

Proton beam radiation for iris melanoma: case series and review of literature

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ABSTRACT

Objective Purpose of this study is to analyse the visual outcomes, the complication and eye retention rate as well as tumour control data of patients treated with proton beam radiation therapy (PBRT) for iris melanoma.

Methods Retrospective case series and review based on patients' records. All tumours were categorised according to the American Joint Committee of Cancer staging criteria for primary iris melanoma and underwent either sectorial or whole anterior segment PBRT.

Results Thirteen cases were identified of which five received PBRT of the whole anterior segment and eight received sectorial PBRT. Local tumour control after a mean follow-up of 25 months was 92%. Complications after PBRT included cataract (46%), secondary glaucoma (31%), superficial keratitis (15%) and madarosis (8%). Complications were more common in patients necessitating irradiation of the entire anterior segment than in patients which received sectorial irradiation. Eye retention was achieved in all cases. No statistically significant difference in the mean best corrected visual acuity (BCVA) and intraocular pressure (IOP) was found before and after treatment. Comparison of mean BCVA and IOP between different treatment groups (complete anterior segment vs sectorial irradiation) at the last follow-up visit were also not significantly different. No patient developed metastatic disease during follow-up.

Conclusion PBRT is a safe and vision preserving therapeutic modality for iris melanoma. Complete irradiation of the anterior segment is associated with higher complication rates.

INTRODUCTION

Uveal melanoma is the most common primary intraocular malignant neoplasia in adults. It arises from melanocytes of the choroid plexus, ciliary body and iris.¹ Approximately 8% of uveal melanomas are located in the iris.² Bright skin colour, bright iris colour, numerous cutaneous nevi, congenital ocular melanocytosis, oculodermal melanocytosis (nevus of Ota), uveal melanocytoma, dysplastic cutaneous nevi, familiar cutaneous melanoma and neurofibromatosis type 1 are predisposing factors for the development of iris melanoma.³

Iris melanomas carry a much better prognosis than ciliary body or choroidal

Key messages

What is already known about this subject?

- ▶ Proton beam radiation therapy is an established treatment method for iris melanoma concerning local tumour control and eye retention rate.

What are the new findings?

- ▶ Complications are limited and early treatment results in preservation of visual acuity.
- ▶ Irradiation of the entire anterior segment carries a higher complication rate compared with sectorial irradiation.
- ▶ No significant difference was found between the different treatment strategy groups concerning final intraocular pressure.

How might these results change the focus of research or clinical practice?

- ▶ Although serious complications are seldom, early recognition and treatment can result in excellent visual acuity for the patients.
- ▶ As secondary glaucoma after complete proton beam radiation therapy turned out to be quite common, early recognition of this complication and sufficient treatment can result in an excellent visual outcome.

melanomas.⁴ A published study of Lumbroso-Le Rouic *et al* showed no metastatic disease or fatal courses for patients suffering of iris melanoma excluding ciliary body melanomas with iris involvement or tumours with extrascleral invasion (n=21, median follow-up time 33 months (8–72 months)).⁵

Treatment options for iris melanoma include iridectomy for small circumscribed tumours, Naumann block excision technique for iridociliary body melanoma, iridocyclectomy in the case of limited ciliary body involvement and radiotherapy (brachytherapy, proton beam and stereotactic radiation therapy). Enucleation should be performed in diffuse growing or diffusely relapsing tumours if radiotherapy is not possible.^{6–10}

MATERIALS AND METHODS

In this retrospective study, we analysed 13 patients with iris melanoma, iris melanoma

Table 1 Iris melanoma based on AJCC eighth edition classification

T category	T criteria	(n)
T1	Tumour limited to the iris	3
T1a	Tumour limited to the iris, not more than three clock hours in size	3
T1b	Tumour limited to the iris, more than three clock hours in size	2
T1c	Tumour limited to the iris with secondary glaucoma	
T2	Tumour confluent with or extending into the ciliary body, choroid, or both	2
T2a	Tumour confluent with or extending into the ciliary body, without secondary glaucoma	1
T2b	Tumour confluent with or extending into the ciliary body and choroid, without secondary glaucoma	1
T2c	Tumour confluent with or extending into the ciliary body, choroid, or both with secondary glaucoma	
T3	Tumour confluent with or extending into the ciliary body, choroid, or both, with scleral extension	
T4	Tumour with extrascleral extension	1
T4a	Tumour with extrascleral extension ≤ 5 mm in largest diameter	0
T4b	Tumour with extrascleral extension > 5 mm in largest diameter	
Total		13

