Effect of Radiation Dose on Ocular Complications after Iodine Brachytherapy for Large Uveal Melanoma: Empirical Data and Simulation of Collimating Plaques

Ilkka Puusaari, Jorma Heikkonen, and Tero Kivelä

**Purpose.** To calculate radiation doses to intraocular tissues in iodine brachytherapy (IBT) for large uveal melanoma, to study their relationship to ocular complications, and to assess a modified plaque design to reduce doses to the macula and optic nerve.

**Methods.** Ninety-six patients with a uveal melanoma, classified as large according to the Collaborative Ocular Melanoma Study criteria, underwent primary IBT. Median tumor height and diameter were 10.7 mm (range, 4.5–16.8) and 16.5 mm (range, 7.3–25.0) mm, respectively, and median follow-up was 3.5 years (range, 0.3–10.4). Each IBT was retrospectively modeled with a plaque simulator to calculate doses and dose rates to ocular tissues. Cox proportional hazards regression was used to assess their association with time to ocular complications, low vision, and blindness (20/70 or worse and loss of 20/400, respectively). A collimating plaque design was assessed by replacing the actual plaque with the modified one in each model.

**Results.** Median doses to tumor apex and base were 81 Gy (range, 40–158 Gy) and 384 Gy (range, 188–1143 Gy), respectively, and the median dose rates at these points were 53 Gy/h (range, 11–204) and 289 Gy/h (range, 84–1213) Gy/h, respectively. Median doses to the lens, macula, and optic disc were 69 Gy (range, 20–141), 79 Gy (range, 12–632), and 83 Gy (range, 10–377) Gy, respectively. Dose to the lens was associated with cataract (hazard ratio [HR] 1.15 for each 10-Gy increase, P = 0.002), and dose to the optic disc with optic neuropathy (HR 1.08, P = 0.001). Dose to the macula predicted low vision (HR 1.06, P = 0.025) and blindness (HR 1.10, P < 0.001). A collimating design provided a median reduction of 36% (range, 19% to 198%) and 30% (range, 9% to 160%) Gy in modeled doses to the macula and optic disc, respectively.

**Conclusions.** Simulated dose distribution together with tumor height predicts major complications and vision loss after IBT. Simulation suggests that clinically meaningful dose reduction to normal tissues is feasible with a redesigned brachytherapy protocol, which may help to reduce complications and vision loss after IBT of large uveal melanoma. (Invest Ophthalmol Vis Sci. 2004;45:3425–3434) DOI:10.1167/iovs.04-0066

**Episceral plaque brachytherapy has been proposed as an alternative to enucleation for selected patients with large uveal melanoma.** In terms of survival, enucleation and iodine-125 brachytherapy (IBT) appear comparable in this group of patients, based on data from the Collaborative Ocular Melanoma Study (COMS) and a retrospective, consecutive series of 97 patients who fulfilled the COMS inclusion criteria and in whom the melanoma was managed with IBT. Local tumor recurrence rate was 6% at 5 years after IBT, and chances of conserving the eye were fair. By survival analysis, it was estimated that the proportion of patients who avoid low vision and blindness would be 11% and 26% at 2 years after treatment, respectively.

After IBT of large uveal melanoma, vision is threatened by frequent side effects, many of which are likely related to radiation damage to ocular tissues uninvolved by the tumor. This is now potentially possible, with conformal positioning of iodine seeds and collimating plaque design that are made practical by improved computerized therapy planning systems. To exploit this potential, the ocular oncologist would benefit from empirical data on the actual dose distribution and the effects of different doses on ocular tissues.

We retrospectively investigated the radiation dose to various ocular tissues in a population-based cohort of 96 patients who underwent primary IBT between November 1990 and June 2001 for a uveal melanoma that was large according to the COMS criteria. We also evaluated the association between these doses and ocular complications and assessed the potential for realistic improvement in dose distribution with modified plaque design and standardized grading of prescription dose according to tumor height to reduce complications in future IBT of patients with large uveal melanoma.

**Patients and Methods**

**Goals of the Study**

The goals were to model radiation dose to intraocular tissues after primary IBT for large uveal melanoma; to assess the relationship between dose, ocular complications, and visual loss; and to test, by simulation, a modified plaque design to reduce the doses to the fovea and macula.

**Inclusion Criteria**

Eligible for this study were patients who had a uveal melanoma that met the COMS criteria for a large tumor (largest basal diameter [LBD] >16.0 mm and height >2.0 mm, height >10.0 mm, regardless of LBD, or a peripapillary tumor >8.0 mm by height and located within <2.0 mm of the optic disc), and whose disease had been managed with IBT between November 1, 1990, and June 1, 2001. Unlike COMS, we did not consider patients ineligible if they had a history of other coexisting disease that threatened survival, another cancer, or metastatic mela-
noma at the time of diagnosis, provided that treatment was otherwise indicated.

