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Horizon Scanning Report

Proton beam therapy for the treatment of uveal melanoma

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ASERNIP-S

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Table of Contents

Tables

Figures

Executive Summary

Uveal melanoma is the most common primary intraocular malignant tumour with an incidence of 6 to 7 cases per 100,000 population. Therefore, approximately 5,000,000 individuals worldwide are affected by this tumour (Dendale et al. 2006, Damato 2004). In Australia, 233 new cases of ocular cancers were reported in 2001; however, unlike other cancers (e.g. skin melanoma), the incidence of malignant ocular tumours is projected to remain relatively stable. Before the development of modern eye conserving treatment modalities, identification of uveal melanomas is usually followed with enucleation (removal of the eye). However, with the development new techniques, current treatment is aimed at conserving comfortable and cosmetically acceptable eye with useful vision whenever possible. Radiotherapy in particular has gained substantial popularity as one of the main treatment modalities for uveal melanoma at the time of writing, the two methods commonly utilised is brachytherapy (plaque radiotherapy), which involves the implantation of radioactive seeds to destroy the tumour, and external beam therapy (utilising photons and charged particles). One of the key difficulties in utilising radiotherapy for the treatment of uveal melanomas is confining the radiation dose to the target tumour. Photon radiotherapy is particular has dose-distribution characteristics that leads to the irradiation of healthy tissue adjacent to the target tumour, potentially leading to substantial radiation-induced damage which may result in long-term morbidity or the development secondary tumours (see Figure 1).

An alternative form of external beam radiotherapy, proton beam therapy, was developed to treat tumours in patients where surgical excision is deemed impossible, too dangerous or unsuccessful. The key advantage of protons compared to photons is its superior dose-distribution profile (see Figure 1), protons have a very rapid energy loss in the last few millimetres of penetration and therefore has a sharply localised peak dose known as the Bragg peak. By modulating the penetration depth of the protons (determined by the initial energy of the proton), it is possible to target the Bragg peak precisely to the target tumour while sparing the healthy tissue beyond the tumour from radiation. This could prove to be very useful in the case of uveal melanomas, where sensitive structures (fovea, optic disc etc.) are often located in close proximity to the tumour. Patients undergoing proton beam therapy are required to undergo a surgical procedure to suture tantalum clips onto the sclera around the tumour base to identify the tumour margins. In addition to this, a 3D model of the patient's eye will be constructed with a treatment planning program in order to precisely identify the location of the tumour and to ensure than the proton beam is targeted accurately.

Studies have shown that a considerable amount of complications can occur when treating uveal melanomas with radiotherapy, and proton beam therapy is of no exception. Some of the common complications reported include rubeosis, neovascular glaucoma, cataract and vision loss. Overall, studies have shown that patients treated with proton beam therapy for uveal melanoma experience substantial complications. However, due to the lack of comparative studies and the large variation between existing proton beam therapy studies, no firm conclusion can be deduced on the relationship of proton beam therapy and these ocular complications. Most of the studies included in the report are confident that proton beam therapy is capable of

achieving good tumour control rates (~ 95%), which is at least comparable to brachytherapy. In addition, patient survival rates are similar to brachytherapy a well. In one comparative study, enucleation rates appear to be higher for proton beam therapy patients compared to patients treated with ^{125}I and ^{106}Ru brachytherapy (Wilson and Hungerford 1999); however there was a significant variation in pre-treatment prognostic variables between the patient groups. It should be noted that studies on proton beam therapy for the treatment of uveal melanomas varied substantially with regards to patient characteristics, tumour size, treatment margins and total apical radiation dose. Therefore, comparisons across studies are often difficult and the lack of high-quality evidence prevents the elucidation of the advantages of proton beam therapy compared to other existing radiotherapy techniques.

At the time of writing, there were no cost-effectiveness studies on the utilisation of proton beam therapy for uveal melanoma. However, one study on the general costs associated with the installation and the operation of a proton beam facility was retrieved. Goitein and Jermann (2003) estimated that the construction of a two-gantry proton facility would cost approximately €62,500,000; in comparison construction of an X-ray facility would cost €16,800,000. Operational costs per fraction were estimated to be €1025 for proton therapy and €425 for X-ray/photon therapy. It is likely that proton beam therapy will continue to be substantially more expensive compared to conventional photon therapy despite accounting for future cost reductions.

In conclusion, the evidence on the safety and effectiveness of proton beam therapy for the treatment of uveal melanomas is mixed. The local tumour control rates achieved are remarkably consistent across studies despite the heterogeneity across study cohorts and methodology, and at the very least appears to be comparable to brachytherapy. Meanwhile, the incidence of metastasis and overall patient survival is comparable to brachytherapy as well. However, it is unclear if proton beam therapy results in a substantial improvement of eye preservation rates and the ocular complications observed post-treatment are of concern. Further studies are required to address the limitations of previous studies and to compare proton beam therapy to existing techniques.

HealthPACT Advisory

The use of proton beam therapy as another form of radiotherapy for intraocular melanoma has theoretical appeal but insufficient comparative clinical evidence to contemplate its routine application at this time. Australia should maintain a watching brief on the ongoing international research, and revisit the evidence when contemplating the development of new radiotherapy or synchrotron facilities in the major capital cities.

Its introduction into Australia for treatment of intraocular melanoma could only be considered in the context of research, and it would be more prudent to await the outcome of international research involving larger numbers of patients, preferably in randomised trials, before contemplating a commitment to such a substantial capital investment. The magnitude of the required capital investment, the strategic siting of such a facility, and the clinical governance arrangements would dictate the need for a national summit if the use of proton beam therapy was to be seriously considered in this country.

Introduction

The Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S), on behalf of the Medical Services Advisory Committee (MSAC), has undertaken a Horizon Scanning Report to provide advice to the Health Policy Advisory Committee on Technology (HealthPACT) on the state of play of the introduction and use of proton beam therapy for the treatment of uveal melanoma.

Proton beam therapy was developed as a means of treating tumours located adjacent to critical structures. If approved, this technology will be offered through a radiologist or specialist medical institutions.

This Horizon Scanning Report is a preliminary statement of the safety, effectiveness, cost-effectiveness and ethical considerations associated with proton beam therapy.

Description of the Technology

The Procedure

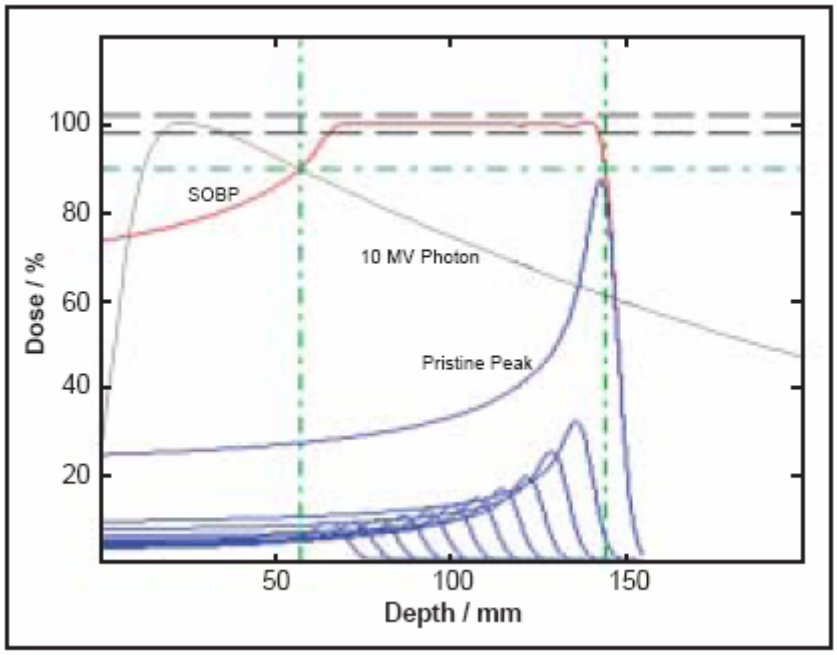
Malignant melanoma is the most common primary intraocular malignancy and arises due to a neoplasm of the uveal tract, the pigmented layer of the eye that includes the iris, ciliary body, and choroid. Despite the fact that malignant uveal melanomas are the most common ocular tumour, it remains relatively uncommon compared to other cancers (Damato 2004). Melanomas of the ciliary body or choroid typically appear as discrete solid tumours with a secondary serous sensory retinal detachment adjacent to the tumour which can potentially result in loss of vision. In some cases, the choroidal melanoma breaks through the Bruch's membrane, extending to the subsensory retinal space. These tumours have a distinct mushroom or collar-button shape and may cause vitreous haemorrhage with symptoms of sudden visual loss. Iris melanomas appear as single or multiple elevated lesions arising in the iris stroma. In comparison to choroidal and ciliary melanomas, iris melanomas are usually benign and are more readily detected due to their visibility (Kincaid 1998).

