Proton or Stereotactic Photon Irradiation for Posterior Uveal Melanoma?

A Planning Intercomparison

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Background and Purpose: Proton and stereotactic radiotherapy with photons (SRT) are both used to treat choroidal melanomas in proximity to optic disk and fovea centralis, a situation where plaque therapy is prone to complications. A comparative treatment-planning study was done to assess the capability of both modalities to preserve vision.
Patients and Methods: In ten patients treated with 68-MeV protons, SRT with 6-MV photons was planned. Structures most important for visual acuity (fovea and optic disk, optic nerve) were contoured identically for both therapies. Safety margins of 1.5 mm for proton therapy were reduced to 1.0 mm for SRT.
Results: Proton-beam therapy was superior in eight of ten situations, and this result did not differ significantly by changes in the weighting of the different parameters analyzed.
Conclusion: When dose deposition to those structures most important for the preservation of vision is taken into account, under the conditions examined proton therapy offers an advantage in the majority of the patients evaluated.

Key Words: Proton therapy · Stereotactic radiotherapy · Comparative planning study · Uveal melanoma

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Protonen- oder stereotaktische Photonenbestrahlung für posteriore Aderhautmelanome? Ein Planungsvergleich

Hintergrund und Ziel: Für Aderhautmelanome am hinteren Augenpol, die nicht mit Plaques behandelt werden können, stehen Protonentherapie und stereotaktische Bestrahlung mit Photonen (SRT) zur Verfügung. In einer vergleichenden Therapieplanungsstudie wurden die Aussichten beider Verfahren untersucht, den Visus bestmöglich zu erhalten.
Patienten und Methodik: Bei zehn mit 68-MeV-Protonen behandelten Patienten wurde alternativ eine SRT mit 6-MV-Photonen geplant. Die für das Sehvermögen bedeutsamsten Strukturen, Macula, Papille und Sehnerv, wurden identisch konturiert. Der Sicherheitssaum von 1,5 mm bei der Protonentherapie wurde für die SRT auf 1,0 mm reduziert.
Ergebnisse: Die Protonentherapie war in acht von zehn Fällen überlegen, und dieses Ergebnis änderte sich auch durch eine unterschiedliche Gewichtung der einzelnen untersuchten Parameter nicht wesentlich.
Schlussfolgerung: Wenn die Dosisbelastung der für den Erhalt des Sehvermögens bedeutsamsten Strukturen als entscheidend betrachtet wird, ist die Protonentherapie unter den für die Untersuchung gewählten Bedingungen in der Mehrzahl der Fälle überlegen.

Schlüsselwörter: Protonentherapie · Stereotaktische Bestrahlung · Vergleichende Planungsstudie · Aderhautmelanom

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Introduction

Uveal melanoma is a very rare malignant tumor with an estimated incidence of only 0.6–0.8 per 100,000 per annum in Western Europe [5]. Radiation therapy nowadays is one of the cornerstones of therapy. Tumors of the posterior aspect of the globe are difficult to treat because of the proximity to those structures most relevant for preservation of visual acuity [1]. The general perception is, that tumors located within 2 mm of the optic disk or fovea centralis should not be treated with radioactive plaques due to the high doses at areas in close proximity to the surface of the plaque applicator and hence an inevitable risk of radiation damage to these structures [2, 7]. Proton-beam therapy not only in this situation offers many advantages by the very sharp distal fall-off, enabling homogeneous treatment of the tumor without excessive risks of damage to organs or structures nearby [10, 14, 17, 22, 24].

Excellent local control rates of approximately 95% at 5 years have been reported from most of the centers, but proton therapy centers are rare with only some ten centers in Europe and Russia, a population of about 0.5 billion inhabitants, and due to the enormous costs in building and maintenance and the manpower necessary to run them, therapy is expensive [6, 11, 15]. Other forms of high-precision conformal radiotherapy have developed over the years and nowadays gamma knife as well as linear accelerator-based stereotactic radiotherapy or radiosurgery are broadly available. It was therefore not unexpected to find these modalities expanding their field of interest into ocular radiation therapy [4, 18]. Although compelling results in regard of tumor control have been reported in some series, others where rather disappointing [5, 23].

Comparison of the published series is a difficult matter, as there are many interdependent risk factors for not achieving tumor control as well as for developing sequelae and there are merely no prospective studies. The major goal in therapy is to achieve local tumor control and to preserve the organ and its function. We therefore decided to do a comparative study with all the tools and additional diagnostic procedures, that have made proton therapy that successful, available for both modalities.

