Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original Article

Local tumour control and radiation side effects for fractionated stereotactic photon beam radiotherapy compared to proton beam radiotherapy in uveal melanoma

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ARTICLE INFO

ABSTRACT

Purpose: To compare the adverse side effects of fractionated stereotactic photon beam radiotherapy (fSRT) with proton beam radiotherapy (PBR) in patients with uveal melanoma (UM).

Methods: A retrospective study investigating 306 UM patients treated with fSRT (N=153) by the Rotterdam Ocular Melanoma Study group (ROMS), The Netherlands, between 1999–2014 or with PBR (N=153) at the Royal Liverpool University Hospital and the Clatterbridge Cancer Centre, Bebington, United Kingdom, between 1993–2014. The tumours treated with fSRT were matched with tumours treated with PBR based on sex, left or right eye, TNM classification, posterior margin ≤ or > 3mm of the fovea and of the optic disc.

Results: The five-year actuarial rates of tumour recurrence were 4.5% for fSRT and 6.1% for PBR. For fSRT and PBR, the five-year actuarial rates of maculopathy were 14.9% and 12.4%, and for vitreous haemorrhage were 29.4% and 4.7%, respectively. Only vitreous haemorrhage (HR: 0.19, 95% CI: 0.07–0.56) was more common after fSRT compared to PBR. Overall, larger tumours were risk factors for maculopathy and secondary enucleation.

Conclusions: Both treatments have excellent local tumour control. In matched groups, vitreous haemorrhage was the only adverse side effect showing a significant difference between groups.

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Fractionated stereotactic photon beam radiotherapy (fSRT) and proton beam radiotherapy (PBR) are both eye-sparing forms of radiotherapy to treat uveal melanoma (UM). These therapeutic modalities provide excellent tumour-control while conserving the eye, usually with useful vision [1–3]. Several studies have concluded that radiotherapy is as effective as enucleation concerning metastatic disease and death [4,5]. Therefore, enucleation is now reserved for eyes with a tumour deemed too large for radiotherapy [6].

FSRT is suitable for small- and medium-sized melanomas up to approximately 12 mm in thickness and a diameter less than 16 mm. An advantage of fSRT over PBR is that it does not require surgical insertion of fiducial markers for tumour localization and that it is more readily available than PBR. Reported complications of fSRT are neovascular glaucoma, cataract, vitreous haemorrhage, optic neuropathy, maculopathy, retinopathy, and secondary enucleation is required in 3–16% patients [1,7–9]. Local tumour control rates have been reported as high as 96–100% after fSRT [1,7,8,10].

PBR is available in a growing number of centres in Europe. Some ocular oncologists administer this treatment to all patients, while others reserve it for patients whose tumour is considered unsuitable for brachytherapy. With PBR, radiation is delivered homogenously to the tumour with the dose rapidly falling to zero distal to the tumour [11]. PBR is generally reserved for tumours not exceeding 20 mm in diameter and/or 12 mm in thickness, so as to avoid severe exudative and neovascular complications resulting in a blind and painful eye ('toxic tumour syndrome') [12]. The reported local tumour control rates are 96% at 5 years and 94–95% at 10 years after PBR [13–15]. Secondary enucleation rates

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are 5–16% due to local recurrence or toxic tumour syndrome [14,16,17]. Ocular morbidity can also occur as a result of collateral damage to lens, optic nerve, macula and development of glaucoma or vitreous haemorrhage [15,18].

Although, outcomes of fSRT and PBR for UM have been evaluated, fSRT and PBR have not previously been compared with respect to ocular outcomes of matched data in a large study population [19]. As treatment indications, tumour control rates and adverse side effects overlap between fSRT and PBR, we conducted a retrospective study to compare fSRT with PBR for UM with respect to local tumour control and ocular morbidity.

Materials and methods

A retrospective study was conducted in 163 patients with choroidal and/or ciliary body UM treated with fSRT by the Rotterdam Ocular Melanoma Study group (ROMS), The Netherlands, between December 1999 and January 2014, and 912 patients treated with PBR in the Royal Liverpool University Hospital, United Kingdom, between January 1993 and January 2014 in Liverpool. In order to assess the differences in survival and to study the complications between two treatments (fSRT and PBR) for UM, we matched both cohorts of each 153 patients. The local medical ethical committees of both institutes approved the study protocol. Informed consent was obtained prior to treatment and the study was performed according to guidelines of the Declaration of Helsinki.

