The Lens Opacities Classification System III Grading in Irradiated Uveal Melanomas to Characterize Proton Therapy-Induced Cataracts

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• PURPOSE: To evaluate the use of the Lens Opacities Classification System III grading (LOCS III) for the characterization of radiation-induced cataract, and to correlate the proton beam projection onto the lens with cataract location and grade as defined by the LOCS III.

• DESIGN: Prospective, interventional case series.

• METHODS: Fifty-two consecutive patients with cataract following proton therapy were included. All cataracts were graded using LOCS III. Relationships between proton beam and cataract subtypes, as well as between dose, proportion of lens irradiated, and extent of cataracts, were assessed.

• RESULTS: Tumor diameter, volume, stage, and equatorial tumor location were associated with extent of posterior subcapsular cataracts (PSC) that were diagnosed at a median (interquartile range) 36 months (22;83) after treatment. In multivariate analysis, the tumor volume ($P < .01$) and an equatorial tumor location ($P = .01$) were risk factors for extensive PSC. Lens irradiation was avoided in 10 patients. In the remaining 42 patients (81%), the extent of PSC significantly correlated with the dose to the lens receiving 10, 26, and 47 Gy ($P = .03$, $P = .03$, and $P = .04$, respectively), the dose to the lens periphery receiving 10 and 26 Gy ($P = .02$ and $P = .02$, respectively), and the dose to the ciliary body receiving 10 and 26 Gy ($P = .03$ and $P = .02$, respectively). Nuclear color significantly correlated with the dose to the ciliary body receiving 10 Gy ($P = .03$) and 26 Gy ($P = .02$). After adjustment of the results on tumor volume and tumor location, the volume of lens receiving 10 Gy ($P = .04$) and 26 Gy ($P = .03$) remained significantly associated with the extent of PSC.

• CONCLUSIONS: Proton dose correlated with the occurrence of PSC and nuclear color cataracts as defined by LOCS III grading. Better characterization of cataracts with the LOCS III after irradiation may help to further fill gaps in the current understanding of the mechanisms of radiation-induced cataracts. (Am J Ophthalmol 2019;201:63–71. © 2019 Elsevier Inc. All rights reserved.)

MANAGEMENT OF UVEAL MELANOMAS IS INCREASingly conservative, and proton beam therapy (PBT) and brachytherapy are the most frequently used techniques.[1,2] However, radiation-induced toxicities such as optic neuropathy, retinopathy/maculopathy, dry eye syndrome, and cataracts can compromise vision.[3–5] As the lens is one of the most radiosensitive tissues among the ocular structures, cataracts are a frequent complication after ocular radiation therapy. Their incidence varies from 45% to 100% after ocular radiation therapy.[1,6,7] Radiation cataracts typically include posterior subcapsular lens clouding caused by damage to the subcapsular epithelium. However, there is neither absolute phenotypic conformity for the subtype of cataracts nor pathognomonic signs of radiation-induced cataracts. Senile, traumatic, or iatrogenic cataracts may also occur after radiation therapy. Full analysis of how exposure to therapeutic ionizing irradiation correlates and colocalizes with subsequent lens opacification is warranted to better establish causality. Such colocalization between radiation beam and opacities is only possible with specific forms of radiation modalities, in particular particle therapy that yields sharp dose distributions. Another important gap in current knowledge is that radiation cataracts are not graded like nononcologic cataracts.[7] The international Common Toxicity Criteria (CTC) classification does provide grades of severity in terms of visual acuity and cataracts but is not appropriate for uveal melanomas, as it does not distinguish between vision loss owing to maculopathy or cataracts and does not describe lens opacities accurately. Depending on their location in the lens, opalescence, color, and proportion of lens involved, lens opacifications can variably affect the vision. The international Lens Opacity Classification System (LOCS) defines a score based on the anatomic location and extent of cataracts on slit-lamp

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examination. The third version of the LOCS (LOCS III) is a robust and accurate means to classify cataracts as nuclear color (NC), nuclear opalescence (NO), cortical (C), and posterior subcapsular (P) cataracts, and grade them in terms of extent into the lens based on an atlas of standardized slit-lamp retroillumination images.[8] Assessing LOCS III in radiation-induced cataract could provide a better way to describe the effect of the proton beam on lens opacities.

This study was designed to evaluate the feasibility of using the LOCS III for radiation-induced cataracts and to examine correlations between the proton beam impact onto the lens and anatomic subtypes and extent of cataracts according to the LOCS III after PBT for uveal melanomas.

METHODS

• **PATIENT SELECTION AND CATARACT GRADING:** This interventional case series included consecutive patients with cataract from 1 hospital (Eye Clinic, Bordeaux, France) who underwent PBT for eye tumor between January 2007 and December 2016. Patients who already had cataracts or were pseudophakic prior to PBT, and patients who had intravitreal, sub-Tenon, or subconjunctival corticosteroid use, were excluded from the study.

All included patients provided fully informed consent before participation and an international review board approved the study (Ethics Committee of the French Society of Ophthalmology, IRB 00008855 Société Française d'Ophtalmologie IRB#1).

