Palladium-103 Plaque Radiation Therapy for American Joint Committee on Cancer T3- and T4-Staged Choroidal Melanomas

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IMPORTANCE Patients with larger choroidal melanomas are being treated with plaque radiation therapy.

OBJECTIVE To report the methods and results of palladium-103 brachytherapy for American Joint Committee on Cancer, 7th edition, T3- and T4-sized choroidal melanomas.

DESIGN, SETTING, AND PARTICIPANTS A retrospective analysis of the results of a clinical case series over a 10-year period of 47 consecutive patients with uveal melanoma. The patients were treated at The New York Eye Cancer Center, Beth Israel Comprehensive Cancer Center, or The New York Eye and Ear Infirmary between 2002 and 2012 and had a minimum follow-up of 6 months. Tumors had a mean preoperative apical tumor height of 8.6 mm and a mean largest basal diameter of 15.8 mm.

MAIN OUTCOMES AND MEASURES We analyzed, but were not limited to, data on the methods of radiation therapy, local tumor control, adverse effects, vision retention, and metastatic rate.

RESULTS All patients completed therapy and received the prescribed tumor apex dose. At a median of 47 months (range, 6-125 months), the rate of local control was 91% and the rate of eye retention was 89%. The most common long-term brachytherapy-related complication was radiation maculopathy (66% of patients), followed by radiation optic neuropathy (51% of patients). One or both of these complications were diagnosed at a mean time of 16 months (range, 2-36 months) after brachytherapy. Secondary cataract developed in 36% of patients. Glaucoma developed in 17% of patients and resulted in enucleation in 4% of patients. The mean pretreatment visual acuity was 20/50 (range, 20/12.5 to hand motions), which evolved to a mean visual acuity of 20/100 (range, 20/20 to no light perception). Overall, 25 of 47 patients (53%) maintained 20/200 or better vision. Metastatic melanoma developed in 32% of patients.

CONCLUSIONS AND RELEVANCE Palladium-103 ophthalmic plaque radiation therapy can be used as an eye- and vision-preserving treatment for relatively large American Joint Committee on Cancer T3- or T4-sized choroidal melanomas.

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ophthalmic plaque brachytherapy has become the most widely used eye- and vision-sparing treatment for uveal melanomas. First used to sterilize posterior choroidal melanomas, plaque techniques have expanded to new frontiers, allowing treatment of both iris and circumpapillary melanomas. Similarly, a large tumor size has limited the use of ophthalmic plaque brachytherapy. For example, in 1985, the Collaborative Ocular Melanoma Study (COMS) placed limits on the size of choroidal melanomas amenable to plaque brachytherapy. Large choroidal melanomas defined by the COMS as having a basal dimension of 16.0 mm or greater or an apical height of 10.0 mm or higher were only treated by enucleation. However, in 2003, the American Brachytherapy Society sanctioned plaque brachytherapy for select COMS large-sized choroidal melanomas.

Informed consent is more complicated in the treatment of large choroidal melanomas. For example, in comparison with radiation of medium-sized choroidal melanomas, radiation of large melanomas is associated with greater risks of tumor regrowth, radiation complications, and metastatic disease. Patients must consider that the COMS comparison of iodine 125 (125I) plaque brachytherapy vs enucleation for the prevention of metastasis was limited to select COMS medium-sized (not large) melanomas. Furthermore, large choroidal melanomas are more likely to exhibit additional risk factors for metastasis, including ciliary body involvement, extrascleral tumor extension, epithelioid cell type, high mitotic rate, chromosome 3 monosomy, chromosome 8q gain, and an increased standardized uptake value detected by 18 fluorodeoxyglucose positron emission tomography/computed axial tomography (PET/CT). That said, when confronted with the choice between eye- and vision-sparing radiation or enucleation, patients typically prefer to keep their eye.

