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# Cataract Avoidance With Proton Therapy in Ocular Melanomas

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**PURPOSE.** The lens is a radiosensitive organ. Any dose of cephalic irradiation can give rise to radiation-induced cataracts. Contrary to other forms of radiotherapy, proton therapy (PT) can spare all or part of the lens due to accurate dose deposition. We investigated whether a lens-sparing approach was relevant to avoid cataracts in uveal melanoma patients.

**METHODS.** Patients were referred for PT from onco-ophthalmologists of private and academic institutions. Patients without preexisting cataracts or implants were entered in a prospective database. Dose thresholds responsible for cataracts were investigated in volumes of lens or lens periphery. Lens opacifications and de novo vision-impairing cataracts (VICs) had biannual follow up by ophthalmologists blinded to lens dose. Correlations between dose-volume relationships and VICs were assessed using univariate/multivariate regressions.

**RESULTS.** Between 1991 and 2015, 1696 uveal melanoma patients were consecutively treated with PT. After a median follow up of 48 months, 14.4% and 8.7% of patients had cataracts and VIC within median times of 19 and 28 months, respectively. Median values of mean lens and lens periphery doses were 1.1 (radiobiologically effective [RBE] dose in photon-equivalent grays [GyRBE]) and 6.5 GyRBE, respectively. The lens received no dose in 25% of the patients. At an irradiated lens volume of  $\leq 5\%$ , there was no significantly increased risk for VIC below a dose of 10 GyRBE.

**CONCLUSIONS.** A lens-sparing approach is feasible and results not only in reduced need for cataract surgery but also in better fundus-based tumor control. Reassessment of radioprotection rules for lens dose thresholds may follow.

**Keywords:** radiotherapy, proton therapy, toxicity, cataracts, dose, volume, lens

Radiation therapy is used in 60% of patients with cancer. As the eye lens is one of the most radiosensitive organs, any type of irradiation involving the head triggers radiation-induced cataracts. Historically, 10 and 18 Gy were considered tolerance dose levels for vision-impairing cataracts (VICs), requiring surgery in, respectively, 5% and 50% of cases at 5 years after irradiation.<sup>1,2</sup> More recently, the International Commission on Radiological Protection (ICRP) defined 0.5 Gy as the new threshold.<sup>3,4</sup> However, minor lens opacities do not necessarily progress into VICs. In radiotherapy, the lens dose is usually minimized according to the ALARA (as low as reasonably achievable) principle. Due to dose distribution characteristics of conventional radiation therapy (using photons), sparing such a small organ as the eye lens is unlikely.

In ocular tumors, the high radiation doses delivered over several days with low-dose rate brachytherapy or high-dose rate proton therapy (PT) may increase the risk for cataracts. Cataract incidence at 5 years reaches up to 83% after I-125 brachytherapy, with a need for surgery in 12% of cases.<sup>5,6</sup> With PT, the finite range and increasing energy loss per unit path

length of protons penetrating in the body result in a steep depth-dose deposition, with a sharp final peak known as the Bragg peak. The proton beam is spread out in depth to cover the entire tumor thickness. Both lateral and distal penumbrae are sharp, that is, the dose decreases from 90% to 10% within approximately 1 mm. Thus, PT planning can be optimized to spare all or part of the lens in most situations. Cataract surgery following radiation-induced VIC is frequent and oncologically safe.<sup>7,8</sup> However, it is potentially associated with a higher risk of postoperative complications.

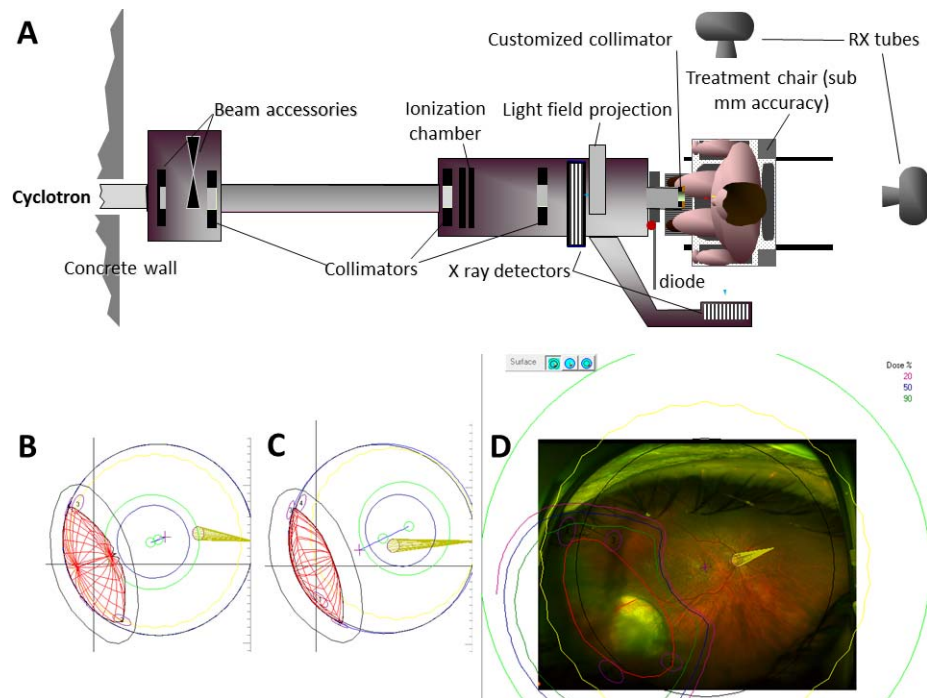
We evaluated the impact of a lens-sparing PT approach on the risk for VICs based on lens dose in patients treated for ocular melanomas.

