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ROLE OF VITREORETINAL SURGERY IN MAXIMIZING TREATMENT OUTCOME FOLLOWING COMPLICATIONS AFTER PROTON THERAPY FOR UVEAL MELANOMA

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préparée sous la direction du Professeur Thomas J. Wolfensberger

(avec la collaboration du Docteur Ann Schalenbourg, du Docteur Etienne Bovey et du Professeur Léonidas Zografos)

et présentée à la Faculté de biologie et de médecine de l'Université de Lausanne pour l'obtention du grade de

DOCTEUR EN MEDECINE

par

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Médecin diplômé de la Confédération Suisse
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Role of vitreoretinal surgery in maximizing treatment outcome following complications after proton therapy for uveal melanoma

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pour Le Doyen
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Madame le Professeur Stephanie Clarke
Directrice de l'Ecole doctorale

Rôle de la chirurgie vitro-rétinienne dans la prise en charge des complications induites par la protonthérapie dans le cadre du mélanome de l'uvée

Résumé

L'utilisation de faisceaux de protons accélérés dans le traitement des mélanomes de l'uvée a été utilisée pour la première fois en Suisse (et par ailleurs en Europe) en 1984. Depuis, la protonthérapie a constamment évolué avec des logiciels toujours plus performants et précis pour devenir à l'heure actuelle le traitement de référence pour ce type de tumeurs. Ainsi, jusqu'à ce jour, l'Institut Paul Scherrer à Villigen a traité plus de 7000 cas de tumeurs oculaires.
Mais la protonthérapie, aussi efficace soit-elle avec un taux de guérison de plus de 98%, comporte malheureusement un certain nombre d'effets secondaires et indésirables pouvant parfois mener le patient jusqu'à l'énucléation secondaire. De la simple dermatite actinique à l'hémorragie intravitréenne massive, les complications induites sont pour la plupart bien connues et documentées mais leurs prises en charge, notamment sur un organe préalablement irradié diffèrent. Alors que nous avons beaucoup de recul sur la protonthérapie, la gestion de ses complications reste propre à chaque centre de soin et n'est que très peu documentée.

Les complications majeures de la protonthérapie qui ont nécessité une prise en charge par le chirurgien vitrorétinien représentent souvent un défi majeur. Bien que rares, puisqu'elles ne représentent que 2% de notre collectif, celles-ci peuvent avoir de lourdes conséquences. Par exemple, une hémorragie intravitréenne massive, complication la plus fréquente dans notre série, compromet l'observation de la tumeur au fond d'œil et empêche le bon suivi oncologique.
La chirurgie vitrorétinienne a alors pour mission, de restaurer la transparence des milieux, élément indispensable à l'ophtalmologue pour le suivi clinique, iconographique et radiologique des mélanomes de l'uvée. Secondairement, cette chirurgie permet parfois d'augmenter l'acuité visuelle de l'œil malade.

La chirurgie vitrorétinienne est un précieux atout pour l'oncologue et permet d'éviter une énucléation secondaire. Elle participe ainsi à la prise en charge globale du patient atteint de mélanome de l'uvée.

ROLE OF VITREORETINAL SURGERY IN MAXIMIZING TREATMENT OUTCOME FOLLOWING COMPLICATIONS AFTER PROTON THERAPY FOR UVEAL MELANOMA

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Purpose: To assess the role of vitreoretinal surgery in maximizing treatment outcome following complications after proton therapy for uveal melanoma and to evaluate its safety.

Methods: Retrospective chart study on 21 patients (2% of a total of 1,005 treated by proton therapy between January 2003 and August 2007) who had developed a complication requiring vitreoretinal surgery. Mean/median total follow-up after irradiation was 43/43 months (range, 12–70 months).

Results: Indications for surgery included vitreous hemorrhage (n = 13), epimacular membrane (n = 5), rhegmatogenous retinal detachment (n = 1), combined vitreous hemorrhage with total serous retinal detachment (n = 1), and vitritis (n = 1). Mean/median interval for vitreoretinal surgery after irradiation was 21/20 months (range, 4–45 months), and mean/median follow-up after pars plana vitrectomy was 22/23 months (range, 2–56 months). Pars plana vitrectomy was combined with retinal photocoagulation (n = 5), air/gas (n = 5), or silicone oil tamponade (n = 1). Mean Snellen visual acuity was 20/200 (0–20/40) before and 20/100 (0–20/25) after pars plana vitrectomy. A transient postoperative rise in intraocular pressure was measured in seven patients. Four patients developed phthisis bulbi.

