Tumor Regression After Brachytherapy for Choroidal Melanoma: Reduction of Thickness and Cross-Sectional Area by Shape and Regression Pattern

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PURPOSE. To model regression rate of thickness and cross-sectional area of choroidal melanomas after ruthenium and iodine brachytherapy by shape and regression pattern (RP).

METHODS. We enrolled 330 of 388 consecutive uveal melanomas from 2000 to 2008 and analyzed images from I3 System-ABD 10-MHz B-Scan at diagnosis and during a 3-year-long follow-up. We classified tumor shape by Collaborative Ocular Melanoma Study definitions and RP according to an earlier study. We plotted regression over time and compared thickness and cross-sectional area.

RESULTS. The observed RP by thickness was classified as decrease (D) in 43%, stable (S) in 5%, increase (I) in 1%, and other in 40% of eyes; main subpatterns were decrease-stable (DS) in 16% and zigzag in 10% of eyes. The corresponding percentages by area were 42%, 3%, 1%, 45%, 16%, and 14%. Regression pattern was discordant in 34% of eyes for thickness versus area. Area reduced faster than thickness when shape was oval to dome or mushroom and if RP was D. Pooled patterns D, DS, decrease-increase (DI), and zigzag corresponded with progressive but increasingly less pronounced regression for 3 years (56% by thickness and 69% by area), 2 years (50% and 52%), 6 months (29% and 33%), and 6 months (19% and 23%), respectively. First-order exponential decay function fitted thickness and area regression for every shape and for patterns D, DS, DI, and zigzag.

CONCLUSIONS. Heterogeneity in RP variation in shape, and tumor cross-sectional area as an alternative measure must be considered when tumor regression rate is used in outcome analysis.

Keywords: brachytherapy, tumor regression, iodine, ruthenium, exponential decay

Radiotherapy is currently the most common treatment for uveal melanoma. Although enucleation may be indicated for large tumors, some of them1 and most medium-sized and small tumors are generally treated with radiation therapy. Radiotherapy initiates tumor regression that is routinely evaluated in clinical practice as change in tumor thickness measured by B-scan ultrasonography.2 This is reasonable because the diameter of the tumor base does not change.3 If the treatment is successful, the tumor flattens to where it arose.

The regression of uveal melanoma as evaluated by change in tumor thickness measured by ultrasonography following brachytherapy with cobalt,3–7 iodine,7–11 and ruthenium,10,12–23 plaques, teletherapy with charged particles,24–27 gamma knife,17,28 and linear accelerator,29 sometimes in combination with transpupillary thermotherapy,8,19,21–23 has been addressed in many studies over three decades, often with contradicting results. In particular, although several studies have suggested that rapid initial or overall regression would be associated with higher mortality,6,9,15,20,24 not all have confirmed such a difference.3,14,18 Moreover, some studies have recently reported that uveal melanomas with monosomy 3 or class 2 gene expression profile, which would be expected to lead to metastasis, did not regress faster than disomy 3 and class 1 tumors regressed,10,11,20 whereas others have in fact found a difference.8,9

These contradictory results have raised the suspicion that the apparent association of melanoma-related mortality with rapid tumor regression8,9,15,20,24 might be a spurious finding, reflecting different case mix with regard to thickness, cell type, and other tumor characteristics.11 Most studies agree that large uveal melanomas regress faster than smaller ones,5,7,9,16,24,27 and some have found that those with epithelioid cells14 and high metabolic activity25 may also regress faster. Additional factors likely contribute to the contradicting results, however. With one exception,7 data from all treated tumors have been pooled for analysis, which results in a curve with progressively decreasing tumor thickness. However, some studies have revealed that the regression pattern of an individual uveal melanoma after irradiation in fact varies widely, from more or less rapid decrease through no change to even increase in thickness.7,10,11,18 Secondly, uveal melanomas come in a number of shapes, such as flat, crescent, oval, dome, mushroom (collar button), lobulated, and irregular10,31; and when they grow and regress, their shape may change. For these reasons, it is not obvious that measurement of pooled tumor thickness would accurately reflect the regression relative to
tumor characteristics such as its genetic profile or propensity to spread.

In general, one-dimensional measurement of maximal tumor diameter is thought to be sufficient to assess the response of a solid tumor to treatment, and agreement between one- and two-dimensional measurements has been close. Indeed, the current version of the Response Evaluation Criteria In Solid Tumors (RECIST), which the majority of clinical trials in oncology use, has now adopted a one-dimensional measurement. However, in a number of patients the response to treatment may still be classified differently based on volumetric as opposed to one- or two-dimensional imaging.

Because the shape of uveal melanomas varies more widely than that of a typical solid tumor in other organs, tumor thickness is not necessarily the best surrogate measure for tumor volume, and especially for a change in tumor volume. For example, the base of a mushroom-shaped melanoma seems to regress to a different extent than the part that has broken through Bruch's membrane. Although volume measurements of uveal melanoma have been obtained from time to time, none of these methods has become routine. Formulas for estimating tumor volume from two-dimensional measurements of uveal melanoma have proved inconsistent and largely unsatisfactory.

We address the hitherto unexplored relationship between the height and cross-sectional area of choroidal melanomas and their regression after brachytherapy, and analyze the rate and pattern of regression of both measures relative to tumor shape. We use cross-sectional area as a presumed closer surrogate for tumor volume than tumor thickness.

**Patients and Methods**

**Aims of the Study**

The aims of this study were to analyze regression of tumor thickness and cross-sectional area of choroidal melanomas based on their shape and pattern of regression in order to gain a better understanding of these relationships, with the aim of developing better statistical models for assessing the contribution of tumor biology and genetics to tumor regression and that of regression to survival.

**Eligibility Criteria**

Eligible for this study were all consecutive patients who had a choroidal melanoma with or without ciliary body and iris extension that was measured at diagnosis and at least twice during follow-up with the 10-MHz probe of the System-ABD B-Scan (Innovative Imaging, Inc., Sacramento, CA, USA) and who were treated with primary brachytherapy between September 14, 2000, and June 30, 2008, at the Ocular Oncology Service, Helsinki University Central Hospital, Finland. We excluded patients with iris and primary ciliary body melanomas, which were measured using other equipment, and tumor eyes that had silicone oil tamponade at the time of diagnosis.

