Plaque Radiotherapy of Uveal Melanoma With Predominant Ciliary Body Involvement

Kaan Gündüz, MD; Carol L. Shields, MD; Jerry A. Shields, MD; Jacqueline Cater, PhD; Jorge E. Freire, MD; Luther W. Brady, MD

Background: There are several options for management of ciliary body melanoma, including plaque radiotherapy, charged particle irradiation, local resection, and enucleation. The choice of therapy depends on many factors, and plaque radiotherapy is often used.

Objectives: To determine the outcome of plaque radiotherapy in the management of ciliary body melanoma and to identify the risk factors associated with the development of radiation complications, tumor recurrence, metastasis, and melanoma-related death after plaque radiotherapy of ciliary body melanoma.

Methods: We analyzed the clinical records of 136 patients with ciliary body melanoma who were treated with plaque radiotherapy between July 1976 and June 1992.

Results: The median follow-up period was 70 months. Using Kaplan-Meier survival estimates, the most frequent radiation complication at 5 years’ follow-up was cataract, developing in 48% of the patients, followed by neovascular glaucoma (21%), retinopathy (20%), scleral necrosis (12%), and vitreous hemorrhage (11%). Visual acuity decrease (by ≥3 Snellen lines) was noted in 40% of the patients at 5 years. Kaplan-Meier estimates showed that 8% of the patients developed recurrence, 28% had metastasis, and 22% died of melanoma-related causes by 5 years. Univariate analysis demonstrated that the factors predictive of radiation cataract were superonasal (P = .003) and inferior tumor meridian (P = .02) compared with inferonasal meridian and apex dose rate greater than 57 cGy/h (P = .05). The development of neovascular glaucoma was significantly related to iris involvement with the ciliary body tumor (P < .001).

Conclusions: Plaque radiotherapy offers 92% 5-year local control rate for ciliary body melanoma. Metastasis occurs in 28% of the patients treated with this method by 5 years. Patients with tumors greater than 7 mm in thickness are at greater risk than patients with thinner tumors for metastatic disease and melanoma-related death. Major radiation complications include radiation cataract, neovascular glaucoma, retinopathy, tumor recurrence, and metastasis in multivariate analysis.


The factors predictive of development of radiation retinopathy were base dose rate greater than 230 cGy/h (P = .03) and the presence of diabetes mellitus (P = .05). The only predictor of metastasis was tumor thickness greater than 7 mm (P = .02). The risk factors for melanoma-related death were the presence of metastasis (P < .001), tumor thickness greater than 7 mm (P = .02), and recurrence (P = .02). Multivariate analyses showed that the most significant variables predictive of the development of scleral necrosis were intraocular pressure greater than 15 mm Hg (P < .001) and tumor thickness greater than 7 mm (P = .007). The most significant predictive factors for vitreous hemorrhage were visual acuity of 20/40 to 20/200 (P = .02) and intraocular pressure greater than 15 mm Hg (P = .02). The best subset of independent predictors of vision decrease were mushroom tumor shape (P = .002), age older than 61 years (P = .006), and superonasal meridian (P = .04). The risks for melanoma-related death were presence of metastasis (P < .001) and tumor thickness greater than 7 mm (P = .01). There was no group of significant variables predictive for radiation cataract, neovascular glaucoma, retinopathy, tumor recurrence, and metastasis in multivariate analysis.

The management of ciliary body melanoma is controversial. In view of the controversy regarding enucleation, there has been increasing interest in conservative forms of management including plaque radiotherapy, charged particle (helium ion and proton beam) irradiation, and surgical resection. It is not known whether different treatment methods (enucleation vs plaque radiotherapy, enucleation vs proton beam irradiation, local resection vs plaque radiotherapy, and helium ion irradiation vs plaque radiotherapy) have any advantageous effect on survival in patients with ciliary body and choroidal melanoma.