The files of the Ocular Oncology Service, Department of Ophthalmology, Helsinki University Central Hospital, a tertiary referral center that managed 90% of uveal melanomas in Finland (population, 5.2 million) during the study period, identified 121 patients with large uveal melanoma, of which 96 (79%) received IBT as the primary treatment. The primary treatment given to the remaining 25 patients who did not undergo IBT and the elements of informed consent and counseling of the patients have been described in detail.\(^1\) The study protocol adhered to the provisions of the Declaration of Helsinki.

**Clinical Evaluation**

The variables recorded included tumor height and LBD, best corrected visual acuity (VA), and intraocular pressure (IOP).\(^1\) Distance from the posterior tumor margin to the foveola and optic disc and the presence of exudative retinal detachment (RD) and vitreous hemorrhage were assessed with biomicroscopy, using a 90.0-D lens (Volk Optical, Mentor, OH) and binocular indirect ophthalmoscopy. Gonioscopy was used to determine the anterior tumor margin and to detect neovascularization of the iris and chamber angle.

**Iodine Brachytherapy**

Iodine-125 applicators were crafted in 1991 by a goldsmith to conform with ruthenium-106 plaques already in use.\(^9\) Four 0.5-mm-thick, unrimmed, noncollimating plaques were used: CCB (diameter 20 mm, circular, 10 seeds), CCC (Fig. 1A; 25 mm, circular, 12 seeds), COB (20 mm, notch for the optic nerve, 9 seeds), and CIB (diameter 20 mm, notch for the limbus, 8 seeds). Seeds were attached with silicone rubber (RTV 3140; Dow Corning, Midland, MI) that increased plaque thickness to 1.0 to 1.5 mm. The first treatments of the series used either 10 or 15 mCi seeds (model 6702; Mediphysics, Arlington Heights, IL) but since August 1994, 15 mCi was the standard seed intensity.

The dose to tumor apex was calculated at the time of the treatment with commercial brachytherapy software (Cadplan; Varian Dosetek, Helsinki, Finland). The angular and distance dependence dose rates were determined from tabulated correction matrices that included absorption and scatter correlations.\(^9\)–\(^11\) In 1995, the software was modified according to American Association of Physicists in Medicine Radiation Therapy Committee Task Group No. 43.\(^12\)

The prescription point was tumor height plus 1 mm for the sclera. Prescription dose was initially 100 Gy–80 Gy if the tumor was very thick in an effort to limit complications. Since 1997, the prescription dose has been 80 Gy to the apex, and very thick tumors have received a prescription dose of 70 to 60 Gy. Treatment time was calculated from the central axis depth dose curve. Seeds were replaced when the time approached 2 weeks. Some treatments that took place just before application of a fresh batch of seeds were performed by loading the plaque with additional seeds from the old batch to shorten treatment time. Three patients had treatment times in excess of 450 hours when delivery of seeds was delayed.

The tumor was localized with transillumination, using a fiberoptic probe, indirect ophthalmoscopy with scleral indentation, or both. A minimum safety margin of 2 mm around the tumor was desirable, but not an absolute requirement. Tumors close to the optic disc and macula were often irradiated with a smaller or no safety margin toward these structures. The intended position of the plaque relative to tumor margins, the macula, and the optic disc was checked at the end of the procedure by indenting the plaque to visualize its margin directly, transscleral illumination with a bent vitrectomy light probe positioned in contact with the plaque margin, or both.
Six patients received brachytherapy more than once. Three of these treatments were a planned continuation to, and took place within 12 weeks of, primary IBT, to cover an exceptionally large or inconveniently shaped tumor. The remaining three brachytherapies were secondary treatments warranted by local tumor recurrences. The former were delivered with two ruthenium-106 (CCB and CCC) and one iodine-125 (CCB) plaque, whereas the recurrences were treated with iodine plaques.

**Retrospective Analysis of Dose Distribution**

All treatments were retrospectively modeled with therapy-planning software, (Bebig Plaque Simulator [BPS], ver. 4.12; Bebig GmbH, Berlin, Germany) based on prospectively collected data in the registry of the ocular oncology service on the size, shape, and location of the tumor and the axial length (AL) of the eye at the time of primary treatment. In 50 models, these data and the shape of the eye were obtained from computed tomography and magnetic resonance images. Otherwise, the model was based on clinical and ultrasonographic data obtained from computed tomography and magnetic resonance images.

Each plaque and seed combination was created in the BPS. Templates provided for the ruthenium plaques, and a beta version (5.0.9B3) of the software was used to model two secondary ruthenium treatments for optimal accuracy.13 The plaques in the model were positioned by consensus of two investigators, based on location of the plaque, transillumination shadow, extraocular muscles, and the limbus, as recorded in the patient charts. Typically, the surgeon recorded distance of the tumor shadow and anterior plaque margin from the limbus and the insertions and margins of adjacent extraocular muscles, and the position of the fixation holes of the plaque relative to extraocular muscles. In five models, it was necessary to presume that the plaque had slid along the optic nerve, and offset from scleral surface (wobble) was applied accordingly.