► The corresponding number of patients (n) of our series is documented in the right column

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AJCC, American Joint Committee of Cancer.

extending into the ciliary body or irido-ciliary ring tumour, that is, with 360° angle invasion, which were treated at the Department of Ophthalmology-Innsbruck Medical University, in the period from January 2008 to May 2019. Data acquisition was performed in an anonymised way from patient-file data. Patient demographics, melanoma type, clinical features, functional and visual outcomes after therapy were evaluated.

Tumours were classified concerning their location according to the revised classification for primary iris melanoma of the American Joint Committee on Cancer (AJCC), which allows a more detailed description of tumour size and anatomic localisation (table 1).¹¹

All patients underwent either sectorial or complete anterior segment proton beam radiation therapy (PBRT). In most cases (77%) where PBRT was to be performed, this was preceded by tantalum clip marker surgery to mark tumour margins and ensure precise irradiation. At the tantalum clip marker surgery, after 360° conjunctival peritomy and anchoring of the recti muscles, four tantalum markers were sutured on the sclera with non absorbable sutures, one marker in each quadrant between the muscle insertions 3–6 mm posterior to the limbus. The bowstring distance from each marker to the closest tumour margin was measured with callipers. In the case of whole anterior segment irradiation, tantalum markers were put in each quadrant in the same way and the bowstring distance of each marker to the limbus was noted. In all cases the pupil was not dilated.

All patients underwent complete clinical examination, Snellen best-corrected visual acuity (BCVA) testing and intraocular pressure (IOP) measurements, slit lamp photography, ultrasound biomicroscopy (UBM) and anterior segment optical coherence tomography (AS-OCT) prior to treatment and during follow-up visits. The mean time interval between tantalum marker clip surgery and PBRT was 2 weeks. PBRT was performed

at the Hahn-Meitner Institute in Berlin-Germany or at the Paul-Scherrer Institute in Villigen-Switzerland and consisted of a total radiation dose of 60 (4×15) Grey (Gy). For irradiation planning, intraoperative tantalum marker data, axial length and horizontal corneal diameter of the treated eye as well as maximum tumour thickness (measured by UBM or AS-OCT) were used by the irradiation planning software ‘OCTOPUS’ or ‘EYEPLAN’ to create a virtual model of the eye and calculate the irradiation volume and isodose distribution. A safety margin of 2 mm was added to the calculated tumour volume. In the case of whole anterior segment radiation, the entire iris, cornea, lens and approximately 60% of the ciliary body were irradiated implementing a frontal plane irradiation projection strategy. In all cases, the pupil was not dilated during irradiation.

Patients underwent ophthalmologic follow-up in 3–6 monthly intervals, unless complications required more frequent visits. Six-monthly abdomen sonography as well as liver function plasma testing were additionally performed, to exclude metastasis.

All data were analysed for normal/non-n.d. (n.d./n.n.d.) and equal variances with the Kolmogorov-Smirnov-test by SPSS V.24.0.0.1 software (IBM). Wilcoxon signed-rank test was used to compare pretreatment to post-treatment measurements. Mann-Whitney U test was used to compare post-treatment measurements between subgroups. Comparison in complications between complete PBRT and sectorial PBRT was calculated using Fisher’s exact test. Statistical significance was set to < 0.05 .

Patients or the public were not involved in the design, conduct, reporting or dissemination plans of our research.

RESULTS

From the 13 patients identified, 62% were male and 38% female. All patients had unilateral eye involvement.