In 2009, the American Joint Committee on Cancer (AJCC) published a universal staging system for eye cancers. This was the work of a combined AJCC and Union for International Cancer Control Ophthalmic Oncology Task Force consisting of 46 eye cancer specialists from 11 countries. This collaboration resulted in a new TNM universal staging system for uveal melanomas based, in part, on a retrospective review of the tumor size–related mortality of 7369 patients. In the resultant AJCC Uveal Melanoma Staging System, tumors were staged according to the AJCC Uveal Melanoma Staging System, 7th edition.

Tumor basal dimensions were determined during clinical examination primarily using information gathered by ultrasonographic imaging, fundus photography, fluorescein angiography, optical coherence tomography, and transilluminometry. The distances from the posterior tumor edge to the optic disc and macula were aided by eye-map measurements originally provided by the COMS.

Pretreatment tumor staging aided by whole-body PET/CT or abdominal radiographic imaging (CT or magnetic resonance imaging) was performed. Follow-up metastatic surveys were repeated every 6 months for 3 years and yearly thereafter.

Radiation Dosimetry
In our study, we used standard 16- to 20-mm COMS plaques and custom-made 22-mm diameter gold plaques (without side walls). Palladium-103 seeds (Theragenics) were used to load the plaques. The dose to the tumor and critical normal ocular structures were calculated by certified medical physicists.

The Dose Gradient and Large Intraocular Tumors
Our study recognizes and exploits the ophthalmic plaque “dose gradient” originally described in 1997 and recognized by the American Association of Physicians in Medicine Task Group 129 and the American Brachytherapy Society in analyses of dosimetry related to plaque radiation therapy in 2012. By exploiting the dose gradient, we were able to reduce the measured uveal melanoma apex dose to the

Methods
Our study adhered to the Declaration of Helsinki and the Health Insurance Portability and Accountability Act of 1996. We obtained approval from the New York Eye Cancer Center internal review board to perform this retrospective medical record review. Our study was a retrospective evaluation of the results of ophthalmic plaque brachytherapy of AJCC T3- and T4-sized choroidal melanomas (Figure 1) treated in the New York Eye Cancer Center and affiliated hospitals between 2002 and 2012 (with a follow-up of ≥6 months).

Informed Consent
All patients were informed of the risks and potential benefits related to observation, radiation therapy (plaque or proton), surgical excision, and enucleation surgery. This included discussing the potential risks associated with minimal extrascleral extension with the 2 affected patients. All patients were informed that the COMS found no survival advantage related to enucleation vs plaque brachytherapy for COMS medium-sized choroidal melanomas. Thus, all patients in our study refused enucleation and were informed of the known risks related to eyesparing treatment of larger choroidal melanomas.

Ophthalmic Examinations
Initial diagnostic and follow-up ophthalmic examinations included a best-corrected visual acuity, tonometry, slit-lamp biomicroscopy, gonioscopy, and ophthalmoscopy. Tumors were measured using 20-MHz B-scan and/or 35-MHz high-frequency ultrasonographic imaging. Fluorescein angiography and optical coherence tomography were used to evaluate the tumors and their related vasculopathies (Figure 2). Tumors were staged according to the AJCC Uveal Melanoma Staging System, 7th edition.

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minimum targets used in external beam radiation therapy for cutaneous melanoma. The dose gradient can be explained by comparing 2 hypothetical choroidal melanomas treated with ophthalmic plaque radiation therapy. Both measured to have a rather average 12-mm largest basal dimension, but one with a relatively large 10 mm in height and the other just 3 mm in height. If both are given an equivalent 85-Gy prescription dose to each tumor apex, the base of the 10-mm–high tumor will be calculated to receive nearly 644 Gy (with a base to apex ratio of 8 to 1), whereas the base of the 3-mm–high tumor will be calculated to receive only 166 Gy (with a base to apex ratio of 2 to 1). Thus, for an equivalent apex dose, the smaller tumor receives just one-fourth the base dose compared with the larger tumor. Also, the average dose within the large tumor will be 365 Gy vs 126 Gy for the smaller tumor (Table 1). Therefore, in plaque brachytherapy for different size tumors, there can exist strikingly different doses within the tumor volume. In this case, we see no reason why the larger tumor would require 3 times more radiation than the smaller tumor to be sterilized.