In practice, the positioning of the seeds in the plaque may have varied up to 1 mm radially. We estimated that the position of a round plaque on the scleral surface may have deviated from the modeled position up to 2 mm radially and circumferentially. As a sensitivity analysis, a subgroup of 20 eyes irradiated with the round CCB and CCC plaques (which were used in 80 of the 96 treatments) was chosen at random, and doses to tumor apex and the center of the lens, macula, and optic disc were recalculated after a random displacement of either the seeds or the plaque within these limits.

Dose distribution was modeled using linear source approximation, correction for anisotropy, silicon carrier, and gold shell collimation. The following parameters were recorded from the program output: dose and dose rate at tumor base (inner scleral surface) and apex, at the center of the macula and the optic disc, at the posterior pole and center of the lens, at the nearest and farthest point of the chamber angle, and, when applicable, at the retina opposite the plaque’s center. Ratios of tumor apex dose to tissue dose, including the previously introduced T:M (tumor apex relative to the macula) and T:D (tumor apex relative to the optic disc) ratios,14 were calculated.

If a patient had undergone secondary brachytherapy within 3 months of the primary treatment, the doses were added for analysis. If secondary brachytherapy was given later, the patient was censored from analysis at that time.

**Extrapolated Response Dose**

To take into account the biological effects of dose rate and tissue susceptibility, extrapolated response doses (ERD) for each tissue were calculated from a linear-quadratic equation appropriate for nonpermanent implants with a decaying radiation source15:

\[
ERD = D \cdot (1 + \frac{(2R_A)}{(\mu - \lambda)} \cdot \frac{\beta}{\alpha} \cdot [1 - \exp(-\lambda T)]^{-1} \times \left\{ \frac{1}{2\lambda} \cdot [1 - \exp(-2\lambda T)] - (\mu + \lambda)^{-1} \cdot [1 - \exp(-T(\mu + \lambda))] \right\}
\]

where \(D\) is BPS dose, \(R_A\) is dose rate at start of treatment, \(T\) is treatment time, \(\lambda\) is radioactive decay constant (0.693/the half-life of the isotope), \(\alpha/\beta\) is a tissue-specific ratio of two constants representing cell damage and repair, and \(\mu\) is a time constant (0.46 hours\(^{-1}\)). A small \(\alpha/\beta\) ratio is typical of healthy, late-reacting tissues capable of repairing radiation damage, whereas a large \(\alpha/\beta\) ratio is typical of early reacting malignant tumors with limited repair capability. An \(\alpha/\beta\) ratio of 9.75, based on an average \(\alpha/\beta\) of various uveal melanoma cell lines,16 was used for tumor tissue, 1.2 for the lens,17 and 2.5 was assumed for retina, optic nerve, and other late-reacting normal tissues. Patients who underwent secondary brachytherapy were excluded from the analysis.

**Clinical Outcome Variables**

Patients were followed up at 3, 6, and 12 months after IBT, biannually for at least 5 years and at least once a year thereafter. Time to the following outcomes was assessed, the evaluation criteria of which have previously been described in detail1,18: treatment-related cataract (consisting of or including posterior subcapsular opacity); neovascularization of the iris, chamber angle, or both; glaucoma (IOP >24 mm Hg); radiation optic neuropathy; radiation maculopathy; exudative RD (one quarter or more in size, progressive or persisting at least 6 months); vitreous hemorrhage; low vision (World Health Organization definition, visual acuity 20/70 or lower); and blindness (loss of 20/400) of the tumorous eye.

**Simulation of Treatment with Collimating Plaques**

A collimating design for the round CCB and CCC plaques was created with the BPS. Notched COB and CIB plaques were not redesigned, because dose to the optic nerve would be high despite collimation, and collimation at the limbus would have small effect on already low doses to the fovea and optic disc. Furthermore, the margins of ciliary body tumors are difficult to localize accurately and, in both locations, scattered radiation outside the plaque margins is likely to improve local tumor control. Patients managed with two sequential plaques or who received secondary brachytherapy were excluded from the analysis.

The CCB and CCC plaques were redesigned to have the same diameter, external shape, and number of seeds as the plaques used in the actual treatments, but to be 1.0 mm thicker (Fig. 1B). Along the plaque margin, six (CCB) or eight (CCC) seeds were placed in 5.0-mm-long and 1.1-mm-deep slots (offset, 0.6 mm) in the gold shell, to obtain a collimating effect that reduces laterally directed radiation. The four seeds in the plaque center were not placed in collimating slots, to ascertain adequate radiation of the entire tumor base. They were arranged as a cross to take advantage of seed anisotropy in reducing radiation to adjacent tissues (Fig. 1).