Regardless of the treatment method used, ciliary body melanoma generally has a poor prognosis compared with uveal melanoma in general. The overall 5-year metastatic rate for patients with poste-
All patients who were diagnosed as having ciliary body melanoma and were treated with plaque radiotherapy on the Ocular Oncology Service at Wills Eye Hospital, Philadelphia, Pa, between July 1976 and June 1992 were included in our study. For purposes of this study, a ciliary body melanoma was defined as a melanoma that had its center in the ciliary body and in which more than 50% of the tumor was located in the ciliary body. Tumors with a center in the choroid or in the iris and that had minor ciliary body involvement were excluded from this study.

The baseline clinical variables evaluated included age, sex, race, patient history of diabetes mellitus, systemic hypertension, best-corrected initial visual acuity (>20/40, 20/40-20/200, <20/200), and baseline intraocular pressure. (The variables marked with an asterisk were used as reference for later statistical analysis). Tumor data included tumor location (ciliary body, ciliochoroidal, intraocular, ciliooculochoroidal), tumor meridian (superior, superotemporal, temporal, inferotemporal, inferior, inferonasal, nasal, supranasal, or macular), the distance of the posterior edge of the tumor to the optic nerve and foveola, maximum basal tumor diameter (from indirect opthalmoscopy and B-scan ultrasonography), thickness (from A-scan and B-scan ultrasonography), shape (dome, mushroom, diffuse, and plateau, as defined by indirect opthalmoscopy and B-scan ultrasonography), the presence of subretinal fluid (from indirect opthalmoscopy and A-scan and B-scan ultrasonography), retinal invasion (from indirect opthalmoscopy, B-scan ultrasonography, and fluorescein angiography), and extrachoroidal extension (from slitlamp biomicroscopy and A-scan and B-scan ultrasonography).

The plaque size was selected to be 2 mm larger than the tumor on all the sides. The plaque radiotherapy data included radioactive isotope used (iodine 125, rhenium 106, cobalt 60, and iridium 192); plaque shape (round, notched, boomerang, postage stamp); plaque size; hours of radiation; radiation dose to the apex, base, optic disc, fovea, and lens (in centigrays); and dose rate to apex, base, optic disc, fovea, and lens (in centigrays per hour).

The follow-up examinations were generally made at 3- to 6-month intervals up to 5 years and at 6- to 12-month intervals thereafter. Information on the Snellen visual acuity and the development of radiation retinopathy, papillopathy, cataract, neovascular glaucoma, scleral necrosis, vitreous hemorrhage, recurrence, and metastasis was recorded. The time interval to the development of each event was determined.

Nonproliferative radiation retinopathy was diagnosed if capillary bed changes (nonperfusion, dilation, microaneurysms), retinal hemorrhage, retinal exudation, retinal edema, vascular sheathing, or nerve fiber layer infarctions were found. Radiation maculopathy was diagnosed when any of these changes occurred within 3 mm from the foveola. A diagnosis of proliferative radiation retinopathy was made when there was retinal neovascularization or optic disc neovascularization. Radiation papillopathy was diagnosed when peripapillary exudates, hemorrhages, or optic disc swelling was present.

Radiation cataract was defined as the development of a lens opacity, especially posterior subcapsular cataract, which was not present before radiation treatment. The diagnosis of neovascular glaucoma was made based on the presence of iris and/or angle neovascularization and intraocular pressure rise. Radiation scleral necrosis was diagnosed when there was sufficient scleral erosion to allow direct visualization of uveal tissue. A diagnosis of radiation vitreous hemorrhage was made when there was vitreous blood detectable with slit-lamp biomicroscopy, indirect ophthalmoscopy, or A-scan and B-scan ultrasonography.

Tumor recurrence was defined as any degree of documented tumor growth (in thickness or base) detected by opthalmoscopy and A-scan and B-scan ultrasonography. The final tumor thickness (as measured by A-scan and B-scan ultrasonography), final best-corrected Snellen visual acuity, and presence of metastasis (documented by physical examination and laboratory studies and proven by histopathological assessment) were determined. Melanoma-related deaths and deaths from other causes were recorded.

