The Effectiveness and Safety of Proton Radiation Therapy for Indications of the Eye

A Systematic Review

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Background and Purpose: Proton radiation has been used for the treatment of uveal melanoma since 1975, but few studies have been conducted to assess its efficacy and safety. This paper aims to systematically review the effects and side effects of proton therapy for any indication of the eye.
Material and Methods: A range of databases were searched from inception to 2007. All studies that included at least ten patients and that assessed the efficacy or safety of proton therapy for any indication of the eye were included.
Results: The search generated 2,385 references, of which 37 met the inclusion criteria. Five controlled trials, two comparative studies and 30 case series were found, most often reporting on uveal melanoma, choroidal melanoma and age-related macular degeneration (AMD). Methodological quality of these studies was poor. Studies were characterized by large differences in radiation techniques applied within the studies, and by variation in patient characteristics within and between studies. Results for uveal melanoma and choroidal melanoma suggest favorable survival, with, however, significant rates of side effects. Results for choroidal hemangioma and AMD did not reveal beneficial effects from proton radiation.
Conclusion: There is limited evidence on the effectiveness and safety of proton radiation due to the lack of well-designed and well-reported studies. There is a need to lift evidence on proton therapy to a higher level by performing dose-finding randomized controlled trials (RCTs), comparative studies of proton radiation versus standard given alternatives and prospective case studies enrolling only patients treated with up-to-date techniques, allowing extrapolation of results to similar patient groups.

Key Words: Proton therapy · Effectiveness · Safety · Eye melanoma

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Wirksamkeit und Verträglichkeit von Protonenstrahltherapien für ophthalmologische Indikationen. Eine systematische Übersicht

Hintergrund und Ziel: Protonenstrahlen werden seit 1975 zur Behandlung von Uveamelanomen eingesetzt, aber nur wenige Studien haben die Wirksamkeit und Verträglichkeit der Behandlung untersucht. Ziel dieser Studie war die Erstellung einer systematischen Übersicht der Wirksamkeit und Verträglichkeit von Protonenstrahltherapien für alle ophthalmologischen Indikationen.
Material und Methodik: Suche in diversen Databanken über den Zeitraum von der Einführung bis zum Jahr 2007. Einbezogen wurden alle Studien, in die mindestens zehn Patienten eingeschlossen wurden und deren Ziel es war, die Wirksamkeit oder Verträglichkeit der Protonenstrahltherapie für beliebige ophthalmologische Indikationen zu untersuchen.
Ergebnisse: Die Suche ergab 2 385 Treffer; davon erfüllten 37 Studien die Selektionskriterien. Es handelte sich um fünf kontrollierte Studien, zwei vergleichende Studien und 30 Fallstudien. Die meisten Arbeiten betrafen Uveamelanome, Aderhautmelanome und altersbedingte Makuladegeneration (AMD). Die methodische Qualität dieser Studien war niedrig. Es bestanden große Unterschiede bei den angewendeten Strahlungsprotokollen und den Patienteneigenschaften, nicht nur zwischen, sondern auch innerhalb der Studien. Die Resultate für Uveamelanome und Aderhautmelanome wiesen auf einen positiven Effekt bezüglich der

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Überlebensrate hin, allerdings in Verbindung mit beachtlichen Komplikationsraten. Die Ergebnisse für Aderhautmelanome und AMD zeigten keine günstigen Auswirkungen der Protonstrahlbehandlung.

Schussfolgerung: Aufgrund des Mangels an gut geplanten und gut dokumentierten Studien ist die Evidenz für die Wirksamkeit und Sicherheit der Protonenstrahlbehandlung gering. Um einen höheren Evidenzgrad zu erreichen, ist es erforderlich, randomisierte, kontrollierte Studien (RCTs) zur Dosisfindung und zum Vergleich zwischen Standard- und Protonenstrahltherapie in einem prospektiven Design unter Anwendung moderner Techniken durchzuführen, was die Extrapolation der Daten auf ähnliche Patientengruppen zulässt.

Schlüsselwörter: Protonenstrahltherapie · Wirksamkeit · Verträglichkeit · Uveamelanom

Introduction

Proton radiation has been used for the treatment of uveal melanoma, the most frequent primary malignant tumor of the eye, since 1975 [34]. The energy distribution of proton radiation is characterized by a Bragg's peak, which refers to a low dose at entry reaching a maximum at the stopping region with a non-existent exit dose [1]. Consequently, a large dose of radiation is delivered to the portion of the eye involved by the tumor but the dose delivered to the rest of the eye and to adjacent normal structures can be limited. This promises greater dose conformity and should results in a wider therapeutic window by yielding high tumor control with less side effects.