For a period of time, surgical enucleation was considered as the standard treatment for uveal melanomas. However, a study in 1978 challenged this traditional approach by suggesting that enucleation may accelerate death from metastatic disease. This was based on the conjecture that compression of the globe during enucleation can cause tumour cells to exit via the vortex veins, thus causing metastasis (Zimmerman et al. 1978). The data supporting this theory was ambiguous at best and have been contested by other clinicians. Nevertheless, the medical field adopted a more cautious approach in the treatment of uveal melanomas after the publication of this paper. To date, various eye-preserving treatment modalities have subsequently been developed, such as local resection, plaque brachytherapy, external beam radiotherapy with photons using a linear accelerator, helium ions and proton beam therapy. At the time of writing, the optimal management of uveal melanomas remains undefined. As technology improved, radiation therapy, delivered via charged particle beams or by episcleral radioactive plaques (brachytherapy), has grown to be the most popular alternative treatment modality for uveal melanomas. External beam radiotherapy in particular has garnered substantial interest due to its potential advantages in delivering optimal and uniform radiation doses to the target tumour and reducing the handling time of radioactive materials by ophthalmologists (Egger et al. 2003).

Photon beam radiotherapy is the most commonly utilised form of external beam radiotherapy and was developed for the locoregional treatment of cancer. As with all radiation based therapies, destruction of the tumour is achieved via radiation-induced DNA damage of the tumour cells, vascular fibrosis and secondary hypoxia. However, researchers and clinicians have recognised that the precise administration of radiation dose to the target tumour is challenging due to the inherent nature of photons. As illustrated in Figure 1, photon therapy delivers the maximum radiation dose to the surrounding normal tissue instead of the tumour itself, therefore exposing the healthy tissue to potential radiation-induced damage. In contrast, the physical characteristic of

proton should permit the achievement of superior dose distributions. As illustrated in Figure 1, protons deposit very little radiation into the surrounding tissues until the end of the proton energy range, resulting in a sharply localised peak of radiation dose known as the Bragg peak (Figure 1). This inherent characteristic of protons makes them particularly promising in the treatment of ocular tumours as the superior dose-distribution should theoretically enable clinicians to administer higher doses of radiation to the target tumour (thus leading to a consequent higher tumour control probability) without compromising healthy tissues (Suit et al. 1990). The penetration depth of the Bragg peak is directly related to the initial energy of the charged particle, therefore the desired dose can be precisely targeted to the culprit tumour. When proton beams are utilised for tumour irradiation, the beam energy is modulated by superimposing multiple Bragg peaks of descending energies and weights to create a spread (spread Bragg peak) of uniform radiation dose over the depth of the target tumour (DeLaney et al. 2005). A spread Bragg peak is essential for the successful application of this technology in tumour control as a single concentrated Bragg peak is considered too narrow for practical clinical applications (Figure 1) (DeLaney et al. 2005). Importantly, the application of multiple Bragg peaks does not alter the proton's dose distribution and it is still characterised by a lower-dose region in the healthy tissue proximal to the tumour, a uniformly high-dose region within the tumour and zero dose beyond the tumour (DeLaney et al. 2005). Protons are accelerated with cyclotrons, basically an accelerator for atomic and sub-atomic charged particles.

Figure 1: Depth-dose curve



Depth-dose distributions for a spread-out Bragg peak (SOBP), its constituent pristine proton Bragg peaks and a 10MV photon beam.

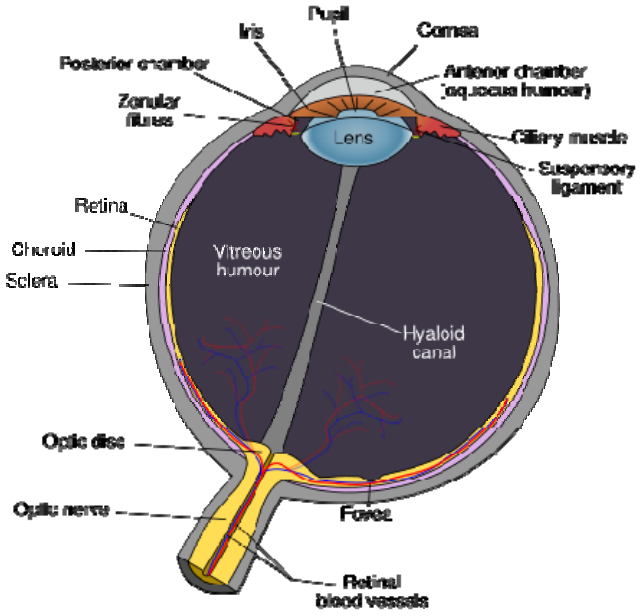
DeLaney et al. (2005)

After clinical diagnosis of uveal melanoma, patients who have consented to proton beam therapy will be required to undergo a surgical procedure for precise demarcation of tumour margins by an ophthalmologist. This procedure involves the suturing of tantalum clips onto the sclera (Figure 2) around the tumour base while the limits of the tumour base will be determined by transillumination or ophthalmoscopy and

scleral pressure. A clinician will also define the tumour position and size (diameter, elevation, distance to optic disc, distance to macula and distance to limbus), eye measurements (axial length, transverse diameter, thickness of the coats, distance between anterior cornea and posterior lens, limbus diameter, inter-pupillary distance), and clip measurements (distance between clip to limbus, clips to clips and clips to tumour) in order to develop a precise fundus view model with tumour and clip locations. This information is then relayed into a dedicated treatment planning program (EYEPLAN) which will schematically display a model of the patient's eye, including the lens, optic nerve and fovea. The tumour margins will be drawn on this 3-D diagram by the ophthalmologist and verified by the radiation oncologist to maximise accuracy (Höcht et al. 2004, Dendale et al. 2006, Damato et al. 2005a).

Patients undergoing proton beam therapy are immobilised to ensure the same position is maintained throughout the treatment with respect to the proton beam. In the case of ocular tumours, the fixation device would usually consist of a customised thermoplastic mask and bite block. The patient's eyelids are retracted with the use of retractors or with sticky tape.

Figure 2: Anatomy of the eye



Intended Purpose

Proton beam therapy was developed to treat tumours in patients where surgical excision is deemed impossible, too dangerous, or unsuccessful. The first published use of proton beam therapy was in 1954 (Chalmers 2003), however the high cost of producing charged particles like protons has inhibited its widespread usage.

The improved dose-distribution that can be achieved with proton beam therapy enables this form of radiotherapy to be used for the treatment of tumours that are located close to critical structures such as the spinal cord, eyes and brain. In the case of uveal melanomas, tumours may arise in close proximity to the optic disk, optic nerve and fovea, structures vital for visual function. Proton beam therapy was first utilised for the treatment of uveal melanomas in 1975 (Kodjikian et al. (2004).

Clinical Need and Burden of Disease

Uveal melanoma is the most frequently reported ocular tumour but remains relatively rare compared to other cancers, with a reported incidence of 6 to 7 cases per 100,000 inhabitants (Dendale et al. 2006). This infers an overall incidence of approximately 5,000,000 per year worldwide. Uveal melanomas arise in the iris in approximately 3% of patients, the ciliary body in 5-10%, and the choroid in about 90% (Damato 2004). Uveal melanomas tend to cause exudative retinal detachment, astigmatism, cataract, secondary glaucoma from angle invasion, and in advanced stages, neovascular glaucoma and uveitis (Damato 2004). Uveal melanomas are more common in older individuals and in Caucasians, particularly those with blue/grey irises (Damato 2004).

The incidence and hospital separations of eye cancers in Australia and New Zealand are summarised in Table 1. The incidence of eye cancer is projected to remain stable at around current rates for both women and men. For women, the number of new cases of eye cancer is projected to increase by 36% from 96 in 2001 to 131 in 2011, with a 95% prediction interval from 89 to 195. For men, the number of new cases is projected to increase by 39% from 137 in 2001 to 190 in 2011, with a 95% prediction interval from 133 to 279 (AIHW 2006b)

Table 1: Incidence rates of eye cancers in Australia and New Zealand.

Principal diagnosis	Number of new cases, Australia (2001)	Number of public hospital separations, Australia (2001-2002)	Number of registered cases, New Zealand (2002)	Number of public hospital separations, New Zealand (2002)
Eye (C69)	233	609	43	133

AIHW 2006, New Zealand health Information Service 2006

Stage of Development

At the time of writing, over 39,000 patients worldwide have received part or all of their radiation therapy by proton beams (Levin *et al.* 2005). Published scientific literature shows that there is widespread experience from many centres with regards to proton beam treatment of uveal melanomas, with at least 8000 patients treated (Blomquist et al. 2005) since the first inference of utilising this technology to treat uveal melanomas in 1974 (Kodjikian et al. 2004).