The major outcomes analyzed in this study were the development of radiation cataract, neovascular glaucoma, retinopathy, scleral necrosis, vitreous hemorrhage, papillopathy, visual acuity decrement, tumor recurrence, metastasis, and melanoma-related death. The effect of individual clinical variables on the development of each outcome event was analyzed by a series of univariate Cox proportional hazards regressions. The correlation among the variables was determined by using Pearson correlations. All variables were analyzed as discrete variables except for patient age, intraocular pressure, basal tumor diameter, tumor thickness, radiation dose, and radiation rate, which were analyzed as continuous variables and later grouped into discrete categories to derive cutoff values. The variables that were significant on a univariate level (P < .05) were entered into a stepwise regression analysis. For variables that showed a high degree of correlation, only 1 variable from the set of associated variables was entered at a time in subsequent multivariate models. A final multivariate model fitted variables that were identified as significant predictors (P < .05) in the stepwise model as well as variables deemed clinically important for the specific outcome.

Kaplan-Meier survival estimates were used to analyze the development of radiation cataract, neovascular glaucoma, retinopathy, scleral necrosis, vitreous hemorrhage, visual acuity decrement of at least 3 Snellen lines, tumor recurrence, metastasis, and melanoma-related death as a function of time. With respect to visual acuity analysis, patients whose initial visual acuity was 20/200 or worse were not included in the analysis. The time point at which the patient experienced a decrement of at least 3 Snellen lines of acuity was computed and analyzed by a Cox proportional hazards model using time to event as the end point.
patients with ciliary body melanoma has not been studied previously.

RESULTS

There were 136 patients with ciliary body melanoma, as defined in the “Patients and Methods” section, treated with plaque radiotherapy between July 1976 and June 1992. All patients with ciliary body melanoma were white and the median age was 63 years (mean, 62 years; range, 29-91 years). There were 69 women and 67 men. Eleven patients had systemic hypertension, 5 had diabetes mellitus, and 2 had both of these conditions. The initial visual acuity was equal to or better than 20/200 in 49% of patients and better than 20/40 in 24% of the patients and better than 20/200 in 45% of the patients.

TUMOR DATA

Of the 136 patients, 126 (93%) had ciliochoroidal, 7 (5%) had iridociliary, 2 (1%) had iridociliochoroidal, and 1 (0.7%) had a pure ciliary body melanoma. The tumor location was superior in 9 patients (7%), superotemporal in 20 (15%), temporal in 10 (7%), inferotemporal in 20 (15%), inferior in 11 (8%), inferonasal in 34 (25%), nasal in 8 (6%), and superonasal in 24 (18%). The median largest basal tumor diameter was 13 mm (mean, 13 mm; range, 4-20 mm) and the median tumor thickness was 7 mm (mean, 7 mm; range, 2-16 mm). The median distance of the posterior margin of the tumor to the optic nerve was 8 mm (mean, 8 mm; range, 0-20 mm), and to the fovea was 9 mm (mean, 9 mm; range, 0-20 mm). Subretinal fluid was present in 53 patients (39%). The tumor was dome shaped in 123 patients (90%) and mushroom shaped in 13 (10%). Extraocular extension was observed in 4 patients (3%).

PLAQUE RADIOThERAPY DATA

The radioisotope iodine 125 was used in 61 cases (45%), cobalt 60 in 61 (45%), ruthenium 106 in 13 (9%), and iridium 192 in 1 (0.7%). A regular, round plaque was used in 127 cases (93%), a custom-designed curvilinear (boomerang shaped) plaque in 5 (4%), and a notched plaque in 4 (3%). The plaque size ranged from 10 to 25 mm and the 2 most frequently used plaque sizes were 15 mm and 20 mm, used in 98 (72%) and 15 (11%) patients, respectively. The radiation time and dose and rate of radiation to the tumor base, apex, optic disc, fovea, and lens are shown in Table 1. The median radiation time was 149 hours (mean, 162 hours). The median dose to the tumor apex was 8760 cGy (mean, 8463 cGy) and the median dose to the tumor base was 36 750 cGy (mean, 37 291 cGy).