Proton radiation has been available for 40 years. However, few studies have been conducted to assess its efficacy and side effects. As the application of proton therapy requires large investments with regard to hospital resources, equipment and staff, an overview of the evidence of this therapy is warranted.

This study aims to systematically review the effects and side effects of proton therapy for any indication of the eye. Two accompanying papers (in preparation) focus on indications of the central nervous system, skull and neck and on all remaining indications such as cancers of the prostate, lung, pituitary gland, and liver.

Material and Methods

Search Strategy

The following electronic databases were searched for published articles from inception: MEDLINE (OVID), Cinahl, The Cochrane Library (4th quarter, 2006), ISI Web of Science, EMBASE. Searches took place in February 2007. In addition, trial registries were searched and reference lists of included studies and of reviews were screened for missed studies.

The databases were searched for relevant studies on key words "proton$" or "proton". This was combined with searches for radiotherapy using the following key words: "radiotherapy", "radiation", and "irradiation". Finally, the results were combined with the key words "treatment" or "therapy".

Study Selection Criteria and Procedures

All studies assessing the efficacy or safety of proton therapy, evaluating at least ten patients treated with proton therapy for any indication, were included in the review. For this paper, all indications of the eye were selected. No restrictions were applied regarding study design, language or type of publication. Two reviewers screened the title and abstract of all papers located by the search strategies. Reasons for exclusion were noted. Relevant studies, which met the inclusion criteria, together with those whose suitability could not be determined from the abstract or title, were retrieved. Two reviewers read all retrieved papers in full to reconfirm their suitability for inclusion. Where necessary, a third reviewer was consulted to resolve disagreements.

Study Quality Assessment

Table 1 presents the items that were used to assess the methodological quality of the studies (adapted from the Centre for

Table 1. Critera used to assess the methodological quality of the included studies.

Tabelle 1. Kriterien zur Bewertung der methodologischen Qualität der einbezogenen Studien.

(Randomized) controlled trials
1. Was the assignment to the treatment groups really random?
2. Was the treatment allocation concealed?
3. Were the groups similar at baseline in terms of prognostic factors?
4. Was the patient blinded?
5. Were outcome assessors blinded to the treatment allocation?
6. Was the care provider blinded?
7. Did the analyses include an intention-to-treat analysis?
Comparative studies
1. Were data collected prospectively?
2. Is there sufficient (for comparison) description of the groups and the distribution of prognostic factors?
3. Were the groups comparable on all important confounding factors?
4. Are the groups assembled at a similar point in their disease progression?
5. Was there adequate adjustment for the effects of confounding factors?
6. Was the maximum follow-up at least 2 years?
7. Were dropout rates and reasons for dropout similar across intervention and comparison groups?
8. Was outcome assessment blind to exposure status?
Case series
1. Were consecutive or random-selected patients included?
2. Are the criteria for inclusion explicit?
3. Did all individuals enter the study at a similar point in their disease progression?
4. Was the maximum follow-up at least 2 years?
5. Proportion of patients dropped out or lost to follow-up?
6. Were outcomes assessed using objective criteria or was blinding used?
7. Were data collected prospectively?

Reviews and Dissemination guidelines) [9]. In addition, for all studies we recorded whether the authors had assessed or reported any serious adverse events.

Data Extraction Strategy

After a training session, data extraction was performed by one reviewer and checked by a second reviewer using standardized data extraction forms (one for each design). Data on dose and schedule of radiation and period of treatment, co-interventions, study size, loss to follow-up and methodological quality were extracted. In addition, we extracted the following items: age and sex, stage and variant of disease (tumor size), concurrent/previous treatment, and other potentially relevant patient characteristics.

This review focused on survival outcomes, functioning of important organs such as vision or hearing, and side effects. Additional outcomes were extracted whenever relevant. In case of duplicate publications, only the paper that reported the largest number of patients was extracted. Duplicate papers were, however, screened for additional information concerning design and relevant outcomes.

For each unique study, the study characteristics and results were tabulated. Results were analyzed descriptively.

Results

The search generated 2,385 references. In total, 272 papers were included in the review, reporting on 121 studies (Figure 1). The overall agreement between the two reviewers was 92.1% with a kappa value of 0.73 for the title/abstract phase and 94.9% with a kappa value of 0.89 for the full papers. Table 2 illustrates the number of studies included for all indications of the eye. 37 unique studies were included in this review: five controlled trials, two comparative studies, and 30 case series. 13 studies reported on uveal melanoma and ten on choroidal melanoma. This paper focuses on results of studies on uveal melanoma, choroidal hemangioma and age-related macular degeneration (AMD). Tables in this paper present main findings only. Detailed tables on study characteristics, quality assessment, patient characteristics and results as well as results on choroidal melanoma, iris melanoma and other eye tumors are available upon request.

