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Clinical Predictors of Regression of Choroidal Melanomas after Brachytherapy

A Growth Curve Model

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Purpose: To build multivariate models to assess correctly and efficiently the contribution of tumor characteristics on the rate of regression of choroidal melanomas after brachytherapy in a way that adjusts for confounding and takes into account variation in tumor regression patterns.

Design: Modeling of longitudinal observational data.

Participants: Ultrasound images from 330 of 388 consecutive choroidal melanomas (87%) irradiated from 2000 through 2008 at the Helsinki University Hospital, Helsinki, Finland, a national referral center.

Methods: Images were obtained with a 10-MHz B-scan during 3 years of follow-up. Change in tumor thickness and cross-sectional area were modeled using a polynomial growth-curve function in a nested mixed linear regression model considering regression pattern and tumor levels. Initial tumor dimensions, tumor–node–metastasis (TNM) stage, shape, ciliary body involvement, pigmentation, isotope, plaque size, detached muscles, and radiation parameters were considered as covariates.

Main Outcome Measures: Covariates that independently predict tumor regression.

Results: Initial tumor thickness, largest basal diameter, ciliary body involvement, TNM stage, tumor shape group, break in Bruch's membrane, having muscles detached, and radiation dose to tumor base predicted faster regression, whether considering all tumors or those that regressed in a pattern compatible with exponential decay. Dark brown pigmentation was associated with slower regression. In multivariate modeling, initial tumor thickness remained the predominant and robust predictor of tumor regression ($P < 0.0001$). In addition, use of ruthenium isotope as opposed to iodine isotope ($P = 0.018$) independently contributed to faster regression of tumor thickness. For both isotopes considered alone, initial tumor thickness was the sole clinical predictor of regression ($P < 0.0001$).

Conclusions: Regression of choroidal melanoma after brachytherapy was associated with several clinical tumor and treatment parameters, most of which were shown to reflect initial tumor size. An independent predictor of regression of tumor thickness was the isotope used. These 2 covariates need to be adjusted for when exploring the associations with the rate of regression of histopathologic or genetic features of the tumor. Our model allows such future analyses efficiently without matching. *Ophthalmology 2018;■:1–8 © 2018 by the American Academy of Ophthalmology*

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Radiotherapy is the leading method of treatment for uveal melanoma, and the most common irradiation method is plaque brachytherapy.[1] In North America and Australia, γ-ray–emitting iodine 125[2,3] or, in some centers, palladium 103[4,5] is the most frequently used isotope, whereas in Europe and some Asian countries, the β-ray source ruthenium 106 is most common.[6–11] When both types of source are available, ruthenium plaques typically are used to irradiate melanomas less than 5 to 6 mm thick,[12] and iodine plaques are used primarily for larger tumors.[13] Ruthenium offers a possibility for less frequent radiation-related complications[14] as compared with γ-ray sources,[4] especially in treating small choroidal melanomas close to the fovea and optic disc.[15]

Because a prognostic biopsy sample is not obtained from every irradiated uveal melanoma, the regression rate of the tumor—how fast it shrinks in size after radiotherapy—has been explored as a potential surrogate marker for known histopathologic and genetic factors that predict the risk of metastasis and death. Many studies of response of uveal melanomas to radiotherapy have suggested that rapid initial or eventual regression may be associated with higher mortality from metastases,[6,16–19] but the results have not been consistent.[12,20,21] More recently, uveal melanomas with monosomy 3 or class 2 gene expression profile (GEP), which would be expected to seed metastases more often, likewise have been reported to regress faster than disomy 3 or class 1 tumors by some[19,22,23] but not all[24–28] authors.

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Some have even found that class 1 melanomas regressed faster than class 2 tumors.[24,27,29] The contradictory results likely reflect in part a variable case mix regarding the size, cell type, and other characteristics of the tumor[25] and in part different methods of irradiation, which include both brachytherapy and proton beam therapy.[17,30] Many of these studies concluded that larger uveal melanomas regress faster than smaller ones,[17,19,26,28,30–33] and some have suggested that those with epithelioid cells[12] and high metabolic activity,[34] both of which may signify a higher risk of metastases, also may regress faster.

With one exception,[32] the authors pooled data from all treated tumors, which yields a plot of regression in tumor thickness that follows first-order exponential decay. In reality, the regression pattern of an individual uveal melanoma varies widely, from more or less rapid decrease through no change to even an increase in thickness.[21,25,32,35] We recently showed that no more than 48% of 330 uveal melanomas regressed progressively after brachytherapy. Although an additional 35% of them regressed according to 1 of 3 other patterns that, as a group, legitimately could be modeled as first-order exponential decay, the decay functions differed in their plateaus, corresponding to the eventual percentage of regression at 3 years after irradiation.[36] It has been suggested that the plateau may provide an estimate of the proportion of more radioresistant tumor cells.[30,33] Moreover, we found that regression of tumor thickness differed from that of cross-sectional area, a closer surrogate for tumor volume.[36] Thus, we proposed that studies of regression of uveal melanomas should be stratified by regression pattern and that they additionally should consider tracking the cross-sectional area.