FOLLOW-UP DATA AND STATISTICAL ANALYSIS

The follow-up periods ranged from 25 to 212 months, with a median follow-up of 70 months (mean, 75 months). The proportion of patients in the various visual acuity ranges at baseline and at 12, 24, 36, 48, and 60 months’ follow-up after plaque radiotherapy are shown in Table 2. The final visual acuity was equal to or better than 20/200 in 49% of patients and better than 20/40 in 24% of the patients. The final median tumor thickness was 3 mm (mean, 4 mm; range, 1-7 mm).

Table 3 depicts the interval (median, mean, and range) for the development of radiation complications, tumor recurrence, metastasis, and melanoma-related death. Radiation cataract was the most frequent complication, noted in 65 patients (48%) at a median interval of 35 months. By using Kaplan-Meier survival esti-
mates, we found that the proportion of patients with radiation cataract was 10% at 1 year and 48% at 5 years (Figure 1). Neovascular glaucoma was diagnosed in 21 patients (15%) at a median interval of 32 months. Kaplan-Meier estimates showed that 2% of the patients developed neovascular glaucoma at 1 year and 21% at 5 years (Figure 1). Seven of 21 patients with neovascular glaucoma had associated retinal neovascularization. In the remaining 14 patients, there was no posterior segment neovascularization.

Radiation retinopathy was observed in 20 patients (15%) at a median interval of 20 months. All the patients had nonproliferative radiation retinopathy. In addition, proliferative retinopathy was noted in 7 patients (5%) and maculopathy in 7 (5%). Kaplan-Meier estimates showed that the proportion of patients with radiation retinopathy was 2% at 1 year and 20% at 5 years (Figure 2). Radiation papillopathy was observed in 4 patients (3%) at a median interval of 24 months. Scleral necrosis was diagnosed in 15 patients (11%) at a median interval of 32 months. Kaplan-Meier estimates showed that the proportion of patients with scleral necrosis was 5% at 1 year and 12% at 5 years (Figure 2).

Vitreous hemorrhage was documented in 13 patients (10%) at a median interval of 32 months. By using Kaplan-Meier estimates, we found that the proportion of patients with vitreous hemorrhage was 6% at 1 year and 11% at 5 years. Three of 13 patients with vitreous hemorrhage had preexisting proliferative radiation retinopathy. In the remaining 10 patients, vitreous hemorrhage was presumably due to tumor necrosis. Vision decrement by 3 or more Snellen lines was documented in 53 (56%) of 95 patients with an initial visual acuity better than 20/200. The proportion of patients with at least 3 Snellen lines of vision decrease was 5% at 1 year and 40% at 5 years (Figure 3).

Local tumor recurrence was found in 10 patients (7%) at a median interval of 32 months. Kaplan-Meier estimates showed that 2% of the patients developed recurrence at 1 year and 8% at 5 years (Figure 4). Seven of 10 patients were treated with enucleation and 3 were treated with a second plaque application. There was no recurrence after the second plaque treatment. Overall, plaque radiotherapy achieved local tumor control in 95% of the patients with ciliary body melanoma.

Of the 136 patients, 43 (32%) developed metastasis at a median interval of 56 months. Kaplan-Meier estimates showed that the proportion of patients who developed metastasis was 1% at 1 year and 28% at 5 years (Figure 4). There were 32 melanoma-related deaths (24%) and 3 deaths from other causes at a median interval of
68 months. The proportion of patients who died from melanoma-related causes was 0% at 1 year and 22% at 5 years (Figure 5).

Enucleation was performed in 20 (15%) of 136 patients with ciliary body melanoma because of tumor recurrence in 7 cases, patient preference in 5 cases, neovascular glaucoma in 4 cases, and scleral necrosis in 4 cases. Recurrence was a significant risk factor for enucleation (P = .002). There was no effect of enucleation on the subsequent development of metastasis or melanoma-related death.

