

# Radiation-induced optic neuropathy following brachytherapy of uveal melanomas

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**Abstract.** In a prospective study the incidence of optic neuropathy following <sup>106</sup>Ru/<sup>106</sup>Rh-brachytherapy of uveal melanomas was evaluated. Pattern visual evoked potentials (VECP) were measured before radiation and at regular follow-up intervals. Patients were grouped according to tumor location in peripheral melanomas with a central tumor margin of more than 60° to the optic disc (*n*=11) and central melanomas with a tumor within 15° to the optic disc (*n*=28). No patient with peripheral tumor had clinical signs of optic neuropathy or pathological VECPs after radiation. In patients with central melanomas clinical signs were seen in 5/28 (18%), but pathological VECPs developed in 14/28 (50%). The visual loss after radiation was greater in patients with pathological VECPs (*P*<0.03). Radiation-induced optic nerve damage depends on tumor location and is more frequent than clinically expected.

## Introduction

Brachytherapy is widely used for the treatment of uveal melanomas in several centers throughout the world [14, 18, 21]. Long-term local tumor control can be achieved in about 85% [4, 14]. Major complications are the development of radiation-induced cataract, retinopathy, and optic neuropathy. While cataracts can be treated successfully, retinopathy and optic neuropathy may lead to severe functional loss despite the tumor being successfully treated.

Radiation-induced optic neuropathy has been described following either external radiation of pituitary adenomas [19] and periorbital tumors [2] or radiation

of intraocular tumors with external beam [5], helium ion therapy [6, 12, 16], proton beam [10, 20] and <sup>60</sup>Co- [5, 7, 17], <sup>125</sup>I- [9, 16] or <sup>106</sup>Ru/<sup>106</sup>Rh-brachytherapy [8, 14, 15]. The incidence of optic neuropathy is variable between these studies due to differences concerning treatment modalities, tumor size and location, follow-up time or no differentiation between retinopathy and neuropathy. In most cases optic neuropathy developed within 1–2 years after radiation.

In previous clinical studies the overall risk for development of optic neuropathy following <sup>106</sup>Ru/<sup>106</sup>Rh-brachytherapy was 4.1% after a follow-up of more than 1 year [8] and 9.7% after a follow-up of more than 5 years [14]. Clinical findings indicate that the optic neuropathy preferably occurs following treatment of juxtapapillary tumors and may be dose-dependent. Clinical signs identifying optic neuropathy are optic disc swelling, peripapillary hemorrhages, venous stasis and cotton wool spots. The evaluation of clinical signs, however, is somewhat speculative. To evaluate the incidence of optic nerve damage after  $\beta$ -ray brachytherapy and to receive better data for treatment planning, we examined optic nerve function with electrophysiological methods.

## Materials and methods

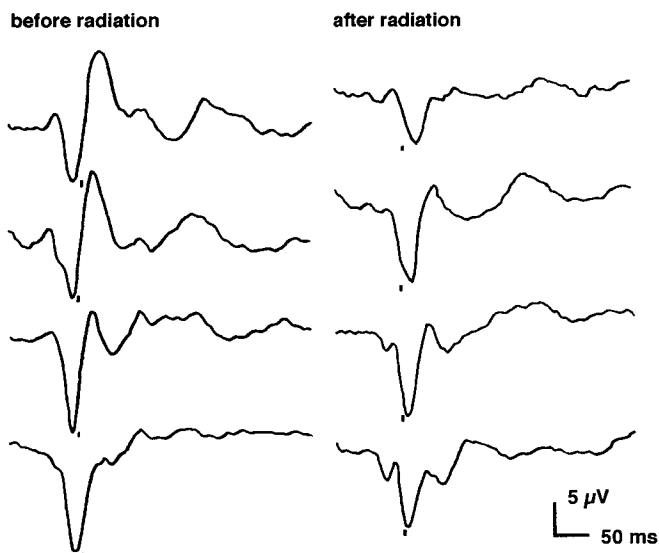
A consecutive series of 45 patients was examined after informed consent was obtained. Inclusion criteria were absence of any retinal pathology within the temporal vascular arcades, normal optic disc, clear media, normal preoperative visual evoked cortical potentials (VECP) and no history of glaucoma. These criteria were chosen to eliminate optic nerve damage due to other causes or VECP alterations due to difficulties of pattern recognition because of media opacities or macular pathology. Six patients who developed secondary glaucoma or severe media opacities after radiation were excluded from the study. Therefore, the results of 39 patients were evaluated.