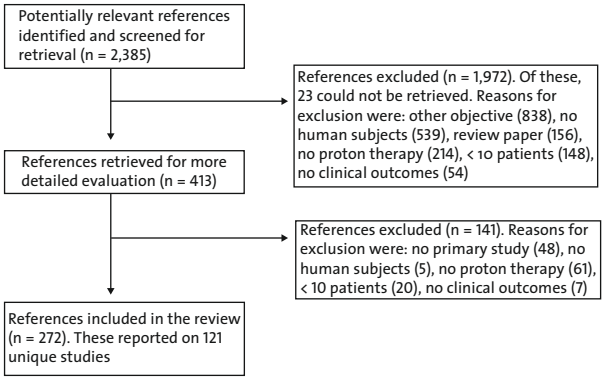

Figure 1. Flow chart of number of references and studies through the review.

Abbildung 1. Flussdiagramm zur Anzahl von Referenzen und Studien dieser Übersichtsarbeit.

Table 2. Number of studies included in the review per indication.

Tabelle 2. Anzahl der in die Übersicht einbezogenen Studien nach Indikation.

	Controlled trials	Comparative studies	Case series
Uveal melanoma	1	0	12
Choroidal melanoma	0	1	9
Iris melanoma	0	0	2
Choroidal hemangioma	0	1	2
Other eye tumors	0	0	4
Age-related macular degeneration (AMD)	4	0	1
Total	5	2	30

Methodological quality of the included studies was poor. None of the controlled trials reported concealment of allocation and only two blinded their patients. Neither of the comparative studies used prospective data collection. Ten of 30 case series included a consecutive patient sample and eight reported a prospective design. There was heterogeneity with respect to the included patients: in two trials, the groups were not similar at baseline, in both comparative studies, patients were not comparable, and in only seven of 30 case series, the patients entered the study at a similar point in their disease spectrum. Serious adverse events were reported or assessed in 15 of 37 studies.

Uveal Melanoma[7]

One randomized controlled trial (RCT) and twelve case series were found reporting on uveal melanoma (Tables 3 and 4). One study was found on recurrent uveal melanoma (# 13).

The RCT including 188 patients, aimed to determine if a reduction in proton radiation dose would decrease radiation-induced complications for patients with uveal melanoma at high risk of these complications (# 1). All tumors were located within four disk diameters of optic disk and/or the macula. The study showed no reduction of visual loss when reducing dose from 70 to 50 CGE proton radiation.

Twelve case series were located (# 2–13). The two largest series included over 2,000 patients who were treated over a period of at least 15 years (# 2 and 3). Survival rates were infre-

[7] Uveal melanoma includes tumors of the choroid, ciliary body, and iris. The majority of uveal melanomas originate in the choroid or ciliary body. Studies that included patients with choroidal and/or ciliary body melanomas were therefore combined with studies that included patients with uveal melanoma. Studies solely reporting on choroidal melanoma are described separately below.

Table 3. Description of studies assessing proton therapy for uveal melanoma. CG: comparison group; EG: experimental group; FU: follow-up; RCT: randomized controlled trial; ?: not clear.

Tabelle 3. Beschreibung der Studien zur Bewertung der Protonentherapie bei Uveamelanomen.

