Management of Iris Melanomas With $^{125}$Iodine Plaque Radiotherapy

BRUNO F. FERNANDES, HATEM KREMA, EMILIANO FULDA, CHARLES J. PAVLIN, DAVID G. PAYNE, HUGH D. MCGOWAN, AND ERNEST RAND SIMPSON

- **PURPOSE:** To report the experience of the Princess Margaret Hospital/University Health Network with the treatment of iris melanoma (IM) with $^{125}$Iodine plaque brachytherapy.
- **DESIGN:** Retrospective noncomparative case series.
- **METHODS:** All cases of IM submitted to $^{125}$Iodine plaque radiotherapy were included. Patients’ demographic, clinical, management, and follow-up data were reviewed. Outcome measures included rates of tumor control, eye preservation, systemic metastases, and brachytherapy-related complications.
- **RESULTS:** Fourteen IMs were included in the study. All patients had blue/green irises. Mean largest basal dimension and thickness were 7.1 ± 2.1 mm (range, 4.0 to 11.5 mm) and 2.2 ± 0.8 mm (range, 1.0 to 3.5 mm), respectively. Ten patients (71%) had seeding and 2 (14%) had glaucoma at presentation. Median follow-up was 26.6 ± 19.5 months (range, 6 to 72 months). Tumor control was achieved in 100% of the cases and no eye was enucleated because of radiation-induced complications. At last visit, all patients were alive and free of metastasis. Final visual acuity was the same as or better than before treatment in 9 patients (75%). Cataract was the most common complication (8; 75%), followed by persistent glaucoma (2; 17%) and anterior uveitis (1; 8%). No other significant complication was seen during the follow-up period.
- **CONCLUSIONS:** Plaque radiotherapy is a safe and effective conservative treatment option for IM, although cataract is a common, yet treatable, complication. This treatment scheme circumvents an intraocular procedure and may avoid the dissemination of malignant cells, and provides a margin of safety in the treatment of clinically undetectable disease. (Am J Ophthalmol 2010;149:70–76. © 2010 by Elsevier Inc. All rights reserved.)

Iris melanoma (IM) is the least common of uveal melanomas. It comprises less than 3% of all intraocular melanomas and carries the best prognosis. Metastatic rates are 3%, 5%, and 10% on 5-, 10-, and 20-year follow-ups, respectively.

Proper management of IM is still controversial. Malignant lesions of the iris are usually followed until growth is detected. Natural history studies have shown that only a few of those cases change over time (4.6% at 3.9-month mean follow-up). The classical approach to enlarging lesions of the iris is surgical resection. Since surgical resection of the melanoma carries the risks associated with an invasive intraocular procedure and incomplete tumor excision, different irradiation modalities have been advocated. The experience with $^{125}$Iodine plaque brachytherapy in the treatment of IM at the Princess Margaret Hospital/University Health Network is the subject of the report to follow.

METHODS

We retrospectively reviewed all cases of IM treated with $^{125}$Iodine plaque radiotherapy over the past 10 years. Contraindications for plaque treatment were ring melanoma (more than 180 degrees), tumor-induced glaucoma in an eye with low visual potential, peripheral corneal disease, and seeding of tumor cells away from the planned area of treatment. Only cases with documented growth and suggestive clinical features were treated and consequently included in the study. Large tumor size, prominent tumor vascularity, tumor seeding, elevated intraocular pressure (IOP), and tumor-related ocular complications are some of the described suspicious features. Even though cases with minimal ciliary body involvement were included, we did exclude cases that originated from the ciliary body, or when the bulk of the lesion was not in the iris. Patients who had no available follow-up information were excluded from the study.

- **BASELINE CHARACTERISTICS:** Medical records were reviewed in order to retrieve the following information: age, gender, laterality, symptoms, past ocular history, visual acuity (VA) and IOP at presentation, iris color, pupil distortion, presence of hyphema, location of the tumor (quadrant involved), degree of pigmentation, presence of seeding, and prominent vascularity.
- **ULTRASOUND BIOMICROSCOPIC FEATURES:** Ultrasound biomicroscopy (UBM) was performed in all patients to determine the largest tumor dimension (LTD),
thickness, extension, and ultrasonographic features of the tumor; internal reflectivity (high or low, homogeneous or heterogeneous); shape; presence of intralenticular cavitations or associated cysts; anterior surface plaque; tumor touching the cornea; anterior and posterior tumor contour (smooth or irregular); and iris pigment epithelium breaks.

