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Combined iodine-125 plaque irradiation and indirect ophthalmoscope laser therapy of choroidal malignant melanomas: comparison with iodine-125 and cobalt-60 plaque radiotherapy alone

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Abstract. The authors studied the short-term impact of combined episcleral iodine-125 plaque radiotherapy and argon laser treatment in a series of 24 patients with choroidal malignant melanoma. All patients underwent plaque therapy prior to their initial laser session. All laser treatments were performed with an indirect ophthalmoscope argon green laser, using low-power, long-duration exposures. The endpoint of laser therapy was a well-defined atrophic circumbasal chorioretinal laser scar and complete or nearly complete nonfluorescence of the lesion on fluorescein angiography. In a case-by-case matched comparison study, the authors evaluated the relative local regression of tumors treated by combined plaque-laser therapy, iodine-125 plaque therapy alone, and cobalt-60 plaque therapy alone. The tumors treated with supplemental laser regressed substantially faster and more completely than did those treated by either type of plaque therapy alone. However, the short-term visual loss was greater in eyes treated by the combined therapy.

Introduction

The combined use of episcleral plaque radiation therapy and photocoagulation for choroidal malignant melanomas is not new. Photocoagulation has been used as a planned supplement to episcleral plaque therapy for such tumors since at least the mid-1970s. Boniuk and Cohen [4] were the first to describe combined plaque radiotherapy and photocoagulation, in 1978. These authors summarized their experience with xenon arc photocoagulation as a planned supplement to gold plaque radiotherapy in 40 eyes. Subsequently, Zygulska-Mach et al. [21] reported their use of xenon arc photocoagulation following cobalt plaque radiotherapy in 77 eyes, and Moura et al. [17] described their experience with argon laser photocoagulation after gold plaque radiotherapy in 21 eyes. More recently, Lee and coworkers [14] reported their experience with dye laser therapy as a supplement to iodine-125 plaque treatment in 17 eyes. All of these authors were pleased with their results and recommended more widespread use of combined plaque-laser therapy.

Our group has been using iodine-125 plaque radiotherapy followed by indirect ophthalmoscope argon laser treatment in selected patients with choroidal malignant melanoma since October 1990. The purpose of this paper is to describe our therapeutic approach, to summarize our preliminary results on local tumor regression and visual acuity, and to compare them with the results obtained following iodine-125 and cobalt-60 plaque radiotherapy alone.

Materials and methods

Patients

Between October 1990 and July 1992, the senior author treated 56 patients with a choroidal or ciliochoroidal melanoma by planned sequential iodine-125 plaque radiotherapy and indirect ophthalmoscope argon laser therapy. The current analysis concerns the first 25 patients in this series, all of whom were treated prior to July 1991. All of these patients underwent a comprehensive baseline ophthalmologic and systemic assessment prior to the initiation of treatment. The methods of clinical examination, diagnosis, and follow-up used in this group of patients have been published previously [1, 3].

One of the 25 patients was lost to follow-up shortly after her initial laser treatment. This patient was therefore excluded from the present study. The remaining 24 patients (Table 1) ranged in age from 30 to 85 years and had a mean age of 56.8 years. Nine of the 24 patients were male and 15 were female. The 24 tumors ranged from 5.5 to 17.0 mm in maximal basal diameter (mean 9.8 ± SD 3.1 mm) and from 2.0 to 8.6 mm in thickness (4.1 ± 1.6 mm). Five of the tumors were located within 3 mm of both the foveola and optic disc margin, while nine were located over 3 mm from both the foveola and the optic disc.

All 24 patients underwent iodine-125 episcleral plaque radiotherapy with an apical target dose of 80–100 Gy. Patients having

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Table 1. Baseline demographic features and tumor characteristics of matched patient groups

Variable	Categories	Combined plaque-laser group			Iodine-125 plaque alone group			Cobalt-60 plaque alone group		
		No.	(%)	Mean	No.	(%)	Mean	No.	(%)	Mean
Age	≤58 years	12	(50)		12	(50)		12	(50)	
	>58 years	12	(50)		12	(50)		12	(50)	
				56.8 ± 14.9			57.3 ± 13.0			56.8 ± 11.5
Sex	Male	9	(38)		12	(50)		10	(42)	
	Female	15	(62)		12	(50)		14	(58)	
Eye	Right	13	(54)		13	(54)		14	(58)	
	Left	11	(46)		11	(46)		10	(42)	
Visual acuity										
	≤20/30	14	(58)		9	(38)		11	(46)	
	>20/30	10	(42)		15	(62)		13	(54)	
Largest linear basal tumor diameter										
	≤8.5 mm	12	(50)		9	(38)		11	(46)	
	>8.5 mm	12	(50)		15	(62)		13	(54)	
				9.8 ± 3.1			10.0 ± 2.6			9.8 ± 3.1
Tumor thickness										
	≤4 mm	8	(33)		12	(50)		13	(54)	
	>4 mm	16	(67)		12	(50)		11	(46)	
				4.1 ± 1.6			4.0 ± 1.3			4.4 ± 1.5
Location of anterior tumor margin relative to ocular equator										
	At or posterior to equator	18	(75)		13	(54)		16	(67)	
	Anterior to equator	6	(25)		11	(46)		8	(33)	
Location of posterior tumor margin relative to optic disc										
	Within 3 mm of disc	8	(33)		11	(46)		11	(46)	
	Over 3 mm from disc	16	(67)		13	(54)		13	(54)	
Location of posterior tumor margin relative to foveola										
	Within 3 mm of foveola	13	(54)		11	(46)		12	(50)	
	Over 3 mm from foveola	11	(46)		13	(54)		12	(50)	

Categories of continuous numeric variables are dichotomized at the median values; mean values are shown only for the continuous numeric variables

a tumor located 3 mm or less from the optic disc were treated with a posteriorly notched plaque.

