Metastatic Melanoma Death Rates by Anatomic Site After Proton Beam Irradiation for Uveal Melanoma

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Background: Ciliary body location is an established prognostic factor for metastasis-related death from uveal melanoma. We evaluated alternative approaches for classifying this covariate when constructing predictive models of patient survival.

Methods and Design: The analyses were based on a consecutive series of 1848 primary choroidal and/or ciliary body melanoma patients treated with proton beam irradiation (70 cobalt gray equivalent in 5 fractions) at the Harvard Cyclotron Laboratory, Boston, Mass, between July 1975 and December 1995. For each patient, the anatomic site of the tumor was classified according to an estimate of the proportion of the tumor base lying anterior to the ora serrata. Using proportional hazards regression, we estimated relative risk ratios and death rates from melanoma metastasis according to the extent of ciliary body involvement. All estimates were adjusted for other established prognostic factors.

Results: Patients were followed up through April 30, 1998; none were lost to follow-up. Of 1848 patients analyzed, 378 died of melanoma metastasis. The median follow-up period among survivors was 9.5 years. Ciliary body origin (>/=50% of tumor base anterior to the ora serrata) was positively associated with tumor pigmentation (P<.001), tumor height (P<.001), and extraocular extension of the tumor (P<.001). Compared with tumors involving only the choroid, melanoma-associated death rates increased with the proportion of the tumor base lying within the ciliary body (P=.006); the multivariate-adjusted relative risk ratio for greater than 75% involvement was 2.30 (95% confidence interval [CI], 1.26-4.23). The covariate-adjusted 5-year death rates for ciliary body origin and choroidal origin were 15.9% (95% CI, 11.3%-21.2%) and 9.8% (95% CI, 8.3%-11.7%), respectively.

Conclusion: Patients with melanomas of presumed ciliary body origin seem to be subject to a higher risk of death resulting from melanoma metastasis.

Arch Ophthalmol. 2000;118:1066-1070

ANTEOR TUMOR location is an adverse prognostic factor for patient survival after treatment for intraocular melanoma.1-30 In past studies, tumor location has been classified according to the location of the most anterior margin,1-14 presence or absence of ciliary body involvement,15-20,21,22,23,24,25,26,27,28,29,30,31,32 anatomic location,33-35 or a combination of these.13,14,25,26 The location of the most anterior margin has generally been classified as iris, ciliary body, or anterior or posterior to the equator.

Recent cytogenetic and tumor vascular studies provided a biological explanation for the prognostic importance of tumor location. It has been shown that tumors involving the ciliary body have a predilection for 2 chromosomal abnormalities (monosomy 3 and multiple copies of 8q),18,33-39 that are associated with a poor prognosis.35-37 Tumors with ciliary body involvement also express vascular patterns17,28,40 that are correlated with decreased patient survival.17,27,28,31,40-43

If a single site of origin is assumed for ciliochoroidal tumors, the presumed anatomic site of origin determined by the proportion of the tumor base lying anterior to the ora serrata might better reflect a differential path of disease progression and clinical course of these tumors. In this article, we describe the importance of considering the extent of ciliary body involvement in prognostic models of metastasis-free survival in an analysis based on a large series of patients treated by proton beam irradiation.

RESULTS

There were no losses to follow-up. Of 1848 patients analyzed, 378 died of melanoma metastasis. The median follow-up among survivors was 9.5 years. The unadjusted
SUBJECTS AND METHODS

The subjects consisted of a consecutive series of 1848 patients treated with proton beam irradiation for uveal melanoma between 1975 and 1995. Patients were United States or Canadian citizens with unilateral tumors, having no evidence of metastasis at pretreatment examination. Irises-only melanomas were excluded from analysis. Most patients were treated with the standard therapeutic dose of 70 cobalt gray equivalents (CGE) (96.5%) (range, 54-100 CGE [3.5%]) at the Harvard Cyclotron Laboratory, Boston, Mass. All patients were treated by the same physician (E.S.G.) and were followed up annually through April 30, 1998. The study protocol was approved by the Massachusetts Eye and Ear Infirmary Human Studies Committee, and written informed consent was obtained from all patients.