Conclusion: Vitreoretinal surgery was efficient in maximizing treatment outcome after proton therapy, as it allowed a better oncologic follow-up. Pars plana vitrectomy permitted panretinal photocoagulation to avoid neovascular glaucoma or retinal detachment repair. Macular surgery improved visual acuity, especially in anterior melanoma, whereas repeated surgery may increase the risk of enucleation.

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Uveal melanoma (UM) is the most frequent intraocular malignancy in ophthalmologic practice, mainly encountered in adult white populations with an annual incidence of six new cases per million.[1] Standard treatment is radiotherapy, using plaques or proton beam, or enucleation with similar survival rates for both methods.[2] External proton beam radiotherapy delivers a uniform irradiation to the target volume, with a good sparing of uninvolved eye tissues. As UM is a radioresistant tumor requiring high radiation doses, proton therapy allows for tumors with a large volume or a shape or location unfit for brachytherapy, also being treated conservatively.[3]

The results of proton therapy figure among the best of any conservative oncologic treatment techniques, with local tumor recurrence only ranging from 1% to 5%.[3] Eye retention rate varies from 85% to 100% and is mainly related to tumor size, proximity to the disk, and the extent of retinal detachment (RD) at treatment time. The main cause of secondary enucleation is neovascular glaucoma.[3–5] Functional prognosis is often

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poor, with a final Snellen visual acuity of 20/100 in <50% of the patients.[6]

Sight-threatening tumor and radiation-induced complications include RD, maculopathy, papillopathy, cataract, glaucoma, vitreous hemorrhage (VH), and the recently described "toxic tumor syndrome."[7] Their occurrence depends primarily on tumor location and size. There are to date no precise data available on the surgical management of vitreoretinal (VR) complications after proton therapy. The aim of this study was therefore to assess the role of VR surgery in maximizing treatment outcome following complications after proton beam irradiation for UM.

Patients and Methods

We scanned retrospectively through the data of 1,005 consecutive patients who were treated for UM between January 2003 and August 2007. We identified and investigated 21 patients/21 eyes (2%) that had required VR surgery for a tumor or radiation-related complication. All patients were seen at the Ocular Oncology Unit of the Jules-Gonin Eye Hospital (Lausanne, Switzerland), and investigations and treatment included the following: confirmation of UM diagnosis, tantalum clip surgery, ophthalmic oncologic follow-up, and VR surgery. Proton beam radiotherapy was performed at the Paul Scherrer Institute (Villigen, Switzerland), according to a standard protocol prescribing 60 cobalt gray equivalent in 4 fractions on 4 consecutive days.[8] Pars plana vitrectomy (PPV) was performed according to the same standardized protocol as for eyes without an intraocular tumor by two surgeons (E.B. and T.J.W.). In the cases presenting an anterior ciliochoroidal tumor, the insertion of the PPV instruments was planned in a manner as to avoid the tumor site.

The mean age of our 21 patients (male to female ratio: 12:9) at the time of melanoma diagnosis was 53 years (range, 19–69 years). The main outcome measures were indications for surgery, time interval after proton therapy, and specific VR surgical modalities. We also analyzed clinical follow-up data, including Snellen best-corrected visual acuity, intraocular pressure (IOP), and final eye retention. The mean/median total follow-up time after irradiation was 43/43 months (range, 12–70 moths).