Patients were diagnosed with UM by ophthalmic examination and underwent full systemic examination. The fSRT patient data were collected in a customised database application based on File-maker 16 (FileMaker Inc, Santa Clara, California, United States). All clinical data and follow-up data were collected for PBR and fSRT patients. UM were categorised according to the TNM classification, 8th edition [20]. This classification is the same as the 8th edition of the AJCC Classification of posterior uveal melanoma, T category [21]. The following adverse outcomes were documented: local recurrence, neovascular glaucoma, vitreous haemorrhage, optic neuropathy, maculopathy and enucleation. Neovascular glaucoma presented with open or closed angle, depending on the extent of neovascularization. Optic neuropathy was defined as visual loss caused by collateral optic nerve damage and diminished colour vision (tested with Ishihara plates) with or without an afferent pupillary defect. Maculopathy was diagnosed by the presence of haemorrhages, hard exudates, and (non)-cystoid edema, which was identified by ophthalmoscopy, optical coherence tomography or fluorescein angiography when available. We excluded cystoid macula edema developing after cataract extraction. Local recurrence of UM was determined clinically with or without ultrasonography and by sequential fundus photography.

The fSRT and PBR protocols have been described previously [1,3]. The stereotactic radiation dose is given in 5 fractions of 10 Gray (total 50 Gray), at the 80% isodose over five consecutive days and the proton radiation dose is 53 proton Gray in 4, daily fractions.

Statistical analyses

Matching was based on the following variables: age, sex, TNM-classification, tumour distances to the fovea and optic disc. For age we applied a window of 5 years, however the other variables required an exact match. As a consequence, 10 of the 163 patients treated with fSRT could not be matched and were excluded; this resulted in 153 fSRT and 153 PBR patients. Differences in complications (i.e., after treatment) between patients treated with fSRT and PBR were analysed using independent t-tests and Chi-square statistics.

The risk of a complication caused by a tumour characteristic was analysed by applying Cox proportional hazard models in the unmatched complete dataset to calculate hazard ratios (HR) with corresponding 95% confidence intervals (CI). Follow-up duration, used as the time variable, was measured from the date of treatment to the latest visit. The models were adjusted for age, sex, and often for type of treatment (i.e., fSRT or PBR). The risk of a complication caused by treatment (fSRT of PBR) was analysed in a matched dataset [N = 306] by applying "non-conditional" and conditional Cox proportional hazard models. Follow-up duration was used as the time variable.

Cumulative incidence analyses were performed on the matched dataset and the log-rank test was used to assess statistical significance between the curves. Actuarial rates were calculated at 1, 3, 5, and 10 years of follow-up. We used complete case analysis and considered p-value ≤ 0.05 as statistically significant. All statistical analyses were performed using IBM SPSS Statistics version 22.0 for Windows (SPSS inc., Chicago, IL, USA) and R statistical package version 3.6.1 for Mac (http://www.r-project.org).

Results

Our study cohort included, 153 UM patients of whom were treated with fSRT and 153 with PBR (Table 1). The two treatment groups were matched, based on the significant differences in tumour characteristics between the fSRT and PBR group.