The position of the plaque and the activity of the seeds were taken from the actual IBT. If other than the default number of seeds had been used in the actual treatment (two with less, five with more than the default), the redesigned plaque was loaded with the default number, adjusting the reference date to keep treatment time within 2 weeks. If the plaque apparently had slide along the optic nerve, the redesigned plaque was moved to avoid the slide.

The end date of treatment was altered, if necessary, to deliver the following prescription dose to the tumor apex: 80 Gy to tumors 12 mm or less in height, 70 Gy to tumors from 12 to 14 mm, and 60 Gy to tumors more than 14 mm. Doses to the macula and optic disc were calculated with the BPS and compared with corresponding doses from the actual treatment, based on both absolute doses and the T:M and T:D ratios, which are not influenced by any change in the prescription dose.

**Statistical Methods**

Follow-up data up to the date of analysis on November 30, 2001, were collected prospectively into a dedicated database (developed with
Results

Median age at diagnosis of the 96 patients (male:female, 48:48), all white, was 64 years (range, 24–82). Median follow-up time was 3.5 years (range, 0.3–10.4).

Median tumor height and LBD were 10.7 (range, 4.5–16.8) and 16.5 (range, 7.3–25.0) mm, respectively. Ten (10%) of the tumors were classified as large, on the basis of their peripapillary location, and 61 (64%) involved the ciliary body. The posterior margin of the tumor touched the optic disc in 13 (14%) eyes and extended to within 2 mm of it in 10 (10%) eyes in the computer model. The median distance from posterior tumor margin to the center of the fovea was 6.0 mm (range, 0–17.0).

Dose Distribution and Dose Rate

The tumor apex (prescription point) was a median of 11.3 mm from the outer scleral surface. The median prescribed dose was 87 Gy (range, 42–109) at a median dose rate of 57 cGy/h (range, 13–217; Fig. 2A). Median treatment duration was 147 hours (range, 42–599).

The median BPS doses at tumor apex and tumor base were 81 and 384 Gy, respectively (Fig. 3). The median dose rates at these points were 53 (range, 11–204) and 289 (range, 84–1213) cGy/h, respectively. The range of dose rates at tumor apex was 53 (range, 11–204).
Association between Dose and Ocular Complications

Cataract progressed in 65 patients, including those who received the lowest doses to the lens (Fig. 4A). By univariate Cox regression, time to progression was associated with dose to the center (HR 1.15 for each 10-Gy increase, $P = 0.002$) and posterior pole (HR 1.14 for each 10-Gy increase, $P = 0.003$) of the lens, but not with corresponding dose rates ($P = 0.44$ and 0.67, respectively). A trivariate model, which combined dose to the lens center with age at diagnosis and diabetes as confounders (Table 1), did not fit the data better than a model based on the same confounders and tumor height\(^\text{17}\) ($–2 \log$ likelihood $472.83$ vs. $472.40$, $P = 0.56$, $\chi^2$ test, 1 df).

Iris neovascularization (Fig. 4B) was associated with dose to the Macrophage retina in the 87 eyes for which this variable was applicable (HR 1.72 for each 10-Gy increase, $P = 0.018$), but was unassociated with dose to chamber angle and dose rate at all points measured. In trivariate models, dose to the opposite retina (Table 1) and tumor height provided a similar fit ($–2 \log$ likelihood $358.89$ vs. $358.74$, $P = 0.70$, $\chi^2$ test, 1 df) when combined with two known confounders, presence of RD at diagnosis and diabetes.\(^\text{18}\)

Secondary glaucoma (Fig. 4C) was associated with dose to the opposite retina (HR 1.90 for each 10-Gy increase, $P = 0.025$), even when adjusted for tumor height and IOP at diagnosis ($P = 0.024$, Table 1), two clinical predictors of glaucoma after IBT.\(^\text{18}\)

Macrophage developed in one patient when the dose to the macula was less than 40 Gy or the T:M ratio was more than 2.0 and in five patients when the dose was less than 50 Gy (Figs. 4D, 4E). A statistical association with dose to ($P = 0.47$), or dose rate at ($P = 0.34$), the center of the macula was not evident. Distance of the posterior tumor margin to the center of the fovea was significantly associated with development of macrophage,\(^\text{18}\) even when adjusted for dose to the macula (HR 0.84 for each 1-mm increase, $P = 0.015$; Table 1).

Optic neuropathy developed in two patients when the dose to the optic disc was less than 50 Gy or the T:D ratio was more than 1.5 (Figs. 4F, 4G) and was associated with dose to (HR 1.08 for each 10-Gy increase, $P = 0.001$), and dose rate at (HR 1.06 for each 10-Gy/h increase, $P = 0.002$), the optic disc. Patients with a T:D ratio less than one were four times as likely to have optic neuropathy as those with a higher ratio (HR 4.37, $P = 0.004$). In a bivariate model which adjusted for distance from the posterior tumor margin to the optic disc,\(^\text{18}\) dose to the optic disc remained significant (Table 1).