## METHODS

### Patients

Between 1994 and 2015, an institution review board approved this cohort study of all consecutive patients with neither





**FIGURE 1.** An illustration of treatment planning Optimization. (A) Schematic of the proton beam line. (B) Optimized treatment plan including the lens in the proton beam projection. (C) Optimized proton therapy plan sparing the lens. (D) Isodose lines on fundus view of the optimized plan.

preexisting cataracts nor implants and for whom lens dose-volume metrics and occurrence of de novo cataracts and VICs were collected prospectively.

### Treatment Planning and Delivery

Ocular PT used a 65-MeV dedicated hospital-based cyclotron.<sup>8–10</sup> Ocular proton therapy has a steep dose gradient and very narrow penumbra, with 1.4 mm laterally and 0.8 mm posteriorly, which corresponds to the distance at which the dose decreases from 90% to 10% of the prescribed dose. Briefly, four tantalum fiducials were positioned on the sclera under general anesthesia by the ophthalmologist using transillumination to define tumor borders. Ocular structures and tumor characteristics were defined on transillumination, fundus (retinography/angiography), ultrasound, ultrabiomicroscopy, and optical coherence tomography (OCT). PT was performed 2 to 4 weeks after fiducial placement. The Eyeplan ocular PT-planning system software (v1-3; Nice, France) was used. Starting in 1994, ocular computed tomography (CT) scans were performed to measure eye lengths and the delineation of critical normal structures, such as the optic nerve, lens, eyeball, and clips. The range and modulation width of the spread-out Bragg peak plateau were set. Additional beam modifiers were designed, depending on tumor thickness and diameter/shape and the position respective to critical structures. Lateral conformation was achieved with a brass collimator adjusted to tumor contours, using 2.5-mm lateral safety margins. The papilla, optic nerve, and macula were preserved whenever possible without compromising tumor control. In case of equatorial/pre-equatorial tumors, treatment planning optimization was performed with the lens as a critical organ. The lens was preserved whenever possible using adapted gaze, but without risking tumor undercoverage or sacrificing the optic nerve or macula (Fig. 1). The patient's gaze was directed using a light-emitting diode located in a plane perpendicular to the beam. Patient and tumor setup was controlled using online

orthogonal X-ray images. The eye position was monitored by video camera during the 10-second treatment at a dose rate of 75 GyRBE/min (radiobiologically effective [RBE] dose), corresponding to the physical proton dose by a factor of 1.1 compared to photons; eye movements triggered immediate beam interruption.

### Eye Lens State During Planning and Treatment

All patients were requested to fix on a red-emitting diode at the scanner and during treatment at a distance of about 20 cm from their eyes. Thus, patients were not at rest, and the lens was not in a stretched state. Average lens volume for patients with ocular tumors was 158.9 mm<sup>3</sup>, minimum was 105.7 mm<sup>3</sup>, and maximum was 266.2 mm<sup>3</sup> in the accommodation state on CT scanner.

### Eye Gazing and Lens

The lens was delineated on all axial slices where it was visible. The center of the lens was considered the center of the ellipse seen as largest on either of the delineated slices. The PT-planning software performed automatic volumetric reconstruction based on lens dimensions. It was able to reconstruct all structures of the ocular system and to recalculate the center of each structure when changing the gaze angle for the purpose of normal tissue sparing, as is done during PT planning.

### Eye Lens Delineation

The lens delineation method was established before 1994, that is, before the start of the current study, and has not been changed during the time lapse of the current study using the same software for delineation and dosimetry. The eye lens was imaged by a CT scan with a slice thickness of 1 mm and spaced every 1 mm. In each slice, the eye lens was manually delineated where it was visible. The software then modeled the eye lens and reconstructed its volume. The eye lens was

one among the different structures delineated to prepare a radiation therapy plan. Those structures are either targets to be irradiated or healthy tissues to be spared from radiation. The recognition of a given structure (either a target structure, such as a tumor or an organ at risk, that is, an organ or tissue to be spared from radiation if possible) is based on the knowledge of the anatomy of the given structure and known differences in density compared to adjacent tissues on CT scans. As for the eye lens, it is characterized by a higher density compared to the anterior and posterior chambers and the iris. It appears as a white structure on axial CT scan slices. Given the craniocaudal length of the lens and the CT scan-slice thickness, five slices were sufficient in all cases to delineate the lens on all slices where it was visible. The same two persons (dosimetrist experts in the field) have delineated patients' lenses throughout the study period. Furthermore, the treatment planning system that we use for ocular PT could reconstruct the lens volume, shape, and position to produce dose-volume histograms (DVH), that is, relationships between doses and volumes of the lens to be correlated with clinical outcomes such as cataracts.