Patients were evaluated for cataract development at a single ophthalmology hospital (Eye Clinic, Bordeaux, France), expert in LOCS III grading (LR), after pupil dilation with 0.5% tropicamide and 10% phenylephrine hydrochloride 30 minutes before examination. A pupil diameter of more than 8 mm was considered as appropriately dilated for cataract evaluation. LOCS III grading scales include lens opacities defined as NO, NC, C, and P cataracts with 6 degrees of extent (ie, severity). The LOCS III uses a set of 6 slit-lamp images of nuclear cataracts and 5 retroillumination images of cortical or posterior subcapsular cataracts. Patient characteristics, tumor, and cataract grading were prospectively recorded in a case report form (CRF), which was filled out immediately after the medical appointment. Collected data included age, sex, initial and final visual acuity, and tumor characteristics (diagnosis, TNM staging, ultrasound thickness and diameter, volume, topography, and ciliary involvement).

• **TREATMENT:** Irradiation was conducted with a 65 MeV dedicated hospital-based cyclotron at the Cancer Center in Nice, France. Four tantalum fiducial markers were positioned under anesthesia onto the sclera using transillumination to define tumor borders. After surgery, topical corticosteroids were administered for 2 weeks. Tumor characteristics and associated signs were reported on ophthalmology reports based on transillumination, fundus (or retinography/angiography), ultrasound, and/or optical coherence tomography depending on tumor position relative to the equator of the eye. PBT was performed 2-4 weeks after fiducial placement. The Eyeplan treatment planning system software (v1-3) was used. Ocular computed tomography (CT) scan with clips was performed for the delineation of normal structures and treatment plan optimization. The tumor was delineated and 2.5-mm lateral safety margins were added around the tumor. Beam modifiers were designed depending on the target range and lateral conformation was performed using a brass collimator adjusted to the tumor contours. The papilla, optic nerve, and macula were preserved whenever possible without compromising tumor control. In case of equatorial and preequatorial tumors, optimization using CT scan modeling was performed on the anterior chamber with the lens as a surrogate. The lens was preserved whenever possible using adapted gaze, but not at the cost of tumor under-coverage or sacrifice of optic nerve or macula. The patient's gaze was focused using a light-emitting diode located in a plane perpendicular to the beam. Proper projection of the beam using light field projection was systematically verified. Patient and tumor setup were controlled using online orthogonal radiographic images. Eye position was monitored using video camera surveillance during the 10-second treatment, eye movements triggering immediate beam interruption. The gaze direction was chosen to minimize the dose to the optic nerve and macula and, when possible, the dose to the lens and retina. Each tumor was irradiated by 4 fractions of 13 Gy physical dose; the corresponding radiobiologically equivalent dose was 15 GyRBE, which corresponds to the dose that would be given with conventional photon-based irradiation. Patients had antibiotic and corticosteroid eye drops for a period of 1 month after the end of treatment. All data concerning irradiation planning were collected in patient medical charts.

• **DOSE-VOLUME ANALYSIS:** Lens periphery and lens core volumes were generated from the outer contours of the lens, which were delineated with a similar method throughout the study. Given the craniocaudal length of the lens and the CT scan slice thickness, 5 slices were sufficient in all cases to delineate the lens on all slices where it was visible. The same 2 investigators (dosimetrists, expert in the field) delineated patient lenses throughout the study. The treatment planning system for ocular PBT was able to reconstruct the lens volume, shape, and position to produce dose-volume histograms, that is, relationships between doses and volumes of the lens to be correlated with clinical outcomes such as cataracts. Computer-generated dose-volume histograms of the tumor and other structures (eyeball, ciliary body, etc) were also extracted using the Eyeplan software. Graphic displays of treatment plans were analyzed for collimator aperture and isodose projections onto the eye. The volume of the eye lens and periphery lens that received at least 20%, 50%, and 90% of the maximum prescription dose (52 Gy), defined as V10 Gy, V26 Gy, and V47 Gy,

were calculated from full dose-volume histograms. Additionally, the volume of the ciliary body V10 Gy, V26 Gy, and V47 Gy was reported.

• **ANALYSIS OF CATARACT SUBTYPES ACCORDING TO THE LENS OPACITIES CLASSIFICATION SYSTEM III:** All cataracts were graded by a single trained ophthalmologist (L.R.). Description of cataracts with slit-lamp examination was performed by an ophthalmologist masked to lens irradiation avoidance on the proton therapy plan. We examined whether the proton beam anterior projection included the lens on graphic displays and, if so, what proportion of lens was irradiated. We correlated the beam projection with grade of severity, defined by the extent of the lens opacities after PBT. We then established whether the LOCS III locations of cataracts were consistent with radiation damage, that is, whether the classical anatomic subtype of cataracts, such as the posterior subcapsular subtype, was located within the beam projection. Similarly, we examined whether cataract subtypes atypical with respect to radiation-induced damage (nuclear, for example) could be attributed to the proton beam in the terms of beam projection and location of opacities. Finally, we analyzed the extent of cataracts and correlated them with dose-volume histograms of the lens periphery or core volume.