Previous analyses have tried to control for the association of regression rates with tumor size by using either matching, which has led to exclusion of a large number of cases, or 2-way analysis of variance, both of which ignore the diversity of regression patterns. In the present study, we pursued a universal growth curve model that allows inclusion of all cases and multiple predictors and takes different regression patterns into account. We confirmed the dependence of regression rate on initial size of choroidal melanomas and excluded additional tumor- and treatment-related characteristics that independently might have been associated with the rate of regression after brachytherapy. Our growth curve model can be applied in the future to determine the effect of histopathologic, genetic, and other characteristics of uveal melanomas on their regression rate in an appropriate and efficient fashion, and it should aid in either discarding or accepting with confidence tumor regression rate as a surrogate or additional independent clinical prognostic indicator for local recurrence, metastasis, and death.

Methods

Aim of the Study

This study aimed to build a versatile multivariate model to allow efficient assessment of the impact of tumor characteristics on regression of choroidal melanomas after radiotherapy without matching.

Eligibility Criteria

Eligible for this study were consecutive patients who had a choroidal melanoma with or without ciliary body or iris extension measured at diagnosis and after primary brachytherapy with I^3 System ABD 10-MHz B-scan (Innovative Imaging, Inc., Sacramento, CA) at the Helsinki University Hospital, Helsinki, Finland, between September 14, 2000, and June 30, 2008.[36] Tumors measured with a 20-MHz B-scan, eyes with silicon oil, and the second tumor of a patient with bilateral uveal melanoma were excluded. The study was approved by the institutional review board of the Operative Section of the Helsinki University Hospital and followed the tenets of the Declaration of Helsinki. Of 388 consecutive tumors diagnosed, 330 (85%) fulfilled the other inclusion criteria and represented 92% of those treated with brachytherapy.

Ultrasonography

The I^3 System was introduced in the Ocular Oncology Service in September 2000.[36] Images were filed digitally at the time of each visit. Normally, the tumor was measured 8 times within 3 years from irradiation (at 0, 3, 6, 12, 18, 24, 30, and 36 months). Thereafter, patients residing elsewhere generally were referred to their regional hospital for further follow-up, and later scans were not available consistently. We measured tumor thickness and cross-sectional area from the most similar projection at each visit using image analysis software (Olympus DP-10 Soft version 3.0; Soft Imaging System GmbH, Muster, Germany) and classified each tumor by its shape according to an adaptation of definitions in an ancillary Collaborative Ocular Melanoma Study report[37] as described.[36] In cases of local recurrence, we excluded measurements from the visit when the recurrence was diagnosed and from subsequent visits. One of the authors (M.R.) used a mouse-driven cursor to mark the inner scleral surface of the tumor and its apex to measure the thickness of the tumor and then traced the boundary of the tumor to obtain its cross-sectional area. All measurements were verified by consensus with the senior author (T.T.K.).

We classified the tumor regression pattern by plotting its thickness and cross-sectional area over time according to a system originally developed by Abramson et al,[32] expanded to 8 categories as we previously described[36]: decrease (D; progressive decrease in thickness by at least 15% after brachytherapy), stable (S; less than 15% thickness change), increase (I; progressive increase in thickness by at least 15%), D followed by S, D followed by I, I followed by D, S followed by D, and zigzag (alternating measurements with less evidence of a trend).

Of the 330 tumors, 244 (74%) regressed in thickness and 257 (78%) in cross-sectional area by a pattern that as a group legitimately can be modeled as first-order exponential decay (D, D followed by S, D followed by I, or zigzag) according to our previous analysis[36] and were analyzed separately in addition to models considering all tumors. The tumors that regressed by other patterns (S, S followed by D, I followed by D, I, or undefined) were smaller in thickness and cross-sectional area, less often demonstrated broken Bruch's membrane, received higher radiation doses, and had undergone fewer measurements after irradiation than the enrolled ones (Table S1, available at www.aaojournal.org). Regarding regression of thickness, they also were smaller in largest basal diameter (LBD) and lower in American Joint Committee on Cancer (seventh edition) tumor–node–metastasis (TNM) classification of tumor size category and stage.[38]

Brachytherapy

Ruthenium 106 and iodine 125 radioactive plaques were used to treat up to 5- to 6-mm (median, 2.7-mm) and thicker (median,