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Retina dose as a predictor for visual acuity loss in ^{106}Ru eye plaque brachytherapy of uveal melanomas

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ABSTRACT

Background and purpose: To evaluate the retina dose as a risk factor associated with loss of visual acuity (VA) in ^{106}Ru plaque brachytherapy.
Material/methods: 45 patients receiving ^{106}Ru plaques brachytherapy (median follow-up 29.5 months) were included in this study. An in-house developed treatment planning system with Monte Carlo based dose calculation was used to perform treatment planning and dose calculation. Risk factors associated with loss of VA were evaluated using the Cox proportional hazards models, Kaplan–Meier estimates and Pearson correlation coefficients.
Results: A significant correlation was found between VA loss and mean ($r = 0.49$, $p = 0.001$) and near maximum ($r = 0.47$, $p = 0.001$) retina dose $D_{2\%}$ and tumor basal diameter ($r = 0.50$, $p < 0.001$). The Kaplan–Meier and Cox proportional hazards model yielded a significantly higher risk for VA loss (>0.3 Snellen) for patients receiving a maximum dose of >500 Gy ($p = 0.002$). A Cox multivariate analysis including the macula dose ($p = 0.237$) and basal diameter ($p = 0.791$) showed that a high maximum retinal dose is the best risk factor ($p = 0.013$) for VA loss.
Conclusion: The study showed that retina dose ($D_{2\%}$ and D_{mean}) is a suitable predictor for VA loss.

The preservation of visual acuity is a major objective in conservative treatments of uveal melanoma, such as brachytherapy using either ^{106}Ru or ^{125}I plaques and external beam stereotactic radiotherapy with photons or charged particle therapy [1–10]. Among these techniques brachytherapy using ^{106}Ru or ^{125}I plaques achieves excellent local control while providing a treatment option that allows to preserve useful vision, good cosmetic and quality of life results [2,7,11].

However, the loss of visual acuity is a common side effect of these techniques and can be associated with different factors [11–14]. In ^{106}Ru brachytherapy, mainly geometric characteristics of the tumor were identified to be associated with worse visual outcome in earlier studies [1,11,15]. Only recent publications were able to correlate the loss of visual acuity to dosimetric parameters such as the dose to the fovea [13]. Increased tumor height and basal diameters were both associated with a decreased visual acuity [13,15]. But while both parameters directly affect the overall dose to the retina, the retina dose itself was not found to be a risk factor for bad visual outcome in past studies [11].

The present study is focusing on the effect of retina dose on visual acuity and secondary toxicities after ^{106}Ru plaque brachytherapy using a newly developed treatment planning system.

Materials and methods

Patient cohort and data collection

In this retrospective study patients with choroidal and/or ciliary body melanoma were included who had been treated with ^{106}Ru eye plaque brachytherapy at the Department of Ophthalmology and the Department of Radiotherapy, Medical University, Vienna, between 1995 and 2015. Patients were selected for ^{106}Ru eye plaques according to common recommendations [16,17]. Patients were treated with ^{106}Ru plaques unless tumor height was above 7 mm or in case of centrally located tumors (distance to macula and/or optic disk < 3 mm) – in these cases, patients were treated

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using hypofractionated stereotactic photon radiotherapy [10,18]. The presence of metastatic disease was an exclusion criterion for this study. Of all these patients 45 patients could be used for dose recalculation. The remainder had to be excluded due to a lack of follow-up data.

Standard A- and B-scan echography was performed to assess tumor dimensions. The tumor location was determined using A- and B-scan echography, ophthalmoscopy, funduscopy (using wide angle contact glasses if necessary) and diaphanoscopy.

^{106}Ru plaque treatment protocol

All patients in this retrospective study were treated with ^{106}Ru plaques manufactured by BEBIG (Eckert & Ziegler BEBIG GmbH, Berlin, Germany). Depending on tumor size and location one of two available plaque types (CCB, CCA) with diameters of 19.8 and 15.3 mm was chosen. Typically, tumors up to around 11 mm were treated with the CCA type plaque. Larger tumors were treated with the CCB type plaque. The treatment was aimed to deliver a minimum of 100 Gy to the tumor apex [19]. The required treatment time was calculated using the specification data provided by the manufacturer. The surgical implantation for all patients was done by the same physician.