**SURGICAL TECHNIQUE:** Collaborative Ocular Melanoma Study (COMS)-designed plaques were used in all cases,
with diameters of 12- or 14-mm depending on the size of the tumor. Plaque size was determined according to the tumor's largest basal dimension; a safe margin of 2 mm was added in all directions. Radiation dose was calculated considering the maximum thickness of the lesion. The energy, number, and distribution of the radioactive seeds were adjusted for each individual case so as to provide a total dose of 8500 cGy to the tumor apex at a dose rate of 50 cGy/hour over 7 days, which is the time allocated for plaque surgery in our institution. Calculations were made using the Plaque Simulator software distributed by BEBIG GmbH (Berlin, Germany). Briefly, the tumor was transilluminated after a conjunctival peritomy. Two scleral sutures were placed in the sclera and tied to 2 plaque islets. The conjunctiva was then sutured over the plaque to avoid scleral exposure and displacement of the plaque. The plaque was left in place for a week and during that time the eye was patched with a special dressing to prevent further pressure on the globe. A tobramycin 0.3%-dexamethasone 0.1% ophthalmic suspension (Isopto Homatropine; Alcon Laboratories Inc., Fortworth, Texas, USA) and homatropine (Tobradex; Alcon Laboratories Inc.) were used 3 times a day during this week, and also for the following 2 weeks after plaque removal. At that time, the patient was examined to assess corneal integrity and conjunctival healing.

● OUTCOME: The first postoperative tumor measurements were accomplished at 3 and 6 months postoperatively and every 6 months thereafter. Tumor response was defined by loss of vascularity, decrease in tumor thickness, and UBM changes, such as an increase in internal reflectivity. At each visit, the patient was screened for metastatic disease (liver enzymes and abdominal ultrasound) and a complete ophthalmologic evaluation, including VA, IOP, presence of complications, and tumor measurements by UBM, was performed. Subsequent surgical interventions were also recorded. A list of potential complications included: delayed corneal and/or conjunctival healing; corneal epitheliopathy; scleral and/or corneal necrosis; endothelial decom-
FIGURE 2. Amelanotic IM. Slit-lamp (Top left) and goniscopic (Top middle) view. Note the prominent tumor vascularity. (Top right) Ultrasound biomicroscopy (UBM) shows the mass in contact with the cornea but without extension to the ciliary body. (Bottom left and middle) Six months after plaque brachytherapy, the tumor is smaller and less vascularized. (Bottom right) UBM confirms the decrease in size and also reveals an increased internal reflectivity after treatment.
pensation; persistent anterior uveitis and/or glaucoma; cataract; radiation retinopathy; radiation optic neuropathy; and neovascular glaucoma.

**RESULTS**

- **CLINICAL FEATURES:** Fourteen IMs were included in the study. On average, patients were followed for 32 ± 43 months before treatment was indicated. Age at presentation was 51.0 ± 13.8 years (range, 27 to 72) and 11 of the patients (79%) were women. All patients had blue/green irises. Eight patients (57%) had the left eye affected. The majority of patients had no symptoms at presentation (n = 11, 79%). Three patients had vision blurring, 2 attributable to hyphema and 1 attributable to cataract. One other patient was pseudophakic with a posterior chamber intraocular lens implanted. Mean IOP was 16 ± 4 mm Hg. Two patients presented with unilateral glaucoma. Other clinical features are detailed in Table 1.

- **TUMOR CHARACTERISTICS:** Thirteen of the IMs (93%) were located at sun-exposed areas of the iris. Mean largest basal dimension and thickness were 7.1 ± 2.3 mm (range, 4.0 to 11.5 mm) and 2.3 ± 0.7 mm (range, 1.0 to 3.5 mm), respectively. Ten IMs (71%) were pigmented, 2 (14%) showed varied pigmentation, and 2 (14%) were amelanotic. Ten cases (71%) showed seeding on the adjacent iris surface and/or angle. Prominent intrinsic vasculature was seen in 8 cases (57%), and 5 of the tumors (36%) caused distortion of the pupil. Eleven cases (79%) showed involvement of the pupillary margin, while in 13 cases (93%) the root of the iris was compromised (10 cases [71%] had both). UBM showed extension to the ciliary body in 5 cases (36%). All (2) amelanotic tumors had low internal reflectivity. Among the (10) melanotic ones, 3 had high and 7 had low internal reflectivity. Other UBM features are exposed in Table 2.

