LONG-TERM RISK OF LOCAL FAILURE AFTER PROTON THERAPY FOR CHOROIDAL/CILIARY BODY MELANOMA

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ABSTRACT

Purpose: To quantitate long-term risk of local treatment failure after proton irradiation of choroidal/ciliary body melanomas and to evaluate risk of metastasis-related deaths after local failure.

Methods: We followed prospectively 1,922 patients treated at the Harvard Cyclotron between January 1975 and December 1996 for local recurrences of their tumors. Mortality surveillance was completed through June 1999. For analysis, patient follow-up continued until tumor regrowth was detected or, in patients without recurrence, until the date of the last dilated examination prior to April 1998. Actuarial methods were used to calculate rates of recurrence and metastatic deaths. Cox regression models were constructed to evaluate risk factors for these outcomes.

Results: Median ocular follow-up after irradiation was 5.2 years. Local recurrence was documented in 45 patients by ultrasound and/or sequential fundus photographs; in 17 more patients, the eye was enucleated due to suspected but unconfirmed tumor growth. Recurrences were documented between 2 months and 11.3 years after irradiation. The 5- and 10-year rates of regrowth, including suspected cases, were 3.2% (95% confidence interval [CI], 2.5%-4.2%), and 4.3% (95% CI, 3.3%-5.6%). Among the 45 documented recurrences, about one half (21) occurred at the margin, presumably due to treatment planning errors. The remaining cases represented extrascleral extensions (nine cases), ring melanomas (six cases), or uncontrolled tumor (nine cases). Recurrence of the tumor was independently related to risk of tumor-related death.

Conclusion: These data, based on relatively long-term follow-up, demonstrate that excellent local control is maintained after proton therapy and that patients with recurrences experience poorer survival.

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INTRODUCTION

Uveal melanoma is the most common primary intraocular malignancy, with an annual incidence of six cases per million persons, or approximately 1,500 new diagnoses each year in the United States.[1] Over the past several decades, radiotherapy (external beam charged-particle therapy [eg, protons, helium ions] or episcleral plaque therapy) has replaced enucleation as the preferred treatment for most patients with this tumor. With radiotherapy, eye salvage is achieved, and particularly for cases in which the tumor is located away from the optic disc or macula, useful vision can be retained after treatment.[2-6] High rates of local control are also achieved, with 5-year control rates exceeding 95% in patients treated with charged particles.[7-9] Somewhat lower rates are reported for plaque therapy, ranging from 81% to 86%[10-13] in patients treated with cobalt 60 or iodine 125, now the most commonly used plaque. Survival rates do not appear to be compromised with conservative therapy when compared to enucleation.[14-17] However, some investigators have reported an increased risk of death from metastasis when the treatment has failed to control local tumor growth.[7,9,18,19] Previous studies evaluating local failure have been limited by small numbers and relatively short-term follow-up.

In this study, we evaluated local failure as an end point in a large series of uveal melanoma patients treated by proton irradiation, with long-term follow-up having accrued at the time of analysis. Identification of modifiable risk factors may reduce the rates of recurrence and lead to fewer complications, preservation of the eye, improved visual function and, potentially, better survival outcome.[20] Additionally, we evaluated local failure as a risk factor for metastatic death. Longer-term results may provide additional data that may aid in clarifying the association between local failure and metastatic risk.

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METHODS

We evaluated local control in a series of 1,922 patients with intraocular melanomas treated with proton therapy at the Harvard Cyclotron between 1975 and 1996 and followed prospectively through April 1998. Patients living outside the United States or Canada, patients with bilateral or iris melanomas, and patients diagnosed with metastasis at time of presentation were excluded from analysis. Additionally, patients who had received previous therapy for their tumor or adjuvant therapy after proton irradiation were excluded.

Tumor characteristics determined during the initial ophthalmologic examination included tumor size (based on indirect ophthalmoscopy, transillumination, and echography) and tumor location in relation to the optic disc, macula, equator, and ora serrata. Tumor shape and pigmentation also were estimated during the examination. Demographic and patient characteristics, including patient age, gender, and eye color, were recorded. Pretreatment workup, including liver function studies and chest x-rays, were routinely performed to rule out systemic metastasis. When liver function tests were abnormal, a liver scan was also performed.