One of the pioneering centres of proton beam therapy for the treatment of tumours was the Harvard Cyclotron Laboratory in Cambridge, Massachusetts. Patient treatment with proton therapy began in the centre in 1961 up to 2002; at that point the

clinical programme was transferred to the Northeast Proton Therapy Centre at Massachusetts General Hospital (Levin *et al.* 2005). Eventually, hospital-based cyclotrons were developed and were capable of producing higher energy beams (hence deeper penetration) with field sizes comparable to linear accelerators and rotational gantries that assist in ensuring accurate targeting of the tumour. One of the first hospital-based facilities was opened at the Loma Linda University in California, 1990 (Levin *et al.* 2005, LLUMC 2006), a list of operational proton therapy centres is provided below (Table 2):

Table 2: Operational proton therapy centres

Country/Facility	Date of first treatment	Recent patient total	Date of total
Canada			
TRIUMF	1995	89	December 2003
England			
Clatterbridge	1989	1287	December 2003
France			
Nice	1991	2555	April 2004
Orsay	1991	2805	December 2003
Germany			
HMI, Berlin	1998	439	December 2003
Italy			
INFN-LNC, Catania	2002	77	June 2004
Japan			
Chiba	1979	145	April 2002
NCC, Kashiwa	1998	270	June 2004
HIMBC, Hyogo	2001	359	June 2004
PMRC, Tsukuba	2001	492	July 2004
WERC	2002	14	December 2003
Shizuoka	2003	69	July 2004
Russia			
ITEP, Moscow	1969	3748	June 2004
St. Petersburg	1975	1145	April 2004
Dubna	1999	191	November 2003
South Africa			
iThemba Labs	1993	446	December 2003
Sweden			
Uppsala	1989	418	January 2004
Switzerland			
PSI	1984	4066	June 2004
PSI	1996	166	December 2003
United States			
Loma Linda	1990	9282	July 2004
UCSF-CNL	1994	632	June 2004
NPTC, MGH	2001	800	July 2004

Levin et al. 2005

Australian Therapeutic Goods Administration approval

At the time of writing, proton beam therapy is not available in Australia or New Zealand in for the treatment of uveal melanomas in clinical practice or trials. However, cyclotrons capable of producing the high-energy protons required for this

treatment have been installed in several Australian states. At the time of writing, functioning cyclotrons are available in Victoria, New South Wales, Queensland and Western Australia.

Treatment Alternatives

Existing Comparators

As stated previously, the optimal management of uveal melanomas remain undefined. The comparators to proton beam therapy are presented below, only treatment modalities that aim to conserve the affected eye will be considered:

a) Other forms of external beam therapy
Photons, helium ions and carbon ions can be utilised in external beam therapy to treat uveal melanomas in the same way that protons are utilised. However, photon beam therapy has been associated with excessive radiation dosage to the surrounding tissue, therefore increasing the risk of damage and development of secondary tumours. Stereotactic radiotherapy was designed to reduce the amount of radiation imposed upon adjacent healthy tissue during radiotherapy. It involves the administration of radiation from multiple directions utilising a gamma knife of with a linear accelerator (Damato 2004).

b) Plaque radiotherapy
Plaque radiotherapy of brachytherapy involves the utilisation of a metal shield which contains small radioactive seeds. This shield is sutured to the outside of the sclera overlying the tumour; therefore the radiation dose is principally delivered to the base of the tumour. Plaque sizes are designed to include a margin of 2 mm around the tumour and are left in place until the intended dose has been delivered. To date, several different isotopes have been utilised: cobalt 60, ruthenium 106, iodine 125, and palladium 103 (Finger 1997).

c) Transpupillary thermotherapy
Transpupillary thermotherapy involves 1 minute applications of 3 mm spots of low-energy diode laser to the tumour and the surrounding choroid. Tumour regression with this technique occurs slowly, usually resulting in a white scar. The developers of this technique have recommended the use of brachytherapy as an adjunct to this technique (Damato 2004).

d) Sclerouvectomy (eyewall resection)
Sclerouvectomy is a method of excising small ocular tumours, especially those located relatively anteriorly. The entire tumour is removed en bloc and a replacement piece of banked sclera is used to repair the surgical defect. Lamellar sclerouvectomy is a modification of en bloc resection which preserves the outer sclera and therefore helps maintain the integrity of the eye. However, research has raised concerns with regards to the fact that melanoma cells usually invade the adjacent sclera and therefore may be present at the margin of the resected tissue (Robertson et al. 1991).

e) Endoresection
Endoresection involves citrectomy; tumour removal with a vitrector either via a retinotomy or after lifting a retinal flap; fluid-air exchange to drain any subretinal fluid; endolaser photocoagulation, to destroy any residual tumour in the sclera and to achieve retinoplexy; air-silicone exchange; and adjunctive brachytherapy if required. This technique is controversial due to the potentially devastating risk of seeding tumour cells. In an effort to reduce the risk of local recurrence and seeding, researchers have recommended the use of stereotactic radiotherapy prior to endoresection (Damato 2004).

Clinical Outcomes

There is a considerable amount of literature describing the use of proton beam therapy in the treatment of patients with uveal melanoma. Twenty-five studies are included in this assessment based on the quality of evidence and the number of patients enrolled. The majority of these provide case series evidence (level IV Intervention evidence). A combination of high/moderate quality studies and low quality case series are presented and analysed. Readers should note that several case series studies retrieved were excluded from assessment due to relatively small patient cohorts of ≤ 20 patients.

It is important to note that due to the heterogeneity between the included studies, it may be impossible to compare results in a meaningful manner. A large proportion of existing studies on proton beam therapy for uveal melanoma are quasi-anecdotal due to the fact that treatment parameters and patient selection are so variable. Among the problems encountered when attempting to compare across studies are disparities in total apical radiation dose, varying tumour locations relative to sensitive structures, substantial difference in dose rates, lack of standardisation of treatment margins, and no uniform definition of what constitutes continued tumour growth or regrowth.

The radiation dose administered is reported in Gy (Grays) or CGE (Cobalt Gray Equivalent). CGE is defined as 'Gy x Relative Biological Effectiveness (RBE)[1]'. The RBE for protons is 1.1 (photon RBE: 1.0). In some studies, results were analysed according to the Kaplan-Meier method, which computes survival taking account of the different lengths of follow-up and any censoring due to dropout.

Specific characteristics of the studies are presented for the key outcomes of interest in the following sections. Full study characteristics are presented in Appendix B.

Safety

Research has revealed that radiotherapy for the treatment of uveal melanomas is often associated with substantial levels of complications. Some of the complications that may arise after proton beam therapy includes: glaucoma, rubeosis, cataract,

[1] RBE: A measure of the capacity of a specific ionising radiation to produce a specific biological effect, expressed relative to a reference radiation.

intraocular inflammation (uveitis), optic disc neuropathy, radiation retinopathy, loss of visual acuity, keratopathy and lash loss. Among these potential complications neovascular glaucoma and rubeosis are among the most severe, while cataract is common and contributes to loss of visual acuity, which itself is another common complication which arises from this treatment modality. These complications will be discussed in greater detail below to highlight some of the major detrimental effects associated with the use of proton beam therapy for the treatment uveal melanomas.

a) Glaucoma

As stated previously, external beam radiotherapy has been known to induce a range of ocular complications. The most significant complications, which may lead to enucleation (removal of the eye) after proton beam therapy, are rubeosis and neovascular glaucoma (Gragoudas et al. 1987). Glaucoma is a condition whereby the optic nerve is subjected to gradual damage due to increased intraocular pressure; while rubeosis refers to abnormal blood vessel growth on the iris/structures in front of the eye which may obstruct the drainage of aqueous fluid; causing elevation of intraocular pressure and eventually glaucoma.

Studies have shown that the presence of rubeosis is indicative of severe ocular damage while neovascular glaucoma is stated within the literature to be the most common cause of subsequent enucleation after proton beam therapy (Foss et al. 1997), and has been associated to 71% to 100% of complication-related enucleation (Dendale et al. 2006). To date, the pathogenic mechanisms of these two complications are not clear, researchers have postulated that it may be due to angiogenic factors elaborated by the melanomas, retinal ischemia from irradiation and inflammation from necrosis of the tumour (Gragoudas et al. 1987). Daftari et al. (1997) attributed the occurrence of neovascular glaucoma to extensive irradiation of anterior ocular structures and have suggested anterior segment sparing to reduce this complication. The retrospective analysis by Foss et al. (1997) revealed that large tumour size and the presence of retinal detachment were significant, independent risk factors for the development of rubeosis. In addition, these factors were shown to be predictive of subsequent enucleation for uncontrollable ocular pain (Foss et al. 1997). Meanwhile, Gragoudas et al. (1987) reported that the significant factors for development of rubeosis were the size of the tumour (diameter and height), and the percent of irradiation of the anterior segment ($p = 0.0003$, $p = 0.0003$, $p = 0.0001$, respectively).

