Radiation Retinopathy Following Plaque Radiotherapy for Posterior Uveal Melanoma

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

Objective: To identify the risk factors that lead to the development of radiation retinopathy following plaque radiotherapy for posterior uveal melanoma. Radiation retinopathy is a slowly progressive, occlusive vasculopathy characterized by radiation-induced endothelial damage.

Methods: Review of the medical records of patients with posterior uveal melanoma treated with plaque radiotherapy.

Results: Of 1300 patients with posterior uveal melanoma treated with plaque radiotherapy from July 1, 1976, through June 30, 1992, radiation retinopathy developed in 560 (43.1%). By using Kaplan-Meier survival estimates, we found that 5% of the patients had nonproliferative radiation retinopathy at 1 year (95% confidence interval [CI], 3%-6%) and 42% at 5 years (95% CI, 38%-45%). The proportion of patients with proliferative retinopathy was 1% at 1 year (95% CI, 0.2%-1.5%) and 8% at 5 years (95% CI, 5%-10%). Multivariate analyses showed that the subset of clinical variables best related to the development of nonproliferative radiation retinopathy were tumor margin of less than 4 mm from foveola (P < .001), tumor limited to the choroid (P = .002), and radiation dose rate of greater than 260 cGy/h to the tumor base (P = .02). The best subset of independent variables related to the development of radiation maculopathy were tumor of less than 4 mm to foveola (P < .001) and the use of radioisotope iridium 192 (192Ir) (P = .02) compared with iodine 125 (125I). From a multivariate model, the most important factors for the development of proliferative radiation retinopathy included diabetes mellitus (P = .01), radioisotope 192Ir (P = .01) compared with 125I, and tumor base of greater than 10 mm (P = .02).

Conclusions: Radiation retinopathy is a common finding after plaque radiotherapy for choroidal melanoma, occurring in 42% of patients at 5 years. The main predictors of radiation retinopathy are posterior tumor location with margin near the foveola and high radiation dose rate to the tumor base.


First described in 1933 by Stallard, radiation retinopathy is characterized by a slowly progressive, occlusive vasculopathy with a delayed onset after irradiation. The pathologic hallmark of this condition seems to be radiation-related endothelial changes in the retinal vessels, leading to occlusive vascular disease. Radiation retinopathy usually leads to irreversible visual impairment.

Radiation retinopathy can occur after external beam irradiation of the eye, orbit, eyelids, face, paranasal sinuses, nasopharynx, and brain. The incidence of radiation retinopathy is greater when the treatment site is closer to the eye and the cephalic radiation dose is high. Although radiation retinopathy has been more commonly observed in patients treated with external beam irradiation, it can also occur after episcleral plaque radiotherapy.

There have been a few reports specifically addressing the role of risk factors for the development of radiation retinopathy after plaque radiotherapy in patients with posterior uveal melanoma. Although radiation retinopathy is a potential cause of visual loss in this group of patients, it nevertheless represents a balance between the treatment of a life-threatening ocular tumor and vision-threatening ocular complications. We herein aim to identify the factors that led to the development of radiation retinopathy following plaque radiotherapy in a large group of patients with posterior uveal melanoma.

RESULTS

Five hundred sixty (43.1%) of 1300 patients with posterior uveal melanoma and treated with plaque radiotherapy from July
PATIENTS AND METHODS

We reviewed the medical records of patients with posterior uveal melanoma who were treated with plaque radiotherapy from July 1, 1976, through June 30, 1992, at the Ocular Oncology Service of Wills Eye Hospital, Philadelphia, Pa, and retrieved those of patients in whom radiation retinopathy developed. We analyzed the risk factors that led to the development of radiation retinopathy after plaque radiotherapy in this group.

