUS CATARACT EXTRACTION (N=81)	PREVIOUS FAILED FILTER (N=27)	TOTAL (N=108)
1	.77 (.05)	.88 (.07)	.80 (.04)	.59 (.06)	.63 (.09)	.60 (.05)
1.5	.69 (.05)	.79 (.08)	.72 (.04)	.45 (.06)	.52 (.10)	.47 (.05)
2	.59 (.06)	.71 (.09)	.62 (.05)	.39 (.06)	.33 (.09)	.38 (.05)
3	.54 (.06)	.62 (.10)	.56 (.05)	.29 (.05)	.26 (.08)	.28 (.05)
4	.48 (.06)	.62 (.10)	.51 (.05)	.28 (.05)	.26 (.08)	.27 (.04)
5	.48 (.06)	.47 (.11)	.48 (.05)	.23 (.05)	.17 (.08)	.21 (.04)

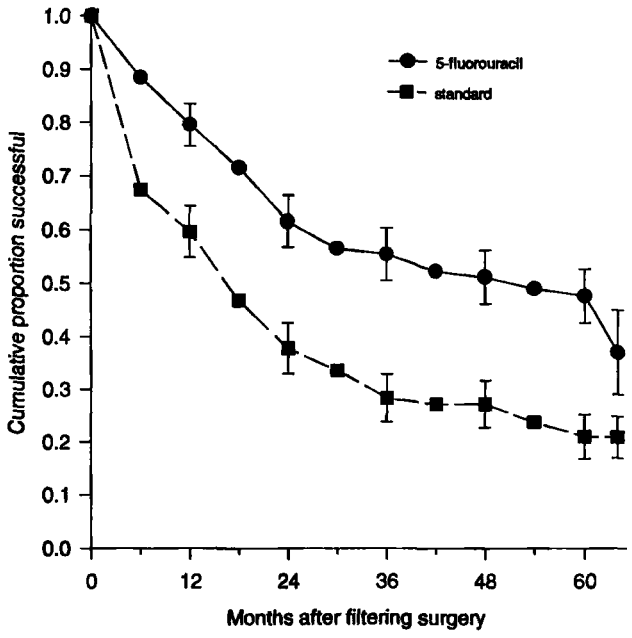

Fig. 1 (The Fluorouracil Filtering Surgery Study Group). Cumulative proportion of patients who did not undergo a reoperation and who did not have an intraocular pressure greater than 21 mm Hg in months after trabeculectomy by treatment group (5-fluorouracil group, 105 patients; standard group, 108 patients). Bars indicate ± standard error.

trabeculectomy, we compared the percentage of patients in each treatment group who did not require additional medical therapy at the time of each annual examination (Table 3). All patients, regardless of outcome, were included. As information on glaucoma medications frequently could not be obtained from nonstudy ophthalmologists, this outcome was more likely to be unknown than the status of reoperation, intraocular pressure, or visual acuity. At the five-year examination, 41% (32 of 78) of the patients in the 5-fluorouracil group were not taking any glaucoma medications, and 21% (15 of 71) of the patients in the standard filtering surgery group were not using any medications ($P = .015$; χ^2). If only patients with controlled intraocular pressure (intraocular pressure 21 mm Hg or less) without reoperation are considered, 58% (21 of 36) of patients in the 5-fluorouracil group were taking no glaucoma medication compared to 41% (seven of 17) of similar patients in the standard filtering surgery group ($P = .383$, χ^2) at the five-year examination.

During the five years of follow-up, patients in each treatment group experienced a gradual loss of vision from their visual acuity at the qualifying examination (Table 4 and Fig. 3). The mean decrease in visual acuity was 0.7 logMAR unit ($P < .001$, paired *t*-test). Patients in the 5-fluorouracil group lost significantly more vision than those in the standard filtering surgery group at one month ($P < .001$) but recovered visual acuity by six months and had significantly less visual acuity loss than those in the standard filtering surgery group at one ($P = .046$), two ($P = .047$), and three ($P = .030$) years after trabeculectomy. Although a significant difference in visual loss did not persist at five years (Table 4 and Fig. 3), the 95% confidence interval does not exclude a clinically

TABLE 2

CUMULATIVE PROPORTION (STANDARD ERROR) OF PATIENTS WITHOUT REOPERATION

	5-FLUOROURACIL GROUP			STANDARD FILTERING SURGERY GROUP		
FOLLOW-UP (YRS)	PREVIOUS CATARACT EXTRACTION (N=81)	PREVIOUS FAILED FILTER (N=24)	TOTAL (N=105)	PREVIOUS CATARACT EXTRACTION (N=81)	PREVIOUS FAILED FILTER (N=27)	TOTAL (N=108)
1	.82 (.04)	.92 (.06)	.85 (.04)	.60 (.06)	.63 (.09)	.61 (.05)
1.5	.82 (.04)	.83 (.08)	.83 (.04)	.53 (.06)	.56 (.10)	.54 (.05)
2	.81 (.04)	.83 (.08)	.82 (.04)	.53 (.06)	.48 (.10)	.52 (.05)
3	.77 (.05)	.70 (.09)	.75 (.04)	.47 (.06)	.37 (.09)	.44 (.05)
4	.73 (.05)	.70 (.09)	.72 (.05)	.45 (.06)	.30 (.09)	.41 (.05)
5	.69 (.05)	.66 (.10)	.69 (.05)	.42 (.06)	.30 (.09)	.39 (.05)

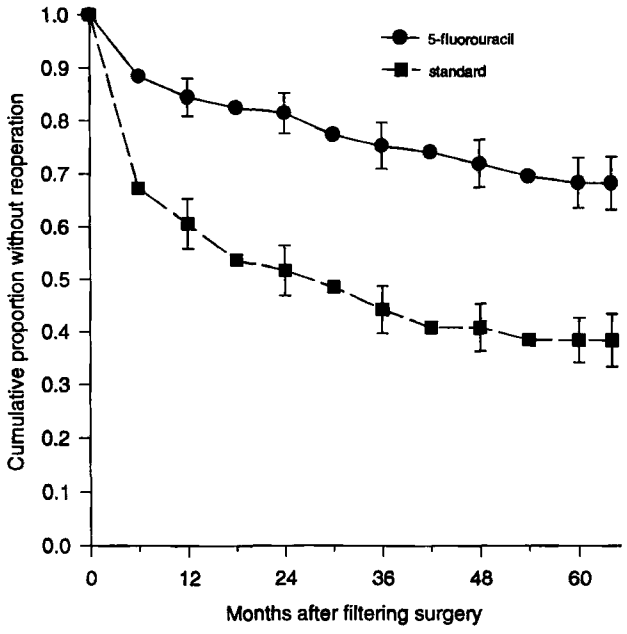

Fig. 2 (The Fluorouracil Filtering Surgery Study Group). Cumulative proportion of patients who did not undergo a reoperation for control of intraocular pressure in months after trabeculectomy by treatment group (5-fluorouracil group, 105 patients; standard group, 108 patients). Bars indicate ± standard error.

important effect (−0.20 to 0.40 logMAR unit). The distribution of visual acuity loss in each group at five years is shown in Figure 4.