Results

Indications for VR surgery (Table 1) included VH (n = 13), rhegmatogenous RD (n = 1), combined VH with total serous RD (n = 1), vitritis of undetermined

Table 1. Indications for PPV After Proton Therapy for UM Were Correlated With Tumor Location, Defined as Posterior (Including Tumors With the Optic Nerve Receiving a Full-Dose Irradiation), Anterior (Including Tumors Involving the Ciliary Body), and Equatorial (Including the Remaining "Intermediate" Tumors)

	Indications for VR Surgery						Mean Snellen BCVA (Range)		
Tumor Location (Number With Retinal Invasion)	VH	Rhegmatogenous RD	Total Serous RD + VH	Vitritis	EMM	Total Number	At Diagnosis	Before Vitrectomy	After Vitrectomy
Posterior	9 (7)	1 (1)			1	11 (8)	20/32 (20/100–20/20)	20/1,000 (0–20/125)	20/200 (0–20/40)
Equatorial	2 (1)		1 (1)			3 (2)	20/32 (20/200–20/20)	20/2,000 (20/2,000–20/2,000)	20/400 (20/2,000–20/250)
Anterior	2 (1)			1	4	7 (1)	20/32 (20/2,000–20/20)	20/63 (20/200–20/40)	20/50 (20/200–20/25)
Total number	13 (9)	1 (1)	1 (1)	1	5	21 (11)			
Total average							20/32 (20/2,000–20/20)	20/200 (0–20/40)	20/100 (0–20/25)

Twelve of 21 patients presented a melanoma with retinal invasion (number between brackets). Posterior melanomas tended to be more complicated by vitreous hemorrhage, whereas anterior melanomas had more macular surgery. At the left, evolution of BCVA is correlated with tumor location, indicating that anterior melanomas tended to have a better visual outcome.

EMM, epimacular membrane; BCVA, best-corrected visual acuity.

origin (n = 1), and epimacular membrane (n = 5), 2 of which were associated with a lamellar macular hole. Indications for PPV were correlated with tumor location, revealing that posterior melanomas tended to lead more often to VH, whereas anterior melanomas were associated more often with macular surgery. From the 14 patients presenting a VH, 9 were presumed to come from tumor vessels or retinal vessels overlying a tumor with retinal invasion (of which the posterior melanomas were originally called "Knapp-Ronne" type melanoma[9]) (Figure 1), 3 were only associated with ischemic retinopathy, and 2 cases presented both complications. The former were treated with vitrectomy only, in one case with coagulation of visible tumor vessels, the others presumably having scarred after radiotherapy. The latter five cases, presenting proliferative radiation retinopathy, were at the end of their PPV treated with panretinal photocoagulation and one of them also with bevacizumab. This was the only case that ultimately developed neovascular glaucoma. Three of the five patients presenting VH and ischemia had at the same time rubeosis iridis without glaucoma, and in one of those three, the angle was involved.

The mean/median interval for the appearance of these complications following proton therapy and the subsequent VR surgery was 21/20 months (range, 4–45 months), with a mean/median follow-up time after PPV of 22/23 months (range, 2–56 months). Diagnosis was usually made after visual symptoms had been noticed by the patient, although some complications were only discovered during a routine oncologic follow-up examination.

Seven patients (33%) presented an anterior ciliochoroidal tumor. Table 2 summarizes the variations on standard PPV that were applied and the corresponding number of patients. One patient with an anterior melanoma and chronic inflammation had a second vitrectomy to remove membranes provoking pupillary seclusion around his lens implant. The three other patients, having had repeated PPV because of recurrent VH (average VH duration 4.5 months, range, 3–6 months), ultimately all developed phthisis

