Tumor Basal Area and Metastatic Death After Proton Beam Irradiation for Choroidal Melanoma

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Background: Tumor dimension is an established prognostic factor for metastasis-related death after radiotherapy for uveal melanoma.

Objective: To compare various methods of modeling the relationship between tumor dimension and metastatic death.

Patients and Methods: The analyses were based on a consecutive series of 1204 patients with primary choroidal melanoma treated with proton beam irradiation (70 cobalt-gray equivalent in 5 fractions) at the Harvard Cyclotron Laboratory, Boston, Mass, between January 1985 and December 1998. Largest basal diameter and largest perpendicular basal diameter were recorded at the time of surgical placement of tantalum rings used for tumor localization during proton treatment. The height of the tumor and the axial diameter of the eye were measured by ultrasonography prior to treatment. Using proportional hazards regression, we compared the prognostic influence of different indices of tumor size with estimated risk ratios and death rates according to tumor basal area and largest basal diameter. All estimates were adjusted for other established prognostic factors.

Results: Patients were followed up annually through June 30, 2000. Of the 1204 patients analyzed, 193 died of melanoma metastasis. The median follow-up among survivors was 7.9 years. The 5- and 10-year metastatic death rates were 12.8% and 20.7%, respectively. Among various approaches for modeling tumor dimension, the logarithm of tumor basal area had the highest log-likelihood and performed better than other approaches in 85% of the simulations. Based on this model, the covariate-adjusted rate ratio for any doubling in tumor basal area was 1.92 (95% confidence interval, 1.62-2.28).

Conclusion: Tumor basal area is a better prognostic indicator than largest tumor diameter and tumor volume in the prediction of metastatic death after proton beam irradiation for uveal melanoma.

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SEVERAL METHODS for modeling the relationship between patient survival time and tumor dimension in ocular melanoma have been proposed in the literature.[1-9] Although there is no consensus on the optimal approach, the linear form of the largest tumor diameter (LTD) in contact with the sclera has been most commonly adopted.[10-20] Both LTD and tumor volume are considered to be correlated with the time since tumor onset or with its aggressiveness and thus its metastatic potential. Compared with other solid tumors, choroidal tumors have only their base in contact with the ocular blood supply and thus, the ratio between the basal area in contact with surrounding tissues and tumor volume tends to be much smaller. Intuitively, an area measure would more adequately characterize a tumor's access to the vascular system (ie, for nutrient supply and dissemination via the bloodstream). Tumor basal area thus may provide better prediction of a patient's risk for metastatic death. In this article, we evaluate the prognostic value of tumor basal area and other indices of tumor size in a large series of patients treated for ocular melanoma with proton irradiation.

METHODS

Subjects in the analysis consisted of patients with primary choroidal melanoma treated with proton beam irradiation (70 cobalt-gray [7000 rad] equivalent in 5 fractions) at the Harvard Cyclotron Laboratory (Boston, Mass) between 1985 and 1998. All patients were US or Canadian residents under the care of a single ophthalmologist (E.S.G.). Of 1539 patients meeting these criteria, 1204 patients were included in the analysis following exclusions due to 1 or more of the following reasons: evidence of metastasis (n=6), signs of extrascleral extension (n=49), bilateral involvement (n=19), irregular topography (n=102),
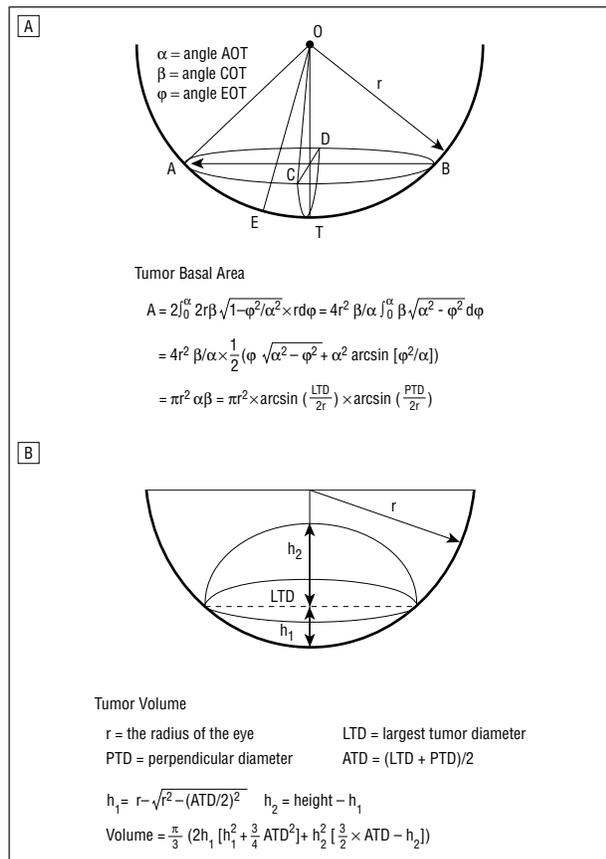
Figure 1. Calculations for tumor basal area and volume based on spherical segments.