In our study, you will note a trend toward apical dose reductions (for the taller tumors) toward the end of what is con-
Plaque Surgery

The insertion of large plaques presented unique challenges. For example, the extraocular muscles were invariably relocated, and the exposed portion of the anterior plaques were covered with Gunderson flaps. In this series, no patient required a temporary displacement of more than 2 rectus muscles and 1 oblique muscle.

After 2006, when tumors extended into the anterior segment, plaques were placed on the cornea and sutured to adjacent sclera. In these cases, fresh-frozen amniotic membrane grafts (Bio-Tissue) were used to buffer the cornea.²⁹ Patients were treated for 5 or 7 consecutive days, after which the plaque was removed.

Statistical Analysis

Data were summarized as minimum, maximum, and mean or median values with 95% CIs for the following variables: patient age, observation period, tumor dimensions, and radiation dosage. The number and percentage were tabulated for categorical data. Visual acuity data at baseline and at last visit were summarized as mean, median, minimum, and maximum values. Comparative analyses were performed using the Mann-Whitney U test, and \( P < .05 \) was considered to be statistically significant. Kaplan-Meier estimates were performed for analysis of radiation-related complications and melanoma-specific survival (Statistica; StatSoft Inc).

Results

Forty-seven patients with an AJCC T3-sized (\( n = 38 \)) or T4-sized (\( n = 9 \)) uveal melanoma were treated with \(^{125}\)Pd plaque brachytherapy between 2002 and 2012 (Table 2). The observation period after the treatment ranged from 6 to 125 months (median, 47 months) (Table 2). In this series, 19 patients were men and 28 were women, with ages ranging from 31 to 89 years (mean age, 65 years [95% CI, 61-70 years]). Tumors involved the iris, the ciliary body, and the choroid (Table 2). Two patients had a minimal extrascleral tumor extension at the time of plaque therapy.

Preoperative tumor heights (thickness) varied from 3.8 to 12.3 mm (mean height, 8.6 mm [95% CI, 8.0-9.2 mm]). Base diameters were 12.1 to 19.9 mm in size (mean diameter, 15.8 mm [95% CI, 15.3-16.4 mm]). Of the 47 patients, 45 (96%) had a secondary exudative retinal detachment prior to treatment.

Initial whole-body PET/CT imaging was performed for 32 patients.³⁰ Of these patients, 26 (81%) had uveal melanomas that were reported to exhibit increased standardized uptake values varying between 1.8 and 15.1 (mean value, 5.1).¹² Fifteen patients did not undergo PET/CT but were examined by use of contrast-enhanced chest and abdominal CT or magnetic resonance imaging. All the results of preoperative metastatic surveys were negative.

Complications After Plaque Radiation Therapy

Short-term Findings

Of the 47 patients, 30 (64%) had no short-term complications after treatment (Table 3). Local corneal complications included transient corneal epithelial defects and edema. These were primarily associated with plaque placement onto the cornea for the treatment of anterior uveal melanomas. Amniotic membrane grafts were placed between the plaque and the corneas after 2006 (for 9 of 22 patients [41%]). This offered subjective comfort during treatment and diminished the risk of anterior segment complications.²⁹
Long-term Findings
Of the 47 patients, 4 (9%) experienced no long-term complications and have maintained their pretreatment visual acuity over 9 to 68 months (Figure 2). A secondary cataract developed in the phakic eye of 16 of 44 patients (36%) and at a mean time of 26 months (range, 2-45 months) after irradiation. There were no reported difficulties associated with postirradiation cataract surgery. Of 45 patients with preexisting exudative retinal detachments, 14 (31%) maintained persistent detachments that significantly affected visual acuity outcomes. For example, 8 of 14 patients (57%) with persistent retinal detachments lost more than 3 lines of visual acuity. Secondary glaucoma developed in the eyes of 8 out of 47 patients (17%), and 2 patients (4%) required enucleation.31 Vitreous hemorrhage developed in 6 patients (13%), and secondary vitritis developed in 2 patients (4%). Scleral melting developed in the eyes of 2 patients (4%) 17 and 31 months after irradiation, respectively, and was associated with scleral doses of 463 and 633 Gy, respectively.32