Nine eyes in the 5-fluorouracil group and 12 in the standard filtering surgery group lost visual acuity to the level of no light perception. Four eyes of the 12 in the standard filtering surgery group had received postoperative 5-fluorouracil after reoperation for intraocular pressure control. No eyes in the 5-fluorouracil group were enucleated. Four eyes in the standard filtering surgery group were enucleated, and one underwent a retrobulbar alcohol injection. One of the enucleated eyes received 5-fluorouracil at reoperation and was later removed for an invasive orbital basal cell carcinoma; one of the enucleated eyes received 5-fluorouracil at a reoperation; and two never received 5-fluorouracil.

To define the possible relationship between visual acuity loss and intraocular pressure control, patients were classified into the following three groups on the basis of intraocular pressure control, independent of treatment group: (1) intraocular pressure controlled at every study examination at and after the one-year examination (success); (2) intraocular pressure greater than 21 mm Hg at one or more examinations in patients who did not undergo reoperation (intraocular pressure failure); and (3) patients who required reoperation for pressure control (reoperation). Patients were classified as unknown and excluded from this analysis if they were not reoperated on and had no intraocular pressure measurement greater than 21 mm Hg, had no examination at or after the three-year examination, and did not have at least three examinations at or after the one-year examination. For patients without a five-year examination, the four-year visual acuity measurement was used, and for patients without a four-year examination, the three-year visual acuity measurement was used. The average loss of visual acuity in logMAR units from the qualifying examination through the five-year follow-up examination in these three groups increased significantly from best to worst outcome: mean intraocular pressure success, 0.30 ± 0.73 (N = 65); intraocular pressure failure, 0.64 ± 1.04 (N = 38); and reoperation, 0.97 ± 1.05 (N = 88) ($P < .001$, test of linear trend in one-way analysis of variance). The relationship of visual acuity loss to outcome was of similar magnitude and statistical significance in the aphakic stratum, where change in visual acuity was not confounded by the development of cataracts or cataract surgery.

TABLE 3

PERCENTAGE OF PATIENTS TAKING NO GLAUCOMA MEDICATION

	5-FLUOROURACIL GROUP		STANDARD FILTERING SURGERY GROUP		P
FOLLOW-UP	%	(NO./TOTAL)*	%	(NO./TOTAL)*	VALUE
1 mo	87	(88/101)	47	(49/104)	<.001
6 mos	61	(61/100)	37	(37/100)	.001
1 yr	58	(57/98)	29	(27/93)	<.001
1.5 yrs	58	(53/92)	38	(32/85)	.012
2 yrs	47	(43/91)	33	(29/88)	.072
3 yrs	46	(42/91)	32	(26/81)	.084
4 yrs	42	(34/82)	33	(24/73)	.349
5 yrs	41	(32/78)	21	(15/71)	.015

*Numerator indicates number of patients taking no medications, and denominator indicates the total number of patients for whom follow-up data are available.

TABLE 4

VISUAL ACUITY CHANGE (LogMAR)

FOLLOW-UP	5-FLUOROURACIL GROUP NO.	5-FLUOROURACIL GROUP MEAN (S.D.)	STANDARD FILTERING SURGERY GROUP NO.	STANDARD FILTERING SURGERY GROUP MEAN (S.D.)	P VALUE*
1 mo	101	.35 (.45)	102	.06 (.31)	<.001
3 mos	100	.09 (.56)	100	.04 (.41)	.451
6 mos	101	.08 (.53)	99	.17 (.64)	.269
1 yr	98	.13 (.66)	96	.32 (.68)	.046
1.5 yrs	93	.18 (.72)	87	.36 (.72)	.103
2 yrs	93	.26 (.73)	91	.49 (.83)	.047
3 yrs	94	.29 (.78)	87	.55 (.86)	.030
4 yrs	86	.51 (.92)	82	.69 (.84)	.211
5 yrs	88	.67 (1.03)	86	.77 (.99)	.521

*t-test.

The relationship of the extent of visual acuity loss to the maximum intraocular pressure measured at a study examination at or after one year is shown in Figure 5. Missed examinations precluded the use of either the average intraocular pressure or the sum of intraocular pressures as reliable indicators of exposure to high intraocular pressure. A similar correlation was found with the amount of visual acuity loss and the maximum intraocular pressure in the aphakic patients who did not undergo reoperation for intraocular pressure control.

Visual fields were measured preoperatively and at six months, one year, 18 months, two, three, four, and five years postoperatively. If a patient did not have a five-year examination, the four-year visual field score was used, and for those without a four-year examination, the three-year score was used. If no visual field test was performed because visual acuity was no light perception or light perception, a visual field score of 16 (the worst score) was assigned; if visual acuity was hand motions, a score of 15 was assigned. Figure 6 shows the distributions of the preoperative and the five-year visual field scores for all patients. The mean preoperative visual field score was 9.3 ± 3.9 (N = 210) and the mean five-year visual field score was 12.0 ± 3.8 (N = 186). The change in visual field score was not significantly different between treatment groups (P = .8, two sample *t*-test). The mean visual field score decrease from the preoperative to the five-year examination in patients in both treatment groups combined was 3 units, which was statistically significant (P < .001; paired *t*-test).