Details concerning the treatment of intraocular melanomas at the Harvard Cyclotron Laboratory have been described previously.[21-23] Early in the program, doses as high as 100 Gy were administered in efforts to determine the optimal dose, while recently a lower dose of 50 Gy was administered to patients in a randomized clinical trial to establish safety and efficacy of a dose reduction.[24] The standard protocol requires delivery of 70 Gy in five equal fractions over 7 to 10 days. In this study most patients (94%) received the standard dose, while 5% received 50 Gy as participants in our dose reduction trial.

Ocular outcomes, including tumor regrowth, were ascertained through April 1998. The majority of patients returned to the Massachusetts Eye and Ear Infirmary (MEEI) for at least one follow-up examination after treatment. Mortality surveillance was current through June 1999. For patients not returning to MEEI, active surveillance was performed to ascertain outcomes data from referring ophthalmologists and vital status from ophthalmologists, internists, patients, or other sources (eg, the National Death Index) on an annual basis. Local recurrences were documented by ophthalmologic examination, ultrasonography, and/or sequential fundus photography for all patients evaluated at MEEI. Whenever possible, documentation of recurrences by ultrasonography and photography was also obtained from the referring ophthalmologists.

Patients were followed from completion of proton therapy to the date of diagnosis of recurrence or, in censored observations, until the date of the last dilated examination. For tumor-related mortality, patients were followed to the date of death or, for patients still alive, until the earlier of the date of last prior contact or June 30, 1999.

Using Kaplan-Meier methods,[25] we estimated annual incidence rates and cumulative rates at 5, 10, and 15 years after treatment, with corresponding 95% confidence intervals (CI). We calculated relative risk (RR) estimates using Cox proportional hazards regression[26] to determine statistically significant factors independently related to risk of tumor regrowth. Using a time-varying covariate approach, we compared risk of death from metastasis in patients with and without tumor regrowth.

SUBJECTS

Approximately equal numbers of males (49%) and females (51%) were treated. There was no predilection for either eye to be affected, with 50% of cases involving the right eye. As expected, this cohort was racially homogeneous, with the proportion of Caucasian subjects approaching 100%. Median age at time of treatment was 60 years. Mean tumor dimensions were 13 mm and 5.3 mm for diameter and height, respectively. Tumors were predominantly located in the posterior fundus, and about one quarter (26%) involved the ciliary body.

RESULTS

Tumor regrowth occurred in 62 patients, approximately 3% of the cohort. Of these, 45 were documented by ultrasonography and/or sequential fundus photography. A total of 17 cases were enucleated outside the Ocular Oncology Unit at MEEI. Of the confirmed cases, 27 eyes were enucleated. Median follow-up was 5.2 years. Time to recurrence ranged between 2 months and 11.3 years after proton irradiation. Of the 45 documented cases, close to half (47%) occurred at the tumor margin. The remaining cases included nine extrascleral extensions, six ring melanomas, and nine tumors exhibiting growth in all dimensions.

As shown in Table I, the highest rate of failure, 1.0%, was observed during the first year after therapy. Annual rates declined thereafter to less than 1% in subsequent years after therapy (Figure 1). Late recurrences were rare and occurred as long as 11 years after therapy. Cumulative rates of recurrence, illustrated in Table I and Figure 2, were likewise low. By 5 years after irradiation, approximately 3% of tumors had recurred. After 5 years, the cumulative rate increased little over time, with 10- and 15-year rates at 4% and 5%, respectively.

Statistically significant prognostic factors (Table II) identified in the univariate regression analysis were tumor diameter, tumor height, ciliary body involvement of the tumor, and tumor pigmentation. Factors of borderline significance included symptoms at presentation (P=.09)

TABLE I: ANNUAL AND CUMULATIVE RATES OF LOCAL FAILURE*

YEAR AFTER THERAPY	NO. AT RISK	NO. OF FAILURES	ANNUAL RATES (%)	CUMULATIVE RATES (%)	95% CI
1	1,917	19	1.02	1.02	0.65-1.60
2	1,791	16	0.95	1.96	1.41-2.72
3	1,563	8	0.55	2.50	1.86-3.36
4	1,333	6	0.48	2.97	2.24-3.92
5	1,172	3	0.28	3.24	2.47-4.24
6	975	6	0.67	3.88	2.99-5.03
7	822	0	0.00	3.88	2.99-5.03
8	690	1	0.16	4.03	3.10-5.23
9	578	0	0.00	4.03	3.10-5.23
10	477	1	0.23	4.25	3.25-5.55
11	386	1	0.29	4.53	3.43-5.98
12	299	1	0.38	4.90	3.64-6.57
13	221	0	0.00	4.90	3.64-6.57
14	148	0	0.00	4.90	3.64-6.57
15	95	0	0.00	4.90	3.64-6.57

CI, confidence interval.
*Includes documented and suspected cases.