Laser treatments were begun in every case after completion of plaque therapy. All laser treatments were performed with an indirect ophthalmoscope argon green laser (Coherent, Inc.) under retrobulbar anesthesia. The first laser treatment was usually performed immediately following plaque removal, but it was delayed for up to 3–4 months in patients with bullous retinal detachment to allow at least some of the subretinal fluid to be reabsorbed.

The first laser treatment session entailed creation of a confluent, gray-white burn 2–3 burn diameters wide around the tumor base (Figs. 1a, 2a, 3a). This confluent circum-marginal burn was made with a "continuous" laser exposure of relatively low power, typically in the range of 200–400 mW. The continuous exposure was interrupted only briefly from time to time to allow the surgeon to change viewing position. Using the low-power, continuous-exposure technique, the surgeon was able to "paint" the selected tissues to a desired level of whiteness by adjusting the speed with which he moved the aiming beam arround the tumor's margin. The total duration of treatment was usually 15–20 min. By keeping the power settings relatively low, the surgeon could usually avoid occlusion of the larger-caliber retinal arteries and veins crossing over the barrier burn.

The second and any subsequent laser sessions (if needed) entailed retreatment of the tumor margin by the same technique described in the preceding paragraph followed by low-power, continuous-exposure treatment of the entire surface of the tumor (Fig. 1b). The second treatment session was usually performed within 1 month after the initial photocoagulation, although occasionally it was delayed for up to 3 months. Subsequent treatment sessions, if necessary, also usually took place within 1–3 months after the prior laser session. All of these sessions were also performed under retrobulbar anesthesia. For the circumbasal retreatment, we generally used laser power settings about the same as or slightly higher than those used in the initial session. For the direct tumor treatment, however, we usually employed laser power settings lower than those used for the initial circumbasal photocoagulation. When treating the tumor proper, we slowly "painted" its surface concentrically from its periphery to its center. In every case, we attempted to render the surface of the tumor confluently and homogeneously gray-white.

In eyes with a juxtapapillary tumor, the second and subsequent laser sessions commonly occluded the large-caliber retinal arterioles and venules. If such occlusion was obvious, we usually performed sectorial scatter laser therapy (Fig. 4a) to the retina peripheral to the treated tumor to reduce the likelihood of subsequent retinal neovascularization.