Brachytherapy was performed with <sup>106</sup>Ru/<sup>106</sup>Rh-plaques (Isocommerz, Berlin) in all patients [3, 8]. Different plaque types, variable in size (CCA or CCB) or with a notch for treatment of juxtapapillary tumors (COB), were chosen according to tumor location [13]. In addition to the regular tests, VECPs were recorded before radiation and at regular follow-up examinations about every

The authors do not have any commercial or proprietary interest in <sup>106</sup>Ru/<sup>106</sup>Rh-plaques. Preliminary data of this study have been reported at the meeting of the Association of Research in Vision and Ophthalmology in 1990

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**Fig. 1.** VECP recording of a patient of group B prior to and 1 year after radiation. The marks below each recording indicate the upper limit of the normal range. Before radiation the P100 latencies and amplitudes were normal at all check sizes. One year after radiation the P100 latencies were delayed at all check sizes. The delay was most distinct at the smallest check size. An amplitude reduction was obvious at the smallest check size and less distinct in other check sizes

3 months during the first half year following radiation and every 6 months thereafter.

Checkerboard-pattern-reversal VECPs were recorded with four check sizes (15', 30', 1° and 2° of arc, Fig. 1). The contrast was 68%. In every recording 128 sweeps were averaged. The P100 latency and amplitude were measured in all recordings. In all patients the response to the smallest check size was the most sensitive one. Therefore, in the following evaluation only the results of the smallest check size are shown. The upper normal limit of the P100 latency at this check size was 119 ms (mean value + 2 standard deviations).

The patients were grouped according to tumor location. Group A ( $n=11$ ) included patients with a melanoma of the peripheral choroid and the anterior uvea with a posterior margin more than 60° to the optic disc. Group B ( $n=28$ ) included patients with a posterior tumor margin less than 15° to the optic disc. There was no tumor extension within the temporal vascular arcades. Between groups there was no difference in the mean follow-up period and radiation dose. The mean follow-up time was  $424 \pm 209$  days (range 144–814 days) in group A and  $563 \pm 259$  days (range 190–974 days) in group B. In group A the mean scleral contact dose was  $991 \pm 102$  Gy and in group B  $937 \pm 210$  Gy. There was also no difference in mean radiation dose at the tumor apex or in the mean dose rate of the plaques.

## Results

### Group A

The pretreatment mean visual acuity was 20/25. Visual loss occurred after radiation and at the last follow-up examination the mean visual acuity was 20/40 (Table 1). None of the patients developed clinical signs of optic neuropathy during the follow-up period. There was no difference in mean latencies of the VECP prior to radiation and at the last follow-up examination ( $106 \pm 6$  ms

**Table 1.** Visual acuity before and after radiation

Visual acuity	Group A		Group B			
	$(n=11)$		Normal VECP $(n=14)$		Pathological VECP $(n=14)$	
	pre	post	pre	post	pre	post
>20/40	9	6	11	5	9	1
20/40–20/80	2	3	3	7	4	7
<20/80	0	2	0	2	1	6

pre, before radiation; post, at last follow-up examination

vs  $104 \pm 7$  ms). No patient showed delayed P100 latencies at any follow-up examination.

### Group B

The mean visual acuity was comparable to group A prior to treatment (20/30) and a similar visual loss occurred after radiation (20/50, Table 1). Five of 28 patients (18%) developed optic disc swelling, peripapillary hemorrhages, venous stasis or cotton wool spots.

The mean P100 latency was normal before radiation with  $107 \pm 9$  ms. At the last follow-up examination it was delayed over the upper limit of the normal range with  $122 \pm 30$  ms. Pathological VECPs were seen in 14 patients (50%). In 3 patients no measurable VECP responses were found and 11 patients developed delayed P100 latencies (Fig. 1). In the other half of the patients the P100 latencies remained normal ( $104 \pm 8$  ms). Interestingly, delayed latencies were found even in eyes with normal optic disc and unchanged visual acuity of 20/20.

All 5 patients with clinical signs of optic neuropathy developed delayed VECP latencies. In 1 patient the delayed latency occurred 3 months before the clinical signs; in the remaining patients there was no time difference. The mean time interval between radiation and clinical signs of optic neuropathy was  $385 \pm 226$  days ( $n=5$ ) and between radiation and delayed VECP latencies  $342 \pm 232$  days ( $n=14$ ). The shortest time period for the development of clinical signs and delayed VECPs was 55 days.