During the study period, 388 consecutive patients (190 men, 198 women) with a uveal melanoma were diagnosed and imaged with the ABD scan. One of them had bilateral uveal melanoma managed with brachytherapy, and we drew one eye at random into this study. Two small tumors were under follow-up without treatment at the closing date; 1 tumor was primarily managed with transpupillary thermotherapy; 5 with local resection, 21 with enucleation, and 2 with exenteration; 13 eyes were imaged with other equipment and 2 had silicon oil. Four patients died before their first review at the Ocular Oncology Service; two had not yet attended their first review, two with poor general health were reviewed elsewhere; and four patients were excluded because no comparable projection was available in follow-up scans. A total of 330 patients and tumors were thus enrolled in this study (inclusion ratio, 85% of all uveal melanomas and 92% of those that were irradiated during the study period).

The study was approved by the Institutional Review Board and followed the tenets of the Declaration of Helsinki.

**Ultrasonography**

The System-ABD scan was introduced in the Ocular Oncology Service in September 2000. One of two ocular oncologists measured the thickness of the tumor from the inner surface of the sclera to tumor apex and the largest basal diameter (LBD) using a gain of 60 dB. Thickness was measured from two meridians, along the LBD and perpendicular to it. Representative digitized scans were prospectively stored at the time of each diagnostic and follow-up visit.

Generally, patients were reviewed seven times in the Ocular Oncology Service clinically and by ultrasonography during the first 3 years after irradiation (at 3, 6, 12, 18, 24, 30, and 36 months). Patients from the catchment area of the Helsinki University Central Hospital attended also a 1-month visit and continued follow-up after 3 years, generally annually; patients residing elsewhere were similarly reviewed in other university or central hospitals. In case the tumor had developed a local recurrence, we excluded measurements from the visit when the recurrence was diagnosed and from subsequent visits.

For the purpose of this study, we classified the tumors by their ultrasonographic shape according to the Collaborative Ocular Melanoma Study (COMS) definitions. We adopted ours from the scheme of eight standard shapes defined in the ancillary COMS study that compared transillumination and histologic slide measurements of choroidal melanomas. It provided more detail than the one in the COMS Manual of Procedures that illustrated dome, mushroom, peaked, and lobulated as the most common shapes, although the Study Forms additionally listed the shapes flat, irregular, and other. No textual guidance was provided as to how to apply this classification. In the ancillary histopathological study, crescent, oval, and oval with extension were introduced; peaked was dropped; and irregular included also tumors that could not otherwise be classified. An illustration was provided as guidance for each shape. Using this system, intra- and intergrader agreement were 90% and 93%, respectively.

We measured tumor thickness and cross-sectional area from stored scans of most similar projections using image analysis software (Olympus DP-10 Soft, Version 3.0; Soft Imaging System GmbH, Munster, Germany). We selected the projections by consensus of two investigators. We used a mouse-driven cursor to manually mark the inner scleral surface of the tumor and its apex to measure the linear distance between these points, and we then traced the boundary of the tumor (Fig. 1). The coordinates of each point on the boundary provide the tumor cross-sectional area as an n-sided polygon. We used the millimeter scale on the ultrasound scans to calibrate the software so as to obtain all results in square millimeters.

Additional clinical data, including the status of Bruch's membrane (unbroken, broken, or indeterminate), were taken from the prospective database of the Ocular Oncology Service.

**Brachytherapy**

Ruthenium-106 (EBIG GmbH, Berlin, Germany) and iodine-125 radioactive plaques (crafted by a local goldsmith) were...
We generally aimed to deliver a dose of 100 and 80 Gy to the tumor apex with ruthenium and iodine plaques, respectively, in a maximum of 14 days. Very thin tumors received a minimum scleral dose of 250 Gy\(^5\) and very thick tumors a reduced apical dose.\(^1\) In 158 single ruthenium plaque treatments, the median delivered dose to apex and base were 102 Gy (range, 62–194) and 361 Gy (range, 192–1212), respectively; and in 165 single plaque iodine treatments the median delivered apical dose was 80 Gy (range, 49–164). The corresponding median delivered dose rates to tumor apex were 112 cGy/h (range, 22–400) and 68 cGy/h (range, 14–550) for ruthenium and iodine, respectively. The corresponding median treatment durations were 95 hours (range, 28–407) and 119 hours (range, 27–467), respectively (in five instances, the treatment time exceeded 14 days).

**Statistical Analysis**

We analyzed follow-up data up to the date of analysis on September 30, 2008, with Stata (version 13; StataCorp, College Station, TX, USA) and Prism (release 6; GraphPad Software, San Diego, CA, USA) statistical software. All tests were two-tailed, and a \( P \) value \(< 0.05\) was taken to indicate statistical significance.

We give the median and range for skewed and the mean and standard deviation (SD) for normally distributed variables, respectively, and the 95% confidence interval (CI) for main findings. Wilcoxon matched-pairs signed-ranks test was used to compare regression of thickness and cross-sectional area at a specific time point. Kruskal-Wallis test and nonparametric test for trend were used to compare regression between unordered and ordered categories, respectively. Our study was an explorative one. No compensation was made for multiple comparisons, which must be taken into account when interpreting \( P \) values.

We constructed Bland-Altman plots\(^49\) to assess agreement between the prospective I\(^3\) System-ABD B-Scan and the retrospective Olympus DP-10 software (ODS) thickness measurement.