Our endpoint for stopping laser therapy was a well-defined,

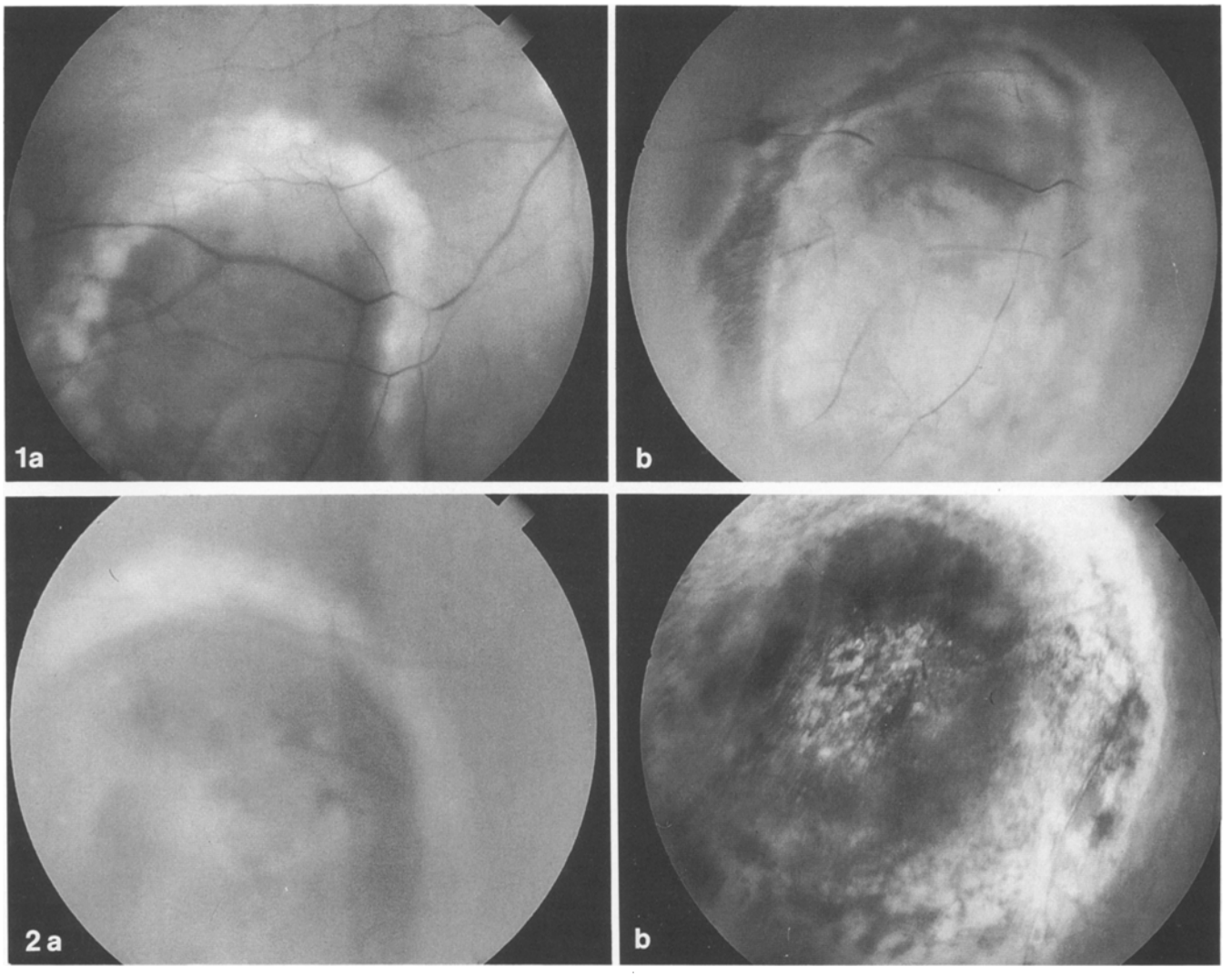

Fig. 1a, b. Combined plaque-laser therapy of choroidal melanoma. **a** Confluent deep white circum-marginal laser burn immediately after initial laser session. **b** Whitish discoloration of tumor with partial occlusion of overlying large-caliber retinal arterioles and venules immediately after second laser session

Fig. 2a, b. Combined plaque-laser therapy of choroidal melanoma. **a** Confluent deep white laser burn along margin of tumor immediately following initial laser session. **b** Regressed tumor 18 months after initial treatment and following two additional laser sessions

atrophic, circumbasal chorioretinal laser scar (Figs. 2b, 3b, 4a) and complete or nearly complete nonfluorescence of the treated tumor on fluorescein angiography (Figs. 3c, 4b, 5a).

Following plaque therapy, the patients underwent from one to five laser treatments (with a median of 2 and a mean of 2.5 sessions) over a median postirradiation interval of 16.5 weeks. Three patients had one laser session, while ten patients had two, nine patients had three, and one patient each had four and five laser treatments.

Matching groups

For each of the 24 patients in our combined plaque-laser group, we identified two "matched" patients, one each from our concurrent and antecedent iodine-125 and cobalt-60 plaque radiotherapy alone groups. The matching patients from the iodine-125 plaque alone group were selected from a total of 100 cases treated between May 1982 and July 1991. The matching patients from the cobalt-60 plaque alone group were selected from a total of 486 patients treated between May 1976 and December 1983. Each of the patients in both comparison groups was identified by computer-assisted case-by-case matching. The clinical variables used to match the patients were the following: age at the time of treatment (within $\pm$ 10 years); largest linear basal tumor diameter (within $\pm$ 3 mm); tumor thickness (within $\pm$ 1.5 mm); location of the posterior tumor margin relative to the optic disc (within $\pm$ 3 mm); and location of the posterior margin tumor relative to the foveola (within $\pm$ 3 mm). Patient matching was performed in a masked fashion, using computer-generated listings of the five matching variables that did not include patient names or outcomes. The patient who most closely met all of the matching criteria was selected. Once a patient from the iodine-125 or cobalt-60 plaque alone groups had been selected, that patient was removed from the list so as not to be selected again.

The patients in each matched group were similar in mean age, age range, and sex distribution to the patients in the combined plaque-laser group (Table 1), and the tumors in the matched patient groups were almost identical in mean largest basal diameter (approximately 10 mm) and thickness (approximately 4 mm) to the tumors in the combined plaque-laser group (Table 1).

All patients in each comparison group underwent conventional episcleral plaque therapy with the respective isotope. As in the combined plaque-laser group, the apical radiation target dose was 80–100 Gy. The patients in the iodine-125 plaque alone group who had a tumor $\leq$ 3 mm from the optic disc were treated with a