Eye surface and a lens periphery volume were generated from the outer contours of the eyeball and lens, respectively. The lens volume represented the lens core (further called lens) defined as the whole lens minus the lens periphery. The lens periphery contains the radiosensitive germinal cell layer, while the lens contains the nucleus sensitive to biochemical modifications.

### Dose-Volume Relationships

All tumors were prescribed a dose of 60 GyRBE delivered over 4 days. Mean doses to the lens and lens periphery were calculated from full DVHs collected prospectively. Additionally, the doses at 2% (D2), 5% (D5), and 10% (D10) were also evaluated to determine the role of high doses in small portions of the lens and lens periphery. The following dose intervals were chosen a priori: (0;0.5), (0.5;5), (5;10), (10;60) Gy.

### Analysis of Cataracts and Toxicity Scoring

After PT, patients underwent follow-up visits with onco-ophthalmologists every 6 months for 5 years and once yearly thereafter to assess both tumor control and side effects, including lens opacities.

### Diagnosis of Radiation-Induced Cataracts

The diagnosis of cataract was made prospectively on the presence of lens opacities on slit lamp examination at each visit. The degree and extent of lens changes present was also examined. The first evaluation was made before proton beam therapy for both eyes. Patients were classified as phakic with or without cataract or pseudophakic for both eyes. At each follow-up visit, the crystalline lens was evaluated (both eyes) and compared to the evaluation before PT. In case of a bilateral phakic patient, the crystalline lens changes were also compared between each. In case of a unilateral phakic patient (with the other eye pseudophakic), the crystalline lens opacification was compared to the preproton evaluation. Tumor eyes were compared to healthy eyes at diagnosis and during follow-up visits, although this information did not appear in our prospectively collected tumor database.

The aim of our study was to estimate cataract prevalence after a lens-sparing approach of PT. We therefore excluded from analysis all patients for whom cataract was present at or already were pseudophakic at baseline. We also excluded patients for whom cataract status was not recorded at baseline.

The likelihood of bilateral radiation-induced cataracts is null with protons while senile cataracts are often bilateral, and thus they have other causes such as diabetes mellitus, bilateral steroid drops, or treatments. Ocular traumatism is an exception but is easily recognized on anamnesis when interviewing patients. Thus, in the absence of a pathognomonic sign of radiation-induced cataracts, a diagnosis of radiation-induced cataracts was considered if the delay was short (usually less than 3 years in the absence of other causes) until cataract occurred in a tumor eye without cataract before PT and/or if the healthy eye did not exhibit similar types of lens opacities. We then made the assumption that de novo cataracts were radiation induced. In such cases, subcapsular, cortical, or nuclear opacities could be considered as radiation induced.

### Cataract Grading

Cataracts were graded as minor and were then surveilled or were vision impairing/important to the point that fundus surveillance was rendered difficult. Clinical findings were recorded on a prospectively collected clinical assessment form. VICs were defined as cataracts needing cataract surgery or showing a marked decrease in visual acuity corresponding to grade  $\geq 3$  and visual acuity below 20/40 using the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 (<http://evs.nci.nih.gov/ftp1/CTCAE/About.html>; provided in the public domain by the National Cancer Institute). The time of onset of cataracts was defined as the interval between PT and first diagnosis of cataracts or VICs.

### Statistical Analysis

Quantitative parameters were described by mean and standard deviation or by median and interquartile range according to the normality of distributions assessed by the Shapiro-Wilk test. Qualitative parameters were described by frequency and percentage. The cumulative incidence was assessed using the Kaplan-Meier method. The start date was the end of PT, and analyses were censored at 5 years or at the date a VIC was first diagnosed. While standard onco-ophthalmology visits were planned every 6 months, interval events such as deterioration of vision due to cataracts could be diagnosed and operated on by ophthalmologists at standard practice facilities and not necessarily at hospitals specialized in onco-ophthalmology. The relationship between demographic or clinical parameters was investigated by univariate Cox proportional hazard regression analysis. The linearity assumption was checked using martingale residuals. If this hypothesis was not verified, the quantitative parameter was transformed into binary variables using the assessment of known clinical significance. The validity of the proportional hazard (PH) assumption was checked by determining the scaled Schoenfeld residuals (SSR). The PH assumption was tested for each covariate by correlating the corresponding SSR with the rank of time. The results were expressed as a hazard ratio (HR) (95% confidence interval [CI]). The prevalence of eye complications arising over the whole follow up was compared according to VIC status by the  $\chi^2$  test. Impact of each dose parameter on VIC was investigated by the univariate Cox PH model. The analysis was then adjusted on demographic and clinical parameters with a *P* value less than 0.1 in univariate analysis and noncorrelated with this dose parameter in order to avoid overfitting. The adjusted analysis was performed for each dose parameter using a multivariate Cox PH model. The Harrell's *C*-statistic (concordance index) was computed for each multivariate model in order to investigate the discriminant power corresponding to the probability of concordance between observed and predicted VIC according to the multivariate