• **STATISTICAL ANALYSIS:** The patient sample size was determined to evaluate the feasibility of integrating the LOCS III in patients with cataracts in a routine onco-ophthalmology practice with sufficient sampling of the various cataract subtypes. Visual acuity was converted to logMAR units for statistical investigations. Quantitative parameters were described by median and interquartile range (IQR) according to the normality of distributions assessed by the Shapiro-Wilk test. Qualitative parameters were described by frequency and percentage. For each of the 4 features of the lens (the extent of nuclear opalescence, nuclear color, cortical cataract, and posterior subcapsular cataract), the relationship between extent and patient characteristics was investigated using bivariate analyses. For binary parameters the Wilcoxon test was used, and for qualitative parameters with more than 3 levels the Kruskal-Wallis test was used. To test the relationship between the extent and quantitative parameters, the Spearman correlation coefficient was computed. When several patients or dose-volume characteristics were predictive of the extent with a significance level less than 0.1, they were included in a multivariate linear model. The multicollinearity was assessed with the variance inflation factor (VIF) and parameters with a VIF ≥3 were excluded. The stability of the final model was investigated with the bootstrap resampling method. The validity of the final model was checked by the Studentized residuals and Cook's distance. All analyses were performed using SAS 9.4 software (SAS Institute Inc, Cary, North Carolina, USA).

TABLE 1. Patient and Tumor Characteristics

Characteristic	Result
Patient characteristics	
Median age in years (IQR)	65 (57;71)
Sex, % (n)	
Female	52% (27)
Male	48% (25)
Diabetes mellitus, % (n)	15% (8)
Lens thickness (mm), median (IQR)	4.5 (4;5)
Initial visual acuity, median (IQR)	0.95 (0.10–1.00)
Final visual acuity, median (IQR)	0.5 (0.01–1.00)
Tumor characteristics	
Melanoma type, % (n)	
Choroidal melanoma	75% (39)
Ciliary body melanoma	8% (4)
Iridociliary melanoma	5% (3)
Choroidociliary melanoma	10% (5)
Iris melanoma	2% (1)
UICC staging, % (n)	
T2a	69% (36)
T3	31% (16)
Tumor diameter (mm), median (IQR)	13.4 (11.25;16.9)
Tumor volume (cm^3), median (IQR)	0.34 (0.17;0.79)
Tumor topography, % (n)	
Anterior	33% (17)
Equatorial	11% (6)
Posterior	56% (29)
Ciliary body involvement, % (n)	
Yes	31% (16)
No	69% (36)

IQR = interquartile range.

RESULTS

• **POPULATION:** Fifty-two patients were included. Patient characteristics are reported in Table 1. Melanoma types were choroidal (75%), choroidociliary (10%), ciliary (8%), iridociliary (5%), and iris (2%). For choroidal melanomas, the anterior edge of the tumor was posterior to the equator in 29 patients (56%) and on the equator for 6 patients (11%). None of the tumors were in contact with the lens at diagnosis and at the time of cataract grading. All patients were treated by PBT after tantalum fiducial placement and none of them had any complications related to this surgery.

• **CATARACT ANALYSES ACCORDING TO THE LENS OPACITIES CLASSIFICATION SYSTEM III:** The median (IQR) time to diagnosis of cataracts after PBT was 36 months (22;83). Different subtypes of cataracts were graded accorded to the LOCS III at the slit-lamp examination (Figure 1) and are reported in Figure 2. The crystalline lenses were outside or within the anterior projection of the proton beam in 10 patients (19%) and 42 patients

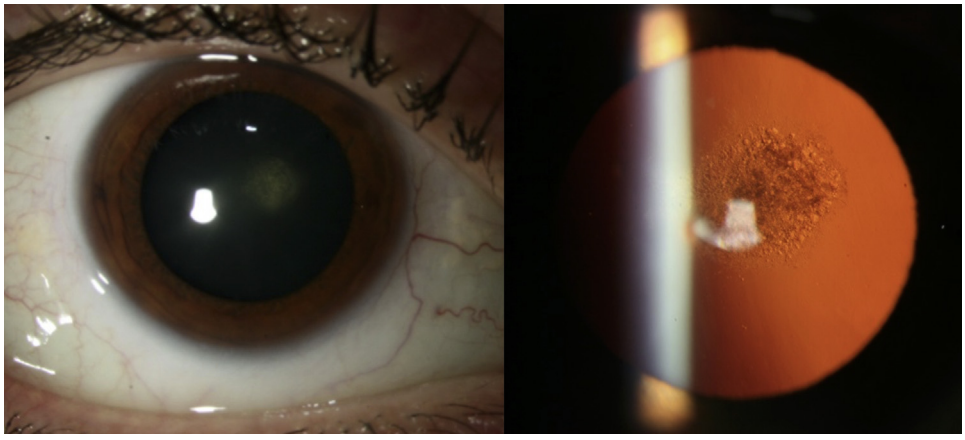

FIGURE 1. Cataract grading according to the Lens Opacities Classification System III grading system at 3 years after proton beam therapy for choroidal melanoma. NO 0, NC 1, C 0, P 3. C = cortical cataract; NO = nuclear opalescence; NC = nuclear color; P = posterior subcapsular cataract.

(81%), respectively. The proportion of lens in the proton beam projection was variable depending on tumor volume and location. This proportion exceeded 50% in 8 patients (15%), was between 25% and 50% in 22 patients (42%), and was less than 25% in 22 patients (42%).

