LOCAL TUMOR CONTROL AFTER $^{106}$Ru BRACHYTHERAPY OF CHOROIDAL MELANOMA

BERTIL DAMATO, Ph.D., F.R.C.Ophth.,* IMRAN PATEL, M.Sc.,† IAN R. CAMPBELL, B.Sc.,‡ HELEN M. MAYLES, M.Sc.,† AND R. DOUGLAS ERRINGTON, F.R.C.R.§

*Ocular Oncology Service, St. Paul’s Eye Unit, Royal Liverpool University Hospital, Liverpool, United Kingdom; Departments of †Physics and §Radiotherapy, Clatterbridge Centre for Oncology, Bebington, Wirral, United Kingdom; ‡IC Statistical Services, Wirral, United Kingdom

Purpose: To report on local tumor control after $^{106}$Ru brachytherapy for choroidal melanoma.

Methods and Materials: A total of 458 patients with choroidal melanoma were treated at a single institution between January 1993 and December 2001. The tumors had a median longest basal dimension of 10.6 mm and a median height of 3.2 mm. The brachytherapy was administered using a 15- or 20-mm plaque. For posterior tumors, the plaque was positioned eccentrically with its posterior edge aligned with the posterior tumor margin to reduce the radiation dose to the optic disk and fovea. A minimal scleral dose sufficient to cause visible choroidal atrophy provided a permanent ophthalmoscopic record of the distribution of choroidal irradiation. If radiotherapy to the posterior tumor was uncertain, adjunctive transpupillary thermotherapy was administered 6 months postoperatively.

Results: The actuarial rates of tumor recurrence were 1%, 2%, and 3% at 2, 5, and 7 years, respectively. Local tumor recurrence correlated with the longest basal tumor dimension (Cox univariate analysis, $p = 0.02$, risk ratio 1.41, 95% confidence interval 1.06 – 1.88). Seven of the nine eyes with recurrent tumor were salvaged with additional conservative therapy.

Conclusion: The low rate of local tumor recurrence suggests that ruthenium plaque radiotherapy is effective with good case selection and if special measures are taken to ensure that the plaque is positioned correctly.

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Uveal melanoma, $^{106}$Ru, Plaque brachytherapy, Local control.

INTRODUCTION

Enucleation for uveal melanoma has largely been replaced by therapies aimed at destroying the primary tumor while conserving the eye with as much useful vision as possible. Such “conservative” modalities include plaque brachytherapy, proton beam radiotherapy, stereotactic radiotherapy, transpupillary thermotherapy, cryotherapy, transscleral local resection, and transretinal endoresection (1). $^{106}$Ru plaques emit $\beta$-radiation so that tumors up to 5.4 mm in height can be treated reliably. Several investigators have independently published the results of plaque radiotherapy, administered alone or in combination with transpupillary thermotherapy (2–14). The survival rates have not been significantly different from those reported after enucleation (15–17). The conventional practice is to position the plaque centrically over the tumor so that it overlaps the visible tumor margins by at least 2 mm in all directions (10, 18). The wide radiation safety margin inevitably increases ocular morbidity, especially when the tumor extends close to optic disk or fovea. Since 1993, we have, whenever possible, treated such posterior choroidal melanomas with the posterior edge of the plaque aligned with the posterior tumor margin. This practice developed from the experience of one of us (B.D.) in treating juxtapapillary tumors with an anteriorly positioned $^{106}$Ru plaque combined with low-energy, long-duration photocoagulation (19) to the posterior part of the tumor. To ensure accurate positioning of the plaque in relation to the tumor, any overlying extraocular muscles were routinely disinserted and both plaque and tumor were localized by indentation and transillumination. Furthermore, a minimal scleral radiation dose of 300 Gy was delivered so that choroidal atrophy developed, which enabled correct positioning of the plaque to be verified ophthalmoscopically during subsequent surveillance of the patient.

Reprint requests to: Bertil Damato, Ph.D., F.R.C.Ophth, St. Paul’s Eye Unit, Royal Liverpool University Hospital, Prescott St., Liverpool L7 8XP, UK. Tel: (+44) 151-706-3973; Fax: (+44) 151-706-5436; E-mail: Bertil@damato.co.uk

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The aim of this study was to document the incidence of local tumor recurrence after $^{106}$Ru brachytherapy of choroidal melanoma at our center.

