Early Photocoagulation for Diabetic Retinopathy

ETDRS Report Number 9

EARLY TREATMENT DIABETIC RETINOPATHY STUDY RESEARCH GROUP*

Abstract: The Early Treatment Diabetic Retinopathy Study (ETDRS) enrolled 3711 patients with mild-to-severe nonproliferative or early proliferative diabetic retinopathy in both eyes. One eye of each patient was assigned randomly to early photocoagulation and the other to deferral of photocoagulation. Follow-up examinations were scheduled at least every 4 months and photocoagulation was initiated in eyes assigned to deferral as soon as high-risk proliferative retinopathy was detected. Eyes selected for early photocoagulation received one of four different combinations of scatter (panretinal) and focal treatment. This early treatment, compared with deferral of photocoagulation, was associated with a small reduction in the incidence of severe visual loss (visual acuity less than 5/200 at two consecutive visits), but 5-year rates were low in both the early treatment and deferral groups (2.6% and 3.7%, respectively). Adverse effects of scatter photocoagulation on visual acuity and visual field also were observed. These adverse effects were most evident in the months immediately following treatment and were less in eyes assigned to less extensive scatter photocoagulation. Provided careful follow-up can be maintained, scatter photocoagulation is not recommended for eyes with mild or moderate nonproliferative diabetic retinopathy. When retinopathy is more severe, scatter photocoagulation should be considered and usually should not be delayed if the eye has reached the high-risk proliferative stage. The ETDRS results demonstrate that, for eyes with macular edema, focal photocoagulation is effective in reducing the risk of moderate visual loss but that scatter photocoagulation is not. Focal treatment also increases the chance of visual improvement, decreases the frequency of persistent macular edema, and causes only minor visual field losses. Focal treatment should be considered for eyes with macular edema that involves or threatens the center of the macula. *Ophthalmology 1991; 98:766–785*

The Early Treatment Diabetic Retinopathy Study (ETDRS), a multicenter, collaborative, clinical trial sponsored by the National Eye Institute, was motivated principally by three clinical questions:

1. When in the course of diabetic retinopathy is it most effective to initiate photocoagulation therapy?
2. Is photocoagulation effective in the treatment of macular edema?
3. Is aspirin effective in altering the course of diabetic retinopathy?

This report focuses on the first two questions. Specific approaches were developed during the design of the ETDRS to provide information relevant to these questions. A brief summary of the design and methods is given below; a more detailed explanation is available elsewhere in this issue.[1]

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* A list of the ETDRS Research Group investigators appears at the end of ETDRS report number 7 in this supplement to *Ophthalmology*.

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Table 1. Definitions of Commonly Used Terms

A. Macular edema
   Thickening of retina within 1 disc diameter of the center of the macula; and/or hard exudates ≥ standard photograph 3[11] in a standard 30° photographic field centered on the macula (field 2), with some hard exudates within 1 disc diameter of the center of the macula
B. Clinically significant macular edema (CSME)
   Retinal thickening at or within 500 μm of the center of the macula; and/or hard exudates at or within 500 μm of the center of the macula, if associated with thickening of the adjacent retina; and/or a zone or zones of retinal thickening 1 disc area in size at least part of which was within 1 disc diameter of the center
C. Mild nonproliferative retinopathy
   At least one microaneurysm; and definition not met for D, E, F, or G below
D. Moderate nonproliferative retinopathy
   Hemorrhages and/or microaneurysms ≥ standard photograph 2A[11]; and/or soft exudates, venous beading, or intraretinal microvascular abnormalities definitely present; and definition not met for E, F, or G below
E. Severe nonproliferative retinopathy
   Soft exudates, venous beading, and intraretinal microvascular abnormalities all definitely present in at least two of fields 4 through 7; or two of the preceding three lesions present in at least two of fields 4 through 7 and hemorrhages and microaneurysms present in these four fields, equaling or exceeding standard photo 2A in at least one of them; or intraretinal microvascular abnormalities present in each of fields 4 through 7 and equaling or exceeding standard photograph 8A in at least two of them; and definition not met for F or G below
F. Early proliferative retinopathy (i.e., proliferative retinopathy without DRS high-risk characteristics)
   New vessels, and definition not met for G below
G. High-risk proliferative retinopathy (proliferative retinopathy with DRS high-risk characteristics)
   New vessels on or within 1 disc diameter of the optic disc (NVD) ≥ standard photograph 10A[11] (about ¼ to ⅓ disc area), with or without vitreous or preretinal hemorrhage; or vitreous and/or preretinal hemorrhage accompanied by new vessels, either NVD < standard photograph 10A or new vessels elsewhere (NVE) ≥ ¼ disc area
H. Less severe retinopathy
   Mild or moderate nonproliferative retinopathy
I. More severe retinopathy
   Severe nonproliferative or early proliferative retinopathy
J. Severe visual loss
   Visual acuity < 5/200 at two consecutive follow-up visits (scheduled at 4-month intervals)
K. Moderate visual loss
   Loss of 15 or more letters between baseline and follow-up visit, equivalent to a doubling of the initial visual angle (i.e., 20/20 to 20/40 or 20/50 to 20/100)

METHODS

From April 1980 to July 1985, the ETDRS enrolled 3711 patients with diabetes mellitus who met the following criteria: (1) no macular edema, visual acuity of 20/40 or better, and moderate or severe nonproliferative diabetic retinopathy or early proliferative diabetic retinopathy, or (2) macular edema, visual acuity of 20/200 or better, and mild, moderate, or severe nonproliferative diabetic retinopathy or early proliferative diabetic retinopathy (definitions of retinopathy severity categories and other terms used in this report are given in Table 1). Patients meeting eligibility requirements in both eyes and with favorable prognosis for survival and follow-up for at least 5 years were enrolled in the ETDRS and assigned randomly to aspirin 650 mg per day or matching placebo. As shown in a companion report,[2] aspirin had no effect on the course of retinopathy, either in eyes assigned to deferral of photocoagulation or in those assigned to early photocoagulation. Therefore, in this report, the results for patients assigned to aspirin and placebo have been combined.

To assess the effect of the timing of photocoagulation, one eye of each patient was assigned randomly to early photocoagulation (scatter and/or focal) and the other eye was assigned to "deferral of photocoagulation" (Figs 1–3). Follow-up visits were scheduled at 4-month intervals. The primary endpoint used to compare early photocoagulation with deferral of photocoagulation was the rate of development of "severe visual loss," i.e. (Table 1, item J), visual acuity less than 5/200 at two consecutive follow-up visits. The primary endpoint for assessing the effects of photocoagulation on macular edema was the occurrence of "moderate visual loss," i.e. (Table 1, item K), loss of 15 or more letters (equivalent of 3 lines) between baseline and follow-up visit on the visual acuity charts used in the ETDRS.

STRATEGIES FOR PHOTOCOAGULATION

The specific techniques for photocoagulation have been described previously and are summarized in Table 2.[3–6] For eyes assigned to deferral, the protocol specified that full scatter be applied as soon as high-risk proliferative retinopathy was detected. If clinically significant macular edema (CSME) was present at that time, focal photocoagulation was initiated also, but only for those patients whose strategy for early photocoagulation for the fellow eye included delayed focal photocoagulation. After 5 years in this 9-year study, the accumulating data showed focal photocoagulation was effective in reducing moderate visual loss. Therefore, the protocol for all eyes assigned to deferral was modified to allow focal photocoagulation for CSME whenever it occurred.[6] This report presents anal-

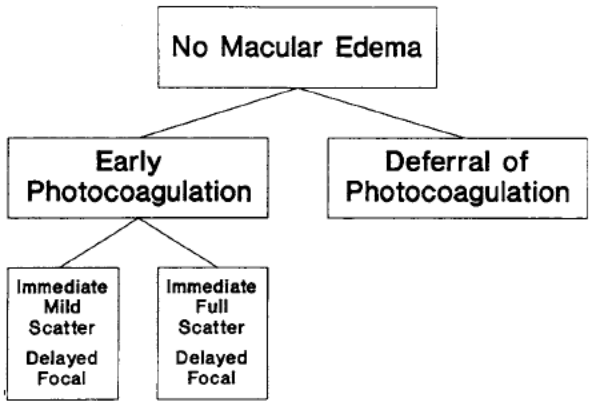


Fig 1. Early Treatment Diabetic Retinopathy Study photocoagulation treatment scheme for eyes without macular edema with moderate-to-severe nonproliferative or early proliferative retinopathy. Eyes were assigned randomly to early photocoagulation or deferral of photocoagulation. Eyes assigned to early photocoagulation were further assigned randomly to either mild or full scatter (panretinal) photocoagulation.

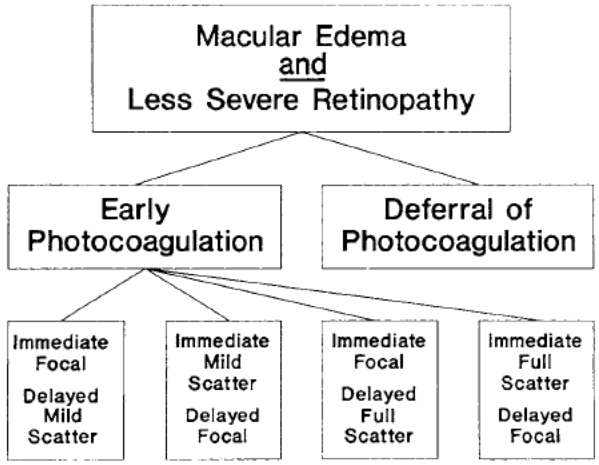


Fig 2. Early Treatment Diabetic Retinopathy Study photocoagulation treatment scheme for eyes with macular edema and *less severe retinopathy*. Eyes were assigned randomly to early photocoagulation or to deferral of photocoagulation. Eyes assigned to early photocoagulation were further assigned randomly to either mild or full scatter (panretinal) photocoagulation and to either immediate focal or delayed focal treatment. In eyes assigned to immediate focal treatment, the assigned scatter treatment was not applied initially, but only if severe nonproliferative retinopathy or worse developed during follow-up.

yses of all eyes according to their original randomized assignment of treatment; observations made after the modification of the protocol are included.

Initiation of early photocoagulation differed depending on the retinopathy at baseline (Figs 1–3). Three categories were defined on the basis of preliminary grading of fundus photographs and fluorescein angiograms; these differed in retinopathy severity and presence or absence of macular edema (Table 3). The strategies for early photocoagulation for each category are outlined in the following sections.

CATEGORY 1: EYES WITHOUT MACULAR EDEMA

Eyes in this category (Fig 1) had moderate-to-severe nonproliferative or early proliferative retinopathy and did not have macular edema. "Immediate" strategies for photocoagulation for these eyes were either mild or full scatter. "Delayed" focal photocoagulation was to be initiated during follow-up if macular edema developed that involved or threatened the center of the macula (CSME).

