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Choroidal melanoma

Dose–response of critical structures in the posterior eye segment to hypofractioned stereotactic photon radiotherapy of choroidal melanoma

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ABSTRACT

Purpose: To identify modifying factors and dose–/volume–response relationships for the retina and optic nerve related to highly conformal hypofractionated radiotherapy.

Patients and methods: Seventy-three patients undergoing hypofractionated stereotactic photon radiotherapy of choroidal melanoma were included in this retrospective study.

The volumes of the optic nerve receiving doses of more than 7.5 or 12 Gy, respectively, were defined. Optic nerve circumference included in the 30%, 40%, 50%, or 80% isodose ($ON_{\%}$) and retina included in 30% or 40% were determined as quantal effects.

Univariate and multivariate analyses were performed for clinical variables as well as probit analysis to define ED*x* (doses where a positive response is expected in *x*% of the cases).

Results: Median follow-up was 90.0 (interquartile range 69.0–98.0) months. Fifty-two (71%) and 49 (67%) patients developed radiation retinopathy and optic neuropathy (any grade). Age, length of follow-up and diabetes were significant parameters regarding retinopathy. Optic neuropathy was significantly influenced by age, length of follow-up, and ON_{30}.

The probability of optic neuropathy (any grade and grade $\geqslant 2$) significantly increases with the dose (*p* ranges from 0.0126 to 0.0211).

Conclusion: Treatment planning should aim at minimizing encompassing isodoses particularly in the low dose region, without compromising PTV coverage.

Choroidal (uveal) melanoma is the most common intraocular malignancy in adults [7]. Besides surgical intervention, radiotherapy is a highly effective curative primary treatment modality. As an alternative to brachytherapy or external beam proton therapy, stereotactic radiotherapy with high-energy photons may be administered [4–6,12,14]. At the Medical University of Vienna linear accelerator-based hypofractionated stereotactic radiotherapy is applied in patients with posterior tumor localization unsuitable for brachytherapy or surgical resection [5,6]. High precision target positioning is guaranteed with a dedicated automated eye monitoring and surveillance system. This system was designed to be utilized already during imaging for treatment planning (CT- and MR) as well as during treatment delivery [2,16]. With this image-guided stereotactic radiotherapy technique using online target position monitoring, high local tumor control rates of 95.9% after 5 years and 92.6% after 10 years, respectively, were achieved, with acceptable treatment-related morbidity rates [5,6].

As this treatment technique was based on three-dimensional imaging and three-dimensional dose calculation, dose–volume information can be extracted retrospectively from treatment plans [8]. Furthermore, ocular structures involved in the treatment of uveal melanoma are rather stable in terms of geometry. Spatially invariant structures and dose distributions facilitated the correlation of observed side effects with dose and dose–volume parameters. As far as dose–volume effects of the optic nerve and other posterior parts of the eye are concerned, literature is limited. The QUANTEC chapter on the optic nerve only deals with standard fractionation schemes or single fraction therapy [11], concluding in existing literature dose reporting for the optic nerve is generally limited to the maximum dose. There is a lack of data from hypofractionated treatments for the optic nerve and other ocular structures in general.

The aim of the present study was therefore to identify modifying factors and to establish dose–/volume–response relationships for critical structures in the posterior segment of the eye (retina

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and optic nerve), related to highly conformal hypofractionated radiotherapy.

Material and methods

Patient cohort and treatment technique

Seventy-three patients with unilateral, predominantly posterior choroidal melanoma were included in this retrospective analysis. The study was approved by the Ethics Committee of the Medical University of Vienna.

The initial diagnosis included baseline tumor dimensions, tumor shape (dome vs. mushroom), retinal detachment around the tumor, number of quadrants affected by retinal detachment and distance to macula and optic disc. Tumor size was classified according to the Collaborative Ocular Melanoma Study (COMS) protocol (as 'nevus' (tumor height $\leqslant$1 mm and tumor base $\leqslant$5 mm), 'small' (tumor height $\leqslant$3 mm and tumor base $\leqslant$16 mm), 'medium' (tumor height $\leqslant$10 mm and tumor base $\leqslant$16 mm) or 'large' (tumor height >10 mm or tumor base >16 mm).

Patients at our institution were treated with hypofractionated stereotactic photon radiotherapy if: (1) the initial height of the choroidal melanoma was $\geqslant$7 mm, (2) in cases of juxtapapillary and/or juxtamacular tumors with a height of $\geqslant$2.5 mm and if the central tumor distance to the optic disc and/or the macula was less than 3 mm and (3) if other forms of conservative or surgical treatment were not possible. No hypofractionated stereotactic photon radiotherapy was performed if either extrascleral tumor extension, neovascular glaucoma or metastatic disease was detected before treatment or if the patient had undergone any form of pretreatment for the disease.