**METHODS AND MATERIALS**

**Patients and data collection**

Patients were included in the study prospectively and consecutively if they had been treated with a $^{106}$Ru plaque for choroidal melanoma between 1993, when the Liverpool Ocular Oncology Centre was established, and December 2001. They were excluded if the tumor had previously been treated by other methods; the tumor did not extend posterior to the ora serrata; the tumor was bilateral (1 patient) (20); or if a notched plaque or a 25-mm plaque was used (because <10 patients were treated with such plaques). Our criteria for diagnosing a choroidal tumor as melanoma were thickness >2.0 mm; serous retinal detachment; confluent orange pigment; a history of recent visual symptoms; and tumor growth, documented photographically. As a rule, brachytherapy using a 15- or 20-mm $^{106}$Ru plaque (BEBIG, Berlin, Germany) was our choice of treatment unless the longest tumor basal dimension was >16 mm, the tumor height was >5.4 mm, or the posterior tumor margin extended close to the optic disk so that we believed that plaque radiotherapy could not be administered reliably without causing optic neuropathy. Eccentric plaque placement was performed with full patient consent if the tumor extended postequatorially and if it did not appear to be diffuse.

Preoperative and follow-up assessments were performed, as described previously (21). Follow-up assessments alternated between our center and the referring ophthalmologist until the probability of complications was considered low (i.e., <1%, when patients were discharged to their ophthalmologist for annual review. If no follow-up information was automatically received from the referring ophthalmologist, it was requested by mail. Data regarding patient demographics, ocular and tumor characteristics, primary treatment, and all outcomes were collected prospectively. In patients with local tumor recurrence or enucleation, the case notes were reviewed. The tenets of the Helsinki Declaration were followed. Institutional ethical committee approval for outcomes analysis was not required.

**Treatment protocol**

Any rectus muscle overlying the tumor was disinserted after placing two 6-0 Vicryl sutures in the muscle tendon and measuring the knot-to-limbus distances. The inferior oblique muscle was disinserted if it impeded contact of the plaque with the sclera and was held in its anatomic position by a sling. The tumor margins were identified by transpupillary transillumination or binocular indirect ophthalmoscopy with indentation. In general, tumors up to 10 mm in diameter were treated with a 15-mm plaque and those with a wider base were treated with a 20-mm plaque. Tumors extending postequatorially were treated by placing the posterior edge of the plaque over the posterior margin of the tumor. This was achieved by marking the sclera with a pen at a point corresponding to the difference between the ultrasound longitudinal basal tumor dimension and the plaque diameter. A transparent plastic template was first sutured to the sclera with bows, and correct positioning was confirmed by indenting the eye with the posterior margin of the template while performing binocular indirect ophthalmoscopy. In the latter part of the study, three small holes were drilled into the template, close to its posterior margin, so that positioning of the template with respect to the tumor could be checked by inserting the tip of a fine right-angled transilluminator through each hole and observing its location by indirect ophthalmoscopy. The template was then replaced with the radioactive plaque, using the same sutures. A mattress suture was placed over the plaque to ensure that it was firmly applied to the globe. Any disinserted muscles were returned to their correct anatomic position by slings attached to the sclera, the lugs of the plaque, or the mattress suture.

Six months postoperatively, the distribution of any visible radiation-induced choroidal atrophy was assessed. If the tumor extended more than one disk diameter beyond the visible choroidal atrophy, the suspicious area was treated with transpupillary thermotherapy in the conventional fashion. A few patients received phototherapy as a treatment for exudative maculopathy or to prevent recurrent vitreous hemorrhage from tumor that had perforated the retina. In these cases, transpupillary thermotherapy was administered to the tumor without any safety margin.

The plaque was removed after delivering a minimal scleral radiation dose of 300–400 Gy and a minimal apex dose of 80–100 Gy, using the manufacturer’s ASMW specifications (ASMW is the standardization office of the former German Democratic Republic). In 2002, BEBIG, the plaque manufacturer, changed the calibration procedure and adopted a new standard: the National Institute for Standards and Technology (NIST; http://www.bebig.de/downloads/augen_info_dosimetrie_engl.pdf). All dose data for the patients in this study were retrospectively recalculated using the NIST calibrated dose rates for the plaques.

**Outcomes measures**

Local treatment failure was diagnosed if unequivocal expansion of any tumor margin was seen when comparing the ophthalmoscopic appearances with previous color photographs, or when a definite increase in tumor height was seen on ultrasonography, if necessary confirmed by sequential examination.

**Statistical analysis**

All outcomes analyses were based on data computerized by October 16, 2003. The time to tumor recurrence was measured to the date of diagnosis of this complication. The follow-up period was measured to the latest date at which the ocular status was known. The results were analyzed with the Statistical Package for Social Sciences, version 11.0, software (SPSS, Chicago, IL). Cox’s univariate proportional hazards model was used to identify associations between the baseline variables (Table 1) and the time to local treatment failure. Kaplan-Meier estimates were used to draw survival curves for the time to this outcome. Statistical significance was taken as $p < 0.05$.