Persistent exudative RD (Fig. 4H) was associated only with dose to the opposite retina (HR 1.87 for each 10-Gy increase, $P = 0.07$). In a bivariate model with location of the anterior tumor margin in the ciliary body, dose to the opposite retina did not improve the fit of the model compared with a model that replaced it with tumor height\(^\text{18}\) ($–2 \log$ likelihood $157.57$ vs. $136.24$, $P = 0.29$, $\chi^2$ test, 1 df). Vitreous hemorrhage was not associated with any dose or dose rate analyzed.

**Association between Dose and Loss of Vision**

By univariate regression, low vision and blindness of the tumorous eye (according to WHO definitions) were associated with dose to the optic disc (HR 1.04 and 1.06 for each 10-Gy increase, $P = 0.055$ and $P = 0.001$, respectively, Table 2), and macula (HR 1.06 and 1.10 for each 10-Gy increase, $P = 0.025$ and $P < 0.001$, respectively). In bivariate models with tumor height, dose to the macula independently predicted low vision and blindness, whereas dose to the optic disc independently predicted only blindness (Table 2).

Dose to the macula showed no association with low vision in a trivariate model with tumor height and location of the...
anterior tumor margin in the ciliary body (Table 2)—another factor associated with vision loss in this data set. This model did not provide a better fit than the corresponding bivariate model without ciliary body involvement ($P = 0.76, \chi^2$ test, 1 df) and was not preferred to the latter one. Dose to the macula remained associated with blindness in a similar trivariate model.

![Figure 4. Kaplan-Meier curves showing the proportion of patients with large uveal melanoma who were free of (A) cataract, (B) iris neovascularization, (C) glaucoma, (D, E) radiation maculopathy, (F, G) radiation optic neuropathy, and (H) persistent exudative retinal detachment after iodine brachytherapy. The time scale is logarithmic. The curves are superimposed on a scatterplot coded to show the type of observation and the dose to (A) lens center, (B, C) chamber angle, (D) fovea, (E) disc, and (H) opposite retina (or the ratio of dose to tumor apex relative to dose to (E) the macula and (G) the optic disc. Solid dot: the event of interest. Censored observations: open dot, end of follow-up; +, death; triangle, secondary brachytherapy; box, secondary enucleation; and \(\times\), fundus view lost.]

<table>
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<tr>
<th>Variable</th>
<th>Coefficient (SE)</th>
<th>Wald $\chi^2$</th>
<th>$P$</th>
<th>Hazard Ratio (95% CI)</th>
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<tr>
<td>Cataract $-2 \log$ likelihood = 472.83 (65 events)</td>
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<tr>
<td>Dose to lens center*</td>
<td>0.158 (0.044)</td>
<td>9.67</td>
<td>0.002</td>
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<td>Age†</td>
<td>0.006 (0.011)</td>
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<td>0.59</td>
<td>1.01 (0.98-1.05)</td>
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<td>Diabetes‡</td>
<td>0.154 (0.600)</td>
<td>0.05</td>
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<td>Iris neovascularization $-2 \log$ likelihood = 358.89 (54 events)</td>
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<td>Dose to opposite retina*</td>
<td>0.056 (0.025)</td>
<td>5.81</td>
<td>0.016</td>
<td>1.76 (1.11-2.77)</td>
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<td>Retinal detachment‡</td>
<td>0.447 (0.420)</td>
<td>1.12</td>
<td>0.29</td>
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<td>Diabetes‡</td>
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<td>2.05 (0.46-9.08)</td>
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<td>Dose to opposite retina*</td>
<td>0.756 (0.325)</td>
<td>5.11</td>
<td>0.024</td>
<td>2.09 (1.10-3.95)</td>
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<td>Tumor height§</td>
<td>-0.038 (0.110)</td>
<td>0.12</td>
<td>0.73</td>
<td>0.96 (0.78-1.19)</td>
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<td>IOP at diagnosis§</td>
<td>0.070 (0.047)</td>
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<td>0.14</td>
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<td>Dose to disc*</td>
<td>0.062 (0.031)</td>
<td>4.12</td>
<td>0.042</td>
<td>1.06 (1.00-1.15)</td>
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<td>Distance to disc§</td>
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<td>1.61</td>
<td>0.20</td>
<td>0.92 (0.82-1.04)</td>
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<td>Maculopathy (tumors located $\geq$ 2 mm from fovea) $-2 \log$ likelihood = 175.64 (25 events)</td>
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<td>Dose to macula*</td>
<td>-0.008 (0.007)</td>
<td>1.21</td>
<td>0.27</td>
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<td>Distance to macula§</td>
<td>-0.178 (0.073)</td>
<td>5.90</td>
<td>0.02</td>
<td>0.84 (0.75-0.97)</td>
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* Continuous variable (10 Gy).
† Continuous variable ($y$).
‡ Coding no = 0; yes = 1.
§ Continuous variable (mm).
∥ Continuous variable (mm Hg).
model, but this model did not improve fit \((P=0.10)\). Tumor height retained an independent association with loss of vision in all models. Dose to the optic disc showed a weaker association with low vision than dose to the macula, and provided a poorer fit as regards blindness (Table 2).