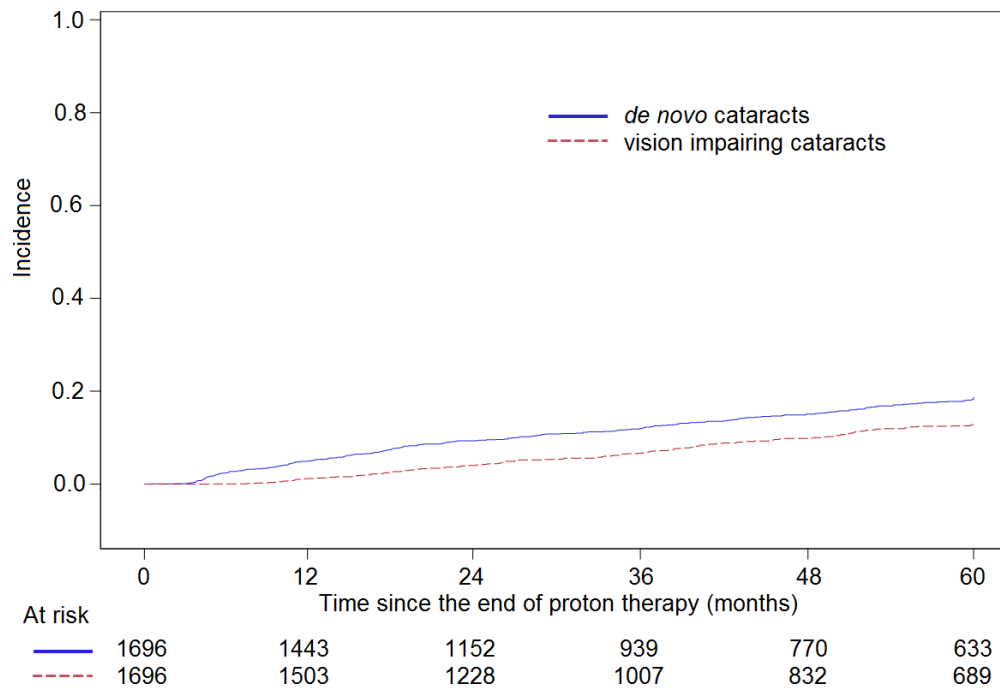


FIGURE 2. Incidence of de novo cataracts and de novo VICs for the 1696 patients after the end of PT (Kaplan-Meier method).

model. All analyses were done using SAS 9.4 software (SAS Institute Inc., Cary, NC) and statistical software R (version 3.3.2; <https://www.r-project.org/>, in the public domain).

## RESULTS

### Patient Characteristics and Incidence of VICs

Patient characteristics are reported in [Supplementary Table S1](#). Median follow up was 49 months with an interquartile range (IQR) from 23 to 90 months. At 5 years, overall survival was 87.4% (95% CI: 85.4%–89.2%). The crude relapse and enucleation rates were 5.7% and 8.6%, respectively. Median time to cataracts and VICs was 18 months (IQR [9;36]) and 29 months (17;41), respectively. The 1-, 3-, and 5-year cumulative incidences of cataracts (Fig. 2) were, respectively, 4.9% (95% CI: 4.0%–6.1%), 12.0% (95% CI: 10.4%–13.8%), and 18.7% (95% CI: 16.5%–21.1%). The corresponding VIC rates (Fig. 2) were 1.2% (95% CI: 0.8%–1.9%), 6.7% (95% CI: 5.5%–8.1%), and 12.8% (95% CI: 10.9%–14.9%). Among 233 patients with cataracts at 5 years, 147 (63.1%) had VICs.

Risk factors for VIC are described in [Supplementary Table S1](#). Age above 60 years was a predictive factor for VIC (HR 1.72, 95% CI [1.23;2.41]), as was diabetes (HR 2.21, 95% CI: [1.27;3.83]). The larger the tumor diameter, the greater the risk for VIC (HR 1.18, 95% CI: [1.13;1.23]). The larger the distance to the macula, the lower the risk for VIC (HR 0.96, 95% CI: [0.93;0.99]). Ocular complications (mainly glaucoma and retinopathy) following treatment in patients with VIC are presented in [Supplementary Table S2](#).

### Dose-Volume Response Analyses

Among 1696 patients, 419 (24.7%) and 241 (14.2%) had no irradiation (0 Gy) to their lens and lens periphery, respectively. The median value of mean lens dose was 1.1 GyRBE (IQR [0;12.3]) and the median value of mean lens periphery dose was 6.5 GyRBE (0.8;17.7) ([Supplementary Table S3](#)). The distribution of the mean doses received by 2%, 5%, and 10% of

the lens and lens periphery is described in [Supplementary Table S4](#).

In univariate analysis (Table), a mean lens dose between 0.5 and 5 GyRBE was a risk factor for VIC compared to a mean lens dose of less than 0.5 (HR 2.56, 95% CI [1.57;4.18]). The risk increased with any increase in mean lens dose (HR 3.69, 95% CI [1.99;6.83] for a dose between 5 and 10 GyRBE). The corresponding HR was 4.63, 95% CI [3.03;7.09] for a dose above 10 GyRBE. While irradiation of 2% of the lens (D2) between 0.5 and 5 GyRBE was not significantly associated with VIC (HR 1.24, 95% CI [0.56;2.73]), a lens D2 between 5 and 10 GyRBE was a risk factor for VIC (HR 2.41, 95% CI [1.19;4.88]) and so was the case for higher dose levels (Table). The critical dose at which the risk became significant was thus between 5 and 10 GyRBE when 2% of the lens was in the proton beam. When 10% of the lens was in the proton beam, all dose categories greater than 0.5 were significantly associated with VIC compared to doses below 0.5 GyRBE.