CATEGORY 2: EYES WITH MACULAR EDEMA AND LESS SEVERE RETINOPATHY

Eyes in this category (Fig 2) had macular edema and mild-to-moderate nonproliferative retinopathy (*less severe retinopathy*, Table 1). Early photocoagulation for these eyes was: (1) immediate focal photocoagulation, with scatter photocoagulation (mild or full) added if severe nonproliferative or early proliferative retinopathy developed during follow-up; and (2) immediate scatter photocoagulation (mild or full), with focal photocoagulation delayed for at least 4 months. Eyes assigned to delayed focal photocoagulation received treatment at the 4-month visit if the macular edema had not improved and the visual acuity score had not increased by five or more letters by that time. Focal photocoagulation was initiated at the 8-month visit if the edema was not substantially improved,

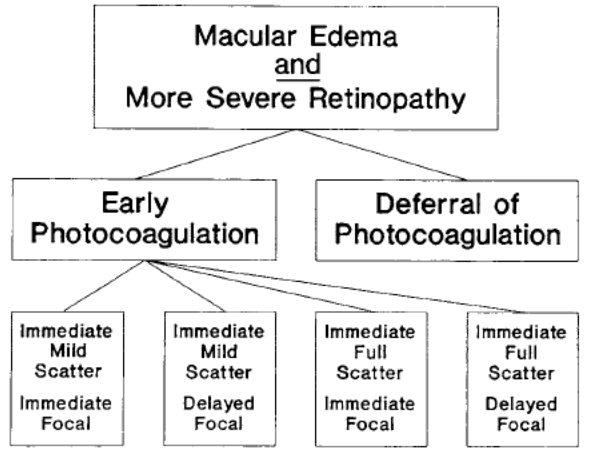


Fig 3. Early Treatment Diabetic Retinopathy Study photocoagulation treatment scheme for eyes with macular edema and *more severe retinopathy*. Eyes were assigned randomly to immediate photocoagulation or to deferral of photocoagulation. Eyes assigned to immediate photocoagulation were further assigned randomly to either mild or full scatter (panretinal) photocoagulation, and to either immediate focal treatment or to deferral of focal treatment for at least 4 months.

as demonstrated by either a return of an initially thickened macular center to normal thickness or improvement in visual acuity score by 10 or more letters. At and after the 12-month visit, initiation of focal photocoagulation was required for all eyes assigned to early photocoagulation if they had CSME and had not yet received focal photocoagulation.

Table 2. Major Features of ETDRS Early Photocoagulation Treatment

Scatter	Full	Mild
Burn characteristics		
Size	500 μm (at retina)	500 μm (at retina)
Exposure	0.1 seconds	0.1 seconds
Intensity	Moderate	Moderate
Number	1200–1600	400–650
Placement	½ burn apart > 2 disc diameters from fovea out to equator	≥1 burn apart > 2 disc diameters from fovea out to equator
Number of episodes	≥2	1
Lesion treated directly	Patches of NVE < 2 disc areas	Patches of NVE < 2 disc areas
Indications for follow-up treatment	Recurrent or new NVE or high-risk proliferative retinopathy	Recurrent or new NVE or high-risk proliferative retinopathy
Focal	**Direct**	**Grid**
Burn characteristics		
Size	50–100 μm	<200 μm (at retina)
Exposure	0.05–0.1 seconds	0.05–0.1 seconds
Intensity	Sufficient to whiten or darken large microaneurysms	Mild
Number	Sufficient to satisfactorily treat all focal leaks	Sufficient to cover areas of diffuse leakage and non-perfusion
Placement	500–3000 μm from center of fovea	Spaced greater than one burn width apart 500–3000 μm from center of fovea
Number of episodes	1	1
Indications for follow-up treatment	Presence of CSME and treatable lesions at ≥ 4 months	Presence of CSME and treatable lesions at ≥ 4 months

NVE = new vessels elsewhere; CSME = clinically significant macular edema.

Table 3. Numbers of Eyes in Each Baseline Retinopathy Category

	Photocoagulation Treatment Strategy				
	Early* Full Scatter		Early* Mild Scatter		
Baseline Retinopathy Category	Immediate Focal	Delayed Focal	Immediate Focal	Delayed Focal	Deferral
Eyes without macular edema		583		590	1179
Eyes with macular edema and *less severe retinopathy*	362	356	365	365	1429
Eyes with macular edema and *more severe retinopathy*	272	270	276	272	1103
Total	634	1209	641	1227	3711

* See Figures 1 to 3.

CATEGORY 3: EYES WITH MACULAR EDEMA AND MORE SEVERE RETINOPATHY

Eyes in this category (Fig 3) had macular edema and severe nonproliferative or early proliferative retinopathy (*more severe retinopathy*, Table 1). Early photocoagulation for these eyes was (1) immediate focal and scatter photocoagulation (mild or full); or (2) immediate scatter photocoagulation (mild or full), with focal photocoagulation delayed for at least 4 months. The same procedure described in Category 2 for initiating focal photocoagulation at or after 4 months was used.

These strategies for early photocoagulation were based on the following considerations: (1) for eyes with macular edema and *less severe retinopathy*, macular edema was considered the more immediate threat to vision, and the primary focus of early photocoagulation was on the treatment of the macular edema. Delaying scatter photocoagulation in eyes with macular edema and *less severe retinopathy* assigned to immediate focal photocoagulation

provided a group of eyes in which the effects of focal photocoagulation without concurrent scatter photocoagulation could be assessed. Because this was early treatment, scatter photocoagulation was delayed only until the development of severe nonproliferative or early proliferative retinopathy rather than until the development of high-risk proliferative retinopathy. Similarly, by delaying focal photocoagulation for at least 4 months in eyes assigned to immediate scatter photocoagulation, the effects of immediate scatter photocoagulation without concurrent focal photocoagulation could be assessed. (2) For eyes with macular edema and *more severe retinopathy,* an increased rate of progression to high-risk proliferative retinopathy was expected compared with the rate for eyes that had *less severe retinopathy.* For these eyes, strategies for early photocoagulation could not focus primarily on the treatment of macular edema. Scatter photocoagulation, if it was to be considered "early," could not be delayed, and thus immediate scatter photocoagulation (mild or full) was specified for all eyes with macular edema and *more severe retinopathy* assigned to early photocoagulation.

Best corrected visual acuity was measured and ocular examinations were performed according to a standardized protocol at baseline and at 6 weeks and 4 months after randomization. This procedure was repeated every 4 months thereafter. The visual acuity score was defined as the total number of letters that could be read correctly from the logarithmic visual acuity charts used in the ETDRS. A score of 100 corresponds to a visual acuity of 20/10, and the visual angle doubles with each decrement of 15 letters.[7] When one or more visual acuity scores were missing, scores from the preceding and following visits were averaged to replace the missing score(s).

Visual field scores were calculated by totaling the peripheral extent of the visual fields in degrees, obtained using the I/4e and I/2e test objects with the Goldmann perimeter, on each of 12 meridians after subtracting any scotomas encountered along them. Color vision was assessed with the Farnsworth-Munsell 100-Hue Test, scored by the method of Farnsworth. The square root of the score was calculated and used to assess change between baseline and follow-up visits. Stereoscopic fundus photographs and fluorescein angiograms taken at baseline and periodically during follow-up were graded centrally at the ETDRS Fundus Photograph Reading Center.

Table 4. Patient Enrollment and Close-out

		Patients			
			Survival through Close-out		
Enrollment Year	Follow-up* (yrs)	Number Enrolled	No.	Complete Close-out Examinations	Deaths
1980	8	366	251	234 (93%)	115
1981	7	780	579	538 (93%)	201
1982	6	761	621	567 (91%)	140
1983	5	874	719	672 (93%)	155
1984	4	669	590	562 (95%)	79
1985	3	261	245	234 (96%)	16
Total	—	3711	3005	2807 (93%)	706

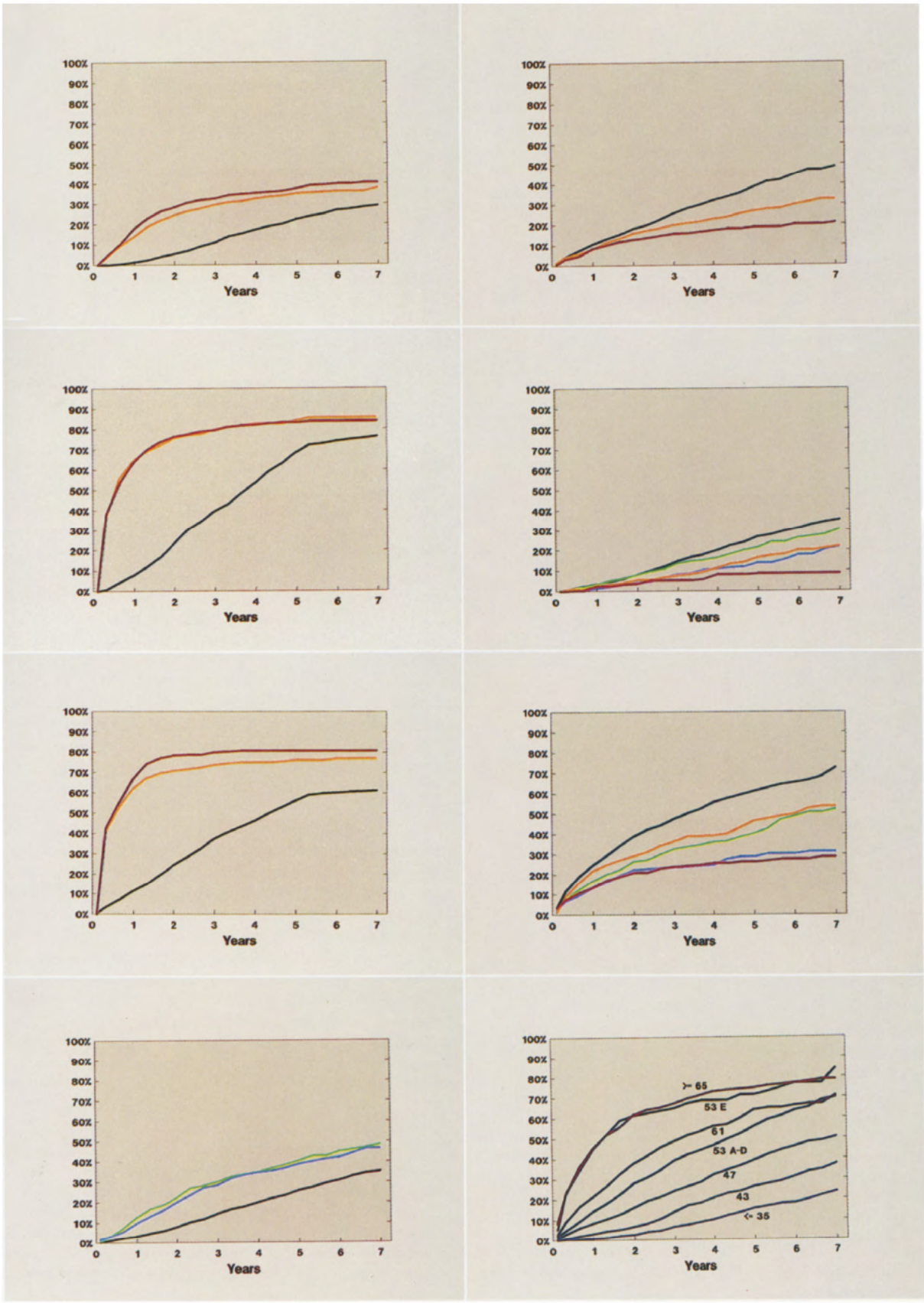
* Close-out visits occurred between August 1, 1988 and June 30, 1989.