## Extrapolated Response Dose

Optic neuropathy and blindness, which were strongly associated with dose to the optic disc and dose to the macula, respectively, were also associated with corresponding ERD, but the association was weaker (HR 1.02 vs. 1.08 for neuropathy and 1.01 vs. 1.10 for blindness). In all other analyses, replacing dose with ERD resulted in loss of a significant association with the outcome of interest, if present.

## Simulated Treatment with Collimating Plaques

Simulated treatments with collimating plaques and standard prescription doses graded according to tumor height were modeled in 77 patients (58 managed with a CCC plaque and 19 with a CCB). These models suggest a median decrease of 56 Gy (range, 19-Gy increase to 198-Gy decrease) in dose to the center of the macula and a median decrease of 30 Gy (range, 9-Gy increase to 160-Gy decrease) in dose to the optic disc, when compared with the BPS doses of the actual treatments (Fig. 5). The median T:D and T:M ratios, based on these 77 patients, improved from 0.94 (range, 0.39–3.15) to 1.61 (range, 0.35–5.27) and from 0.99 (range, 0.27–2.59) to 1.81 (range, 0.36–4.04), respectively.

Of 69 patients whose BPS dose to the macula had exceeded 50 Gy, 45 (65%) avoided this level of radiation in the simulation with collimating plaques, and 23 (38%) of 60 patients avoided an identical dose to the optic disc.

## Discussion

The dose to tumor apex as modeled with the BPS corresponded well with the originally calculated dose obtained from general radiotherapy-planning software, provided that ultrasoundography was accurate, which supports the validity of the BPS4,24 in eyes in with large uveal melanoma. When IBT with two sequential plaques is planned for a particularly broad tumor or when the posterior margin of a large plaque extends close to the optic nerve, the BPS appears to be particularly useful for obtaining an accurate dose and placement of the plaque. A limitation of the BPS software in planning IBT for large uveal melanoma is that it currently does not allow tumor modeling when tumor height exceeds the radius of the eye and, hence, automatic prescription to tumor apex.

The BPS depends on the accuracy of clinical examination and, in retrospective studies, on the quality of the patient’s records. The position of the plaque in the model cannot be completely controlled retrospectively, and the results should thus be interpreted with caution until confirmed by prospective studies. Using extraocular muscles and limbus as landmarks, we found that retrospective positioning of the plaque with little ambiguity was possible in most cases, with sufficient

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### Table 2. Cox Proportional Hazards Regression of Time to Low Vision (20/70 or worse) and Blindness (loss of 20/400) in the Tumorous Eye of 96 Patients with a Large Uveal Melanoma who Underwent Iodine Brachytherapy