#	Design	Location (unique characteristic[a])	Period	Experimental intervention/ description (dose)	Comparison intervention/ description (fractions and duration)	Patients (n)/ FU duration	Extracted references – (not extracted)
1	RCT	NPTC MGH, USA	1989–1994	Lower-dose proton radiotherapy 50 CGE	Conventional dose proton radiotherapy 70 CGE	EG: 94; CG: 94 Maximum 6 years	[37]
2	Case series	PSI, Switzerland	1984–1999	Proton radiotherapy Mode 54.5 Gy[b] (= 60 CGE)	4 fractions on 4 days	2,645 (2,648 eyes) Median 44 months	[19, 20] – [18, 76, 79]
3	Case series	NPTC MGH, USA	1975–1997	Proton radiotherapy 70 CGE	5 fractions on 7–10 days	2,069 Median 9.4 years	[15, 16, 28] – [13, 14, 17, 26, 29–36, 38–41, 52, 57–60, 65–67, 70]
4	Case series	Orsay, France	1991–2001	Proton radiotherapy 60 CGE	4 fractions on 4 days	1,406 Median 73 months	[10, 43] – [11, 54]
5[c]	Case series	Orsay France (RCT)	1999–2003	(1) Proton radiotherapy; (2) Proton radiotherapy + transpupillary thermotherapy 60 CGE	4 fractions on 4 days	151 Median 38 months	[12]
6	Case series	Nice, France	1991–1996	Proton radiotherapy 57.2 CGE	4 fractions on 4 days	538 Maximum FU range 1–6 years	[8] – [42, 50, 69]
7[d]	Case series	UCSF – CNL, USA	1978–2000	Proton radiotherapy Range 48–80 GyE	4–5 fractions on 5–7 days	199 Up to 15 years	[4] – [7]
8	Case series	HMI, Berlin, Germany	1998–2003	Proton radiotherapy 60 CGE	4 fractions on 4 days	245 Median 18.4 months	[47] – [45]
9	Case series	Clatterbridge, UK	1989–1992	Proton radiotherapy 52 CGE	4 fractions on 4 days	127 Median 36 months	[24]
10[d]	Case series	Clatterbridge, UK	1993–1995	Proton radiotherapy 53 Gy	4 days	17 Median 268 days (n = 57)	[49]
11	Case series	ITEP, Moscow, Russia	?1974–?	Proton radiotherapy 10,000–12,500 rad (= 100–125 Gy)	4–5 fractions with intervals of 1–2 days	63 Mean 33.8 months	[3]
12	Case series	Uppsala, Sweden	1989–1991	Proton radiotherapy 54.6 Gy	4 fractions on 4 days	20 5 years	[61]
Recurrent uveal melanoma							
13	Case series	NPTC MGH, USA	1980–2000	Proton radiotherapy 70 CGE	5 fractions	31 Median 36 months	[55]

[a]Only extracted for studies that were conducted in the same location and period

[b]Treatment started with dose of 70 CGE, this dose was lowered to 65 CGE in a first step, then to 63 CGE, and, finally, to 60 CGE

[c]This study is an RCT comparing proton radiation vs. proton radiation + transpupillary thermotherapy. As the primary outcomes are reported for the two arms combined, the study is extracted as case series

[d]Paper reports also case series on other interventions, only results for proton therapy are displayed. However, where indicated results apply to the entire patient sample

Table 4. Description of results of studies assessing proton therapy for uveal melanoma. KM: Kaplan-Meier; CF: counting fingers; CI: confidence interval; Q1: first quartile; Q3: third quartile; TTT: transpupillary thermotherapy.

Tabelle 4. Ergebnisse der Studien zur Bewertung der Protonentherapie bei Uveamelanomen.