The proportion of lens within the proton beam projection was significantly correlated with the extent of P cataracts according to the LOCS III ($P = .01$; Table 2).

• **CATARACTS ACCORDING TO THE LENS OPACITIES CLASSIFICATION SYSTEM III AND TO CLINICAL PARAMETERS:** No relationship was found between time to diagnosis and cataract subtype according to LOCS III grading. In bivariate analysis, a significant correlation was observed between tumor volume, maximum tumor diameter, and the occurrence of P cataracts. The initial thickness of lens was not significantly associated with postproton cataracts. Tumor stage was a significant predictive factor for the extent of P cataracts according to the LOCS III; T3 stage was significantly associated with the extent of P cataracts ($P < .01$). There was no significant correlation between tumor type (iris, ciliary body, or choroidal melanoma) and cataract subtype. However, for choroidal melanomas, an equatorial tumor correlated with the extent (grade of LOCS III severity) of P cataracts ($P < .01$) (Table 3).

After a multivariate analysis, tumor volume ($P < .01$) and an equatorial tumor location ($P = .01$) were found to be independently associated with the occurrence of P cataracts.

• **CATARACTS ACCORDING TO THE LENS OPACITIES CLASSIFICATION SYSTEM III AND DOSE-VOLUME PARAMETERS IN PATIENTS WITH AN IRRADIATED LENS:** Focusing on the 42 patients whose crystalline lens was at least partially in the proton field, dose-volume characteristics are described in Table 4. The extent/severity of P and NC cataracts was significantly correlated with the volume of ciliary body receiving 10 Gy and 26 Gy, which corresponded to 20% and 50%, respectively, of the maximum prescribed dose. Thus, the higher the dose to the ciliary body, the more severe the P and NC cataracts. Dose to the ciliary body was not significantly correlated with other subtypes of cataracts (NO and C) ($P > .05$). In addition, it was observed that the extent of P cataracts was significantly correlated with the proportion of lens periphery receiving at least 10 Gy, 26 Gy, and 47 Gy. The larger the volume of lens irradiated, the more severe the P cataracts.

After adjustment of the results of dose-volume parameters on tumor volume and a posterior tumor location, the volume of lens receiving 10 Gy and 26 Gy remained significantly associated with the extent/severity of P cataracts (respectively, $P = .04$ and $P = .03$). The other parameters were no longer significantly associated after adjustment: volume of ciliary body receiving 10 Gy ($P = .09$) and that receiving 26 Gy ($P = .06$), the volume of lens periphery receiving 10 Gy ($P = .07$) and that receiving 26 Gy ($P = .053$), and the volume of lens receiving 47 Gy ($P = .13$). No stable multivariate model was found for the extent/severity of NC cataracts owing to strong collinearity.

DISCUSSION

OCULAR PROTON THERAPY USING A DEDICATED OCULAR cyclotron has physical properties that allow a lens-sparing approach owing to more accurate dose distribution, and which are not found in other photon-based modalities. This is owing to a small lateral penumbra to the order of 1 mm or less at the radiation field edges. Radiation-induced cataracts were first described in 1952.[9] Until very recently, the threshold for detectable lens opacities was assumed to be on the order of 2 Gy (with conventional x-ray photon irradiation) for acute exposure to ionizing

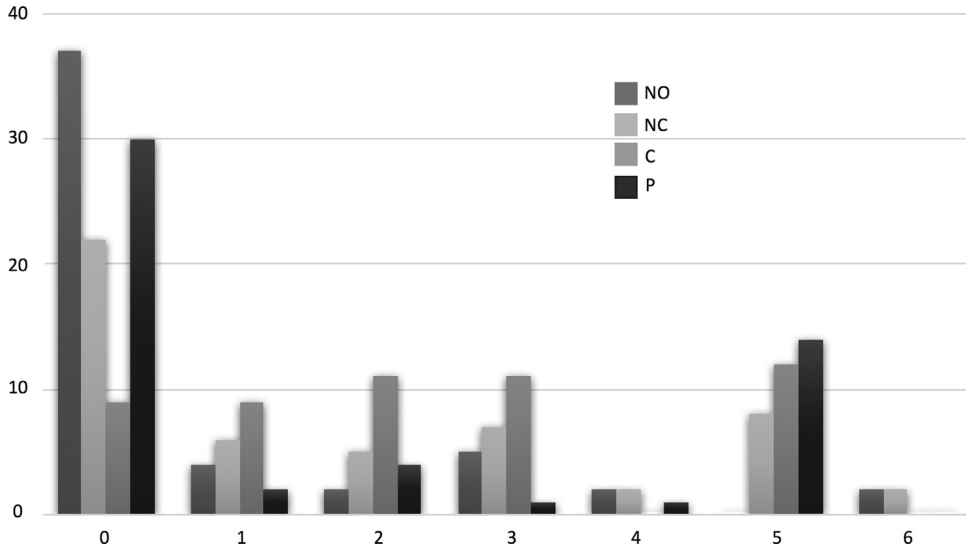

FIGURE 2. Cataract extent and anatomic location according to the Lens Opacities Classification System III grading system (LOCS III) in 52 patients. The x-axis corresponds to the cataract score according to the LOCS III. The y-axis corresponds to the frequency of the different cataract subtypes observed in the study population. C = cortical cataract; NO = nuclear opalescence; NC = nuclear color; P = posterior subcapsular cataract.