lengths of the spheroid are determined by LTD, PTD, and height. Tumor volume may be approximated by

$$V = \frac{\pi}{3}\left(2h_1\left[h_1^2 + \frac{3}{4}ATD^2\right] + h_2^2\left[\frac{3}{2}\times ATD - h_2\right]\right)$$

where h_1 is the convex height, h_2 is the height elevated above the convex plane, and ATD is the arithmetic average of the LTD and PTD.[23] Derivations of these 2 formulas are shown in **Figure 1**.

The end point in this study was metastasis-related death. The prognostic value of alternative indices of tumor size were evaluated with the Cox proportional hazards models[24,25] and adjusted for established prognostic factors, ie, sex, age at treatment, symptoms at initial examination, tumor pigmentation, iris color, and time from initial examination to treatment.[21] Nonlinearity of the LTD and tumor basal area was investigated using multiple fractional polynomial regression and the partial likelihood ratio test.[26] The proportional hazard assumption was evaluated via the procedure by Grambsch and Therneau.[27] Model adequacy was examined using the May-Hosmer goodness of fit test.[28] Performance of the models was evaluated using log-likelihood criteria, ie, better fitting models achieve a higher likelihood.

However, when 2 models do not share any covariate or have the same number of covariates, partial likelihood ratio test cannot be used to evaluate whether the difference in log-likelihood between 2 models are statistically significant. Instead, we used a bootstrap method[29,30] to evaluate the variation of such a comparison in log-likelihood and to ensure that the differences in log-likelihood were not particular to this data. The bootstrap is a data-based simulation method for statistical inference. In each replication, we draw with replacement a sample of fixed size (n = 1204) from the total cohort, each constituting a bootstrap sample. We then fitted each candidate regression model with the bootstrap sample and identified the best performing model based on log-likelihood criteria (ie, the model with the maximum log-likelihood). We repeated this procedure 10 000 times and counted the number of times each candidate model performed the best.

Based on these models, we estimated regression coefficients and their SEs (**Table 1**). The hazard ratios and their 95% confidence intervals (CIs) were computed by $HR_i = \exp(\Delta \times \beta_i)$ and $\exp(\Delta_i \times [\beta_i \pm 1.96\ SE_i])$, where i equals 1, 2, . . . , and 6 indexes in each of the 6 models, Δ_i is the change in the i-th tumor indices, and β_i is the coefficient, with SE corresponding to the i-th tumor size index. For example, if tumor basal area changes from $100\ mm^2$ to $125\ mm^2$, based on model 1, the hazard ratio and its 95% CIs are estimated by $HR_1 = \exp([\log_2 (125) - \log_2 (100)] \times \beta_1)$ and $HR_1 = \exp([\log_2 (125) - \log_2 (100)]$

history of other treatment (n = 117), nonstandard dose (n = 105), or presumed ciliary body origin of the tumor (eg, >50% of LTD falling anterior to the limbus) (n = 103).[21] Patients were followed up annually for metastasis-free survival through June 30, 2000.

The LTD and the largest perpendicular tumor diameter (PTD) were recorded at the time of surgical placement of tantalum rings used for tumor localization during proton treatments. The height of the tumor and the anteroposterior axial length of the eye (APD) were measured by ultrasonography (A-scan) before proton beam irradiation.