The studies included within this assessment reported large variations in the incidence of glaucoma/rubeosis post-proton beam treatment, ranging from 5% to 29% for glaucoma and 7% to 34% for rubeosis (Table 3). It is plausible that this variation was due to the heterogeneity of tumour characteristics and radiation dose administered between the study cohorts. This heterogeneity between studies also makes it difficult to compare results across studies in a meaningful manner.

Wilson and Hungerford (1999) retrieved hospital records from the prior 8 years for people with choroidal melanoma who had been treated with two forms of brachytherapy or proton beam therapy. They reported that patients treated with proton beam therapy had higher incidence of refractory neovascular glaucoma (5.7%) compared to patients who were treated with ^{125}I (2.1%) and ^{106}Ru (0%) brachytherapy. This was partly responsible for the higher enucleation rates observed

among patients treated with proton beam therapy in this study (Wilson and Hungerford 1999). However, tumour characteristics between treatment groups varied to an extent, especially with regards to tumour height (mean of 6.6 on proton beam vs 5.9 on ^{125}I and 4.2 on ^{106}Ru in the other groups) which has been implicated as a key predictor of rubeosis (Gragoudas et al. 1987, Foss et al. 1997).

Meanwhile, a randomised controlled trial (Gragoudas et al. 2000) showed that patients treated with a higher dose of proton beam therapy (70 CGE) had similar rates of rubeosis/neovascular glaucoma compared to patients receiving a lower radiation dose (50 CGE), 7% (7/94 patients) and 10% (9/94 patients) respectively. These results indicate that radiation dosage may play a lesser role compared to the size and location of the tumour in causing neovascular glaucoma or rubeosis.

Table 3: Neovascular glaucoma/rubeosis incidence after proton beam therapy for uveal melanoma.

Study	Study design	Glaucoma/Neovascular glaucoma incidence	Rubeosis incidence
Brovkina and Zarubei (1986) Follow-up Mean: 33.8 months	Case series (Level IV intervention evidence) 63 patients with uveal melanoma (ciliochoroidal)	Secondary post-radiation glaucoma reported in 11 eyes (17.5%)	Not reported
Dendale et al. (2006) Follow-up Median: 73 months	Case series (Level IV intervention evidence) 1406 patients with uveal melanoma	Glaucoma observed in 28.6% of patients at 5-years.	Not reported
Desjardins et al. (2006) Follow-up Median: 38 months	Randomised controlled trial (Level II intervention evidence) 151 patients with large (≥ 7mm thick *or* ≥ 15 mm diameter) uveal melanoma	No significant difference in glaucoma rates between the proton therapy group (41 patients, 27.2%) and the proton therapy + tranpupillary thermotherapy group (35 patients, 23.2%).	Not reported
Foss et al. (1997) Follow-up Unclear	Case series (Level IV intervention evidence) 127 patients with uveal melanoma	Not reported	42 patients (34%) developed rubeosis.
Gragoudas et al. (1987) Follow-up Median: 5.4 years	Case series (Level IV intervention evidence) 128 patients with uveal melanoma	Rubeosis iridis and neovascular glaucoma were the most serious complications, observed in 19 eyes (15%). Six eyes (4.7%) were enucleated due to glaucoma.	
Gragoudas et al. (2000) Follow-up 5 years	Randomised controlled trial (Level II intervention evidence)	Rubeosis/neovascular glaucoma incidence 50 CGE group: 9 patients (10%) 70 CGE group: 7 patients (7%)	

	188 patients with uveal melanoma (choroidal)		
Höcht et al. (2004) Follow-up Median: 18.4 months	Case series (Level IV intervention evidence) 245 patients with uveal melanoma	Estimated glaucoma incidence was 8.7% at 19.8 months (median follow-up); this increased to 10.9% at 36 months.	Estimated rubeosis iridis incidence was 7.8% at 19.1 months (median follow-up); this increased to 19.5% at 36 months.
Mosci et al. (2001) Follow-up Mean: 21 ± 5 months	Case series (Level IV intervention evidence) 127 patients with uveal melanoma (choroidal)	7.4% of patients had neovascular glaucoma. 4 eyes (3.1%) were enucleated due to neovascular glaucoma which was highly correlated with proton treatment.	Not reported
Wilson and Hungerford (1999) Follow-up (mean ± SD) ^{125}I: 47.3 ± 22 months ^{106}Ru: 45.3 ± 29.7 months Proton beam: 43 ± 20.6 months	Retrospective comparative study (Level III-2 intervention evidence) 597 patients with uveal melanoma (choroidal)	Incidence of glaucoma ^{125}I: 4/190 patients (2.1%) ^{106}Ru: 0/140 patients (0%) Proton beam: 15/267 patients (5.6%)	Not reported

In an effort to decrease the risk of exudative phenomena and glaucoma, the randomised controlled trial (n = 756) by Desjardins et al. (2006) examined if the systematic addition of transpupillary thermotherapy (TTT) after proton beam therapy would have a beneficial effect towards these ocular complications. No significant difference reduction in the incidence of glaucoma was noted between the two treatment groups (Desjardins et al. 2006). However, the investigators noted that patients who received TTT had less severe glaucoma, with intraocular pressure that tended to return to normal after several months of treatment. In addition, patients treated with TTT had significantly lower secondary enucleation rates ($p = 0.02$).

Overall, the incidence of glaucoma and rubeosis after proton beam therapy is largely inconsistent between studies. However, most studies agree that neovascular glaucoma and rubeosis contribute significantly to secondary enucleation after proton beam therapy.

b) Cataract

Another complication that threatens vision or necessitates further treatment after charged-particle radiotherapy is cataract. Research has revealed the causal role of ionising radiation in the development of cataract since the late 20th century. Cataract can be divided into various subtypes (nuclear, cortical, posterior subcapsular), but only posterior subcapsular changes had been linked to microwave and ionising radiation exposure (Gragoudas et al. 1995). As observed with glaucoma, a substantial variation in the incidence of cataract was apparent from the included studies, ranging from 6% to 62% (Table 4) post-treatment. One study (Brovkina and Zarubei 1986)

reported that proton beam therapy appears to accelerate the progression of pre-existing cataract as well.

Table 4: Cataract incidence after proton beam therapy for uveal melanoma.

Study	Study design	Cataract incidence
Brovkina and Zarubei (1986) Follow-up Mean: 33.8 months	Case series study (Level IV intervention evidence) 63 patients with uveal melanoma	Radiation-induced cataract observed in 4 eyes (6.3%). More rapid than normal progression of pre-existing sectorlike complicated cataract observed in 11 eyes (17.5%).
Dendale et al. (2006) Follow-up Median: 73 months	Case series study (Level IV intervention evidence) 1406 patients with uveal melanoma	Actuarial 5-year cataract rate of 61.8%.
Gragoudas et al. (1987) Follow-up Median: 5.4 years	Case series study (Level IV intervention evidence) 128 patients with uveal melanoma	43 eyes (33%) developed cataract.
Gragoudas et al. (1995) Follow-up Mean: 37 months	Case series study (Level IV intervention evidence) 383 patients with uveal melanoma	3-years post-treatment: Posterior subcapsular opacity observed in 42% of patients.
Gragoudas et al. (2000) Follow-up 5 years	Randomised controlled trial of 2 proton beam doses (Level II intervention evidence) 188 patients with uveal melanoma (choroidal)	Posterior subcapsular opacity incidence: 50 CGE group: 13 patients (14%) 70 CGE group: 7 patients (7%)
Höcht et al. (2004) Follow-up Median: 18.4 months	Case series study (Level IV intervention evidence) 245 patients with uveal melanoma	Kaplan-Meier estimate of cataract was 18.7% at a median follow-up of 19.6 months; this increased to 39.2% at 36 months post-treatment.

In the case series study by Gragoudas et al. (1995), the 3-year post-proton beam therapy lens opacification rate was 42% and was shown to be highly dependant on the amount of dose received by the lens. Cox's modelling of potential independent predictors of subcapsular opacities revealed that lens dose and tumour height were found to be statistically significant determinants of this complication (Gragoudas et al. 1995). When the rates of posterior subcapsular opacity was analysed among risk groups defined on the basis of the 2 independent risk factors (tumour height and lens dose), 80% of patients in the high-risk group developed posterior subcapsular opacity by 36 months, compared to < 25% in low-risk patients (Gragoudas et al. 1995).

Studies on other treatment modalities, such as cobalt 60 brachytherapy, revealed that the probability of developing vision detrimental cataract was 57% at 5-years and 84% at 10-years (Kleineidam et al. 1993). Meanwhile Meecham et al. (1994) reported that after an average of 5-years post-helium ion therapy, 44% of patients developed

radiation-induced cataract. These results are somewhat comparable to the upper-end of the range derived from the included studies for cataract incidence post-proton beam therapy (6% to 62%).