In our analyses, tumor location was defined according to the extent of ciliary body involvement (Figure 1).44,45 Tumors were classified into 6 groups according to the location of the tumor with respect to the equator. Ciliary body–involved tumors were classified according to the proportion of the anteroposterior axis of the tumor base lying anterior to the ora serrata: (I) posterior to the equator, (II) anterior to the equator but posterior to the ora serrata, or (III) involving the ciliary body and anterior to the ora serrata by 1% to 25%, (IV) 26% to 50%, (V) 51% to 75%, or (VI) greater than 75% of the anteroposterior tumor diameter.

Margins and anteroposterior diameter were obtained from surgical reports. For tumors extending posterior to the equator, distances between the anterior margin and limbus, posterior margin to limbus, and anteroposterior axial diameter of the tumor (APD) were recorded at the time of surgical placement of tantalum rings used for tumor localization during proton treatments. For ciliary body tumors treated without prior surgical localization, these distances were estimated by transillumination of the eye during pretreatment simulation. In both cases, the proportion of the tumor base lying within the ciliary body was estimated as the ratio between the anteroposterior axial length of the tumor lying anterior to ora serrata (LAO) and the APD:

\[
\text{LCB} = \frac{\text{Patient's Eye Diameter}}{\text{APD}} \times \text{LCB of a Standard Eye (6.5 mm)}
\]

Ciliary body–only and iridociliary tumors were classified as having 100% of the tumor base lying within the ciliary body. For analysis purposes, a tumor was considered to have a ciliary body origin if more than 50% of its anteroposterior axis fell anterior to the ora serrata.

The end point in this study was death from melanoma metastasis after irradiation (documented by autopsy, biopsy, death certificates, or reported by physicians or next of kin). The prognostic value of anteroposterior tumor location was evaluated with multivariate Cox proportional hazards models46 and adjusted for established prognostic factors, ie, sex, age at treatment, time from first visit to treatment, iris color, symptoms at first visit, tumor basal area, presence or absence of extrascleral extension, and tumor pigmentation. Interaction terms were evaluated using the procedures outlined by Hosmer and Lemeshow.47 The proportional hazard assumption was examined via the Grambsch and Therneau48 procedure. The covariate-adjusted 5-, 10-, 15-, and 20-year death rates were computed using the modified risk score method,49 and associated 95% confidence intervals (CIs) were constructed using bootstrap methods.49 The baseline survivorship function was estimated for 60-year-old women with dark- or moderate-colored irises, no symptoms at first visit, and a time from first visit to treatment of 3 months, whose tumors had heavy tumor pigmentation, no extrascleral extension, and a tumor basal area of 125 mm².

Table 1 gives a comparison of patient and tumor characteristics according to presumed ciliary body origin (>50% of tumor base). Ciliary body origin was associated with greater tumor pigmentation (P < .01), female sex (P < .04), larger tumor height (P < .001), and extrascleral extension (P < .001).

Multivariate relative risk (RR) ratios for anterior location are given in Table 2. Compared with choroid-only tumors, the rate of metastatic death increased with the proportion of the tumor base lying within the ciliary body (PR = .006, based on 4 categories of >0% of tumor base lying anterior to the ora serrata); the RR ratios for 51% to 75% and greater than 75% were 1.62 (95% CI, 1.06-2.47) and 2.30 (95% CI, 1.26-4.23), respectively. The RR for tumors with 100% ciliary body involvement (ciliary body–only or iridociliary tumors; n = 31) was 3.61 (95% CI, 1.74-7.47). Patients with choroidal tumors having only peripheral involvement of the ciliary body (<50%) had no greater risk for metastatic death (P > .75) than patients with lesions confined to the posterior pole. The covariate-adjusted 5-, 10-, 15-, and 20-year death rates and associated 95% CIs for tumors with presumed ciliary body origin (n = 145) and choroidal origin (n = 1703) are listed in Table 3, and the covariate-adjusted cumulative failure function is shown in Figure 2. The relation of ciliary origin (>50% of the tumor base within the ciliary body) to melanoma-free survival was similar across categories of other prognostic factors (data not shown).