- **OUTCOME:** Median follow-up was 26.6 ± 19.5 months (range, 6 to 72 months). Tumor control was achieved in 100% of the cases and no eye was enucleated because of radiation-induced complications. Mild keratitis was evident in most cases during the first week after surgery, but no long-term corneal complications were observed (Figure 1). All tumors showed a decrease in size after treatment. Mean tumor thickness decreased from 2.32 ± 0.69 to 1.55 ± 0.89 mm. On UBM, the internal reflectivity of the tumor tended to increase, and the tumor structure was more homogeneous after treatment (Figure 2). Internal structure was homogenous in 5 (35%) at presentation, and in 7 (50%) after treatment (P = 0.09). Only 3 (8%) tumors showed high internal reflectivity before treatment, compared to 8 (58%), after radiation (P = 0.01). Of 12 patients who had clear lens before radiation, 8 (75%) developed some degree of radiation-induced lens opacification. Cataract surgery was performed in 3 of those cases. Ten patients (71%) had final VA of 20/30 or better. At last follow-up visit, visual acuity was better in 1 (7%), the same in 10 (71%) and worse in 3 (21%) patients. In the 3 patients (21%) who had VA worse than before treatment, cataract surgery had not been performed; thus vision is likely to improve.8 One patient had persistent anterior uveitis, controlled with topical steroids. The 2 cases (17%) that presented with unilateral glaucoma were the only ones with persistently high IOP. At last visit, the IOP was 24 mm Hg in 1 and 14 mm Hg in the other, with medication. No cases of delayed corneal and/or conjunctival healing, corneal epitheliopathy, scleral and/or corneal necrosis, endothelial decompensation, neovascular glaucoma, or radiation retinopathy/optic neuropathy were detected. At last visit, all patients were alive and free of metastases.

**DISCUSSION**

PLAQUE BRACHYTHERAPY OF IMS IS A SAFE AND EFFECTIVE alternative therapy to resection. Even though most cases had mild keratitis after plaque removal, at 2-week follow-up all corneas were clear. Two cases had glaucoma before the procedure and persisted with increased IOP at last visit. In both cases the angle was open without evidence of neovascularization. IOP was controlled with topical medication and no other procedures were needed. One patient needed long-term use of topical steroids for chronic anterior uveitis, which was also present before radiation. There were no cases of neovascular glaucoma, radiation retinopathy, or optic neuropathy. No eye had to be enucleated because of recurrence or radiation-related complications. The only significant long-term side effect in our series was cataract, which is in agreement with other series.8–10 Also in keeping with the current literature, radiotherapy for IM rarely incurs long-term corneal or scleral complications. Damato and associates had 1 case with bullous keratopathy caused by the tumor and 2 cases of mild keratitis.8 Shields and associates reported a 9% incidence of corneal epitheliopathy but no cases of corneal stromal edema or corneal or scleral necrosis.10 A comparison of recent reports on surgical excision12,13 or radiotherapy8,10,11 for IM suggests that there is less ocular morbidity with the latter. Plaque radiotherapy, being an extraocular procedure, avoids some of the complications inherent to an intraocular intervention. Operative complications related to local resection include vitreous loss, retinal detachment, lens subluxation, traumatic cataract, hemorrhage, persistent wound leak, and prolonged endothelial decompensation.12 These complications were not seen in our series. Another frequent complication of local resection is symptomatic postoperative photophobia and glare, which is seen in 25% of patients. Despite pupil reconstruction, some patients would still complain of postoperative glare requiring the
use of tinted glasses.\textsuperscript{12} Such visual symptoms are usually unavoidable because the vast majority of IMs are located inferiorly between the 3- and 9-o’clock positions.

In addition to all complications related to the surgical resection, there is the questionable wisdom of invading an eye harboring an intraocular malignancy. Manipulation of the tumor has the potential to disseminate malignant cells in the anterior chamber and indeed increases the risk of metastases.\textsuperscript{4} In some cases, it might be difficult for the surgeon to ensure tumor-free margins. Lateral margins are difficult to determine in diffuse, flat tumors and the posterior margin is not always clearly defined by UBM. Transillumination is helpful but, unfortunately, thin tumors do not produce a distinct shadow. Tumor seeding in the angle or adjacent iris and tumor touching the cornea are other factors that increase the risk of leaving cells behind. As well, “brushing” the tumor mass against adjacent tissues during removal may play a role in increasing the chances of recurrence. Recurrences after tumor excision are seen in up to 11.8% of cases.\textsuperscript{14} Data from large series show a better tumor control with radiation therapy. Damato and associates, using proton beam radiotherapy, obtained a 3.3% recurrence rate at 4 years.\textsuperscript{5} Shields and associates, using \textsuperscript{125}Iodine custom-designed plaques, had a slightly higher recurrence rate of 8% at 5 years.\textsuperscript{10} However, their sample included only nonresectable cases; thus, a selection bias towards more aggressive cases is likely present. In our series, during the study period, no recurrences were seen. Tumor recurrence not only implies another visit to the operating room, but also is associated with a worse prognosis. Geisse and associates studied 1,043 IMs and 62% of the metastatic cases were associated with either previous incomplete excision or inadvertent transection of the lesion.\textsuperscript{15}