A dedicated, specially designed eye monitoring and surveillance system was applied for all imaging procedures (CT, MRI) as well as for the administration of irradiation [2,16]. In brief, a stereotactic mask fixation system (Brainlab Germany, Feldkirchen, Germany) was combined with a tube that carried a light source and a micro video camera for monitoring of the position and the orientation of the eye.

The clinical target volume (CTV) was defined as the contrast medium-enhancing macroscopic tumor volume on MRI images, and delineated accordingly. A 1.5 tesla MRI system was used. The treatment planning and delivery procedures are described detailed elsewhere [3,5,8]. In brief, for dose calculations the MR images were merged with the radiotherapy planning CT images by rigid registration. The automatically generated planning target volume (PTV) comprised the CTV plus a 2-mm safety margin in all directions.

Radiotherapy doses were prescribed to the 80% isodose. Five fractions of 12 or 14 Gy were applied in 57 and 16 patients, respectively. All treatments were completed within 7 days. The treatment was delivered via 10–12 static, micro-MLC shaped 6 MV photon beams. A commercially available treatment planning system (BrainScan®; Brainlab Germany, Feldkirchen, Germany) was used. Dose calculations were performed with a pencil beam algorithm on a 2×2 mm^2 grid with an algorithm specifically designed for this treatment technique [17]. Treatment plans were optimized with regard to the steepness of the dose gradient toward the optic nerve, optic chiasm and eye lens.

Organs at risk

The organs at risk (OAR) considered in the posterior eye were: the entire posterior eye segment, optic nerve and chiasm, and retina. In order to achieve comparable optic nerve volumes with similar number of voxels for dose–volume statistics in all patients, a virtual optical nerve was created with a standard length of 2 cm (to account for a dose gradient to 10% of the prescribed dose). The dosimetric parameters with their definitions are summarized in Supplementary file 1.

For the posterior segment of the eye, the volumes receiving doses of 7.5, 12 or 15 Gy ($V_{ps7.5}$, V_{ps12} and V_{ps15}) were defined. The volumes of the (virtual) optic nerve receiving doses of more than 7.5 or 12 Gy, respectively, were defined ($V_{on7.5}$ and V_{on12}). Furthermore, inclusion of the entire optic nerve circumference within the 30%, 40%, 50%, or 80% isodose (ON_{30}, ON_{40}, ON_{50} and ON_{80}) was determined as a quantal effect. The latter procedure is illustrated in Fig. 1.

The retina was delineated as a whole, and inclusion of more than 30% or 40% of the retinal volume in the PTV (R_{30} and R_{40}) was defined as a quantal effect.

In addition, the entire anterior eye segment, lens, iris and lacrimal gland were delineated for further analyses (results to be reported independently). Patient characteristics including standard parameters (gender, age, and weight) and the presence of diabetes were documented at the onset of radiotherapy. The tumor-related parameters are listed in Table 1 (upper part).

Patient follow-up

All ophthalmologic procedures were performed at the Department of Ophthalmology of the Medical University of Vienna/AKH Wien. After a baseline examination before the onset of radiotherapy, follow-up comprised visits in 3-monthly intervals for the first two years, in 6-monthly intervals for further 3 years, and subsequently every 12 months. Follow-up examinations are described

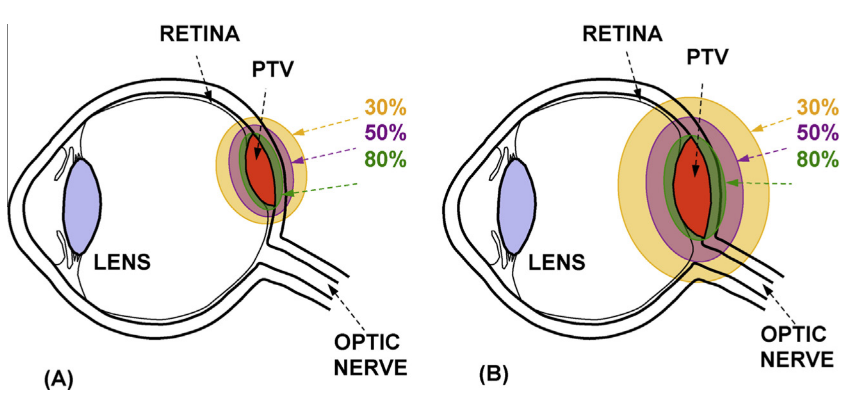

Fig. 1. Treatment planning for uveal melanoma. Illustration showing treatment planning for a smaller (left, 'A') and a larger (right, 'B') uveal melanoma with the respective isodoses.