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<th>Variable</th>
<th>Coefficient (SE)</th>
<th>Wald ( \chi^2 )</th>
<th>( P )</th>
<th>Hazard Ratio (95% CI)</th>
<th>Coefficient (SE)</th>
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<td>Dose to tumor apex*</td>
<td>0.045 (0.081)</td>
<td>0.30</td>
<td>0.580</td>
<td>0.96 (0.82–1.12)</td>
<td>0.045 (0.081)</td>
<td>0.30</td>
<td>0.580</td>
<td>0.96 (0.82–1.12)</td>
</tr>
<tr>
<td>Dose to tumor base*</td>
<td>0.002 (0.007)</td>
<td>0.06</td>
<td>0.081</td>
<td>1.00 (0.99–1.01)</td>
<td>0.002 (0.007)</td>
<td>0.06</td>
<td>0.081</td>
<td>1.00 (0.99–1.01)</td>
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<td>Dose to lens center*</td>
<td>0.048 (0.055)</td>
<td>0.81</td>
<td>0.370</td>
<td>1.05 (0.95–1.16)</td>
<td>0.048 (0.055)</td>
<td>0.81</td>
<td>0.370</td>
<td>1.05 (0.95–1.16)</td>
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<tr>
<td>Dose to optic disc*</td>
<td>0.037 (0.018)</td>
<td>4.41</td>
<td>0.055</td>
<td>1.04 (1.00–1.07)</td>
<td>0.037 (0.018)</td>
<td>4.41</td>
<td>0.055</td>
<td>1.04 (1.00–1.07)</td>
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<td>Dose to macula*</td>
<td>0.056 (0.025)</td>
<td>5.02</td>
<td>0.025</td>
<td>1.06 (1.01–1.11)</td>
<td>0.056 (0.025)</td>
<td>5.02</td>
<td>0.025</td>
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<td>T:D ratio</td>
<td>-0.256 (0.104)</td>
<td>6.10</td>
<td>0.013</td>
<td>0.77 (0.65–0.95)</td>
<td>-0.256 (0.104)</td>
<td>6.10</td>
<td>0.013</td>
<td>0.77 (0.65–0.95)</td>
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<td>T:M ratio</td>
<td>-0.446 (0.155)</td>
<td>8.47</td>
<td>0.004</td>
<td>0.64 (0.47–0.86)</td>
<td>-0.446 (0.155)</td>
<td>8.47</td>
<td>0.004</td>
<td>0.64 (0.47–0.86)</td>
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<td>Bivariate analysis</td>
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<tr>
<td>Dose to macula*</td>
<td>0.048 (0.028)</td>
<td>3.06</td>
<td>0.081</td>
<td>1.05 (0.99–1.11)</td>
<td>0.048 (0.028)</td>
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<td>1.05 (0.99–1.11)</td>
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<tr>
<td>Dose to macula*</td>
<td>0.054 (0.029)</td>
<td>3.46</td>
<td>0.063</td>
<td>1.06 (1.00–1.12)</td>
<td>0.054 (0.029)</td>
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<tr>
<td>Tumor height‡</td>
<td>0.273 (0.082)</td>
<td>10.96</td>
<td>0.001</td>
<td>1.31 (1.12–1.54)</td>
<td>0.273 (0.082)</td>
<td>10.96</td>
<td>0.001</td>
<td>1.31 (1.12–1.54)</td>
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<td>Model 4</td>
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<tr>
<td>Dose to optic disc*</td>
<td>0.022 (0.018)</td>
<td>1.49</td>
<td>0.221</td>
<td>1.02 (0.99–1.06)</td>
<td>0.022 (0.018)</td>
<td>1.49</td>
<td>0.221</td>
<td>1.02 (0.99–1.06)</td>
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<td>Model 5</td>
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<tr>
<td>Tumor height‡</td>
<td>0.270 (0.084)</td>
<td>10.24</td>
<td>0.001</td>
<td>1.31 (1.11–1.54)</td>
<td>0.270 (0.084)</td>
<td>10.24</td>
<td>0.001</td>
<td>1.31 (1.11–1.54)</td>
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<td>Trivariate analysis</td>
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<tr>
<td>Dose to macula*</td>
<td>0.042 (0.027)</td>
<td>1.85</td>
<td>0.173</td>
<td>1.04 (0.98–1.11)</td>
<td>0.042 (0.027)</td>
<td>1.85</td>
<td>0.173</td>
<td>1.04 (0.98–1.11)</td>
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<tr>
<td>Dose to optic disc*</td>
<td>0.021 (0.021)</td>
<td>1.06</td>
<td>0.304</td>
<td>1.02 (0.98–1.06)</td>
<td>0.021 (0.021)</td>
<td>1.06</td>
<td>0.304</td>
<td>1.02 (0.98–1.06)</td>
</tr>
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</table>

SE, standard error; CI, confidence interval; T:M, tumor:macula; T:D, tumor:optic disk.

* Continuous variable (10 Gy).
† Continuous variable (mm).
‡ Categories: 0 = in the ciliary body; 1 = behind the ora serrata.
accuracy to suggest unobserved tilting of some posteriorly placed plaques from the scleral surface along the optic nerve. Sensitivity analysis suggested that the retrospective BPS doses to tumor apex reported in our study should be essentially unaffected by error in placement of the seeds and the plaque in the model, and that the mean doses to the lens, macula, and optic disc are unlikely to deviate more than 5 Gy from actual mean doses. The BPS off-axis doses are also subject to up to 11% deviation due to the mathematical approximations used by the software. In general, this error is reported to be 5% or less. 

Further limitations of our study are retrospective coding of some complications such as persistence of RD, missing observations at some visits, and the fact that posterior pole complications could have been missed after visibility to the fundus was compromised. The latter problem was taken into account by censoring patients from analysis at that point. However, censoring in such instances probably was not independent of the outcome of interest, which introduces bias.

Because of the large size of the tumor and use of a noncollimating plaque, adjacent ocular tissues often received a high dose of radiation. Of the complications analyzed, optic neuropathy and cataract were most strongly associated with dose. Furthermore, loss of visual acuity was strongly related to the dose to the macula and optic disc. Tumor height, which correlates with dose to adjacent tissues and to tumor volume, remained independently associated with loss of vision, even when adjusted for dose to the macula and optic disc. Moreover, substituting tumor height with dose to the lens, chamber angle, and opposite retina did not significantly improve the fit of multivariate models predicting development of cataract, neovascularization of the iris, and secondary glaucoma. Thus, for clinical purposes, tumor height remains a robust predictor of a high risk of major complications and vision loss after IBT of a large choroidal and ciliary body melanoma.