Moreover, in the review of 169 lesions from Shields and associates, surgical intervention before referral was statistically associated with a worse prognosis.\textsuperscript{10} Ultrasound biomicroscopy is the most useful ancillary test for the evaluation of iris lesions. It provides not only tumor measurements but also the relationship of the tumor with other ocular structures, extent of the malignant process, and information concerning the internal structure of the mass. In addition, UBM is a reliable tool to follow tumor changes after radiation. Besides a decrease in thickness, we could see changes in the internal reflectivity of these lesions. After treatment, the internal reflectivity tended to increase and become more homogeneous. These changes are particularly valuable for the follow-up of thin and/or diffuse tumors, when the thickness is not expected to alter greatly. These are important findings that reflect a response to radiation even when the lesion does not decrease in size.

A limitation of our study was the lack of histopathologic confirmation. Diagnosis was made based on previously described clinical and UBM features.\textsuperscript{4,8,11,16,17} Even though it is known that benign uveal nevi may grow over time, documented growth is the single most important determinant of malignancy.\textsuperscript{1,16} Growing iris lesions are usually considered to be malignant and treated accordingly.\textsuperscript{7} In our sample, all cases showed documented growth before treatment was indicated. We might, however, have included cases of iris nevi that had suspicious features of IM, which could have overestimated the effectiveness of the procedure. The rate of radiation-induced complications, however, would have remained unaffected. Nevertheless, the fact that all cases responded to radiation by showing a decrease in tumor size further supports the presumption that all cases were indeed composed of radiosensitive malignant melanoma cells. Another limitation of our study is the relatively short follow-up time. IM is known to have a good prognosis and whenever metastases occur, they do so long after the treatment of the primary tumor. Thus, conclusions regarding the impact of our study on survival are limited.

Plaque radiotherapy is a safe and effective conservative treatment option for IMs, although cataract is a common, yet treatable, complication. This management option, by circumventing an intraocular intervention, may avoid the dissemination of malignant cells and provides a margin of safety in the treatment of clinically undetectable disease.


REFERENCES


Biosketch

Bruno F. Fernandes, MD, PhD, received his medical degree in 2001 from Federal University of Rio de Janeiro, Brazil and completed his residency in Rio de Janeiro, Brazil. He then enrolled in the PhD program at the Federal university of Sao Paulo, obtaining his degree in 2006. After his PhD, he completed a one-year post-doctoral research fellowship focusing on the ocular cancers. He had subspecialty training in Ocular Pathology under the supervision of Dr. Miguel N. Burnier Jr. at McGill University and Ocular Oncology under the supervision of Dr. Ernest Rand Simpson at The Princess Margaret Hospital/University of Toronto.

Dr. Fernandes has published more than 30 peer-reviewed publications in the areas of ocular pathology and oncology. He has served as a reviewer for major journals in the field of pathology, ophthalmology and oncology. He is also a member of 12 professional associations and has given presentations all-over the world in major international and regional meetings. Dr. Fernandes is currently based at McGill University, Montreal. Canada.
Biosketch

Hatem Krema, MD, is currently an Assistant Professor in the department of Ophthalmology and Vision Sciences of University of Toronto, Ontario, Canada. He received his medical degree from Cairo University in Egypt, and he obtained a Masters of Science degree in ophthalmology from the same university. He became a fellow of the Royal College of Surgeons of Edinburgh, United Kingdom in 1997. He was trained in ocular oncology in Liverpool, England and completed fellowship training in ocular oncology at Wills Eye Hospital, Philadelphia, Pennsylvania, and Princess Margaret Hospital, Toronto, Ontario, Canada. Dr Krema is an active presenter in International ophthalmology conferences. He is an author and coauthor of several articles in ocular oncology, and an ad-hoc peer-reviewer of several scientific journals. His clinical and research interests are focusing on the management of intraocular and extra ocular tumors and the control of treatment related complications.