Other endpoints evaluated were the occurrence of either severe visual loss or vitrectomy, visual acuity worse than 20/100 (equivalent to "legal blindness"), and change between baseline and follow-up visits in visual field, color vision, or retinopathy.

A two-sample z-test of equality of proportions[8] was used when comparing proportions of eyes with a given endpoint. The Cutler-Ederer life table method[9] was used to estimate rates of first occurrence of certain events. In the absence of the specified event, observations were censored at the patient's last visit or at death. The Mantel-Cox statistic[10] was used to provide probabilities for tests of significance for the comparison of life table results for the entire period of follow-up. Because multiple endpoints were compared at frequent intervals during the course of the study, a 0.01 probability level, rather than 0.05, was considered statistically significant for the primary endpoints. For other comparisons, P-values between 0.01 and 0.001 provided some evidence of differences between treatments, and P-values less than 0.001 provided stronger evidence of such differences.

The Cox proportional hazards model with adjustment for retinopathy severity and presence or absence of macular edema was used to assess the relative risk (along with the 99% confidence interval)[10] of some primary endpoints

Fig 4. Life table cumulative event rates of first application of focal photocoagulation treatment for macular edema in eyes assigned to *immediate mild scatter/delayed focal* (orange), *immediate full scatter/delayed focal* (red), or *deferral of photocoagulation* (black). *Top left,* A, eyes without macular edema. *Second row left,* B, eyes with macular edema and *less severe retinopathy. Third row left,* C, eyes with macular edema and *more severe retinopathy.* **Fig 5.** *Bottom left,* life table cumulative event rates of first application of scatter treatment in eyes with macular edema and *less severe retinopathy* assigned to *immediate focal/delayed mild scatter* (green), *immediate focal/delayed full scatter* (blue), or *deferral of photocoagulation* (black). **Fig 6.** Life table cumulative event rates of high-risk proliferative retinopathy. *Top right,* A, eyes without macular edema assigned to *immediate mild scatter/delayed focal* (orange), *immediate full scatter/delayed focal* (red), or *deferral of photocoagulation* (black). *Second row right,* B, eyes with macular edema and *less severe retinopathy* assigned to *immediate focal/delayed mild scatter* (green), *immediate mild scatter/delayed focal* (orange), *immediate focal/delayed full scatter* (blue), *immediate full scatter/delayed focal* (red), or *deferral of photocoagulation* (black). *Third row right,* C, eyes with macular edema and *more severe retinopathy,* assigned to *immediate focal/immediate mild scatter* (green), *immediate mild scatter/delayed focal* (orange), *immediate focal/immediate full scatter* (blue), *immediate full scatter/delayed focal* (red), or *deferral of photocoagulation* (black). **Fig 7.** *Bottom right,* life table cumulative event rates of high-risk proliferative retinopathy by level on retinopathy severity scale[13] at baseline in eyes assigned to deferral of photocoagulation.



for the entire period of follow-up for eyes assigned to early photocoagulation compared with eyes assigned to deferral. Terms for two- and three-way interactions were included and if ascertained to be nonsignificant ($P > 0.01$) were omitted from the model. A relative risk significantly less than 1.0 indicates a reduced risk of the endpoint for eyes assigned to early photocoagulation compared with eyes assigned to deferral. A relative risk significantly greater than 1.0 indicates an increased risk of the endpoint for eyes assigned to early photocoagulation compared with eyes assigned to deferral. In these analyses, a 99% confidence interval of the relative risk that included 1.0 indicated that the observed data were consistent with no difference between the strategies for photocoagulation.

RESULTS

COMPLETENESS OF FOLLOW-UP

Results presented in this report include all data processed at the ETDRS Coordinating Center as of November 8, 1990, when all collected ETDRS data up to and including all close-out visits (scheduled between August 1, 1988 and June 30, 1989) were available for analysis. Table 4 shows the distribution of the 3711 patients by each year of enrollment, including the number of deaths and the length of follow-up.

At close-out, 706 patients were dead, 2971 patients were known to be alive, and vital status of 34 patients (1%) was unknown. Of the 2971 patients known to be alive, only 164 patients did not have an eye examination at the close-out visit, and only 11 of the patients did not have at least a nonprotocol estimate of visual acuity (e.g., a home visit, a non-ETDRS ophthalmologist assessment, or other assessment).

During the first 3 years of follow-up, 90 to 95% of expected follow-up visits were completed. This rate decreased to 80 to 90% for follow-up longer than 3 years. The proportions of patients missing visits were similar in all treatment groups.

Of 130,980 expected visual acuity scores, all but 1.5% were available. Ninety percent of the 129,054 available visual acuity scores were from measurements made according to the protocol; another 9% were estimated by averaging the two measured visual acuities bracketing those unavailable due to missed visits; and 1% were estimated using nonprotocol measurements from eye examinations or using answers to questions—for example, about the patient's ability to read, watch television, or walk through doorways. During the follow-up period, 50% of the patients had measurements of visual acuity obtained according to the protocol for every expected visit; 30% missed only one or two measurements.

FREQUENCY AND TIMING OF DELAYED PHOTOCOAGULATION

Several groups of eyes were not assigned to receive focal photocoagulation as part of their initial treatment, i.e., eyes without macular edema at baseline, eyes with macular edema assigned to immediate scatter photocoagulation and delayed focal photocoagulation (Figs 1–3), and all eyes assigned to deferral of photocoagulation. Figure 4 presents cumulative rates of the first application of focal photocoagulation for macular edema to these eyes.

Eyes without macular edema at baseline that were assigned to early photocoagulation received focal photocoagulation when CSME developed during follow-up. After 5 years, approximately one third of such eyes had received focal photocoagulation, and there was little difference between eyes assigned to mild scatter initially and those assigned to full scatter (Fig 4A). Among eyes in this category assigned to deferral of photocoagulation, 22% had received focal photocoagulation within 5 years; in 91% of these eyes, focal photocoagulation was initiated after the change in the protocol in 1985 allowing focal photocoagulation for CSME.

More than one third of the eyes with macular edema that were assigned to immediate scatter and delayed focal photocoagulation had focal photocoagulation initiated at the 4-month visit. By the 1-year visit, approximately two thirds of these eyes had received focal photocoagulation (Figs 4B, C). Among eyes with macular edema assigned to deferral of photocoagulation, approximately two thirds had received focal photocoagulation within 5 years; in 87% of these eyes, focal photocoagulation was initiated after the change in protocol that allowed focal photocoagulation for CSME.

Analyses restricted to follow-up before the 1985 change of protocol showed the following 48-month rates of the first application of focal photocoagulation in eyes assigned to deferral: 3.5% for eyes without macular edema; 5.5% for eyes with macular edema and *less severe retinopathy*; and 16.7% for eyes with macular edema and *more severe retinopathy*.

Two groups of eyes did not receive scatter photocoagulation initially. Eyes with macular edema and *less severe retinopathy* assigned to immediate focal photocoagulation had scatter photocoagulation (either mild or full) delayed until severe nonproliferative or early proliferative retinopathy developed. Eyes assigned to deferral of photocoagulation had scatter photocoagulation initiated only when high-risk proliferative retinopathy developed.

Figure 5 shows the cumulative rates of first application of scatter photocoagulation by assigned treatment for eyes with macular edema and *less severe retinopathy* that did not receive scatter photocoagulation initially. After 1, 3, and 5 years, approximately 10%, 30%, and 40%, respectively, of the eyes assigned to early photocoagulation ("immediate focal/delayed mild scatter" or "immediate focal/delayed full scatter") had received their assigned scatter photocoagulation because of progression to severe nonproliferative or early proliferative retinopathy (57%) or high-risk proliferative retinopathy (43%). These rates were approximately double the rates for comparable eyes assigned to deferral of photocoagulation, which had to progress to the high-risk proliferative stage before becoming eligible for scatter photocoagulation.

Table 5. Development of High-risk Proliferative Retinopathy*

Baseline Retinopathy Category	Photocoagulation Treatment Strategy				
	Early† Full Scatter		Early† Mild Scatter		
	Immediate Focal	Delayed Focal	Immediate Focal	Delayed Focal	Deferral
No macular edema					
5-yr rate (%)		18.8		26.9	38.5
Relative risk‡		0.41		0.64	
99% CI		0.31–0.55		0.51–0.81	
No. of eyes		583		590	1179
Macular edema and *less severe retinopathy*					
5-yr rate (%)	13.7	8.5	21.4	16.6	26.7
Relative risk	0.52	0.27	0.81	0.56	
99% CI	0.36–0.75	0.16–0.44	0.59–1.11	0.39–0.80	
No. of eyes	362	356	365	365	1429
Macular edema and *more severe retinopathy*					
5-yr rate (%)	28.8	26.3	40.3	46.7	61.3
Relative risk	0.36	0.34	0.59	0.67	
99% CI	0.26–0.49	0.25–0.47	0.46–0.77	0.53–0.87	
No. of eyes	272	270	276	272	1103

CI = confidence interval.

* Life table event rates of first occurrence of high-risk proliferative retinopathy using Cutler-Ederer actuarial estimates.

† See Figures 1 to 3.

‡ Relative risk of high-risk proliferative retinopathy for each early treatment strategy versus deferral was estimated for the entire period of follow-up for each baseline retinopathy category. A Cox model with time to high-risk proliferative retinopathy as the dependent variable was used. The 99% CI for the estimate of the relative risk was calculated.

DEVELOPMENT OF HIGH-RISK PROLIFERATIVE RETINOPATHY

Life table rates for the development of high-risk proliferative retinopathy are shown in Figure 6 and Table 5 according to baseline retinopathy. Compared with deferral of photocoagulation, early photocoagulation reduced the rate of progression to the high-risk stage in each baseline category (Mantel-Cox; $P < 0.001$ for each strategy of early photocoagulation compared with deferral, except for immediate focal and delayed mild scatter photocoagulation in eyes with macular edema and *less severe retinopathy*, $P = 0.09$). Within all categories, the 5-year rate of developing high-risk retinopathy was lowest in eyes assigned to immediate full scatter, highest in eyes assigned to deferral, and intermediate in eyes assigned to immediate mild scatter.

Among eyes with macular edema and *more severe retinopathy* (Fig 6C), the timing of focal photocoagulation (immediate versus delayed) had no apparent effect on the rate of development of high-risk retinopathy. However, among eyes with macular edema and *less severe retinopathy* (Fig 6B), the rates of development of high-risk retinopathy for eyes assigned to immediate focal and delayed scatter photocoagulation were intermediate between those for immediate scatter and delayed focal and those for deferral of photocoagulation.

Life table rates showing the development of high-risk proliferative retinopathy for all eyes assigned to deferral (classified by baseline retinopathy, as derived from detailed gradings of color fundus photographs[11]) are given in Figure 7 and Table 6. The risk of progression to the high-risk stage increased substantially with increasing severity; 5-year life table rates rose from 15% in eyes with the least severe retinopathy in ETDRS (level ≤ 35) to more than 70% in eyes with very severe nonproliferative (level 53e) or moderate proliferative retinopathy (level ≥ 65).