The diameter of the choroidal sphere was estimated based on the APD as determined by ultrasonography. On average, the APD was 21.5 mm for male eyes and 21.3 mm for female eyes. The ratio of the average transverse and vertical diameter to the anteroposterior diameter is 0.9634 for male eyes and 0.9748 for female eyes.[22] The thickness of the sclera averages 0.5 mm across regions.[22] Therefore, the diameter of the choroidal sphere (D), adjusted for the scleral thickness, may be estimated as D = $(0.9634 \times APD) - (2 \times 0.5)$ for male eyes and D = $(0.9748 \times APD) - (2 \times 0.5)$ for female eyes.

Assuming isotropic growth of the tumor, the tumor basal area in contact with the sclera must be an ellipse on its equidistant projection plane. The axial length of the ellipse is equal to the projection length of the LTD and PTD on the plane, respectively. Thus, tumor basal area is estimated by the equation

$$\text{Area} = \pi r^2 \times \arcsin\left(\frac{LTD}{D}\right) \times \arcsin\left(\frac{PTD}{D}\right).^{23}$$

Similarly, a tumor may be seen as a part of a spheroid intersected by a sphere with a diameter equal to D. The semiaxial

Table 2. Summary Statistics of Tumor Size Indices

Indices	Mean (SD)	Median	Minimum	First Quartile	Third Quartile	Maximum
LTD, mm	12.7 (3.6)	12.0	6.0	10.0	16.0	22.0
PTD, mm	10.4 (3.2)	10.0	4.0	8.0	13.0	21.0
Height, mm	5.1 (2.8)	4.2	1.0	2.9	7.0	15.0
Basal area, mm^2	137.3 (98.0)	109.5	22.6	65.0	184.5	762.4
Tumor volume, mm^3	854.7 (988.3)	463.3	24.8	179.4	1188.2	7832.9
Uveal tract involvement, %*	9.40 (6.6)	7.5	1.6	4.4	12.6	38.8

Abbreviations: LTD, largest tumor diameter; PTD, perpendicular tumor diameter.
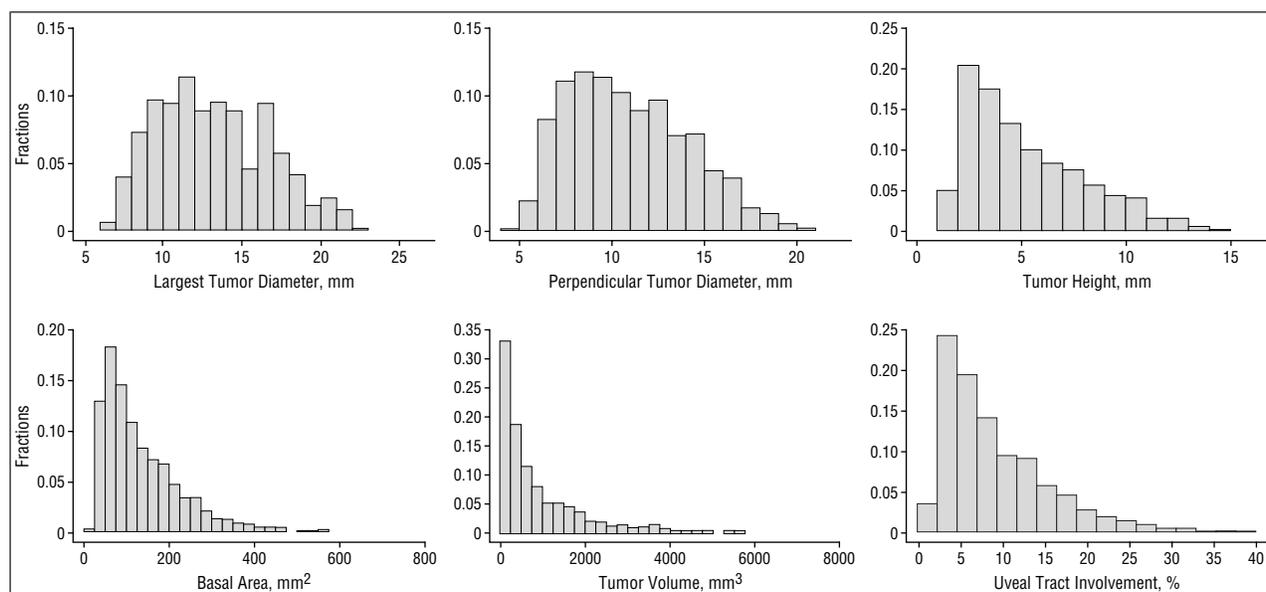*Ratio of tumor basal area to the total surface area of uveal tract (basal area–uveal tract area × 100%).