The median follow-up times of the fSRT and PBR groups were 58.5 months (IQR: 26.1–95.2 months) and 40.0 months (IQR: 19.1–70.0 months) respectively ($p < 0.001$). The 5-year local tumour control rates were 96.1% for fSRT and 96.1% for PBR. At the end of the study, the local tumour control was 94.1% after fSRT with 15 years of follow-up and 95.4% after PBR with 15 years (and 20 years) of follow-up, respectively ($p = 0.798$; Table 1). The actuarial rates of tumour recurrence are presented in Table 2. The median interval between fSRT and tumour recurrence ($N = 9$) was 19.8 months (IQR: 14.0–72.7 months). The median interval between PBR and tumour recurrence ($N = 7$) was 29.4 months (IQR: 15.3–36.7 months). Three tumours treated with fSRT developed a recurrence after more than five years (i.e., after 5.3, 6.8 and 7.0 years). These were T3, T2 and T1 class tumours of the TNM classification respectively. One T1 tumour treated with PBR developed a recurrence after more than five years (i.e., after 9.2 years). However, greater tumour size and tumour location (≤ 3 mm to the fovea and ≤ 3 mm to the optic disc) were not associated with a higher incidence of tumour recurrences irrespective of treatment (Table 3). Furthermore, local tumour recurrence was not significant associated with a type of treatment (Table 4). Secondary enucleation for tumour recurrence was performed in 8 (5.3%) patients after fSRT and 3 (2.0%) after PBR. One fSRT patient with a tumour recurrence received additional fSRT. Four PBR patients with tumour recurrence received additional treatment, such as trans pupillary thermotherapy, iodine plaque radiotherapy, ruthenium plaque radiotherapy or adjunctive PBR. The 5-year enucleation rate is higher in patients treated with fSRT (12.4%) than in patients treated with PBR (5.9%). Multivariate analyses showed in the study population ($N = 306$) that the incidence of vitreous haemorrhages (VH) was significantly higher after fSRT than PBR (HR: 0.19; 95% CI 0.07–0.56) ($p < 0.0001$) (Table 4 and Fig. 1). Fig. 1 shows the cumulative incidence of all complications and complications during follow-up.

Regardless of treatment, neovascular glaucoma was 2.0 times significantly more common in tumours that were further than 3 mm of the fovea (Table 3). The rate of neovascular glaucoma was higher in fSRT patients (17.6%) than in PBR patients (8.5%) ($p = 0.027$). The median time to develop neovascular glaucoma

Table 1

General characteristics of the study population and complications after treatment with fSRT or PBR.

	fSRT (N = 153)	PBR (N = 153)	P-value
Age (mean ± SD) in years	61.8 ± 11.1	61.6 ± 10.6	
Female (N [%])	72 (47.1)	72 (47.1)	
Tumour characteristics			
TNM class (N [%])			
1	34 (22.2)	34 (22.2)	
2	64 (41.8)	64 (41.8)	
3	55 (35.9)	55 (35.9)	
4	0 (0.0)	0 (0.0)	
Margin to the fovea ≤ 3 mm (N [%])	88 (57.5)	88 (57.5)	
Margin to the optic disc ≤ 3 mm (N [%])	77 (50.3)	77 (50.3)	
Complications			
Recurrence (N [%])	9 (5.9)	7 (4.6)	0.798
Neovascular glaucoma (N [%])	27 (17.6)	13 (8.5)	0.027
Vitreous haemorrhage (N [%])	28 (18.3)	5 (3.3)	<0.001
Optic neuropathy (N [%])	11 (7.2)	14 (9.2)	0.677
Maculopathy (N [%])	17 (11.1)	19 (12.4)	0.859

fSRT = fractionated stereotactic photon beam radiotherapy.
PBR = proton beam radiotherapy.
SD = standard deviation.

was 20.6 months for fSRT patients (IQR: 13.3–33.3 months) and 26.5 months for PBR patients (IQR: 13.2–32.2 months). The actuarial rates of neovascular glaucoma are presented in Table 2. After developing neovascular glaucoma, enucleation was required in 4 and 13 patients after PBR and fSRT respectively.

More fSRT patients (18.3%) developed a VH than PBR patients (3.3%) (p < 0.001) (Table 1). VH was not associated with tumour characteristics for the total study population (Table 3). We found that patients treated with fSRT had significant greater risk of VH compared to PBR (HR 0.19; 95% CI 0.07–0.56) (Table 4). The median time to develop a VH was 24.8 months for fSRT patients (IQR: 9.6–33.4 months) and 11.6 months for PBR patients (IQR: 4.7–35.0 months). Eleven of the 35 patients treated with fSRT had a VH at baseline. Of those 11 patients, four VH resolved and seven VH remained. After we excluded the seven fSRT patients with a remaining VH from baseline, we found 28 VH that developed after treatment (HR 0.25; 95% CI 0.08–0.75, p < 0.013). The actuarial rates of VH are presented in Table 2.

Optic neuropathy developed in 7.2% and 9.2% of patients treated with fSRT and PBR, respectively (p = 0.677) (Table 1). Tumours extending within 3 mm of the optic disc were significantly associated with optic neuropathy (HR: 0.24, 95% CI 0.09–0.62) (Table 3). There was no difference in the rate of optic neuropathy between fSRT and PBR (Table 4). The median time to optic neuropathy was 17.6 months in fSRT patients (IQR: 12.3–26.4 months) and

Table 3

The risk of a complication caused by a tumour characteristic in the study population (N = 306). Presented as hazard ratio with corresponding 95% CI*.

