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Choroidal melanoma

Hypofractionated stereotactic photon radiotherapy of posteriorly located choroidal melanoma with five fractions at ten Gy – Clinical results after six years of experience

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ABSTRACT

Purpose: To evaluate long-term safety and efficacy of hypofractionated stereotactic photon radiotherapy with 5 five fractions at 10 Gy each in patients with centrally located choroidal melanoma.

Materials and Methods: Ninety-one patients with centrally located choroidal melanoma were treated stereotactically at a linear accelerator with 6 MV photon beams with 5 fractions at 10 Gy each. Examinations were performed at baseline and every 3 months in the first 2 years, then every 6 months until 5 years and yearly thereafter. Median follow-up was 37.8 months (IQR 19.2–49.9). They included visual acuity assessment, routine ophthalmological examinations with fundoscopy, echography for measurement of tumor dimensions, medical examinations and, if necessary, fluorescein angiography.

Results: Initial tumor base diameters, height and volume were 11.20 mm (IQR 9.10–13.70), 9.80 mm (IQR 7.80–11.70), 4.53 mm (IQR 3.33–6.43) and 253.8 mm^3 (IQR 127.5–477.0).

Local tumor control and eye retention rates were 97.7% and 86.4% after 5 years, respectively. Eight patients developed metastatic disease and 3 of them died due to metastatic disease during the follow-up period. Median visual acuity decreased from 0.67 initially to 0.05 at the last individual follow-up ($p < 0.001$).

The most common toxicities (any grade) were radiation retinopathy ($n = 39$), optic neuropathy ($n = 32$), radiogenic cataract ($n = 21$), neovascular glaucoma ($n = 15$) and dry eye syndrome ($n = 10$). The 5 year probabilities to remain free of these side effects (any grade) were 26.0%, 45.4%, 55.4%, 72.6% and 80.5%, respectively. The most important prognostic factors for toxicities were the largest tumor base diameter, tumor height and tumor distance to the optic disk.

Conclusion: Hypofractionated stereotactic photon radiotherapy with a total dose of 50 Gy delivered in 5 fractions is a highly effective treatment option in patients with centrally located choroidal melanoma and has a moderate toxicity profile.

Modern treatment options for choroidal melanoma depend on size and location of the tumor as well as available resources. They include radiotherapy as well as various surgical techniques, with primary enucleation being required mainly in cases presenting with large tumors. Regarding brachytherapy (BT), episcleral plaques with ruthenium-106 and iodine-125 are the most widespread alternatives [3,25,27]. Alternative external beam therapy techniques include charged particle therapy using protons (or helium ions), stereotactic radiosurgery (SRS) at a Gamma Knife as well as linear accelerator (LINAC) based stereotactic radiotherapy [4,6–9,15,17,19,20,26]. Hypofractionated stereotactic photon therapy with a LINAC has been demonstrated to be safe and effective in the treatment of uveal melanoma over the last decade [10,11,21]. The main advantages of LINAC radiotherapy are that surgical placement of tantalum markers prior to radiotherapy is not necessary when compared to proton beam therapy and a more convenient eye fixation technique than with Gamma Knife SRS.

At our institutions, hypofractionated stereotactic photon radiotherapy has been employed successfully in the treatment of choroidal melanoma. Long-term treatment results regarding local tumor control, visual acuity, metastatic disease, survival and radiogenic side effects were published earlier for patients treated with five fractions at 14, 12 and 10 Gy each, respectively [10,11].

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However, at that time, only preliminary results were available for patients treated with five fractions at 10 Gy each.

This paper reports the clinical results in patients with centrally located choroidal melanoma treated with hypofractionated stereotactic photon radiotherapy at a LINAC with five fractions at 10 Gy each after dose deescalation from 5×14 to 5×12 Gy. The results are critically discussed regarding comparability of local tumor control and morbidity to the higher dose fractionation schedules.

Materials and methods

Since 2005, 91 patients with malignant melanoma of the choroid unsuitable for ruthenium-106 BT or local resection were treated stereotactically at a LINAC with 6 MV photon beams at the Department of Radiotherapy and the Department of Ophthalmology, Medical University of Vienna, Austria.

Before radiotherapy, patients were examined ophthalmologically including best-corrected distance visual acuity using Snellen charts, applanation tonometry, anterior segment examination with slit-lamp biomicroscopy and gonioscopy, if indicated, as well as fundoscopy, fundus photography and fluorescein angiography after pupil dilation. Standardized A- and B-scan echography was performed to assess tumor dimensions. Furthermore, to exclude metastatic disease, blood tests (blood count, renal function parameters, liver enzymes and inflammatory parameters), chest X-ray, abdominal echography and physical examination were done in all patients before radiotherapy.