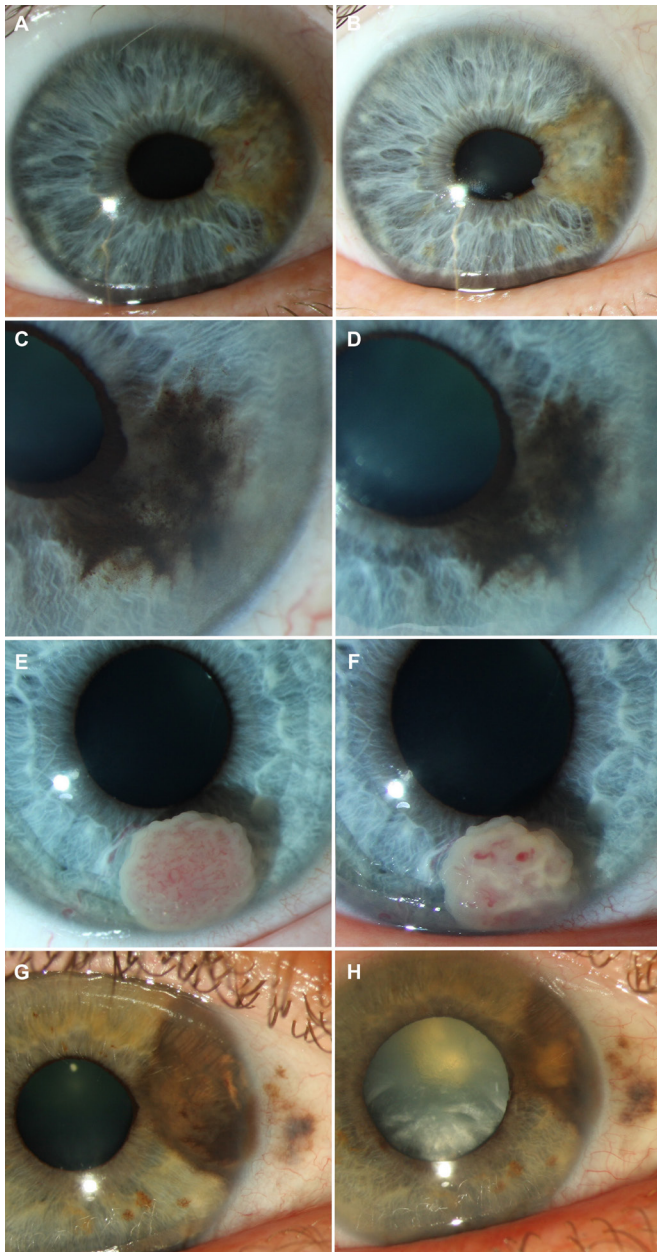


Figure 1 T1a tumour before (A) and after (B) sectorial PBRT. T1b tumour with seeding cells over the entire iris before (C) and after (D) PBRT of the whole anterior segment. Amelanotic T1a tumour before (E) and after (F) sectorial PBRT. T4a tumour before (G) and after (H) PBRT of the whole anterior segment. PBRT, proton beam radiation therapy.

Median age at presentation was 53 (range 23–80) years. According to the updated AJCC classification, following types concerning localisation were identified: T1a (n=3), T1b (n=3), T1c (n=2), T2a (n=2), T2b (n=1), T2c (n=1) and T4a (n=1) (table 1).

All cases received PBRT (figure 1). Sectorial PBRT was applied in T1a, T1b, T2a and T2b tumours (eight cases), whereas irradiation of the whole anterior segment was chosen for T1b, T1c, T2c and T4a tumours (five cases).

All patients with sectorial PBRT but only 2 out of 5 with complete anterior segment PBRT received tantalum markers.

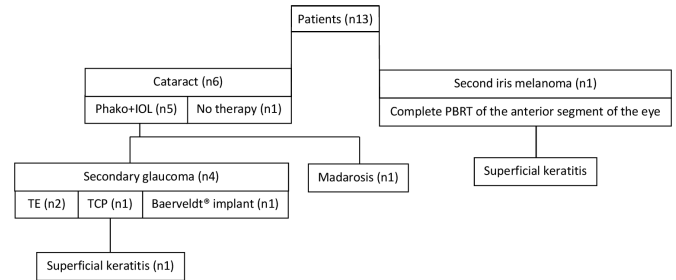


Figure 2 Postirradiation complications and their management. TCP, transscleral cyclophotocoagulation; TE, trabeculectomy.