Patients of group B were divided in subgroups either having always a normal VECP response ( $n=14$ ) or showing delayed latencies at one or more follow-up examinations ( $n=14$ ). There was no difference in mean radiation dose between the two subgroups. Patients with normal VECP received a mean scleral contact dose of  $919 \pm 187$  Gy and patients with delayed VECP latencies  $993 \pm 189$  Gy. There was also no difference in mean dose at tumor apex, in the mean dose rate or in the plaque types used. The preoperative visual acuity was similar in both subgroups (Table 1). Visual loss after radiation was significantly pronounced in patients with delayed P100 latencies ( $P < 0.03$ ).

Three of the 14 patients with delayed VECP latencies during the follow-up period had normal VECPs at the

last examination. In all cases, the improvement of VECP was accompanied by an increase in visual acuity.

## Discussion

The development of radiation-induced optic neuropathy after brachytherapy of uveal melanomas depends on the tumor location. In our series patients with anterior melanomas never developed clinical or electrophysiological signs of optic nerve damage. This is in accordance with other studies, which have found an increased risk for visual loss in eyes with tumors near the optic disc [12, 15, 20]. No comparison with other radiation modalities concerning the incidence of optic neuropathy was possible because no other studies used electrophysiologic methods.

Electrophysiological evaluation of optic nerve function revealed that radiation damage occurs considerably more frequently than expected from the clinical findings (50% vs 18%). This may be an explanation for the patients who had visual loss without clinically visible pathology. However, good visual acuity may be retained in eyes with pathological VECP recordings. Delayed VECP latencies were found even when the optic disc and visual acuity were normal. The divergence between VECP and visual acuity may depend on the location of the optic nerve damage. On the other hand, the delayed latencies may indicate a beginning optic neuropathy in these patients.

The cause for optic neuropathy is vascular endothelial damage, which results in a vasculopathy and in a delayed onset of visual loss [1, 5]. The vasculopathy may be repairable, because three of our patients had delayed VECP latencies that turned to normal during follow-up. It may be speculated that in these cases the optic nerve dysfunction was not due to axon destruction but to a disturbance of the axoplasmic transport due to edema of the optic nerve. Using ultrasound, Lovato [16] has demonstrated a swelling of the optic nerve during the acute phase of optic neuropathy. Regression of edema may lead to normalization of the axoplasmic transport and the VECP. The course of the vasculopathy, however, cannot be determined, and radiation retinopathy has been found up to 15 years following radiation [22]. Therefore, the incidence for optic nerve damage may be even higher with a longer follow-up.

In contrast to our prior statement in a preliminary report of our study [11], we could not find a dose relationship for the risk for optic neuropathy. Eyes with delayed VECPs received a higher dose at the sclera and tumor apex and a higher dose rate; however, after a longer follow-up and inclusion of more patients there was no longer a significant difference compared to the eyes with normal VECPs.

It is not possible to calculate the radiation dose delivered to the optic nerve exactly. There is a steep decrease in radiation at the margin of the plaque [13]. The distance between optic nerve and the margin of the plaque, however, cannot be defined sufficiently either clinically or echographically. The placement of the plaque is diffi-

cult near the optic nerve [23]. A tilting of the posterior part of the plaque may occur. This would increase the radiation dose received by the optic nerve. Therefore, any estimation of the radiation dose delivered to the optic nerve is arbitrary. One would expect that plaques with a notch would deliver more radiation dose to the optic nerve. Delayed VECPs, however, developed in a similar frequency following treatment with plaques with and without a notch. This finding may indicate that the dosage level was sufficient for development of optic nerve dysfunction in most of our patients. In the dose range used in our series optic nerve dysfunction may have been more dependent on interindividual variances than on radiation dose.

Although eyes with central melanomas have a high risk for optic nerve damage due to radiation, treatment of juxtapapillary melanomas using  $^{106}\text{Ru}/^{106}\text{Rh}$  brachytherapy may result in a good visual outcome. Half of the patients in our series did not show optic nerve dysfunction and had a mean visual acuity with an average of 20/40 at the last follow-up examination. This visual acuity, however, cannot be expected for most patients with tumors near the optic disc, and visual prognosis should even be worse in patients with tumors within the vascular arcades, which were not included in our series.

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