We partially collapsed the COMS shapes for statistical analysis as follows: group 1, flat and crescent; group 2, oval with or without extension and dome; group 3, mushroom; group 4, lobulated; and group 5, other or indeterminate. For each shape group, we fitted a least squares linear regression model for tumor cross-sectional area according to tumor thickness based on the ODS measurements.\(^47\) We assessed the appropriateness of linear fit using the goodness-of-fit statistic and runs test, and by comparing the regression line visually with a corresponding locally weighted scatterplot smoothing (lowess) curve.\(^48\)

We plotted the thickness and the cross-sectional area of each individual tumor over time and categorized the tumor regression pattern according to Abramson et al.\(^7\) into four main patterns: D (decrease; progressive decrease in thickness by at least 15% after brachytherapy), S (stable; less than 15% change in thickness), I (increase; progressive increase in thickness by at least 15%), and other. We further subdivided other into five subtypes: DS (D followed by S), DI (D followed by I), ID (I followed by D), SD (S followed by D), and zigzag (alternating measurements with little evidence of a trend). We excluded from this analysis 18 patients who had only two acceptable follow-up measurements and 19 patients who had been followed for less than 6 months.

We calculated the initial thickness (height) regression rate (ITRR) according to Kaiserman et al.\(^20\) defined as the mean decrease at ODS measurement 3 months after brachytherapy, and we defined initial cross-sectional area regression rate (IARR) accordingly.
We plotted mean tumor ODS thickness and cross-sectional area over time according to status of Bruch’s membrane, shape group, and regression pattern to identify any difference between regression of thickness and cross-sectional area. Finally, we fitted first- and second-order exponential decay or linear functions to the plotted data by tumor shape and regression pattern using least squares nonlinear regression. Goodness-of-fit statistic and runs test were used to evaluate model fit.

RESULTS

The median age of the 330 patients (166 males, 164 females) at diagnosis was 61 years (range, 18–93). According to the Tumor, Node, Metastasis (TNM) classification, 91 (28%) of the 330 choroidal melanomas represented size category T1 or small; 107 (32%) were T2 or medium-sized; 95 (29%) were T3 or large; and 37 (11%) were T4 or very large (Supplementary Table S1). Eighty-nine (27%) were TNM stage I, 166 (50%) stage II, 70 (21%) stage III, and 5 (2%) stage IV (metastases at the time of diagnosis).

The patients had a median of five follow-up visits with an acceptable measurement of tumor thickness and area from a comparable projection (Supplementary Table S1) during the first 3 years after brachytherapy (range, 2–12; interquartile range, 5–7).

Tumor Dimensions and Shape

The median tumor LBD and thickness at diagnosis as measured with ABD were 11.7 mm (range, 3.2–24.5) and 4.9 mm (range, 1.0–16.8), respectively (Supplementary Table S1). The corresponding ODS measurement of median thickness was 4.7 mm (range, 1.0–15.5). The mean difference between the two measurements was 0.06 mm (95% CI, −0.97 to +1.09; Supplementary Fig. S1) by the Bland-Altman analysis. The median cross-sectional area of the tumor was 38 mm² (range, 5–294) as measured with ODS.

Eighty tumors (24%) extended to the ciliary body, and two (0.6%) had anterior extraocular extension. Bruch’s membrane was intact in 165 (50%) and broken in 119 (36%) eyes (Supplementary Table S1). The COMS shape group was flat to crescent in 97% (50%), oval with or without extension to dome in 132 (39%), mushroom in 55 (17%), lobulated in 38 (12%), and other or indeterminate in 8 eyes (2%).

Tumor Thickness Relative to Cross-Sectional Area at Diagnosis

The slope of the linear regression line of tumor cross-sectional area by ODS thickness at the time of diagnosis varied within narrow limits from 14.2 to 15.4 (Supplementary Fig. S1) for the main COMS shape groups except for the flat to crescent (slope, 9.6). The other three shape groups taken together, a 1-mm increase in tumor thickness was associated, on average, with a 14.8-mm² increase in cross-sectional area (flat-to-crescent shape, 9.6 mm²).

The r² statistic was 0.82 for the flat-to-crescent shape and ranged from 0.90 to 0.93 for the other three shape groups, indicating that linear regression on tumor thickness captured 82% to 93% of total variation in tumor cross-sectional area (Supplementary Fig. S1). Runs test indicated no significant deviation from linearity for any shape (P > 0.05 for all; Supplementary Fig. S1). The lowess plot deviated from the regression line for flat-to-crescent shapes when tumor thickness exceeded 3.5 mm because of two outliers that could alternatively have been classified as dome, and for oval-to-dome shapes that showed more variation when thickness exceeded 10 mm (Supplementary Fig. S1).

Across all shape groups, linear regression explained 91% of total variation in tumor cross-sectional area (Supplementary Fig. S1). The lowess curve approximated the regression line when thickness was smaller than 10 mm, but runs test indicated nonlinearity (P = 0.0014) because of lower initial slope due to flat-to-crescent tumors and presence of outliers among tumors of other shapes thicker than 10 mm.

Tumor Regression Patterns

The tumor regression pattern based on ODS thickness was D in 141 (43%), S in 18 (5%), I in 2 (1%), and other in 132 (40%) eyes (Table 1). Corresponding figures for tumor cross-sectional area were 137 (42%), 7 (5%), 2 (1%), and 147 (45%). The pattern could not be determined for 27 (8%) tumors because of insufficient sequential data. The most common subpattern was D5 in 54 (16%) eyes, followed by zigzag in 35 (10%), SD in 20 (6%), DI in 16 (5%), and ID in 9 (3%) eyes, based on thickness. According to cross-sectional area, the corresponding figures were 54 (16%), 45 (14%), 19 (6%), 21 (6%), and 8 (2%).

The regression types for thickness and cross-sectional area were concordant in 192 (66%) tumors with a known pattern...
and discordant for 101 (34%; Table 1). Patterns D and zigzag were most concordant, in 78% and 81% of eyes, respectively. Patterns DS, DI, and SD were concordant in approximately one-half of the eyes, and types S, I, and ID were mostly discordant.