When the same outcome categories for intraocular pressure control that were used to analyze the visual acuity data were applied to visual field scores, no significant differences were found (P = .18, one-way analysis of variance) among the groups. The largest mean visual field loss was in the reoperation group, with a score of 3.3 ± 3.3 (N = 84), as opposed to those in the intraocular pressure failure group, with a score of 2.2 ± 2.8 (N = 36), and those in the intraocular pressure success group, with a score of 2.8 ± 3.1 (N = 64). We expected that any differences in visual fields among these three intraocular pressure groups would be clearest in the aphakic stratum, where visual function changes would not be confounded by the development of cataracts or cataract surgery. When the analysis was performed on these patients, the reoperation group showed greater mean losses in visual field scores (3.9 ± 3.4 [N = 57]) than the other two groups (P = .005, one-way analysis of variance), the intraocular pressure failure group (2.1 ± 2.4 [N = 29]), and the intraocular pressure success group (2.2 ± 2.7 [N = 48]). If the patients with

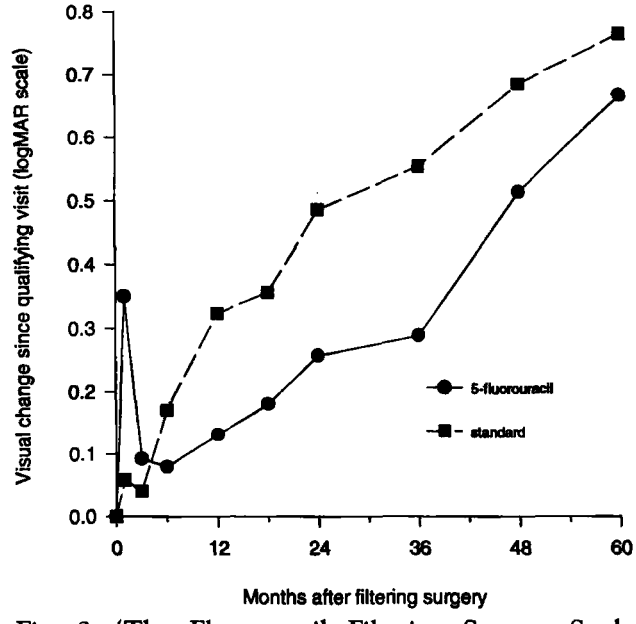

Fig. 3 (The Fluorouracil Filtering Surgery Study Group). Mean change in visual acuity (logMAR) from preoperative examination at each postoperative study examination, by treatment group (5-fluorouracil group, 105 patients; standard group, 108 patients).

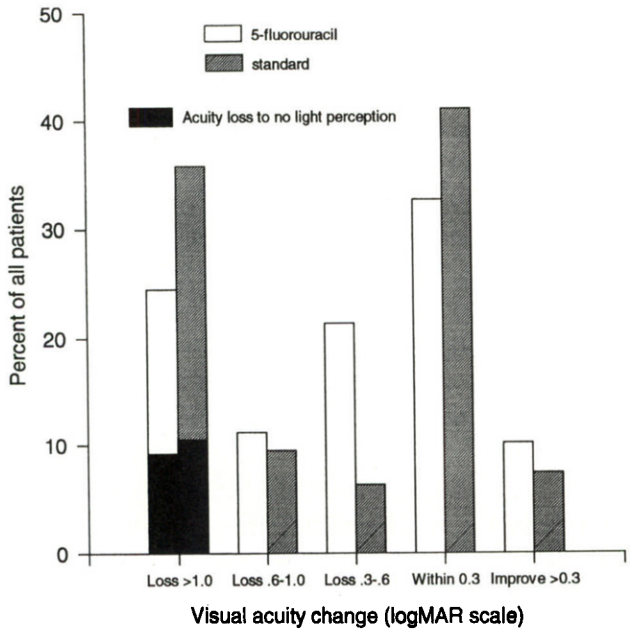

Fig. 4 (The Fluorouracil Filtering Surgery Study Group). Frequency distribution of change in visual acuity (logMAR) from the preoperative examination to the five-year examination, by treatment group (5-fluorouracil group, 88 patients; standard group, 86 patients).

hypotony, that is, no intraocular pressure measurement greater than 10 mm Hg, are omitted, the visual field score loss is statistically significantly associated with increasing maximum intraocular pressure measured for each patient between one and five years after trabeculectomy, for the aphakic stratum (P = .033, analysis of variance with orthogonal polynomial test for linear trend) as illustrated in Figure 7.

All suprachoroidal hemorrhages occurred in patients with previous cataract extractions. The incidence of suprachoroidal hemorrhage was equal in the two treatment groups: five of 81 eyes in the 5-fluorouracil group and five of 81 eyes in the standard filtering surgery group. The risk of suprachoroidal hemorrhage was strongly associated with the level of preoperative intraocular pressure. A suprachoroidal hemorrhage developed in none of the 63 patients with a preoperative intraocular pressure less than 30 mm Hg, three (6%) of the 47 patients with a preoperative intraocular pressure between 30 and 39 mm Hg, four (11%) of the 36 patients with a preoperative intraocular pressure between 40 and 49 mm Hg, two (17%) of the 12 patients with a preoperative intraocular pressure between 50 and 59 mm Hg, and one of four patients with an intraocular pressure greater than 60 mm Hg.[10]

Of the 105 eyes in the 5-fluorouracil group, 31 underwent additional surgery to decrease intraocular pressure after trabeculectomy. Sixteen of these 31 eyes underwent implantation of a drainage device, two eyes had cyclodialysis, six were treated with a cyclodestructive procedure (Nd:YAG cyclophotoablation, five eyes; ultrasonic therapy, one eye), two trabeculectomies were revised, and five eyes underwent additional trabeculectomy, either alone (three eyes) or as a part of a combined cataract extraction (one eye) or penetrating keratoplasty (one eye).

Of the 108 eyes in the standard filtering surgery group, 63 underwent additional surgery after trabeculectomy failure. One eye was enucleated, 14 eyes underwent implantation of a drainage device, six eyes were treated with a cyclodestructive procedure (Nd:YAG cyclophotoablation, two eyes; cyclocryotherapy, four eyes), six trabeculectomies were revised, 32 eyes underwent additional trabeculectomy either alone (31 eyes) or as a part of a combined cataract extraction (one eye), and four eyes were treated with an unguarded or full-thickness filtering procedure.

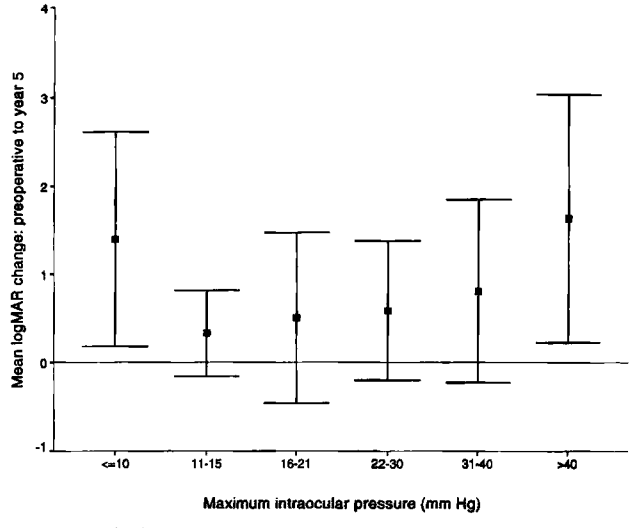

Fig. 5 (The Fluorouracil Filtering Surgery Study Group). Mean change in visual acuity (logMAR) from preoperative examination to five-year examination by maximum intraocular pressure (mm Hg) reached at a study examination at or after the one-year examination. A positive change reflects a loss of visual acuity. Bars indicate ± standard deviation.