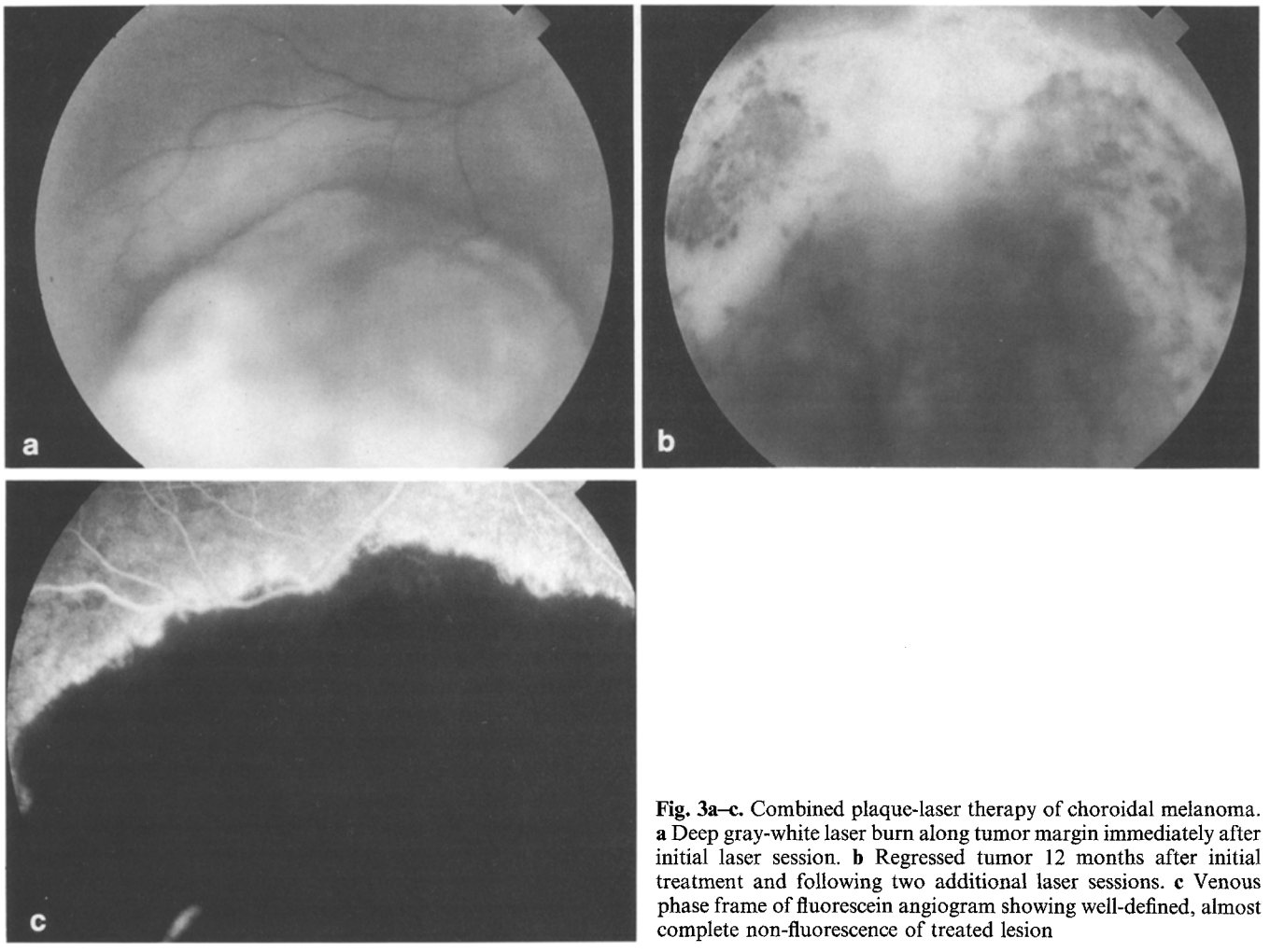

Fig. 3a–c. Combined plaque-laser therapy of choroidal melanoma. **a** Deep gray-white laser burn along tumor margin immediately after initial laser session. **b** Regressed tumor 12 months after initial treatment and following two additional laser sessions. **c** Venous phase frame of fluorescein angiogram showing well-defined, almost complete non-fluorescence of treated lesion

posteriorly notched plaque. In contrast, all patients in the cobalt-60 plaque group received a non-notched plaque regardless of the tumor's location relative to the optic disc.

Post-treatment follow-up

Following plaque radiotherapy, the patients were reevaluated at least every 1–3 months during the first 12 months after treatment. Each of these reevaluations included comprehensive binocular indirect ophthalmoscopy with assessment of tumor margins and an estimation of residual tumor thickness. In addition, B-scan ophthalmic ultrasonography (Fig. 6a, b) with tumor biometry was performed at each visit. Fluorescein angiography was performed on a case-by-case basis as indicated by ophthalmoscopic findings.

Assessment of event rates in study groups

We evaluated the relative local regression of the tumors in the three groups graphically by plotting the mean fractional tumor thickness (i.e., the tumor's thickness at follow-up divided by its initial thickness) in each group over time following treatment (PATPLOT routine, MEDLOG Clinical Data Management System, Information Analysis Corporation, Incline Village, Nev.). We also compared the mean thickness of matched tumors in the three groups at the 12-month interval using intergroup paired *t*-testing.

We evaluated the visual loss rates of the treated eyes in the three groups using product-limit (Kaplan-Meier) failure time analysis [13a]. For this analysis, we evaluated (1) the length of time until visual acuity decreased to $\leq 20/200$ and (2) the length of time until visual acuity decreased by more than two Snellen lines. We compared the event rate curves in the three groups using the logrank test [13b].

Results

Local tumor regression was substantially more rapid and more complete in the patients treated by combined plaque-laser therapy than in those treated by either form of plaque radiotherapy alone. The time course of the changes in tumor thickness in the three groups is illustrated by a plot of the relative fractional thickness of the tumors over the first 12 months following therapy (Fig. 7). At 12 months after irradiation, the mean residual tumor thickness was 1.8 mm in the plaque-laser group versus 2.9 mm in the iodine-125 plaque alone group and 2.8 mm in the cobalt-60 plaque alone group. The differences in mean residual tumor thickness between the plaque-laser treated tumors and the tumors treated by either method of plaque alone at the 12-month follow-up visit are substantial (approximately 1 mm) and statistically significant ($P \approx 0.01$ for both comparisons, paired *t*-test).