ENDPOINTS

Severe visual loss. The cumulative rates of the development of severe visual loss for eyes assigned to deferral of photocoagulation and for all eyes assigned to early photocoagulation are shown in Figure 8 (Mantel-Cox; $P = 0.035$ for the entire period of follow-up). The relative risk of severe visual loss for the entire period of follow-up in eyes assigned to early photocoagulation compared with eyes assigned to deferral of photocoagulation was 0.77 (99% confidence interval, 0.56 to 1.06, calculated using a Cox proportional hazards model with retinopathy severity and presence or absence of macular edema at baseline as covariates). The rates of severe visual loss were low; 5-year rates were 3.7% for eyes assigned to deferral of photocoagulation and 2.6% for eyes assigned to early photocoagulation.

Comparison of either early full scatter or early mild scatter with deferral resulted in similar relative risks and 99% confidence intervals that also included 1.0. The 5-year rates of severe visual loss in eyes assigned to early full or early mild scatter were 2.5% and 2.7%, respectively,

Table 6. Development of High-risk Proliferative Retinopathy in All Eyes Assigned to Deferral by Baseline Retinopathy Severity Level*

Baseline Retinopathy Severity (Level)	No. of Eyes	Cumulative Rate (%) of High-risk Proliferative Retinopathy at Visit		
		1-Year	3-Years	5-Years
Level ≤ 35 (mild NPDR)	609	0.8	6.7	15.5
Level 43 (moderate NPDR)	906	3.3	14.2	26.5
Level 47 (moderately severe NPDR)	938	8.6	24.4	39.4
Level 53a–d (severe NPDR)	500	14.6	39.5	56.0
Level 53e (very severe NPDR)	92	45.0	64.9	71.3
Level 61 (mild PDR)	339	21.7	48.6	63.8
Level ≥ 65† (moderate PDR)	327	45.5	67.2	74.7
Total	3711	12.1	28.0	40.7

NPDR = nonproliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy.

* Levels defined in retinopathy severity scale in ETDRS Report 12.[13]

† Includes eight eyes classified as not having high-risk proliferative retinopathy by the preliminary eligibility grading, but classified as having high-risk proliferative retinopathy on subsequent detailed grading.

compared with 3.7% in eyes assigned to deferral. The relative risk of severe visual loss for the entire period of follow-up in eyes assigned to early full scatter compared with eyes assigned to deferral was 0.69 (99% confidence interval, 0.45 to 1.05); in eyes assigned to mild scatter, the relative risk was 0.84 (99% confidence interval, 0.57 to 1.25).

Both the severity of retinopathy and the presence of macular edema at baseline were associated with the development of severe visual loss. The relative risk (adjusting for the presence or absence of macular edema) for the development of severe visual loss for eyes with *more severe retinopathy* compared with eyes with *less severe retinopathy* was 2.41 (99% confidence interval, 1.73 to 3.37). The relative risk (adjusting for severity of retinopathy) for the development of severe visual loss for eyes with macular edema compared with eyes without macular edema was 1.73 (99% confidence interval, 1.17 to 2.57).

The development of severe visual loss for all baseline categories is shown in Figure 9 and Table 7. Analyses that included the entire follow-up period demonstrated no statistically significant differences between any of the strategies for early photocoagulation and deferral within each category. For each of the three categories, the estimates of the relative risk of severe visual loss for eyes assigned to early photocoagulation (combining all strategies for early photocoagulation) compared with deferral were as follows (with 99% confidence intervals): eyes without macular edema, 1.37 (0.67 to 2.77); eyes with macular edema and *less severe retinopathy* at baseline, 0.59 (0.32 to 1.09); and eyes with macular edema and *more severe retinopathy* at baseline, 0.70 (0.44 to 1.11).

Severe visual loss or vitrectomy. Some eyes in the ETDRS eventually required vitrectomy for complications of diabetic retinopathy. The cumulative rates of vitrectomy in eyes assigned to deferral and early photocoagulation are shown in Figure 10. The 5-year rates of vitrectomy are 3.9% and 2.2% for deferral and early photocoagulation, respectively. These rates are about the same as the 5-year rates of severe visual loss. However, only 32% of the eyes that underwent vitrectomy had severe visual loss.

Because vitrectomy saved an unknown number of eyes from severe visual loss, and because vitrectomy could be considered a bad outcome for eyes eligible for the ETDRS, one endpoint was defined as the first occurrence of either severe visual loss or vitrectomy. The cumulative rates of the occurrence of this endpoint for eyes assigned to deferral of photocoagulation and early photocoagulation are shown in Figure 11. The relative risk of this endpoint for the entire period of follow-up for eyes assigned to early photocoagulation compared with eyes assigned to deferral was 0.67 (99% confidence interval, 0.52 to 0.87).

The development of this endpoint by baseline category is shown in Figure 12 and Table 8. Analyses that included the entire follow-up period demonstrated no statistically significant differences within each category for the comparison of a specific strategy of early photocoagulation with deferral. The estimates of the relative risk of the occurrence of the endpoint for eyes assigned to early photocoagulation (combining all strategies for early photocoagulation within each of the three categories) compared with the eyes assigned to deferral were as follows (with 99% confidence intervals): eyes without macular edema, 0.78 (0.47 to 1.29); eyes with macular edema and *less severe retinopathy* at baseline, 0.55 (0.33 to 0.94); eyes with macular edema and *more severe retinopathy* at baseline, 0.68 (0.47 to 0.99).

Moderate visual loss. For each baseline category, percentages of eyes in which moderate visual loss occurred at specified follow-up visits are presented in Figure 13 and Table 9. An adverse effect of full scatter photocoagulation was apparent at both the 6-week and 4-month follow-up visits in each category, with visual loss occurring more frequently in eyes assigned to this strategy than in those assigned to deferral.

There was less evidence for moderate visual loss associated with mild scatter than with full scatter photoco-

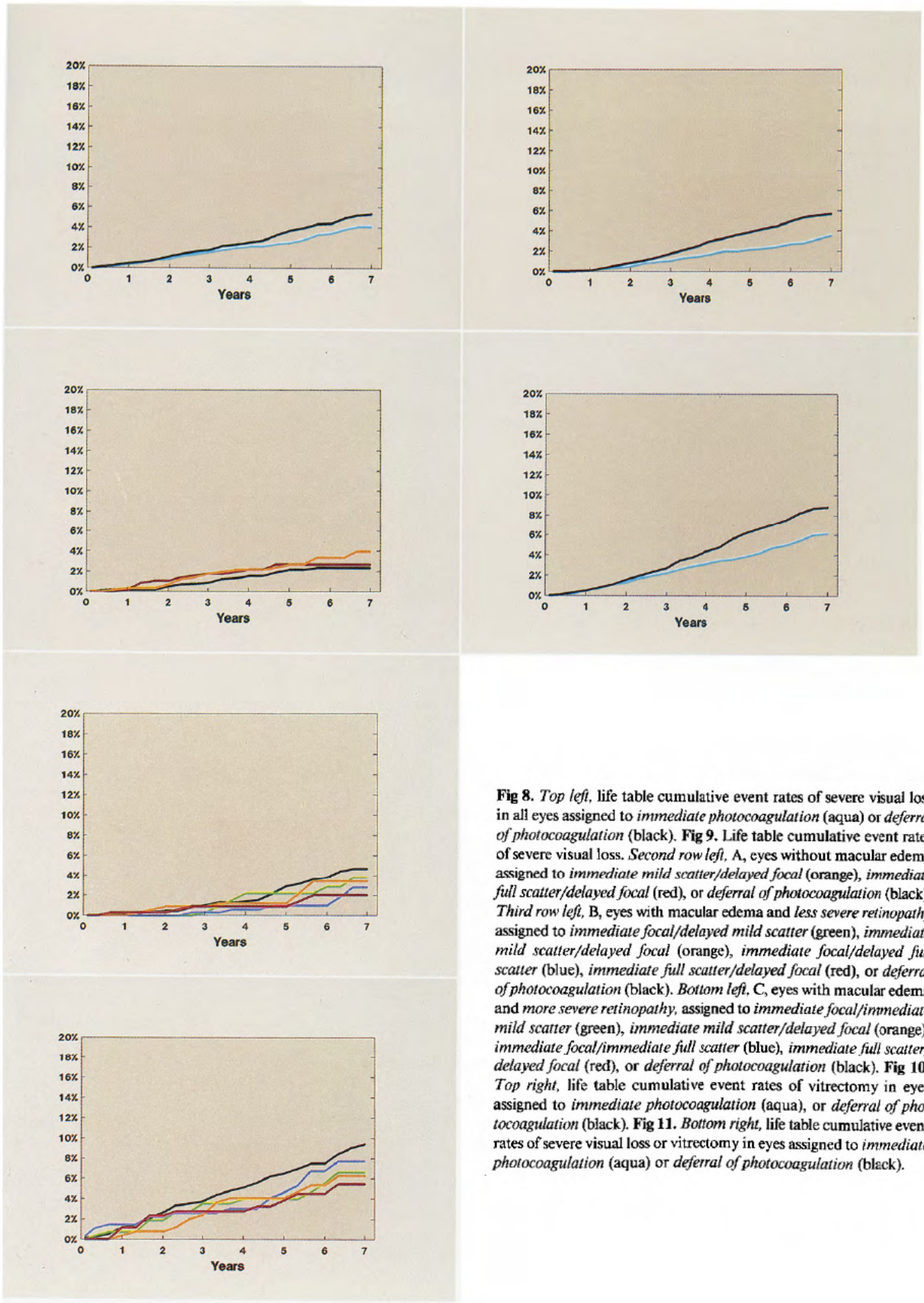


Fig 8. *Top left,* life table cumulative event rates of severe visual loss in all eyes assigned to *immediate photocoagulation* (aqua) or *deferral of photocoagulation* (black). **Fig 9.** Life table cumulative event rates of severe visual loss. *Second row left,* A, eyes without macular edema assigned to *immediate mild scatter/delayed focal* (orange), *immediate full scatter/delayed focal* (red), or *deferral of photocoagulation* (black). *Third row left,* B, eyes with macular edema and *less severe retinopathy* assigned to *immediate focal/delayed mild scatter* (green), *immediate mild scatter/delayed focal* (orange), *immediate focal/delayed full scatter* (blue), *immediate full scatter/delayed focal* (red), or *deferral of photocoagulation* (black). *Bottom left,* C, eyes with macular edema and *more severe retinopathy,* assigned to *immediate focal/immediate mild scatter* (green), *immediate mild scatter/delayed focal* (orange), *immediate focal/immediate full scatter* (blue), *immediate full scatter/delayed focal* (red), or *deferral of photocoagulation* (black). **Fig 10.** *Top right,* life table cumulative event rates of vitrectomy in eyes assigned to *immediate photocoagulation* (aqua), or *deferral of photocoagulation* (black). **Fig 11.** *Bottom right,* life table cumulative event rates of severe visual loss or vitrectomy in eyes assigned to *immediate photocoagulation* (aqua) or *deferral of photocoagulation* (black).