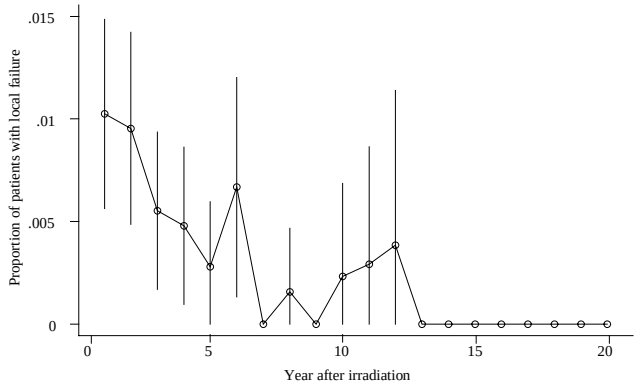

FIGURE 1
Annual rates of local failure after proton therapy, with 95% confidence intervals. Documented and suspected cases of recurrence are included.

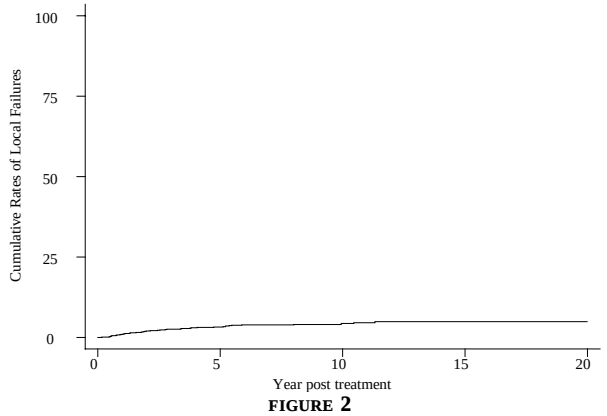

FIGURE 2
Cumulative rates of local failure after proton therapy. Documented and suspected cases of recurrence are included.

and presence or absence of extrascleral extension of the tumor (P=.06). Eye color, age at treatment, and male or female gender were not associated with local failure.

In a multivariate analysis, we selected variables that were statistically significant ($P \leq .05$) in univariate regression to enter in our model. These included tumor pigmentation, a composite tumor size variable (tumors >15 mm in diameter and >5 mm in height were defined as large), and ciliary body involvement, the strongest predictor of regrowth of the three variables. Tumor pigmentation was not independently associated with recurrence and was dropped from the model. Large tumors and tumors involving the ciliary body continued to be significant risk factors for recurrence in the multivariate analysis. Patients with large tumors had more than double the risk of recurrence of patients with smaller tumors (RR, 2.4; 95% CI, 1.4-4.1). Similarly, a patient's risk of treatment failure was more than doubled if the tumor involved the ciliary body rather than the choroid only (RR, 2.3; 95% CI, 1.3-4.1).

Patients experiencing tumor regrowth were at greater risk of death from metastasis. After adjustments for known risk factors for metastatic death (eg, tumor size, age, location of tumor), tumor growth was demonstrated to be highly predictive of metastatic death in a Cox regression model. The relative risk of metastasis-related death was 4.1 (95% CI, 2.6-6.6) for patients with documented growth as compared to patients who did not experience recurrence.

DISCUSSION

Results of this study confirm reports of our previous studies[7,27] and demonstrate that rates of regrowth decrease

TABLE II: UNIVARIATE ANALYSIS OF PROGNOSTIC FACTORS FOR LOCAL FAILURE*

RISK FACTOR	LEVEL	RR	95% CI	*P* VALUE
Age	1 yr	1.01	0.99-1.03	.34
Gender	Male vs female	0.93	0.57-1.54	.79
Largest tumor diameter	1 mm	1.16	1.09-1.23	.000
Tumor height	1 mm	1.18	1.09-1.28	.000
Ciliary body involvement	No vs yes	3.35	2.03-5.51	.000
Symptoms	No vs yes	1.32	0.96-1.81	.09
Extrascleral extension	No vs yes	2.60	0.94-7.17	.065
Tumor pigmentation	None/minimal	Ref†	. . .	. . .
	Moderate	2.88	0.82-10.11	.10
	Heavy	4.74	1.44-15.64	.01
Eye color	Brown	Ref†	. . .	. . .
	Green, hazel	1.36	0.63-2.94	.44
	Blue, gray	1.31	0.63-2.71	.47