Figure 2. Distribution of tumor size indices.

$\times \beta_{1\pm}1.96 \times SE_1$), respectively. Based on model 4, the hazard ratio and its 95% CI are estimated by $HR_4 = \exp([125-100] \times \beta_4)$ and $\exp([125-100] \times [\beta_{4\pm}1.96 \times SE_4])$, respectively.

RESULTS

A total of 20 subjects were not followed up for 12 or more months preceding June 30, 2000. For these patients, we consulted the Social Security Death Index, and finding no matches, assumed the patients to be alive as of June 30, 2000. The vital statuses of the other 1184 patients are known through annual follow-up. In total, 363 patients died; among them, 193 died of melanoma metastasis, 161 died of another known cause, and 9 died of an unknown cause. The median follow-up among survivors was 7.9 years. The 5- and 10-year metastatic death rates were 12.8% and 20.7%, respectively. Summary statistics of LTD, tumor basal area, and tumor volume are presented in **Table 2**. The distributions of the indices are shown in **Figure 2**.

We evaluated several approaches for modeling tumor dimension, including the linear form of LTD, the logarithm of LTD, additive effects between LTD and PTD and tumor height, and linear and logarithm functions of tumor basal area and tumor volume. After including LTD in the model, adding both PTD and tumor height, or add-

ing either PTD or tumor height alone, did not significantly improve model performance (likelihood ratio tests: $P=.23$, $P=.40$, and $P=.10$, respectively), nor did the inclusion of a quadratic term of LTD (likelihood ratio test: $P=.58$). Among all possible power transforms of LTD, basal area, and volume, only the logarithmic transform of these 3 tumor size indices increased the log-likelihood significantly. **Table 3** presents a comparison of the performance of these models. Based on 10 000 bootstrap replications, the logarithm of tumor basal area outperformed the logarithm of LTD and that of tumor volume in 92% and 95% of the replications, respectively (Table 2).

The results further indicate that the relationship between tumor dimension and patient survival time is nonlinear (Table 3). The multivariate rate ratio for any doubling in tumor basal area, based on the model of the logarithmic transformation of tumor basal area, is 1.92 (95% CI, 1.62-2.28). Relative risk ratios for 25 mm^2 increased from basal area values of 25, 50, 100, 200, and 400 mm^2, are 1.62, 1.33, 1.17, 1.09, and 1.04, respectively (**Figure 3**). Likewise, based on the logarithmic LTD model, rate ratios for a 1-mm increase from an LTD value of 5, 10, 15, and 20 mm are 1.52, 1.25, 1.16, and 1.12 mm, respectively (**Figure 4**). Thus, as demonstrated, the magnitude of risk ratios for each unit increase

Table 3. Comparison of Methods for Modeling Tumor Dimension in Relation to Metastatic Death After Proton Beam Irradiation for Choroidal Melanomas*

| Method | Tumor Size Indices | Log-Likelihood | Pairwise Comparison† | | | | | % of Best Performances |
			2	3	4	5	6	
1	Log_2 (basal area)	−1191.6	92.9	95.1	98.1	93.2	99.9	84.60
2	Log_2 (LTD)	−1200.3	. . .	25.2	38.1	57.1	63.3	4.99
3	Log_2 (volume)	−1194.5	. . .	. . .	79.5	76.0	99.2	4.28
4	Basal area (25 mm^2)	−1197.3	. . .	. . .	. . .	62.4	99.8	1.74
5	LTD (1 mm)	−1200.6	. . .	. . .	. . .	. . .	63.0	4.39
6	Volume (100 mm^3)	−1202.4	. . .	. . .	. . .	. . .	. . .	0.02