#	Results survival (experimental vs. comparison intervention)	Functional results/recurrence/metastases/local control (experimental vs. comparison intervention)	Adverse effects (experimental vs. comparison intervention)
1	None reported	Visual acuity: median letters decline 13 (Q1–Q3 0–56) vs. 27 (2–55) at 5 years (p = 0.61); proportion preserving useful vision (≥ 20/200) 33 vs. 24 (p = 0.82) Recurrence 2 vs. 3 at 5 years (p > 0.99)	Rubeosis/neovascular glaucoma 9 vs. 7 Enucleation 4 vs. 5
2	KM survival rate subgroup tumor controlled 72.6% ± 1.9% and subgroup tumor not controlled 47.5% ± 6.5% at 10 years Cancer-related mortality 338/2,645 (12.8%)	Actuarial eye retention rate: 88.9% ± 0.8% at 5 years, 86.2% ± 1.0% at 10 years, and 83.7% ± 1.6% at 15 years Recurrence rate 95.8% ± 0.5% at 5 years and 94.8% ± 0.7% at 10 years	Eye enucleation 218/2,648 eyes (8.2%) Causes: confirmed recurrence 38, suspected recurrence 13, tumor evolution not evaluable 11, eye symptoms 65, glaucoma 131, functional loss 146, unknown 4 (there could have been multiple causes)
3	Overall survival 78% at 5 years and 63% at 10 years Disease-specific survival in subgroup parous women 77%, subgroup nulliparous women 75%, and subgroup men 75% at 10 years	Visual acuity < 20/100 14% Local recurrence 45, suggested recurrence in additional 15	Eye enucleation 179/2,069 (8.7%) Causes: glaucoma 46%, blind uncomfortable eye 31%, local recurrence 23%
4	Overall survival 79% (range 77.8–80.2%) at 5 years and 62.9% at 10 years (10-year figure based on subgroup of 167 patients) Metastasis rate 31% at 10 years (based on subgroup of 167 patients)	Visual acuity improved 6%, stable 38%, deteriorated 56% compared to baseline Visual acuity ≥ 20/40 24.4%, 20/200–< 20/40 21.5%, < 20/200 54% at 5 years Recurrences 52 (3.7%)	Eye enucleation for complications 7.7% (range 6.7–8.7%) at 5 years Actuarial rate of glaucoma 28.6% (95% CI 26–31.2) at 5 years Actuarial rate of maculopathy 66.5% (95% CI 63.3–69.7) at 5 years (most fequent complication) Other complications at 5 years: papillopathy 23.4%, cataract 61.8%, keratitis 11.5%, vitrous hemorrhage 13.9%, intraocular inflammation 27.5%
5	Overall survival 126/151 (83.4%) at median 38 months Disease-free survival 116/151 (76.8%) at median 38 months	Preservation eye rate 81% for proton radiation group and 97% for proton radiation + TTT at 5 years (p = 0.02); data read of figure	Glaucoma 76/151
6	Cause-specific survival 96% at 2 years, 87.6% at 4 years, 86.3% at 5 years, and 77.4% at 6.5 years	Eye retention rate 88% Visual acuity (n = 284): improved 54 (19.1%), stable 41 (14.4%), deterioriated 189 (66.5%)	Eye enucleation 38 (7.1%) Causes: tumor progression 15, glaucoma 12, both 6 Glaucoma 55 (10.2%)
7	None reported	Intraocular recurrence 7/199 (3.5%)	None reported
8	None reported	Eye retention 92.6% at median 20 months and 87.5% at 3 years Local recurrence 7 at median 18.4 months	Any grade of (at 3 years) retinopathy 55.7%; optic disk neuropathy 59.8%; rubeosis 19.5%; glaucoma 10.9%; cataract 39.2%
9	Metastatic death 16 (12.6%)	None reported	Eye enucleation 17 (13.4%) Causes: treatment-related morbidity 15, tumor progression 1, unknown 1 Rubeosis 43 (33.9%)
10	Metastatic death 1/17 (5.9%)	Visual acuity: improved 1, stable 12, deteriorated 4 Visual acuity 6/6–6/12 4 (23.5%), 6/18–6/36 7 (41.1%), 6/60–CF 5 (29.4), worse than CF 1 (5.9%)	Eye enucleation: none Main complications: cataract 1, keratopathy 2, maculopathy 1, radiational optic neuropathy 2

(continued next page)

Table 4. *Continued*

#	Results survival (experimental vs. comparison intervention)	Functional results/recurrence/metastases/local control (experimental vs. comparison intervention)	Adverse effects (experimental vs. comparison intervention)
11	Overall survival 29 (46%) at 3 years and 10 (15.9%) at 5 years	Preservation eye 47/63 (74.6%) Intact visual function (not defined) 29 (46.0%) at mean 27 months (range 0.3–4 years)	Eye enucleation 16/63 (25.4%) Causes: 15 presumed failure, 3 either complications or proven failure Complication 12/63 (19.0%) at mean 27 months (radiation-induced cataract in 4, cataract progression in 11, postradiation glaucoma in 11, retinopathy in 3, retinal detachment in 3, and hemophthalmos in 1; multiple complications in 10 eyes)
12	None reported	Recurrence 2/20 (10%) Preservation of vision depended on tumor localization	Acute changes: redness and dryness of skin, no ulceration, no evidence of damage Painful hemorrhagic glaucoma combined with total retinal detachment 7 eyes Eye enucleation 9/20 eyes (45%) Causes: painful glaucoma 7, tumor recurrence 2
Recurrent uveal melanoma			
13	Overall survival 23 (64%) at 5 years	Retained useful vision ($\geq$ 20/200): 27% at 5 years Eye retention rate 55% (95% CI 25.2–77.4) at 5 years	Eye enucleation 9 (29%) Causes: local recurrence 5, intractable pain 4 Complications: glaucoma 4 (treated conservatively, radiation-induced cataract 12 (of which 3 were later enucleated)

quently reported; disease-specific survival was at least 75% at 3–10 years in three studies (# 3, 5, and 6). Overall survival varied between 15.9% and 83% at 3–5 years (# 3, 4, 5, and 11). Significant rates of impaired vision (up to 54%) and secondary enucleation rates (up to 45%) were reported. Specific eye complications such as glaucoma, optic disk neuropathy and maculopathy were prevalent in up to 66% of the patients after proton radiation. Glaucoma seemed to be an important reason for eye enucleation.