Reference level	TNM-classification 1	Margin to the fovea ≤ 3 mm	Margin to the optic disc ≤ 3 mm
Recurrence	1.69 (0.81–3.51)	1.36 (0.50–3.70)	2.46 (0.77–7.88)
Neovascular glaucoma	1.50 (1.00–2.34)	2.04 (1.07–3.90)#	1.40 (0.72–2.70)
Vitreous haemorrhage	0.94 (0.62–1.41)	0.93 (0.48–1.78)	0.83 (0.43–1.59)
Optic neuropathy	1.31 (0.77–2.23)	0.72 (0.31–1.68)	0.24 (0.09–0.62)#
Maculopathy	1.99 (1.21–3.26)#	0.96 (0.48–1.91)	1.52 (0.75–3.09)
Enucleation	1.91 (1.14–3.22)#	1.00 (0.50–2.01)	1.20 (0.59–2.44)

CI = confidence interval.
* = adjusted for age and gender.
# = Significant values.

Table 4

The risk of a complication caused by treatment (fSRT or PBR; fSRT served as the reference) in the matched study population. Presented as hazard ratio with corresponding 95% CI*.

	Matched study population (N = 306)
Recurrence	1.50 (0.42–5.32)
Neovascular glaucoma	0.50 (0.23–1.11)
Vitreous haemorrhage	0.19 (0.07–0.56)#
Optic neuropathy	1.67 (0.61–4.59)
Maculopathy	1.18 (0.53–2.64)
Enucleation	0.47 (0.19–1.15)

fSRT = fractionated stereotactic photon beam radiotherapy.
PBR = proton beam radiotherapy.
CI = confidence interval.
* = Adjusted for age, gender, TNM-classification, margin to the fovea, and margin to the optic disc.
# = Significant values.

18.8 months in PBR patients (IQR: 11.7–28.3 months). The actuarial rates of optic neuropathy are presented in Table 2.

Maculopathy occurred in 11.1% and 12.4% of patients after fSRT and PBR, respectively (Table 1). T2 and T3 tumours were 2.0 times more likely to develop maculopathy compared to T1 tumours (Table 3). There was no difference in the incidence of maculopathy (Table 4). The median time to maculopathy was 24.3 months in fSRT patients (IQR: 10.7–49.0 months) and 19.4 months in PBR patients (IQR: 14.2–61.0 months). The actuarial rates of maculopathy after fSRT and PBR are presented in Table 2.

Discussion

To our knowledge, this is the first study to compare outcome of fSRT with PBR as a treatment for UM. We found that high 5-year local tumour control rates were achieved by both methods of

Table 2

Actuarial rates (%) of complications at 1, 3, 5, and 10 years of follow-up for fSRT and PBR.

	1 year	3 years	5 years	10 year
fSRT				
Recurrence	0.65	3.49	4.52	9.84
Neovascular glaucoma	3.33	15.65	20.22	24.54
Vitreous haemorrhage	9.29	22.21	29.42	29.42
Optic neuropathy	1.32	7.50	8.52	8.52
Maculopathy	2.65	8.85	14.94	14.94
PBR				
Recurrence	0.00	3.62	6.06	11.93
Neovascular glaucoma	1.43	10.24	11.58	14.04
Vitreous haemorrhage	2.25	3.29	4.69	4.69
Optic neuropathy	3.08	11.91	13.15	13.15
Maculopathy	2.93	10.99	12.43	30.37

fSRT = fractionated stereotactic photon beam radiotherapy.
PBR = proton beam radiotherapy.

radiotherapy treatment (i.e., after 96.1% in PBR patients and 96.1% in fSRT patients). In a matched study population (N = 306), the most common complications were maculopathy (12.4%) after PBR and vitreous haemorrhage (18.3%) after fSRT (p < 0.001) (Table 1 and 4). Maculopathy and enucleation were significantly and neovascular glaucoma was nearly significant associated with large tumour size. As expected, with tumour proximity to optic disc more optic neuropathy was observed. Neovascular glaucoma was associated with tumours located further than 3 mm of the fovea.