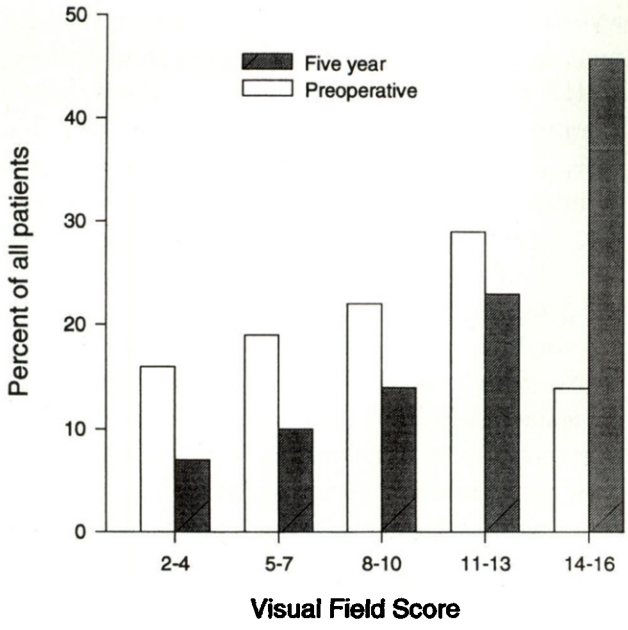

Fig. 6 (The Fluorouracil Filtering Surgery Study Group). Frequency distribution of visual field scores at the preoperative and five-year examinations (preoperative, 210 patients; five-year, 186 patients).

Of the 31 eyes in the 5-fluorouracil group that underwent a reoperation for intraocular pressure control, 20 underwent one procedure, five were treated with two reoperations, and six were treated with three reoperations, for a total of 48 surgical procedures. No eye in the 5-fluorouracil group received more than three operations for intraocular pressure control, and no eye was enucleated or treated with retrobulbar alcohol. The 63 eyes in the standard filtering surgery group underwent a total of 114 additional surgical procedures to decrease intraocular pressure; 39 eyes underwent one procedure; seven eyes, two procedures; ten eyes, three procedures; four eyes, four procedures; and three eyes, five procedures. Thirty-four eyes in the standard filtering surgery group received 5-fluorouracil after a reoperation for intraocular pressure control. After the first reoperation, two patients underwent enucleation and one received a retrobulbar alcohol injection. Of first reoperations in both treatment groups, 13% (12 of 94) were cyclodestructive, whereas 56% (38 of 68) of subsequent reoperations were cyclodestructive.

An aqueous leak in the filtering bleb, characterized by positive results of a Seidel test, that was first noted after the 14th postoperative day was more likely to occur in eyes in the 5-fluorouracil group. Nine (9%) of 105 eyes in the 5-fluorouracil group as opposed to two (2%) of 108 eyes in the standard filtering surgery group (P = .032, Fisher's exact test, two-tailed) had a leak in the filtering bleb. Patients in the 5-fluorouracil group developed leaks at three, eight (two patients), 25 (three patients), 28, 35, and 51 months after surgery. Patients in the standard filtering surgery group developed leaks 30 and 59 months later. Four (5.3%) of the 76 inferonasally or inferotemporally positioned blebs as opposed to seven (5.1%) of the 137 superiorly positioned blebs (P = .784; χ^2) developed leaks.

In two patients in the 5-fluorouracil group and in one patient in the standard filtering surgery group, complications of endophthalmitis developed. In one patient in the 5-fluorouracil group, *Staphylococcus aureus* endophthalmitis developed in an eye with an inferiorly positioned bleb that had been noted to leak eight months after trabeculectomy and six months before the development of the infection. The patient was treated with a pars plana vitrectomy and intravitreal antibiotics and recovered visual acuity of 20/30. The other patient in the 5-fluorouracil group developed a long-standing bleb leak two years after surgery

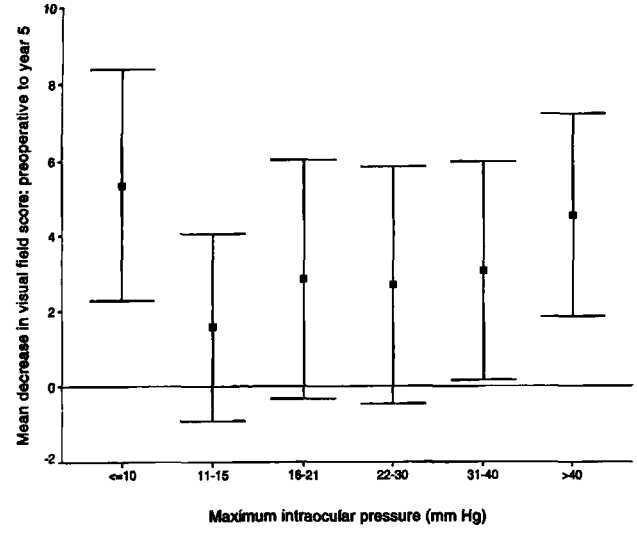

Fig. 7 (The Fluorouracil Filtering Surgery Study Group). Mean decrease in visual field score among aphakic patients from preoperative examination to five-year examination by maximum intraocular pressure (mm Hg) reached at a study examination at or after the one-year examination (134 patients). Bars indicate ± standard deviation.

and complained of ocular pain in the eye five years after trabeculectomy, at which time visual acuity was hand motions. He underwent a pars plana vitrectomy with irrigation of the anterior chamber and an aqueous and vitreous tap, with injection of intravitreal antibiotics. *Moraxella catarrhalis* and *Streptococcus sanguis* were cultured from the vitreous. His visual acuity improved after the end of the study to 20/60. The patient in the standard filtering surgery group developed endophthalmitis two years after trabeculectomy. No bleb leak had been noted on previous examinations. A nonstudy ophthalmologist performed an anterior vitrectomy with injection of intravitreal antibiotics, and no culture information was available. The patient recovered visual acuity of 20/30. All eyes that were treated for presumed endophthalmitis were noted to have functioning filtering blebs at the last study examination before the development of the infection.

