Survival Implications of Enucleation After Definitive Radiotherapy for Choroidal Melanoma

An Example of Regression on Time-Dependent Covariates

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Objective: To evaluate whether the removal of the eye after radiotherapy alters the rates of metastatic death in patients with melanoma of the choroid.

Patients and Methods: Using an extension of the Cox model, we based our analysis on a cohort of 1541 consecutive patients with unilateral choroidal or ciliary body melanoma treated with protons (70 cobalt-gray equivalent in 5 to 7 fractions) at the Harvard University (Boston, Mass) cyclotron between July 1, 1975, through December 31, 1993, and who were observed prospectively up to September 30, 1995. Patient survival and the status of the treated eye were updated annually.

Results: By September 1995 (median follow-up among survivors, 8 years), 137 patients underwent enucleation after radiotherapy for complications (n=103) or tumor regrowth (n=34). The overall 10-year rate of eye retention was 89% (95% confidence interval, 87%-91%). Of the 1541 patients, 300 died of tumor metastasis, 38 following enucleation of the affected eye (mean interval from enucleation to death, 25 months). The multivariate rate ratio for metastatic death associated with enucleation (modeled as a time-dependent covariate) was 0.9 (95% confidence interval, 0.6-1.4) for enucleation due to complications and 3.8 (95% confidence interval, 2.3-6.3) for enucleation associated with tumor regrowth.

Conclusions: In the absence of tumor viability, enucleation after primary irradiation for choroidal melanoma has no deleterious effect on patients’ survival. Enucleation concurrent with tumor regrowth is associated with high death rates; growth of the tumor in the eye may presage systemic recurrence and death from metastasis.


The prognostic influence of enucleation in the treatment of choroidal melanoma has long been debated.1-5 Zimmerman et al2 proposed that enucleation could be a causal factor in early metastasis based on their demonstration of a peak in the annual death rates 2 to 3 years after the surgery. As additional evidence, they cited the low prevalence of metastasis before any intervention is initiated and anecdotal reports of long-term survival in patients refusing treatment. The experimental work of Niederkorn6,7 provided additional support that enucleation through mechanical means could provoke the seeding of metastatic emboli into the circulation. Others8-9 suggested, however, that the patterns noted by Zimmerman et al reflect the natural history and growth kinetics of the tumor.8-9 By this view, the onset of symptoms triggered by the growth of the tumor coincides with its metastasis from the eye, which explains the temporal association of diagnosis and enucleation with death from the tumor. Support for this alternative view is the transient rise in tumor mortality in other primary tumors regardless of treatment.9 Also, similar survival patterns have been noted in patients with choroidal melanomas treated by irradiation.10

We examined the prognostic influence of enucleation in patients for whom radiotherapy has failed. The analysis was based on a large series of patients treated initially for choroidal melanoma with proton irradiation, a proportion of whom at varying intervals had enucleation for complications or regrowth of the tumor.11 We hypothesized that enucleation should pose no additional hazard for metastasis or provide any net benefit if the tumor has been destroyed by irradiation. Reciprocally, locorecurrence, valid evidence of active tumor, should increase death rates. To model the effect of the surgery on survival, we demonstrate the specialized procedures needed for modeling “time-dependent” prognostic indicators whose status may change after the start of follow-up.
PATIENTS AND METHODS

PATIENTS

From a total cohort of 1864 patients with eye melanoma treated with protons at the Harvard University (Boston, Mass) cyclotron through December 1993, 1533 patients were eligible for this analysis. Exclusions included patients who had bilateral melanoma (n=8), iris-only tumors (n=5), residency in other countries (n=133), any prior treatment of the tumor (n=44), and treatment with a nonstandard proton dose (eg, more or less than 70 cobalt-gray equivalent) (n=121). Details concerning the treatment of intraocular melanomas at the Harvard University facility have been described elsewhere.12,13 A primary aim of the study was to evaluate the possible effect of cause-specific enucleation on tumor mortality. Therefore, we excluded from analysis 2 patients in whom metastasis was diagnosed concurrent with tumor regrowth and 1 patient whose eye was removed after the diagnosis of metastasis. Because nearly all patients with local recurrence were treated by enucleation, we further excluded the few patients with recurrences re-treated successfully by proton irradiation (n=2) or photocoagulation (n=7). The remaining 1541 patients were included in the analysis.

Information collected at baseline on these patients has been described elsewhere.14 In brief, the initial size of the tumor was estimated on the basis of indirect ophthalmoscopy, transillumination, and echography. The tumor's location in relation to the optic disc, macula, equator, and ora serrata also was determined. Demographic information, including age and sex, was available for all patients.

