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Proton Beam Therapy for Iris Melanomas in 107 Patients

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Purpose: To report on the clinical characteristics and outcomes for patients with iris melanoma using proton therapy.

Design: Retrospective study.

Participants: One hundred seven patients with iris melanoma from 3 regional ophthalmologic centers.

Methods: A retrospective study was conducted for iris melanoma patients from 3 regional ophthalmologic centers referred to and treated at a single proton therapy facility between 1996 and 2015.

Main Outcome Measures: At each follow-up visit, examinations included measurement of best-corrected VA, slit-lamp, examination, indirect ophthalmoscopy, and ultrasound biomicroscopy.

Results: With a median follow-up of 49.5 months, 5 of 107 patients experienced a local relapse within a median of 36.3 months. The cumulative incidence of relapse was 7.5% at 5 years. All 5 patients showed involvement of the iridocorneal angle ($P = 0.056$). Diffuse iris melanoma showed a higher risk of relapse ($P = 0.044$). Four patients showed out-of-field relapse and 1 showed angular relapse. Three patients were retreated with proton therapy, whereas 2 other patients, one with T1b disease and another with diffuse T3 disease, underwent secondary enucleation. None of the patients experienced metastases nor died of iris melanoma. Vision improved in 59.4% of patients (n = 60/101). However, cataracts occurred in 57.4% of the 54 patients (n = 31) without cataract or implant at diagnosis. Secondary glaucoma was reported in 7.6% of the patients (n = 8), uveitis in 4.7% (n = 5), and hyphema in 3.7% (n = 4). All but 5 cases of complications were mild, transient, and not sight limiting after treatment. Five cases of glaucoma, including 1 with uveitis, were severe and associated with visual deterioration.

Conclusions: Proton therapy showed efficacy and limited morbidity in iris melanomas. *Ophthalmology 2017;■:1–9 © 2017 by the American Academy of Ophthalmology*

Iris melanomas are rare uveal tumors that develop from neuroectodermal cells. They represent approximately two thirds of all primary iris tumors, but only approximately 5% of uveal melanomas.[1,2] Their annual incidence varies between 2 to 6 cases per 10 million persons.[3,4] Their prognosis seems more favorable than that of choroidal melanomas, with local control rates of approximately 95% and much lower metastatic rates on the order of 5% or less, in contrast to 30% or more for choroidal melanomas. Iridectomy or sectorial iridocyclectomy has been the mainstay of treatment of small iris or iridociliary melanomas, whereas enucleation was the rule for larger tumors.[5–8] However, iridectomy is associated with substantial morbidity and complications, such as cataracts, hypotonia, corneal damage, retinal detachment, phthisis,[9] and debilitating photophobia, as reported by patients. Moreover, iridectomy is not exempt from tumor seeding.[10] In view of the excellent oncologic outcomes of iris melanomas, more conservative treatments with less morbidity have been investigated. Conservative ocular treatments were based on similar survival outcomes with brachytherapy or enucleation with choroidal melanomas from the 1970s.[11,12] Brachytherapy also has been applied to iris melanomas requiring enucleation.[13,14] Complications after brachytherapy include cataracts and significant inflammation of the anterior segment as well as corneal damage. Proton therapy is a type of radiotherapy characterized by a very sharp dose deposition and is a standard treatment for uveal melanomas. It initially was performed by Damato et al[15] for the treatment of iris melanoma in 1994. Since then, only a limited number of studies have reported the long-term outcomes of such an approach for the management of iris melanomas.[15–18]

The goals of this study were to evaluate these outcomes, such as local control of the treatment site, and to report the side effects and ocular complications of proton therapy for iris melanomas. The study's treatment facility is 1 of 12 proton therapy centers performing ocular treatments worldwide.[19]

Methods

Patients

All consecutive iris melanoma patients underwent proton therapy between 1996 and 2015. Patients were referred from 3 oncology

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reference centers (Nice and Lyon, France, and Genoa, Italy). The patients underwent physical examination, ultrasound eye examination, and ultrasound biomicroscopy before treatment. The tumor was diagnosed as a melanoma, either clinically or histologically (either with fine-needle aspiration biopsy or iridectomy). Identification of the clinical features suspicious for melanoma remains challenging. However, positive clinical criteria, as defined by Shields et al,[20] are pigmented iris lesions of 3 mm or more in diameter, 1 mm in thickness, or both by ultrasound biomicroscopy. Any of the following signs could be associated with confirmed growth: a pre-existing nevus, pupillary deformation, uveal ectropion, tumoral neovessels, sectorial cataract, and elevated intraocular pressure (Fig 1). Achromic lesions could be diagnosed as melanoma in the presence of 1 of these associated signs. *Diffuse melanoma* refers to iris melanomas presenting as flat with infiltrating growth pattern or with seeding through the anterior chamber with confluent or multifocal iris involvement.[21] Only patients treated for a primary iris melanoma were included. Ciliary body melanomas with iris involvement were excluded; these presented as a main cellular nodule in the ciliary body, infiltrating the iris root on ultrasound biomicroscopy.