Based on the findings by Gragoudas et al. (1995), the large variation of cataract incidence observed between studies may be due to the heterogeneity of tumour height and lens dose between study cohorts. Curiously, a more recent study by Garoudas et al. (2000) appears to contradict the relationship of radiation dose and the occurrence of cataract. Comparisons between the randomised patient groups who received 70 CGE or 50 CGE revealed that the incidence of posterior subcapsular opacity was two times higher in patients who received the lower dose of 50 CGE (Table 4), but this difference was reported as not statistically significant (Gragoudas et al. 2000).

Overall, the incidence of cataract, although varied across studies, continues to be a significant contributor to vision loss after proton beam therapy. The effect of proton beam therapy on visual acuity will be explored further in the following section.

c) Visual acuity/Visual field

The visual outcome of the proton beam treated eye is a key safety measure of this treatment modality. Presumably, due to the better dose-distribution that can be achieved with proton beam therapy, deleterious consequences to visual acuity and visual field should be reduced, especially in tumours located near the optic disc of fovea. Once again, the results across studies could not be utilised for meaningful comparisons due to the large variation in pre-treatment visual and tumour characteristics across the study cohorts, which is evident from the summary of results in Table 5 (Note: Visual acuity of 20/20 is considered perfect vision).

Table 5: Visual acuity/field after proton beam therapy for uveal melanoma.

Study	Study design	Visual acuity/field outcomes
Damato et al. (2005a) Follow-up Median: 3.1 years	Case series study (Level IV intervention evidence) 349 patients with uveal melanoma (choroidal)	In 346 patients with visual acuity of counting fingers or better at treatment: 89.2% conservation at 2-years 79.1% conservation at 5-years 72.9% conservation at 8-years In 301 patients with visual acuity 20/200 or better at treatment: 81.9% conservation at 2-years 61.1% conservation at 5-years 41.7% conservation at 8-years In 212 patients with visual acuity 20/40 or better at treatment: 63.5% conservation at 2-years 44.8% conservation at 5-years 32.2% conservation at 8-years
Damato et al. (2005b) Follow-up Median: 2.7 years	Case series study (Level IV intervention evidence) 88 patients with uveal	Latest recorded visual acuity (%, acuity): 28%, 20/17 30%, 20/20 22%, 20/30

<table>
<tr><td></td><td>melanoma (iris)</td><td>7%, 20/40
1%, 20/60
2%, 20/100
1%, 20/200
2%, counting fingers
2%, hand movements
1%, light perception</td></tr>
<tr><td>Dendale et al. (2006)

<u>Follow-up</u>
Median: 73 months</td><td>Case series study (Level IV intervention evidence)

1406 patients with uveal melanoma</td><td>At 5-years, visual acuity was:
stable in 38% of patients
decreased in 56%
improved in 6%.</td></tr>
<tr><td>Gragoudas et al. (1987)

<u>Follow-up</u>
Median: 5.4 years</td><td>Case series study (Level IV intervention evidence)

128 patients with uveal melanoma</td><td>Percentage of treated eyes retaining visual acuity of 20/200 or better:
<table><tr><th>Year</th><th>%</th><th>±SE%</th></tr><tr><td>6 months</td><td>94</td><td>2</td></tr><tr><td>1</td><td>89</td><td>3</td></tr><tr><td>2</td><td>82</td><td>4</td></tr><tr><td>3</td><td>77</td><td>4</td></tr><tr><td>4</td><td>73</td><td>5</td></tr><tr><td>5</td><td>69</td><td>6</td></tr></table>
Eyes with large diameters, large height and located within 2 disc diameters (DD) from the optic disc and fovea were more likely to have worse than 20/200 visual acuity (p = 0.04, p = 0.01 and p = 0.0008, respectively).</td></tr>
<tr><td>Gragoudas et al. (2000)

<u>Follow-up</u>
5 years</td><td>Randomised controlled trial (Level II intervention evidence)

188 patients with uveal melanoma (choroidal)</td><td>Visual outcome was similar between patients randomised to 50 CGE or 70 CGE proton beam therapy.

At 5-years, median visual acuity was:
20/160 in 50 CGE group
20/100 in the 70 CGE group

Approximately 55% of patients in both groups retained visual acuity of 20/200 or better.

Visual field in the 50 CGE group experienced less deterioration. Over time, the mean increase in defect was 2.3 to 3.2 times higher in the 70 CGE group compared to the 50 CGE group.</td></tr>
<tr><td>Mosci et al. (2001)

<u>Follow-up</u>
21 ± 5 months</td><td>Case series study (Level IV intervention evidence)

127 patients with uveal melanoma (choroidal)</td><td>At 2-years:
Visual acuity better than 2/10 was retained in 30% of cases in T1/T2 group.
Visual acuity better than 2/10 was retained in 21% of cases in T3 group.</td></tr>
<tr><td>Park et al. (1996)

<u>Follow-up</u>
Patients who developed papillopathy (mean): 48 months
Patients who did not develop papillopathy</td><td>Case series study (Level IV intervention evidence)

59 patients with uveal melanoma (parapapillary choroidal)</td><td><u>Visual field</u>
Progressive visual field loss:
67% (12/18) of patients with radiation papillopathy.
73% (30/41) of patients without papillopathy.</td></tr>
</table>

(mean): 42 months		
Seddon et al. (1987) <u>Follow-up</u> Median: 20.4 months	Case series study (Level IV intervention evidence) 666 patients (667 eyes) with uveal melanoma	In 74 patients with pre-treatment acuity worse than 20/200: 35 eyes (47%) did not improve to 20/200 after treatment. 36 eyes (49%) improved to 20/200 but improvement was temporary in 25 eyes. In 165 patients with tumours near the disc or fovea (≥2 years follow-up): 17 (10.3%) improved 99 (60%) worsened 49 (29.7%) remained stable <u>Visual loss to worse than 20/200</u> 228/562 eyes with initial acuity of 20/200 or better declined to worse than 20/200. Of the 228 eyes with visual decline: 171 (75%) had tumours near the disc/fovea.
Wilson and Hungerford (1999) <u>Follow-up (mean ± SD)</u> ^{125}I: 47.3 ± 22 months ^{106}Ru: 45.3 ± 29.7 months Proton beam: 43 ± 20.6 months	Retrospective comparative study (Level III-2 intervention evidence) 597 patients with uveal melanoma (choroidal)	<u>Visual acuity for each treatment group</u> 106Ru: 55% had 6/12 or better 125I: 39% had 6/12 or better Proton: 15% had 6/12 or better

The included studies reported that the most important prognostic factors for visual loss to worse than 20/200 are: 1) tumour height (Wilson and Hungerford 1999, Seddon et al. 1987) and 2) the proximity of the tumour to the optic disc or fovea or both (Seddon et al. 1987). Other factors that may be predictive of visual loss were the presence of macular detachment, poor pre-treatment vision and high radiation dose to the disc, fovea or lens (Seddon et al. 1987). In the study by Seddon et al. (1987), patients treated with proton beam therapy for uveal melanoma near the optic disc or fovea (or both) was examined to determine the rate of visual loss in comparison to patients where the tumour was located further from these critical structures. As expected, Seddon and colleagues showed that patients with tumours near the optic disc *and* fovea are at a higher risk of visual deterioration after proton beam therapy as a result of the location and radiation dose delivered to sensitive structures. Overall, only 53% of patients with 20/200 of better pre-treatment vision managed to retain 20/200 or better vision 2 years post-treatment. In comparison, patients with tumours located greater than 2 DD from the disc and fovea achieved a corresponding visual conservation rate of 72%. However, despite the higher risk of visual deterioration, Seddon and colleagues highlighted that most of these patients retained useful vision (53%) despite the unfavourable location of their tumours. Multivariate analysis

showed that proximity to the fovea was associated with a slightly higher risk (hazard ratio: 1.34; 95% CI: 0.83-2.18) compared to proximity to the optic disc, but this was not statistically significant (Seddon et al. 1987). Höcht et al. (2004) suggested that there was a strong inverse correlation between the changes in visual acuity during follow-up with the distance of the tumour to the fovea, but no data were presented.

The randomised trial by Gragoudas et al. (2000) in patients with tumours less than 4 DD to the optic disc and/or the macula showed that despite a 30% reduction in radiation dose (70 CGE to 50 CGE), there were no statistically significant differences in retention of visual acuity between patients treated with 70 CGE or 50 CGE proton beam therapy from 12 months post-treatment to 60 months post-treatment. At 5-years post-treatment, approximately 55% of patients in both groups retained visual acuity of 20/200 or better in the treated eye (Gragoudas et al. 2000). This could suggest that radiation dose is a less important factor in predicting loss of visual acuity, compared to proximity to the disc/fovea and tumour height (Seddon et al. 1987). Conversely, the findings of this randomised trial may suggest that 50 CGE exceeds the threshold of radiation effects in the macula, therefore further dose reduction may be required before substantial improvements in conserving visual acuity is achieved. However, any reduction of radiation dosage to conserve vision should not take precedence over local tumour control.

