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CLINICAL INVESTIGATION **Eye**

NEOVASCULAR GLAUCOMA AFTER STEREOTACTIC RADIOTHERAPY FOR JUXTAPAPILLARY CHOROIDAL MELANOMA: HISTOPATHOLOGIC AND DOSIMETRIC FINDINGS

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Purpose: Enucleation after stereotactic radiotherapy (SRT) for juxtapapillary choroidal melanoma may be required because of tumor progression (TP) or the development of intractable radiation-induced neovascular glaucoma (NVG). We compare pathologic changes and dosimetric findings in those eyes enucleated secondary to NVG as opposed to TP to better understand potential mechanisms.

Methods and Materials: Patients with juxtapapillary choroidal melanoma treated with SRT (70 Gy in 5 fractions, alternate days over a total of 10 days) at the Princess Margaret Hospital, Toronto, Ontario, Canada, who underwent enucleation between 1998 and 2006 were selected. We correlated dosimetric data based on the patient's original SRT treatment plan with histopathologic findings in the retina, optic nerve head, and anterior chamber. A dedicated ocular pathologist reviewed each case in a blinded fashion.

Results: Ten eyes in ten patients were enucleated after SRT. Six were enucleated secondary to NVG and four secondary to because of TP. Aggressive tumor features such as invasion of the sclera and epithelioid cell type were observed predominantly in the TP group. Retinal damage was more predominant in the NVG group, as were findings of radiation-related retinal vascular changes of fibrinoid necrosis and hyalinization. No conclusive radiation-related effects were found in the anterior chamber. The maximum point dose and dose to 0.1 cc were lower for the anterior chamber as compared with the dose to the tumor, retina, and optic nerve head. The mean 0.1-cc doses to the retina were 69.4 Gy and 73.5 Gy and to the anterior chamber were 4.9 Gy and 17.3 Gy for the NVG group and tumor progression group, respectively.

Conclusions: Our findings suggest that NVG is due to radiation damage to the posterior chamber of the eye rather than primary radiation damage to the anterior segment.

Neovascular glaucoma, Stereotactic radiotherapy, Complications, Choroidal melanoma, Histopathology.

INTRODUCTION

Juxtapapillary choroidal melanoma poses a challenge to the ocular oncologist, given greater recurrence rates, a higher likelihood of extraocular extension, an overall worse visual prognosis, and a greater risk of treatment-related complications (1, 2). With respect to treatment modalities, brachytherapy with standard plaque radiotherapy has been cautioned against because of the physical difficulty of positioning a plaque close to the optic nerve head where tilting can result in tumor underdosing (3). Alternatively, external beam radiotherapy has been used successfully with protons or charged particles (4), Gamma Knife technology (5), or linear accelerator–based stereotactic radiotherapy (SRT) (6–8). The aim of radiation as opposed to enucleation is tumor control with organ preservation; however, radiation-induced complications can still result in enucleation. Radiation-induced neovascular glaucoma (NVG) diagnosed by neovascularization of the iris or angle and elevated intraocular pressure is the main radiation-induced complication requiring enucleation (9).

On the basis of our reported experience with SRT for juxtapapillary melanoma (6–8), we present a detailed pathologic analysis of eyes enucleated for NVG or tumor progression and correlate these findings with dose–volume histogram (DVH) data based on relevant contoured anatomy features (optic nerve head, retina, and anterior