The most common long-term complications were radiation maculopathy (RM) and/or radiation optic neuropathy (RON), seen in 34 patients (72%). Intraocular radiation vasculopathy was characterized by early vascular transudation with edema followed by vascular occlusions associated ischemia. For example, early RM and RON were seen as retinal or optic disc edema with hemorrhages and exudates. Cotton-wool spots, capillary dropout, and large vessel closures (ghost vessels) were best seen by use of fluorescein angiography. Intra-retinal fluid and loss or shallowing of the optic disc cup were best seen on optical coherence tomographic scans.27 Overall, RM was diagnosed in the eyes of 31 patients (66%) at a mean time of 15 months (range, 2-36 months). In those patients, the mean dose to the fovea was 49.8 Gy (range, 14.5-545.2 Gy). Similarly, RON was noted in the eyes of 24 patients (51%) at a mean time of 16 months (range, 2-36 months). In those patients, the center of the optic disc was calculated to receive a mean dose of 63.3 Gy (range, 14.0-257.0 Gy). The nearer the tumor was to the macula or optic disc, the higher radiation dose was delivered to these structures. There was a statistically significant correlation between radiation dose to the tumor and development of RON or RM (P = .002 and P = .003, respectively, determined by use of the Mann-Whitney U test). The Kaplan-Meier estimates for the risk of developing the most common treatment-related complications are shown in Figure 3.

Anti–Vascular Endothelial Growth Factor Intervention
Overall, 34 patients developed RM and/or RON during our study, 21 patients developed RM and/or RON prior to the advent of anti–vascular endothelial growth factor therapy, and all lost some of their vision (range, 1-14 lines to no light perception). The remaining 13 patients were treated with monthly intravitreal injections of anti–vascular endothelial growth factor agent, which were extended to 6- to 8-week intervals depending on response to treatment.33-35 Of those 13 patients, 7 (54%) were able to improve (n = 3) or maintain (n = 4) their pretreatment visual acuity, and 6 (46%) lost vision despite treatment (ranging from 1 line loss to no light perception).

Overall Visual Acuity
Pretreatment visual acuities ranged from 20/12.5 to hand motion (mean visual acuity, 20/50; median visual acuity, 20/32), and 32 of 47 patients (68%) had an initial visual acuity of 20/200 or better. Overall, the final vision at last examination improved for 9 patients (19%), remained unchanged for 7 patients (15%), and decreased for 31 patients (66%). At last follow-up, visual acuities ranged from 20/20 to no light perception (mean visual acuity, 20/100; median visual acuity, 20/50). A visual acuity of 20/200 or better was preserved for 25 of 47 patients (53%). Patients with a higher mean radiation dose to the tumor, macula, and optic disc had a greater chance of developing treatment-related complications and poor vision.

Tumor Regression and Local Control
The mean tumor thickness over time demonstrated a gradual regression, slowing 3 years after radiation (Figure 4). Local tumor control was achieved in 43 cases (91%). Among the 4 patients whose treatment could not maintain local control, 1 tumor was successfully retreated with plaque brachytherapy, and 3 eyes were enucleated 1.5, 4, and 8.5 years after initial treatment (Table 4). In these cases, the apical prescription dose was 72.6, 75, 75, and 50.2 Gy, respectively. Neither the radiation dose to the tumor apex nor the mean dose to the tumor was significantly correlated with failure of local control (P = .78 and P = .38, respectively, determined by use of the Mann-Whitney U test).

Eye Conservation
The reasons for enucleation were tumor recurrence and intractable secondary glaucoma. In this series, 4 patients (9%) had tumor recurrence at a mean follow-up of 36 months.
Among these 4 patients, the eyes of 3 patients were enucleated. An additional 8 patients (17%) developed secondary glaucoma. Among these 8 patients, enucleation was performed in 2 cases (12 and 48 months after brachytherapy, respectively) for blind and painful eyes. The other 6 patients’ glaucoma was medically controlled. Overall, eye preservation was achieved for 42 patients (89%). In that only 5 eyes were removed, a statistical analysis of the risk of enucleation according to preexisting or treatment-related conditions was not performed.