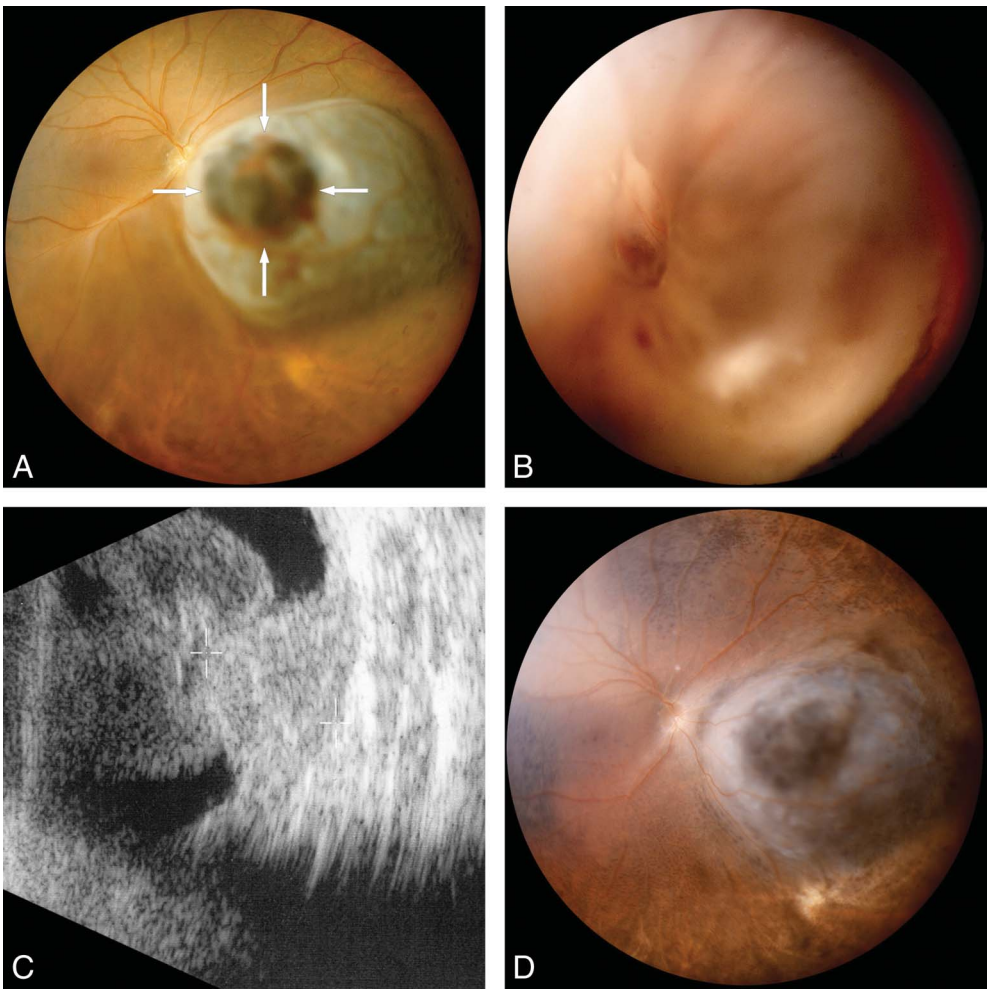

Fig. 1. Panoramic fundus pictures (Panoret camera) of a VH after proton therapy of a Knapp-Ronne type melanoma. **A.** A 55-year-old man had a parapapillary, nasal choroidal melanoma, presenting a hemorrhage at its surface and an invasion of the retina (white arrows). Despite the presence of a secondary serous RD, his best-corrected visual acuity (BCVA) was 20/25. He was treated with proton therapy. **B.** Six months later, his BCVA had dropped to light perception, related to a VH. **C.** On B-scan ultrasonography, the VH was shown to originate from the apex of the tumor, which had regressed from an original thickness of 8.4 mm to 7.8 mm. A simple uneventful vitrectomy was performed. **D.** Five months later, the tumor scar remained perfectly visible, with a BCVA at 20/400, related to retinal atrophy.

Table 2. Summarizes the Technical Variations on Standard PPV Applied During the First Vitrectomy and the Corresponding Number of Patients, Including the Number of Phacoemulsifications and Intravitreal Injections of Anti-VEFGs and Triamcinolone

First Vitrectomy Procedure	Number	+Phaco	+Bevacizumab	+Triamcinolone	2nd PPV	3rd PPV	Phthisis Bulbi
Simple vitrectomy	10	1		1	2		1
Vitrectomy with silicone tamponade	1						
Vitrectomy with air/gaz tamponnade	5						
Vitrectomy with laserphotocoagulation	4	1	1		1		2
Vitrectomy with air tamponnade and laserphotocoagulation	1	1		1	1	1	1
Total number	21	3	1	2	4	1	4

There were 4 patients requiring a second and one a third vitrectomy, 3 of whom developed phthisis bulbi.

bulbi. No internal tumor resection was performed in this series.

Pars plana vitrectomy and phacoemulsification were combined in 3 cases (14%) during the first and in 2 cases (10%) during the second vitrectomy, when lens opacities were too significant to allow correct fundus visualization.