**RESULTS**

**Patient population and treatment**

On October 16, 2003, when the analysis was started, 458 patients had been followed for up to 9.7 years (median 3.9). Of the 458 patients treated >1 year before analysis, follow-up information at 1 year was available for 427 (93%). The corresponding figures at 2 years were 364 (81%) of 448 and at 5 years, 153 (53%) of 289. During the recruitment period of this study, 1,212 patients with choroidal melanoma were treated at our center using other methods, including proton beam radiotherapy, iodine plaque radiother-
apy, 25-mm ruthenium plaque radiotherapy, notched-plaque ruthenium plaque radiotherapy, transscleral local resection, transretinal enucleation, transpupillary thermotherapy, photocoagulation, and enucleation.

Patient demographics and tumor characteristics are provided in Table 1. The mean age was 61 years (SD, 13.5; range, 21–94). The median tumor diameter was 10.6 mm (range, 5.0–16.6), and the median tumor height was 3.2 mm (range, 0.7–7.0). In the tumors extending anterior to the ora serrata, 44 reached pars plana, 12 involved pars plicata, and 6 reached the anterior chamber angle. Of the tumors extending anterior to the ora serrata, 44 reached pars plana, 12 involved pars plicata, and 6 reached the anterior chamber angle. Of the tumors extending anterior to the ora serrata, 44 reached pars plana, 12 involved pars plicata, and 6 reached the anterior chamber angle. Of the tumors extending anterior to the ora serrata, 44 reached pars plana, 12 involved pars plicata, and 6 reached the anterior chamber angle. Of the tumors extending anterior to the ora serrata, 44 reached pars plana, 12 involved pars plicata, and 6 reached the anterior chamber angle.
successful in 7. Of the patients with recurrent tumor, 3 died of metastatic disease (Patients 2, 4, and 7), and 1 died of pancreatic carcinoma.

DISCUSSION

This study reports a high rate of local tumor control after treatment of choroidal melanoma with $^{106}\text{Ru}$ brachytherapy by a single surgeon at one center. This was despite the omission of a 2-mm physical safety margin with posterior tumors whenever possible. Our results suggest that when a minimal scleral dose of 300 Gy is administered, the side scattering of radiation is sufficient to deliver an adequate safety margin even when the edge of the plaque is aligned with the tumor margin, without any physical overlap. This finding is important, because it allows smaller radiation...
doses to be delivered to the optic nerve and macula when treating posterior choroidal melanoma. Our study is timely because of the recent discovery that the manufacturer’s ASMW dosimetry was inaccurate when the NIST calibration was used as the standard, with most patients receiving greater radiation doses than intended. We have corrected for the ASMW dosimetry errors when analyzing and reporting our results, so that our study should be relevant to future patients.

A possible criticism of our study is that the proportion of patients with follow-up data exceeding 5 years was only 53%. Any error should be small, however, because local tumor recurrence is rare >5 years after treatment (10). The reason for the incomplete long-term follow-up information was that if patients lived far from our center, we delegated surveillance to the referring ophthalmologist once the chances of local tumor recurrence were considered small (i.e., <1%). It would have been unethical to review the patients ourselves, purely for research or audit purposes, without providing reimbursement for travel and accommodation expenses and for lost earnings. Our experience has been that ophthalmologists tend to refer patients back to our care if they have any concerns about tumor activity or other significant complications. The chances of underestimating local tumor recurrence were, therefore, small.

The degree of eccentricity of the plaque placement varied with the posterior tumor extension, type of tumor margin (i.e., discrete or diffuse), patient preference, and confidence about the plaque and tumor locations while inserting the plaque. This strategy allowed us to deliver a high radiation dose to the tumor without a corresponding increase in radiation to the disk and macula. The apex dose, which was especially high with small tumors, reduced the chances of local recurrence from any radioresistant tumor. The high scleral doses provided a permanent visual record of the choroidal distribution of radiation actually delivered so that