Of tumors with an unbroken, indeterminate, and broken Bruch’s membrane, increasing proportions regressed according to the D pattern (Table 2; 39%, 50%, and 60% analyzed by thickness; $P = 0.0008$ Kruskal-Wallis test; and 36%, 58%, and 56% analyzed by cross-sectional area; $P = 0.0009$). Of the other two regression patterns observed in over 25 patients, DS did not show a significant trend ($P = 0.83$ and $P = 0.13$, respectively), whereas decreasing proportions showed a zigzag pattern ($P = 0.074$ and $P = 0.0010$, respectively).

By COMS shape group, D was always the most common regression pattern and increased in frequency category by category from 31% by thickness and 34% by cross-sectional area for flat-to-crescent tumors to 65% and 72%, respectively, for lobulated ones (Table 2; $P = 0.0001$ and $P = 0.0002$ nonparametric test for trend, respectively). The DS pattern was generally the second most common one but did not show any frequency trend. The zigzag pattern was observed mainly in the flat-to-crescent and oval-to-dome shape groups, with a decreasing trend toward mushroom and lobulated ones ($P = 0.017$ and $P = 0.0010$, respectively).

### Tumor Regression Rate by Tumor Shape

The overall median ITRR and IARR by 3 months were 4.4% and 6.0% per month, respectively (Table 3). Both the ITRR (median, 2.4% vs. 7.4%) and IARR (4.2% vs. 9.8%) were slower when Bruch’s membrane was intact rather than broken (both $P = 0.0001$, Kruskal-Wallis test). According to the COMS shape group, ITRR (median, 1.4% vs. 4.3% vs. 8.1%) and IARR (2.7% vs. 5.9% vs. 9.9%) increased significantly from flat to crescent shaped to oval and dome shaped to mushroom tumors (both $P < 0.0001$ nonparametric test for trend).

Except for tumors with indeterminate Bruch’s membrane, as well as those that were flat to crescent or lobulated in shape, IARR was larger, but the difference was of borderline significance for tumors with unbroken Bruch’s membrane (Table 3).

During the first year after brachytherapy, the thickness of a uveal melanoma reduced on average more slowly than its cross-sectional area (Fig. 2A; median, 26% vs. 30% at 6 months, $P < 0.0001$ Wilcoxon signed-ranks test; and 32% vs. 58% at 1 year, $P < 0.0001$). This was true irrespective of the status of Bruch’s membrane or shape group (Table 3). With the exception of indeterminate Bruch’s membrane, the difference ranged from 4 to 9 percentage points, which amounted to a 16% to 24% difference. By 3 years, the difference ranged from ~6% to 17%, and was no longer significant for tumors without broken Bruch’s membrane or those that were flat to crescent or lobulated in shape. Thereafter, the data were biased by partial referral of patients to follow-up elsewhere (Fig. 2A). Analysis was thus based on the first 3 years.

Thickness and cross-sectional area reduction rates were slower when Bruch’s membrane was intact (Table 3; Fig. 2B; 25% and 29% at 1 year; and 37% vs. 36% at 3 years) as compared to indeterminate (Fig. 2C) or ruptured Bruch’s (Fig. 2D; 41% and 48% at 1 year, both $P = 0.0001$ Kruskal-Wallis test; and 55% and 61% at 3 years, both $P = 0.0001$). Compared with the flat-to-crescent group (22% and 26% at 1 year, and 36% and 34% at 3 years), the oval-to-dome group (33% and 41% at 1 year, $P = 0.0022$ and $P = 0.0011$; and 42% vs. 49% at 3 years, $P = 0.14$ and $P = 0.048$) and the mushroom shape (41% and 50% at 1 year, both $P = 0.0001$; and 67% and 74% at 3 years, both $P = 0.0001$) had a faster rate of reduction (Figs. 2E–G). The

### Table 2
Regression Type by Thickness and Cross-Sectional Area Against Tumor Shape and Status of Bruch’s Membrane Among 330 Choroidal Melanomas

<table>
<thead>
<tr>
<th>Variable</th>
<th>DS</th>
<th>DI</th>
<th>ID</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bruch’s membrane, no. (%)</td>
<td>13 (9)</td>
<td>35 (47)</td>
<td>8 (6)</td>
<td>56 (80)</td>
</tr>
<tr>
<td>Unbroken</td>
<td>12 (8)</td>
<td>28 (39)</td>
<td>7 (6)</td>
<td>47 (64)</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>1 (1)</td>
<td>7 (10)</td>
<td>1 (1)</td>
<td>9 (12)</td>
</tr>
<tr>
<td>Broken</td>
<td>3 (2)</td>
<td>7 (10)</td>
<td>5 (6)</td>
<td>15 (20)</td>
</tr>
<tr>
<td>COMS shape group, no. (%)</td>
<td>10 (12)</td>
<td>19 (25)</td>
<td>7 (9)</td>
<td>36 (47)</td>
</tr>
<tr>
<td>Flat to crescent</td>
<td>15 (13)</td>
<td>30 (38)</td>
<td>7 (9)</td>
<td>52 (66)</td>
</tr>
<tr>
<td>Oval to dome</td>
<td>5 (4)</td>
<td>12 (16)</td>
<td>2 (2)</td>
<td>19 (25)</td>
</tr>
<tr>
<td>Lobulated</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Total, no. (%)</td>
<td>35 (11)</td>
<td>54 (18)</td>
<td>16 (5)</td>
<td>105 (32)</td>
</tr>
</tbody>
</table>