Table 1. Patient characteristics.

Tabelle 1. Patientencharakteristika.

Patient #	Tumor volume[a] (mm^3)	Tumor base (mm)	Tumor apex (mm)	Distance to optic disk[a] (mm)	Distance to fovea[a] (mm)
1	1,340	20 × 19	7.5	1.9	1.1
2	120	10 × 8	4.2	3.5	0
3	520	15 × 13	7.1	3.6	0
4	780	15 × 12	10.1	6.6	3.7
5	620	16 × 13	6.5	5.2	1.4
6	30	7 × 6	1.8	0	2.1
7	1,350	18 × 16	11.8	1.3	4.7
8	30	6 × 5	2.7	0	2.7
9	140	14 × 11	2.6	4.2	0
10	240	15 × 11	4.4	0	0

[a]values generated by the EYEPLAN program

Patients and Methods

In ten patients treated consecutively with 68-MeV protons from June to September 2003, SRT with 6-MV photons was planned additionally. Relevant patient and tumor characteristics are listed in Table 1. Treatment planning for proton irradiation was done with the EYEPLAN program as previously described [14, 15]. High-resolution computed tomography of the involved eye in each case was done (Somatom Volume Zoom, Siemens AG Medical Solutions, Erlangen, Germany; slice thickness and collimation 1.0 mm, 120 kV, 100 mA, reconstruction increments of 1.0 mm; kernel H 50).

For proton therapy a safety margin of 1.5 mm surrounding the tumor outline was applied and adjusted manually, as the EYEPLAN program does not support modern ICRU-based volume definitions. Treatment optimization had to be done manually. Planning CTs for this study were performed in a modified headrest of a stereotactic treatment system (BrainLAB AG, Heimstetten, Germany) which had been supplemented for these purposes by an adjustable LED light for eye fixation as shown in Figure 1. As it was not intended to treat patients with stereotactic photon irradiation (SRT) but solely to compare treatment plans, no fixation mask for SRT was built. Otherwise, additional technical adjustments and equipment in analogy to the details of the proton therapy setup would have been necessary. To make all the information which form the basis of treatment plan generation in proton therapy available for SRT planning, based on the program Image Pro Plus 4.0 (Media Cybernetics, Silver Spring, MD, USA) a tool was developed to export the information used for proton therapy treatment planning into the planning CTs on a slice-by-slice basis as shown in Figure 2. This enabled to take dose deposition on optic disk and fovea centralis into account for SRT planning. These structures are not visible in the routine CT or MRI diagnostics done for SRT planning.

SRT was planned with a straightforward view without globe rotation, and therefore a reduction of the safety margin in PTV (planning target volume) delineation to 1.0 mm was made, taking into account that the direction on which the globe is rotated for proton therapy (in general approximately 30°) sometimes leads to inconsistencies and rapid correctional movements that cannot be compensated otherwise, thus giving need for a somewhat larger safety margin.

To be comparable with the restricted possibilities of the EYEPLAN program, only the first 10 mm of the optic nerve were contoured without surrounding fibrovascular or connective tissue for SRT. SRT planning was done with the program BrainScan 4.03 (BrainLAB AG) for a 6-MV photon linear accelerator (CLINAC 600 CD, Varian Medical Systems, Palo Alto, CA, USA). Conformal microcollimators, a micro-multi-

leaf collimator with 1 mm leaf width at isocenter, static arc techniques were available for SRT planning. After extensive pretesting as a class solution all patients were planned with five conformal static beams. Five to twelve SRT plans were calculated per patient. Minimum allowed distance between PTV contour and beam aperture was set to 2.0 mm.

To achieve a dose homogeneity comparable to proton treatment, constraints were set as follows: at least 97% of the PTV should be encompassed with at least 90% and at most 110% of the reference dose (for reasons see Discussion). Dose prescription for SRT was 4 × 15 Gy, as it was in proton therapy where 4 × 15 CGE (Cobalt Gray Equivalent) were given. For comparison of the results dose-volume histograms (DVHs) were used, where possible. Due to the tiny size of fovea and optic disk no DVHs could be generated for them with the SRT program, instead point doses were measured with the program tool available for these purposes. A difference of at least 15% in minimum or maximum dose was considered relevant for optic disk and fovea. For the optic nerve a 15% difference in minimum or maximum dose or a significant difference in the integrated dose was chosen as cutoff point for evaluating differences, whereas the criteria applied to dose deposition to the lens were no versus any dose deposition or a significant reduction in the maximum dose.