**Metastatic Disease**

Fifteen patients (32%) developed metastatic melanoma. As predicted by use of the AJCC staging system, 4 of the 9 patients (44%) with T4-sized tumors developed metastasis compared with 11 of 38 patients (29%) with T3-sized tumors (Figure 3). One patient died of breast cancer, and another died of a cerebral vascular accident. There was no evidence of metastasis in the remaining 30 patients (64%) for a median time of 53 months (range, 6-125 months). Kaplan-Meier estimates for melanoma-specific death are shown in Figure 3.

**Discussion**

Conservative treatments for large uveal melanoma present unique clinical challenges. For example, our study shows that patients with large uveal melanomas have high mortality rates. Furthermore, increased tumor size was associated with relatively high radiation doses to normal ocular structures and thus more cases of RM, RON, neovascular glaucoma, and secondary enucleation (Tables 2 and 3).
Therefore, informed consent was more complex for patients with large uveal melanomas. In consideration of these challenges, patients with T3- and T4-sized uveal melanomas were made cognizant that their prognosis for useful vision after brachytherapy was relatively guarded (compared with the eyes with smaller tumors). They were told that their vision would likely be affected by preexisting retinal detachments, tumor hemorrhages, and exudation. In addition, should their vision be preserved, these eyes harbored a long-term dose-related risk of RM and RON. \(^{25,34,36,37}\) Lastly, patients were informed that periodic intravitreal injections of anti-vascular endothelial growth factor agents were available to suppress certain complications related to intraocular radiation. \(^{33-35}\)

Our study indicates that in treatment of T3- and T4-staged uveal melanomas, Kaplan-Meier estimates of the risk for developing radiation-induced complications at 5 years are 76% for RM, 58% for RON, 27% for secondary glaucoma, and 15% for vitreous hemorrhage (Figure 3). Partly as a result of this experience, our current contraindications for plaque brachytherapy for large uveal melanomas include tumors with gross (T4e or >5 mm) extraocular extension, blind painful eyes, and those with no light perception vision. However, there will be

### Table 4. Analysis of Failures of Local Control

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
<th>Patients With No Recurrence, Mean (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor height, mm</td>
<td>6.5</td>
<td>5.5</td>
<td>10.8</td>
<td>7.9</td>
<td>8.7 (3.8-12.3)</td>
</tr>
<tr>
<td>Maximum tumor width, mm</td>
<td>14.0</td>
<td>12.5</td>
<td>13.9</td>
<td>13.8</td>
<td>16.0 (12.1-19.0)</td>
</tr>
<tr>
<td>T category</td>
<td>T3a</td>
<td>T3b</td>
<td>T3b</td>
<td>T3b</td>
<td>T3a, T3b, T3c, T3d, T4a, T4b</td>
</tr>
<tr>
<td>Tumor location</td>
<td>Choroid</td>
<td>Ciliochoroidal</td>
<td>Ciliochoroidal</td>
<td>Ciliochoroidal</td>
<td>Iris, ciliary body, choroid</td>
</tr>
<tr>
<td>Dose to tumor apex, Gy</td>
<td>72.6</td>
<td>75.0</td>
<td>50.2</td>
<td>75.0</td>
<td>69.4 (49.0-87.2)</td>
</tr>
<tr>
<td>Dose to tumor base (sclera), Gy</td>
<td>332.7</td>
<td>240.5</td>
<td>509.7</td>
<td>421.0</td>
<td>181.9 (130.8-698.0)</td>
</tr>
<tr>
<td>Mean dose to tumor, Gy</td>
<td>202.7</td>
<td>157.8</td>
<td>280.0</td>
<td>248.0</td>
<td>254.0 (116.5-382.8)</td>
</tr>
<tr>
<td>Tumor relapse time, y</td>
<td>4.5</td>
<td>4.0</td>
<td>2.0</td>
<td>1.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Additional treatment</td>
<td>TTT twice (relapsed), enucleation (4 y after TTT)</td>
<td>103Pd plaque brachytherapy</td>
<td>Enucleation</td>
<td>Enucleation</td>
<td>None</td>
</tr>
<tr>
<td>Total observation period, y</td>
<td>10.0</td>
<td>6.5</td>
<td>3.5</td>
<td>2.0</td>
<td>3.9 (0.5-10)</td>
</tr>
<tr>
<td>Metastasis</td>
<td>No</td>
<td>Liver</td>
<td>Lungs</td>
<td>No</td>
<td>30%*</td>
</tr>
</tbody>
</table>