Mean follow-up time of the complete cohort was 25 (range 5–66) months. Follow-up time for the group which received PBRT of the whole anterior segment was 40 (range 5–66) months whereas for the group with sectorial PBRT was 16 (range 8–30) months.

No statistically significant difference was found in the mean BCVA between pretreatment and post-treatment eyes (Wilcoxon test (0.79 ± 0.4 vs 0.76 ± 0.4 , $n=13$ vs 13 , $p=0.8$, n.n.d.)). Comparison of mean IOP showed no statistically significant difference between baseline and last follow-up visit (Wilcoxon test ($17.8 \text{ mm Hg} \pm 6$ vs $15 \text{ mm Hg} \pm 4$, $n=13$ vs 13 , $p=0.08$, n.n.d.)). Between the two treatment groups (sectorial vs whole anterior segment irradiation) no statistically significant difference in the mean BCVA at the last follow-up visit was noted (Mann-Whitney U test, complete PBRT: 0.56 ± 0.4 vs sectorial PBRT: 0.88 ± 0.4 , $p=0.29$, n.n.d., respectively). Similarly, mean IOP between these two different treatment groups was not statistically different at the last follow-up visit (Mann-Whitney U test, complete PBRT: $15 \text{ mm Hg} \pm 5$ vs sectorial PBRT: $15 \text{ mm Hg} \pm 3.3$, $p=0.94$, n.n.d., respectively).

Postinterventional complications occurred in 7 (54%) of 13 patients (figure 2). These occurred in 80% of our patients with complete irradiation of anterior eye segment, whereas in only 38% of patients with sectorial irradiation. Comparison between complications in complete and sectorial PBRT showed no statistical significance ($n=13$, $p=0.266$, figure 3).

After PBRT, 6 (46%) patients developed cataract, of which 4 (31% of total PBRT cases) had additionally secondary glaucoma; 3 of them had secondary glaucoma

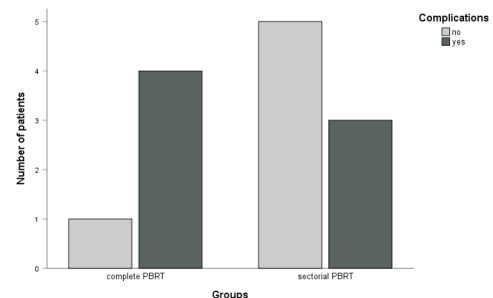


Figure 3 Comparison of complications between complete and sectorial PBRT. PBRT, proton beam radiation therapy.

already at presentation, that is, before PBRT. The TNM staging of these glaucoma patients was: T1c (n=2), T2c (n=1) and T4a (n=1). All 4 patients with glaucoma had to undergo complete anterior segment PBRT, because of tumour localisation and/or size. In all of these patients local IOP-lowering medication was not sufficient to control IOP after PBRT. As a result, two patients underwent trabeculectomy, one received a Baerveldt tube and one had a single session of transscleral cyclophotocoagulation. One trabeculectomy patient developed postoperative ocular hypotonia due to insufficient healing of the conjunctiva at the area of the bleb and required surgical revision twice. This patient had undergone previous tantalum clip marking surgery, so his conjunctiva had been surgically manipulated and in addition irradiated, this could have led to healing problems. IOP could be controlled in all cases at the end of the follow-up. Cataract surgery was also performed in these 4 patients, as well as in another patient without glaucoma, thus in total 5 patients underwent cataract surgery post PBRT. Mean time interval from PBRT to cataract surgery was 20 (range 8–30) months.

One patient was diagnosed with madarosis after sectorial PBRT. In 2 patients (15%) superficial keratitis developed, which was treated with lubricating eye-drops.

Local tumour control is defined as the absence of tumour growth and absence of any new lesion in the treated eye.¹² Local tumour control was achieved in 12 out of 13 (92%) patients after a single treatment during follow-up. Only one patient (8%) developed a second iris melanoma at a non-irradiated area after sectorial PBRT (out-of-field recurrence) and was re-irradiated with complete anterior segment PBRT (figure 4).

No patient in our study showed metastatic disease during a follow-up.