In the comparative study by Wilson and Hungerford (1999) between proton beam therapy (n = 267), ^{106}Ru brachytherapy (n = 140) and ^{125}I brachytherapy (n = 190), visual acuity retention of 6/12 or better was observed in 55% ^{106}Ru patients, 29% of ^{125}I patients and 15% of proton beam therapy patients at the last examination. Patients treated with ^{106}Ru lost an average of 1.08 lines of visual acuity while patients treated with ^{125}I lost an average of 2.1 lines. In comparison, proton beam patients lost an average of 3.27 lines of visual acuity. Overall, patients treated with proton beam therapy were found to be at *significantly greater risk of visual loss* after treatment. In addition, when lines of visual loss were examined as a function of time, patients receiving proton beam therapy were shown to have a *more rapid loss of vision* as well (Wilson and Hungerford 1999). The only significant covariate was tumour height ($p = 0.0001$), which coincides with the results of Seddon et al. (1987). It is important to note that the average tumour height was slightly higher in the proton beam cohort (mean ± standard deviation; 6.6 ± 3.4 mm) compared to the ^{106}Ru cohort (4.2 ± 1.5 mm) and the ^{125}I cohort (5.9 ± 2.3), which may explain the higher risk and rate of visual loss observed (Wilson and Hungerford 1999). This infers that the results of this study may have been confounded by the pre-treatment tumour height of the included patients.

With regards to visual field outcomes (measured in terms of average increase in the threshold for light perception in decibels), Gragoudas et al. (2000) reported that there appears to be some benefit in dose reduction as patients treated with 50 CGE experienced less deterioration compared to those treated with 70 CGE. At 1-year post-treatment, the mean increase in visual field defect between groups was less than 1 decibel[2]; however visual field defects increased markedly to 3.2 times higher in the 70

[2] Average increase in the threshold for light perception was measured in decibels

CGE group at 72 months port-treatment (Gragoudas et al. 2000). Park et al. (1996) examined the extent of visual field deficit after proton beam therapy in 59 patients with parapapillary choroidal melanoma 18 months after treatment and found that visual field deficits was very common after proton irradiation. Analysis showed that progressive visual field loss was correlated to the area of the retina exposed to proton beam irradiation (Park et al. 1996).

Effectiveness

The effectiveness of proton beam therapy for the treatment of uveal melanoma was assessed primarily via local control, metastasis, survival and eye retention. Most studies included within this assessment reported the key effectiveness outcomes mentioned, however there are selected studies where the investigators decided to focus their efforts on specific outcomes (such as local control only etc.). Each of these key outcomes will be assessed separately, keeping in mind that the composition of studies across each section will differ to an extent.

a) Local control

Overall, most of the included studies reported good local tumour control rates after treatment with proton beam therapy (most ≥ 95% local control) (Table 6). Of the seven studies that reported 5-year actuarial local control rates, six reported local control ranging from 96% to 97% (Gragoudas et al. 2002, Munzenrider et al. 1989, Egger et al. 2001, Dendale et al. 2006, Damato et al. 2005a, Gragoudas et al. 1992). The remaining study (Marucci et al. 2006), reported substantially lower 5-year local control rate of 69%. However, this study cohort was restricted to patients with recurrent uveal melanomas after primary treatment with proton beam therapy. The tumour control rates therefore reflect the outcomes of a second course of proton beam therapy in a group of patients with tumours that appear to be more radioresistant (Marucci et al. 2006). Conversely, the higher rate of local recurrence after retreatment may suggest that there was difficulty in defining the target volume for irradiation in these patients. Nevertheless, Marucci and colleagues have shown that a second course of proton beam therapy in recurrent tumours could be considered as over 2/3 of this markedly 'difficult' tumours achieved local control. Brovkina and Zarubei (1986) reported markedly lower local control rates at the time of analysis as well (71.4%), however the dosage regimen for this study was substantially different and baseline tumour characteristics were not clearly defined.

The randomised controlled trial by Gragoudas et al. (2000) revealed that there was no difference in local tumour control rate in patients treated with 70 CGE or 50 CGE proton beam therapy. However, the patients treated within this randomised trial had tumour heights that tended to be lower (median: 3mm in both 70 CGE and 50 CGE groups) compared to the other included studies (Table 6). Considering the fact that tumour height appears to be predictive of local recurrence (Gragoudas et al. 2002, Gragoudas et al. 1992), the lower values of this tumour characteristic in the cohort treated by Gragoudas et al. (2000) may have diluted the potential difference in control rates between the two doses. Other predictive factors of recurrence include; large tumour diameter (Dendale et al. 2006, Gragoudas et al. 2002), small macular area

(Dendale et al. 2006), ciliary body involvement (Gragoudas et al. 2002) and tumour pigmentation (Gragoudas et al. 2002). In contrast to these studies, Wilson and Hungerford (1999) reported that smaller (diameter) and thinner (height) tumours were more likely to recur in the patient cohort they examined.

Table 6: Local control and metastatic disease after proton beam therapy for uveal melanoma.

Study	Tumour type	No. of patients (eyes)	Tumour size	Dose (Gy/CGE)	Local control	Metastases
Brovkina and Zarubei (1986) Follow-up Mean: 33.8 months	Uveal melanoma (ciliochoroidal)	63 patients (63 eyes)	Largest diameter: 8 to 20 mm Height: 3 to 13.7 mm	1500 rad per session at intervals of 1-2 days for 4/5 sessions **Dose:** 10,000 to 12,500 rad	At the time of analysis: 71.4% control	Four patients died of metastasis (6.3%).
Damato et al. (2005a) Follow-up Median: 3.1 years	Uveal melanoma (choroidal)	349 patients (349 eyes)	Diameter: N/A Height: > 5.5 mm	4 fractions over 4 consecutive days **Dose:** 53.1 Gy	At the time of analysis: 97.4% control 5-years: 96.5% control	In 285 patients: 2-years metastatic death rate: 2.5% 5-years metastatic death rate: 10.0% 8-years metastatic death rate: 14.1%
Damato et al. (2005b) Follow-up Median: 2.7 years	Uveal melanoma (Iris)	88 patients (88 eyes)	Median diameter: 4.3 mm Height: N/A	4 fractions over 4 consecutive days **Dose:** 53.1 Gy	Not reported	At the time of analysis, metastatic survival: 98.9%
Dendale et al. (2006) Follow-up Median: 73 months	Uveal melanoma	1406 patients (1406 eyes)	Mean diameter: 13.3 mm Mean height: 5.4 mm	4 fractions over 4 consecutive days **Dose:** 60 CGE	At the time of analysis: 96.3% 5-year: 96%	5-year metastasis free survival: 80.6%
Egger et al. (2001) Follow-up Median: 40 months	Uveal melanoma	2432 patients (2435 eyes)	Small (diameter ≤ 10mm, thickness ≤ 3mm): 126 patients Mid-sized (10mm < diameter ≤ 15mm and/or 3mm < thickness ≤ 5mm): 581 patients Large (15mm < diameter ≤ 20mm and/or 5mm < thickness ≤ 10mm): 1185 patients Extra-large (diameter > 20mm and/or thickness > 10mm): 543 patients	4 fractions in 4 consecutive days **Dose:** 54.5 Gy (60 CGE)	5-years: 95.8 ± 0.5% control 10-years: 94.8 ± 0.7% control 2 extra cases of recurrence after 10-years, 130 months: 92.4 ± 1.8% control	Not reported
Gragoudas et al. (1987) Follow-up Median: 5.4 years	Uveal melanoma	128 patients (128 eyes)	Largest tumour diameter Small: ≤ 10 mm Medium: 10.1-15 mm Large: ≥ 15.1	5 fractions over 7 to 10 days **Dose:** 70 CGE (63.6 Gy)	At the time of analysis, all tumours showed regression in size.	At the time of analysis: 20.5% metastases Metastases free survival