CI, confidence interval; RR, relative risk.
*Includes documented and suspected cases.
†Referent.

with time after therapy for patients treated by protons for intraocular melanoma. Tumor recurrences may occur many years after therapy, but in this patient series none was observed after 12 years. Our findings are also consistent with reports of our group[19] and others,[28,29] identifying local recurrence after radiotherapy as a prognostic indicator for tumor-related survival.

We found that patients with ciliary body involvement and large tumors were at increased risk of local failure. One possible explanation for an increased risk of regrowth in tumors involving the ciliary body may be the increased likelihood of treatment planning errors, since visualization of the tumor margins by transillumination is more difficult when the ciliary body is involved. If this were the case, one would expect to find an overrepresentation of ciliary body tumors classified as marginal recurrences. Although over 50% of marginal recurrences involved the ciliary body, the majority of all other types of recurrences also involved the ciliary body (78%, 67%, and 44% for extrascleral extensions, ring melanomas, and uncontrolled tumors, respectively); this fact suggests that factors other than–or in addition to–inadequate radiation of the tumor are responsible for the tendency of ciliary body tumors to grow.

Studies by Folberg and colleagues[30,31] have demonstrated that tumor vascular networks are associated with an increased risk of metastasis and that these markers of a more aggressive tumor are found more often in ciliary body tumors.[32] It is possible that these vascular networks enhance the tumor's ability to regrow as well as to disseminate to other organs. Additionally, certain genetic aberrations–monosomy 3, losses of chromosome arms 6q and 1p, and additional copies of arm 8q–have been shown to be associated with metastatic uveal melanoma,[33,34] and alterations on chromosomes 3 and 8 in particular appear more commonly in ciliary body tumors.[33,35] Similar cytogenetic analyses have not been performed with samples from patients with tumor recurrences. These same mutations may be identified in association with regrowth if such analyses were to be completed.

Large tumors may be at increased risk of regrowth because they may be less radiosensitive than smaller tumors. This decrease in radiosensitivity may occur if tumor growth outpaces proliferation of tumor vasculature, thereby reducing its blood supply and the oxygenation that is necessary to optimize radiation effects.[36] Smaller tumors are less likely to be rendered radioresistant because they may have a more viable vasculature and thus the ability to reoxygenate. In this series, over half (56%) of the true in-field recurrences ("uncontrolled tumors" [ie, tumors with growth in height and diameter] and tumors developing extrascleral extension) occurred in larger tumors. Marginal recurrences were only somewhat less likely to involve tumors of this size (48%). In contrast, most patients with large tumors (94%) in this series did not experience local failure. This is not unexpected, given that these patients were treated with a total dose of 70 Gy in five fractions, one of the highest doses used in external beam irradiation for any malignancy.[37] It may be that only a small subset of these larger tumors is radioresistant, and it is these tumors that recur.

Patients with large tumors and tumors involving the ciliary body are at increased risk not only for tumor regrowth but also for metastasis, and this increased risk is independent of local failure status.[38-41] Further, local recurrence is an independent prognostic factor for metastasis-related death. This suggests that local recurrence and metastasis are not interdependent outcomes. We can speculate that underlying mechanisms, which optimize viability and proliferation of these tumors, may affect malignant potential at both local and distant sites. Underlying angiogenic mechanisms may play a role by controlling growth of the primary tumor as well as growth in metastatic foci.[42] Primary tumors may produce angiogenic factors that inhibit angiogenesis at distant sites.[43] In the case of enucleation, removal of the primary tumor may halt production of angiogenesis inhibitors, allowing metastasis to occur in the presence of local control. On the other hand, patients who experience local failure after radiotherapy harbor tumors that continue to proliferate, with a higher risk of dissemination of tumor cells to distant sites. This may explain why we continue to observe rates of metastasis-related death in patients treated by enucleation that are similar to those rates achieved with radiation,[14-17] and suggests that metastases may develop through several mechanisms. An alternative explanation may be that tumors that recur are highly malignant and have already developed preclinical metastases before any therapeutic intervention, irradiation, or enucleation.