DISCUSSION

Despite being the rarest form of uveal melanoma, iris melanoma is a disease with which every ophthalmologist will be confronted at some point in his practice. This underlines the necessity of proper diagnosis and treatment, as the tumour can cause local and systemic complications or even death if left untreated.¹³

Using the AJCC classification system allows a more anatomically accurate description of iris melanomas



Figure 4 T1B tumour before sectorial PBRT (A). Second iris melanoma in non-irradiated area (arrow) (B). PBRT, proton beam radiation therapy.

and might help in prognosticating metastatic risk in the future.¹⁴ Unfortunately this classification system is not entirely appropriate when used on its own in determining the best therapeutic option. This is obvious in our series, since different patients with the same T category might require different irradiation strategies. In our series, 2 patients with T1b tumours underwent sectorial irradiation whereas another patient with the same T1b category had to undergo irradiation of the whole anterior segment to treat the entire tumour adequately. Future studies might be necessary to develop a revised classification system that incorporates treatment strategies.

PBRT is a game-changer in the treatment of tumours of the anterior uvea, due to the absence of invasiveness, which is leading progressively more physicians to consider it as the primary therapeutic option, especially in the case of diffuse iris melanoma.^{4–8 12 14–17} It achieves a high level of local tumour control and eye preservation rate, as no surgical tumour manipulation takes place, which could, at least theoretically, lead to iatrogenic tumour spread.¹⁴ The physical properties of protons (Bragg peak) allow for selective tumour treatment with minimal collateral damage to the surrounding tissues, that no other treatment modality offers.¹⁰ Because of that, critical structures for vision, such as the macula and optic nerve, are spared from irradiation, as they receive 0% of the irradiation dose. This explains why in our series no difference was found in BCVA before and after treatment. The usage of tantalum marker clips further increases the accuracy of PBRT, as it helps radiotherapists to define the target volume better. Tantalum marker placement is optional in the case of planned whole anterior segment irradiation, since anatomic landmarks such as the limbus and visual axis can be used to define target volume and eye position. In our series, all patients planned to receive sectorial PBRT underwent tantalum marker surgery. In the case of whole anterior segment irradiation, the decision on tantalum marker surgery was taken in a case per case manner, depending on the requirements of the radiotherapists and the ability to accurately model the eye in the irradiation planning software.

In our series, primary local tumour control could be achieved in 92% during a mean follow-up of 25 months, which is in coordination with data from the literature.^{4 5 12 15 18} PBRT allows homogenous dosage distribution across the entire target volume, which further contributes to the extremely high local tumour control rate.¹⁰ There was only one case of local tumour recurrence due to tumour development in the non-irradiated area (out-of-field recurrence). This underlines the significance of thorough clinical examination to identify possible tumour seeding on the iris surface or the angle and adequate irradiation planning to cover all areas of tumour occurrence. After local recurrence, secondary PBRT of the whole anterior segment can be indicated and it is a beneficial therapeutic option, nevertheless, it may significantly increase complication rate.

Forty-six per cent of our patients showed no complications during follow-up. Irradiation of the entire anterior segment has been shown to be associated with a significant higher rate of complications.¹⁵ This finding could also be shown with our data although due to the low number of cases no statistical significance could be reached. Furthermore, this result could be the reason for the more than twice as long follow-up time in the whole anterior segment irradiation group compared with the sectorial irradiation group.

Glaucoma is possibly the most significant vision-threatening complication after PBRT for iris melanoma. Glaucoma at presentation or after PBRT is more common in tumours that are spreading more than three clock hours in size (previously called 'diffuse' melanomas) or that are extending into the angle and ciliary body in a circular manner (previously called 'ring' melanomas),⁷ due to the more extended angle infiltration and the scarring that occurs after irradiation of the complete anterior segment. In our series, patients that developed glaucoma had more advanced disease: 2 had stage T1c, 1 had T2c and 1 had T4a. In the case of uncontrolled IOP, surgery or cyclodestructive procedures are necessary. There is some concern about tumour seeding after filtering procedures but taking into consideration the fact that excellent local control rates are achieved with PBRT, this risk seems not significant. Larger series with tubes have not shown any tube-related metastasis.^{18 19} Filtering procedures in the perilimbal conjunctiva and sclera, such as trabeculectomy, have the disadvantage that they involve previously irradiated and surgically manipulated (in the case of tantalum clip marking) tissue. This significantly increases the possibility of scarring and surgical failure. In our series, all patients with glaucoma (either pre-existing or after PBRT) required glaucoma shunt surgery or cyclodestruction to control IOP.