Abbreviations: LTD, largest tumor diameter.
*All models were adjusted for sex, age, presence of symptoms, iris color, tumor pigmentation, and duration of time between initial examination and treatment. Ellipses indicate not applicable.
†Percentage of better performance of model number in the first column vs model number in the first row based on 10 000 replications. For example, model 1 (log_2 [basal area]) outperforms model 2 (log_2 [LTD]) in 92.9% of the occasions.
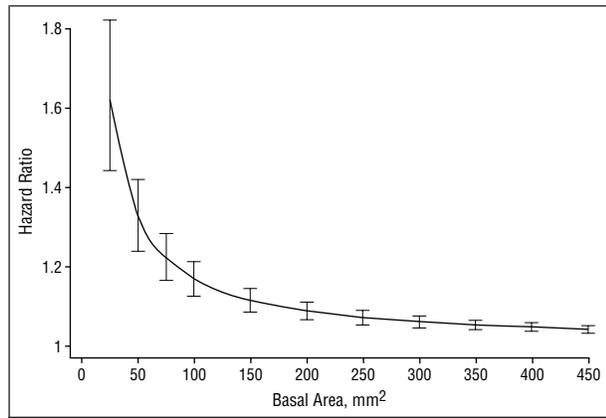

Figure 3. Hazard ratios and 95% confidence intervals for a 25-mm^2 increase in basal area from the labeled values.
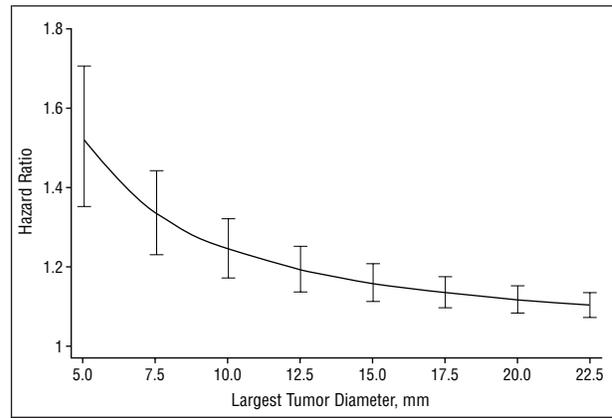

Figure 4. Hazard ratios and 95% confidence intervals for a 1-mm increase in basal diameter from the labeled values.

in LTD declines progressively from small to larger values of LTD.

COMMENT

Uveal melanoma disseminates hematogenously,[31-34] and access to the vascular system may be a determining factor in the metastasis of such tumors.[32,34] In addition, tumor growth depends on a nutrient supply from the choroid, which is limited by the basal area of the tumor in contact with sclera, particularly before tumor neovascularization has taken place. Based on these concepts, tumor basal area would be expected to perform best in the prediction of metastatic death among alternative approaches for modeling tumor dimension.

The nonlinearity of the LTD in relationship to survival was first reported by Gamel and McLean.[6] In their report, LTD was defined as the largest dimension of the tumor (height or basal diameter) recorded at the time of gross examination or measured from the histologic slide. These authors determined that the formula $\beta_1 \times LTD + \beta_2 \times LTD^2$ was the best transformation based on sum of squared error criteria. Our results indicate that logarithmic transformation of the largest basal diameter provides better prediction than a 2-term quadratic model, at least among patients treated by proton irradiation (in the earlier report, patients had been treated by enucleation). Such a non-

linear relationship suggests that a 1-unit increase in tumor size at an early stage of tumor development may elevate the relative risk of metastasis more substantially than a 1-unit increase at a later stage in tumorigenesis. This makes sense biologically because a 1-mm increase in a 20-mm tumor represents a much smaller increase proportionally (5%), relative to the same 1-mm increase in a 5-mm tumor (20%). As opposed to relative risk differences, the elevation in absolute risk for a 1-mm increase in LTD is far greater in larger than in smaller tumors (10-year death rates increase from 23% to 27% for a 15-mm tumor and from 2% to 3% for a 5-mm tumor, respectively).

The analysis has several limitations. To simplify the predictive models, we considered the choroid to be a section of a perfect sphere, when the structure is known to follow the shape of an ellipsoid. In addition, we assumed a scleral thickness of 0.5 mm, which may not have been accurate for all patients. However, the error is presumably random and would not have introduced distortion in the relative risks. Furthermore, assuming substantial error in these assumptions, the true predictive power of the model would have been underestimated relative to the other approaches.

In summary, we found that tumor basal area provides better prediction of tumor-related mortality than a linear form of tumor dimension (LTD, PTD, and height) or tumor volume. However, a drawback of this approach

is that it requires measures of the axial length of the eye, LTD, PTD, and height, which may not be routinely available. The LTDs and PTDs are generally recorded, and the product of these 2 measures should provide a reasonable approximation.

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