Patients were treated with hypofractionated stereotactic radiotherapy if: (1) initially the height of the choroidal melanoma was 7 mm or higher, (2) initial tumor height was >2.5 mm and the central tumor distance to the optic disk and/or the macula was <3 mm and (3) if other conservative or surgical treatment methods were not possible [9,10]. Hypofractionated stereotactic photon radiotherapy was not performed if: (1) any form of pre-treatment had been performed or metastatic disease had been detected at baseline, (2) extrascleral tumor extension or (3) neovascular glaucoma was diagnosed before treatment [9,10]. Radiotherapy planning and follow-up schedule were described in earlier publications [9,10]. A fractionation schedule of 5×10 Gy encompassing the planning target volume with the 80% isodose was given to all patients within 5–7 days.

At each follow-up visit the following parameters were evaluated and noted in a database: best-corrected distance visual acuity, applanation tonometry, slit-lamp examination, fundoscopy, A- and B-scan echography and, if necessary, fundus photography and fluorescein angiography. The Collaborative Ocular Melanoma Study classification of choroidal melanoma was used to classify tumors 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). The ellipsoidal solid model was used to calculate tumor volumes.

As described in [11], the presence or absence of each of the following radiogenic side effects was noted prospectively in the database: radiogenic dermatitis of the eyelid or around the eye, alopecia, eyelash loss, diseases of the lacrimal drainage system, uveitis (anterior chamber flare > Tyndall 0), cataract development, neovascular glaucoma (intraocular pressure > 21 mmHg, iris neovascularization and/or need for antiglaucomatous medication in a previously normotensive eye), dry eye syndrome with corneal surface defects, corneal ulcer, optic neuropathy (hyperemia, hemorrhages, narrowing of optic disk vessels, partial or total atrophy) and ischemic retinopathy (intraretinal hemorrhages, cotton wool spots, hard exudates, neovascularizations and macular edema). Grading was done according to the Common Terminology Criteria for Adverse Events (CTCAE; U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute; latest Version 4.0 published May 28th 2009) [22]. The occurrence of a respective toxicity (any grade) as well as the occurrence of grade $\geqslant$3 toxicities (ranging from 'visual acuity worse than 20/40 Snellen' and 'limiting self care activities of daily living' to 'blindness', see [22]) were noted in the database. Blood tests (blood count, renal function parameters, liver enzymes and inflammatory parameters), chest X-ray, abdominal echography and physical examination were done every 6 months to screen for metastatic spreading of the disease. The majority of follow-ups were done at our institution (>95%), or, in rare cases, by two referring eye departments using the same examination regimen and reported back to our database.

End points were enucleation of the affected eye, tumor recurrence (defined as an increase in tumor volume of more than 25% over two examination intervals at least 6 months after radiotherapy), occurrence of metastatic disease, death and the respective radiogenic side effects.

Statistical analysis

Continuous variables are presented as mean and standard deviation if the data are approximately normally distributed and as median and interquartile range (IQR) otherwise, whereas categorical variables are presented as absolute and relative frequencies. The inverse Kaplan–Meier (KM) method was used to estimate median follow-up times. Regarding tumor dimensions and visual acuity, differences between the individually last measurement and the baseline value were calculated. The individually last measurements for all patients without enucleation or death are presented as median and quartile and tested against baseline using the sign test. The times until visual acuity drops below 0.1 Snellen, until the occurrence of recurrent tumor growth and the various side effects are given as Cumulative Incidence Functions (CIF) due to the presence of enucleation and death due to metastatic disease as competing risks [23,24]. The KM estimate for an event without competing risks (time to overall death) is presented as 1-survival instead of probability to maintain comparability with CIF. Percentages of event-free survival after 3, 12, 30 and 60 months and 95% confidence intervals (CIs) as well as estimates of median and quartile times until occurrence of a respective event are based on these KM and CIF estimates. Univariate competing risk regression models were used to identify potential risk factors (presence of retinal detachment before treatment, baseline largest tumor diameter, baseline tumor height, pre-treatment visual acuity, distance to macula and distance to the optic disk) for complications with at least 10 events in an exploratory manner. For each of the tested complications, the Bonferroni–Holm method was used to adjust the p-values of the four potential risk factors for multiple testing.

p-Values smaller than 0.05 were considered statistically significant. Calculations were performed using SAS 9.2 (with the % cuminc macro) and R 2.13.0 with the cmprsk package (version 2.2–1).

Results

Patient data

Median follow-up was 37.8 months (IQR 19.2–49.9). Mean pre-treatment patient age was 62.3 (±12.2) years. Table 1 summarizes patient and tumor characteristics. Ten tumors (11.0%) were classified as 'small', 74 (81.3%) as 'medium' and 7 (7.7%) as 'large' according to the COMS tumor size classification.

Before radiotherapy serous retinal detachment around the tumor was observed in 33 (36.3%) patients. In 18 of these patients,