Mean lens dose was correlated to diameter ( $r = 0.387$ ,  $P < 0.001$ ), distances to the optic disk ( $r = 0.118$ ,  $P < 0.001$ ), and macula ( $r = 0.140$ ,  $P < 0.001$ ). Thus, the search for a dose effect dependent on the percentage of lens or lens periphery irradiated was not adjusted to these three factors. It was then adjusted on age (60 years old), diabetes, hypertension, and stage. After adjustment in multivariate analysis (Table), the results remained the same: the risk for VIC significantly increased when 2% of the lens (D2) received a 5- to 10-GyRBE dose (2.05 [1.01;4.16]). Similarly, 10% of the lens (D10) receiving a 0.5- to 5-GyRBE dose was a risk factor for VIC (2.27 [1.24;4.17]). HRs and 95% CI of each lens periphery dose parameter on VIC are illustrated Figure 3. The results obtained for the mean lens periphery dose were comparable to those for the mean lens dose ([Supplementary Table S5](#)). The risk for VIC was significantly increased when 5% of the lens periphery (D5) received above 10 GyRBE or when 10% of the lens periphery (D10) received above 5 GyRBE (Fig. 4). VICs are shown in Figures 3 and 4. The concordance index for lens dose ([Supplementary Table S4](#)) and lens periphery dose ([Supplementary Table S5](#)) ranged from 0.731 to 0.749. The discrim-

**TABLE.** Impact on VICs of Each Lens Dose Parameter in Univariate Analysis and After Adjustment for Age, Diabetes, Hypertension, and UICC Staging in Multivariate Cox Analyses

	Univariate Analyses		Multivariate Analyses		
	HR (95% CI)	P Value	HR (95% CI)	P Value	Concordance Index
Mean lens dose, Gy					
(0;0.5)	1		<b>1</b>		0.745
(0.5;5)	2.9 (1.5;5.6)	0.001	<b>2.2 (1.4;3.7)</b>	<b>0.001</b>	
(5;10)	5.0 (2.6;9.9)	<0.001	<b>2.9 (1.6;5.5)</b>	<b>0.001</b>	
(10;60)	7.6 (4.0;14.6)	<0.001	<b>3.5 (2.2;5.6)</b>	<b>&lt;0.001</b>	
Age, y ≥60			1.6 (1.1;2.3)	0.007	
Diabetes			2.1 (1.2;3.8)	0.01	
Hypertension			1.8 (1.2;2.8)	0.005	
UICC staging T3–T4			2.3 (1.6;3.4)	<0.001	
Lens D2, Gy					
(0;0.5)	1		<b>1</b>		0.742
(0.5;5)	1.0 (0.3;3.2)	0.986	1.1 (0.5;2.5)	0.785	
(5;10)	3.0 (1.3;6.7)	0.007	<b>2.0 (1.1;4.2)</b>	<b>0.046</b>	
(10;60)	6.4 (3.0;13.9)	<0.001	<b>3.3 (1.9;5.8)</b>	<b>&lt;0.001</b>	
Age, y ≥60			1.6 (1.2;2.3)	0.005	
Diabetes			2.1 (1.2;3.7)	0.012	
Hypertension			1.8 (1.2;2.8)	0.007	
UICC staging T3–T4			2.5 (1.7;3.6)	<0.001	
Lens D5, Gy					
(0;0.5)	1		<b>1</b>		0.748
(0.5;5)	1.9 (0.7;4.7)	0.185	1.4 (0.7;2.8)	0.327	
(5;10)	4.2 (2.0;8.8)	<0.001	<b>2.9 (1.5;5.7)</b>	<b>0.002</b>	
(10;60)	7.7 (3.7;16.0)	<0.001	<b>3.7 (2.2;6.2)</b>	<b>&lt;0.001</b>	
Age, y ≥60			1.6 (1.1;2.3)	0.006	
Diabetes			2.1 (1.2;3.8)	0.009	
Hypertension			1.8 (1.2;2.8)	0.006	
UICC staging T3–T4			2.4 (1.7;3.5)	<0.001	
Lens D10, Gy					
(0;0.5)	1		<b>1</b>		0.748
(0.5;5)	2.0 (1.1;4.9)	0.035	<b>2.3 (1.2;4.2)</b>	<b>0.008</b>	
(5;10)	3.7 (1.9;7.1)	<0.001	<b>2.8 (1.4;5.6)</b>	<b>0.004</b>	
(10;60)	6.5 (3.5;12.3)	<0.001	<b>3.9 (2.3;6.4)</b>	<b>&lt;0.001</b>	
Age, y ≥60			1.6 (1.1;2.3)	0.007	
Diabetes			2.1 (1.2;3.6)	0.013	
Hypertension			1.8 (1.2;2.8)	0.007	
UICC staging T3–T4			2.4 (1.6;3.4)	<0.001	

D2, D5, and D10 represent the volume of the organ receiving a given dose; for example, lens D2 stands for 2% of the lens receiving *X* Gy, concordance index corresponds to Harrell's *C*-statistic and estimates the probability of concordance between observed and predicted VICs according to the multivariate model (discriminant power). Doses are given in GyRBE. Bolded values indicate statistical significance. UICC, Union for International Cancer Control.

inant power of dose parameters was then comparable whatever the volume or the organ (lens or lens periphery).

