

CLINICAL INVESTIGATION

Eye

RISK FACTORS FOR CATARACT AFTER PALLADIUM-103 OPHTHALMIC PLAQUE RADIATION THERAPY

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Purpose: To examine how tumor characteristics and dose affect cataract development after plaque radiation therapy.

Methods and Materials: Three hundred and eighty-four patients were diagnosed with uveal melanoma and treated with palladium-103 (¹⁰³Pd) plaque radiation therapy. Of these, 282 (74%) inclusion met exclusion criteria for follow-up time, tumor location, and phakic status. Then patient-, ophthalmic-, and radiation-specific factors (patient age, diabetes, hypertension, tumor location, tumor dimensions, and lens dose) were examined (by a Cox proportional regression model) as predictors for the development of radiation-related cataract.

Results: Radiation cataract developed in 76 (24%) of patients at a mean follow-up of 39.8 months (range, 1–192). Patients with anteriorly located tumors were noted to have a higher incidence of cataract at 43.0% (43 of 100 patients) vs. 18.1% (33 cataracts per 182 patients) for posteriorly located tumors ($p < 0.0001$). However, multivariate Cox proportional modeling showed that increasing patient age at time of treatment (p for trend = 0.0003) and higher lens dose (p for trend = 0.001) were the best predictors (biomarkers) for radiation cataract.

Conclusions: Although anterior tumor location, greater tumor height, and increased patient age (at treatment) were associated with significantly greater risk for radiation cataract, dose to lens was the most significant factor. © 2011 Elsevier Inc.

Cataract, Lens, Dose, Radiation, Choroidal melanoma.

INTRODUCTION

Cataract is a common complication after radiation therapy for ocular tumors. It can be reported after external beam modalities (*e.g.*, stereotactic radiosurgery, gamma knife, linear accelerator based intensity modulated [IMRT], and particle irradiation) as well as ophthalmic plaque brachytherapy (1, 2). Although all these techniques can be used to deliver therapeutic quantities of radiation to ocular and orbital tumors, they differ in their pattern of dose (and dose rate) delivered to normal ocular structures.

Ophthalmic plaque brachytherapy remains the most common and widely used eye- and vision-sparing technique for treatment of choroidal melanoma (2). Regardless of radionuclide (*e.g.*, iodine-125 [¹²⁵I], ruthenium-106 [¹⁰⁶Ru], or palladium-103 [¹⁰³Pd]) secondary radiation cataracts are common and can limit a patient's visual acuity and quality of life (2).

Radiation therapy plans are designed to focus radiation within the tumor (targeted zone) with maximum sparing of normal structures (outside the targeted zone). The goal of each treatment is a highly conformal dose to the tumor with

simultaneous sparing of adjacent normal tissues. With this in mind, it is important to consider that all radiation sources used for plaque brachytherapy (¹²⁵I, ¹⁰⁶Ru, ¹⁰³Pd) are affected by two dominant characteristics: first, the “inverse square law” dictates that the dose to tissue is inversely related to the square of the distance from the source. Thus, structures (tumor) close to the source (seeds) absorb much more radiation than those tissues at farther locations (*e.g.*, lens). Second, the greater the dose to normal ocular tissues, the greater the risk of radiation-related side effects.

This study examines radiation dose as a biomarker for cataract formation. In addition, both univariate and multivariate Cox model analysis were used to examine patient age, diabetes, hypertension, and tumor size and location as they relate to radiation cataract formation.

METHODS AND MATERIALS

Patient selection

We report on 384 consecutive uveal melanoma patients treated with ¹⁰³Pd ophthalmic plaque radiation therapy. Our methods of

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diagnosis, informed consent, treatment, and follow-up have been previously described (3, 4). Aspects of particular importance to this study include that tumor basal dimensions were determined by ophthalmoscopy, transillumination, fluorescein angiography (FA), and ultrasonography. Intervening patients who underwent enucleation, were enrolled in the Collaborative Ocular Melanoma Study (COMS) and treated with ^{125}I , as well as those who received adjuvant microwave hyperthermia, were excluded from this analysis (5, 6). Each patient participated in a detailed discussion of the relative risks and benefits of each treatment form as it related to their tumor size, tumor location, and risk for ocular complications and metastatic disease. This study was conducted in compliance with the Tenets of the Declaration of Helsinki and approved by the Institutional Review Board of The New York Eye Cancer Center.

Tumor classification

Intraocular tumor locations were defined according to the COMS. Posterior uveal melanomas were centered in the posterior pole (P), posterior equator (PE), or equator posterior (EP). Equatorial tumors (E) were centered at the equator. The categories of anterior uveal melanomas were equator anterior (EA), ciliary body (CB), iridociliary (ICB), and iris (I) (7). Further, melanomas were classified according to the 7th Edition, American Joint Committee on Cancer/International Union Against Cancer Staging System (8).