- $P < 0.0001$ nonparametric test for trend.
<table>
<thead>
<tr>
<th>Variable</th>
<th>ITRR Mean (SD)</th>
<th>Median %</th>
<th>IARR Mean (SD)</th>
<th>Median %</th>
<th>P†</th>
<th>1 y %</th>
<th>3 y %</th>
<th>1 y %</th>
<th>3 y %</th>
<th>1 y pp (%)</th>
<th>P†</th>
<th>3 y pp (%)</th>
<th>P†</th>
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<tbody>
<tr>
<td>All tumors</td>
<td>5.0 (7.6)</td>
<td>4.4</td>
<td>6.0 (10.0)</td>
<td>6.0</td>
<td>&lt;0.0001</td>
<td>32</td>
<td>43</td>
<td>38</td>
<td>52</td>
<td>6 (19)</td>
<td>&lt;0.0001</td>
<td>7 (16)</td>
<td>0.0017</td>
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<td>Bruch’s membrane</td>
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<tr>
<td>Unbroken</td>
<td>2.9 (7.5)</td>
<td>2.4</td>
<td>3.8 (9.8)</td>
<td>4.2</td>
<td>0.037</td>
<td>25</td>
<td>37</td>
<td>29</td>
<td>36</td>
<td>4 (16)</td>
<td>0.012</td>
<td>−1 (−3)</td>
<td>0.73</td>
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<tr>
<td>Indeterminate</td>
<td>6.8 (6.6)</td>
<td>7.5</td>
<td>7.5 (7.7)</td>
<td>8.4</td>
<td>0.15</td>
<td>35</td>
<td>50</td>
<td>51</td>
<td>47</td>
<td>16 (46)</td>
<td>0.018</td>
<td>−3 (−6)</td>
<td>0.35</td>
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<tr>
<td>Broken</td>
<td>7.5 (6.7)</td>
<td>7.4</td>
<td>9.7 (7.2)</td>
<td>9.8</td>
<td>&lt;0.0001</td>
<td>41</td>
<td>55</td>
<td>48</td>
<td>61</td>
<td>7 (17)</td>
<td>&lt;0.0001</td>
<td>6 (11)</td>
<td>&lt;0.0001</td>
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<td>COMS shape group</td>
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<tr>
<td>Flat to crescent</td>
<td>1.3 (7.4)</td>
<td>1.4</td>
<td>1.9 (10.2)</td>
<td>2.7</td>
<td>0.18</td>
<td>22</td>
<td>36</td>
<td>26</td>
<td>34</td>
<td>4 (18)</td>
<td>0.048</td>
<td>−2 (−6)</td>
<td>0.74</td>
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<tr>
<td>Oval to dome</td>
<td>5.0 (7.0)</td>
<td>4.5</td>
<td>6.7 (7.8)</td>
<td>5.9</td>
<td>0.0001</td>
<td>33</td>
<td>42</td>
<td>41</td>
<td>49</td>
<td>8 (24)</td>
<td>&lt;0.0001</td>
<td>7 (17)</td>
<td>0.0054</td>
</tr>
<tr>
<td>Mushroom</td>
<td>8.6 (6.5)</td>
<td>8.1</td>
<td>10.6 (7.9)</td>
<td>9.9</td>
<td>0.0001</td>
<td>41</td>
<td>67</td>
<td>50</td>
<td>74</td>
<td>9 (22)</td>
<td>&lt;0.0001</td>
<td>7 (10)</td>
<td>0.006</td>
</tr>
<tr>
<td>Lobulated</td>
<td>8.7 (6.5)</td>
<td>9.6</td>
<td>7.2 (15.5)</td>
<td>9.3</td>
<td>0.34</td>
<td>39</td>
<td>55</td>
<td>45</td>
<td>62</td>
<td>6 (15)</td>
<td>0.054</td>
<td>7 (13)</td>
<td>0.31</td>
</tr>
<tr>
<td>Regression pattern</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>7.0 (6.5)</td>
<td>7.4</td>
<td>9.6 (7.5)</td>
<td>9.7</td>
<td>&lt;0.0001</td>
<td>41</td>
<td>56</td>
<td>52</td>
<td>69</td>
<td>11 (27)</td>
<td>&lt;0.0001</td>
<td>13 (25)</td>
<td>0.002</td>
</tr>
<tr>
<td>S</td>
<td>−2.7 (3.4)</td>
<td>−3.0</td>
<td>0.1 (4.1)</td>
<td>1.2</td>
<td>0.0061</td>
<td>1</td>
<td>4</td>
<td>0.3</td>
<td>0</td>
<td>1 (1)</td>
<td>0.48</td>
<td>4</td>
<td>0.65</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DS</td>
<td>6.7 (7.3)</td>
<td>7.3</td>
<td>7.7 (8.3)</td>
<td>7.7</td>
<td>0.43</td>
<td>38</td>
<td>51</td>
<td>41</td>
<td>56</td>
<td>3 (8)</td>
<td>0.16</td>
<td>5 (9)</td>
<td>0.68</td>
</tr>
<tr>
<td>DI</td>
<td>6.2 (7.4)</td>
<td>5.4</td>
<td>7.1 (6.0)</td>
<td>6.1</td>
<td>0.13</td>
<td>23</td>
<td>29</td>
<td>32</td>
<td>42</td>
<td>9 (39)</td>
<td>0.60</td>
<td>13 (15)</td>
<td>0.062</td>
</tr>
<tr>
<td>SD</td>
<td>1.2 (5.1)</td>
<td>0.2</td>
<td>−3.2 (5.4)</td>
<td>−3.4</td>
<td>0.15</td>
<td>5</td>
<td>34</td>
<td>13</td>
<td>26</td>
<td>8 (160)</td>
<td>0.0002</td>
<td>−8 (−24)</td>
<td>0.070</td>
</tr>
<tr>
<td>ID</td>
<td>−8.3 (5.4)</td>
<td>−9.0</td>
<td>−5.5 (9.0)</td>
<td>−5.6</td>
<td>0.21</td>
<td>24</td>
<td>−8</td>
<td>−17</td>
<td>5</td>
<td>−7 (−29)</td>
<td>0.036</td>
<td>−3 (−38)</td>
<td>0.18</td>
</tr>
<tr>
<td>Zigzag</td>
<td>3.3 (6.1)</td>
<td>3.5</td>
<td>1.5 (10.0)</td>
<td>2.5</td>
<td>0.66</td>
<td>17</td>
<td>31</td>
<td>17</td>
<td>28</td>
<td>0</td>
<td>0.81</td>
<td>−3 (−9)</td>
<td>0.77</td>
</tr>
</tbody>
</table>

