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Literature Review

Comparing plaque brachytherapy and proton therapy for choroidal melanoma: a review of the literature

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Abstract

The aims of conservative treatment in patients with ocular melanoma are globe retention, good visual acuity (VA) and local control. Two well-established radiation conservative treatment options are proton beam radiotherapy and episcleral plaque brachytherapy (EPB). Patients who receive treatment with either of these options will experience some degree of radiation-related ocular complications and poor VA. The purpose of this review of the literature is to establish whether there is a significant clinical difference in normal tissue morbidity and local tumour control between proton therapy and EPB, and whether this difference can justify the purchase and implementation of additional proton therapy facilities. Based on this review, evidence suggested that both treatment options are comparable, and that neither proton therapy nor EPB is clinically superior than the other regarding normal tissue morbidity and local tumour control. This review highlighted the need for further research on a larger scale in order to bridge the gap that is apparent within the literature.

Keywords

Ocular melanoma; brachytherapy; proton therapy; choroidal melanoma

INTRODUCTION

Malignant tumours of the eye are classified as ''orbital'' (involving the bone surrounding the orbital cavity) or ''intraocular'' (in the eye). Ocular melanoma comes under the intraocular classification, mostly affecting the uveal tract, in particular the choroid.[1] Uveal melanoma is the most common type of ocular melanoma, arising along the uveal tract of the eye, specifically affecting the choroid, ciliary body and iris, and accounts for 5% of all melanomas.[2] Each of these structures is heavily coloured with melanin. Malignant melanoma of the uveal tract affects six in every million people per annum, with 15% arising in the ciliary body and the remaining 85% in the choroid.[3]

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Treatment options

When considering the treatment option for uveal melanoma, factors such as tumour size, activity, location, growth pattern, the patient's general health, age and status of the fellow eye must be taken into consideration.[4] Table 1 demonstrates the treatment options according to tumour size.

Of these, episcleral plaque brachytherapy (EPB) and proton therapy are commonly

Table 1. *Treatment options according to tumour size*

Small melanomas (<10 mm in diameter and <3 mm thick)	Medium melanomas (10–15 mm in diameter and 3–8 mm thick)	Large melanomas (>15 mm in base diameter and >8 mm thick)
Observation	Plaque brachytherapy	Local resection
Laser photocoagulation*	Proton therapy	Plaque brachytherapy
Thermotherapy*	Carbon ion radiotherapy	Enucleation**
Charged particle radiotherapy*	Local resection	
Plaque brachytherapy*	Ablative laser therapy	
Local resection*	Thermotherapy	
Cryotherapy	Stereotactic radiosurgery	
	Enucleation	4–8

*Used for tumours that show clinical risks for metastasis.
**Preferred method due to ocular intolerance of conservative methods.[4,30,45–48]

Table 2. *Brachytherapy and proton therapy studies*

	Study dates	Plaque brachytherapy (no. of patients enrolled)	Proton beam radiotherapy (no. of patients enrolled)
Wilson, 1999	1990–1994	190 ^{125}I, 140 ^{106}Ru	267
Damato, 2005	1993–2001	458 ^{106}Ru	349
Desjardins, 2003	1989–1998	346 ^{125}I	926
Gerard, 2000	1983–1998	219 ^{106}Ru	226
		1,353	1,768

accepted treatment options, as summarised in Table 2, and are more favourable than conventional radiotherapy due to their physical characteristics.[5–7] EPB treats a small volume with an extremely heterogeneous dose distribution. A radioactive plaque is used to produce γ or β rays. The dose to the tumour base can be greater than or equal to the dose to the tumour apex. The plaque is placed directly over the tumour allowing a high dose to be delivered with rapid fall off in dose to adjacent normal tissue.

Proton therapy involves highly conformal target volume shapes. Clinically useful protons are produced using a particle accelerator such as cyclotron or synchrotron. The high-dose region or ''Bragg peak'' is narrow due to the proton beams being monoenergetic; this allows for a uniform dose to be delivered to the entire tumour with minimal entrance and exit dose (Figure 1).