Five of the 105 patients in the 5-fluorouracil group underwent penetrating keratoplasty after trabeculectomy. Four additional patients underwent penetrating keratoplasty after reoperation for intraocular pressure control, and one patient underwent penetrating keratoplasty at the time of a first reoperation for intraocular pressure control. Three of the 108 patients in the standard filtering surgery group underwent penetrating keratoplasty after trabeculectomy. Five additional patients in the standard filtering surgery group underwent penetrating keratoplasty after reoperation for intraocular pressure control (5-fluorouracil was used after the reoperation in two patients), and one patient in the standard filtering surgery group underwent a penetrating keratoplasty at the time of the third reoperation for intraocular pressure control. This patient had received subconjunctival 5-fluorouracil after a previous procedure. Two patients underwent application of a bioadhesive as treatment for a perforated corneal ulcer. One perforation occurred in a patient in the 5-fluorouracil group who developed a *Haemophilus influenzae* corneal ulcer four months after trabeculectomy. The other patient in the standard filtering surgery group had a sterile corneal perforation 28 months after trabeculectomy.

In addition to procedures to decrease intraocular pressure, eyes also underwent other procedures. During the first 14 postoperative days, conjunctival wound leaks or buttonholes that required surgical revision occurred in seven of 105 patients (eight procedures) in the 5-fluorouracil group, and in three of 108 patients (three procedures) in the standard filtering surgery group ($P = .309$; χ^2). During this time, anterior chamber reformation with or without drainage of serous or hemorrhagic choroidal effusion was performed in 11 of 105 patients in the 5-fluorouracil group (15 total procedures) and in four of 108 patients in the standard filtering surgery group (six total procedures) ($P = .096$; χ^2). Three patients in the 5-fluorouracil group underwent three other procedures (two laser peripheral iridotomies and an intracapsular cataract extraction with anterior vitrectomy for treatment of malignant glaucoma), and one patient in the standard filtering surgery group underwent one procedure (aqueous and vitreous tap for presumed endophthalmitis). During the first 14 postoperative days, 18% (19 of 105) of the patients in the 5-fluorouracil group and 7% (eight of 108) in the standard filtering surgery group underwent other ocular procedures, which included, in addition to the aforementioned wound leak repairs and anterior chamber reformation, aqueous and vitreous taps, and a cataract extraction ($P = .033$, χ^2 test).

After the first 14 postoperative days, two of 105 patients in the 5-fluorouracil group underwent a total of six needling procedures to promote aqueous flow from an encysted bleb to the surrounding conjunctival space, and five of 108 patients in the standard filtering surgery group underwent five needling procedures ($P = .465$; χ^2 test). Four patients in the 5-fluorouracil group and one in the standard filtering surgery group underwent repair of a bleb leak ($P = .349$, χ^2 test). Laser treatments, such as peripheral iridectomy, Nd:YAG capsulotomy, and panretinal photocoagulation, excluding cyclophotoablative procedures, were performed in 12 patients in the 5-fluorouracil group and in 20 of the patients in the standard group ($P = .209$; χ^2 test). Other procedures involving conjunctival incisions not performed for the purpose of decreasing intraocular pressure, such as cataract extraction, retinal detachment repair, and vitrectomy, were performed in 26 of the 105 patients in the 5-fluorouracil group (39 total procedures) and in 28 of the 108 patients in the standard filtering surgery group (35 total procedures) ($P = .970$; χ^2 test). Thus, after the immediate postoperative period, 31% (33 of 105) of the patients in the 5-fluorouracil

group and 43% (46 of 108) of the patients in the standard filtering surgery group underwent further ocular procedures (P = .122; χ^2 test). Ten patients in the 5-fluorouracil group and 15 in the standard filtering surgery group underwent cataract extraction (six patients in the 5-fluorouracil group and five in the standard filtering surgery group underwent cataract extraction before a reoperation for intraocular pressure control, and the remainder occurred either at or after a reoperation for intraocular pressure control).

The median survival time and P value for each risk factor adjusted for treatment (log-rank test) are given in Table 5. Table 6 gives the risk ratios for the continuous risk factors. In addition to treatment with

TABLE 5

CATEGORICAL RISK FACTORS AND OUTCOME

RISK FACTOR	TOTAL NO. OF PATIENTS	MEDIAN TIME FROM TRABECULECTOMY TO FAILURE (MOS)*		LOG-RANK TEST P VALUE (STRATIFIED BY TREATMENT GROUP)
		5-FLUOROURACIL GROUP	STANDARD FILTERING SURGERY GROUP	
Stratum				.77
Previous cataract extraction	162	37	13	
Phakic, failed filter	51	60	18	
Race				.92
Black	41	59	18	
Not black	169	45	13	
Age (yrs)				.71
<50	49	59	7	
≥50	164	36	16	
Conjunctival status of filtration site				.44
Scarred	94	—†	18	
Unoperated	119	36	13	
Type of glaucoma				.0002
Primary open angle	73	61	23	
Secondary angle closure	68	23	5	
Other types	72	47	13	
Ocular inflammatory disease				.36
History	38	19	14	
No history	175	61	13	
Gender				.57
Male	110	51	13	
Female	103	37	14	
Ethnicity				.006
Hispanic	27	16	12	
Non-Hispanic	183	61	16	
Iris color				.0209
Blue	62	—†	21	
Brown or hazel	149	28	13	
Surgical location				.0206
Superior	137	63	18	
Inferior	76	20	12	
Diabetic status				.069
Diabetic	32	20	12	
Nondiabetic	181	53	14	

*Failure time is defined as time to reoperation or time to intraocular pressure >21 mm Hg at or after one year.
†Less than 50% failed.

TABLE 6

CONTINUOUS RISK FACTORS AND OUTCOME ADJUSTED FOR TREATMENT GROUP

RISK FACTOR	COX PROPORTIONAL HAZARDS RISK RATIO (95% CONFIDENCE INTERVAL)	MAXIMUM LIKELIHOOD P VALUE
Age (10-year increase)	1.02 (0.92–1.13)	.7
Number of previous procedures with conjunctival incisions	1.24 (1.09–1.41)	.002
Time (days in log scale) since last procedure with a conjunctival incision (30-day increment)	0.30 (0.19–0.47)	<.0001
Preoperative intraocular pressure (10 mm Hg)	1.35 (1.13–1.60)	.001
Preoperative visual acuity (one-logMAR-unit difference)	1.32 (1.06–1.64)	.018

5-fluorouracil, the following variables demonstrate statistically significant effects ($P < .05$ by Kaplan-Meier univariate survival analysis) on the time from trabeculectomy to failure: (1) time elapsed since the last ocular procedure involving a conjunctival incision (Fig. 8); (2) secondary angle-closure glaucoma as opposed to primary open-angle glaucoma (Fig. 9); (3) number of previous procedures involving conjunctival incisions (Fig. 10); (4) self-reported Hispanic ethnicity; (5) high preoperative intraocular pressure (Fig. 11); (6) poor preoperative visual acuity; (7) trabeculectomy performed in an inferior location as opposed to superior location; and (8) brown or hazel iris color as opposed to blue. Other variables examined, which do not demonstrate a difference in risk, are stratum (aphakic or previously failed filter), race, age, gender, presence of ocular inflammatory disease, diabetic status, and presence of conjunctival scarring at the filtration site.