Complications resulting from the extent of the iris tumor were noted as well as best-corrected visual acuity (VA) using the Monoyer's scale. Our onco-ophthalmology proton therapy database has been compiled prospectively in since 1991 to include patient, tumor thickness, diameter, location, and treatment characteristics. Meanwhile, associated signs and follow-up were filled in by each of the 3 referring ophthalmologic centers. Informed consent with information on the risks and benefits of proton therapy was obtained from all of the patients. The ethical review board of Centre Lacassagne, Nice approved the study, with consideration to the tenets outlined in the Declaration of Helsinki.

Irradiation Technique

Implantation of 4 radio-opaque (tantalum) fiducial markers at the surface of the sclera was performed under local anaesthesia 1 to 4 weeks before administration of proton therapy. Atropine drops were prescribed for 1 month from the implantation of fiducial placement by ophthalmologists from Genoa and Lyon, but not by the third team from Nice. Using a treatment planning system dedicated to ocular proton therapy, fiducials were used for stereotactic modelling of eye orientation starting from the virtual eye model in macular fixation proposed in the treatment planning system. Fiducials also were used to define tumor borders. An ocular planning computed tomography scan was used for eye, lens, and nerve delineation. The treatment planning software EyePlan version 1-3.6 (Douglas Cyclotron Centre, Clatterbridge, UK) aimed to reproduce the true patient gaze and lens position and thus to generate optimized sparing of anterior chamber structures rather than those used from a virtual eye only. All patients were treated with a 65-MeV proton fixed horizontal beam line in a seated position. For head immobilization, a custom-made thermoplastic mask and a dental impression (bite block) were used for reliable and reproducible positioning. Local anesthetic eye drops were used before blepharostat placement to avoid cutaneous eyelid toxicity. Being radio-opaque, the fiducials also were used to control eye positioning using orthogonal radiographs in the treatment room so as to ensure online image-guided irradiation immediately before proton beam delivery. Then, during the 10 seconds of beam-on treatment time, an infrared camera (with images projected on a screen outside the treatment room for immediate interruption in case of gaze deviation) was used for gaze monitoring. This full process allows treatment delivery with submillimetric accuracy. The beam range was usually selected to place a 90% isodose of the distal fall of 2.5 mm beyond the tumor. The 90% isodose of the proximal spread-out-Bragg-peak was placed 2.5 mm in front of the tumor. The collimator border defined the location of the 50% isodose. The dose delivered was 60 relative biological effectiveness in 4 fractions of 15 Gy over 4 days (relative biological effectiveness is defined as the physical proton dose multiplied by the relative biological effectiveness [relative to dose delivered with photons] of 1.1).

Follow-up

Follow-up times were measured from the date of proton therapy to the date of treatment failure or the last known status. Patients were reviewed at 1 and 6 months after proton therapy, then twice yearly for 5 years, and then annually. At each follow-up visit, examinations included measurement of best-corrected VA, slit-lamp examination, indirect ophthalmoscopy, and ultrasound biomicroscopy. Patients alternately were examined by their general ophthalmologists and onco-ophthalmologists. Local control was defined as the absence of tumor growth and absence of any new lesion on the treated eye. Ocular complications, such as cataract, hyphema, elevated intraocular pressure, response to treatment, palpebral sequelae, dry eye syndrome, keratitis, posterior synechiae, uveitis, and tantalum ring exteriorization were collected. The tumor was classified either as stable with partial response (reduction of tumor thickness) or complete response (flat lesion) or as progressive (increased tumor thickness or diameter). Detection of metastases was based on 6-month hepatic ultrasound or computed tomography scan.

Statistical Analysis

Quantitative parameters were described with median and range and qualitative parameters with frequency and percentage. The cumulative incidence of relapse was assessed using Kaplan-Meier survival estimates and was capped after 5 years. The log-rank test was used to assess prognostic factors among initial patient and tumor characteristics. The degradation of VA, defined by a decrease of VA in logarithm of the minimum angle of resolution (logMAR) units between baseline and last follow-up, was described by frequency. Prognostic factors of VA were investigated through a logistic regression to adjust analyses on VA at baseline and time of follow-up. Results were explained by an adjusted odds ratio and 95% confidence interval. P values of less than 0.05 were considered significant. All analyses were carried out using SAS software version 9.2 (SAS Institute, Inc., Cary, NC).

Results

Patient and Tumor Characteristics

One hundred seven consecutive patients were treated between 1996 and 2015 and were included in the study. Fifty-nine were women (55.6%; Table 1). Patients were referred by ophthalmologists from Nice, Lyon, and Genoa in 27.1% (n = 29), 33.6% (n = 36), and 39.3% (n = 42) of cases, respectively. This group represented 4.6% of all uveal melanomas in our population of ocular tumor patients treated with proton therapy. Median age was 57.0 years (range, 22.8−86.7 years). Iris color was blue, green, or brown in 46.2% (n = 48), 15.4% (n = 16), and 38.5% (n = 40) of patients, respectively. These distributions were different among the centers, with more blue eyes in patients from Nice and Lyon, representing 59.3% and 55.6% of patients, respectively, whereas 30% of patients from Genoa had blue eyes ($P = 0.003$). Median VA before treatment was 1.00 (range, 0−1.00).

All lesions were unilateral and equally distributed on either side (51 right eyes, 56 left eyes). Tumors were centered on the inferior

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