TABLE 2. Extent of Lens Opacities Classification System III Cataract Types According to the Proportion of Lens Within the Proton Beam Projection in Bivariate Analysis in 52 Patients

	NO	NC	C	P
Proportion of lens within proton beam projection	-0.21[a] *P* = .130	0.27[a] *P* = .06	0.22[a] *P* = .12	0.34[a] *P* = .01*

C = cortical; NC = nuclear color; NO = nuclear opalescence; P = posterior subcapsular cataracts.
Asterisk (*) indicates statistical significance.
[a]Results presented with Spearman correlation coefficient.

radiation and 5 Gy for highly fractionated or protracted, chronic, exposure[10]; for vision-impairing cataracts, these thresholds were on the order of 5 Gy.[10] More recent epidemiologic studies have demonstrated that doses of conventional radiation therapy on the order of 1 Gy can lead to detectable lens opacities.[11,12] Several other radiation-related factors have been involved in the occurrence of radiation cataracts, such as the type of irradiation, total dose, dose per fraction, and time since exposure. Although, with PBT, lens irradiation was completely avoided in about a fifth of the 52 consecutive patients included in the present study, all patients had cataracts per study selection criteria. Despite the possibility to avoid lens irradiation with PBT for uveal melanomas, radiation-induced cataracts are, however, frequent, as there are numerous situations where the lens is next to the tumor or within the anterior projection of the proton beam. Similar results have also been reported in other series of uveal melanoma patients after PBT.[7,13,14] In this cohort, all patients were treated uniformly with a similar method, total prescription dose, and lens-sparing approach.

The LOCS III has been validated in both clinical and epidemiologic studies of cataracts of various origins[8,15,16] but is not commonly used in ocular oncology. We showed herein the feasibility of using the LOCS III to evaluate cataracts after PBT for uveal melanomas. In particular, we found correlations between the proton beam projection and the anatomic location of the lens opacities (ie, LOCS III subtypes NC, NO, C, and P). We also found relationships between the volume of lens included in the proton field and extent of lens opacities as defined by the LOCS III severity. It was beyond the scope of the current study to correlate cataract severity and the deterioration of the visual acuity after PBT owing to major confounding factors such as radiation maculopathy and optic neuropathy, which, unlike cataracts, are often irreversible.[17] Additionally, the patient sample size was designed neither to assess the influence of ocular radiation

TABLE 3. Prognostic Factors of Cataract Extent According to the Lens Opacities Classification System III in Bivariate Analysis in the 52 Patients

	Cataract Subtype According to LOCS III			
	NO	NC	C	P
Time to diagnosis[a]	0.07	-0.03	0.18	0.015
	$P = .58$	$P = .78$	$P = .19$	$P = .91$
Age[a] (years)	0.20	0.26	0.22	0.01
	$P = .15$	$P = .05$	$P = .11$	$P = .89$
Thickness of lens[a]	0.17	0.04	0.06	-0.06
	$P = .21$	$P = .76$	$P = .64$	$P = .67$
Tumor volume[a]	-0.28	0.18	0.007	0.47
	$P = .03$*	$P = .19$	$P = .95$	$P < .01$*
Maximum tumor diameter[a]	-0.26	0.15	-0.08	0.35
	$P = .06$	$P = .27$	$P = .52$	$P < .01$*
UICC stage[b]				
T2a (n=36)	0 (0;1.5)	1 (0;3)	2 (1;3)	0 (0;1.5)
T3 (n=16)	0 (0;0)	2.5 (0;5)	1.5 (0;5)	4.5 (0;5)
	$P = .37$	$P = .22$	$P = .73$	$P < .01$*
Tumor type[b]				
Choroidal melanoma (n = 39)	0 (0;1)	2 (0;4)	2 (1;5)	0 (0;5)
Other (n = 13)	0 (0;0)	1 (02)	2 (1;3)	0 (0;0)
	$P = .61$	$P = .35$	$P = .52$	$P = .15$
Tumor location[b] with respect to ocular equator (for choroidal melanoma only)				
Anterior	0 (0;1)	2 (1;3)	2 (1;3)	0 (0;4)
Equatorial	0 (0;0)	2.5 (0;5)	5 (0;5)	5 (3;5)
Posterior	0 (0;1)	2 (0;3)	2 (1;3)	0 (0;2)
	$P = .73$	$P = .76$	$P = .54$	$P < .01$*

C = cortical; LOCS = Lens Opacities Classification System; NC = nuclear color; NO = nuclear opalescence; P = posterior subcapsular cataracts.

Asterisk (*) indicates statistical significance.

[a]Results presented with Spearman correlation coefficient.