A weakness of the study is that fSRT and PBR were performed in different centres, which may not have measured baseline features and outcomes in the same way. It would have been ideal if both centres had randomised patients, however, neither centre had access to both forms of radiotherapy. As in other retrospective studies, our study may have also suffered from bias caused by missing data and loss of patients from follow-up. In order to compare the different complications of both treatments we performed analyses on matched data to have equal groups regarding: sex, age and tumour characteristics (TNM-classification, tumour distances to fovea and optic disc).

An excellent 5-year tumour control rate was achieved with either treatment and was comparable to previous studies [15,19,22,23]. When we analysed the matched population only VH was significant more common after fSRT than after PBR (Table 4). Of note, 11 of the 35 patients treated with fSRT already had VH at baseline; however, this had no influence on the development of new VH after treatment. PBR patients had no VH at baseline, as good tumour visualization was needed to perform clip surgery prior to PBR. We are unable to explain why VH was more
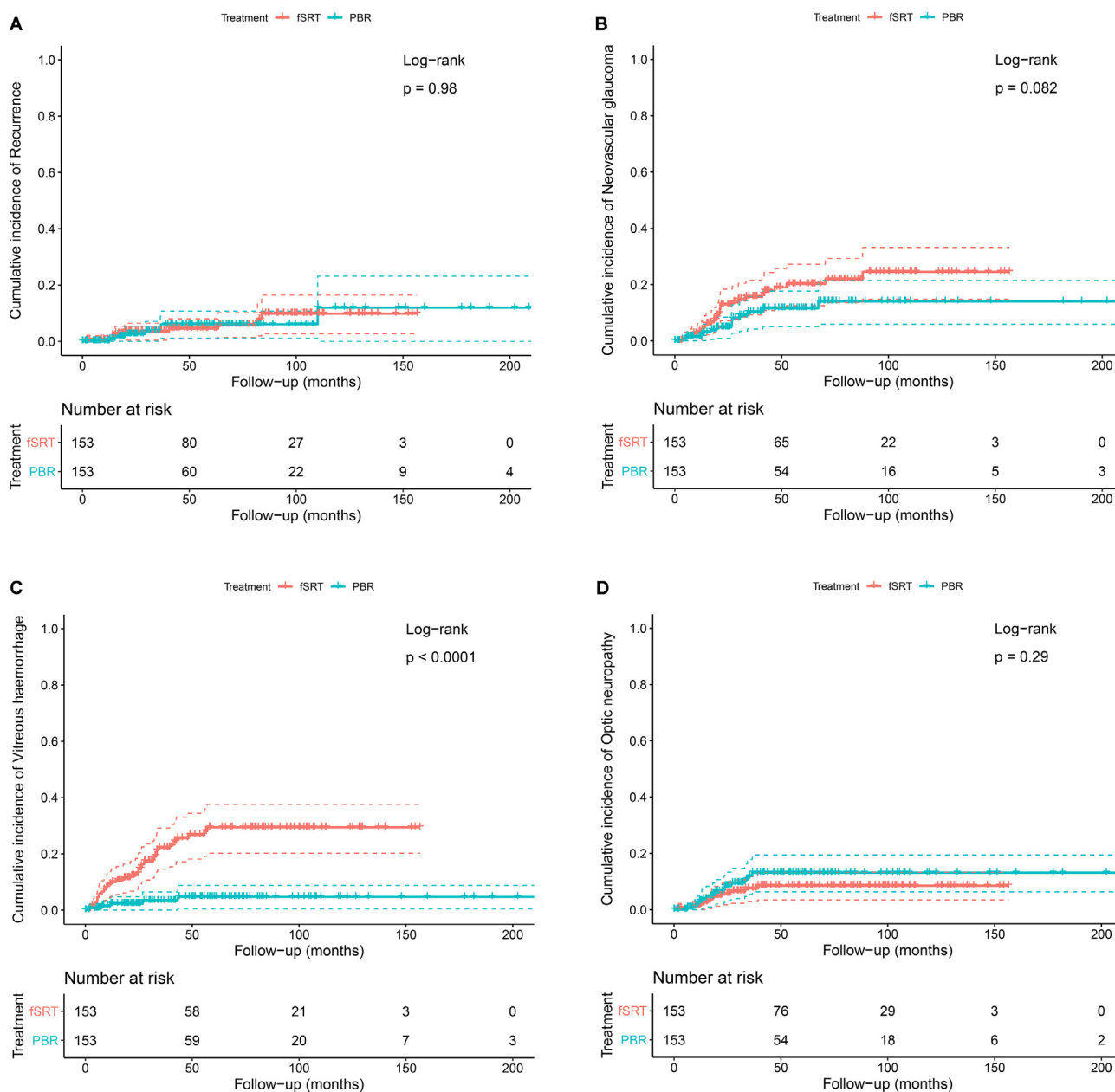

