Long-term Risk of Melanoma-Related Mortality for Patients With Uveal Melanoma Treated With Proton Beam Therapy

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**IMPORTANCE** Little is known about the long-term risk of dying of uveal melanoma after treatment with radiotherapy.

**OBJECTIVE** To determine the long-term risk of dying of this disease, we evaluated melanoma-related mortality rates up to 25 years after proton beam therapy in a large series of patients with uveal melanoma.

**DESIGN, SETTING, AND PARTICIPANTS** In this analysis, we included 3088 patients with uveal melanoma, identified from a hospital-based cohort and treated with proton irradiation between January 1975 and December 2005. Vital status and cause of death were ascertained through active follow-up and searches of government databases (the Social Security Death Index and the National Death Index) through December 31, 2008. Cumulative rates of melanoma-related mortality were calculated using the Kaplan-Meier method. Patient and tumor characteristics of known prognostic significance for melanoma-associated death were evaluated, including patient age and tumor dimensions.

**MAIN OUTCOMES AND MEASURES** The primary outcome measure was cumulative rates of melanoma-specific mortality, and secondary measures included annual melanoma-specific mortality hazard rates and cumulative all-cause mortality rates.

**RESULTS** Of 1490 deceased patients, 620 (41.6%) died of ocular melanoma. In addition, 19 patients were alive, but their melanoma metastasized, by the end of the observation period (mean follow-up after diagnosis of metastasis, 5.3 years). All-cause mortality rates in this cohort were 49.0% (95% CI, 47.0-51.1) at 15 years, 58.6% (95% CI, 56.4%-60.8%) at 20 years, and 66.8% (95% CI, 64.2%-69.4%) at 25 years. Melanoma-related mortality rates were 24.6% (95% CI, 22.8-26.4) at 15 years after treatment, 25.8% (95% CI, 24.0-27.8) at 20 years after treatment, and 26.4% (95% CI, 24.5-28.5) at 25 years after treatment. The 20-year mortality rate was 8.6% (95% CI, 6.2-11.9) for younger patients (<60 years) with small tumors (<11 mm) and 40.1% (95% CI, 36.1-44.3) for older patients (>60 years) with large tumors (>11 mm).

**CONCLUSIONS AND RELEVANCE** In this large series of patients with ocular melanoma treated conservatively with proton beam irradiation, the cumulative melanoma-related mortality rates continued to increase up to 23 years after treatment. Annual rates decreased considerably (to <1%) 14 years after treatment. Information regarding the long-term risk of dying of uveal melanoma may be useful to clinicians when counseling patients.
Published data on survival after enucleation indicate that the long-term risk of dying of uveal melanoma continues many years after diagnosis and treatment. In one study, metastasis was detected 23 years after diagnosis, and in another study, 34 years after diagnosis. In both studies, the 25-year mortality rate for patients with uveal melanoma was 50% or more.

It has now been more than 30 years since radiotherapy was established as a standard of care for uveal melanoma, yet little is known about the long-term risk of melanoma-related death for patients treated with proton beam irradiation of their tumors. Twelve-year melanoma-related mortality rates have been presented from the Collaborative Ocular Melanoma Study, with similar rates observed between patients who were randomly assigned to receive plaque radiotherapy with iodine 125 and those who were randomly assigned to receive enucleation. Gragoudas et al calculated rates of several patient outcomes after proton beam irradiation using risk scores based on Cox regression models; 15 years after treatment, melanoma-related mortality rates of more than 50% were only observed among patients with the highest-risk scores.

In 1975, the first patient was treated with proton beam radiotherapy for uveal melanoma at the Massachusetts Eye and Ear Infirmary (MEEI) in Boston, and since then, more than 4000 patients have been treated. The majority of these patients are monitored throughout their lives as part of a Uveal Melanoma Registry established at the MEEI in the 1980s. As a result, mature data are now available from the registry allowing for evaluation of mortality rates up to 25 years after treatment in a large series of patients to determine whether rates are similar to those observed after enucleation or whether late-occurring differences emerge. We also evaluated known prognostic factors for melanoma-related deaths to explore whether the magnitude of effect for these factors varies over time.