Univariate Cox proportional hazards regression analyses (Table 4) demonstrated that the factors predictive of radiation cataract were superonasal (P = .003) and inferior tumor meridian (P = .02) compared with inferonasal meridian, and apex dose rate greater than 57 cGy/h (P = .05). The development of neovascular glaucoma was significantly related to iridociliary and iridociliochoroidal compared with ciliochoroidal tumor location (P < .001). The factors predictive of development of radiation retinopathy were base dose rate greater than 230 cGy/h (P = .03) and the presence of diabetes mellitus (P = .05). The factors predictive of development of radiation scleral necrosis were intraocular pressure greater than 15 mm Hg (P < .001) and tumor thickness greater than 7 mm (P = .05). Radiation vitreous hemorrhage were base dose rate greater than 230 cGy/h (P = .03) and visual acuity greater than 20/40 (P = .02). The factors predictive of vision decrease were mushroom tumor shape (P = .002), superonasal meridian (P = .046), and superonasal meridian (P = .04). The risks of melanoma-related death were presence of metastasis (P < .001) and tumor thickness greater than 7 mm (P = .01). There was no group of significant variables predictive for radiation cataract, neovascular glaucoma, retinopathy, tumor recurrence, and metastasis.

Plaque radiotherapy is currently the most common treatment for posterior uveal (ciliary body and choroidal) melanoma. It seems to provide equivalent tumor control and patient survival comparable to charged particle irradiation,7 partial lamellar sclerouvectomy,6 and enucleation.4 Plaque radiotherapy for posterior uveal melanoma may lead to a number of early and late complications.16 Early complications are few and include ocular irritation and diplopia especially if an extraocular muscle is disinserted to position the plaque. Late complications include radiation retinopathy, papillopathy, cataract, neovascular glaucoma, scleral necrosis, and vitreous hem-

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Factors Predictive of Radiation Cataract</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Base dose rate greater than 230 cGy/h</td>
</tr>
<tr>
<td></td>
<td>Superonasal meridian (P = .003)</td>
</tr>
<tr>
<td></td>
<td>Inferior meridian (P = .02)</td>
</tr>
<tr>
<td></td>
<td>Apex dose rate greater than 57 cGy/h</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 5</th>
<th>Factors Predictive of Neovascular Glaucoma</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Base dose rate greater than 230 cGy/h</td>
</tr>
<tr>
<td></td>
<td>Visual acuity greater than 20/40</td>
</tr>
</tbody>
</table>

Figure 4. Plaque radiotherapy of ciliary body melanoma. Kaplan-Meier estimates of patients free of recurrence and metastasis over time.

Figure 5. Plaque radiotherapy of ciliary body melanoma. Kaplan-Meier estimates of patients free of melanoma-related deaths over time.
orrhage. Radiation retinopathy and papillopathy are the most common reasons for permanent decreased vision following plaque radiotherapy of posterior uveal melanoma. The present study excluded melanoma located predominantly in the choroid and included only ciliary body melanoma, as defined in the "Patients and Methods" section. Plaque radiotherapy of ciliary body melanoma may be associated with a higher frequency of anterior segment complications compared with choroidal melanoma. After iodine 125 plaque radiotherapy, radiation cataract was observed in 14% of all patients with posterior uveal melanoma as compared with 48% of those with ciliary body melanoma in this study. Similarly, radiation papillopathy was noted in 11% of all patients with posterior uveal melanoma who received plaque radiotherapy vs 3% of those with ciliary body melanoma reported herein.

Radiation cataract, noted in 48% of our patients, was the most frequent complication of plaque radiotherapy in ciliary body melanoma. The factors predictive of radiation cataract were superonasal and inferior tumor meridian and apex dose rate greater than 57 cGy/h. Radiation dose and rate to the lens were not statistically important factors. Similar findings have been previously reported and there are several possible explanations for this. First, although dose and rate of radiation to the lens were calculated as accurately as possible, the theoretical method of dose estimation may be less accurate than planned due to many variables, including unaccounted displacement of lens by the tumor. Second, the dose and rate may be altered because of even slight movements of the lens during plaque placement. Additionally, the tumor may obstruct or displace the lens, resulting in an altered dose distribution.