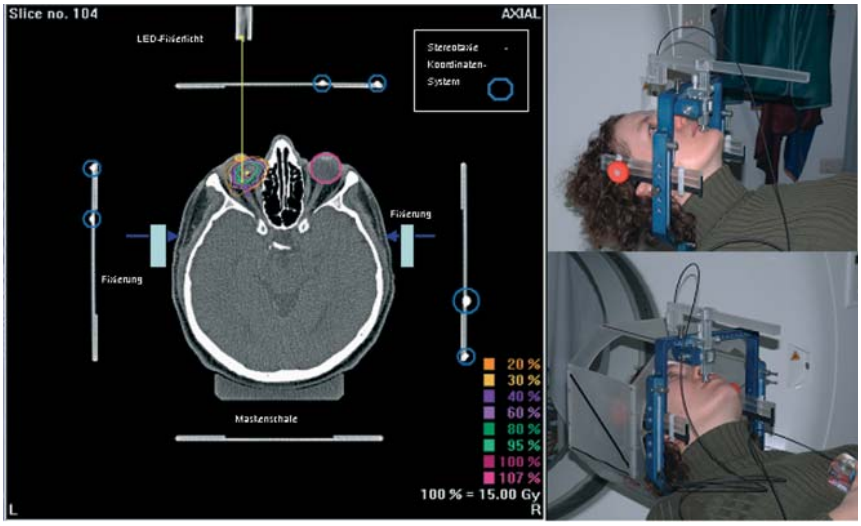

Figure 1. Modified stereotactic mask system with adjustable LED-fixation light.

Abbildung 1. Modifiziertes Stereotaxie-Maskensystem mit verstellbarem LED-Licht.

Comparison of the doses to the optic nerve was complicated twofold, first by the fact that the program EYEPLAN on the one hand uses a simplification showing only 10 mm of its length and on the other hand it does not show the anatomy as seen in CT or MRI examinations, as only the central parts are shown and not the surrounding tissues. To alleviate analysis and comparisons, the SRT contours were drawn in analogy. The EYEPLAN program for proton therapy does not display a DVH for the optic nerve, instead a dose-length histogram (DLH) is plotted. To keep results comparable for SRT, the optic nerve was therefore contoured with a constant width.

Results

In detail, the results of dose deposition to the structures fovea centralis, optic disk, optic nerve, and lens are shown in Table 2, and a summary of the results achieved is given in Table 3. The doses to *fovea centralis* for patients #1, 3, 5, 6, 9, and 10 were equal for both modalities, protons were superior in patients #4, 7, and 8, whereas SRT was superior in patient #2. In the analysis of dose deposition to *optic disk* results for patients #1, 6, 7, 8, and 9 were without relevant differences, in patients #2, 3, 4, and 5 protons were better, in patient #10 SRT fared favorable. The steep distal fall-off of proton beams showed advantages in the calculated doses applied on the *optic nerve*. In patients #2, 3, 4, and 5 there was no dose delivery; in patients #1 and 9, although comparable in their minima and maxima, the integrated dose over volume was by far lower for protons (making them advantageous). Thus, solely in patients #6 and 8 SRT was better.

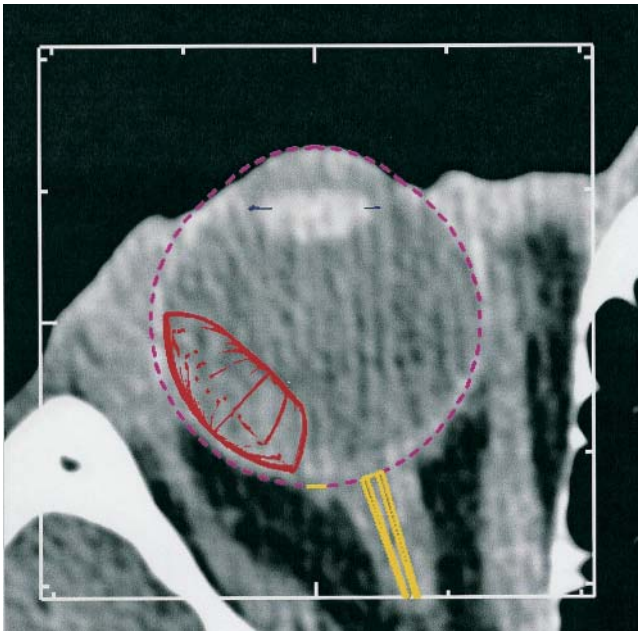

Figure 2. Export of the EYEPLAN contours into the planning CT for stereotactic radiotherapy with photons.