## DISCUSSION

Our study suggests that a lens-sparing approach is feasible for patients undergoing PT for uveal melanomas. Radiation-induced cataracts, although curable, are involved in vision deterioration in 30% to 80% of uveal melanoma patients after PT, brachytherapy, or stereotactic irradiation.<sup>11–14</sup> Cataracts are usually considered a minor complication of cancer treatments because VICs are easily manageable with extracapsular lens extraction and intraocular lens implant placement. However, Gragoudas et al.<sup>7</sup> reported significant postoperative complications in 16% of patients following PT for ocular melanomas. In the Collaborative Ocular Melanoma Study,<sup>15</sup> 27% of patients underwent cataract surgery after brachytherapy and suffered

from postoperative complications. Moreover, in our experience, cataract surgery years after radiation therapy is more subject to zonular lysis and capsular rupture, leading to peroperative lens subluxation or total posterior luxation. Posterior phacophagy may be difficult in ocular melanomas due to fibrotic transformation and weakness of the zonular fibers. Even if morbidity has improved over the past 20 years due to the modernization of phacoemulsification techniques, cataract surgery following ocular PT remains risky (Figure 5). Thus, cataract surgery is reserved only for patients with visual potential. In uveal melanoma patients, however, the visual prognosis is mostly due to other complications (retinopathy, neuropathy, neovascular glaucoma)<sup>7,14,16</sup> rather than cataracts. In such cases, cataract surgery is also useful to ensure proper fundus examination to detect local relapse and prevent complications (such as ischemic retinopathy) that may become irreversible at a later stage. Thus, cataract surgery is critical both in patients losing their vision solely because of VIC or

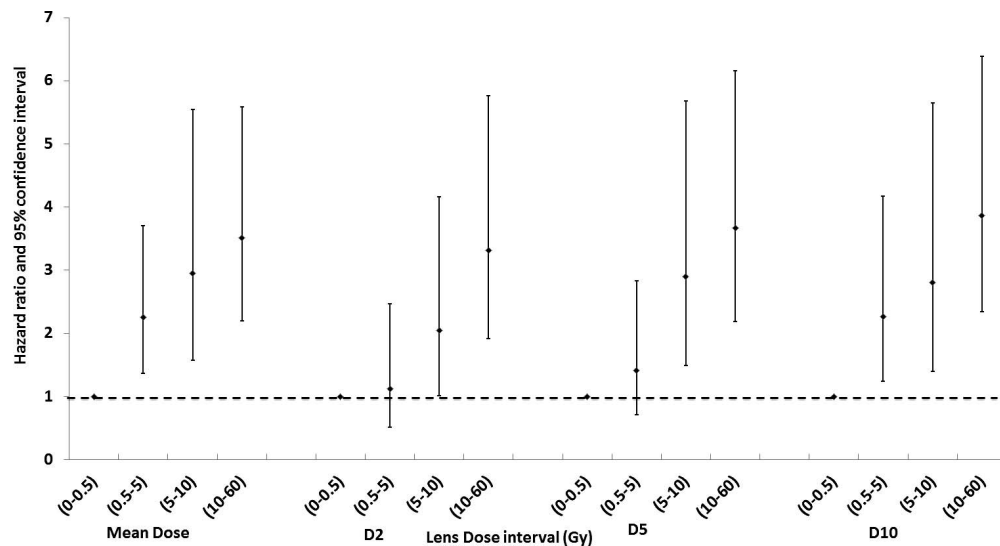


FIGURE 3. HR and 95% CI of each lens dose parameter on VCs after adjustment for age, diabetes, hypertension, and UICC staging in multivariate Cox analyses. Impact on VCs of lens dose interval is statistically significant if the 95% CI excludes 1 (black). The lens dose interval from 0 to 0.5 is taken as the reference. For each dose parameter, the risk of VCs increased with any increase in lens dose.

with lens opacities with no impact on vision per se but in whom fundus-based tumor control is mandatory.

We also showed that median time to occurrence of VIC was 29 months after high-dose rate PT (75 GyRBE/min). High-dose rate irradiation has previously been associated with short latency. With a median follow up of 48 months, we showed that a lens-sparing approach resulted in relatively low cataract rates compared to historical series.<sup>7,15</sup> Using a large cohort of uveal melanoma patients treated uniformly, we could investigate the combination of both lens volume and absorbed doses to study cataractogenesis more accurately than has been done previously with other ionizing radiation modalities. We specifically addressed the effects of irradiation on the occurrence of VIC not only with respect to mean lens dose but also more accurately with respect to subvolumes of lenses irradiated at a given dose. After partial lens irradiation using high doses per fraction, the risk for VIC only increased significantly in the 5- to 10-Gy range if no more than 2% of the