[b]Results presented with median and interquartile range.

side effects nor to show the importance of well-known confounding factors (age, diabetes, etc) on visual acuity. However, to the best of our knowledge, this is the only study that assessed correlations between accurate characteristics of cataracts using the LOCS III and the ballistics of the proton beam, taking advantage of its excellent lateral dose distribution. We showed that cataracts were diagnosed at a median 36 months post treatment, which is earlier than with more fractionated dose regimens[18] but consistent with other hypofractionated high-dose proton therapy series.[19]

Radiation-induced cataracts are typically reported to be of subcapsular type.[20,21] Pathogenesis suggests that radiation damages the DNA of proliferative cells that will migrate posteriorly, leading to deformed lens fiber and debris accumulation in the subcapsular regions, especially posteriorly.[22] However, we did not exclusively observe posterior subcapsular cataract, which is consistent with a study investigating brachytherapy that found that among the 85% of anterior ocular tumor patients who had cataracts, only 52% were of subcapsular type, but no detailed description of plaque placement and type/severity of cataracts was reported.[23] This observation highlights the complexity of the mechanisms involved in postradiation cataracts. Moreover, we cannot exclude that so-called radiation-induced cataracts may indeed be attributable to classical confounding factors but also other iatrogenic causes (traumatic cataracts by tumor compression or during clip placement, use of topical steroids, etc). Furthermore, it is unlikely that the small dose received by secondary neutrons contributed to cataracts,[18,19] but bystander effects on cells that are not directly irradiated but are at short distances from irradiated cells and communicate between each other by means of intercellular junctions or cytokines[20] is possible.

Among the 42 patients with an irradiated lens, the proportion of lens in the proton beam was significantly correlated with the occurrence of P cataracts according to the LOCS III. In addition, the extent of posterior P and NC cataracts was also significantly correlated with the dose to the ciliary

TABLE 4. Description of Dose-Volume Characteristics and Analysis as Prognostic Factors of Cataract Occurrence[a] in 42 Patients Whose Crystalline Lens Was in the Proton Field

		Spearman Correlation Coefficient (N = 42) Bivariate Analysis			
	Volume, % (IQR)	NO	NC	C	P
Volume of lens receiving 10 Gy[b]	18 (3;39)	-0.24	0.20	0.19	0.32
		$P = .11$	$P = .18$	$P = .20$	$P = .03$*
Volume of lens receiving 26 Gy	11 (0;28)	-0.09	0.18	0.22	0.33
		$P = .54$	$P = .23$	$P = .15$	$P = .03$*
Volume of lens receiving 47 Gy	0 (0;10)	-0.21	0.28	0.17	0.30
		$P = .17$	$P = .07$	$P = .25$	$P = .04$*
Volume of lens periphery receiving 10 Gy[c]	30 (21;40)	-0.28	0.26	0.16	0.35
		$P = .06$	$P = .09$	$P = .28$	$P = .02$*
Volume of lens periphery receiving 26 Gy	23 (11;35)	-0.28	0.23	0.14	0.34
		$P = .06$	$P = .12$	$P = .36$	$P = .02$*
Volume of lens periphery receiving 47 Gy	0 (0;25)	-0.21	0.25	0.12	0.21
		$P = .16$	$P = .10$	$P = .41$	$P = .16$
Volume of ciliary body receiving 10 Gy[d]	31 (25;38)	-0.24	0.30	0.19	0.30
		$P = .08$	$P = .03$*	$P = .16$	$P = .03$*
Volume of ciliary body receiving 26 Gy	26 (21;33)	-0.25	0.30	0.20	0.33
		$P = .07$	$P = .02$*	$P = .14$	$P = .02$*
Volume of ciliary body receiving 47 Gy	15 (0;27)	-0.19	0.24	0.09	0.18
		$P = .17$	$P = .07$	$P = .52$	$P = .17$

C = cortical; IQR = interquartile range; NC = nuclear color; NO = nuclear opalescence; P = posterior subcapsular cataracts.
Asterisk (*) indicates statistical significance.
[a]According to the Lens Opacities Classification System III.
[b]The crystalline lens volume receiving X Gy.
[c]The crystalline lens periphery volume receiving X Gy.
[d]The ciliary body volume receiving X Gy.

body. Ciliary body involvement of the tumor or close proximity between the tumor and ciliary body can result in radiation damage to the ciliary body. Such damage may result in intraocular inflammation and secondary posterior subcapsular cataracts, as already reported.[21] Because ciliary body melanomas are anterior tumors in close proximity with the lens, gazing angle cannot be fully optimized to entirely avoid the lens and to exclude the lens nucleus from the proton beam projection. Moreover, ciliary body melanomas are peripheral tumors that are generally thicker than posterior or equatorial tumors, as they are diagnosed later, and thus require higher dose. For these reasons, lens exclusion from the proton beam projection can rarely be done in such localizations.

We also observed that posterior tumor location was significantly correlated with the appearance of posterior subcapsular cataracts. This may be owing to the fact that when tumors are very close to the posterior structures, treatment plan optimization is performed to spare the macula/optic disk rather than the lens.

While we did not find any correlation between uveal melanoma types treated (choroidal, iris, or ciliary body involvement) and LOCS III subtype, we observed a significant correlation between T3 stage and the occurrence of P cataracts. This finding may be a consequence of the volume of tumor and lens irradiated but also of inflammation associated with significant tumor necrosis, as well as vessel damage in the treated eyes.[24] Kleineidam and associates also reported thickness and the anterior tumor location as prognostic factors of cataractogenesis after cobalt 60 brachytherapy of 370 uveal melanomas.[25] However, use of corticosteroids to control intraocular inflammation was not reported,[25] but prolonged use of these drugs is required to induce cataracts.