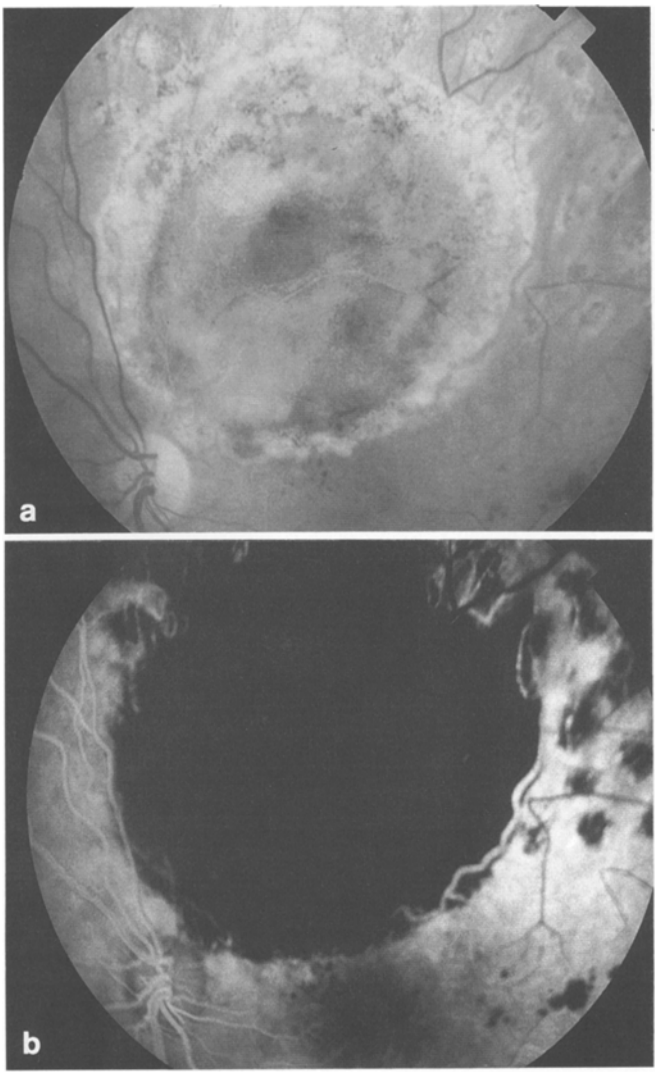

Fig. 4a, b. Combined plaque-laser therapy of choroidal melanoma. **a** Regressed tumor 12 months after irradiation and following two supplemental laser treatment sessions. Note multifocal atrophic retinal laser burn scars peripheral to regressed tumor. **b** Venous phase frame of fluorescein angiogram showing well-defined, virtually complete non-fluorescence of treated lesion and multifocal discrete hypofluorescent retinal laser burn scars peripherally

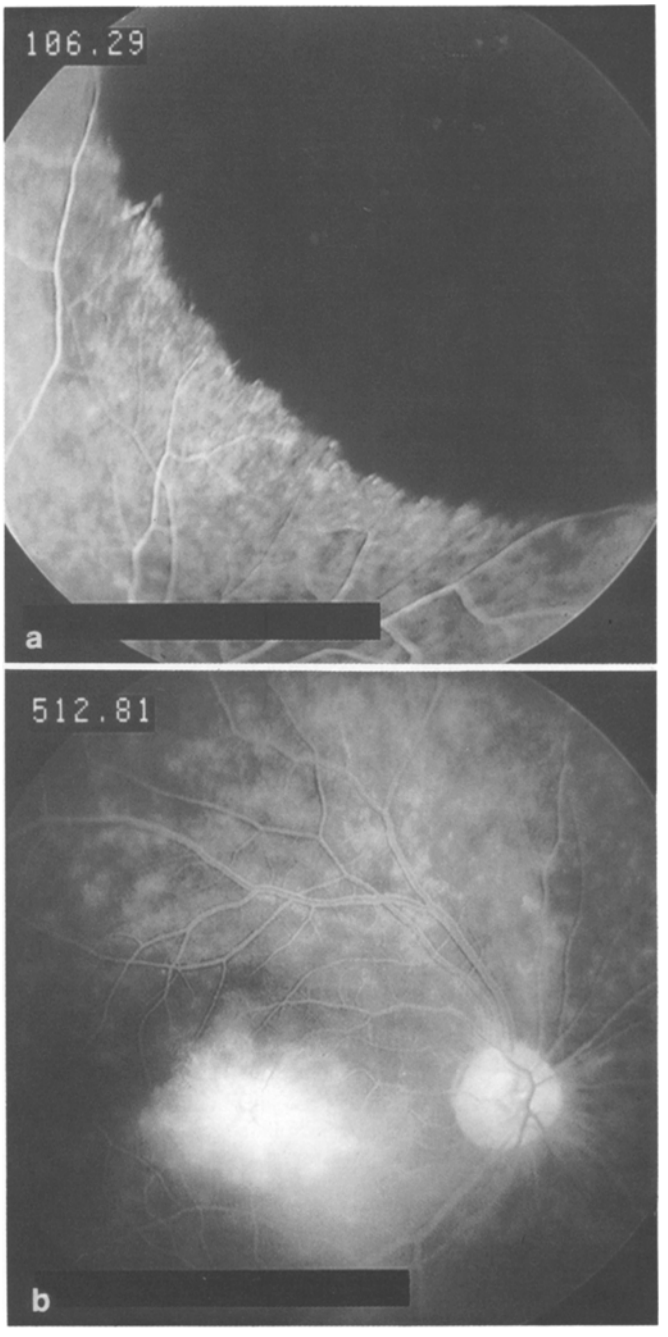

Fig. 5a, b. Fluorescein angiogram of choroidal melanoma 12 months after combined plaque-laser therapy. **a** Venous phase frame showing well-defined, completely non-fluorescent lesion in superonasal midzone. **b** Late phase frame showing pronounced cystoid macular edema