Patients were observed to September 30, 1995. Many patients returned to the Massachusetts Eye and Ear Infirmary (Boston) at regular intervals after irradiation for ocular tumor extension. In the event of a death or the diagnosis of metastasis, medical documentation, including biopsy and autopsy reports, the results of chest x-ray films and computed tomographic scans, discharge summaries, and death certificates, was sought. By September 1993, 484 deaths were documented, 300 due to metastatic melanoma; 14 patients were alive with metastatic disease. Medical documentation for the cause of death was available for 92% of deaths overall (96% for deaths from metastasis). The remaining deaths were classified on the basis of information from the next of kin. The median follow-up among 1057 surviving patients was 8 years (range, 6 months to 18.3 years). The median interval since the last patient contact (before September 30, 1995) was 1 month.

STATISTICAL ANALYSIS

The end points in this analysis were death due to metastatic melanoma and enucleation of the eye. Cumulative proportions of patients with either outcome were calculated using the Kaplan-Meier method.15 The influence of enucleation on prognosis was evaluated using the Cox proportional hazards model,16 treating enucleation as a “time-varying” covariate.17 Models also were fitted that considered enucleation as “time invariant” (ie, fixed at the start of follow-up) to demonstrate how using an inappropriate model may lead to “length bias” in rate ratio estimates. All models were adjusted for established prognostic factors for metastasis in these patients,18 including the largest tumor diameter (in contact with the sclera) and tumor height (as measured by ultrasonography), patient age, location of the anterior tumor margin (ciliary body or anterior or posterior to the equator), and presence or absence of extraocular tumor extension.

RESULTS

All-cause survival rates at 5 and 10 years in this series were 78% and 63%, respectively. The probabilities of death due to metastasis and enucleation by year after radiotherapy are presented in Table 1. Of the 1541 patients, 300 (19.5%) died of metastatic melanoma, and 14 more were alive with metastasis by September 30, 1995. Overall, 75% survived without metastasis for a minimum of 10 years (95% confidence interval, 73%-78%). Enucleation was performed on 137 patients (8.9%) after proton irradiation, for documented or suspected tumor regrowth (n=34), neovascular glaucoma (n=78), or another primary cause (n=23), including blind, painful eye, or another complication. Eighty-nine percent of patients retained the affected eye 10 years after irradiation. Most enucleations (65%) were performed during the first 3 years after irradiation (range, 6 weeks to 14 years).

Table 2 shows the results of Cox regressions when potential baseline prognostic factors for melanoma-related death and enucleation were examined. Melanoma-related death rates increased with patient’s age and tumor diameter, independent of other correlated factors. Tumor height was weakly and inconsistently related to survival after adjusting for tumor diameter and other covariates (P for trend=.72). Other statistically significant predictors of survival were the location of the anterior tumor margin with respect to the equator and the presence or absence of extraocular extension. The risk of enucleation was positively associated with increased tumor height and posterior tumor location.

Patients were observed an average of 3.8 years after enucleation (range, 1 month to 14.4 years). Thirty-eight patients died of metastatic disease following enucleation: 16 (42%) had undergone enucleation for tumor regrowth, 18 (47%) for neovascular glaucoma, and the remaining 4 (10%) for other reasons. The median interval between enucleation and death from metastasis was 24 months (range, 9.6 months to 5.6 years) in the patients with recurrent tumors and 35 months (range, 1.8 months to 7.8 years) in the patients with controlled tumors.

Table 3 shows the rate ratios of melanoma-related death for enucleation under different model assumptions. Using the “naive” approach in which enucleation was modeled as a baseline covariate, tumor recurrence modestly increased the rate ratio for death from metastasis (by 80%), whereas enucleation for reasons other than tumor regrowth was associated with a significant 40% reduction in metastatic death rates. Modeled ap-
propiately as a time-varying covariate, however, the inverse association for enucleation or other causes was greatly attenuated and no longer statistically significant (rate ratio, 0.9; \( P = .65 \)). Enucleation for recurrence in this model emerged as a strong and significant prognostic factor for melanoma-related death: the rate ratio of 3.8 (95% confidence interval, 2.3-6.3) indicates nearly a 4-fold elevation in death rates among patients with tumors not controlled by radiotherapy.

We assessed the effect of enucleation on survival with choroidal melanoma when the surgery follows a definitive course of irradiation. Patients who had enucleation for rubeosis and other complications of irradiation without evidence of tumor growth had rates of metastasis similar to those of patients retaining the eye, the predicted association being manifest.20 In theory, systemic promoters of angiogenesis dictates the rate of growth in the primary tumor and whether dormant metastases will eventually become manifest.20 It has been proposed that the balance of negative and positive regulators of angiogenesis dictates the rate of growth in the primary tumor and whether dormant metastases will eventually become manifest.20 In theory, systemic promoters of angiogenesis could promote growth simultaneously at metastatic sites and in viable primary cells, explaining the close temporal association of local recurrence with death from metastasis in many of these patients.