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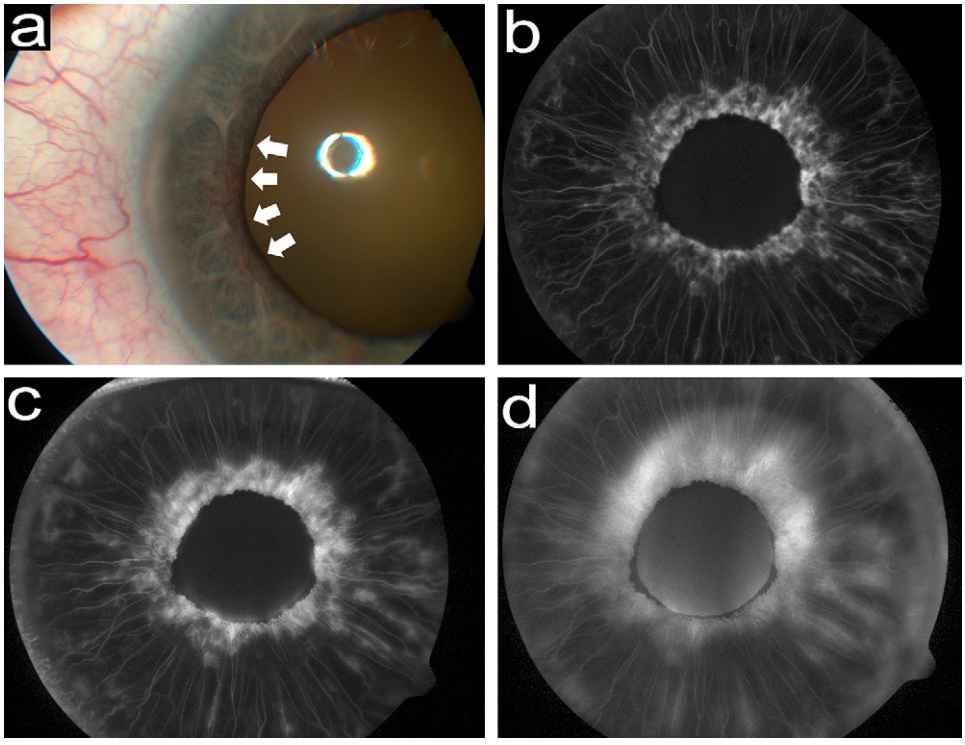

Fig. 1. Eye with neovascular glaucoma due to stereotactic radiotherapy for juxtapapillary choroidal melanoma. (a) Neovascularization of iris surface at pupillary margin (arrows). (b) Early, (c) mid, and (d) late fluorescein angiography of anterior segment showing hyperfluorescence of iris neovascularization. As the angiogram progresses, blurring of the margins of the neovascular fronds occurred from leakage of dye from the new vessels.

chamber). Even though there have been reports on the histopathologic changes of enucleated eyes after different forms of radiotherapy for uveal melanoma (10–15), to our knowledge, this is the first study to detail pathologic changes due to SRT for juxtapapillary tumors.

METHODS AND MATERIALS

Patient selection

Patients with juxtapapillary choroidal melanoma who underwent enucleation after treatment with SRT at the Ocular Oncology Service, Princess Margaret Hospital (Toronto, Ontario, Canada), between October 1998 and January 2006 were selected. Ethics approval was obtained from the institutional research ethics board. Details of the entire cohort of 64 consecutive patients who have received SRT at our institution including their demographics, SRT technique, and outcomes have been previously published (7). Enucleation was indicated in 10 patients. Six cases were because of NVG and four cases because of tumor progression. The clinical diagnosis of NVG was based on the presence of iris or angle neovascularization (Fig. 1), associated with an increase in intraocular pressure. Clinically, local tumor recurrence was defined as tumor enlargement of at least 30% in thickness or 500 μm of tumor base recorded within two successive post-treatment visits.

Other radiation-related complications based on clinical evaluation were also recorded, including radiation cataract, tumor vasculopathy, radiation retinopathy, radiation maculopathy and optic neuropathy. Tumor vasculopathy was defined as the presence of retinal hemorrhage, exudate, or vascular occlusion within one disc diameter of the tumor margin. Radiation retinopathy was defined as the presence of at least two of these findings more than one disc diameter away from the treated tumor margin, with or without macular involvement. Radiation optic neuropathy was defined as optic disc pallor or swelling, without pre-existing peripapillary hemorrhages (7). Radiation maculopathy was defined as the presence of ischemic and/or exudative changes involving the macula secondary to irradiation of a tumour not encroaching on the anatomical macula. Clinical photos of these selected complications are provided in Fig. 2.

Radiation technique

The details of our stereotactic radiation technique and delivery have been described in previous publications (6–8). The total prescribed radiation dose was 70 Gy given in 5 fractions, every alternate day, over 10 days for each patient.

Histopathology

After histopathologic processing, two independent ocular pathologists evaluated each case and were masked to all clinical data and the reason for enucleation. Specific pathologic features related to the tumor, optic nerve, retina, and anterior segment of the eye were described. We also specifically examined each specimen for vessel hyalinization and fibrinoid necrosis. Although these are nonspecific features due to chronic vascular stress, they are histopathologic findings associated with radiation effect. The histopathologic findings were unmasked, and patients were divided into two groups depending on the reason for enucleation (tumor progression or NVG) and analyzed.

Dosimetric analysis and statistics

The original treatment plans were retrospectively reviewed and dosimetric data obtained. Dose–volume histogram analysis was performed for the contoured anatomic features consisting of the tumor,