Abbildung 2. Übertragung der EYEPLAN-Daten in das Planungs-CT der stereotaktischen Bestrahlung mit Photonen.

Table 2. Dose deposition to structures at risk. SRT: stereotactic radiotherapy with photons.

Tabelle 2. Dosisbelastung der Risikostrukturen. SRT: stereotaktische Bestrahlung mit Photonen.

Patient #	Fovea centralis minimum and maximum (dose, %)		Optic disk minimum and maximum (dose, %)		Optic nerve minimum and maximum (dose, %)/length irradiated (mm)		Lens minimum and maximum (dose, %)/ volume irradiated (%)	
	SRT	Protons	SRT	Protons	SRT	Protons	SRT	Protons
1	92–94	97–100	65–86	19–100	23–84/10	0–100/1,2	7–67/100	0–67/37
2	58–84	100–100	9–30	0–0	5–13/10	0–0/0	4–21/100	0–7/5
3	92–98	100–100	40–79	0–0	5–19/10	0–0/0	6–19/100	0–18/28
4	48–74	0–0	13–35	0–0	5–11/10	0–0/0	6–25/100	0–72/28
5	87–94	76–100	17–58	0–0	7–24/10	0–0/0	5–28/100	0–91/48
6	21–69	28–75	96–103	100–100	4–45/10	0–100/2,7	3–5/100	0–2/2
7	68–93	0–0	89–97	100–100	8–91/10	0–100/2,4	7–34/100	0–98/69
8	9–24	0–0	80–103	100–100	5–20/10	0–100/3,9	3–4/100	0–0/0
9	65–94	92–100	8–15	0–5	6–9/10	0–5/0	3–6/100	0–0/0
10	86–99	90–100	48–99	100–100	21–90/10	0–100/3.7	4–23/100	0–22/23

In patients #8 and 9 proton therapy resulted in complete sparing of the *lens*, whereas in patients #4, 5, and 7 SRT plans delivered significantly lower maximum doses to it, making SRT plans advantageous, whereas in the remainders SRT and protons were not different in regard of radiation exposure to the lens (patients #1, 2, 3, 6, and 10). In proton therapy beam homogeneity always is excellent. As all SRT plans were in accordance with the a priori given constraints for *dose homogeneity*, all plans were regarded as equivalent.

To sum up the results, they are depicted in Table 3. If every parameter that has been evaluated is considered equally important, this results in a superiority of proton-beam therapy in eight of the ten patients evaluated. Even if the importance of one of the parameters fovea, optic disk or optic nerve would be weighted twice as their relevance may be judged different, the results would not show major deviations nor would the omission of one of the parameters from the analysis change much, as proton therapy would still be superior in 60–80%.

Table 3. Overview and summary of the results of the parameters evaluated. P: 68-MeV protons superior; –: no relevant differences; SRT: stereotactic radiotherapy with 6-MV photons superior.

Tabelle 3. Zusammenfassung der Ergebnisse der einzelnen Parameter. P: 68-MeV-Protonen überlegen; –: keine wesentlichen Unterschiede; SRT: stereotaktische Bestrahlung mit 6-MV-Photonen überlegen.

Patient #	Fovea	Optic disk	Optic nerve	Lens	Homo-geneity	Summary
1	–	–	P	–	–	P
2	SRT	P	P	–	–	P
3	–	P	P	–	–	P
4	P	P	P	SRT	–	P
5	–	P	P	SRT	–	P
6	–	–	SRT	–	–	SRT
7	P	–	P	SRT	–	P
8	P	–	SRT	P	–	P
9	–	–	P	P	–	P
10	–	SRT	–	–	–	SRT

Discussion

Two alternative radiotherapy strategies exist for the treatment of choroidal melanomas of the eye, if radioactive plaques are considered inadequate. Proton therapy has been in clinical use in this indication for approximately 30 years and many thousands of patients have been treated that way, the majority either at Massachusetts General Hospital – Harvard Cylotron – in Boston, MA, USA, or and at the Paul Scherrer Institute in Switzerland. Extensive documentations on long-term follow-up do exist, and the results could more or less be reproduced by other institutions [6, 11, 15, 16]. With more than 2,000 patients evaluated, statistical power of these reports is to be considered high and the results reported are regarded as very valid. Still all of these publications are retrospective in nature and direct comparisons to the second existing radiotherapeutic modality – stereotactic radiotherapy or radiosurgery – do not exist although many aspects of these modalities have been described [9, 18, 20, 23].