lens was irradiated. This is a much higher dose than the widely accepted threshold of 0.5 Gy associated with a risk for cataracts. This indicates that limiting the volume of lens irradiated is relevant to precise radiation delivery. The ICRP has identified damages to healthy tissues and radioprotection guidelines with respect to radiation-induced risk for cataracts based on exposure to nuclear bombs, X-rays at work, and therapeutic irradiation with photons (X or  $\gamma$ ) or electrons.<sup>12,17-19</sup> While conventional therapeutic irradiation spreads the dose to the whole lens without potential for sparing, PT uses charged particles with sharp dose deposition. Consistent with the ICRP guidelines,<sup>3</sup> we found no significant excess risk for radiation-induced cataracts for doses below 0.5 Gy for up to 5% of lens irradiated. The lens being a very radiosensitive organ, it was assumed that relevant subvolumes should be small and relevant to clinical decisions. On one hand, there are no published data available to define the minimal volume above which lens irradiation results in cataracts. On the

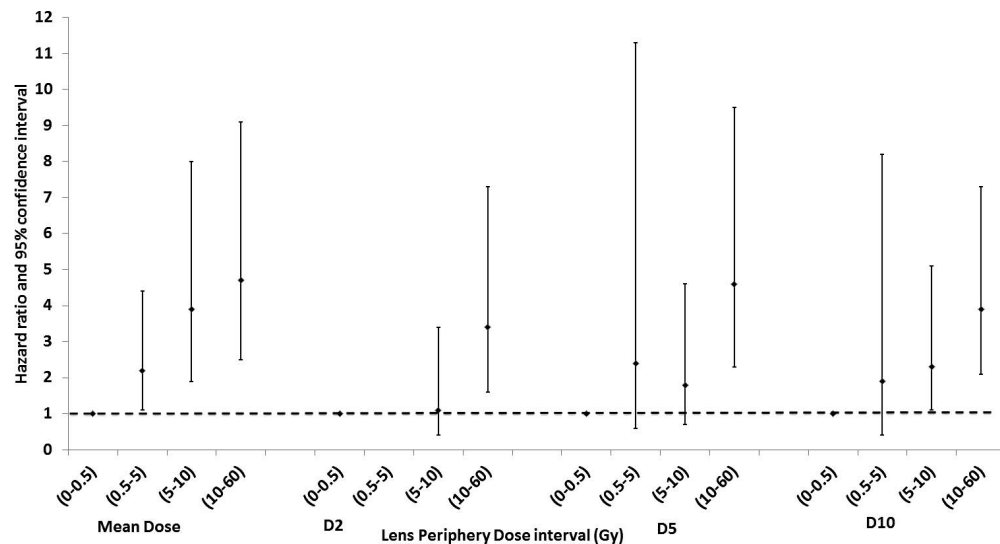
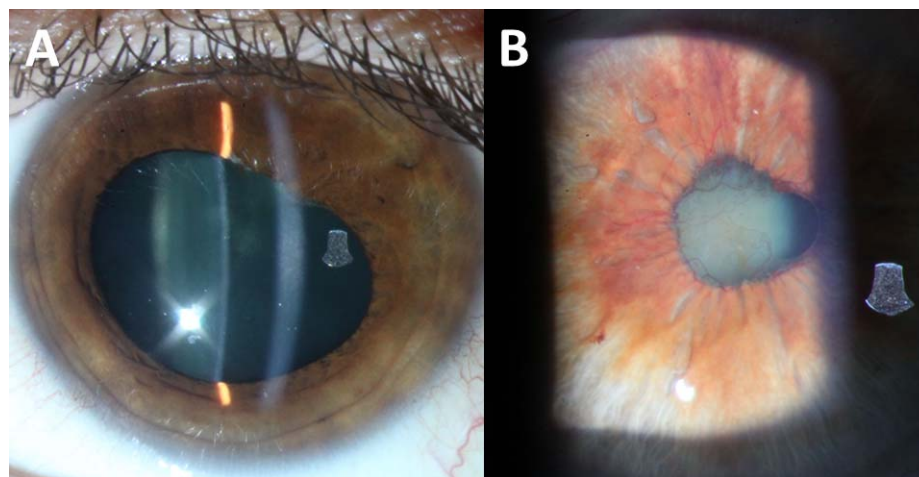


FIGURE 4. HR and 95% CI of each lens periphery dose parameter on VCs after adjustment for age, diabetes, hypertension, and UICC staging in multivariate Cox analyses. Impact on VCs of lens periphery dose interval is statistically significant if the 95% CI excludes 1 (black). The lens dose interval from 0 to 0.5 is taken as the reference. For D2, HR was not computed for (0.5-5) interval since no VCs were found in this interval.



**FIGURE 5.** Radiation cataract after proton beam therapy. (A) Posterior capsular cataract with posterior irido-lenticular synechiae. (B) Total cataract with 360° posterior irido-lenticular synechiae and rubeosis iridis.

other hand, the dose to 2% of an organ is commonly used to account for dose hot spots when evaluating treatment plans. Interestingly, we showed that rather than the dose to such small subvolumes, a relatively high dose situated between 5 and 10 Gy was necessary to induce cataracts if 2% of the lens were irradiated. Above that minimal dose-level threshold, the dose-volume profiles suggested a linear relationship with no superior threshold, consistent with the literature.<sup>2,19,20</sup> PT can spare the lens partially or completely.<sup>10</sup> We were able to fully avoid lens irradiation in 25% of patients. Owing to the very low-dose threshold inducing cataracts, we spared the lens in all other patients whenever possible, according to the ALARA principle. We demonstrated that lens-sparing PT was feasible and translated to low cataract rates, challenging the notion that mean dose to the lens is the sole relevant risk indicator for cataracts.