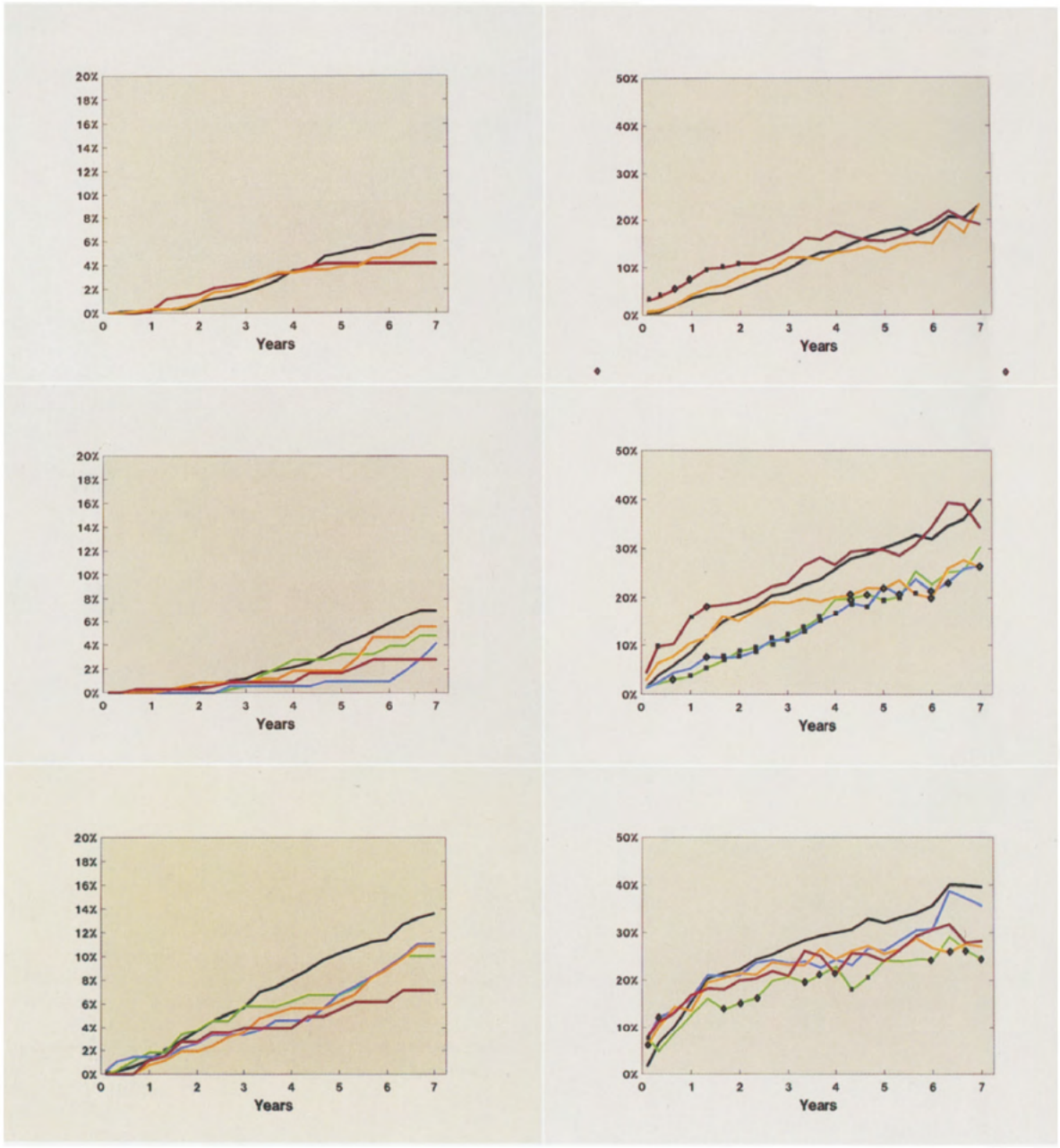


Fig 12. Life table cumulative event rates of severe visual loss or vitrectomy. *Top left,* A, eyes without macular edema assigned to *immediate mild scatter/delayed focal* (orange), *immediate full scatter/delayed focal* (red), or *deferral of photocoagulation* (black). *Center left,* B, eyes with macular edema and *less severe retinopathy* assigned to *immediate focal/delayed mild scatter* (green), *immediate mild scatter/delayed focal* (orange), *immediate focal/delayed full scatter* (blue), *immediate full scatter/delayed focal* (red), or *deferral of photocoagulation* (black). *Bottom left,* C, eyes with macular edema and *more severe retinopathy,* assigned to *immediate focal/immediate mild scatter* (green), *immediate mild scatter/delayed focal* (orange), *immediate focal/immediate full scatter* (blue), *immediate full scatter/delayed focal* (red), or *deferral of photocoagulation* (black). **Fig 13.** Percentage of eyes with moderate visual loss at each follow-up visit. Two-sided test of immediate treatment versus deferral, $P < 0.01$ (diamond), $P < 0.001$ (square). *Top right,* A, eyes without macular edema assigned to *immediate mild scatter/delayed focal* (orange), *immediate full scatter/delayed focal* (red), or *deferral of photocoagulation* (black). *Center right,* B, eyes with macular edema and *less severe retinopathy* assigned to *immediate focal/delayed mild scatter* (green), *immediate mild scatter/delayed focal* (orange), *immediate focal/delayed full scatter* (blue), *immediate full scatter/delayed focal* (red), or *deferral of photocoagulation* (black). *Bottom right,* C, eyes with macular edema and *more severe retinopathy,* assigned to *immediate focal/immediate mild scatter* (green), *immediate mild scatter/delayed focal* (orange), *immediate focal/immediate full scatter* (blue), *immediate full scatter/delayed focal* (red), or *deferral of photocoagulation* (black).

Table 7. Development of Severe Visual Loss*

Baseline Retinopathy Category	Photocoagulation Treatment Strategy				
	Early† Full Scatter		Early† Mild Scatter		
	Immediate Focal	Delayed Focal	Immediate Focal	Delayed Focal	Deferral
No macular edema					
1-yr rate (%)		0.2		0.3	0.2
3-yr rate (%)		1.8		1.8	0.9
5-yr rate (%)		2.7		2.6	2.2
No. of eyes		583		590	1179
Relative risk‡		1.24		1.49	
99% CI		0.52–2.98		0.65–3.39	
Macular edema and *less severe retinopathy*					
1-yr rate (%)	—	0.3	—	—	0.1
3-yr rate (%)	0.3	0.9	0.3	0.9	1.0
5-yr rate (%)	1.0	0.9	2.2	1.2	2.9
No. of eyes	362	356	365	365	1429
Relative risk	0.43	0.43	0.75	0.74	
99% CI	0.13–1.44	0.13–1.44	0.29–1.91	0.29–1.88	
Macular edema and *more severe retinopathy*					
1-yr rate (%)	1.5	1.2	0.7	0.4	1.1
3-yr rate (%)	2.6	2.8	3.5	2.4	3.8
5-yr rate (%)	4.7	3.8	4.0	4.1	6.5
No. of eyes	272	270	276	272	1103
Relative risk	0.78	0.59	0.74	0.68	
99% CI	0.38–1.62	0.26–1.34	0.35–1.57	0.31–1.46	

CI = confidence interval.

* Life table event rates of first occurrence of severe visual loss using Cutler-Ederer actuarial estimates.

† See Figures 1 to 3.

‡ Relative risk of severe visual loss for entire period of follow-up was estimated separately for each baseline retinopathy category and early treatment strategy. A Cox model with time to severe visual loss as the dependent variable was used. The 99% CI for the estimate of the relative risk was calculated.

agulation. In eyes with macular edema and *more severe retinopathy,* there was a statistically significant adverse effect at 6 weeks (Fig 13C) in both strategies for early photocoagulation that included immediate mild scatter.

In both categories of eyes with macular edema (Figs 13B, C), early photocoagulation appeared to reduce the overall risk of moderate visual loss compared with deferral of photocoagulation. This beneficial effect of early photocoagulation was statistically significant, beginning with the first year of follow-up in eyes with macular edema and *less severe retinopathy* assigned to immediate focal photocoagulation with delayed scatter (Fig 13B) and occurred later for eyes with macular edema and *more severe retinopathy* (Fig 13C).

Results presented in Figure 14 are limited to eyes with retinal thickening that involved the center of the macula at the baseline visit (the group of eyes for which focal photocoagulation is generally recommended based on previous ETDRS reports).[3,5,6] The pattern of differences between groups was similar to that seen in Figure 13, but the rates of moderate visual loss were higher, especially for eyes assigned to deferral of photocoagulation.

Retinal thickening at the center of the macula. Degree of change in retinal thickening at the center of the macula, another measure used to assess effects of photocoagulation, is shown in Figures 15 and 16. Figure 15 shows the percentages of eyes without central thickening at baseline that developed central thickening during follow-up. In eyes with *less severe retinopathy* (Fig 15A), the percentage of eyes that developed central thickening during follow-up was lowest for eyes assigned to immediate focal photocoagulation with delay of scatter photocoagulation, either mild or full. Eyes assigned to immediate scatter with delayed focal photocoagulation had the highest percentages of central thickening at the 4-month and 1-year visits, but, by the 3-year visit, these percentages had fallen to the same level as those in the other strategies for early photocoagulation. In eyes with *more severe retinopathy* (Fig 15B), the percentage of eyes that developed central thickening during follow-up was lowest in the eyes assigned to focal photocoagulation and mild scatter. By the 3-year visit, these percentages were similar in all four strategies of early photocoagulation.

Figure 16 shows the percentages of eyes that continued to have central thickening during follow-up in eyes that had central thickening at baseline. Among eyes with *less severe retinopathy* (Fig 16A), thickening persisted during follow-up least frequently in eyes assigned to immediate focal photocoagulation with delay of either full or mild scatter photocoagulation. By the 3-year visit, eyes in all

Table 8. Development of Severe Visual Loss or Occurrence of Vitrectomy*

Baseline Retinopathy Category	Photocoagulation Treatment Strategy				
	Early† Full Scatter		Early† Mild Scatter		
	Immediate Focal	Delayed Focal	Immediate Focal	Delayed Focal	Deferral
No macular edema					
1-yr rate (%)		0.2		0.3	0.3
3-yr rate (%)		2.5		2.3	1.8
5-yr rate (%)		4.2		3.9	5.0
No. of eyes		583		590	1179
Relative risk‡		0.74		0.83	
99% CI		0.39–1.40		0.45–1.52	
Macular edema and *less severe retinopathy*					
1-yr rate (%)	0.0	0.3	0.0	0.0	0.1
3-yr rate (%)	0.6	0.9	0.6	0.9	1.2
5-yr rate (%)	1.0	1.7	3.3	1.9	4.0
No. of eyes	362	356	365	365	1429
Relative risk	0.35	0.42	0.69	0.74	
99% CI	0.12–1.06	0.15–1.16	0.31–1.55	0.34–1.62	
Macular edema and *more severe retinopathy*					
1-yr rate (%)	1.5	1.2	1.9	0.8	1.2
3-yr rate (%)	3.4	4.0	5.9	3.6	5.7
5-yr rate (%)	6.9	5.6	6.8	6.2	10.3
No. of eyes	272	270	276	272	1103
Relative risk	0.72	0.52	0.77	0.72	
99% CI	0.39–1.32	0.26–1.06	0.43–1.41	0.39–1.32	

CI = confidence interval.