Many different factors have potential influence on the results achievable in the treatment of uveal melanomas and some of them are even interrelated, making direct comparisons of the reports on stereotactic radiotherapy and hadron therapy a very difficult topic [6, 8, 12]. As this problem will most probably not dissolve over the next years, there is a substantial need for alternative modes to compare these modalities, although one has to keep in mind, that long-term clinical results are the main objective measure of treatment quality.

Comparison of the results in this report was based on the calculated dose deposition on fovea centralis, optic disk, prox-

imal optic nerve, and lens. Fovea centralis and even the optic disk, which may be positioned eccentric to the optic nerve, are not visible on CT and MRI, and thus they cannot routinely be taken into account in SRT planning, leaving dose deposition to them unaddressed although they are the factors most critical in preserving vision [2, 5, 13, 21]. By the methods employed, we were able to use these anatomic areas and tailor SRT to reduce the probability of side effects to them.

Analysis of treatment plans on the basis of DVHs could not be done by the SRT planning program for fovea and optic disk due to the small size of these structures and point doses had to be used for comparison, which has to be regarded as a drawback of the present study, as more sophisticated tools for comparisons are desirable [19].

Reduction of the safety margin to 1.0 mm for the PTV in SRT planning in this study is down to the level of the resolution of the imaging modalities used, and without technical means to control for setup accuracy as they are used for proton therapy, this would be a very risky strategy, given the known deviations in ocular SRT, where in general safety margins of 1.5–2.5 mm are applied [3, 9, 13, 18, 20, 21]. On the other hand it would not be a major problem to implement clip operation and orthogonal X-ray setup control to SRT. As SRT will not have the necessity to utilize far out view directions as in proton therapy, a smaller safety margin in SRT than in proton therapy helps to compare both modalities under conditions which at least are not putting SRT at a disadvantage.

Due to its characteristic steep distal fall-off proton therapy will always be in favor with respect to dose deposition to the distal aspects of the optic nerve. Evaluation of treatment plans with respect to length of the nerve treated versus maximum dose applied is difficult, as there are merely no data available. Still we would suggest that a reduction of the integrated dose is a criterion that is acceptable in the instance of similar maximum and minimum doses.

We could not evaluate dose distribution to the ciliary body, which is not easily viewable in planning CTs and the representation in EYEPLAN is not precise enough to transfer this information to SRT planning. As a surrogate dose deposition to the lens may be a suitable parameter and there were no major differences in both modalities making it unlikely that analysis of the ciliary body would have much influence on the results. Modern ophthalmic surgery has decreased the importance of a cataract as late effect considerably, questioning the need to take dose deposition to the lens into account. Moreover, cataract surgery in cases of adequate local tumor control after radiotherapy is regarded to be a safe procedure.

Dose homogeneity is an important factor for the achievement of steep dose fall-off outside the volume treated. Therefore, the tight constraints applied may be seen as impeding SRT. Given the well-documented dose dependency of radiation maculopathy and papillopathy, allowing higher maximum doses in SRT plans might bear severe risks for the preservation of vision [12]. In a series reported by Haas et al., retinopathy was present in > 80% of the patients treated after a median follow-up of only 8 months. Patients had been treated by gamma knife, a method where dose homogeneity typically is very poor [13].

Superiority of proton therapy in the present analysis was obvious under the conditions chosen, and the results achieved were not depending on the weighting of the parameters evaluated. Changes in the weighting of parameters as well as omission of parameters had little influence. Proton therapy was superior in 60–80% of the patients evaluated.

Conclusion

When dose deposition to the structures most relevant for the preservation of vision is taken into account, proton therapy seems to be advantageous over SRT. Whether this translates into a relevant long-term clinical benefit is not known and should be addressed in large-scale phase III trials. Although melanoma of the choroid is a rare disease, the enormous costs associated with the use of proton therapies would make such a study attractive.

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