We also showed that irradiation of the lens periphery itself was responsible for VIC. However, the dose range in which the risk became significant for 2% of the irradiated lens periphery was above 10 Gy. Both apoptosis of proliferative epithelial lens cells<sup>21–23</sup> and metabolic changes of lens components are involved in cataractogenesis.<sup>24,25</sup> Radiation-induced cataracts are typically reported to be subcapsular in type. Thus, lens periphery sparing may theoretically avoid radiation-induced cataractogenesis.<sup>26,27</sup> Our results do not seem to show that irradiation of the lens periphery containing the epithelial cells was more correlated with the risk for cataracts than was irradiation of the lens core. We observed that cataracts were not only of a subcapsular type but also were cortical or total (data not shown). In one brachytherapy series, 85% of anterior ocular tumor patients had cataracts, of which only 52% were of subcapsular type.<sup>5,6</sup> Since the current study, the Lens Opacities Classification System III classification has been implemented by our onco-ophthalmologists to better define cataracts in terms of location and extent of opacities.<sup>28,29</sup>

The incidence of cataracts appears to be smaller than in other radiotherapy series.<sup>5,6,11–15,24,30</sup> This could be partly explained by the relatively short median follow up or by 6-month intervals between exams, which may underestimate this incidence. However, high-dose rate and high radiation dose are associated with short latency rather than with more fractionated dose regimens.<sup>4,31</sup> With respect to the definition of VIC, deteriorated visual acuity according to CTCAE is questionable as other complications are important confounders in this population.<sup>9</sup> A more likely explanation lies in our lens-sparing PT approach (feasible because of the physics of protons).

With respect to study limitations, it is important to note that senile cataracts, posttraumatic cataracts due to mechanical stress on the lens during clip placement, or cataracts due to systemic or ocular steroids cannot be excluded. However, past medical history is usually traceable at 6-month intervals, and causal relationships may be established between occurrence of cataracts and causal factors. Additionally, we cannot eliminate the hypothesis that cataracts occurred during intervals between two onco-ophthalmology visits and that time to VIC was thus significantly overestimated. Patients were seen by onco-ophthalmologists for assessment of tumor response, complications, and toxicities of treatments every 6 months. However, they were also seen by their family doctors (general practitioners) and family ophthalmologists between those visits. With respect to cataracts, patients could be diagnosed with cataracts during visit intervals. They then could be operated on for cataracts impairing their vision at standard practice facilities by their ophthalmologists, even after PT. In such cases, interval cataract surgery and VIC were anticipated, and reports were sent to onco-ophthalmologists. Thus a slight overestimation of the median time to radiation-induced cataracts is possible but probably not the median time to radiation-induced VIC.

It was not the first aim of our study to measure the lens volume. However, it should be noted that CT scan is not the best imaging modality to evaluate small organs such as the lens due to relatively poor spatial resolution compared to MRI or OCT.<sup>32–34</sup> It is currently the only imaging modality used to calculate doses for radiation therapy planning. It should also be noted that our CT scans were performed in accommodating tumor eyes. As a consequence, slightly higher lens volumes were observed in comparison with the MRI/OCT literature.

Finally, it is possible that secondary neutrons may be involved in cataractogenesis. However, we previously measured the dose received due to secondary neutrons in conditions of ocular PT as 2.5 mSv.<sup>35–37</sup> It is possible that we missed other confounding causes of cataracts.<sup>38,39</sup>

## CONCLUSIONS

We showed that a lens-sparing approach is feasible and can not only result in reduced need for cataract surgery but also in better fundus-based tumor control. Furthermore, not only is mean lens dose a surrogate for the risk of radiation-induced VIC but also a dose of 10 GyRBE to 5% of the lens. This is important



to the radioprotection field and not just for PT. Ocular PT has a steep dose gradient and very narrow penumbra. To that extent it is different from conventional irradiation using photons, among those are 3D irradiation, intensity-modulated radiotherapy, and stereotactic irradiation. The latter technique results in large areas of intermediate dose spillage, with little potential to spare the lens. With photon-based techniques, dose-volume analyses to small organs such as the lens are limited by the physics of photons. Studying lens radiosensitivity with PT allowed us to improve the understanding of the sensitivity of the lens and adds important data to the current literature. In particular, another treatment technique for uveal melanomas where these new data may apply is brachytherapy, which also has steep lateral gradients. Plaque placement may be optimized to spare the lens to take advantage of the steep lateral gradients. Thus, the current data should be important to the field of the two main conservative treatments of ocular melanomas: brachytherapy and PT. More charged particle therapies (in addition to PT) are available for the treatment of head and neck or ocular tumors. The current data should be useful for treatment planning for these techniques too.

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