A possible implication of our data is that the growth of the tumor in the eye may prestage the outgrowth of cells in metastatic foci. In patients with locally recurrent tumors, the average interval from enucleation to death was less than 24 months, whereas recurrences were sometimes diagnosed years after primary irradiation (average interval between irradiation and enucleation for recurrence, 36 months; range, 2 months to 11.1 years). In 2 patients (not included in the analysis), the growth of the tumor in the eye was diagnosed simultaneously with liver metastasis. These results are interesting in light of the emerging view that the growth of metastases may be controlled by angiogenic mechanisms.20 It has been proposed that the balance of negative and positive regulators of angiogenesis dictates the rate of growth in the primary tumor and whether dormant metastases will eventually become manifest.20 In theory, systemic promoters of angiogenesis could promote growth simultaneously at metastatic sites and in viable primary cells, explaining the close temporal association of local recurrence with death from metastasis in many of these patients.

Because of the limited number, we could not formally address the question of whether the removal of the eye itself contributed to the high death rates in patients treated with enucleation because of radiotherapy failure. Local failures are uncommon after proton irradiation: the 5-year rate is less than 3%.21 Some arise because of incomplete coverage of the tumor with a full radiation field (mar- ginal miss or “ring melanoma”), whereas a small number appear to be resistant to treatment at conventional doses. The class of tumors most likely to recur is not well-defined; in an earlier analysis,21 large tumor size, ciliary body location, and male sex were associated factors. In this series, most patients with recurrence were treated by enucleation. Of the 9 cases re-treated successfully by a second course of irradiation or by photocoagulation, 4 died of metastatic melanoma compared with 16 of the 34 patients who underwent enucleation after tumor regrowth.

### Table 1. Probability of Death Due to Metastasis and Enucleation by Year After Treatment Among Patients With Choroidal or Ciliary Body Melanomas Treated With Proton Beam Irradiation, 1975 to 1993

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<th>Censored, No.‡</th>
<th>Patients Surviving</th>
<th>% 95% CI</th>
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*CI indicates confidence interval.
†The number of patients dying of metastasis and those undergoing enucleation < 10 years after proton irradiation sum to 294 and 131, respectively. Several patients died of metastasis (n=6) or underwent enucleation (n=6) > 10 years after irradiation.
‡For metastasis, this is the number of patients alive and not observed to the end of the specified interval plus those who died of another cause within the interval; for enucleation, this is the number of patients alive and not observed to the end of the specified interval.
Treatment was more likely to be attempted and to be successful when the lesion was small and posterior. A further limitation of these data was the lack of information on histopathologic features associated with survival in this disease. The cellular type and vascular architecture are each associated independently with the probability for metastasis and could have confounded results if baseline distributions of these factors varied by enucleation status.

In summary, our results provide reassurance that enucleation poses no hazard for metastasis among patients in whom local control has been achieved. Likewise, there is no evidence for a survival advantage associated with the removal of the eye in these patients. Local recurrence is uncommon after charged-particle irradiation, but it is more common after brachytherapy in posterior tumors. These data underscore the importance of attaining local control in irradiated tumors, without which a patient may be at substantial risk for local failure and death from metastasis.

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Presymptomatic Hypertension Is a Major Feature in the Diagnosis of Progressive Supranuclear Palsy
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Objective: To examine the history of hypertension (HT) in patients with parkinsonism (PS) of various causes.

Patients: Nine hundred twenty-three patients with PS listed in a citywide movement disorders registry. Hypertension was defined as blood pressure above 150/90 mm Hg on at least 2 occasions or a history of antihypertensive medication use.

Results: Overall, 184 patients (20.6%) had a history of HT. Fifty-three (16.6%) of 320 patients with levodopa-responsive parkinsonism (PD) had a history of HT; similar prevalence of presymptomatic HT was seen for PS and dementia (22/165 [13.3%]), including probable diffuse Lewy body disease and multiple system atrophy of the nigrostriatal degenerative type (33/171 [19.3%]), olivopontocerebellar atrophy (7/40 [18%]), corticobasal ganglionic degeneration (5/15 [33.3%]), drug-induced PS (9/38 [23.1%]), and the predominantly tremulous forms of Parkinson disease (17/43 [39.5%]) showed a higher prevalence of HT. Patients with familial PS (n=36), early-onset PD (n=14), multiple system atrophy of the Shy-Drager type (n=11), and postencephalitic PS (n=6) had no history of HT. In 100 patients with PS of various rare etiologies, a history of HT was seen in less than 5%. The highest prevalence of HT was seen in patients with clinically diagnosed progressive supranuclear palsy (n=42), of whom 34 (81.0%) had a history of HT.

Conclusions: A presymptomatic history of HT is a major feature in the clinical history of progressive supranuclear palsy and may be a diagnostic criterion. Its significance is unknown, but adrenergic nuclei of the brainstem are severely affected, and HT may be the first symptom arising from involvement of these nuclei. This could also explain the features of small vessel disease seen on computed tomography or magnetic resonance imaging in 50% of our patients, as in previous reports.

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