### Table 4. Significant Variables Leading to an Outcome Event Using Univariate Cox Proportional Hazards Analyses

<table>
<thead>
<tr>
<th>Outcome Event</th>
<th>Significant Variable</th>
<th>P</th>
<th>Relative Risk (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiation event</td>
<td>Cataract</td>
<td>Superonasal meridian</td>
<td>.003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inferior meridian</td>
<td>.02</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Apex dose rate &gt;57 cGy/h</td>
<td>.05</td>
</tr>
<tr>
<td></td>
<td>Neovascular glaucoma</td>
<td>ICB and ICBCH tumor*</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>Retinopathy</td>
<td>Base dose rate &gt;230 cGy/h</td>
<td>.03</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diabetes mellitus present</td>
<td>.05</td>
</tr>
<tr>
<td></td>
<td>Scleral necrosis</td>
<td>Intraocular pressure &gt;15 mm Hg</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Thickness &gt;7 mm</td>
<td>.05</td>
</tr>
<tr>
<td></td>
<td>Vitreous hemorrhage</td>
<td>Intraocular pressure &gt;15 mm Hg</td>
<td>.002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vision 20/40-20/200</td>
<td>.02</td>
</tr>
<tr>
<td></td>
<td>Vision loss (&gt;3 lines)</td>
<td>Mushroom shape</td>
<td>.002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Metastasis</td>
<td>.005</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Age &gt;61 y</td>
<td>.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Superonasal meridian</td>
<td>.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Largest tumor diameter &gt;13 mm</td>
<td>.05</td>
</tr>
<tr>
<td>Tumor event</td>
<td>Recurrence</td>
<td>Largest tumor diameter &gt;13 mm</td>
<td>.06</td>
</tr>
<tr>
<td></td>
<td>Metastasis</td>
<td>Thickness &gt;7 mm</td>
<td>.02</td>
</tr>
<tr>
<td></td>
<td>Melanoma-related death</td>
<td>Metastasis present</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Thickness &gt;7 mm</td>
<td>.02</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Recurrence</td>
<td>.02</td>
</tr>
</tbody>
</table>

*ICB indicates iridociliary; ICBCH, iridociliochoroidal.

### Table 5. Significant Factors Related to an Outcome Event Using Multivariate Analyses

<table>
<thead>
<tr>
<th>Outcome Event*</th>
<th>Variable</th>
<th>P</th>
<th>Relative Risk (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scleral necrosis</td>
<td>Intraocular pressure &gt;15 mm Hg</td>
<td>&lt;.001</td>
<td>1.2 (1.1-1.3)</td>
</tr>
<tr>
<td></td>
<td>Thickness &gt;7 mm</td>
<td>.007</td>
<td>1.3 (1.1-1.6)</td>
</tr>
<tr>
<td>Vitreous hemorrhage</td>
<td>Vision 20/40-20/200</td>
<td>.02</td>
<td>11.8 (1.5-92.5)</td>
</tr>
<tr>
<td></td>
<td>Intraocular pressure &gt;15 mm Hg</td>
<td>.02</td>
<td>1.1 (1.0-1.2)</td>
</tr>
<tr>
<td>Vision loss (&gt;3 lines)</td>
<td>Mushroom shape</td>
<td>.002</td>
<td>3.4 (1.6-7.4)</td>
</tr>
<tr>
<td></td>
<td>Age &gt;61 y</td>
<td>.006</td>
<td>1.1 (1.0-1.2)</td>
</tr>
<tr>
<td></td>
<td>Superonasal meridian</td>
<td>.04</td>
<td>2.1 (1.0-4.0)</td>
</tr>
<tr>
<td>Melanoma-related death</td>
<td>Metastasis present</td>
<td>&lt;.001</td>
<td>5.6 (1.8-9.6)</td>
</tr>
<tr>
<td></td>
<td>Thickness &gt;7 mm</td>
<td>.01</td>
<td>2.5 (1.2-5.2)</td>
</tr>
</tbody>
</table>

*There were no group of significant variables predictive for radiation cataract, neovascular glaucoma, retinopathy, tumor recurrence, and metastasis.
changes in the position of the episcleral plaque. Third, cataract formation may be induced by the direct effect of radiation as well as secondary radiation-induced changes such as vascular damage. Fourth, some ciliary body tumors may touch the posterior lens capsule or slightly indent or subluxate the lens. These mechanical disturbances as well as others may also contribute to cataract development.