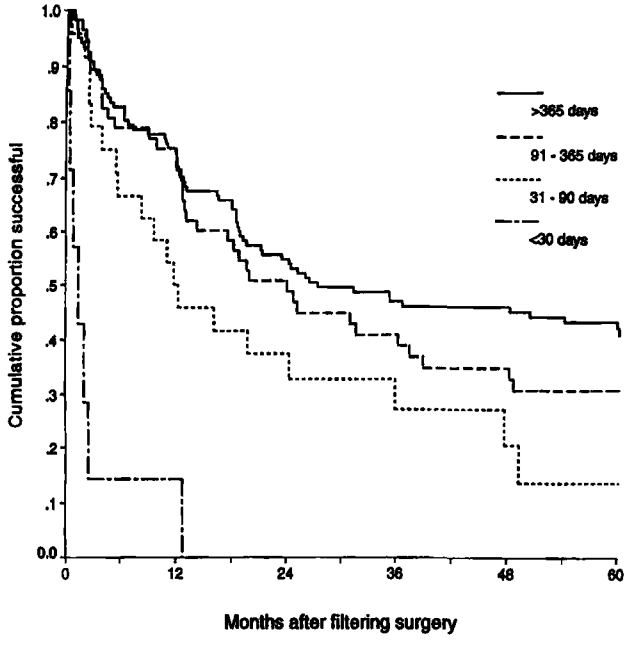

Fig. 8 (The Fluorouracil Filtering Surgery Study Group). **Kaplan-Meier cumulative proportion of patients who did not undergo a reoperation for control of intraocular pressure and who did not have an intraocular pressure greater than 21 mm Hg by months after trabeculectomy for four intervals of time elapsed since previous surgery with a conjunctival incision.**

To clarify the relationships between risk factors and trabeculectomy failure, 5-fluorouracil treatment and all risk factors (significant and nonsignificant in univariate tests) were entered as independent variables in a backward-stepwise Cox proportional hazards regression analysis. Two separate sets of analyses studied failure defined as the following: (1) months until reoperation for intraocular pressure control or an intraocular pressure greater than 21 mm Hg; and (2) months until reoperation for intraocular pressure control. With either definition of failure, 5-fluorouracil treatment, number of previous procedures involving conjunctival incisions, elapsed time since the last procedure involving a conjunctival incision, and preoperative intraocular pressure significantly influenced the trabeculectomy failure times. Model coefficients, standard errors, risk ratios, and P values for each of the variables found to affect significantly the time until trabeculectomy failure by the first of the two definitions are included in Table 7.

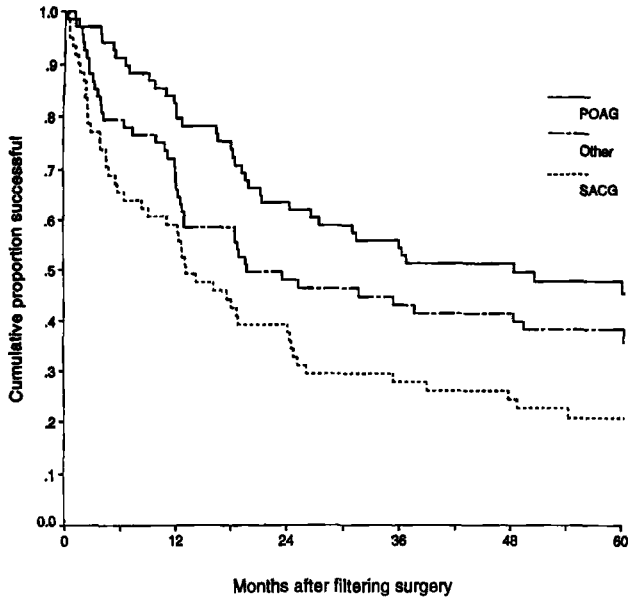

Fig. 9 (The Fluorouracil Filtering Surgery Study Group). Kaplan-Meier cumulative proportion of patients who did not undergo a reoperation for control of intraocular pressure and who did not have an intraocular pressure greater than 21 mm Hg by months after trabeculectomy for glaucoma type. POAG indicates primary open-angle glaucoma; SACG, secondary angle-closure glaucoma; and other, secondary open-angle glaucoma, primary angle-closure glaucoma, and pigmentary glaucoma.

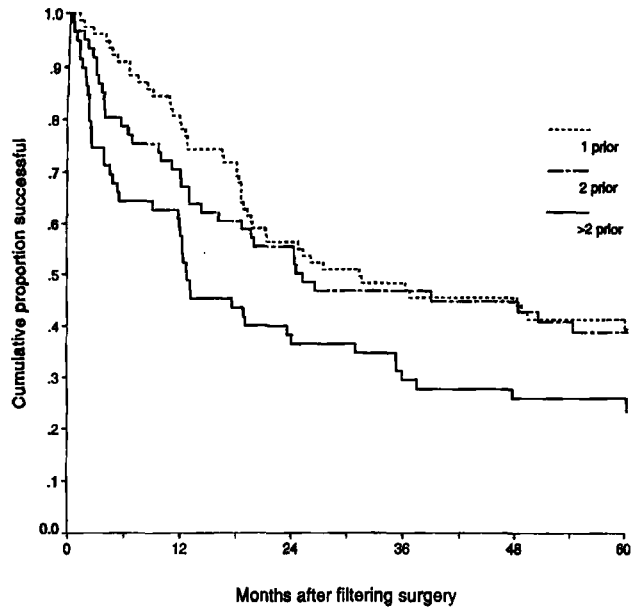

Fig. 10 (The Fluorouracil Filtering Surgery Study Group). Kaplan-Meier cumulative proportion of patients who did not undergo a reoperation for control of intraocular pressure and who did not have an intraocular pressure greater than 21 mm Hg by months after trabeculectomy, by number of previous procedures with conjunctival incision.