Normal tissue morbidity and local tumour control

Due to the anatomical location of ocular melanomas, critical structures are abundant and in close proximity to each other. Radiation damage to key structures within the eye causes increased morbidity and consequent quality-of-life issues.[8] Accurate and highly localised treatment are paramount in order to achieve as little normal tissue morbidity as possible while providing good tumour control probability.[9] Many studies[10–13] have investigated the normal tissue morbidity and local tumour control in patients treated with EPB or proton therapy for choroidal melanoma. Within this review, a comparison of the outcomes in patients treated with the two modalities was made to determine which treatment option is superior. There is currently a lack of clinical availability of proton therapy facilities, and this is largely associated with the cost of proton centres.[14]

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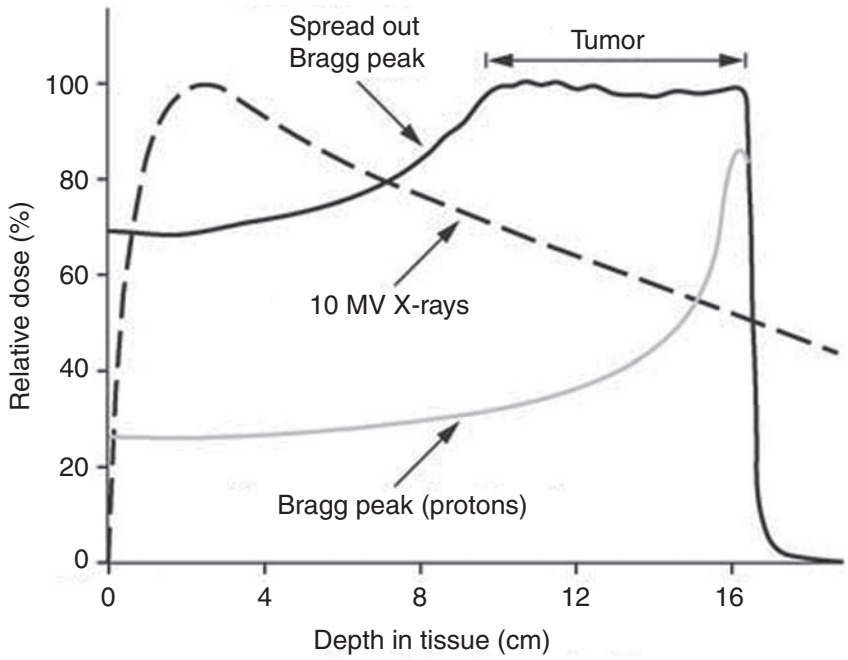

Figure 1. Depth-dose distribution in tissue of a single Bragg peak (grey), a spread-out Bragg peak (black), which consists of multiple Bragg peaks of different energy added together, and a 10 MV X-ray beam (dashed).[41] *Both EPB and proton therapy offer improved conformality and preservation of normal tissue compared to conventional radiotherapy.*[4,42–44] *EPB, episcleral plaque brachytherapy.*

Whether treatment outcomes can justify additional proton centres will also be considered.

METHODS

A literature review was performed to compare normal tissue morbidity and local tumour control for proton therapy and EPB in order to determine optimum treatment choice and inform decisions concerning new equipment purchase.

Design limitations

Much of the literature reviewed consisted of studies that were single centre, retrospective, cohort studies. To generalise findings from a single centre and apply them to other centres can introduce bias into the findings. Retrospective studies use data that was not necessarily collected for research purposes; therefore, they may lack essential information. Reviewed articles were scrutinised for evidence of potential bias during the critical review process.

Reliability and validity

The reliability and validity of the literature reviewed in this research project was ensured by use of the CASP literature appraisal tool.[15] By applying a series of questions to the literature, it was possible to assess the credibility, reliability and validity of the article.

Outcome measures

Ocular preservation, function and cosmesis are important factors for patients with a choroidal melanoma diagnosis.[12] In addition to this, other aims of therapy are to maintain local control, patient survival and good visual acuity (VA).[16] VA is the ability of the eye to perceive details. Evidence indicates that these can be achieved with EPB or proton therapy, which are both well-recognised conservative methods of treatment.[6,10–13,15–17]

Both of these treatment options involve the use of radiation therapy, and consequently,

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radiation damage to surrounding healthy tissue can result in acute and late effects, such as poor VA, ocular pain and discomfort.[18,19] Late effects can develop months or years after treatment; these can be problematic with effects having permanent damage and resulting in partial or complete loss of function.[19] It is the level of normal tissue irradiation that ultimately results in frequency and severity of late effects.