Fig. 1. Cumulative incidence analyses with log-rank test on treatment (i.e., fractionated stereotactic photon beam radiotherapy [fSRT] and proton beam radiotherapy [PBR]) for each complication (i.e., recurrence [A], neovascular glaucoma [B], vitreous haemorrhage [C], optic neuropathy [D], maculopathy [E], and enucleation [F]). Censored patients are denoted by vertical tick marks. The dashed lines around the curve represents the confidence intervals for the point estimates of the cumulative incidence curve.
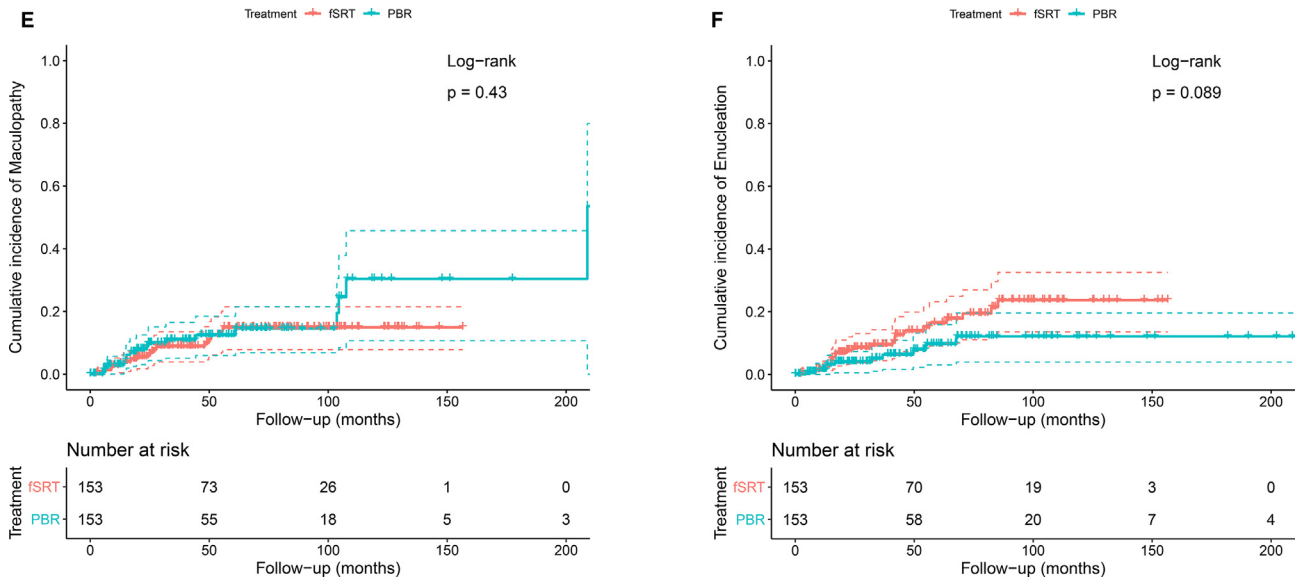
Fig. 1 (*continued*)

common after fSRT than after PBR. This difference may have occurred by chance. In any case, this was not a serious complication as it could easily be treated with vitrectomy. Tumour necrosis, proliferative radiation retinopathy and posterior vitreous detachment have been suggested as a presumed aetiology for VH [24]. In our study we did not take into account the regression rate of the tumour, which might reflect the amount of tumour necrosis and might explain part of the VH. Proliferative radiation retinopathy is not specifically observed within this group of patients. Another study after plaque radiotherapy found underlying diabetic retinopathy, closer tumour proximity to the disc, greater tumour thickness, and break in the Bruch membrane as predictive factors for a VH [24]. In our study we also did not record break of Bruch membrane routinely and did not have complete data on diabetes mellitus status; however, we did not find an effect of tumours closer to optic nerve or tumour thickness as risk factors for vitreous haemorrhages (Table 3).