*Combinations of D, S, and I indicate two sequential regression types; pattern I had too few cases to analyze. RR, regression rate; SD, standard deviation; pp, percentage points.
†Regression pattern could not be determined for 37 of the 330 tumors.
‡Wilcoxon signed-ranks test, two-sided.
FIGURE 2. Measured (left y-axis) and reduction in (right y-axis) thickness (white symbols) and cross-sectional area (black symbols) of 330 choroidal and ciliary body melanomas after brachytherapy, plotted in percentage relative to the time of diagnosis for all tumors (A) and according to the status of Bruch’s membrane (B–D) and the Collaborative Ocular Melanoma Study (COMS) shape group (E–H). The light and dark gray shaded areas indicate 95% confidence intervals, and the dashed and solid red curves are nonlinear regression lines by first-order exponential decay function of tumor thickness and cross-sectional area, respectively. Numbers below graphs are patients under follow-up. Confidence interval too wide to plot in (C).
Regression of lobulated tumors as a group was inconsistent over time with increasing measures between 6 and 18 months without recurrences of individual tumors (Fig. 2H), but their rate of reduction was also faster than that of flat-to-crescent tumors (Table 3; \( P = 0.0034 \) and \( P = 0.0006 \) at 1 year; and \( P = 0.0042 \) and \( P = 0.0032 \) at 3 years).

**Tumor Regression Rate by Regression Pattern**

According to thickness, the median ITRR and IARR were slowest for the S, SD, and zigzag patterns (all less than 3.3%; Table 3). Patterns D, DS, and DI had a faster ITRR (7.4%, 7.3%, and 5.3%, respectively), and the IARR logically decreased from type D to DI (9.7%, 7.7%, and 6.1%, respectively). As expected, the ID pattern was associated with a negative ITRR and IARR, indicating growth by 3 months; the I pattern had too few cases to be representative.

The IARR significantly exceeded ITRR only for the D pattern (\( P < 0.0001 \) Wilcoxon signed-ranks test), and was significantly smaller than ITRR for the S pattern (\( P = 0.0061 \); Table 3).

The thickness of a uveal melanoma reduced on average more slowly than its cross-sectional area by 1 and 3 years if the regression pattern was D (median, 41% vs. 52% at 1 year, \( P = 0.0001 \); and 56% vs. 69% at 3 years, \( P = 0.0002 \)). A significant difference was found at 1 year for SD and ID patterns \( (P = 0.0002 \text{ vs. } P = 0.036, \text{ respectively}) \) and a minor trend at 3 years for SD and DI patterns (Table 3), but no certain difference was observed for any pattern other than D.

The D pattern as a group regressed progressively in thickness and cross-sectional area until 3 years (Fig. 3A); the S pattern (Fig. 3B) did not show any change, whereas the heterogeneous pattern other (Fig. 3C; median, 34% and 35%, respectively) and its DS subpattern (Fig. 3D; 50% and 52%, respectively) showed a slower progressive reduction until 2 years, as did the DI pattern until approximately 6 months (Fig. 3E; 29% and 33%, respectively), all followed by essentially no change thereafter. The SD (Fig. 3E) and ID (Fig. 3F) patterns corresponded to stable or increasing measurements for 6 and 12 months, respectively, followed by approximately 30 percentage point reduction from maximum during the next 2 years, which resulted in 54% and 26% reduction and little or no reduction at 3 years, respectively, relative to measurements at the time of brachytherapy. Although the plots for individual tumors corresponding to the zigzag pattern varied widely, as a pooled group this type also regressed until 6 months (19% and 23%, respectively), followed by stability, similarly to the DI pattern, albeit to a lesser extent (Fig. 3H).

**Modeling of Tumor Regression Rate**

A first-order exponential decay fitted the thickness and cross-sectional area regression curves (Table 4) for all tumors (Fig. 2A), for those with an intact, indeterminate, or broken Bruch’s membrane (Figs. 2B–D); for all COMS shape groups (Figs. 2E–H), and for regression patterns D and other subpatterns DS, DI, and zigzag (Figs. 5A, 3B–E, 3H). Runs test indicated that deviation from the equation was not significant for any of these groups \( (P > 0.05 \) for all; Table 4).

The exponential decay equation could not be legitimately fitted for patterns S, SD, and ID (Figs. 3B, 3E, 3G). Linear regression provided a fit for patterns S and SD (Figs. 3B, 3F; \( r^2 = 0.17 \) and 0.92; \( P = 0.89 \) and \( P = 0.70 \) runs test, respectively).

**Discussion**

Analysis of the regression of 330 population-based, consecutive, unselected choroidal melanomas treated with ruthenium or iodine brachytherapy showed that the regression rate typically was different when the analysis was based on tumor cross-sectional area—a presumed closer surrogate of tumor volume—as compared to tumor thickness that has been the traditional measure. Mushroom-shaped tumors regressed more rapidly than oval-to-dome tumors, with the slowest regression in flat-to-crescent tumors. Regardless of shape, regression of cross-sectional area was faster than regression of thickness at 1 year. However, the timing of regression varied widely between individual tumors, and the resulting pattern of regression, which was associated with tumor shape, was discordant for thickness and cross-sectional area in one-third of the cases. The exponential decay function often used to model regression of uveal melanomas\(^9,16,20,24,27\) was applicable to most, but not all, regression patterns. These main findings should be taken into account when ocular oncologists plan to evaluate any biological differences among uveal melanomas based on their regression after radiotherapy. In particular, our results lend support to multivariate modeling based on exponential decay,\(^9\) but also show that such modeling must take into account that not all tumors fit this pattern, and that tumor area may be an equally relevant endpoint.