In addition, we found ten unique studies reporting on choroidal melanoma[8], among which one comparative study.

Choroidal Hemangioma

We found one comparative study with historical controls and two case series (Tables 5 and 6).

44 consecutive patients were treated in the comparative study with historical controls (# 1). 25 patients received proton radiotherapy and 19 controls received photon radiotherapy. This study showed that proton as well as photon radiation were effective in resolving retinal detachment. Proton therapy, however, appeared to be associated with more side effects.

Two small case series were found; including 53 and 17 patients. The results suggested that vision improved in the majority of patients. Although these studies reported that no radiation-induced complications were found, such complications were reported for a subgroup of eyes that received a higher radiation dose.

Subfoveal Choroidal Neovascular Membranes (CNVM) Associated with Age-Related Macular Degeneration (AMD)

We located four clinical trials and one case series (Tables 7 and 8).

Two RCTs compared proton versus sham radiation or observation (# 1 and 2). The first trial reported no differences between the two groups with regard to visual acuity. The second presented a reduction of vision loss in the proton group compared to controls at 1 year. However, this difference was not significant at 2 years.

Two trials compared two doses of proton radiation (# 3 and 4). The first RCT evaluated 166 patients who were randomized to lower-dose (16 CGE) or to higher-dose (24 CGE) proton radiotherapy (# 3). No differences between the two groups were demonstrated.

The nonrandomized study suggests more favorable results on visual acuity for the high-dose compared to the low-dose groups, however, the rate of adverse events was also higher in the high-dose group.

[8] It should be noted that results of these patients could also be included in the section "Uveal Melanoma" if a specific study reported the results for choroidal melanoma combined with results for other types of eye tumors or in combination with ciliary body tumors. Results of these studies are presented in tables only as the results are very similar to those of uveal melanoma.

Table 5. Description of studies assessing proton therapy for choroidal hemangioma. FU: follow-up.
Tabelle 5. Beschreibung der Studien zur Bewertung der Protonentherapie bei choroidalen Hämangiomen.

#	Design	Location	Period	Experimental intervention/description (dose)	Comparison intervention/ description (fractions and duration)	Patients (n)/ FU duration	Extracted references–(not extracted)
1	Comparative study with historical controls	Berlin, Germany	1993–2002	(a) Proton radiotherapy 20 CGE (4 fractions on 4 days)	(b) Photon radiotherapy 16–30 Gy (5 fractions/week)	(a) 25; (b) 19 (a) Median 23.7 months; (b) median 29 monts	[48]
2	Case series	PSI[a], Switzerland	1988–1997	Proton radiotherapy Range 16.4–18.2 Gy	4 fractions on 4 days	53 (54 eyes) Mean 30.4 months	[77] – [78]
3	Case series	Orsay, France	1995–2000	Proton radiotherapy 20 CGE	4 fractions on 4 days	17 Mean 52 months	[25]

[a]Paper was published by authors of Lausanne that generally cooperate with PSI

Table 6. Description of results of studies assessing proton therapy for choroidal hemangioma.
Tabelle 6. Ergebnisse der Studien zur Bewertung der Protonentherapie bei choroidalen Hämangiomen.

#	Results survival (experimental vs. comparison intervention)	Functional results (experimental vs. comparison intervention)	Adverse effects (experimental vs. comparison intervention)
1	None reported	Retinal detachment resolved in all versus all but 1 Visual acuity stabilized in 93.2% of the patients (in two groups combined)	Grade 4 retinopathy 1 vs. 0 Grade 3 adverse effecs on lens 0 vs. 1 Grade 3 lacrimation 1 vs. 1 Any grade retinopathy 40% vs. 15.7%
2[a]	None reported	Visual acuity improved (n = 22), stable (n = 9), deteriorated (n = 0)	Any radiation-induced vascular alterations: none
3	None reported	Visual acuity improved $\geq$ 2 Snellen lines 9, stable 6, deteriorated 2/17 at 6 months Visual acuity improved 16, stable 1/17 at 2 years Recurrence 1/17	Any complications: none

[a]Results refer to the subgroup of patients that received a treatment dose between 16.4–18.2 Gy and were followed up for at least 1 year (n = 31)

One small prospective case series was found, that reported stable or enhanced visual acuity for 86% at 3 months and 61% at 18 months (# 5). No secondary effects related to the treatment were observed.