Abbreviations: Gy, gray; \(^{103}\)Pd, palladium-103; TTT, transpupillary thermotherapy.

* Thirteen of 43 patients.

### Table 5. Data on Large Choroidal Melanomas: Comparison With Other Published Studies

<table>
<thead>
<tr>
<th>Source</th>
<th>Patients, No.</th>
<th>Mean or Median Follow-up Period, mo</th>
<th>Tumor Thickness, mm</th>
<th>Tumor Diameter, mm</th>
<th>Classification</th>
<th>Treatment Type</th>
<th>Tumor Local Control Rate</th>
<th>Eye Retention Rate</th>
<th>Disease-Specific Survival</th>
<th>Vision of 20/200 or Better</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present study</td>
<td>47</td>
<td>47.0</td>
<td>8.6 [3.8-12.3]</td>
<td>15.8 [12.1-19.9]</td>
<td>AJCC T3 and T4</td>
<td>(^{103})Pd</td>
<td>91.0</td>
<td>89.0</td>
<td>68.0</td>
<td>53.0</td>
</tr>
<tr>
<td>Shields et al(^{38})</td>
<td>344</td>
<td>60.0</td>
<td>9.0 [9.8-16.0]</td>
<td>14.0 [5.0-21.0]</td>
<td>None</td>
<td>(^{125})I</td>
<td>91.0</td>
<td>76.0</td>
<td>70.0</td>
<td>43.0</td>
</tr>
<tr>
<td>Puusaari et al(^{39})</td>
<td>97</td>
<td>43.2</td>
<td>10.7 [4.5-16.8]</td>
<td>16.1 [7.3-25.0]</td>
<td>COMS large</td>
<td>(^{125})I</td>
<td>94.0</td>
<td>84*</td>
<td>65</td>
<td>42b</td>
</tr>
<tr>
<td>Bechrakis et al(^{40})</td>
<td>152</td>
<td>30.1</td>
<td>9.0 (1.1)</td>
<td>14.6 (2.4)</td>
<td>None</td>
<td>(^{125})I</td>
<td>88.8</td>
<td>94.4</td>
<td>89.9</td>
<td>5.5</td>
</tr>
<tr>
<td>Bechrakis et al(^{40})</td>
<td>85</td>
<td>33.1</td>
<td>9.5 (2.1)</td>
<td>14.4 (3.0)</td>
<td>None</td>
<td>Transscleral tumor resection</td>
<td>77.8</td>
<td>89.9</td>
<td>94.4</td>
<td>61.1</td>
</tr>
<tr>
<td>Conway et al(^{41})</td>
<td>21</td>
<td>28.0</td>
<td>8.6</td>
<td>18.7</td>
<td>None</td>
<td>Proton beam</td>
<td>67.0</td>
<td>54.0</td>
<td>90.0</td>
<td>25.0</td>
</tr>
<tr>
<td>Mosci et al(^{42})</td>
<td>132</td>
<td>53.4</td>
<td>9.8 (1.6) [6.2-13.5]</td>
<td>15.2 (2.7) [8.3-21.3]</td>
<td>AJCC T3 and T4</td>
<td>Proton beam</td>
<td>86.0</td>
<td>74.0</td>
<td>61.0</td>
<td>32.0</td>
</tr>
<tr>
<td>Fuss et al(^{43})</td>
<td>78</td>
<td>34.0</td>
<td>6.4</td>
<td>12.2</td>
<td>COMS medium and large</td>
<td>Proton beam</td>
<td>90.5 (3.7)*</td>
<td>75.3</td>
<td>75.6 (7.6)*</td>
<td>49.1</td>
</tr>
<tr>
<td>Kreusel et al(^{44})</td>
<td>31</td>
<td>21.6 (7.8)*</td>
<td>6.8 (1.0) [5.0-8.9]</td>
<td>11.7 (2.40) [7.3-17.6]</td>
<td>None</td>
<td>(^{106})Ru, TTT</td>
<td>96.8</td>
<td>96.8</td>
<td>NA</td>
<td>80.6</td>
</tr>
<tr>
<td>Sarici and Pazarili(^{45})</td>
<td>50</td>
<td>40.0</td>
<td>8.7 [4.1-16.8]</td>
<td>10.3 [7.1-15.7]</td>
<td>COMS</td>
<td>Gamma knife</td>
<td>90.0</td>
<td>82.0</td>
<td>82</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviations: AJCC, American Joint Committee on Cancer; COMS, Collaborative Ocular Melanoma Study; NA, not available; \(^{103}\)Pd, palladium-103; \(^{125}\)I, iodine 125; \(^{106}\)Ru, ruthenium-106; TTT, transpupillary thermotherapy.