We found that only 43% of uveal melanomas progressively regressed over time. Previous studies have assumed for all uveal melanomas a uniform regression pattern that follows a logistic, linear, or more typically, a first-order exponential decay function.\(^9,16,20,24,27\) We noted great variation among the remaining 57% of tumors, confirming an early report by Abramson et al.,\(^7\) who found that no two uveal melanomas regressed exactly according to the same pattern after cobalt or iodine brachytherapy. Of their 82 tumors, 70% regressed progressively, 16% remained stable, 12% increased in size, and 2% showed other patterns. We classified 5% as stable and 1% as increasing in size. Conversely, we assigned 40% of melanomas to other patterns of regression. The disparate percentages reflect a finer analysis of patterns over time rather than underlying differences in the tumors treated or the isotopes used. In particular, we assigned many decreasing tumors to patterns DS and SD, and some increasing ones to patterns DI and ID. Published plots that display regression patterns of uveal melanoma case by case in Abramson et al.\(^7\) and in two later studies\(^11,18\) confirm the existence of these subpatterns and a much wider variation than can accurately be described using four categories.

Except for zigzag, all patterns other than decrease, stable, and increase can be viewed as combinations of these three main patterns. The zigzag pattern, like the DI pattern, was not the result of local recurrence, because we excluded measurements from visits when recurrences were diagnosed. We also excluded overlying retinal detachments, bleeds, and other identifiable sources of bias when measuring the tumor. The zigzag pattern may derive from intermittent intratumoral edema, bleeding, or necrosis; and in some cases the shallowness, anterior location, or the irregular shape of the tumor likely made it more difficult to get a reading from exactly the same meridian. As a pooled group, the zigzag pattern still corresponded to tumor regression over time.

Kaiserman et al.\(^20\) found that the average half-life by first-order exponential decay of tumor thickness after ruthenium brachytherapy was 5.8 months with a plateau at 61%. In our series, the half-life was 5.1 months and the plateau was 59%, a very similar result. However, the half-life and plateau varied 4-fold by tumor shape, being approximately double the average for flat-to-crescent tumors and less than one-half for lobulated ones. The half-life of decay by cross-sectional area was 5.2 months, but the plateau was notably lower at 51%. Interestingly, half-lives of cross-sectional area by shape were much
FIGURE 3. Measured (left y-axis) and reduction in (right y-axis) thickness (white symbols) and cross-sectional area (black symbols) of 293 choroidal and ciliary body melanomas after brachytherapy, plotted in percentage according to the tumor regression pattern (adapted from Abramson et al.7). The main patterns are (A) decrease, (B) stable, and (C) other, the latter further divided into (D) decrease-stable, (E) decrease-increase, (F) stable-decrease, (G) increase-decrease, and (H) zigzag subpatterns. The light and dark shaded areas indicate the 95% confidence intervals, and the dashed and solid red curves the nonlinear regression lines by first-order exponential decay function of tumor thickness and cross-sectional area, respectively. Numbers below graphs are patients under follow-up. Note that exponential decay function could not be fitted to patterns stable (B), stable-decrease (F), and increase-decrease (G). Linear regression is shown instead in (B) and (F). Confidence interval too wide to plot in (G).
more similar and showed a less than 2-fold range, whereas the plateau varied even more widely than for tumor thickness.

The first-order exponential decay with plateau at 52% and 65% of initial thickness and cross-sectional area, respectively, provided an excellent fit for the progressively regressing D pattern. Interestingly, although plots of individual melanomas that regressed according to the DS, ID, and zigzag patterns showed changes in regression rate at widely varying time points, each pattern, when plotted as a group, likewise fitted well a first-order exponential decay function. However, these equations differed in their plateaus, modeling the predicted percentage regression at 3 years, by showing progressively less regression (46% vs. 31% vs. 26% as evaluated by thickness and cross-sectional area) as compared to tumor thickness. Importantly, the exponential decay function was not a reasonable fit for the S, SD, I, and ID patterns that together comprised 14% and 10% of uveal melanomas in our series based on thickness and cross-sectional area, respectively. These patterns may reflect other underlying biological differences.

Our findings also cast doubt on the validity of restricting analysis of regression of uveal melanomas to a specific time point or interval, a method typically used. For example, Kaiserman et al. defined the ITRR as the average monthly regression in thickness during the first 3 months. The median was 5.9% per month for 147 eyes treated with ruthenium plaques as compared to 4.4% for our 330 eyes, a comparable result. However, the ITRR was four times as fast for oval-to-dome-shaped and more than six times as fast for mushroom-shaped and lobulated tumors than for flat-to-crescent ones, and showed even more variation by regression pattern. We observed wide variation in regression patterns after 3 months, indicating that later regression of uveal melanomas cannot be predicted from their ITRR or IARR. This may explain why some studies have found an association with survival based on some but not all time points. Typically, studies on regression of uveal melanomas have failed to report tumor shape or have mentioned only the proportion of dome-shaped or mushroom-shaped melanomas. A different mix of tumor shapes and regression patterns among cases and controls is likely when a nonrandomized, retrospective, comparative analysis is based on specific types of radiotherapy or predictor, and likely will introduce bias to such comparisons. Typically, studies on regression of uveal melanomas have failed to report tumor shape or have mentioned only the proportion of dome-shaped or mushroom-shaped melanomas. A different mix of tumor shapes and regression patterns among cases and controls is likely when a nonrandomized, retrospective, comparative analysis is based on specific types of radiotherapy or predictor, and likely will introduce bias to such comparisons. Typically, studies on regression of uveal melanomas have failed to report tumor shape or have mentioned only the proportion of dome-shaped or mushroom-shaped melanomas. A different mix of tumor shapes and regression patterns among cases and controls is likely when a nonrandomized, retrospective, comparative analysis is based on specific types of radiotherapy or predictor, and likely will introduce bias to such comparisons.