Baseline patient data included age, sex, patient history of diabetes mellitus and 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 analyses. Tumor data consisted of tumor quadrant (superior, superotemporal, temporal, inferotemporal, inferior, inferonasal, nasal, superonasal, and foveal), the distance of the posterior edge of the tumor to the optic disc and fovea, maximum diameter of tumor base (from results of indirect ophthalmoscopy and B-scan ultrasonography), initial thickness (from results of A- and B-scan ultrasonography), shape (dome, mushroom, diffuse, and plateau as defined by results of indirect ophthalmoscopy and B-scan ultrasonography), the presence of subretinal fluid (from results of indirect ophthalmoscopy and B-scan ultrasonography), and retinal invasion (from results of indirect ophthalmoscopy, B-scan ultrasonography, and fluorescein angiography).

Informed consent was obtained before the patients underwent plaque radiotherapy. Plaque radiotherapy data used in this study include radioactive isotope (iodine 125 [125I], ruthenium 106 [106Ru], cobalt 60 [60Co], and iridium 192 [192Ir]); plaque shape (round, noted, rectangular, or curvilinear); plaque size; hours of radiation; radiation doses to the apex, base, optic disc, and fovea; and radiation rates to the apex, base, optic disc, and fovea.

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. The development of radiation retinopathy and the time interval to its onset was determined. Results of indirect ophthalmoscopy, fundus photography, and fluorescein angiography were used to determine the development of radiation retinopathy.

Nonproliferative radiation retinopathy was diagnosed if a group of capillary bed changes (microaneurysms, dilation, and nonperfusion), retinal hemorrhage, retinal exudation, retinal edema, nerve fiber layer infarction, and/or vascular sheathing were found. The presence of at least 2 of these findings was required to make the diagnosis. Radiation maculopathy was diagnosed when these changes occurred 3 mm or less from the foveola. A diagnosis of proliferative radiation retinopathy was made when there was retinal or optic disc neovascularization.

The clinical examination records, color photographs, and fluorescein angiograms were compared with those obtained at baseline to exclude retinal vascular changes due to other causes. Only those retinal vascular changes that developed following plaque radiotherapy were considered significant for our purposes.

The major outcome events of our study were the development of nonproliferative radiation retinopathy, radiation maculopathy, and proliferative radiation retinopathy. The effect of individual variables on the development of each outcome event was analyzed using a series of Cox proportional hazards regressions. The correlation among the variables was determined using Pearson correlations. All variables were analyzed as discrete variables except for age, intraocular pressure, largest basal tumor diameter, tumor thickness, and radiation dose and rates, which were analyzed as continuous variables and later grouped into discrete categories to derive cutoff values. Subsequent multivariate models included variables that were significant on a univariate level (P<.05) and identified the combination of variables best related to the development of events. Kaplan-Meier survival estimates were used to study the development of radiation retinopathy as a function of time.
All patients with radiation retinopathy had nonproliferative changes. Radiation maculopathy was found in 240 patients (42.8%) and proliferative retinopathy in 51 patients (9.1%).

By using Kaplan-Meier survival curves, we found that the proportion of patients in whom nonproliferative radiation retinopathy developed was 5% at 1 year (95% confidence interval [CI], 3%-6%) and 42% at 5 years (95% CI, 38%-45%) (Figure 1). Proliferative radiation retinopathy was observed in 1% of the patients at 1 year (95% CI, 0.2%-1.5%) and 8% at 5 years (95% CI, 5%-10%) (Figure 2).

Of the 560 patients, 222 (39.6%) also had radiation cataract; 106 (18.9%), papillopathy; 43 (7.7%), vitreous hemorrhage; 40 (7.1%), neovascular glaucoma; and 7 (1.2%), scleral necrosis. Twelve patients (2.1%) were treated for recurrence with a second plaque. Forty-seven eyes (8.4%) were enucleated due to recurrence (20 eyes), neovascular glaucoma (14 eyes), vitreous hemorrhage (11 eyes), or scleral necrosis (2 eyes). Fifty-five patients (9.8%) died of melanoma-related causes, and 4 (0.7%) of other causes. Of the 55 patients with mela-
noma-related mortality, 6 previously had undergone enucleation.