The visual loss rate was substantially higher in the combined plaque-laser group than in either of the plaque alone groups. The actuarial event rate curves for visual acuity loss to $\leq 20/200$ are shown for the three groups in Fig. 8. These curves reveal a 12-month cumulative actuarial probability of visual acuity loss to $\leq 20/200$ of approximately 0.36 in the plaque-laser group, 0.17 in the iodine-125 plaque alone group, and 0.04 in the cobalt-60 plaque group. The visual acuity loss curve of the plaque-laser group is significantly different from the curves of either of the plaque alone groups ($P < 0.01$ for both comparisons, logrank test). Comparative actuarial visual loss curves based on the alternative endpoint, visual acuity decrease of more than two Snellen lines, revealed similar results.

The major reasons for severe visual loss in the combined plaque-laser group were cystoid macular edema (which occurred to at least a mild degree in almost all eyes), vitreous hemorrhage (which occurred in seven eyes but was severe in only two eyes), subretinal neovascularization at the margin of the laser scar [which was suspected ophthalmoscopically (Fig. 9a) in six eyes but which was confirmed angiographically (Fig. 9b) in only two eyes], and increase in preexistent retinal detachment following laser treatment (which occurred in three eyes). In addition, one eye each suffered a transient corneal epithelial laser burn and subretinal fibrosis in the macula.

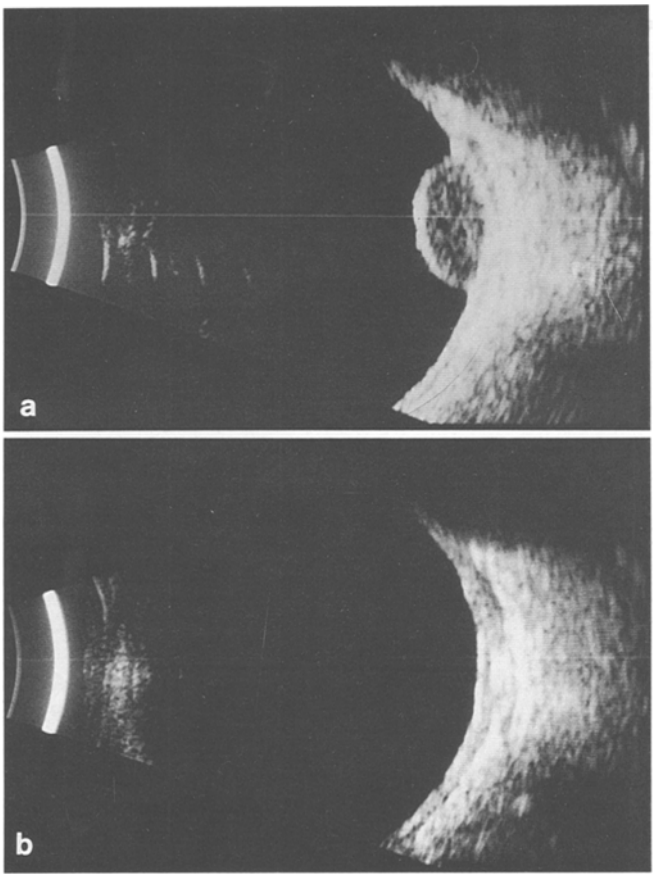

Fig. 6a, b. B-scan ultrasonography of choroidal melanoma treated by combined plaque-laser therapy (same case as shown in Fig. 2). **a** Pre-treatment cross-sectional appearance of nodular tumor. **b** Same location in fundus 18 months following start of treatment. No detectable tumor residue remains

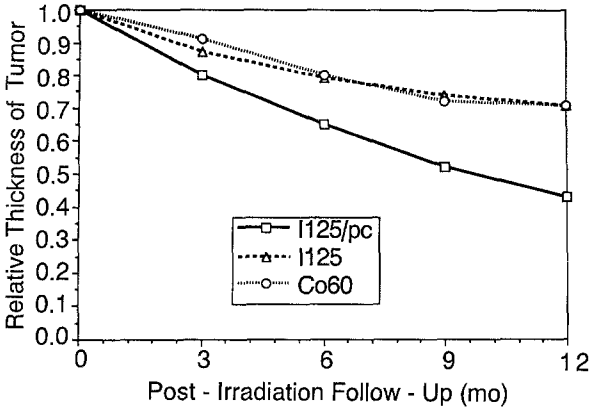

Fig. 7. Mean relative thickness of tumors in three matched groups over first 12 months after irradiation *I125/pc*, combined plaque-laser therapy group; *I125*, iodine-125 plaque radiotherapy alone; *Co60*, cobalt-60 plaque radiotherapy alone. Tumor shrinkage was substantially faster and greater during this interval in the combined plaque-laser group

One of the 24 patients in each of the two plaque alone groups had documented local tumor relapse during the first postirradiation year. In contrast, none of the patients in the combined plaque-laser group developed local tumor relapse during this time. Only one patient (in the iodine-125 plaque therapy alone group) died during the first postirradiation year, and the cause of death was a non-melanoma cancer.