A comparison of 3 methods for classifying tumor location is given in Table 4. Most (77%) of 513 tumors with a margin anterior to the ora serrata likely arose from the choroid (eg, <50% of the tumor base resided in the ciliary body). The effect of such misclassification is bias to the null: the multivariate-adjusted RR ratios for any ciliary body involvement was only modestly and nonsignificantly elevated (RR, 1.16; 95% CI, 0.83-1.62).
In this article, we demonstrate that ciliochoroidal melanomas presumed to have arisen from the ciliary body exhibit more aggressive behavior (with respect to patient survival) than those arising from the choroid. Less quantitative approaches for classifying the anterior extent of the tumor will not adequately reflect this phenomenon, which in turn may lead to misclassification of prognosis. Based on these results, of 513 tumors involving the ciliary body to any extent, 368 (72%) with up to 50% of the tumor base anterior to the ora serrata carried no excess risk of metastatic death (RR, 0.93; 95% CI, 0.70-1.3) compared with tumors posterior to the equator (Table 2). The overall RR for any ciliary body involvement, without regard to extent, was only modestly and nonsignificantly elevated (RR, 1.16; 95% CI, 0.83-1.62). Increasing magnitude of excessive risk with the increasing proportion of the tumor base anterior to the ora serrata is consistent with progressively less misclassification of tumor origin and supports the inherently more aggressive clinical course of tumors originating in the ciliary body. Misclassification may have contributed to the null results in some previous studies\textsuperscript{31,32,50} that found no excess risk for ciliary body location. McLean et al\textsuperscript{6} noted the importance of the extent of ciliary body involvement. These authors reported that only tumors with angle or iris involvement had a significantly worse prognosis, which is consistent with our data showing a worsened prognosis confined to the most anterior tumors. Higher death rates specific to ciliary body origin are consistent with recent reports indicating that genetic defects in ciliary body tumors may be distinct from and carry a poorer prognosis than those giving rise to melanomas in the choroid.\textsuperscript{33,34,37,38,51,52} In addition, microvascular networks linked to poor patient survival\textsuperscript{17,28} tend to develop preferentially in the ciliary body relative to the choroid.\textsuperscript{17,20,60}

We excluded from analysis iris melanomas, which rarely if ever metastasize.\textsuperscript{53,55} However, it is possible that some of the most anterior tumors may have originated in the iris. The fact that the RR ratios for ciliary body–only melanoma (RR, 4.4; 95% CI, 1.6-12.2; n = 10) was substantially higher than the RR for iridociliary tumors (RR, 2.9; 95% CI, 1.1-8.1; n = 21) suggests that RR ratios for presumed ciliary body origin (>50% of the tumor base) were attenuated by the inclusion of some tumors with low malignant potential. Sensitivity analysis, performed

**Table 2. Adjusted Relative Risk Ratios for Metastatic Death by Presumed Anatomic Site of Tumor**

<table>
<thead>
<tr>
<th>Anatomic Site</th>
<th>No.</th>
<th>RR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Posterior to equator</td>
<td>897</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Anterior to equator with no ciliary involvement</td>
<td>438</td>
<td>1.11 (0.83-1.50)</td>
<td>.48</td>
</tr>
<tr>
<td>Anterior to equator with ciliary body involvement (%) of tumor base lying anterior to the ora serrata)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1%-25%</td>
<td>148</td>
<td>1.08 (0.73-1.60)</td>
<td>.70</td>
</tr>
<tr>
<td>26%-50%</td>
<td>220</td>
<td>0.89 (0.61-1.30)</td>
<td>.56</td>
</tr>
<tr>
<td>51%-75%</td>
<td>91</td>
<td>1.62 (1.06-2.47)</td>
<td>.03</td>
</tr>
<tr>
<td>≥76%</td>
<td>54</td>
<td>2.30 (1.26-4.23)</td>
<td>.01</td>
</tr>
</tbody>
</table>

*Test for trend (4 categories for >0% of tumor base lying anterior to ora serrata), P = .006. Ellipses indicate not applicable.
†Relative risk (RR) ratios adjusted for sex, age at treatment, time from first visit to treatment, iris color, symptoms at first visit, extraocular extension and tumor pigmentation, and tumor basal area. CI indicates confidence interval.
by varying reported cutoff points (25%, 50%, and 75%) from 1% to 5%, suggested that the reported estimates and trend of RR ratios for the 4 location categories were robust and not sensitive to slight changes in the cutoff points used.