* At 1 year.

* Mean (SD).
instances when alternative treatments are unacceptable and patient preference for brachytherapy must be considered.

We have used the AJCC staging system rather than the COMS to define a large tumor size in our study because the AJCC T-staging system is more robust, allowing for the inclusion of tumors of any size and in any intraocular location. For example, it allows for tumors with extraocular extension or with ciliary body involvement and for tumors located closer than 2 mm from the optic disc. Furthermore, the AJCC staging system has been adopted by the Union for International Cancer Control and is required or requested in the instructions for authors of most ophthalmic journals (including *JAMA Ophthalmology*). The limitations of our study include its size and retrospective nature. Furthermore, the proportion of patients with follow-up data exceeding 5 years was only 34%. However, local tumor recurrence after 5 years is atypical, and our follow-up is comparable to other reports in the literature (Table 5).

Conclusions

Our study shows that 103Pd ophthalmic plaque radiotherapy can provide local tumor control in 91% of patients and eye retention in 89% of patients with T3- and T4-sized uveal melanomas at a median follow-up of 47 months. Using the dose gradient to adjust the apical tumor dose did not affect local control (P = .78, determined by use of the Mann-Whitney U test). Furthermore, visual acuities of 20/200 or better were preserved in 53% of patients. These rates of local tumor control were as high or higher than those in other “large uveal melanoma” published series, including those using plaque brachytherapy, proton beam radiotherapy, and eye-wall resection (Table 5).

In comparison, proton irradiation for large melanomas provides a high rate of local control. However, there are more reported complications related to anterior ocular and adnexal proton irradiation, a poorer prognosis for vision, and higher rates of secondary enucleation. Compared with protons, 103Pd and 125I brachytherapy studies report fewer anterior segment complications.

The radiation dose to normal ocular structures (macula, optic disc, and opposite eye wall) is typically higher for 125I than for 103Pd. Therefore, 125I-treated patients are at greater risk for RM, RON, and cataract than 103Pd-treated patients. Lastly, 106Ru plaques are limited to the treatment of tumors less than 6.0 mm in thickness. Therefore, some centers that perform 106Ru brachytherapy may add transpupillary thermotherapy to the nonirradiated tumor apex.

Herein, we report our experience with 103Pd plaque radiotherapy as an eye- and vision-sparing alternative treatment for T3- and T4-sized uveal melanomas. This type of radiotherapy resulted in local control and visual acuity and eye retention rates similar to those reported in the treatment of smaller uveal melanomas. We report our results using the AJCC universal staging system, 7th edition, to allow our study to be compared with future radiation studies using alternative radiation delivery systems. In consideration of the trend toward radiation therapy for larger choroidal melanomas, we hope our study is helpful for patients with choroidal melanoma and for the specialists who care for them.
AJCC T3- and T4-Staged Choroidal Melanomas

Original Investigation Research

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