When considering complications of both treatments, we observed that the largest tumour diameter is an important risk factor for adverse outcome. In our population larger tumours required more often an enucleation. This is in contrast to Yazici et al. who found no differences in enucleation rates between eyes with large and small/medium tumours (p = 0.2) after stereotactic radiosurgery and fSRT [9]. In another study large T3 and T4 tumours treated with PBR, 19.5% of the tumours were enucleated, which was higher than in our cohort [25].

We recorded neovascular glaucoma in 8.5% of the PBR-treated patients and 17.6 % in fSRT patients. Most proton beam centres have reported higher percentages of neovascular glaucoma ranging from 12.7% to 47% of the patients [26,27]. FSRT centres report for 24.5–42% neovascula glaucoma [7,22]. A point of attention is that almost 60% of the current study population was in the era before anti-vascular endothelial growth factor (VEGF) intravitreal injections, which could explain the high percentage of neovascular glaucoma in both groups. And with the current treatment options with anti-VEGF we may expect less neovascular glaucoma, however, this has to be evaluated in a prospective study [28].

A tumour within 3 mm of the optic nerve would result in a high dose of radiation of the optic nerve and consequently would lead to a decrease in visual acuity. Juxtapapillary UM are a risk factor for developing optic neuropathy (Table 3). And for those tumours, percentages of optic neuropathy as high as 68% were observed [29]. In tumours treated with fSRT optic neuropathy occurs in 61.5% of patients [22]. In PBR treated eyes comparable and higher percentages (14–68%) of optic neuropathy were found [19,30]. This is in contrast with a study where more than half of their patients had juxtapapillary T3 and T4 UM and only 8.3% developed optic neuropathy [25]. In the end, however, there is no standardized definition of optic neuropathy resulting in different definitions used by different studies.

Maculopathy is another vision threatening complication after radiation. In our population, 57.5% of the UM were closer than 3 mm to the fovea. Despite that, only 11.1% of the fSRT patients and 12.4% of the PBR patients developed a maculopathy and this was not related to the tumour distance to the fovea in the current study. Interestingly, as also observed in other studies, maculopathy occurred more often with an increase in the size of the tumour, history of diabetes mellitus and presence of preoperative subretinal fluid [30,31]. Guyer et al. observed in 89% of the paramacular tumours maculopathy after PBR [32]. After radiation, high doses of VEGF are found in the eye [33]. The treatment of anti- VEGF intravitreal injections seems to limit visual loss associated with radiation maculopathy, although this was analysed after a different form of radiation treatment with plaque therapy [28,34]. Shields et al. observed a decrease in radiation maculopathy with preservation of visual acuity after prophylactic Bevacizumab every four months [28].

An enucleation was performed more often in eyes with a larger tumour. This might be explained by the fact that patients with peripheral tumours often present rather late and may have consequently a larger tumour [35]. The 5-year overall enucleation rate is higher in patients treated with fSRT (12.4%) than in patients treated with PBR (5.9%). However, there is no significant difference between treatments in the risk of enucleating the eye. When comparing different studies, it is important to keep in mind that the indication of a treatment can differ, as fSRT cannot be performed for small tumours whereas PBR can. In other centers where fSRT is performed, the percentages of enucleation were 13.2–17% [22,36]. The same counts for UM treated with PBR, where 7.7% of the eyes were enucleated after 5 years [15].

As the local control in UM patients is high regardless of treatment, the emphasis must lie on limiting the ocular morbidity for patients' quality of life [37]. Moreover, knowledge on the occurrence of complications can help caregivers to apply personalized treatment.

In summary, it can be stated that both treatment options are comparable in their outcome, although fSRT patients developed more vitreous haemorrhages. This is a complication that can be managed very well surgically. As observed in other studies juxta-papillary location has a higher risk of developing optic neuropathy, irrespective of the type of radiation. Overall, in our population, the risk factor for maculopathy and enucleation was the increase in tumour size. A tumour located more than 3 mm from the fovea is more prone to develop neovascular glaucoma.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

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