Postoperative hypotony is a known side effect after trabeculectomy and is more common after PBRT.²⁰ Despite the sclera being relatively radiation tolerant, irradiated tissue on and around the tumour will be altered in a dose-dependent manner. Inflammation of the perilimbal conjunctiva and thinning of the sclera after PBRT, which can affect wound healing, has been reported.¹⁸ The degree to which PBRT affects wound healing after trabeculectomy is still unknown.²¹

Cataract development is common after PBRT for iris melanoma, especially in the case of complete anterior segment irradiation, since part or all the lens lies within the target volume. A retrospective study from Willerding *et al* showed that radiation cataract occurs over time in practically all patients after PBRT of the entire anterior segment.⁷

Madarosis is an uncommon complication of PBRT, as effort is being made to keep the eyelids outside the irradiation plane. In our series, the patient who developed madarosis had closely spaced palpebral fissures, which made it impossible to completely spare the eyelid margin.

Eye retention rate has been reported to be 80%–100% in different studies.^{4 5 12 15 16} In our series, eye retention rate was 100% at the mean follow-up time of 25 months. Despite the differences in the number of eyes, the initial eye status and the different tumour characteristics in the various studies, in most cases eye retention rates are excellent and in coordination with our findings, which underlines the safety of PBRT for iris melanomas.

As already mentioned, there are also other therapy modalities apart from PBRT. Surgical resection was, and still is in the absence of other modalities, a valuable approach to treat localised iris or iridociliary uveal melanoma. Common postoperative complications after iridectomy, anterior irido-trabeculo-cyclectomy and Naumann block excision technique mentioned in the literature include hyphaema (21%), cataract (9%–32%), photophobia (85%), wound leakage (6%), vitreous haemorrhages (2%–35%), vitreous loss (2%), enucleation (2%–6%) and recurrence (3%–8%) with a median follow-up time up to 104 months.^{17 22–25}

In comparison to surgical techniques, the patients treated with PBRT in our study had no photophobia, hyphaema, wound leakage, vitreous haemorrhage, vitreous loss and no patient had to be enucleated.

Local tumour relapse after surgical resection is comparable to that of radiation modalities.²⁴

Metastatic disease is reported in up to 3% of patients at 5 years, 5% at 10 years, and 10% at 20 years of iris melanoma cases, independent of the method of management (resection, radiotherapy or enucleation).¹³ However, no patient of our study showed metastatic disease during follow-up after PBRT. The short follow-up time could be the reason for the low percentage of relapses and metastatic events which can occur very late in this setting as described above. In an analysis of 317 consecutive iris melanoma patients, the main factors found to be predictive for metastasis included extraocular extension and elevated IOP.²⁴ In a previous report of 169 consecutive patients, Shields *et al* found increased age at diagnosis, elevated IOP, angle invasion, extraocular extension and previous surgical intervention before referral to be predictive for metastasis.¹³ In our analysis, only one patient had extrascleral extension (T4a) and glaucoma, but in a follow-up time of 5 years, there was no metastatic disease.

In conclusion, PBRT is a safe, effective and vision preserving therapeutic modality for the treatment of iris melanoma. Our study underlines the clinical significance of PBRT in iris melanoma treatment as the visual outcome and the eye retention rate is excellent and complications are manageable.

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Patient consent for publication Not applicable.

Ethics approval Our retrospective study was approved by the Local Committee for Medical Research Ethics of the Medical University of Innsbruck. There was no objection against the conduct of the study. All procedures involving human participants were performed in accordance with the ethical standards of the institutional and/or national research committee and the 1964 Declaration of Helsinki and its later amendments, or comparable ethical standards.

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Data availability statement All data relevant to the study are included in the article.

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