Definition of radiation cataract

As did the COMS report on cataract outcome, our study defined cataract as a functional or vision-limiting lenticular opacity that developed after plaque brachytherapy (6). Either a loss of line of visual acuity or subjective decrease in visual acuity was recorded. These cataracts were typically asymmetric compared with the nonradiated eye. Therefore, radiation cataracts were defined at the first report of functional vision loss. At that visit, each patient underwent an evaluation that excluded other causes of vision loss (including, but not limited to, radiation maculopathy or optic neuropathy). This determination required a best corrected visual acuity assessment, followed by pupillary evaluation, slit-lamp examination, dilated ophthalmoscopy, fundus photography, fluorescein angiography, and optical coherence tomography (when possible as permitted by the degree of opacity). The date of cataract development was defined as the examination date when the functional vision-limiting cataract was first noted. If the patient was lost to follow-up and later returned with the cataract removed, the date to cataract was recorded as the date the patient returned for examination or the date the patient reported their cataract surgery (as available). Time to cataract surgery was defined as the time from the surgical plaque removal to the date of cataract surgery. Like the COMS study (6), we did not use a standard grading system nor consecutive photographs of affected lenses.

Age-related cataracts were also noted during the study. An age-related cataract was defined as a vision-limiting cataract in the study eye that was not related to plaque radiation. We determined these to be age related if symmetric cataracts were found between the study eye and non-study eye, or if the cataract developed more than 10 years after plaque brachytherapy. These patients typically underwent bilateral cataract surgery.

When any vision-limiting cataract was detected, patients were returned to their local or referring ophthalmologist for cataract extraction.

Visual acuity measurement

Visual acuities were recorded preoperatively and at every posttreatment visit. Visual acuity was recorded as a best-corrected acuity by

a COMS-certified reviewer, in a COMS-certified examination room using Early Treatment Diabetic Retinopathy Study (ETDRS) charts.

Patient exclusion

One hundred two patients were excluded from this analysis because of the presence of aphakia or pseudophakia before plaque brachytherapy ($n = 41$), presence of a dense cataract before surgery ($n = 1$), inability to be assessed for cataract because of lack of follow-up (including unrelated death at time of therapy; $n = 25$), age-related cataract ($n = 17$), and equatorial tumor location ($n = 18$). Tumors centered at the equator were excluded because of the relatively small size of this subgroup.

Radiation treatment

Palladium-103 seeds (model 200) are commercially available (Theragenics Corporation, Buford, GA). They were affixed into gold ophthalmic plaques with a thin layer of acrylic fixative. We do not use COMS-type silicone inserts. The outer dimensions of the ^{103}Pd seeds are almost identical to ^{125}I , and both are cylindrical titanium-encapsulated sources (measuring 0.8 mm in diameter and 4.5 mm in length) and can be used with both the COMS silicone or the newer gold seed-guide inserts (9). The gold seed-guide insert (Trachsel Dental Studios, Rochester, MN) has cutouts that also allow radioactive seeds to be glued directly to the gold backing with dental acrylic (9). The first author has found that the space formerly occupied by the COMS silastic carrier becomes filled with tissue equivalent fluid and clotted blood (unpublished data).

Dosimetry calculations were performed to be comparable to the COMS protocol. Like the COMS, we followed the recommendations of the American Association of Physicists in Medicine (AAPM) Task Groups (10). Seeds were calculated as point sources (no correction for anisotropy). No attenuation effect was attributed to the materials (acrylic or silicone) used to hold the seeds within the plaque or for the (0.5-mm-thick) gold sidewalls of the plaque. "Back-scatter" effects from the posterior wall of the gold plaque were discounted. Dosimetry was adjusted to be compatible with the National Cancer Institute Brachytherapy Contract Group determinations over time. The specific dose rate constant of 1.09 cGy/hr/mCi for ^{103}Pd (as standardized at 1 cm in water) was used for our calculations. Our radial dose function for ^{103}Pd was obtained from published data (3, 4). Unlike COMS, the prescription point for radiation therapy was the tumor apex (defined as the farthest point of intraocular tumor extension from the inner sclera). This is also consistent with the most current recommendation of the American Brachytherapy Society (11).

The first author's surgical techniques for tumor localization and ^{103}Pd episcleral plaque insertion have been previously described (3, 4, 12). Intraoperative two-dimensional and three-dimensional ultrasound-imaging was used to confirm proper plaque placement over choroidal melanomas (13).

Statistical analysis

We estimated the hazard ratios of rate of occurrence of radiation cataract for each factor by a Cox proportional hazard model. To conduct this model analysis, we first established a data set containing covariates of age (<50, 50–69, and ≥ 70 years), diabetes mellitus (yes and no), hypertension (yes and no), tumor location (anterior, or posterior), tumor height (<3.0, 3.0–6.0, and > 6.0 mm), tumor diameter (<8.0, 8.0–11.9, and ≥ 12.0 mm), follow-up time (months), and radiation cataract status (yes = 1 and no = 0). According to the arrangement of data, we estimated corresponding univariate and multivariate-adjusted hazard ratios and 95% confidence

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