Failure rates decreased as the time elapsed after a previous procedure involving a conjunctival incision increased from less than 30 days to greater than one year (Fig. 8). Of the 213 patients, seven underwent trabeculectomy surgery less than one month after a previous procedure with a conjunctival incision. The risk associated with the elapsed time since a previous procedure with a conjunctival incision fit the data best when converted to a logarithmic scale. This finding implies that 30 additional days soon after a previous surgery is associated with a greater reduction in risk than a 30-day wait after many months have already elapsed. Cumulative success rates by glaucoma type, primary open-angle glaucoma, secondary angle-closure glaucoma, and other glaucoma types, including secondary open-angle glaucoma, primary angle-closure glaucoma, and pigmentary glaucoma, are depicted in Figure 9. Survival curves for the patients with one previous procedure involving a conjunctival incision as opposed to those with two as opposed to more than two such procedures are shown in Figure 10. Figure 11 shows that the cumulative success rate decreases as the preoperative intraocular pressure increases.

The stepwise multivariate variable selection procedure eliminated four important univariate risk factors: secondary angle-closure glaucoma, the inferior location of the trabeculectomy, iris color, and preoperative visual acuity. Hispanic ethnicity remained a significant risk factor. The strong association between ethnicity and iris color, (one [4%] of 27 Hispanic patients had blue eyes vs 61 [34%] of 181 non-Hispanic patients with blue eyes [$P = .001$, χ^2] suggested that self-reported Hispanic ethnicity might be a marker for iris color. However, Hispanic ethnicity remained in multivariate models of time to failure and displaced iris color.

DISCUSSION

PATIENTS WITH A HISTORY OF CATARACT EXTRACTION or those who had undergone previous unsuccessful

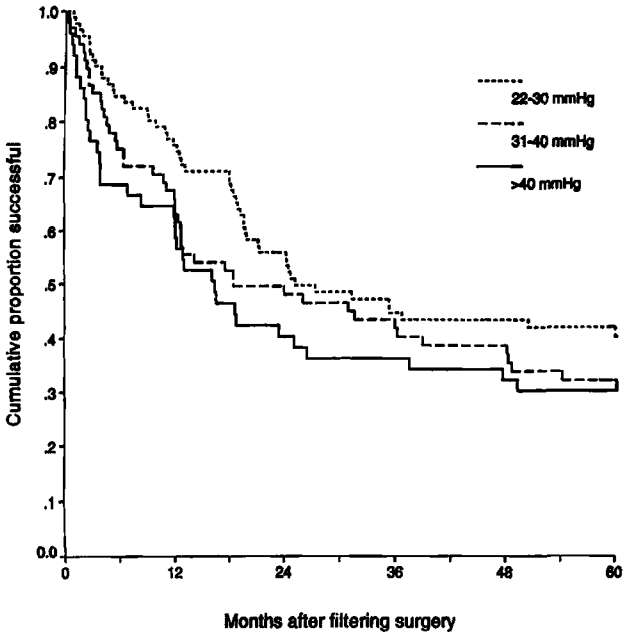

Fig. 11 (The Fluorouracil Filtering Surgery Study Group). Kaplan-Meier cumulative proportion of patients who did not undergo a reoperation for control of intraocular pressure and who did not have an intraocular pressure greater than 21 mm Hg, by months after trabeculectomy for three ranges of preoperative intraocular pressure.

filtering surgery in a phakic eye and who had received 5-fluorouracil were more likely to attain intraocular pressure control and to avoid reoperation for five years. The one-year and three-year follow-up data demonstrated a lower failure rate in the group treated with 5-fluorouracil than in the standard filtering surgery group.[1,2] The present study demonstrated a persistent treatment effect (a lower failure rate) in the group treated with 5-fluorouracil, which continued through the fifth postoperative year. The maintenance of treatment effect most likely reflects the initial benefit of the drug rather than any new benefit occurring later, because failure rates in the two groups appeared similar among patients whose trabeculectomies continued to function successfully 18 months after surgery.[2]

Patients in the 5-fluorouracil group were also more likely to require no glaucoma medications than those in the standard group throughout the five years of the study. Among patients with controlled intraocular pressure without reoperation at five years, the percentage who used no glaucoma medications was similar in both treatment groups, as reported in the three-year results.[2]

Although the primary endpoint of the study was intraocular pressure control rather than preservation of visual function, visual acuity and visual field data were collected prospectively according to study protocol. The average preoperative visual field score for all eyes was 9.3. This value indicates that on average more than half of the visual field function was lost before trabeculectomy, and it reflects an advanced

TABLE 7

COEFFICIENTS AND RISK ESTIMATES FOR COX PROPORTIONAL HAZARDS REGRESSION MODEL RELATING RISK FACTORS TO FAILURE* OF TRABECULECTOMY

VARIABLE OR RISK FACTOR	COEFFICIENT ± STANDARD ERROR	P VALUE	RISK RATIO	95% CONFIDENCE INTERVAL ON RISK RATIOS	
				LOWER	UPPER
5-Fluorouracil treatment	−.869 ± .184	<.001	0.42	0.29	0.60
Elapsed time since the last procedure with conjunctival incision†	−.910 ± .239	<.001	0.40	0.25	0.64
Hispanic ethnicity	.801 ± .247	.003	2.23	1.37	3.62
No. of previous procedures with incisions (for each additional surgery)	.187 ± .071	.012	1.21	1.05	1.39
Intraocular pressure at qualifying visit (for each 10-mm-Hg increase)	.248 ± .096	.012	1.28	1.06	1.55

*Failure is defined as reoperation to control intraocular pressure or intraocular pressure >21 mm Hg.
†Measured on a logarithmic scale, for each 30-day increment.

state of visual impairment. This high degree of preoperative damage reduced the statistical power to detect a treatment effect. However, progressive visual field loss was observed in both treatment groups, with the five-year visual field score decreasing to 12.0, despite aggressive treatment to decrease intraocular pressure. Despite improved success rates of trabeculectomy in the 5-fluorouracil group, both groups continued to lose visual acuity through the fifth postoperative year. Profound loss occurred in the 5-fluorouracil group at the time of the one-month examination but was no longer apparent at the three-month examination. Reversible corneal epithelial toxicity characterized by punctate epitheliopathy and corneal epithelial defects was responsible for the transient decrease in visual acuity.