Results of the univariate Cox proportional hazards regression analyses showed that the factors predictive of the development of nonproliferative radiation retinopathy were tumor of less than 4 mm to foveola (P < .001), tumor limited to the choroid with no anterior uveal involvement (P < .001), tumor of less than 5 mm to optic disc (P < .001), radiation dose rate of greater than 260 cGy/h to the tumor base (P = .002), subretinal fluid (P = .003), supertemporal tumor meridian (P = .005), radiation dose rate of greater than 75 cGy/h to the tumor apex (P = .007), radiation dose rate of greater than 44 cGy/h to the optic disc (P = .01), radiation dose of greater than 4367 cGy to the optic disc (P = .02), radiation dose of greater than 5742 cGy to the fovea (P = .03), and radiation dose rate of greater than 53 cGy/h to the fovea (P = .05) (Table 3). From a multivariate standpoint, the subset of clinical variables best related to the development of nonproliferative radiation retinopathy included tumor of less than 4 mm to foveola (P < .001), tumor limited to the choroid (P = .002), and radiation dose rate of greater than 260 cGy/h to the tumor base (P = .02) (Table 3).

The factors predictive of radiation maculopathy on a univariate level were tumor margin of less than 4 mm to foveola (P < .001), radiation dose rate of greater than 75 cGy/h to the tumor apex (P < .001), radiation dose rate of greater than 260 cGy/h to the tumor base (P < .001), tumor of less than 5 mm to optic disc (P < .001), radiation dose rate of greater than 44 cGy/h to the tumor base (P = .003), tumor limited to choroid (P = .003), diabetes mellitus (P = .02), use of radioisotope 192Ir (P = .03) compared with 125I, diabetes mellitus (P = .04), and largest tumor base of greater than 10 mm (P = .05) (Table 5). By multivariate analysis, the most important factors for the development of proliferative radiation retinopathy included diabetes mellitus (P = .01), use of radioisotope 192Ir (P = .01) compared with 125I, and largest tumor base of greater than 10 mm (P = .02) (Table 5).

Iodine 125 was the most commonly used radioisotope. The risk factors predictive of the development of radiation retinopathy in 329 patients treated with 125I were radiation dose rate of greater than 260 cGy/h to the tumor base (P = .03), tumor limited to choroid (P = .03), largest tumor base of greater than 10 mm (P = .04), and tumor thickness of greater than 5 mm (P = .05) on a univariate level (Table 6). Multivariate analysis showed that the most important factors predictive of the development of radiation retinopathy in this group of patients were tumor thickness of greater than 5 mm (P = .001), tumor limited to choroid (P = .03), and radiation dose rate of greater than 260 cGy/h to the tumor base (P = .05) (Table 6).
nal capillary bed. As areas of capillary loss become confluent, nerve fiber layer infarctions are seen. Larger vessels are involved later in the course of the disease, and vascular sheathing becomes apparent. When there are large or multiple areas of capillary nonperfusion, retinal and disc neovascularization can develop, sometimes leading to vitreous hemorrhage. Occasional associations with radiation retinopathy include choroidal neovascularization,13 choroidal infarction,14 retinal artery occlusion,15 and retinal vein occlusion.16

Results of histopathologic studies of the eyes with radiation retinopathy confirm the vascular nature of damage produced by radiation therapy.17,18 There is an unequivocal loss of endothelial cells with relative sparing of the pericytes. Although small retinal vessels are commonly involved, larger retinal and choroidal vessels can also be affected.18 The inner retinal layers are preferentially damaged as a result of this involvement pattern; however, there may also be destruction of the retinal pigment epithelium.19

The most important predictor of nonproliferative radiation retinopathy in our study was posterior tumor location. From a multivariate model, the factors related to the development of nonproliferative retinopathy included tumor margin of less than 4 mm to the foveola, tumor limited to the choroid without ciliary body and iris involvement, and radiation dose rate of greater than 260 cGy/h to the tumor base. Our results indicate that the peripheral retina may be less susceptible to the damaging effects of irradiation in terms of developing retinopathy. Similarly in diabetes mellitus, retinal vascular changes most often are found posteriorly near the vascular arcades, more so than in the retinal periphery. It has been reported that clinically and angiographically, radiation retinopathy is virtually identical to diabetic retinopathy.20,21