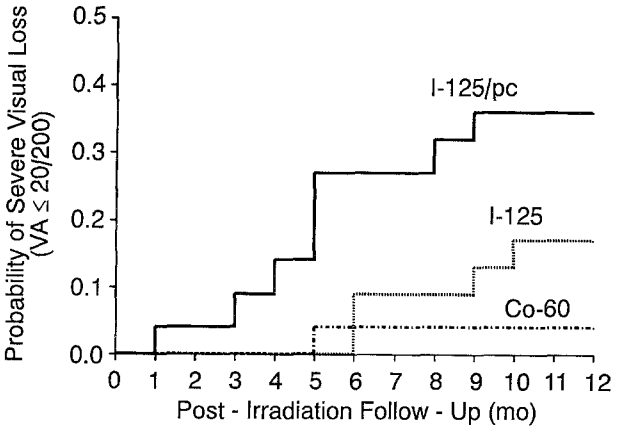

Fig. 8. Cumulative product-limit (Kaplan-Meier) event rate curves for visual acuity deteriation to ≤20/200 during the first year after irradiation in three matched groups. The rate of severe visual loss was substantially greater in the patients treated by combined plaque-laser therapy than in either of the plaque alone groups

Discussion

The results of this comparative local tumor regression study suggest that planned sequential iodine-125 plaque irradiation and indirect ophthalmoscope laser therapy produces faster and more complete local regression of choroidal malignant melanomas than does either iodine-125 or cobalt-60 plaque radiotherapy alone. However, the results also indicate that combined plaque-laser therapy causes more severe early visual loss than does either method of plaque radiotherapy alone.

Radiation therapy is believed to exert its effect on tumors by damaging nuclear DNA [12]. That damage manifests itself principally as a loss of the reproductive integrity of the irradiated cells. Clinically visible evidence of that damage usually does not appear until a substantial proportion of the cells die during attempted mitotic division. The larger the fraction of actively cycling cells in the tumor, the faster and more extensive the observed early postirradiation tumor regression tends to be.

Laser therapy of choroidal melanomas performed by the method described in this report is believed to exert its effect on tumors by two mechanisms [7]. First, the circumbasal laser treatment destroys the tumor's vascular supply and thereby promotes acute tumor necrosis. Second, the direct laser therapy to the tumor coagulates tumor cells by a photothermal mechanism.

When laser therapy follows tumor irradiation within a short time frame, as in the method of combined treatment described in this report, local tumor regression occurs in response to the effects of both therapeutic modalities. Thus, it is not surprising that the combined treatment produces more rapid and more complete local tumor response than does plaque radiotherapy alone.

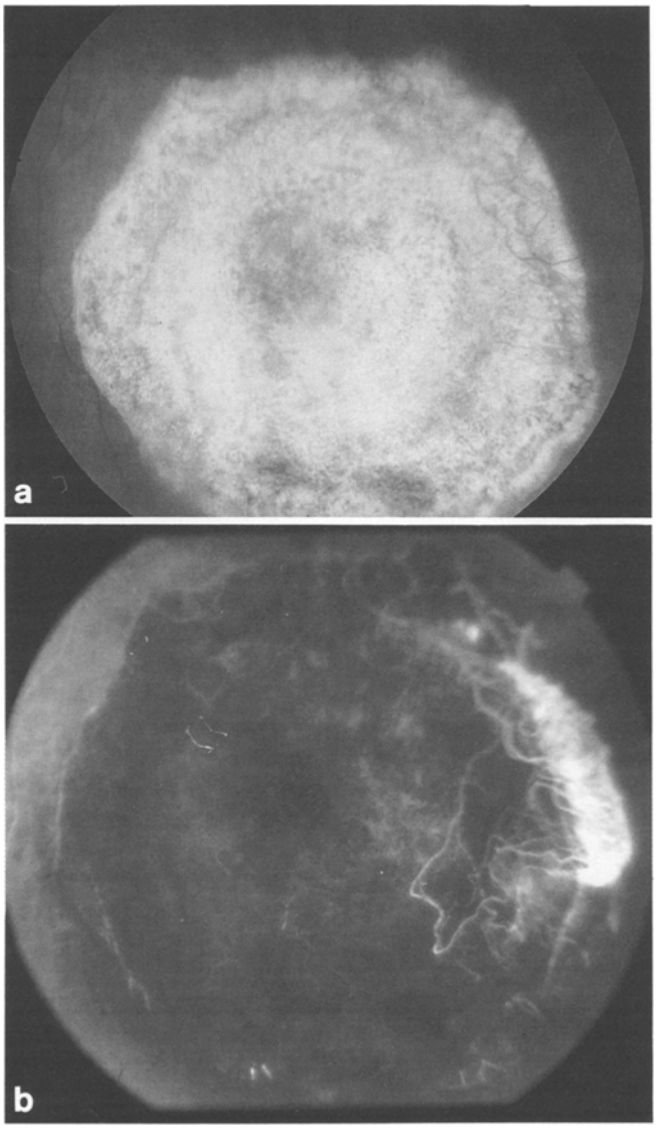

Fig. 9a, b. Neovascularization at margin of regressed choroidal melanoma following combined plaque-laser therapy. **a** Atrophic appearance of regressed tumor 12 months after initial treatment and following two laser treatment sessions. Note faint vascular network involving right-hand edge of post-treatment scar. **b** Early venous phase frame of fluorescein angiogram, showing well-defined, hyperfluorescent, neovascular network involving right-hand margin of treatment scar