Many authors have used radiation-related complication as an outcome measure to determine normal tissue morbidity.[12,13,17,20] Outcome measures of radiation-related complications are presented as ocular complications and tumour events, such as recurrence, metastases and melanoma-related mortality. These outcome measures have been used for both proton therapy and EPB. Normal tissue morbidity can result in conditions that have an impact on the quality of life of a patient.[18,21] Normal tissue morbidity is relative to the level of radiation-related ocular complications, ocular function and VA. These are used as outcome measures to determine the normal tissue morbidity as a result of radiation treatment.[17,20] VA loss has an impact on quality of life as it affects many activities of daily living.[22] VA can be used as a single outcome measure or in addition to radiation-related complication measures to demonstrate normal tissue morbidity. Much of the data and results demonstrate VA as measured using Snellen or Bailey–Lovie charts (Figure 2).[23,24]

Patient condition

Findings suggest that normal tissue morbidity was similar for both types of treatment.[6] Patients with predisposing medical conditions such as diabetes, retinal detachment or glaucoma were more likely to experience a greater degree of normal tissue morbidity, irrespective of modality of choice.[20,25] Other influencing prognostic factors included male gender and a median age of 55 years.[17,25]

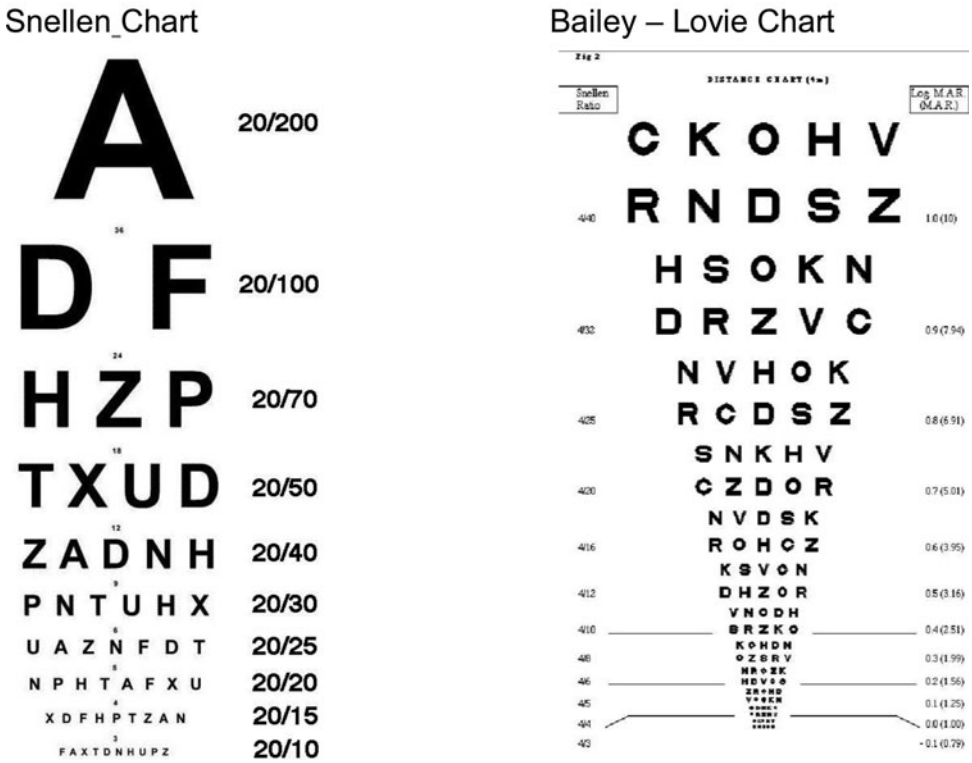

Figure 2. Visual acuity chart.[23,24]

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Tumour location

Tumour location was also found to be a determining factor. A tumour located near to the optic disc or fovea is more problematic and likely to result in greater ocular morbidity.[11,12] With both EPB and proton therapy, ideally a 2–2.5 mm margin is required to ensure adequate tumour coverage.[10,11] Although there was little evidence to indicate that either proton therapy or EPB predominantly results in greater normal tissue morbidity, some findings did suggest that anterior segment complication was higher when using proton therapy.[12,20] This occurs due to the beam having to pass through critical structures within the anterior segment.

VA comparison

The Collaborative Ocular Melanoma Study (COMS)[26] was a large-scale multicentre randomised controlled trials consisting of three arms. The second arm of the COMS compared the effectiveness of brachytherapy to enucleation for treatment of medium-sized choroidal melanomas. Patients with medium choroidal melanomas were randomised to iodine-125 (^{125}I) EPB or enucleation. COMS report no. 16 reported VA during 3 years after treatment in patients in the ^{125}I brachytherapy arm. The sample consisted of 657 randomly assigned patients, of which the VA data of 623 was included in the report. VA was determined using Snellen and Bailey–Lovie charts and standard lighting. A baseline VA was carried out prior to treatment, which was later to be used for comparison. A loss of six or more Snellen VA lines from baseline was defined as VA loss. All 623 patients were enrolled for at least 12 months following treatment; VA follow-up results of 93 and 80% at 2- and 3-year follow-up intervals, respectively, are tabulated below (Table 3).