Methods

Patients (N = 3088) with choroidal and ciliary body tumors who were subsequently treated with proton beam therapy between January 1975 and December 2005, and followed through December 31, 2008, were included in our analysis (see Table for baseline demographics and tumor characteristics). Patients who were not residents of the United States were excluded from analyses. The median follow-up time was 12.3 years (mean follow-up time, 13.4 years; shortest follow-up time, 1.0 year; longest follow-up time, 33.5 years).

Screening for metastasis, performed at the baseline evaluation, includes a physical examination, radiography, and liver function tests. If abnormalities are found, imaging studies (computed tomography, magnetic resonance imaging, or ultrasonography) are completed to further evaluate the patient’s condition. A liver biopsy may be performed if the results of the imaging studies are abnormal. Liver function tests are performed every 6 months for 5 years and annually thereafter. If abnormal results are found, imaging studies and biopsy are performed as indicated.

Vital status was ascertained using several methods, including active surveillance at the MEEI and/or use of online resources (namely, the Social Security Death Index, which is a free online service that uses data provided by the Social Security Administration). Data on cause of death were also obtained through active surveillance at the MEEI and by use of the National Death Index, a federal repository that receives data from death certificates provided by state bureaus. Approximately 6% (n = 180) of patients were lost to follow-up (date of last contact prior to censor date or unable to determine cause of death).

The Kaplan-Meier method was used to calculate cumulative rates of melanoma-related mortality, and annual rates were estimated using actuarial methods. Cox regression analysis was completed to assess prognostic factors for melanoma-related metastasis to determine if influence on risk changes over time.

The MEEI institutional review board reviewed and approved this minimal risk study, and a waiver of informed consent and Health Insurance Portability and Accountability Act authorization was granted.

Results

Overall, 1490 of 3088 patients (48.3%) died by the end of the observation period. Fifteen years after diagnosis and treatment, the cumulative all-cause mortality rate had reached

**Table. Demographic and Tumor Characteristics of 3088 Patients**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis, median (range), y</td>
<td>61.3 (10.3-94.2)</td>
</tr>
<tr>
<td>Male sex, No. (%)</td>
<td>1540 (49.9)</td>
</tr>
<tr>
<td>Tumor size,* No. (%)</td>
<td>Smal 964 (31.2)</td>
</tr>
<tr>
<td></td>
<td>Medium 1287 (41.7)</td>
</tr>
<tr>
<td></td>
<td>Large 835 (27.0)</td>
</tr>
<tr>
<td>Ciliary body involvement, No. (%)</td>
<td>823 (26.7)</td>
</tr>
</tbody>
</table>

* A small-size tumor has a height of 3 mm or less and a diameter of 5 to 16 mm. A medium-size tumor has a height of greater than 3 to 8 mm and a diameter of 16 mm or less. A large-size tumor has a height of greater than 8 mm or a diameter of greater than 16 mm. One patient did not have a tumor height measurement, and another patient did not have the diameter measurement.
Unadjusted cumulative rates of melanoma-related mortality increased very little between 15 and 25 years after proton beam irradiation, from 24.6% (95% CI, 22.8-26.4) to 26.4% (95% CI, 24.5-28.5) (Figure 1). Differences in 20-year melanoma-related mortality rates, adjusted for categories of prognostic factors that were previously evaluated by the Collaborative Ocular Melanoma Study investigators,6 were striking (Figure 2): 8.6% (95% CI, 6.2-11.9) of younger patients (<60 years) with small tumors (<11 mm) had died of uveal melanoma, whereas 40.1% (95% CI, 36.1-44.3) of older patients (>60 years) with large tumors (>11 mm) had died of uveal melanoma.