			mm Height Small: ≤ 3 mm Medium: 3.1-5 mm Large: ≥ 5.1 mm			1-year: 96 ± 2% 2-year: 90 ± 3% 3-year: 86 ± 3% 4-year: 81 ± 4% 5-year: 80 ± 5%
Gragoudas et al. (1992) Follow-up Mean: 4 years	Uveal melanoma	1077 patients (1077 eyes)	Mean diameter: 13.7 mm Mean height: 5.7 mm	Fractionated over 7 to 10 days **Dose:** 70 CGE	At the time of analysis: 98.1% control 5-years: 97% control	At the time of analysis: 16.1% metastases
Gragoudas et al. (2000) Follow-up 5 years	Uveal melanoma (choroidal)	188 patients (188 eyes)	Median largest diameter 50 CGE group: 11.0 (7.0-16.0) mm 70 CGE group: 10.0 (7.0-17.0) mm Median height 50 CGE group: 3.0 (1.2-6.3) mm 60 CGE group: 3.0 (1.0-5.5) mm	5 fractions delivered over 7 days **Dose:** 50CGE/70CGE (depending on group randomisation)	5-years: 50 CGE group: 97.9% control 70 CGE group: 96.8% control *No significant difference between groups*	Not reported
Gragoudas et al. (2002) Follow-up Median: 5.2 years	Uveal melanoma (most tumours located in posterior fundus, 26% involved ciliary body)	1922 patients (1922 eyes)	Mean largest diameter: 13 mm Mean height: 5.3 mm	5 fractions over 7 to 10 days. **Dose:** 70 Gy	At time of analysis: 96.8% control 5-years: ~97% control 10-years: ~96% control 15-years: ~95% control	Not reported
Höcht et al. (2004) Follow-up Median: 18.4 months	Uveal melanoma	245 patients (245 eyes)	Mean diameter: 10.3 mm Mean height: 3.5 mm	4 fractions over 4 consecutive days **Dose:** 60 CGE	At the time of analysis: 96.4% control 3-years: 95.5% control	Not reported
Kodjikian et al. (2004) Follow-up *Varies with outcome measured*	Uveal melanoma (ciliary and choroidal)	224 patients (224 eyes)	Largest basal diameter ≤ 10mm: 145 patients > 10 and ≤ 13mm: 64 patients >15mm: 15 patients Apical height ≤ 3mm: 40 patients >3 and ≤ 15mm: 65 patients > 5mm: 119 patients	Four fractions over 4 consecutive days **Dose:** 52 Gy (60 CGE)	Recurrence-free survival Median 7 months: 95.5%	Metastases free survival At the time of analysis: 82.1% 5-year: 75.6%
Li et al. (2000) Follow-up 9.5 years	Uveal melanoma (ciliary and choroidal)	1848 patients (1848 eyes)	Choroidal origin Mean largest diameter: 13.30 ± 3.73 mm (mean ± SD) Mean height: 5.30 ± 2.82 mm Ciliary body	**Dose:** 70CGE	Not reported	At the time of analysis, metastatic death rate: 20.5% 5-year metastatic death rate: 14.9% 10-year metastatic death rate: 23.9% 15-year metastatic

			origin Mean largest diameter: 13.7 ± 4.02 mm Mean height: 7.10 ± 2.86			death rate: 27.2%
Li et al. (2003) Follow-up Median: 7.9 years	Uveal melanoma (Choroidal)	1204 patients (1204 eyes)	Mean largest diameter: 12.7 ± 3.6 mm Mean height: 5.1 ± 2.8 mm Mean basal area: 137.3 ± 98.0 mm^2	5 fractions **Dose:** 70 CGE	Not reported	5-years metastatic death rate: 12.8% 10-years metastatic death rate: 20.7%
Marucci et al. (2006) Follow-up Mean: 50 months	Uveal melanoma (recurrent tumours re-treated with proton therapy)	31 patients (31 eyes)	Mean largest diameter: 14.6 mm (range: 4.5-24.1 mm) Mean height: 5.5mm (range: 2.0-8.2 mm)	5 fractions **Dose:** 70 CGE	At time of analysis: 83.9% control 5-years: 69% control	At the time of analysis: 25.8% metastasis 5-year metastasis free survival: 73%
Mosci et al. (2001) Follow-up Mean: 21 ± 5 months	Uveal melanoma (choroidal)	127 patients (127 eyes)	Diameter: N/A Height: 1.4-13.0 mm	4 fractions **Dose:** 60 CGE	At the time of analysis: 96.8% control	At the time of analysis: 4.7% death due to metastases.
Munzenrider et al. (1989) Follow-up Median: 16 months	Uveal melanoma (Ciliary and choroidal)	1006 patients (1007 eyes)	Not reported	5 fractions over 7 to 10 days **Dose:** 70 CGE	At time of analysis: 98.8% control 5-years: 96.3 ± 1.5% control 7-years: 95.4 ± 3.3% control	Not reported
Wilson and Hungerford (1999) Follow-up (mean ± SD) ^{125}I: 47.3 ± 22 months ^{106}Ru: 45.3 ± 29.7 months Proton beam: 43 ± 20.6 months	Uveal melanoma (choroidal)	597 patients (597 eyes) **Proton group:** 267 patients **106Ru group:** 140 patients **125I group:** 190 patients	Mean basal diameter **Proton group:** 11.7 mm **106Ru group:** 9.7 mm **125I group:** 10.2 mm Mean height **Proton group:** 6.6 mm **106Ru group:** 4.2 mm **125I group:** 5.9 mm	**Proton group:** 60 CGE, 5 fractions over 7 days **106Ru group:** 100 CGE to tumour apex **125I group:** 100 CGE to tumour apex	At the time of analysis: **Proton group:** 94.8% control **106Ru group:** 89.3% control **125I group:** 95.8% control	**Proton group:** 9.4% metastases **106Ru group:** 5.0% metastases **125I group:** 3.7% metastases

In comparison to other treatment modalities, proton beam therapy appears to be capable of achieving equivalent, if not better local tumour control. The retrospective comparative study by Wilson and Hungerford (1999) showed that patients treated with ^{106}Ru brachytherapy had a significantly greater risk of local tumour recurrence compared to patients treated with ^{125}I brachytherapy ($p = 0.0133$; CI: 1.26-7.02; risk ratio: 2.968) or proton beam therapy ($p = 0.0097$; CI: 1.30-6.66; relative risk: 2.941). Curiously, the tumours within the ^{106}Ru group were smaller and thinner, which typically should translate to lower recurrence (Wilson and Hungerford 1999).

With regards to the incidence of metastasis post-treatment, four studies estimated that the 5-year metastasis free survival rate ranged from 73% to 80% with proton beam therapy (Marucci et al. 2006, Kodjikian et al. 2004, Gragoudas et al. 1987, Dendale et al. 2006). Meanwhile, the 5-year metastatic death rate ranged from 10% to 15% (Damato et al. 2005a, Li et al. 2000). Studies on primary melanomas treated with proton beam therapy have shown that the prognostic factors for metastasis are; tumour diameter (Gragoudas et al. 1987, Damato et al. 2005a), tumour location (Li et al. 2000), tumour basal area (Li et al. 2003) ciliary body involvement (Gragoudas et al. 1987, Li et al. 2000) and local recurrence (Dandale et al. 2006). Ciliary body involvement in particular appears to represent an exceptionally difficult tumour as patients with these melanomas had a worse prognosis for metastasis, regardless of tumour size, compared to those with melanomas involving other regions of the uvea (Kodjikian et al. 2004). It is now known that tumours involving the ciliary body are more likely to harbour monosomy of chromosome 3 and trisomy of chromosome 8q, situations that are associated with a very high risk of metastatic death (Kodjikian et al. 2004, Li et al. 2000). The genetics of tumour and metastatic occurrence is a field that is yet to be clearly elucidated, and therefore may be another confounding factor in studies examining the incidence of metastasis after proton beam therapy.

The only comparative study included (Wilson and Hungerford 1999) reported that patients treated with proton beam therapy had higher rates of metastases (9.4%) compared to patients treated with ^{106}Ru brachytherapy (5.0%) and ^{125}I brachytherapy (3.7%). However the mean maximal basal diameter and the height of the tumours of patients treated with proton beam therapy were greater than patients treated with ^{106}Ru or ^{125}I brachytherapy.

b) Survival

Patient survival will be assessed based on overall survival. A total of 4 studies reported 5-year survival rates (Table 7), ranging from 16% to 85% (Egger et al. 2003, Brovkina and Zarubei 1986, Dendale et al. 2006, Kodjikian et al. 2004). It should be noted that the study which had the lowest survival rate of 16% at 5-years (Brovkina and Zarubei 1986) had large losses to follow-up (only 10 patients remaining from 5 to 7 years). Therefore, a more precise survival range at 5-years would be 78% to 85%.

Multivariate analysis by Kodjikian et al. (2004) revealed that the largest basal diameter of the tumour (LTD) was independently associated with overall survival ($p < 0.05$), an observation supported by other studies that reported significant association between survival and tumour diameter (Dendale et al. 2006). When Kodjikian and colleagues noted that LTD was greater than 10mm, the relative risk of mortality was 3.3 times greater compared to when the LTD was less than 10mm. Apical tumour height only achieved significance when LTD was excluded (Kodjikian et al. 2004). These results meant that the larger the *volume* of the tumour, the worse the prognosis for survival. Other significant prognostic factors include advanced age (Dendale et al. 2006), male gender (Dendale et al. 2006, Kodjikian et al. 2004), median and anterior tumour sites (Dendale et al. 2006), large tumour height (Dendale et al. 2006) and large retinal area (Dendale et al. 2006). It is interesting to note that Kodjikian et al. (2004) reported that tumour size appears to predominate over location for overall survival.

Table 7: Patient survival after proton beam therapy for uveal melanoma.