CONCLUSIONS

These data demonstrate that excellent local control is achieved after proton irradiation of choroidal and ciliary body tumors. In this large series of patients with relatively long-term follow-up, annual and cumulative rates of regrowth were quite low, with most recurrences developing within a few years of treatment. The cumulative rate of recurrence was approximately 3% at 5 years postirradiation. This rate increased 1% between 5 and 10 years posttherapy and increased less than 1% after 10 years. Large tumors and tumors involving the ciliary body were independent predictors of regrowth, and regrowth was associated with poorer survival. It should be noted that because of the infrequency of this outcome, our findings might be due to chance, particularly with regard to multivariate analysis of risk factors. On the other hand, our results are consistent with those in previously published reports.[7,19,27-29]

Future refinements in treatment planning, dosing

regimen, and delivery may reduce the rate of local failure. Further exploration of underlying mechanisms of tumor cell growth is necessary to determine the pathophysiology of local failure. Elucidation of such mechanisms may lead to more effective interventions to arrest progression.

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DISCUSSION

DR JAMES J. AUGSBURGER. The paper you just heard was based on more cases and slightly longer follow-up than prior reports on the same patient group by the same principal author and his coworkers. It otherwise contains no pertinent new information and provides no new insights about local relapses following proton beam irradiation.

The authors show us that the highest annual incidence of local relapses after proton beam irradiation of choroidal and ciliary body melanomas occurs during the first post-irradiation year and that annual incidence then decreases progressively thereafter. They also show us (as they have shown before) that the cumulative actuarial incidence of local relapse after proton beam irradiation is quite low, only about 5% at 15 years. They point out, as they have also done before, that this cumulative actuarial incidence of local relapse after proton beam irradiation is substantially lower than that reported after plaque radiotherapy.

The authors show us that larger tumors and those involving the ciliary body are associated with higher rates of metastasis and metastatic death than are smaller tumors and those that do not involve the ciliary body. Many authors have reported these findings over the past half-century.

The authors show us that patients who experienced local relapse had higher rates of metastasis and metastatic death than did patients who did not experience local relapse. Several groups have also reported this result previously, including Dr Gragoudas's group, since Dr Ulf Karlsson and I first described this phenomenon in 1989. The authors state (but do not present sufficient information to allow readers to verify) that local relapse is a significant prognostic factor for subsequent metastasis and metastatic death even after controlling for tumor size and tumor location in the ciliary body. This result also confirms what others and I have reported previously.

The authors state that they employed a time-varying Cox proportional hazards modeling method to control (adjust) for important prognostic covariates in this study. However, they did not indicate specifically how they set up this analysis or how they evaluated local relapse as a time-varying variable in this study. I suspect that most persons in this audience do not care about this, do not understand why this might be important, or both. Because of this, I will not expand on this point except to call it to the attention of the authors.

None of the foregoing comments should be taken as personal criticism of Dr Gragoudas, his group, or their work. I have the utmost respect for Dr Gragoudas and the work he and his group have done over the years. I am honored to comment on their work.

DR EVANGELOS GRAGOUDAS. I appreciate the opportunity to respond to Dr Augsburger's comments regarding our paper entitled "Long-term Risk of Local Failure after Proton Therapy for Choroidal/Ciliary Body Melanoma." Dr Augsburger states in his discussion that these findings have been reported previously. However, most analyses in previous studies have been limited to small patient series, with actuarial rates beyond 5 years rarely reported. In this large series of 1,922 patients, we demonstrate low rates of recurrence at 10 years (4%) and 15 years (5%) posttherapy, providing evidence that refutes the theory that in these irradiated tumors reproductive activity has not been suppressed.[1]

As Dr Augsburger points out, there have been other studies indicating that ciliary body involvement and large tumors increase risk of metastasis and metastatic death. However, in our paper, we focused our analysis on the influence of local recurrence on metastatic death, while controlling for the already known risk factors. We described using a multivariate Cox regression model to calculate relative risk; we estimated a fourfold increase (RR=4.1, 95% CI, 2.6-6.6) in risk of metastasis-related death for patients with documented tumor recurrence as compared to patients without a recurrence. Further, we used a more accurate statistical approach, evaluating recurrence as a time-varying covariate in a Cox regression model. We have previously demonstrated the value of this approach in measuring relative risk, and interested parties who may want to understand more about this analytic method should refer to the publication by Egan et al.[2]

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