<table>
<thead>
<tr>
<th>Pt. no.</th>
<th>Age (y)</th>
<th>Gender</th>
<th>Eye</th>
<th>Quadrant</th>
<th>Anterior margin</th>
<th>Posterior margin</th>
<th>Longest basal dimension (mm)</th>
<th>Height (mm)</th>
<th>Plaque size (mm)</th>
<th>NIST apex dose (Gy)</th>
<th>NIST dose rate (Gy/h)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>53</td>
<td>Male</td>
<td>Left</td>
<td>Superotemporal</td>
<td>Pars plana</td>
<td>1–2 DD fovea</td>
<td>14.0</td>
<td>5.0</td>
<td>20.0</td>
<td>106</td>
<td>1.04</td>
</tr>
<tr>
<td>2</td>
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<td>Male</td>
<td>Left</td>
<td>Nasal</td>
<td>Postequatorial choroid</td>
<td>13.0</td>
<td>4.4</td>
<td>20.0</td>
<td>235</td>
<td>3.13</td>
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<tr>
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<td>59</td>
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<td>Right</td>
<td>Superotemporal</td>
<td>Postequatorial choroid</td>
<td>13.0</td>
<td>4.4</td>
<td>20.0</td>
<td>152</td>
<td>2.34</td>
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<tr>
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<td>Postequatorial choroid</td>
<td>12.6</td>
<td>3.5</td>
<td>20.0</td>
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<td>Posterior choroid</td>
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<td>3.5</td>
<td>20.0</td>
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<td>Postequatorial choroid</td>
<td>Posterior choroid</td>
<td>12.6</td>
<td>3.5</td>
<td>20.0</td>
<td>204</td>
<td>2.9</td>
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<tr>
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<td>Posterior choroid</td>
<td>10.8</td>
<td>1.6</td>
<td>20.0</td>
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<tr>
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<td>3.5</td>
<td>15.0</td>
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<td>73</td>
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<td>Posterior choroid</td>
<td>Posterior choroid</td>
<td>11.6</td>
<td>2.4</td>
<td>15.0</td>
<td>204</td>
<td>2.9</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: Pt. no. = patient number; NIST = National Institute of Standards and Technology; DD = disk diameter.
traocular muscles impeding accurate tumor localization or ruthenium plaque radiotherapy; (geon believed he could not treat the tumor reliably with methods (particularly proton beam radiotherapy) if the sur-
tion, with our patients treated using other conservative
curve, with the surgeon having extensive experience with
plaque insertion and the absence of a significant learning
greater in our study, including (several reasons why the rate of treatment failure was not
radiotherapy, despite eccentric plaque placement. There are
high rate of local tumor control with ruthenium plaque
results of our study suggest that it is possible to achieve a
radiation if any uncertainty resulted about irradiation
of the posterior tumor region; and (9) the small tumor size
in our sample compared with other studies. Shields et al.
(24) have reported a similar rate of local tumor control after
combined brachytherapy and transpupillary thermotherapy.

Despite irradiating relatively large areas of apparently
normal uvea anterior to the visible tumor, four recurrences
developed at the anterior or anterolateral tumor margins,
and hence beyond the wide radiation safety margins. This
result suggests that some choroidal melanomas tend to show
diffuse spread anteriorly and circumferentially. If this is the
case, perhaps the rate of local tumor recurrence would have
been greater if the plaques had not been offset anteriorly.

Until recently, we administered phototherapy prophylact-
ically if visible choroidal atrophy did not reach the poste-
rior tumor margin. However, we now know that the radia-
tion dose necessary to sterilize choroidal melanoma is less
than that required to cause visible choroidal atrophy. Thus,
we now become concerned only if the tumor extends more
than one disk diameter (1.5 mm) beyond the choroidal
atrophy. The adjunctive transpupillary thermotherapy we
administered in such cases, therefore, was perhaps unnec-
essary. It may also have been less effectual than we had
thought, because a recent study has reported a 22% rate of
local tumor recurrence within 3 years of primary transpu-
illary thermotherapy (25). Serendipitously, the adjunctive
(i.e., preventative) phototherapy may have improved the
visual outcome, because we have found transpupillary ther-
motherapy to be effective at diminishing macular edema.

Three patients with local tumor recurrence died of met-
astatic disease. It might be argued that these fatalities might
have been prevented by central plaque placement. However,
only 1 of these 3 patients developed recurrence where the
safety margin was narrowest. It is not known whether lo-
cally recurrent tumor causes metastatic disease or whether it
only indicates that the tumor was relatively aggressive and,
therefore, more likely to have metastasized before treat-
ment. Of the three recurrences associated with metastases,
two developed beyond the unusually wide safety margins,
perhaps suggesting that these tumors were relatively aggressive.

Because eccentric plaque placement was performed to conserve more vision, we have also assessed the visual acuity in this series of patients. The results have been reported separately. In brief, 8 years postoperatively, visual acuity in this series of patients. The results have been conserve more vision, we have also assessed the visual acuity of 20/40 or better was conserved in approximately 75% of patients if they had presented with such good vision and if the tumor was more than two disk diameters from the disk and fovea (26).

**CONCLUSION**

106Ru brachytherapy can achieve high rates of local tumor control if special measures are taken to ensure that the plaque is positioned accurately in relation to the tumor.

**REFERENCES**