Table 1 summarizes the evolution of mean Snellen best-corrected visual acuity from the time of UM diagnosis to before and after PPV, correlating best-corrected visual acuity with tumor location. Average visual acuity evolved from 20/32 (20/2,000–20/20) at the time of UM diagnosis till 20/200 (0–20/40) before and 20/100 (0–20/25) after vitrectomy. Main causes for loss of visual acuity at the time of UM diagnosis were exudative RD and lens opacities. In this study, visual acuity of 11 patients improved (52%), 5 patients remained stable (24%), and 5 patients deteriorated (24%) after PPV (Figure 2). Radiation retinopathy, macular atrophy, and lens opacities were the main causes preventing visual acuity from improving more than to a mean of 20/100 after PPV.

Figure 3 shows the IOP evolution at the time of UM diagnosis, before, immediately after, and 4 months after vitrectomy, with mean IOP (in red) evolving from 13 mmHg (±3 SD) at the time of diagnosis to 15 mmHg (±3 SD) preoperatively, 20 mmHg (±8 SD) postoperatively, and 15 mmHg (±3 SD) 4 months later. Seven patients presented a transient postoperative rise in IOP above 21 mmHg of which 6 could be normalized with medical treatment. One patient with an inferotemporal anterior ciliochoroidal melanoma received a Baerveldt tube into the anterior chamber 14 months after PPV for an epiretinal membrane related to a "toxic tumor syndrome"[7] with fibrosis and pupillary block.

Postoperative follow-up data showed that 4 of our 21 patients developed phthisis bulbi (19%), 3 of whom underwent secondary enucleation 33, 43, and 47 months after proton therapy (14%), respectively,

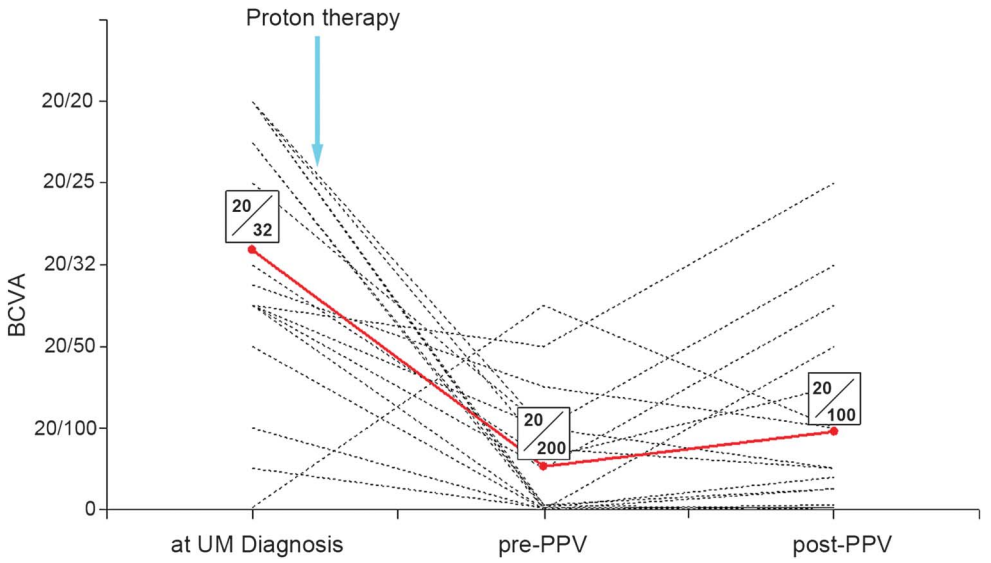

Fig. 2. Graphic illustrating the evolution of Snellen best-corrected visual acuity (BCVA) at the time of UM diagnosis as well as before and after PPV for each of the 21 operated patients with mean visual acuity (red line) evolving from 20/32, to 20/200 before, and 20/100 after PPV, respectively. The only patient with an inversed BCVA curve evolving from hand movements at diagnosis to 20/40 before and 20/100 after PPV had an anterior UM complicated by a dense VH at presentation, and he underwent PPV when the hemorrhage had already partially resolved. At his postoperative control examination, his secondary lens opacities had so much increased that his BCVA was lower than before PPV.