* Life table event rates of first occurrence of severe visual loss or vitrectomy using Cutler-Ederer actuarial estimates.

† See Figures 1 to 3.

‡ Relative risk for entire period of follow-up was estimated separately for each baseline retinopathy category and early treatment strategy. A Cox model with time to severe visual loss or vitrectomy as the dependent variable was used. The 99% CI for the estimate of the relative risk was calculated.

four strategies of early photocoagulation had less central retinal thickening than did eyes assigned to deferral of photocoagulation. Results were similar for eyes with macular edema and *more severe retinopathy* (Fig 16B).

Visual fields and color vision. The cumulative distributions of scores obtained using the Goldmann I/4e test object at the baseline, 4-month, and 48-month visits are given for each baseline category in Figure 17. The distributions did not differ between categories or assigned strategies at baseline. For eyes assigned to deferral, there was no significant change in scores between the baseline and 4-month visits. By the 4-month visit, eyes in all three baseline categories assigned to immediate full scatter photocoagulation had significantly greater loss of visual field than eyes assigned to deferral ($P < 0.001$). There was an intermediate amount of loss for the eyes assigned to mild scatter. The comparison of the loss of visual field between eyes assigned to immediate mild and eyes assigned to immediate full scatter also was statistically significant ($P < 0.001$). Eyes with macular edema and *less severe retinopathy* assigned to immediate focal photocoagulation with delayed scatter had no significant loss of visual field at the 4-month visit. From the baseline to the 4-year visit, scores for visual field worsened in all groups. The scores for eyes assigned to immediate full scatter remained significantly ($P < 0.001$) worse than those for eyes assigned to deferral.

Percentages of eyes with scotomata detected within 20° of fixation with the I/2e test object (or with loss of ability to see this test object) at the 4-month and 4-year follow-up visits in eyes without scotomata at baseline are shown in Table 10. Eyes with macular edema assigned to deferral of photocoagulation were more likely to develop this endpoint by 4 months than were those without macular edema ($P < 0.001$). In eyes without macular edema, there was essentially no difference in the percentages of eyes with this endpoint at the 4-month visit between the eyes assigned to immediate mild scatter and the eyes assigned to deferral, but it was more frequent in the eyes assigned to immediate full scatter ($P < 0.01$ full scatter versus deferral). There were no other statistically significant differences. More sophisticated methods for assessing small scotomas may have shown differences between eyes assigned to early photocoagulation or deferral, but these tests were not included in the protocol.

Percentages of eyes with an increase of 7.5 or greater in the square root of the total error score from the Farnsworth-Munsell 100-Hue test or a score for visual acuity of less than 20 letters (equivalent to less than 10/200, which generally prevented performance of the test) are

Table 9. Occurrence of Moderate Visual Loss* by Visit

Baseline Retinopathy Category	Photocoagulation Treatment Strategy				
	Early† Full Scatter		Early† Mild Scatter		
	Immediate Focal	Delayed Focal	Immediate Focal	Delayed Focal	Deferral
No macular edema					
6-wk rate (%)		3.1§		0.8	0.4
4-mo rate (%)		3.8§		1.0	0.6
1-yr rate (%)		7.5‡		4.3	3.6
2-yr rate (%)		10.8§		8.3	5.9
3-yr rate (%)		13.6		12.1	9.8
5-yr rate (%)		15.5		13.3	17.6
No. of eyes		583		590	1179
Macular edema and *less severe retinopathy*					
6-wk rate (%)	1.4	4.5	1.6	3.0	1.6
4-mo rate (%)	2.5	9.7§	2.2	6.4	3.8
1-yr rate (%)	5.3	15.9§	3.7§	10.5	8.6
2-yr rate (%)	7.6§	19.1	8.9§	15.1	16.6
3-yr rate (%)	11.2§	23.1	12.2§	19.0	21.1
5-yr rate (%)	22.4	29.8	19.5§	21.8‡	30.2
No. of eyes	362	356	365	365	1429
Macular edema and *more severe retinopathy*					
6-wk rate (%)	7.7§	7.8§	7.6§	5.9‡	1.7
4-mo rate (%)	12.2‡	11.2	4.8	10.1	6.5
1-yr rate (%)	16.2	16.9	12.7	13.6	15.5
2-yr rate (%)	21.1	20.0	15.3‡	21.5	22.2
3-yr rate (%)	23.6	20.9	20.7	23.3	27.1
5-yr rate (%)	26.2	24.1	24.1	25.7	32.1
No. of eyes	272	270	276	272	1103

* See Table 1.
† See Figures 1 to 3.
‡ $P < 0.01$.
§ $P < 0.001$ (using a z-test for equality of proportions).

Table 10. Occurrence of Paracentral Scotomata* by Visit

Baseline Retinopathy Category	Photocoagulation Treatment Strategy				
	Early† Full Scatter		Early† Mild Scatter		
	Immediate Focal	Delayed Focal	Immediate Focal	Delayed Focal	Deferral
No macular edema					
4-mo rate (%)		15.5‡		7.5	7.0
No. of eyes		207		227	459
4-yr rate (%)		21.6		18.2	18.0
No. of eyes		292		297	611
Macular edema and *less severe retinopathy*					
4-mo rate (%)	12.9	12.8	16.0	9.5	12.8
No. of eyes	147	133	144	148	572
4-yr rate (%)	24.9	33.9	22.3	19.9	28.4
No. of eyes	173	165	175	171	677
Macular edema and *more severe retinopathy*					
4-mo rate (%)	23.1	19.8	24.1	17.2	15.8
No. of eyes	130	111	112	122	482
4-yr rate (%)	31.6	32.8	37.3	38.0	30.9
No. of eyes	136	125	134	129	540

* The percentage with paracentral scotomata detected within 20° of fixation with the I/2e test object or with a visual acuity less than 5/200 based on the number of eyes with a visual field score or visual acuity less than 5/200.
† See Figures 1 to 3.
‡ $P < 0.01$.

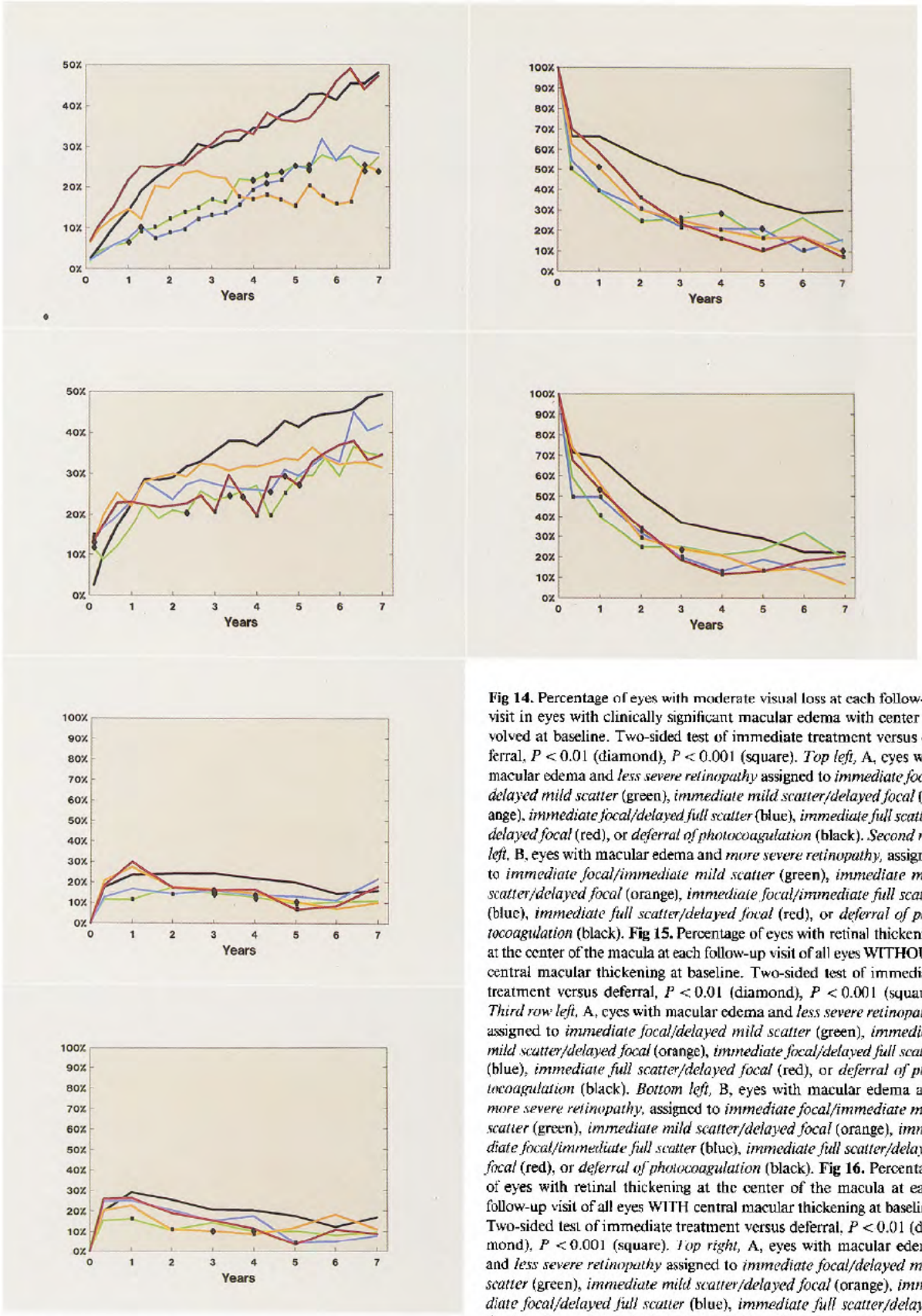


Fig 14. Percentage of eyes with moderate visual loss at each follow-up visit in eyes with clinically significant macular edema with center involved at baseline. Two-sided test of immediate treatment versus deferral, $P < 0.01$ (diamond), $P < 0.001$ (square). *Top left,* A, eyes with macular edema and *less severe retinopathy* assigned to *immediate focal/delayed mild scatter* (green), *immediate mild scatter/delayed focal* (orange), *immediate focal/delayed full scatter* (blue), *immediate full scatter/delayed focal* (red), or *deferral of photocoagulation* (black). *Second row left,* B, eyes with macular edema and *more severe retinopathy,* assigned to *immediate focal/immediate mild scatter* (green), *immediate mild scatter/delayed focal* (orange), *immediate focal/immediate full scatter* (blue), *immediate full scatter/delayed focal* (red), or *deferral of photocoagulation* (black). **Fig 15.** Percentage of eyes with retinal thickening at the center of the macula at each follow-up visit of all eyes WITHOUT central macular thickening at baseline. Two-sided test of immediate treatment versus deferral, $P < 0.01$ (diamond), $P < 0.001$ (square). *Third row left,* A, eyes with macular edema and *less severe retinopathy* assigned to *immediate focal/delayed mild scatter* (green), *immediate mild scatter/delayed focal* (orange), *immediate focal/delayed full scatter* (blue), *immediate full scatter/delayed focal* (red), or *deferral of photocoagulation* (black). *Bottom left,* B, eyes with macular edema and *more severe retinopathy,* assigned to *immediate focal/immediate mild scatter* (green), *immediate mild scatter/delayed focal* (orange), *immediate focal/immediate full scatter* (blue), *immediate full scatter/delayed focal* (red), or *deferral of photocoagulation* (black). **Fig 16.** Percentage of eyes with retinal thickening at the center of the macula at each follow-up visit of all eyes WITH central macular thickening at baseline. Two-sided test of immediate treatment versus deferral, $P < 0.01$ (diamond), $P < 0.001$ (square). *Top right,* A, eyes with macular edema and *less severe retinopathy* assigned to *immediate focal/delayed mild scatter* (green), *immediate mild scatter/delayed focal* (orange), *immediate focal/delayed full scatter* (blue), *immediate full scatter/delayed focal* (red), or *deferral of photocoagulation* (black). *Bottom right,* B, eyes with macular edema and *more severe retinopathy,* assigned to *immediate focal/immediate mild scatter* (green), *immediate mild scatter/delayed focal* (orange), *immediate focal/immediate full scatter* (blue), *immediate full scatter/delayed focal* (red), or *deferral of photocoagulation* (black).