Discussion

This systematic review of the literature aimed to give an overview of evidence around proton radiation for any indication of the eye. Evidence on the efficacy and safety of proton therapy was limited because of the poor standards of conduct and reporting of the included studies. As important health problems and a lot of money are involved in this field, the level of evidence should be lifted to a higher level as soon as possible. Two previously performed systematic reviews were found [53, 62] both stressing the lack of RCTs in this field. Although we do agree with them, we would take our discussion a bit further and formulate suggestions of how to improve this in future.

We identified only five trials and their methodological quality was poor. Goitein & Cox [27] argued that it is unethical to require RCTs comparing protons versus photons as there will never be equipoise. Although we agree that real equipoise is required before an RCT is performed and it may be challenging to perform RCTs on proton therapy, this should not be an excuse to never use this strong design. For eye tumors, for example, dose-finding RCTs with the aim to decrease the side effects would add to the evidence. The limited availability of proton therapy may provide opportunities for comparative studies comparing proton radiation with alternatives given in other treatment centers.

The methodological quality of observational studies was equally poor. The majority of included studies were case series. The use of case series for effectiveness research questions is highly susceptible to bias, mainly because of the lack of a control group [9]. In addition, prospective data collection

Table 7. Description of studies assessing proton therapy for subfoveal choroidal neovascular membranes (CNVM) due to age-related macular degeneration (AMD). FU: follow-up; RCT: randomized controlled trial; ?: not clear.

Tabelle 7. Beschreibung der Studien zur Bewertung der Protonentherapie bei subfovealen, choroidalen neovaskulären Membranen aufgrund altersbedingter Makuladegeneration.

#	Design	Location	Period	Experimental intervention/ description (dose)	Comparison intervention/ description (fractions and duration)	Patients (n)/ FU duration	Extracted references – (not extracted)
1	RCT	?USA	1998–2000	Proton radiotherapy 16 Gy, 2 fractions on 2 days	Sham radiation	37 enrolled, 20 vs. 10 analized Up to 24 months	[5, 6]
2	RCT	?	?	Proton radiotherapy 4 × 4.5 Gy	Observation	39 vs. 28 Not reported	[44]
3	RCT	NPTC MGH, USA	1995–2000	Lower-dose proton radiotherapy 16 CGE	Higher-dose proton radiotherapy 24 CGE	196 enrolled, 87 vs. 79 analized Up to 24 months	[74]
4	Nonrandomized trial	Loma Linda, USA	1994–?	Lower-dose proton radiotherapy 8 CGE	Higher-dose proton radiotherapy 14 CGE	21 vs. 27 eyes Mean 22.1 months	[23] – [72, 73]
5	Case series	Nice, France	1997–1998	Proton radiation 10 CGE	Single dose	58 Up to 18 months	[80]

Table 8. Description of results of studies assessing proton therapy for subfoveal choroidal neovascular membranes (CNVM) due to age-related macular degeneration (AMD). MAR: minimum angle of resolution.

Tabelle 8. Ergebnisse der Studien zur Bewertung der Protonentherapie bei subfovealen, choroidalen neovaskulären Membranen aufgrund altersbedingter Makuladegeneration.

#	Results survival (experimental vs. comparison intervention)	Functional results (experimental vs. comparison intervention)	Adverse effects (experimental vs. comparison intervention)
1	None reported	Average visual acuity (log of MAR) 0.58 (± 0.30, n = 8) vs. 0.67 (± 0.24, n = 5) at 2 years Change in visual acuity (loss in number of lines) 1.25 ± 3.47 vs. 1.63 ± 2.39 at 1 year	Retinal detachment unrelated to treatment 1, non-impairing optic neuropathy 1, no case of radiation retinopathy
2	None reported	Moderate vision loss (≥ 15 log MAR letters) 40% vs. 77% at 12 months (p = 0.01) and 72% vs. 88% at 24 months (p = 0.4)	None reported
3	None reported	Moderate vision loss (≥ 3 lines): 49 eyes (62%) vs. 39 eyes (53%) at 2 years (p = 0.40) Severe vision loss (≥ 6 lines): 19 eyes (25%) vs. 18 eyes (26%) at 2 years (p = 0.82)	Radiation complications 14 vs. 12
4	None reported	Visual acuity stabilized or improved 44% vs. 75% at 1 year Severe vision loss (≥ 6 Snellen lines) 19% vs. 0% at 1 year and 27% vs. 0% at 21 months Local control: decreased area of leakage 50% vs. 95% at 1 year and 27% vs. 100% at 18 months	Radiation retinopathy 0% vs. 48% (11/23) Lash loss, uveitis, conjunctival hyperemia, cataracts or optic nerve margin swelling 0% vs. 0%
5	No survival data nor deaths reported	Vision improved (> 2 lines), unchanged (equal or ± 2 lines), deteriorated (> 2 lines) 10%, 39%, 51% at 18 months (n = 22) and 2%, 84%, 14% at 3 months (n = 50)	No radiation cataracts or retinopathies 4 patients with keratitis, which resolved

was reported by only 24% of the case series and consecutive patient sampling by only 31%. This combination results in an unpredictable impact of selection on survival outcomes or side effects.