There has been more emphasis in the literature on the subject of radiation maculopathy because of its profound visual effects. In our study, the best subset of independent variables related to the development of radiation maculopathy included tumor margin of less than 4 mm to foveola and radioisotope 192Ir compared with 125I on a multivariate level. The higher rate of radiation maculopathy after the use of radioisotope 192Ir can be explained on the basis of its high energy levels (0.38 MeV) compared with 125I (0.032 MeV).22

In 2 previous reports, 18%23 and 23%24 of the patients with posterior uveal melanoma who were treated with plaque radiotherapy were found to have radiation maculopathy. In our study, radiation maculopathy was found in 42.8% of patients developing radiation retinopathy following plaque radiotherapy. Radiation maculopathy can manifest with macular edema if capillary abnormalities and leakage predominate and with macular ischemia if perifoveal capillary loss predominates. In a recent study, focal laser treatment was found to improve visual acuity modestly at 6 months in patients with radiation-induced macular edema, but sustained benefit was not achieved at 2 years.25

Brown et al8 reported that patients in whom radiation maculopathy developed after plaque radiotherapy received a mean radiation dose of 15 000 cGy to the fovea vs 5000 cGy for those who had no maculopathy. They suggested that plaque radiotherapy doses of less than 5000 cGy to the fovea were probably safe. In our study, a fovea radiation dose of greater than 5742 cGy was associated with a significantly higher risk for nonproliferative radiation retinopathy on a univariate level. We agree that a cutoff dose of approximately 5000 cGy or less may be tolerated safely by the fovea following plaque radiotherapy.

After plaque radiotherapy for posterior uveal melanoma, the most important factors for the development of proliferative radiation retinopathy were diabetes mellitus, radioisotope 192Ir compared with 125I, and tumor base of greater than 10 mm. The presence of diabetes mellitus exacerbates the effects of radiation retinopathy.26 Radiation retinopathy causes selective loss of endothelial cells, whereas diabetic retinopathy affects the pericytes. Therefore, the 2 components of the capillary wall are destroyed by the combined effect of diabetes and radiation, leaving little cellular support behind.21 However, Kinyoun et al27 found that diabetic retinopathy was not a risk factor for proliferative radiation retinopathy. The radioisotope 192Ir is associated with a higher risk for proliferative radiation retinopathy compared with 125I, due to its higher energy levels. Larger tumor base is associated with a higher incidence of retinopathy because spill-

### Table 5. Significant Variables Leading to Proliferative Radiation Retinopathy*

<table>
<thead>
<tr>
<th>Significant Variable</th>
<th>RR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Univariate analysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor thickness &gt;5 mm</td>
<td>2.2 (1.2-4.0)</td>
<td>.009</td>
</tr>
<tr>
<td>Radioisotope 192Ir</td>
<td>2.5 (1.2-5.4)</td>
<td>.02</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.9 (1.0-3.6)</td>
<td>.04</td>
</tr>
<tr>
<td>Largest tumor base &gt;10 mm</td>
<td>1.7 (0.9-3.0)</td>
<td>.05</td>
</tr>
<tr>
<td>Multivariate analysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2.2 (1.2-4.4)</td>
<td>.01</td>
</tr>
<tr>
<td>Radioisotope 192Ir</td>
<td>2.7 (1.2-6.0)</td>
<td>.01</td>
</tr>
<tr>
<td>Largest tumor base &gt;10 mm</td>
<td>1.1 (1.0-1.2)</td>
<td>.02</td>
</tr>
</tbody>
</table>

* Determined using univariate and multivariate Cox proportional hazards analyses. RR indicates relative risk; CI, confidence interval; and 192Ir, iridium 192.