With respect to study limitations, the lack of controls was intrinsic to the study selection criteria, as the aim of the current study was to correlate the subtype of cataracts according to LOCS III with the projection of the proton beam onto the crystalline lens and the proportion of lens within the proton field. The small number of cataract subtypes may be considered as a weakness; however, this longitudinal cohort was designed to assess the feasibility of using the LOCS III in oncology.

The design of the study was not appropriate to eliminate confounding factors for cataract development.[26] For instance, examination of the healthy eye would have been useful in identifying cases of bilateral cataracts that are characteristic of senile or diabetic cataracts, but it is unlikely that these would have developed within 36 months, and this

relatively rapid occurrence is more consistent with high-dose radiation-induced cataracts.[7,25,27–29] In addition, the patients included herein are unlikely to have been affected by steroid-induced cataracts because the relatively short prescription of corticosteroids after surgery for fiducial placement is not sufficient to induce cataracts.[27,30] Another potential limitation is that interobserver variability in the slit-lamp evaluation of cataracts may have led to interpretation bias, especially when evaluating the opalescence of the nucleus and severity score. However, the current study was designed to assess cataracts according to the LOCS III by a single ophthalmologist trained in the use of LOCS III for nononcologic cataracts.

Based on the present study, the LOCS III is of potential interest to better characterize and understand the mechanisms of radiation-induced cataracts. These initial findings need further validation in larger prospective cohort studies, and this could lead in the future to promote the use of lens-sparing techniques when possible.[27] The radiation oncology community currently lacks recommendations for dose thresholds to be applied to the lens in therapeutic conditions using high total dose, high dose rate, and hypofractionation. Moreover, there is currently usually no distinction made between the different parts of the lens during PBT planning. Knowing correlations between visual impairment and location of opacifications might be used to optimize fixation angle and beam shaping when such change in planning is neither a risk for tumor coverage nor macula and optic disc sparing. Using LOCS III may even be more relevant to new PBT modalities than passive delivery such as used in the current study and in most international reference centers. Active scanning is the method used in a small but expanding number of new PBT facilities, and it can achieve a slightly better dose sparing at beam entry and thus may allow more personalized lens sparing based on LOCS III grading. Of note, however, such facilities still require adaptations (including energy optimization and lateral collimation) to achieve correct depth dose distribution (tumor and posterior structures). Confirmation of the correlation between visual impairment and the severity of cataracts assessed by the LOCS III[31,32] in an oncology context could also be of great interest in eyes where other radiation complications may occur in view of a potential cataract surgery. More systematic use of the LOCS III in onco-ophthalmology should probably be encouraged.

To conclude, we have shown herein the feasibility of LOCS III grading for radiation cataracts. We also showed that there was a correlation between dose to the lens and occurrence not only of posterior subcapsular cataract subtype but also of nuclear color cataracts, and we report that extent/severity of P cataracts correlated with irradiated lens volume. Better knowledge of correlations between LOCS III and lens dose-volume effects may help to personalize PBT planning, not only with current modalities of delivering PBT but possibly even more with PBT facilities using active scanning (pending some adaptations of equipment used for eye treatment). Prospective studies using the LOCS III are needed to better address the subtype and severity of cataracts in oncology, and to define thresholds for surgery. Better characterization of cataracts after irradiation might also help to further fill gaps in current knowledge of the mechanisms of radiation-induced cataracts.

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REFERENCES

1. Collaborative Ocular Melanoma Study Group. Incidence of cataract and outcomes after cataract surgery in the first 5 years after iodine 125 brachytherapy in the Collaborative Ocular Melanoma Study: COMS Report No. 27. *Ophthalmology* 2007;114(7):1363–1371.
2. Mathis T, Cassoux N, Tardy M, et al. [Management of uveal melanomas, guidelines for oncologists]. *Bull Cancer* 2018;105(10):967–980.
3. Bensoussan E, Thariat J, Maschi C, et al. Outcomes after proton beam therapy for large choroidal melanomas in 492 patients. *Am J Ophthalmol* 2016;165:78–87.
4. Thariat J, Grange J-D, Mosci C, et al. Visual outcomes of parapapillary uveal melanomas following proton beam therapy. *Int J Radiat Oncol Biol Phys* 2016;95(1):328–335.
5. Thariat J, Maschi C, Lanteri S, et al. Dry eye syndrome after proton therapy of ocular melanomas. *Int J Radiat Oncol Biol Phys* 2017;98(1):142–151.
6. Finger PT. Tumour location affects the incidence of cataract and retinopathy after ophthalmic plaque radiation therapy. *Br J Ophthalmol* 2000;84(9):1068–1070.
7. Seibel I, Cordini D, Hager A, et al. Cataract development in patients treated with proton beam therapy for uveal melanoma. *Graefes Arch Clin Exp Ophthalmol* 2016;254(8):1625–1630.
8. Chylack LT, Wolfe JK, Singer DM, et al. The Lens Opacities Classification System III. The Longitudinal Study of Cataract Study Group. *Arch Ophthalmol* 1993;111(6):831–836.
9. Cogan DG, Donaldson DD, Reese AB. Clinical and pathological characteristics of radiation cataract. *AMA Arch Ophthalmol* 1952;47(1):55–70.