In summary, our results confirm recent findings indicating an excess risk for metastatic death in patients with ciliary body tumors linked to specific chromosomal alterations and/or vascular patterns. Since tumor location and chromosome changes are intimately linked, tumor location as classified here may provide a useful surrogate when cytogenetic parameters are not available.

Accepted for publication February 12, 2000.

This study was supported by the Melanoma Research Fund and by the Retina Research Foundation, Houston, Tex.


Dr Gragoudas is a Research to Prevent Blindness Inc, New York, NY, senior scientific investigator.

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Table 3. Adjusted Metastatic Death 22p Rates and Their 95% Confidence Intervals (CIs)* by Presumed Anatomic Site of Tumor†

<table>
<thead>
<tr>
<th>No. of Years</th>
<th>Choroid</th>
<th>Ciliary Body</th>
</tr>
</thead>
<tbody>
<tr>
<td>After Treatment</td>
<td>Crude CI</td>
<td>Covariate-Adjusted CI</td>
</tr>
<tr>
<td>5</td>
<td>13.4 (12.3-15.8)</td>
<td>9.8 (8.3-11.7)</td>
</tr>
<tr>
<td>10</td>
<td>23.0 (20.7-25.4)</td>
<td>17.1 (14.5-19.9)</td>
</tr>
<tr>
<td>15</td>
<td>26.2 (23.8-29.0)</td>
<td>19.9 (16.8-23.1)</td>
</tr>
<tr>
<td>20</td>
<td>27.8 (24.9-32.1)</td>
<td>21.7 (17.6-27.4)</td>
</tr>
</tbody>
</table>

*Death rates were computed using modified risk scores method and adjusted for sex, age at treatment, time between first visit and treatment, iris color, symptoms at first visit, extrascleral extension, tumor pigmentation, and tumor basal area. The 95% CIs were constructed using bootstrap methods and were bias-corrected.
†Originating site of the tumor was defined as choroidal origin (<50% of tumor base lying anterior to ora serrata) and ciliary body origin (=50% of tumor base lying anterior to ora serrata). Ellipses indicate not applicable.

Figure 2. Covariate-adjusted metastatic death rates by anatomic site.

Table 4. Presumed Anatomic Site by Anterior Margin and Area of Involvement of Tumor*

<table>
<thead>
<tr>
<th>Tumor Base Lying Anterior to Ora Serrata, %</th>
<th>Site</th>
<th>0</th>
<th>1-25</th>
<th>26-50</th>
<th>51-75</th>
<th>&gt;75</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior margin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Choroid</td>
<td>1335</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>1335</td>
<td>1335</td>
</tr>
<tr>
<td>CB</td>
<td>.</td>
<td>.</td>
<td>148</td>
<td>57</td>
<td>22</td>
<td>436</td>
<td>.</td>
</tr>
<tr>
<td>Iris</td>
<td>.</td>
<td>.</td>
<td>11</td>
<td>34</td>
<td>32</td>
<td>.</td>
<td>77</td>
</tr>
<tr>
<td>Area of involvement</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Choroid only</td>
<td>1335</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>1335</td>
<td>1335</td>
</tr>
<tr>
<td>CB + Choroid</td>
<td>.</td>
<td>.</td>
<td>148</td>
<td>57</td>
<td>12</td>
<td>426</td>
<td>.</td>
</tr>
<tr>
<td>Iris + CB + Choroid</td>
<td>.</td>
<td>.</td>
<td>11</td>
<td>34</td>
<td>11</td>
<td>56</td>
<td>.</td>
</tr>
<tr>
<td>CB only</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>10</td>
<td>10</td>
<td>.</td>
</tr>
<tr>
<td>Iris + CB</td>
<td>.</td>
<td>.</td>
<td>11</td>
<td>1</td>
<td>1</td>
<td>21</td>
<td>.</td>
</tr>
<tr>
<td>Total</td>
<td>1335†</td>
<td>148</td>
<td>220</td>
<td>91</td>
<td>54</td>
<td>1848</td>
<td>.</td>
</tr>
</tbody>
</table>

*Ellipses indicate not applicable; CB, ciliary body.
†Tumors posterior to equator (n = 897) or anterior to equator with no involvement of ciliary body (n = 438).

REFERENCES