The results showed that treatment using ^{125}I brachytherapy preserved a relatively high level of VA in over 50% of patients within the first year after treatment. This declined at an average rate of approximately two lines per year, with 43–49% of treated eyes having significant VA impairment 3 years after treatment.

In a single centre, retrospective analysis of a series of 136 patients treated with ^{125}I brachytherapy between 1990 and 2000, Lumbroso-Le Rouic et al. found that the mean VA at 5 years was 20/40; this is considerably higher level of VA than the findings in the COMS.[27] Sagoo et al.[28] conducted a retrospective medical record review over 31 years. Although this study had a long review period, it had a limited number of participants. Thirty-seven consecutive patients were involved, who were monitored for long-term VA; the findings were similar to that in the COMS with VA of 20/200 or worse being observed in 62% of patients with 57% losing more than five Snellen VA lines.[28]

Table 3. *COMS visual acuity follow-up*

Months since enrolment	**0**		**12**		**24**		**36**	
Visual acuity	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**
≥20/20	208	33.4	152	24.4	97	16.8	62	12.4
20/25–20/40	230	36.9	203	32.6	136	23.6	93	18.6
20/50–20/80	80	12.8	70	11.2	75	13.0	53	10.6
20/100–20/160	38	6.1	35	5.6	34	5.9	43	8.6
20/200–20/320	25	4.0	37	5.9	39	6.8	32	6.4
20/400–20/640	13	2.1	27	4.3	27	4.7	24	4.8
≤20/800	23	3.7	73	11.7	98	17.0	116	23.2
Enucleated	0	0.0	9	1.4	23	4.0	1	6.2
Not available	6	1.0	17	2.7	48	8.3	47	9.4
Total patients	623	100	623	100	577	100	501	100
Mean visual acuity	20/32		20/40		20/50		20/125 (ref. 25)	

COMS, Collaborative Ocular Melanoma Study.

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Damato et al.[10] used VA as an outcome measure in 349 patients treated with proton beam therapy. This was a single centre study, which was carried out over a period of 10 years. Patients were prospectively and consecutively included. To measure VA, the Snellen chart was used, as well as counting fingers method. Baseline VA in the tumour-affected eye was logged prior to the start of treatment. Two hundred and twelve patients had 20/40 or better vision at this time. VA conservation of this level at follow-up is summarised as follows (Table 4):301 patients had 20/200 or better initial VA. This level of VA was conserved in 81.9% at 2 years, 61.1% at 5 years and 41.7% at 8 years. The study demonstrated that the greater the initial tumour height, the sooner loss of VA occurred.[10]

Courdi et al. looked at VA following proton beam therapy for uveal melanoma.[29] This was a single centre prospective study reporting on 538 patients treated over a period of 5 years; the VA of 284 patients was adequately scored before and during follow-up. Patients were assessed according to a scale other than the Snellen or Bailey–Lovie chart to allow easy estimation of the change in VA following treatment. The scale ranged from 0 (being no light perception) to 14 (being 200/200 vision). The results showed that VA was initially improved in many patients immediately after treatment; however, it became gradually more impaired as length of follow-up time increased.

Table 4. *Visual acuity conservation*

Percentage of patients with 20/40 or better vision	Follow-up (years)
63.5	2
44.8	5
32.2	8

Local control

Local control is defined as tumour shrinkage and growth cessation.[30,31] As an outcome measure, local control failure was considered to be tumour regrowth, recurrence, metastases or the need for enucleation.[10–13,15–21,28,31–36] The review suggested that overall proton therapy was slightly more favourable than EPB (see Table 5) in terms of local control rates at 5- and 10-year follow-up.[12,31,37]

Choice of radioisotope

The local control outcome for proton beam therapy is consistent within the literature; however, EPB outcomes vary depending on radioisotope used. Radioisotopes such as gold-198 (^{198}Au) plaque and palladium-103 (^{103}Pd) plaque are less widely used within clinical practice, with ^{125}I being the most commonly used. Based on the findings in this review, local control rates for patients treated with ^{125}I are lower than those with 103^{Pd} or 198^{Au}. Further research should be carried out to provide a more sound evidence base for the use of 103^{Pd} and 198^{Au}, with a view to these becoming more routinely used over ^{125}I.