The highest annual rates of death from melanoma (approximately 3%-4%) were observed 3 to 6 years after proton beam irradiation. The peak rate was identified 3 years after diagnosis and treatment (3.9% [95% CI, 3.2-4.7]) and varied little through 6 years of follow-up (2.8% [95% CI, 2.2-3.6]). These rates decreased over time but did not drop below 1% until 14 years after treatment. Annual rates of melanoma-related mortality for patients with small tumors remained relatively stable at approximately 1% from 3 to 7 years after diagnosis and treatment (0.87% at 3 years to 0.93% at 7 years), and only the 5-year rate exceeded 1% (1.4% [95% CI, 0.8-2.3]). In contrast, patients with larger tumors experienced greater decreases over time; the 3-year annual rate was 5.9%, whereas the 6- and 10-year annual rates were 4.2% and 2.2%, respectively, suggesting that risk decreases over time (Figure 3). The median time from tumor diagnosis to death from metastasis was 4.8 years for patients 60 years of age or younger and 3.6 years for older patients (P < .001).

Multivariate Cox regression analysis, which included significant prognostic factors based on our previous analyses7 of outcomes after proton beam irradiation (including age at treatment, tumor pigmentation, symptoms at diagnosis, ciliary body involvement, extrascleral extension, and iris color) confirmed that the largest tumor diameter is the most important clinical predictor of melanoma-related mortality, with a 19% increase in risk associated with each 1-mm increase in size (relative risk [RR], 1.19 [95% CI, 1.16-1.23]; P < .001). The addition of tumor height to this model was not informative; height was not found to be a significant predictor of mortality in this cohort (RR, 0.99 [95% CI, 0.97-1.02]; P = .71).

To assess whether the magnitude of effect of risk factors changes over time, we developed 2 regression models defining our end point based on time of occurrence after tumor diagnosis. These analyses revealed that age at diagnosis/treatment is a strong predictor of melanoma-related mortality occurring within 3 years of diagnosis of choroidal melanoma (RR, 1.03 [95% CI, 1.02-1.04]; P < .001), but its association with deaths from melanoma that occur after 3 years is weaker (RR, 1.01 [95% CI, 1.002-1.02]; P = .01). The association between largest tumor diameter and melanoma-related mortality remains significant for both early- and late-occurring deaths: for melanoma-related deaths occurring within 3 years of primary diagnosis, the RR is 1.21 (95% CI, 1.15-1.27) (P < .001), and for melanoma-related deaths occurring after 3 years of the primary diagnosis, the RR is 1.21 (95% CI, 1.17-1.25) (P < .001).

Of the 1490 deceased patients, 620 (41.6%) died of melanoma-related metastasis. In addition, 19 patients were alive, but their melanoma had metastasized by the end of the observation period (the mean follow-up from diagnosis of metastasis to the end of observation was 5.3 years among these patients).
Discussion

The cumulative melanoma-related mortality rate is approaching 27% at 25 years after proton beam therapy and 50% at 25 years after enucleation. It is difficult to explain this strikingly large difference in very long-term mortality when reported rates at 5 or 10 years after enucleation or radiation are quite similar. One possible explanation is that more patients with certain characteristics that increase risk (eg, larger tumors) may have been treated with enucleation than with radiotherapy but the data are not available to evaluate this. A similar rate in the high-risk score group at MEEI supports this explanation, but it is unclear why these differences in mortality associated with uveal melanoma are not observed throughout the entire follow-up period. The 12-year rate of melanoma-related mortality among older patients (≥60 years) with large tumors (largest basal diameter ≥11 mm) treated by plaque radiotherapy in the Collaborative Ocular Melanoma Study was approximately 30%, consistent with our findings.

Both published studies of very long-term follow-up after enucleation included only patients with 20 years or 25 years of follow-up. In contrast, our analyses included all patients treated during a 30-year period. Although the mean follow-up was 12.3 years (interquartile range, 6.6-19.8 years) among living patients, including patients who were treated as recently as 3 years before the end of follow-up (censor date) may have skewed our results toward the observed lower rates of mortality from uveal melanoma. We therefore completed a subgroup analysis of our cohort, including only those individuals who could have had 20 years of follow-up (ie, the 1107 patients treated through December 1988). The 25-year melanoma-related mortality rate was 30.4% (95% CI, 27.6-33.5), somewhat higher than that of our larger cohort but lower than the rates reported after enucleation. Prognostic factors relating to tumor size in our subgroup analysis were similar to those reported by Kujala et al. Largest tumor diameter was significantly associated with melanoma-related mortality in all models, whereas tumor height was not significantly associated with risk in multivariate analysis.