10. Merriam GR, Focht EF. A clinical and experimental study of the effect of single and divided doses of radiation on cataract production. *Trans Am Ophthalmol Soc* 1962;60:35–52.
11. Ainsbury EA, Barnard S, Bright S, et al. Ionizing radiation induced cataracts: recent biological and mechanistic developments and perspectives for future research. *Mutat Res* 2016;770(Pt B):238–261.
12. Bouffler S, Ainsbury E, Gilvin P, Harrison J. Radiation-induced cataracts: the Health Protection Agency's response to the ICRP statement on tissue reactions and recommendation on the dose limit for the eye lens. *J Radiol Prot Off J Soc Radiol Prot* 2012;32(4):479–488.
13. Conway RM, Poothullil AM, Daftari IK, Weinberg V, Chung JE, O'Brien JM. Estimates of ocular and visual retention following treatment of extra-large uveal melanomas by proton beam radiotherapy. *Arch Ophthalmol* 2006;124(6):838–843.
14. Riechardt AI, Cordini D, Willerding GD, et al. Proton beam therapy of parapapillary choroidal melanoma. *Am J Ophthalmol* 2014;157(6):1258–1265.
15. Tang Y, Wang X, Wang J, et al. Prevalence of age-related cataract and cataract surgery in a Chinese adult population: the Taizhou Eye Study. *Invest Ophthalmol Vis Sci* 2016;57(3):1193–1200.
16. Gali HE, Sella R, Afshari NA. Cataract grading systems: a review of past and present. *Curr Opin Ophthalmol* 2019;30(1):13–18.
17. Gragoudas ES, Egan KM, Arrigg PG, Seddon JM, Glynn RJ, Munzenrider JE. Cataract extraction after proton beam irradiation for malignant melanoma of the eye. *Arch Ophthalmol* 1992;110(4):475–479.
18. Carnicer A, Letellier V, Rucka G, Angellier G, Sauerwein W, Herault J. Study of the secondary neutral radiation in proton therapy: toward an indirect in vivo dosimetry. *Med Phys* 2012;39(12):7303–7316.
19. Carnicer A, Letellier V, Rucka G, Angellier G, Sauerwein W, Hérault J. An indirect in vivo dosimetry system for ocular proton therapy. *Radiat Prot Dosimetry* 2014;161(1-4):373–376.
20. Hamada N, Matsumoto H, Hara T, Kobayashi Y. Intercellular and intracellular signaling pathways mediating ionizing radiation-induced bystander effects. *J Radiat Res* 2007;48(2):87–95.
21. Gragoudas ES, Egan KM, Walsh SM, Regan S, Munzenrider JE, Taratuta V. Lens changes after proton beam irradiation for uveal melanoma. *Am J Ophthalmol* 1995;119(2):157–164.
22. Merriam GR, Worgul BV. Experimental radiation cataract–its clinical relevance. *Bull N Y Acad Med* 1983;59(4):372–392.
23. Finger PT, Chin KJ, Yu G-P, Patel NS. Palladium-103 for Choroidal Melanoma Study Group. Risk factors for cataract after palladium-103 ophthalmic plaque radiation therapy. *Int J Radiat Oncol Biol Phys* 2011;80(3):800–806.
24. Saornil MA, Egan KM, Gragoudas ES, Seddon JM, Walsh SM, Albert DM. Histopathology of proton beam-irradiated vs enucleated uveal melanomas. *Arch Ophthalmol* 1992;110(8):1112–1118.
25. Kleineidam M, Augsburger JJ, Hernandez C, Glennon P, Brady LW. Cataractogenesis after Cobalt-60 eye plaque radiotherapy. *Int J Radiat Oncol Biol Phys* 1993;26(4):625–630.
26. Miglior S, Marighi PE, Musicco M, Balestreri C, Nicolosi A, Orzalesi N. Risk factors for cortical, nuclear, posterior subcapsular and mixed cataract: a case-control study. *Ophthalmic Epidemiol* 1994;1(2):93–105.
27. Thariat J, Jacob S, Caujolle J-P, et al. Cataract avoidance with proton therapy in ocular melanomas. *Invest Ophthalmol Vis Sci* 2017;58(12):5378–5386.
28. Thariat J, Racadot S, Pointreau Y, et al. [Intensity-modulated radiotherapy of head and neck cancers: dose effects on the ocular, orbital and eyelid structures]. *Cancer Radiother* 2016;20(6-7):467–474.
29. Thariat J, Rahmi A, Salleron J, et al. Proton beam therapy for iris melanomas in 107 patients. *Ophthalmology* 2018;125(4):606–614.
30. Urban RC, Cotlier E. Corticosteroid-induced cataracts. *Surv Ophthalmol* 1986;31(2):102–110.
31. Grewal DS, Brar GS, Grewal SPS. Correlation of nuclear cataract lens density using Scheimpflug images with Lens Opacities Classification System III and visual function. *Ophthalmology* 2009;116(8):1436–1443.
32. Pan A-P, Wang Q-M, Huang F, Huang J-H, Bao F-J, Yu A-Y. Correlation among lens opacities classification system III grading, visual function index-14, pentacam nucleus staging, and objective scatter index for cataract assessment. *Am J Ophthalmol* 2015;159(2):241–247.e2.