Also, there are reasons to believe that follow-up was inadequate as we noticed short-term follow-up in studies with slow-growing cancer types such as iris melanoma. Some authors expressed concern about studies where study investigators were not the same as the clinicians who would see patients with complications or side effects, and therefore would miss relevant side effects. All these factors could lead to an underreporting of (serious) side effects.

The poor quality and reporting of mainly observational studies are not unique to proton radiation [63, 68]. Several factors specific to this field, however, could be due to this. First, many case series have started ≥ 20 years ago and still continue. Radiation techniques as well as diagnostic possibilities have evolved leading to heterogeneity in intervention and patient characteristics. Although a large size typically is associated with more precise estimate of results, this may not be true for proton therapy. Also, the methodological knowledge has evolved over the past 10 years and, consequently, older studies cannot be accounted for something what was not known at that time. For indications of the eye, smaller case series are indicated to take the heterogeneity into account and provide more worthwhile results.

The implementation of reporting standards [21] will improve reporting of observational studies without major investments. To improve conduct, ideally, a study should be carried out in a setting suitable for complex research such as highly specialized hospitals. The study should be performed by a research team including a radiation oncologist, a clinical epidemiologist, and a specialist in research methods. Future observational studies for indications of the eye should at least use a prospective design, sample patients consecutively and include a patient sample sufficiently homogeneous to answer the research question. When groups are being compared, all efforts must be made to have groups that are comparable on the most important confounding variables.

Survival rates were infrequently reported for uveal melanoma. In general, survival is the most important outcome for malignant disease. However, cumulative uveal melanoma-related mortality increases up to 35 years after surgery [51], meaning that only studies with a long follow-up would be useful for this purpose. In addition, survival will be less relevant for the benign lesions covered in this review. Outcomes such as tumor control and recurrence in these studies should be considered with caution, as a recent discussion showed that the criteria for classifying uveal melanoma regression patterns have changed over time [2, 22], which could lead to inconclusive classifications within the same time series [46]. Therefore, most relevant outcomes in this review may be functioning of the eye, enucleation, and side effects.

This review shows substantial heterogeneity among patients in factors that predict outcome such as tumor size, tumor location, baseline vision, etc. Gragoudas et al. [28] confirmed that, for example, risk factors for eye loss were tumor height and distance of the tumor from the macula and optic disk. These factors are especially relevant when comparing treatments. The lack of adjustment for confounding factors may distort results, especially in observational studies [64]. Thus, such factors should be taken into account when comparing several interventions using observational study designs.

In this review the effect of proton therapy was evaluated. Alternative treatments, currently used most widely for uveal melanomas are ruthenium/rodium-106 applicators and iodine-125 applicators [75]. Based on dose application properties, the treatments have their own advantages, and based on these arguments, patients are selected for the treatments. Ruthenium applicators are suitable for the treatment of dome-shaped melanomas that do not exceed 5 mm in thicknes [75], iodine applicators are used for medium-sized melanomas, and proton radiation is typically used for high-risk cases. A recent study on the effects of ruthenium-106 showed that a higher dose reduces the risk of metastasis, but it may be associated with more side effects [56]. Only one study directly compared the three treatments for uveal melanoma [71]. However, the results of the study may be distorted by selection bias, as treatment selection was based on tumor characteristics. This confirms that, currently, there is too little evidence to make informed decisions on which treatment should be preferred.

Results and Implications for Research

Results on uveal melanoma and choroidal melanoma showed favorable survival outcomes with significant rates of side effects. The challenge for future studies is to investigate how to preserve the encouraging survival outcomes while reducing treatment complications. Dose-finding RCTs and comparative studies should be used for this purpose.

Indications such as hemangiomas and AMD are benign conditions and, therefore, side effects will even be more important. Observational studies to investigate the incidence of side effects would be of benefit here. For all studies there would be a need of a sound design that incorporates adequate follow-up and relevant outcomes such as long-term survival, functional outcomes, and acute and late adverse events with indication of seriousness should be assessed. These developments will bring the evidence on proton radiation to a higher level.

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