We believe that our data are representative of choroidal melanomas in general because they come from a national referral center and cover 92% of all uveal melanomas that underwent brachytherapy. Of our 330 choroidal melanomas with or without ciliary body extension, 28%, 32%, 29%, and 11% represented size categories T1 to T4, as compared to 24%, 34%, 30%, and 12%, respectively, among the 7569 tumors from seven centers used to build the TNM classification. Ciliary body extension was present in 24% of eyes as compared to 25% in TNM data. The thickness measurements obtained with image analysis software also were in excellent agreement with the corresponding clinical measurements. Because of the retrospective

### Table 4. First-Order Exponential Decay Equation Fit Based on Thickness and Cross-Sectional Area Among 330 Choroidal Melanomas

<table>
<thead>
<tr>
<th>Variable</th>
<th>Half-Life (95% CI)</th>
<th>Plateau (95% CI)</th>
<th>P†</th>
<th>Height Regression</th>
<th>Area Regression</th>
</tr>
</thead>
<tbody>
<tr>
<td>All tumors</td>
<td>5.1 (4–9)</td>
<td>59 (55–63)</td>
<td>0.99</td>
<td>5.2 (4–8)</td>
<td>51 (46–55)</td>
</tr>
<tr>
<td>Bruch’s membrane</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unbroken</td>
<td>8.8 (6–16)</td>
<td>61 (55–67)</td>
<td>0.89</td>
<td>4.7 (3–8)</td>
<td>63 (59–67)</td>
</tr>
<tr>
<td>Broken</td>
<td>5.0 (3–9)</td>
<td>51 (45–56)</td>
<td>0.43</td>
<td>3.1 (3–4)</td>
<td>45 (43–48)</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>9.3 (5–14)</td>
<td>49 (27–71)</td>
<td>0.90</td>
<td>8.0 (3–∞)</td>
<td>43 (9–77)</td>
</tr>
<tr>
<td>COMS shape group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flat and crescent</td>
<td>9.6 (4–∞)</td>
<td>64 (44–45)</td>
<td>0.99</td>
<td>4.0 (2–∞)</td>
<td>69 (62–76)</td>
</tr>
<tr>
<td>Oval and dome</td>
<td>4.3 (3–9)</td>
<td>61 (56–66)</td>
<td>0.43</td>
<td>4.7 (4–6)</td>
<td>52 (48–53)</td>
</tr>
<tr>
<td>Mushroom</td>
<td>7.6 (4–25)</td>
<td>36 (23–49)</td>
<td>0.43</td>
<td>5.2 (3–13)</td>
<td>35 (24–43)</td>
</tr>
<tr>
<td>Lobulated</td>
<td>2.3 (1–∞)</td>
<td>53 (40–66)</td>
<td>0.37</td>
<td>2.9 (1–∞)</td>
<td>47 (35–60)</td>
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<td>Tumor regression pattern</td>
<td></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>D</td>
<td>4.4 (3–7)</td>
<td>52 (57–48)</td>
<td>0.43</td>
<td>4.4 (3–7)</td>
<td>65 (70–57)</td>
</tr>
<tr>
<td>S</td>
<td>Not legitimate</td>
<td></td>
<td></td>
<td>Not legitimate</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>4.8 (3–15)</td>
<td>31 (35–26)</td>
<td>0.89</td>
<td>5.6 (2–10)</td>
<td>52 (36–28)</td>
</tr>
<tr>
<td>DS</td>
<td>4.2 (3–8)</td>
<td>46 (51–42)</td>
<td>0.99</td>
<td>4.2 (3–9)</td>
<td>52 (57–46)</td>
</tr>
<tr>
<td>DI</td>
<td>2.6 (1–∞)</td>
<td>31 (38–24)</td>
<td>0.99</td>
<td>3.3 (1–∞)</td>
<td>41 (51–30)</td>
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<td>Not legitimate</td>
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<tr>
<td>ID</td>
<td>Not legitimate</td>
<td></td>
<td></td>
<td>Not legitimate</td>
<td></td>
</tr>
<tr>
<td>Zigzag</td>
<td>5.8 (2–∞)</td>
<td>26 (34–17)</td>
<td>0.43</td>
<td>2.6 (1–∞)</td>
<td>22 (30–14)</td>
</tr>
</tbody>
</table>

Combinations of D, S, and I indicate two sequential regression types. * Regression pattern could not be determined for 37 of the 330 tumors. † Runs test, two-sided.
design, it was not possible to measure cross-sectional area from exactly the same projection at each visit, which introduces some noise into our analysis, although we were careful to select always the image that most resembled the one recorded at diagnosis. In spite of this limitation, our measurements likely reflect the true tumor cross-sectional area more closely than formulas devised to calculate the volume of uveal melanomas reflect their true volume.\textsuperscript{15,17,18} Such formulas often give disparate results because they do not take into account the variable shapes of these tumors.\textsuperscript{51}

A further limitation is that no commonly agreed-upon system was available for classifying the shape of uveal melanomas. Comparison with the main COMS studies,\textsuperscript{5,52} excluding tumors classified as small, shows reasonably similar percentages (Supplementary Table S2), although the proportion of medium-sized tumors was much smaller in the ancillary COMS study. We combined flat with crescent, oval with dome shapes, and lobulated with irregular shapes, which together with the mushroom shape made four main categories of reasonable size. We propose that this classification be adopted for future studies on tumor regression.

We conclude that if exponential decay function (or any other model) is used to analyze regression of uveal melanomas after radiotherapy, such analysis should be stratified by regression pattern and, potentially, by tumor shape. We suspect that the heterogeneity in regression patterns explains the variable results of previous analyses of regression rates such as the apparent presence\textsuperscript{6,9,15,24} or absence\textsuperscript{5,7,14,18} of an association with survival and the presence\textsuperscript{8,9} or absence\textsuperscript{10,11,26} of an association with unfavorable chromosomal and gene expression profiles. Secondly, although we found a linear relationship between the thickness and cross-sectional area of choroidal melanomas at diagnosis, disparate regression rates of these measures indicate that one cannot be substituted for the other. We continue to consider thickness an adequate measure to assess regression in clinical practice, but we cannot presume that thickness alone is an adequate measure for research purposes. We propose that studies on regression of uveal melanomas should use both surrogates until direct measurements of volume are practical. The main disadvantage of analyzing cross-sectional area is that it takes additional time and effort to determine.

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References


Regression After Brachytherapy for Uveal Melanoma