Treatment planning and dose calculation

For this study, post-implantation treatment planning, dose calculation and the calculation of dose-volume metrics were performed using a novel treatment planning system that was described in a previous publication [20]. The underlying Monte Carlo generated dose lookup tables were benchmarked against experimental measurements [21]. Tumor size and location were used to recalculate dose distributions based on a standard 3D model of an eye. Typically, the plaque was centered on the tumor center. In some cases, in which a centered position would expose adjacent critical structures to higher doses, an eccentric plaque placement was chosen if the tumor diameter allowed for such a shift. Dose volume histograms were generated for the organs at risk (e.g. retina, lens, optic nerve, and macula). Doses were reported as near maximum ($D_{2\%}$) and mean doses (D_{mean}). The retina was assumed to be a finite layer with constant thickness of 400 μm, whereas the macula was rendered as a disk of 3 mm diameter and a height of 400 μm. The structures were interpolated from the 3D eye model onto the calculation grid with a voxel size of $200 \times 200 \times 200\ \mu m^3$.

Additionally to the physical dose, biologically equivalent doses (BED) to the OARs were calculated. The treatment planning software allowed to transform physical dose distributions into BED using an equation for temporary brachytherapy implants introduced by Dale and Jones [22]:

$$\mathrm{BED} = \left(\frac{R_0(1-e^{-\lambda T})}{\lambda}\right) \times \left\{1 + \frac{2R_0\lambda}{(\mu-\lambda)(\alpha/\beta)(1-e^{-\lambda T})} \times \left[\frac{1}{2\lambda}(1-e^{-2\lambda T}) - \frac{1}{(\mu+\lambda)}(1-e^{-(\mu+\lambda)T})\right]\right\} \quad (1)$$

Values for the tissue repair constant of sublethal damage μ and α/β values were defined according to studies by Gagne et al. [23,24]. The implant duration T and initial dose rate R_0 were derived from the recorded treatment parameters.

Outcome measures and statistical methods

Visual acuity was documented using Snellen charts. The difference between the baseline visual acuity and visual acuity at the date of the last individual follow-up was considered as visual acuity lost or gained after ^{106}Ru brachytherapy.

Statistical analysis was first done for the entire patient cohort and in a second step for a subgroup of patients with more anteriorly located tumors with a minimum distance of 4 mm or more between tumor base and macula.

Statistical calculations were performed using SPSS software (IBM SPSS Statistics version 21). Descriptive statistics were used to characterize the patient cohort (i.e. median and interquartile ranges (IQR) and mean plus standard deviation (SD) when data was normally distributed). To show differences between normally distributed data sets Student's t-tests were performed as well as Pearson's chi-squared tests for categorized samples. Risk factors were compared to loss of visual acuity by using Pearson correlation coefficients at the time of last follow-up. Predictors for visual acuity loss were evaluated using the Cox proportional hazards models and Kaplan–Meier estimations for loss of visual acuity at each follow-up. Statistical significance was defined to as $p \leq 0.05$.

Results

Patient population and treatment characteristics

The median follow-up time was 29.5 months (IQR 15.0–39.8) for all patients. The median apex dose was 131 Gy (IQR 113.0–150.4). Median tumor height and tumor basal diameters were 4.6 mm (IQR 3.5–6.0), 10.8 mm (IQR 8.3–12.6) and 9.3 mm (IQR 7.9–11.4), respectively. The average distances to the optic nerve and macula were 5.0 mm (IQR 3.5–8.5) and 6.0 mm (IQR 4.0–9.5).

Visual acuity outcome

Visual acuity at baseline was 0.82 (±0.23) Snellen and declined to 0.59 (±0.28) at the last individual follow-up ($p < 0.001$). The results of the Pearson Correlation analysis and respective significance levels are listed in Table 1. A high net loss of visual acuity

Table 1
Summary of parameters associated with loss of visual acuity and worse post treatment visual acuity outcome obtained from Pearson correlation. Both physical ($D_{2\%}$ and D_{mean}) and biological dose ($BED_{2\%}$ and BED_{mean}) were evaluated.

Factors		Loss of visual acuity in Snellen equivalent		Worse post treatment visual acuity in Snellen equivalent	
		Pearson correlation	p	Pearson correlation	p
Max retina dose $D_{2\%}$	$D_{2\%}$	0.472	0.001	−0.538	<0.001
	$BED_{2\%}$	0.381	0.010	−0.414	0.005
Mean retina dose	D_{mean}	0.492	0.001	−0.552	<0.001
	BED_{mean}	0.359	0.015	−0.374	0.011
Basal diameter	Largest	0.503	<0.001	−0.622	<0.001
	Smallest	0.475	<0.001	−0.577	<0.001
Max macula dose $D_{2\%}$	$D_{2\%}$	0.238	0.115	−0.188	0.216
	$BED_{2\%}$	0.265	0.079	−0.195	0.199

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