Table 5. *Enucleation free survival and local control rates*

Author	Proton therapy or plaque	Enucleation free survival (years)	Local control rate (years)
Karvat et al., 2000	^{198}Au plaque	94% (5 years)	98% (5 years)
Shields et al., 2002	Plaque (no specific type)	–	87% (10 years)
Finger et al., 2002	^{103}Pd plaque	94% (mean 4.6 years)	96% (mean 4.6 years)
Rouberol et al., 2004	^{106}Ru plaque	–	82% (5 years), 72% (10 yrs)
Jensen et al., 2005	^{125}I plaque	–	83% (5 years)
Fuss et al., 2001	Proton therapy	75.3% (5 years)	90.5% (5 years)
Höcht et al., 2001	Proton therapy	87.5% (3 years)	96.4% (Med f/u 18.4 months)
Egger et al., 2001	Proton therapy		95.8% (5 years), 94.8% (10 years)

Med f/u, medical follow-up.

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DISCUSSION

Modality choice

Proton beam radiotherapy and EPB are both effective treatment options in the management of choroidal melanoma.[6] The efficacy of each option, measured by comparing normal tissue morbidity and local tumour control, is largely dependent on factors such as tumour size and location, and in EPB, the radioisotope used.[5] The relatively low incidence of choroidal melanoma and the variety of treatment options make it difficult to gather data on long-term results for a large number of equally treated patients.[38] This limitation makes it difficult to establish conclusively which treatment method is most effective.

The literature does, however, suggest that EPB is most effective in the treatment of medium and large posterior choroidal melanoma,[25,30] while proton therapy is most effective for small posterior tumours close to the optic nerve and fovea.[10] Proton is also effective for tumours that are too large for EPB when the patient is unsuitable for surgery. However, given the variability in methods and patient selection criteria in the literature reviewed, a comparison of the results does not provide reliable support for this recommendation. In order to do this, a prospective, multicentre, randomised controlled trial would be necessary. Because treatment outcome is influenced by a variety of prognostic factors, many controls with highly specific inclusion and exclusion criteria would need to be considered in order to ensure reliability.

Clinical availability

The clinical availability of proton therapy is limited due to the small number of clinical sites with proton facilities; there are currently only 26 facilities in operation worldwide.[39] Inevitably, this has an impact on its viability as a treatment option. This limitation is largely associated with the cost of proton centres, including installation fees, equipment and software expenses and personnel to maintain the equipment.[14] Had the findings within this study demonstrated more favourable outcomes in patients treated with proton therapy, a comprehensive cost analysis would have been suggested to consider costs arising as a result of treatment failure using EPB.

Conversely, ophthalmic EPB is a widely available, well-established, conservative treatment option for choroidal melanoma.[18,33] The increased commercial availability of this option compared to proton therapy unsurprisingly makes plaque brachytherapy first-choice option in ocular-conserving treatment for patients with choroidal melanoma.[33] However, this alone should not govern the choice of modality.

CONCLUSION

EPB and proton therapy treatments induce growth arrest and its slow involution over several years.[40] Both are comparable with regards to normal tissue morbidity, as measured by VA and radiation-related complications. Prognostic factors such as gender and predisposed medical conditions influence ocular complications after treatment, more than radiation type.[17] Results suggest proton beam therapy offers better local control at 5- and 10-year follow-up when compared to EPB. This review has highlighted the need for a large-scale, prospective, randomised controlled trial to determine the reproducibility of these results.[12]

Tumour size and location affect local control and normal tissue morbidity outcomes. Tumours located close to the optic nerve can be difficult to plaque, and there is higher risk of developing radiation maculopathy or optic neuropathy, and marginal failure.[20] Proton therapy is indicated for tumours close to critical structures as the beam can be highly focused.[10] Posterior tumours are often best treated with EPB, as anterior segment complications can arise if proton therapy is given.[12,20]

The numbers of requests for an eye-preserving therapy as an alternative to enucleation have increased due to the availability of long-term results of proton therapy.[12] Either treatment option can be routinely used within the

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clinical setting. In order to reap the benefits of each treatment option and achieve ocular retention with good VA and local control, it is necessary to select patients carefully and appropriately when choosing modality.[16] Proton therapy is less routinely used due to the lack of clinical availability; however, 20 new proton therapy facilities are in the planning phase or currently under construction.[39] Based on this review, neither option is significantly superior to the other; clinically, therefore, further research should be undertaken before establishing whether more proton therapy facilities or EPB facilities should be pursued.

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