The rate of developing radiation-induced cataract in patients with posterior uveal melanoma has been reported to be 14% with iodine 125 plaque radiotherapy, \textsuperscript{17} 57% with cobalt 60, \textsuperscript{18} and 44% with helium ion irradiation\textsuperscript{19} at 5 years. Our rate was 48%, similar to prior reports for all patients with posterior uveal melanoma. In our select group of patients with ciliary body melanoma treated with radiotherapy delivered near the lens, one expects a higher rate of cataract formation. However, it is important to realize that the prior reports of a relatively high cataract rate involved cobalt 60 with its deep dose penetration and helium ion with its dose penetrating the lens to treat the posterior tumor.

Iris involvement with ciliary body melanoma was a risk factor for the development of neovascular glaucoma in our series, indicating that location of anterior tumor margin is an important determinant. Of the 21 patients who developed neovascular glaucoma, 7 had associated retinal neovascularization and 14 had iris neovascularization only. It has been reported that iris neovascularization can develop as a response to the rapidly progressive necrosis in ciliary body tumors without disc and retinal neovascularization.\textsuperscript{20,21}

The 5-year risk of developing neovascular glaucoma was 21% in our series compared with the 5-year risk of 43% after helium ion irradiation for ciliary body melanoma.\textsuperscript{13} The mean interval to the development of neovascular glaucoma was 34 months in our series and 14 months after helium ion irradiation.\textsuperscript{22} The risk of developing neovascular glaucoma seems to be higher with charged particle irradiation and the time interval shorter.

The presence of diabetes mellitus allows for a higher risk of radiation retinopathy\textsuperscript{23} and this was confirmed in our study. This finding suggests that eyes with preexisting vascular derangement are more susceptible to the development of radiation retinopathy. The other factor significant in the development of radiation retinopathy was base dose rate greater than 230 cGy/h, attesting to the importance of radiation rate besides the total radiation dose.\textsuperscript{23}

Scleral necrosis following plaque radiotherapy may be due to the disruption of normal blood supply caused by radiation as well as to the release of lysozymatic enzymes from necrotic tumor cells.\textsuperscript{24} The factors that were found to be predictive of scleral necrosis in our study were intraocular pressure greater than 15 mm Hg and tumor thickness greater than 7 mm. Histopathological studies showed that scleral necrosis generally developed in cases where the melanoma had infiltrated the inner scleral lamellae.\textsuperscript{25} Based on this finding, we may speculate that thicker tumors may be more prone to invade the sclera and, therefore, cause scleral necrosis. Our results suggest that intraocular pressure, which probably acts as a mechanical factor, is also significant. Scleral necrosis can be managed successfully by a scleral patch graft but observation or enucleation are alternatives.

In our study, there was only a marginal relationship between recurrence and the largest basal tumor diameter, although this did not reach statistical significance. Previous reports also pointed out the association of larger basal tumor diameter and recurrence.\textsuperscript{25-27} Our recurrence rate of 8% compares favorably to the general recurrence rate of 12% for all posterior uveal melanomas after plaque radiotherapy.\textsuperscript{25} Therefore, ciliary body melanoma is not at particular risk for recurrence. Our recurrence rate is also lower than the recurrence rate of 15% for juxtapapillary melanoma.\textsuperscript{26} This finding may be because plaque placement is more accurate in anteriorly located melanoma compared with juxtapapillary melanoma. The mean interval to recurrence was 33 months in our series in comparison to the mean interval to recurrence of 19 months for all posterior uveal melanomas,\textsuperscript{26} consistent with the difficulty of documenting recurrence in ciliary body melanoma, probably because of its peripheral location.