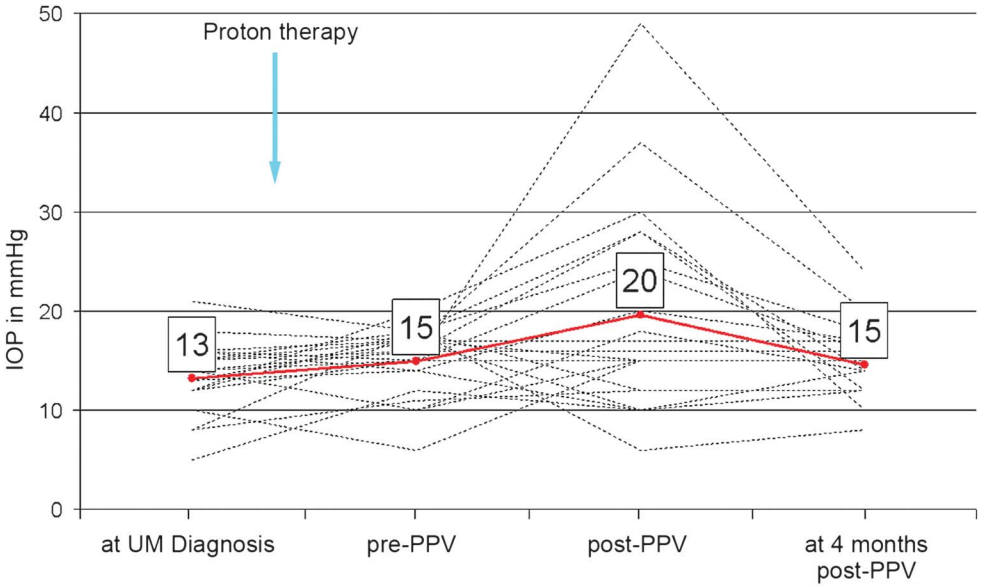

Fig. 3. Graphic showing IOP evolution at the time of UM diagnosis, before, immediately after, and 4 months after PPV, with a mean IOP (red line) of 13, 15, 20, and 15 mmHg, respectively.

and the fourth patient wearing a cosmetic contact lens. Two belonged to the 7 patients with a postoperative rise in IOP. All 4 were women who had undergone vitrectomy, respectively, 6, 3, 5, and 3 months after developing a dense VH. One was related to an anterior tumor recurrence of an equatorial melanoma, treated a second time by proton therapy. The other 3 patients presented a posterior melanoma complicated by uncontrollable proliferative radiation retinopathy, with recurrent VHs, multiple interventions, and one of whom developed neovascular glaucoma. Three of 21 patients presented liver metastases at 11, 24, and 54 months after proton therapy.

Discussion

This study assesses the role of VR surgery in maximizing treatment outcome following complications after proton beam irradiation for UM. Analyzing the indications, surgical technique, results, and safety of VR surgery in the management of these complications, our study of 1,005 consecutive patients, treated between January 2003 and August 2007, showed that only 21 patients (2%) underwent VR surgery, illustrating why very few articles related to the subject exist in the literature. It is interesting to note that the majority of publications on this subject are concerned with complications after plaque radiotherapy or other conservative treatments. In contrast, data on the surgical management of complications after proton therapy are scarce.

Haimovici described 10 patients with UM presenting rhegmatogenous RD simultaneously to (n = 4) or after (n = 6) radiation therapy (protons to iodine plaque ratio: 7:3). Only 1 of 10 had PPV and consequently proton therapy, and the authors concluded that because of the rare occurrence of rhegmatogenous RD in patients with UM, the development of retinal breaks and detachment was unlikely to be related to the tumor or its treatment.[10] The fact that our series contains only one similar case confirms that impression. In 2 recent publications, which addressed the role of PPV performed on patients with UM after plaque radiotherapy, 1 study showed that 74 patients of 3,707 (2%) had undergone vitrectomy because of VH, leading to complete resolution in 53 cases (72%).[11] The other study demonstrated that 29 patients of 3,841 treated UM eyes (0.8%) underwent PPV because of proliferative radiation retinopathy.[12] However, no further details on these "PPV subgroups" are reported. In a case series of 9 treated posterior UM patients (7 with plaque and 2 with transpupillary thermotherapy), Foster et al[13] report a similar indication profile as ours: VH (n = 5), macular surgery (n = 3), and rhegmatogenous RD (n = 1), with vitrectomy being performed at a mean interval of 24.7 months (range, 7–47 months) after melanoma treatment, which is about 4 months longer than our mean interval.