One of the principal goals of combined plaque-laser therapy, as described in this report, is to reduce the frequency of local tumor relapse after plaque radiotherapy. Currently available evidence indicates that the local relapse rate among posterior uveal melanomas treated by episcleral plaque radiotherapy is in the range of 8–10% within 5 years [15, 18] and that the cumulative frequency continues to increase thereafter [16, 19]. Because combined plaque-laser therapy yields more complete local tumor regression than does plaque therapy alone, and because its local tumor effects include acute vasoobliterative and coagulative mechanisms that do not occur with plaque treatment alone, we expect that the frequency of local tumor relapse following our combined plaque-laser therapy will be reduced substantially (hopefully to the range of 2% or less at 5 years). However, only long-term follow-up will reveal whether this expectation is fulfilled.

Unfortunately, combined plaque-laser therapy is not without some important drawbacks. As revealed by our results, the short-term visual loss appears to be substantially greater in eyes treated by combined plaque-laser therapy than in eyes treated by plaque alone. The principal mechanisms responsible for severe early visual loss after combined plaque-laser therapy are cystoid macular edema (which occurs to some degree in virtually all eyes), macular distortion caused by laser-induced vitreoretinal shrinkage (which is observed in eyes with paramacular tumors), and macular chorioretinal destruction produced by the laser burn (which occurs in those eyes with a submacular tumor). Plaque radiotherapy by itself is associated with a high long-term rate of severe visual loss in eyes with posterior uveal melanoma [5, 6, 18], although, early severe visual loss (i.e. within 1 year following irradiation) is relatively uncommon. If one considers the excess severe visual loss that eventually occurs in eyes that develop post-irradiation local tumor relapse and then require additional treatment (typically enucleation, but occasionally a second irradiation), the long-term visual results of combined plaque-laser therapy may well be equivalent to, if not better than, those associated with plaque radiotherapy alone.

In several previous studies, rapid local tumor regression following tumor irradiation was shown to be an unfavorable prognostic factor for survival in posterior uveal melanoma [2, 9, 11]. As mentioned above, the early local tumor regression that occurs after combined plaque-laser therapy is at least in part due to vascular occlusive and coagulative effects of the laser treatment. These effects are probably independent of the underlying malignancy and reproductive integrity of the tumor cells. Moreover, the relative impacts of the two treatments cannot be determined clinically. Consequently, the rate and extent of post-treatment local tumor regression after combined plaque-laser therapy may not prove to be as useful for predicting outcome as they are following plaque radiotherapy alone.

There are a number of important questions about combined plaque-laser therapy of choroidal melanomas that cannot currently be answered. To what extent will this combined treatment really reduce the rate of local tumor relapse? Will the combined treatment improve the survival prognosis compared with that associated with plaque therapy alone? Will the observed improvement in local tumor destruction be worth the excess monetary and visual costs related to this therapy? Will some subgroups of patients with posterior uveal melanoma (e.g., ones with macular and juxtapapillary tumors) benefit more than others? Too few patients have been treated by this method to date, and follow-up on these patients has been too short, to allow any of these questions to be answered definitively.

Recognizing the serious limitations of our current experience in terms of number of patients treated and their length of follow-up, we make no strong recommendation for or against planned combined iodine-125

plaque radiotherapy and indirect ophthalmoscope laser therapy. However, based on our experience, we offer the following advice to those who might be inclined to used combined plaque-laser therapy in their patients with choroidal melanoma: (1) If combined plaque-laser therapy is to be performed, the radiotherapy should *always* precede the laser treatment; this recommendation is based on the well-known fact that hypoxic tumors are less sensitive to a given dose of irradiation than are well-oxygenated ones [20]. (2) If there is substantial subretinal fluid associated with the tumor at the time of plaque radiotherapy, most (if not all) of that fluid should be allowed to resorb prior to embarking on the course of laser treatment. (3) If laser treatment is performed as a supplement to plaque radiotherapy, low-power, continuous laser exposures should be used and intense, short-duration laser bursts avoided [7, 10]. The indirect ophthalmoscope laser appears to be well-suited for use in laser therapy of choroidal melanomas. It is relatively easy to use by any ophthalmologist experienced in binocular indirect ophthalmoscopy [8]; it can be used in both operating room and outpatient settings; it is applicable to the treatment of both posterior and peripheral choroidal tumors; and its optics permit satisfactory viewing of the tumor at all times during treatment, even when using the continuous exposure method.

In conclusion, combined iodine-125 plaque radiotherapy and indirect ophthalmoscope argon laser treatment appears to be a locally effective management method for selected patients with choroidal melanoma. This combined plaque-laser therapy appears to be more effective than plaque radiotherapy alone in terms of completeness of local tumor destruction and rapidity of local tumor regression. On the basis of this evidence, we believe that this combined approach warrants additional consideration as a management option for patients with posterior uveal melanoma.

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