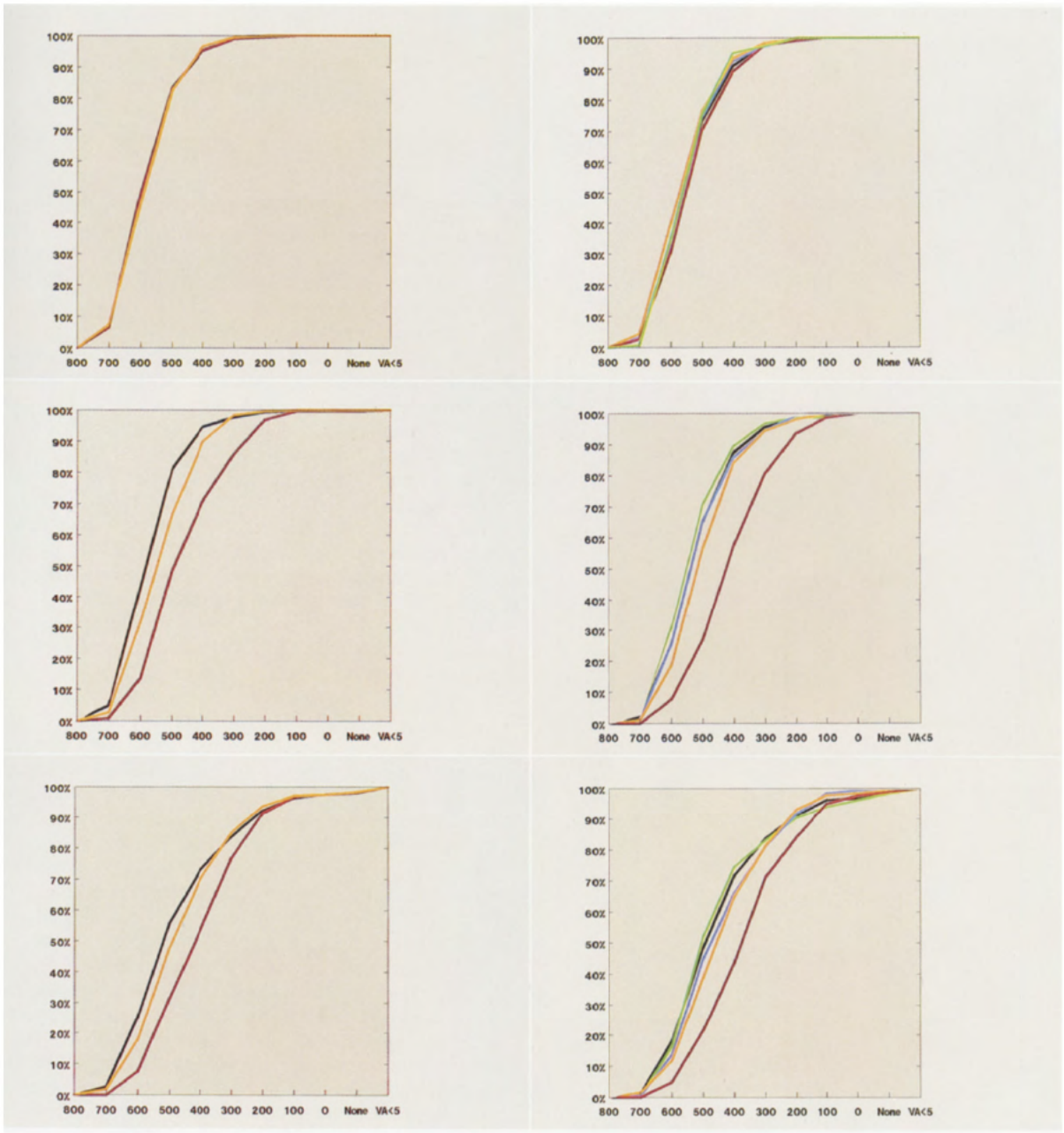


Fig 17. Cumulative percentage distribution of visual field score for all eyes tested at baseline, 4-month and 4-year follow-up visits. *Left,* eyes without macular edema assigned to *immediate mild scatter/delayed focal* (orange), *immediate full scatter/delayed focal* (red), or *deferral of photocoagulation* (black). *Right,* eyes with macular edema and *less severe retinopathy* assigned to *immediate focal/delayed mild scatter* (green), *immediate mild scatter/delayed focal* (orange), *immediate focal/delayed full scatter* (blue), *immediate full scatter/delayed focal* (red), or *deferral of photocoagulation* (black).

presented in Table 11. Between the baseline and the 8-month and 4-year follow-up visits, there were no significant differences between eyes assigned to any strategy of early photocoagulation and eyes assigned to deferral among eyes without macular edema and eyes with macular edema and *more severe retinopathy.* All of the eyes in this category assigned to early photocoagulation had scatter photocoagulation as part of their initial treatment.

For eyes with macular edema and *less severe retinopathy* assigned to immediate focal and delayed scatter photocoagulation, there was less loss of color vision at the 4-year visit ($P < 0.001$ comparing the combination of both groups of eyes assigned to immediate focal photocoagulation with eyes assigned to deferral). This difference was evident but not statistically significant at the 8-month visit. In all three baseline categories, there was a trend at the

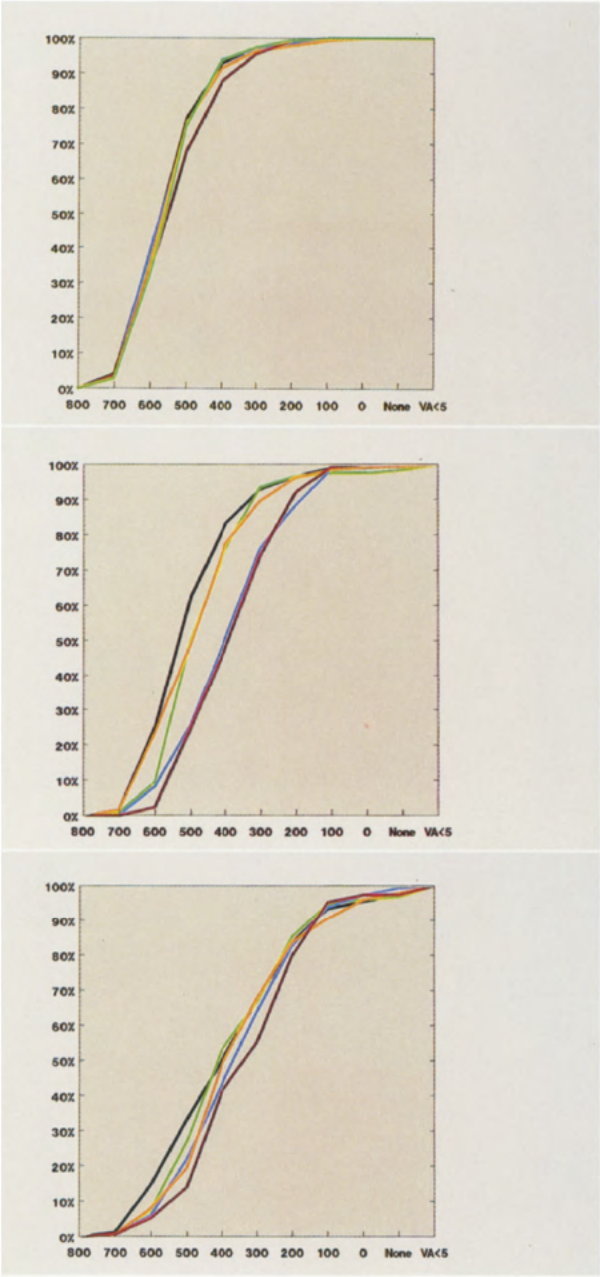


Fig 17. (*Continued*) Eyes with macular edema and *more severe retinopathy,* assigned to *immediate focal/immediate mild scatter* (green), *immediate mild scatter/delayed focal* (orange), *immediate focal/immediate full scatter* (blue), *immediate full scatter/delayed focal* (red), or *deferral of photocoagulation* (black).

8-month visit for a higher percentage of the eyes assigned to immediate full scatter to experience a loss of color vision.

DISCUSSION

As expected from the DRS results, early photocoagulation did result in a marked reduction in the rate of developing high-risk proliferative retinopathy compared with deferral of photocoagulation (Fig 6 and Table 5). When eyes assigned to deferral were stratified according to baseline retinopathy (Fig 7 and Table 6), the rate of progression to the high-risk stage generally increased as the retinopathy increased. Strategies for photocoagulation that included immediate full scatter reduced the rate of developing high-risk proliferative retinopathy by approximately 50%, while strategies that included immediate mild scatter reduced this rate by approximately 25% (Fig 6).

The DRS 4-year rate of severe visual loss in eyes with high-risk proliferative retinopathy (all levels of severity, not just newly developed) that were treated with full scatter was 20.4%. It was anticipated that following eyes carefully and treating at the time of development of high-risk proliferative retinopathy (the ETDRS strategy of deferral of photocoagulation) would reduce this rate, but the degree of reduction was unknown. It was also not known to what degree earlier photocoagulation (the ETDRS strategies for early photocoagulation), which was expected to reduce the rate of development of high-risk retinopathy, would reduce the development of severe visual loss.

As seen in Figure 8, all eyes, whether treated early or followed closely and treated as soon as they reached the high-risk stage, had low rates of severe visual loss. Rates were somewhat higher for the endpoint of severe visual loss or vitrectomy (Fig 11). These rates were highest in eyes with *more severe retinopathy* and macular edema (Fig 12C). However, the 5-year rate of severe visual loss, even among eyes with *more severe retinopathy* and macular edema at baseline, was only 6.5% in eyes assigned to deferral (Table 7) (10.3% for the endpoint of severe visual loss or vitrectomy, Table 8). There was no suggestion that the timing of focal photocoagulation in the eyes with macular edema assigned to early photocoagulation influenced the development of severe visual loss.