In general, the longer the interval since proton therapy, the tougher the vitreous had become to cut during PPV, although it is difficult to translate this observation into statistics. As a consequence, whenever VR surgery now becomes indicated, we tend to intervene as soon as the tumor is locally controlled. In 5 cases, we enlarged our indication and performed simultaneous cataract surgery to reestablish transparency of the visual axis. With a radiation threshold as

low as 0.5 Gy for the induction of cataract to the human lens, this is not surprising.[14]

Anti–vascular endothelial growth factors were scarcely used in this case series, as most of these cases were treated at a time when potential indications for this kind of treatment were only slowly emerging. Although one might speculate that increased use of anti–vascular endothelial growth factors could potentially prevent VH secondary to proliferative radiation retinopathy in the future, it is more difficult to imagine how these treatments will significantly reduce the apparent mechanical effect of a rupture in the retinal barrier. In this context, it is remarkable to note that in our series 11 of 14 cases with VH requiring PPV also presented a tumor breakthrough in the retina, whereas melanomas with retinal invasion were reported to be present in only 7% of a control UM population.[11]

Because of the multitude of factors influencing final visual acuity in UM eyes treated with radiotherapy and consequently PPV, it is difficult to draw universal conclusions from a series of 21 eyes. Initial visual acuity, tumor size and location, extent and duration of the serous RD, radiation retinopathy, and/or neuropathy are all factors that, on top of the other indications for PPV (Table 1), will influence visual acuity after PPV. However, the fact that average visual acuity improved indicates that PPV had been justified in the majority of our cases. Overall, anterior melanomas appear to have a better visual outcome after PPV than posterior melanomas because in the former, the posterior pole has not been irradiated.

Regarding safety of PPV after plaque-irradiated posterior UM, Bansal et al[15] did not report an increased risk of intraocular, local, orbital, or systemic dissemination of the tumor. Our series on PPV after proton therapy indicates that postoperative IOP requires attention, without being a permanent problem in most cases. With a local tumor control after proton therapy of 98.8%,[8] tumor recurrence at the entry ports does not appear to be a problem, in contrast to patients undergoing PPV before tumor treatment.[16] However, the risk does need to be taken into consideration in those cases where ophthalmoscopic or ultrasonographic tumor regression is not convincing. The only case in this series, in which tumor recurrence had been suspected before PPV, was therefore immediately irradiated after surgery.

An interesting observation is that this series appears to indicate that an eye with UM can only support a limited number of surgical procedures before going into phthisis bulbi. Of the 17 eyes treated once with proton therapy, followed by one PPV, 16 eyes survived, whereas of the 4 eyes having had more than one PPV, only one eye, containing an anterior melanoma, did not go into phthisis bulbi.

The fact that 3 patients developed distant metastases is compatible with our overall Kaplan–Meyer survival curve of UM treated with proton therapy.[8]

In conclusion, PPV after proton therapy is rarely indicated (2% in our series). It is a safe procedure and plays a role on 3 levels in the follow-up of patients with UM. First, vitrectomy facilitates tumor surveillance through reestablishing transparency of the visual axis. Second, PPV increases the chances of eye retention as it allows both panretinal photocoagulation to avoid neovascular glaucoma and surgical repair of a rhegmatogenous detachment. And finally, macular surgery or removal of a VH will increase visual acuity, especially when the posterior pole has not been irradiated. Vitreoretinal surgery does thus play an important role in maximizing treatment outcome following complications after proton therapy for UM.

Key words: complications, intraocular pressure, melanoma, proton therapy, radiotherapy, uveal melanoma, visual acuity, vitreoretinal surgery, vitreous hemorrhage.

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