There were several factors that we did not evaluate in our study. Specifically, radiation dose, tumor recurrence, and treatment for metastasis were not evaluated. Tumor recurrence is a well-established risk factor pondering poor prognosis. Our study was not designed to assess recurrences, so the effect that recurrences may have on the long-term mortality findings described here are unknown. However, tumor recurrences after proton beam therapy are quite low, and late-occurring recurrences are rare, suggesting that the effect of this outcome on long-term melanoma-related mortality is minimal.

Likewise, we feel it is unlikely that radiation dose effects melanoma-related mortality. Previous findings of a randomized clinical trial of standard dose (70 Gy) vs lower dose (50 Gy) proton irradiation did not reveal differences in metastasis or tumor regrowth between the 2 dose groups. In addition, the vast majority of patients in this cohort (86.9%) received the standard radiation dose.

Although we did not assess the effects of treatment for metastatic disease, the results of an earlier study by our group did not provide evidence that treatment for metastasis reduces melanoma-related mortality. There was no advantage to early treatment (ie, treatment that was initiated for patients who received a diagnosis before symptoms had developed [presumably “early” treatment] compared with patients who received a diagnosis and were treated after developing symptoms [“late” treatment]).

Underascertainment of patients who were alive with metastasis at the end of our study period is possible. However, we do not feel that the potential of underreporting this group has meaningful implications for the primary goal of our study, which was to determine the long-term risk of dying of uveal melanoma. Given the short survival time between metastasis diagnosis and death, it is likely that any cases of undetected incident metastasis were captured during the observation period as deaths from melanoma metastasis.

Of greater concern is underascertainment of the primary end point (ie, the incidence of melanoma-related mortality in our cohort). We prospectively followed up with patients after their entry into the Melanoma Registry for a number of outcomes that were captured at regular follow-up visits to monitor the tumor. When these active surveillance efforts were unsuccessful, we used a 2-step process to determine deaths and cause of death. The Social Security Death Index was used to determine deaths, matching the records in the Index by personal identifiers such as social security number, name, date of birth, and residence, or a combination of these. A list of the deceased patients identified in this way were then submitted to the National Death Index to determine cause of death. Although complete ascertainment using these indexes cannot be guaranteed, high rates of identification of decedents have been demonstrated, and comparisons of causes of death between the National Death Index and other sources reveal high rates of agreement.

Conclusions

Patients continue to be at risk of death from melanoma more than 20 years after treatment, with the last observed death in this series occurring over 22 years after irradiation. Annual rates of death from melanoma decrease after 6 years but remain 1% or greater until 14 years after irradiation. A total of 216 patients (7.0%) in our cohort died of uveal melanoma between 6 and 14 years after initial diagnosis and treatment, with an additional 18 deaths occurring after 14 years. Given this low risk of death, less frequent monitoring of patients 10 to 15 years after treatment may be appropriate. Patients are at greater risk of dying of nonmelanoma causes if they survive 10 years or more after the diagnosis and treatment of the tumor, with all-cause mortality increasing almost 10% during each 5-year interval. In contrast, melanoma-related rates increase approximately 1% during the same time periods. Nevertheless, it seems prudent to monitor patients for life because new treatments for metastatic melanoma continue to emerge and to be evaluated in clinical trials.
Mortality From Uveal Melanoma After Proton Irradiation

ARTICLE INFORMATION
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Drafting of the manuscript: Lane, Gragoudas. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: Lane. Obtained funding: Gragoudas. Administrative, technical, or material support: Gragoudas. Study supervision: Gragoudas.

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REFERENCES