### Table 6. Significant Variables Leading to Radiation Retinopathy in Patients Treated With Radioisotope 125I*

<table>
<thead>
<tr>
<th>Significant Variable</th>
<th>RR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Univariate analysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor base dose rate &gt;260 cGy/h</td>
<td>1.3 (1.0-1.6)</td>
<td>.03</td>
</tr>
<tr>
<td>Tumor limited to choroid</td>
<td>1.8 (1.0-3.3)</td>
<td>.03</td>
</tr>
<tr>
<td>Largest tumor base &gt;10 mm</td>
<td>1.2 (1.0-1.5)</td>
<td>.04</td>
</tr>
<tr>
<td>Tumor thickness &gt;5 mm</td>
<td>1.2 (1.0-1.5)</td>
<td>.05</td>
</tr>
<tr>
<td>Multivariate analysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor thickness &gt;5 mm</td>
<td>1.1 (1.0-1.2)</td>
<td>.001</td>
</tr>
<tr>
<td>Tumor limited to choroid</td>
<td>2.0 (1.1-3.6)</td>
<td>.03</td>
</tr>
<tr>
<td>Tumor base dose rate &gt;260 cGy/h</td>
<td>1.3 (1.0-1.6)</td>
<td>.05</td>
</tr>
</tbody>
</table>

* Determined using univariate and multivariate Cox proportional hazards analyses. 125I indicates iodine 125; RR, relative risk; and CI, confidence interval.
over radiation energy delivered to the surrounding retina is greater when the tumor base is larger.

During the past decade, we have been using $^{125}$I as the radioisotope of choice because of its availability, ease of shielding, good tissue penetration, and ability to be custom-designed. Our results did not show an increase in the frequency of radiation retinopathy with the radioisotope $^{60}$Co compared with $^{125}$I, despite its considerably higher energy level (1.25 MeV vs 0.032 MeV for $^{125}$I). The radioisotope $^{60}$Co was used in the earlier part of the study, and many eyes with more posterior tumors may have been enucleated rather than treated with plaque radiotherapy during that period. Similar cases recently have been treated with $^{125}$I plaque radiotherapy, altering the relative frequency of radiation retinopathy compared with $^{60}$Co. The multivariate analysis of the patients treated with $^{125}$I plaque radiotherapy showed that the factors related to the development of radiation retinopathy were tumor thickness of greater than 5 mm, tumor limited to choroid, and radiation dose rate of greater than 260 cGy/h to the tumor base. In this subset of patients, tumor proximity to the foveola was not a significant factor.

There are certain limitations of our study that should be considered. First, it is a retrospective study, and more difficult cases may have been sent to us for management because of our special interest in ocular tumors. Second, follow-up may be considered short for a study dealing with posterior uveal melanoma. However, we retrieve from previous reports that radiation retinopathy generally occurs at 1 to 3 years after plaque treatment. Most of our patients had long enough follow-up, adequate to assess the complication. Third, mild degrees of radiation retinopathy, especially in the peripheral retina, not resulting in visual loss may have been overlooked in our study. We suspect that many patients had some radiation-related change on or near the tumor. However, since we did not routinely use 7-field photographs, we may have underestimated the abnormality.

In conclusion, radiation retinopathy is a common finding after plaque radiotherapy for posterior uveal melanoma, occurring in 42% of patients at 5 years. The main predictors of radiation retinopathy are tumor margin near the optic disc and foveola as well as high radiation dose rate to the tumor base. The presence of diabetes mellitus is another major factor that predisposes to the development of radiation retinopathy.

Accepted for publication December 15, 1998.

This study was supported by the Paul Kayser International Award of Merit in Retina Research, Houston, Tex (Dr J. A. Shields); the Eye Tumor Research Foundation and the Pennsylvania Lions Sight Conservation and Eye Research Foundation (Drs Gündüz, C. L. Shields, and J. A. Shields), Philadelphia; and the Macula Foundation, New York, NY (Drs Gündüz and C. L. Shields).

Reprints: Carol L. Shields, MD, Oncology Service, Wills Eye Hospital, 900 Walnut St, Philadelphia, PA 19107.

REFERENCES