Although eyes assigned to the ETDRS strategies of early photocoagulation had somewhat lower rates of severe visual loss or vitrectomy than those assigned to deferral, other effects on visual function and the effect of early photocoagulation in the three different baseline categories must be considered before making clinical recommendations.

For eyes without macular edema, neither of the strategies for early photocoagulation (immediate scatter, mild or full, with delayed focal if needed for clinically significant macular edema) was better than deferral of photocoagulation for preventing either moderate or severe visual loss (moderate visual loss, Fig 13A and Table 9; severe visual loss, Fig 9A and Table 7). Eyes assigned to early full scatter were more likely to have moderate visual loss during the first 2 years of follow-up than eyes assigned to deferral (Fig 13A).

For eyes with macular edema and *less severe retinopathy,* each of the strategies of early photocoagulation had a reduced 5-year risk of severe visual loss compared with eyes assigned to deferral of photocoagulation (Fig 9B and

Table 11. Occurrence of Increase of 7.5 or Greater in Square Root Color Vision Error Score* by Visit

Baseline Retinopathy Category	Photocoagulation Treatment Strategy				
	Early† Full Scatter		Early† Mild Scatter		
	Immediate Focal	Delayed Focal	Immediate Focal	Delayed Focal	Deferral
No macular edema					
8-mo rate (%)		4.3		3.0	1.5
No. of eyes		187		202	399
4-yr rate (%)		17.0		11.2	14.1
No. of eyes		324		321	645
Macular edema and *less severe retinopathy*					
8-mo rate (%)	0.8	6.1	1.4	4.1	2.9
No. of eyes	133	131	145	147	544
4-yr rate (%)	9.4‡	22.9	11.3	14.8	17.9
No. of eyes	191	175	186	182	731
Macular edema and *more severe retinopathy*					
8-mo rate (%)	5.7	8.9	4.3	1.8	5.3
No. of eyes	122	112	115	111	453
4-yr rate (%)	23.1	21.9	20.9	18.9	24.0
No. of eyes	147	146	158	148	600

* The percentage with an increase of 7.5 or greater in the square root of the Farnsworth-Munsell 100-Hue error score or with a visual acuity less than 10/200 based on the combined total of the number of eyes with a color vision score or visual acuity less than 10/200.

† See Figures 1 to 3.

‡ $P < 0.001$.

Table 7), but the risks were low in all groups. The estimate of the relative risk of severe visual loss for the entire period of follow-up for eyes with macular edema and *less severe retinopathy* for all strategies of early photocoagulation combined versus deferral was 0.59 (99% confidence interval, 0.32 to 1.09). If vitrectomy is combined with severe visual loss as an endpoint, the estimate of the relative risk of all strategies of early photocoagulation combined versus deferral is statistically significant (relative risk, 0.55; 99% confidence interval, 0.33 to 0.94).

Immediate focal photocoagulation with delayed scatter (added only if *more severe retinopathy* developed) was the most effective strategy for reducing the risk of moderate visual loss for eyes with macular edema and *less severe retinopathy* (Fig 13B and Table 9). In the first 3 years of follow-up, this strategy resulted in approximately a 50% reduction of moderate visual loss compared with the rate of moderate visual loss in eyes assigned to deferral of photocoagulation. For these eyes, mild scatter with delayed focal photocoagulation was the second best alternative, resulting in rates of moderate visual loss similar to those in eyes assigned to deferral during the first 3 years of follow-up and similar to those in the eyes assigned to immediate focal photocoagulation at and after 4 years. Eyes in this category assigned to immediate full scatter and delayed focal photocoagulation had an increased risk of moderate visual loss during the first 16 months of follow-up ($P < 0.001$ full scatter versus deferral at 4 months and 1 year) and thereafter were similar to the eyes assigned to deferral.

For eyes with macular edema and *more severe retinopathy* (Fig 9C and Table 7), the risk of severe visual loss in eyes assigned to deferral of photocoagulation was relatively high (6.5% at the 5-year visit). This risk was reduced to between 3.8 and 4.7% in the eyes assigned to early photocoagulation. The relative risk of severe visual loss for the entire follow-up period for all strategies of early photocoagulation combined versus deferral was 0.70 (99% confidence interval, 0.44 to 1.11); the relative risk of the endpoint, severe visual loss or vitrectomy, was 0.68 (99% confidence interval, 0.47 to 0.99).

Compared with deferral of photocoagulation, there was an increase in the risk of moderate visual loss soon after early photocoagulation in eyes with macular edema and *more severe retinopathy* (at the 6-week visit, $P < 0.01$ and $P < 0.001$ depending on early strategy; Fig 13C and Table 9). After the first year, all strategies of early photocoagulation for eyes with macular edema and *more severe retinopathy* had a lower risk of moderate visual loss. The strategy associated with the least visual loss (both moderate and severe) was immediate mild scatter combined with immediate focal photocoagulation.

Deferral of photocoagulation in eyes with macular edema and *more severe retinopathy* was the least effective strategy. It was associated with the highest risk of both moderate and severe visual loss, although these differences were not statistically significant at the 0.01 level.

Because the strategies of early photocoagulation in the ETDRS were combinations of focal and scatter photocoagulation, there is no direct method to separate their effects. The following observations help to separate the effects of these two different types of photocoagulation for application of the results of the ETDRS to clinical practice.

The reduced rates of progression to high-risk proliferative retinopathy in eyes assigned to early photocoagu-

lation appear to be due mostly to the effects of the scatter photocoagulation. This reduction was about twice as large with full scatter compared with mild scatter (groups of eyes that were managed identically in regard to focal photocoagulation). Furthermore, this reduction was essentially the same in eyes with and without macular edema (groups of eyes in which the frequency of focal photocoagulation was markedly different—approximately 85% of eyes with macular edema at baseline eventually received focal photocoagulation compared with only 40% of eyes without macular edema at baseline).

The harmful effects of early photocoagulation assessed by moderate visual loss and visual fields also seem to be due mostly to scatter photocoagulation. In the first year, only the groups of eyes receiving immediate scatter photocoagulation showed decreases in these visual functions compared with eyes assigned to deferral, and these decreases were larger in eyes assigned to full scatter than in eyes assigned to mild scatter.

The reduced rates of development of moderate visual loss in eyes with macular edema at baseline assigned to early photocoagulation appear to be due mostly to the effects of the focal photocoagulation. The groups of eyes assigned to immediate focal photocoagulation with delayed scatter demonstrated the largest benefit of early photocoagulation in reducing the risk of moderate visual loss. Although one third of these eyes received scatter photocoagulation during the first 3 years of follow-up, it seems unreasonable to attribute the benefit of early photocoagulation to this delayed scatter photocoagulation.

As recommended in previous ETDRS publications,[3,5,6] and indicated again in this report, focal photocoagulation should be considered for all eyes with clinically significant macular edema. Focal photocoagulation reduced the risk of moderate visual loss, increased the chance of visual improvement, lessened loss of color vision, and was associated with only minor losses of visual field.

Data from the ETDRS demonstrate that early photocoagulation reduces the risk of progression of retinopathy, the risk of vitrectomy, and the risk of developing severe visual loss. However, when making the decision whether to initiate scatter photocoagulation, its side effects on both visual field and central vision must be considered. For most eyes that have not yet reached the high-risk proliferative stage, these side effects of scatter photocoagulation must be balanced with the possible small benefit of early photocoagulation in reducing the risk of severe visual loss. This is largely because the rates of severe visual loss were low in both the early photocoagulation and deferral groups, and because, after 7 years of follow-up, only 50% of eyes assigned to deferral had developed high-risk proliferative retinopathy.

As retinopathy approaches the high-risk stage (very severe nonproliferative retinopathy or moderate proliferative retinopathy[13]), the benefits and risks of early photocoagulation may be roughly balanced. The benefit of a reduction in the risk of severe visual loss from early photocoagulation may be more important in an eye that has almost a 50% chance of reaching the high-risk stage within 1 year (Table 6). Deferral of photocoagulation will save fewer eyes with relatively advanced retinopathy from photocoagulation and its side effects, and the risk of severe visual loss or vitrectomy is higher in these eyes.

Initiating scatter photocoagulation early in at least one eye seems particularly appropriate when both of a patient's eyes are approaching the high-risk stage, because optimal timing of episodes of photocoagulation may be difficult if both eyes simultaneously need photocoagulation. Very few eyes in the ETDRS had more than 2 disc areas of neovascularization elsewhere and the possibility that for these eyes there may be an advantage of prompt scatter photocoagulation cannot be ruled out. Also, prompt scatter photocoagulation should be considered for eyes with new vessels in the anterior chamber angle, whether or not high-risk proliferative retinopathy is present.[12]

Deciding how to treat an eye that has both clinically significant macular edema and retinopathy that is approaching the high-risk stage may be difficult. The most effective strategy used in the ETDRS seemed to be early mild scatter combined with focal photocoagulation for the macular edema. However, the ETDRS did not include evaluation of a strategy that consisted of prompt focal photocoagulation with delayed scatter in such eyes. This was the most effective strategy for eyes with macular edema and *less severe retinopathy* and might be an effective strategy for the more severe eyes. Delaying scatter photocoagulation while focal photocoagulation is being completed, or perhaps until retinal thickening has resolved, is unlikely to increase the risk of severe visual loss, provided the retinopathy is not progressing during this interval, and may reduce the risk of moderate visual loss associated with scatter photocoagulation. When scatter photocoagulation is initiated in these eyes, an approach that limits the amount of photocoagulation in each session and adds photocoagulation only as the retinopathy worsens (similar to the ETDRS mild scatter strategy) may result in the lowest risk of moderate visual loss and no increased risk of severe visual loss.

Delaying scatter photocoagulation while focal photocoagulation is completed in eyes with high-risk proliferative retinopathy should be done with considerable caution. In many such eyes—for example, those with active new vessels and recent vitreous hemorrhage that does not yet preclude scatter photocoagulation—it is probably unwise to defer scatter photocoagulation. For eyes that belong to the high-risk category only because of a small patch of new vessels on the disc, brief deferral of scatter photocoagulation until focal photocoagulation has been initiated may be considered, particularly if the macular edema is severe.

CONCLUSIONS

These and previously published results of the ETDRS indicate that focal photocoagulation with delayed scatter photocoagulation is an effective photocoagulation strategy for eyes with clinically significant macular edema. The beneficial effect of this strategy in reducing the risk of moderate visual loss was decreased or reversed by concurrent scatter photocoagulation. The adverse effects of

scatter photocoagulation were most evident in the months immediately following photocoagulation and were less when it was less extensive.

Based on these results, focal photocoagulation should be considered for eyes with clinically significant macular edema, preferably before scatter photocoagulation for high-risk proliferative retinopathy becomes urgent. The decision of when to initiate focal photocoagulation should take into account the degree to which the center of the macula is involved or threatened and the risks of photocoagulation close to the center.[3,5,6]

Provided careful follow-up can be maintained, scatter photocoagulation is not recommended for eyes with mild or moderate nonproliferative diabetic retinopathy. When retinopathy is more severe, scatter photocoagulation should be considered and usually should not be delayed if the eye has reached the high-risk proliferative stage.

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