The average loss of logMAR visual acuity in the 5-fluorouracil group was significantly less than that in the standard group at one, two, and three years. However, both groups showed progressive loss of visual acuity throughout the study. The loss of visual acuity was more likely to occur in patients with intraocular pressure greater than 21 mm Hg and in patients requiring reoperations for intraocular pressure control. An intraocular pressure that was maintained between 10 and 21 mm Hg throughout the study was associated with less loss of visual acuity. The intuitive rationale for decreasing intraocular pressure in glaucoma patients is supported by the results of this study. Although a dose-response effect of decreasing intraocular pressure has been suggested as a justification for obtaining low intraocular pressure after filtering surgery, this study cannot provide supporting evidence for this claim.[11] Further subdivision of patients with intraocular pressure of less than 21 mm Hg supports the conclusion that not all intraocular pressures in the low range protect eyes from further loss of visual acuity. The higher proportion of patients who lost visual acuity with maximal postoperative intraocular pressures of 10 mm Hg or less compared to those with maximal intraocular pressures of 15 mm Hg or less is most likely explained by complications of profound hypotony, such as suprachoroidal hemorrhage and choroidal detachment.

The following risk factors were statistically significant: the time elapsed since the last procedure involving a conjunctival incision, the number of previous procedures involving conjunctival incisions, secondary angle-closure glaucoma, high preoperative intraocular pressure, trabeculectomy in an inferior location, preoperative visual acuity, and Hispanic ethnicity. Despite identification of these risk factors, it seems unlikely that treatment could be altered by an awareness of the factors. The number of previous procedures involving the conjunctiva and the duration since that procedure cannot be modified, and continued observation of high intraocular pressures may not be safe. Furthermore, no evidence suggests that delaying intervention in these eyes would improve the likelihood of surgical success. Location of trabeculectomy in an inferior conjunctival quadrant was usually performed when scarring precluded filtration in the superior quadrants. A growing concern over the possible increased risk of endophthalmitis associated with inferiorly located trabeculectomies has markedly reduced the number of procedures in this location.[12] Despite previous reports that age and race[13-16] were risk factors for filtering surgery failure, neither was important in this study. Eyes that had undergone cataract extraction, filtering surgery, or both, may have had an altered wound-healing response after trabeculectomy, which masked the possible effect of age and race. This result in these eyes with poor prognoses does not imply that age or race are not important risk factors in eyes that have not been operated on.

Secondary angle-closure glaucoma, inferior trabeculectomy location, and preoperative visual acuity were not statistically significant in multivariate models. The correlation between secondary angle-closure glaucoma with both high preoperative intraocular pressure and the shorter duration from previous procedures involving a conjunctival incision to trabeculectomy (Table 8), and the correlation between inferior location of trabeculectomy and the number of previous procedures involving conjunctival incisions may explain this finding (Table 9). Secondary angle-closure glaucoma may result, as a complication of ophthalmic surgery, and is often associated with high intraocular pressure that necessitates immediate surgical intervention. Similarly, another risk factor, poor preoperative visual acuity, is correlated with higher preoperative intraocular pressure and the number of previous procedures involving a conjunctival incision and with time elapsed since such a procedure.

TABLE 8

RELATIONSHIP OF PREOPERATIVE INTRAOCULAR PRESSURE AND THE TIME FROM THE LAST PROCEDURE WITH CONJUNCTIVAL INCISION TO GLAUCOMA TYPE

GLAUCOMA TYPE	INTRAOCULAR PRESSURE AT QUALIFYING EXAMINATION (MM HG)	TIME ELAPSED SINCE LAST PROCEDURE WITH CONJUNCTIVAL INCISION (MOS)
Primary open angle (N = 73)	31 ± 9	29.0 ± 0.1
Secondary angle closure (N = 68)	37 ± 11	9.0 ± 0.1
Other (N = 72)	35 ± 9	14.0 ± 0.2
P value*	<.001	<.001

*Analysis of variance.

Before this study, the association between high preoperative intraocular pressure and acute postoperative hypotony was not suspected as a possible risk factor for the development of suprachoroidal hemorrhage.[10] This observation has contributed to a change in ophthalmic surgical practice. Patients with high preoperative intraocular pressures now undergo trabeculectomies with multiple tightly tied sutures or with releasable sutures in the scleral flap that have been placed to minimize postoperative hypotony. Postoperative argon laser suture lysis or removal of releasable sutures may reduce the likelihood of large postoperative intraocular pressure decrease and subsequent hypotony.

The beneficial effects of 5-fluorouracil on intraocular pressure control at five years must be interpreted in light of the associated adverse events. The difference in visual acuity and visual field loss between the two groups did not suggest a direct toxic effect to the retina or optic nerve. However, late-onset conjunctival bleb leaks, which may increase the risk of endophthalmitis,[12] were more common in the group that received 5-fluorouracil than in the group that received standard filtering surgery. The 9% incidence of bleb leaks in this study is less than the 25% (five of 20) reported in a series of young patients who underwent initial trabeculectomy with 5-fluorouracil.[13]

TABLE 9

RELATIONSHIP OF TRABECULECTOMY LOCATION TO THE NUMBER OF PREVIOUS PROCEDURES WITH CONJUNCTIVAL INCISIONS*

NUMBER OF PROCEDURES WITH CONJUNCTIVAL INCISIONS	SUPERIOR NO. (%)	INFERIOR NO. (%)
One	65 (48)	19 (25)
Two	36 (26)	28 (37)
Three or more	36 (26)	29 (38)

*P value by χ^2 = .006, by trend in proportion = .004.

Although lower doses and less frequent injections of 5-fluorouracil[17,18] and intraoperative applications[19] have been reported elsewhere to promote intraocular pressure control in similar eyes, we cannot infer a long-term treatment effect of a lower-dose regimen or a different method of drug delivery. Although multiple postoperative subconjunctival injections of 5-fluorouracil have been largely replaced by the single intraoperative application of mitomycin C, on the basis of a clinical trial of postoperative 5-fluorouracil vs intraoperative mitomycin C, we cannot predict the long-term safety or efficacy of any other antimetabolite.[20,21]

The results of clinical trials that demonstrate one treatment to be safe and effective may not be extrapolated as supportive of other treatments, despite widespread clinical acceptance of newer alternative therapies.[22] The Fluorouracil Filtering Surgery Study demonstrated that leaking blebs are more likely to develop in the 5-fluorouracil group. It seems likely that any antimetabolite that enhances bleb formation by reducing scarring at the filtering site may also increase the risk of late-onset bleb leaks. In view of the increased incidence of late-onset conjunctival filtering bleb leaks, we suggest caution in the use of 5-fluorouracil at the dose used in the Fluorouracil Filtering Surgery Study in eyes with good prognoses.

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