Prior studies demonstrated that largest basal tumor diameter,\textsuperscript{3,8,23,29} recurrence,\textsuperscript{23,29} and tumor thickness\textsuperscript{23} were important clinical risk factors for metastasis or melanoma-related death in patients with posterior uveal melanoma. Our study showed that tumor thickness greater than 7 mm was the only significant factor associated with metastasis after plaque radiotherapy of ciliary body melanoma. The risk factors for melanoma-related death were the presence of metastasis and tumor thickness greater than 7 mm. Our 5-year melanoma-related mortality rate was 22%. The 5-year melanoma-related mortality rate after helium ion irradiation was 41%,\textsuperscript{13} confirming the overall poor prognosis of ciliary body melanoma.

The enucleation rate for ciliary body melanoma was 15% in this series and it was reported to be 26% after helium ion irradiation.\textsuperscript{25} The enucleation rate is 6% for all posterior uveal melanoma after plaque radiotherapy.\textsuperscript{31} Therefore, the risk for enucleation seems to be greater for irradiated ciliary body melanoma than posterior uveal melanoma in general. There was no statistical correlation between enucleation and the subsequent development of metastasis and melanoma-related mortality in our study.

Our study has potential limitations that should be considered. This retrospective study might contain a bias in data collection because more difficult cases have been referred to our service for management. Second, treatment preferences may cause a bias in the size of melanoma treated with plaque radiotherapy vs surgical resection, enucleation, or other methods.\textsuperscript{22} Despite these shortcomings, we believe our observations are important. Plaque radiotherapy of ciliary body melanoma has not been previously analyzed in a large number of patients, as in this study. There have been only a few reports on small numbers of patients with ciliary body melanoma treated with plaque radiotherapy.\textsuperscript{23} Second, the median follow-up of 70 months of this study may still be considered short for patients with uveal melanoma and the risk of metastasis may be increased with longer follow-up. However, follow-up data were complete on all the patients. Some of the earlier patients had even longer fol-
low-up times of up to 18 years. Third, our study specifically addresses the role of clinical variables in predicting the development of complications and metastasis following plaque radiotherapy in ciliary body melanoma. Since enucleation is performed less often today, clinical factors rather than histopathological findings will probably be used more often in future studies. 16

The Collaborative Ocular Melanoma Study is currently evaluating the impact of different treatment methods on survival in patients with choroidal melanoma. However, when more than 50% of the melanoma is in the ciliary body, this constitutes a criterion of exclusion in the Collaborative Ocular Melanoma Study. 34 Therefore, our study was designed to address this subset of patients and does not overlap with the Collaborative Ocular Melanoma Study.

In summary, plaque radiotherapy offers a 92% 5-year local control rate in patients with ciliary body melanoma. However, the 5-year metastasis rate remains significant at 28% and the 5-year melanoma-related death rate is 22%. Patients with tumor thickness more than 7 mm have a higher risk for developing scleral necrosis, metastasis, and melanoma-related mortality. Patients with largest basal tumor diameter greater than 13 mm are more likely to develop vision loss. Other radiation complications, including cataract, neurovascular glaucoma, retinopathy, and scleral necrosis, can occur.

Selected cases of ciliary body melanoma with a smaller base (<12 mm) can be treated with local resection. 32 Based on the results of our study, plaque radiotherapy may also be a viable option in these cases. For tumors with a larger base, radiotherapy is preferable to local resection although the risk of radiation complications should be realized. If a ciliary body melanoma exceeds 10 mm in thickness and 20 mm in largest basal diameter, enucleation should be considered because there is little hope for useful vision following radiotherapy.

Accepted for publication September 29, 1998.
This work was supported by the Paul Kayser International Award of Merit in Retina Research, Houston, Tex (Dr J. Shields), the Eye Tumor Research Foundation, Philadelphia, Pa, the Pennsylvania Lions Sight Conservation and Eye Research Foundation, Philadelphia, and the Macula Foundation, New York, NY.
Reprints: Carol L. Shields, MD, Oncology Service, Wills Eye Hospital, 900 Walnut St, Philadelphia, PA 19107.

REFERENCES