Cataract progressed after IBT in almost all tumor eyes in our data set, in support of a low radiation tolerance of the lens, reported to be ~16 Gy, which was invariably exceeded in this cohort with a large melanoma. In eyes that received higher doses, cataract developed earlier, even within months of IBT, which is consistent with the observation that latency of cataract is an inverse function of radiation dose. 

Lack of a significant association between maculopathy and dose to the center of the macula was contrary to some reports. Radiation maculopathy results from damage to vessels that course around the macula to feed the foveal area. These vessels may receive much larger doses than the fovea itself. After proton beam therapy, the risk for maculopathy was reported to level after a radiation exposure of 40 Gy to the fovea. The majority, or 84, of our patients, received at least this dose, weakening the possibility of confirming an association between dose and maculopathy, should the same nonlinear relationship apply to IBT. Moreover, some large melanomas, directly and through exudative RD, damage the macula irrespective of radiation, and many eyes that were censored from analysis after visibility to the fundus was lost had large macular doses, both of which are sources of bias in this analysis.

Optic neuropathy is common after IBT of a large or posteriorly located uveal melanoma, and no effective treatment is available for this condition. Our data suggest that the tolerance of the optic nerve for IBT was between 40 and 60 Gy, in agreement with reports concerning optic neuropathy after other types of irradiation, which have suggested a threshold of 30 to 50 Gy. The sensitivity of the optic nerve to high dose rates has also been documented by others.

Iris neovascularization, glaucoma, and persistent RD were associated with dose to the opposite retina, but this finding must be taken with caution, because tumor height is a confounder. It is probable that tumor height in this model reflects both the dose to adjacent tissues, and the mechanical and physical disturbance before and the amount of tissue undergoing regression after IBT of large uveal melanoma.

The dose rate at the tumor apex in our series varied more widely than the guidelines of the COMS allow and the recent recommendations of the ABS propose. In one series of mainly small to medium-sized uveal melanomas, low dose rate to tumor apex and base, in addition to large tumor dimension, tumor proximity to the optic disc, and low dose to tumor apex, were associated with a higher risk of tumor recurrence. Radiobiological modeling provides theoretical support for an association between low dose rate and local recurrence. The local recurrence rate of 6% at 5 years in our study compares favorably with other series of IBT, despite widely vary-
ing dose rates. However, because all tumors were large and the competing risk of metastatic death was consequently high, some patients may have died before detectable recurrence had time to develop. The small number of recurrences precluded analysis of their association with dose and dose rate.

High dose rates are thought to be more damaging to late-reacting normal tissues than to tumor cells. This effect increases with increasing irradiated volume,\textsuperscript{22} which was large in our study. ERD was designed to take tissue susceptibility and dose rate effect into account.\textsuperscript{15} The lack of association between dose rate and ocular complications other than optic neuropathy, and the fact that ERD was not superior to BPS dose in regression analysis, was unexpected. However, the dose rate effect is reported to be less pronounced at rates of 60 cGy/h or less,\textsuperscript{43} and more than half of the eyes in our data set received a lower apical dose rate. In support of this possibility, a study of smaller melanomas, which reported a comparable mean macular dose (98 Gy vs. 101 Gy in our study) but much higher of smaller melanomas, which reported a comparable mean dose rates. However, because all tumors were large and the competing risk of metastatic death was consequently high, some patients may have died before detectable recurrence had time to develop. The small number of recurrences precluded analysis of their association with dose and dose rate.

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Models of collimating plaques confirmed that small changes in plaque design may notably reduce radiation dose to the optic nerve, macula, and other tissues adjacent to the tumor, increasing the therapeutic ratio without compromising tumor dose. In contrast, such collimating plaques require absolute safety margins. Favorable theoretical dose distributions have been reported with plaques in which each source is individually collimated.\textsuperscript{4} Ensuring an adequate dose to the entire tumor base and underlying sclera using individually collimated seeds would require the use of an increased number of seeds of correspondingly lower intensity. Although a more radical redesign would have further decreased dose to tissues immediately adjacent to the plaque edge, this zone less frequently extends to the macula and optic disc and it acts as a safety border against marginal tumor recurrence.

The reduction in doses to the macula and optic disc achieved with collimating plaques was, in some patients, partly due to the standard prescription dose graded by tumor height, so that very thick tumors received 60 to 70 Gy instead of 80 to 100 Gy in the simulation, as has been our practice more recently. The improvement in T:M and T:D ratios, however, reflects the benefit from plaque redesign only. Although the doses to the macula and optic disc were reduced by a mean of 45% to 38%, doses still exceeded the proposed tolerance limits in many patients. Use of collimating plaques is likely to improve the chances of saving vision in selected patients, but alternative treatments such as transscleral local resection need to be considered.\textsuperscript{47,48} Prospective, preferably randomized clinical trials are needed to translate our simulations to evidence-based benefit to patients with large uveal melanoma.

References