Study	Tumour type	No. of patients (eyes)	Tumour characteristics	Dose (Gy/CGE) and safety margin	Survival
Brovkina and Zarubei (1986) Follow-up Mean: 33.8 months	Uveal melanoma (ciliochoroidal)	63 patients (63 eyes)	Largest diameter: 8 to 20 mm Height: 3 to 13.7 mm	1500 rad per session at intervals of 1-2 days for 4/5 sessions **Dose:** 10,000 to 12,500 rad	At the time of analysis: 93.56% 29 patients survived 3 years (46%). 10 patients survived 5 years (15.9%).
Damato et al. (2005b) Follow-up Median: 2.7 years	Uveal melanoma (Iris)	88 patients (88 eyes)	Median diameter: 4.3 mm Height: N/A	4 fractions over 4 consecutive days **Dose:** 53.1 Gy	At the time of analysis: 96.6%
Dendale et al. (2006) Follow-up Median: 73 months	Uveal melanoma	1406 patients (1406 eyes)	Mean diameter: 13.3 mm Mean height: 5.4 mm	4 fractions over 4 consecutive days **Dose:** 60 CGE	At the time of analysis: 75.7% 5-years: 79%
Egger et al. (2001) Follow-up Median: 40 months	Uveal melanoma	2432 patients (2435 eyes)	Small (diameter ≤ 10mm, thickness ≤ 3mm): 126 patients Mid-sized (10mm < diameter ≤ 15mm and/or 3mm < thickness ≤ 5mm): 581 patients Large (15mm < diameter ≤ 20mm and/or 5mm < thickness ≤ 10mm): 1185 patients Extra-large (diameter > 20mm and/or thickness > 10mm): 543 patients	4 fractions in 4 consecutive days **Dose:** 54.5 Gy (60 CGE)	At the time of analysis Survival of patients with local control: 88.3% (276/2362 patients) Survival of patients with recurrent tumours: 53.4% (34/72 patients) At 10-years: Survival of patients with local control: 72.6 ± 1.9% Survival of patients with recurrent tumours: 47.5 ± 6.5%
Egger et al. (2003) Follow-up Median: 44 months	Uveal melanoma (large tumours or tumours located close to the optic disc or macula)	2645 patients (2648 eyes)	Mean diameter: 16.2 mm (4-27.5 mm) Mean height: 6.5 mm (0.9-15.6 mm)	4 fractions in 4 consecutive days. **Dose**: 54.5 Gy (60 CGE)	At the time of analysis: 87.2% 5-years: 85.1 ± 0.9% 10-years: 74.1 ± 1.6% 15-years: 69.3 ± 2.8%
Kodjikian et al. (2004) Follow-up *Varies with outcome measured*	Uveal melanoma (ciliary and choroidal)	224 patients (224 eyes)	Largest basal diameter ≤ 10mm: 145 patients > 10 and ≤ 13mm: 64 patients >15mm: 15 patients	Four fractions over 4 consecutive days **Dose:** 52 Gy (60 CGE)	Median follow-up to time of analysis: 41 months At the time of analysis: 85.7% 5-year: 78.1% ± 3.7%

			Apical height ≤ 3mm: 40 patients >3 and ≤ 15mm: 65 patients > 5mm: 119 patients		
Marucci et al. (2006) Follow-up Mean: 50 months	Uveal melanoma (recurrent tumours re-treated with proton therapy)	31 patients (31 eyes)	Mean largest diameter: 14.6 mm (range: 4.5-24.1 mm) Mean height: 5.5mm (range: 2.0-8.2 mm)	5 fractions **Dose:** 70 CGE	At the time of analysis: 74.2%
Mosci et al. (2001) Follow-up Mean: 21 ± 5 months	Uveal melanoma (choroidal)	127 patients (127 eyes)	Diameter: N/A Height: 1.4-13.0 mm	4 fractions **Dose:** 60 CGE	At the time of analysis: 95.3% 2-years: 90%
Wilson and Hungerford (1999) Follow-up (mean ± SD) ^{125}I: 47.3 ± 22 months ^{106}Ru: 45.3 ± 29.7 months Proton beam: 43 ± 20.6 months	Uveal melanoma (choroidal)	597 patients (597 eyes) **Proton group:** 267 patients **106Ru group:** 140 patients **125I group:** 190 patients	Mean basal diameter **Proton group:** 11.7 mm **106Ru group:** 9.7 mm **125I group:** 10.2 mm Mean height **Proton group:** 6.6 mm **106Ru group:** 4.2 mm **125I group:** 5.9 mm	**Proton group:** 60 CGE, 5 fractions over 7 days **106Ru group:** 100 CGE to tumour apex **125I group:** 100 CGE to tumour apex	Kaplan-Meier survival curves indicated no significant difference between the treatment groups with regards to survival (p = 0.0567) up to 80 months. *Individual group survival data not presented*

Wilson and Hungerford (1999) noted no difference in survival rates between patients treated with ^{106}Ru brachytherapy, ^{125}I brachytherapy or proton beam therapy. Comparisons with other brachytherapy studies (range: 78% to 89.6%), revealed that proton therapy achieves comparable results (Kodjikian et al. 2004).

c) Eye preservation

Reasons for enucleation varied substantially across studies, among the reasons stated includes: neovascular glaucoma, rubeosis, total retinal detachment, loss of vision, ocular discomfort and tumour recurrence. Overall, most of the studies reported eye preservation rates of approximately 90% at the time of analysis (Table 8). Some studies only reported enucleation rates due to recurrence (Gragoudas et al. 1992, Egger et al. 2001). The 5 studies that provided 5-year eye preservation rates revealed that 55% to 90% of patients managed to retain their treated eye (Egger et al. 2003, Marucci et al. 2006, Kodjikian et al. 2004, Egan et al. 1989, Munzenrider et al. 1988). However, the study by Marucci et al. (2006) only examined patients who underwent re-treatment with proton beam therapy for recurrent tumours; therefore a more reasonable range for eye preservation would be 69% to 90% at 5-years post-treatment after the exclusion of this study.

Munzenrider et al. (1988) found that patients with large tumours had a significantly lower probability of retaining the eye at 5-years compared to those with intermediate size tumours ($p < 0.0001$); no significant difference was found between those with small and intermediate tumours (refer to Table 9 for definition of tumour sizes). Munzenrider and colleagues also noted that both tumour height and diameter were associated with enucleation, with significant reduction in risk when tumour height was ≤ 8 mm and diameter was ≤ 16 mm ($p = <.0001$ for both), an observation partly supported by Egan et al. (1989) where the largest tumour diameter was not predictive of enucleation after adjusting for tumour height. Four other studies have reported an association between tumour size and enucleation (Kodjikian et al. 2004, Damato et al. 2005a, Dendale et al. 2006, Egger et al. 2003). Patients with tumours which involved the ciliary body had a significant risk of eye loss as well ($p = <.0001$), however this association did not apply to small and intermediate tumours (Munzenrider et al. 1988). The role of ciliary body involvement was supported by Damato et al. (2005a). Meanwhile, Egan et al. (1989) reported that the size of the tumour was less important in comparison to its distance of the tumour from the edge of the fovea when considering the possibility of enucleation. Analyses revealed that tumours within 2 DD of the fovea, or both disc and fovea, were 5 and 7 times more likely to experience enucleation compared to tumours located further from these structures, regardless of tumour size (Egan et al. 1989). Likewise, Egger et al. (2003) stated that eye retention was poorer for tumours located close to or infiltrating the optic disc.

Table 8: Eye retention after proton beam therapy for uveal melanoma.

Study	Tumour type	No. of patients (eyes)	Tumour characteristics	Dose (Gy/CGE)	Eye preservation
Brovkina and Zarubei (1986) Follow-up Mean: 33.8 months	Uveal melanoma (ciliochoroidal)	63 patients (63 eyes)	Largest diameter: 8 to 20 mm Height: 3 to 13.7 mm	1500 rad per session at intervals of 1-2 days for 4/5 sessions **Dose:** 10,000 to 12,500 rad	At the time of analysis: 74.6% preservation
Damato et al. (2005a) Follow-up Median: 3.1 years	Uveal melanoma (choroidal)	349 patients (349 eyes)	Diameter: N/A Height: > 5.5 mm	4 fractions over 4 consecutive days **Dose:** 53.1 Gy	At the time of analysis: 90.5% *8 enucleated for recurrence (2.3%)* *25 enucleated for complications (7.2%)*
Dendale et al. (2006) Follow-up Median: 73 months	Uveal melanoma	1406 patients (1406 eyes)	Mean diameter: 13.3 mm Mean height: 5.4 mm	4 fractions over 4 consecutive days **Dose:** 60 CGE	At the time of analysis: 90.6% preservation *33 enucleated for recurrence (2.3%)* *99 enucleated for complications (7%)*
Egan et al. (1989) Follow-up Median: 2.7 years	Uveal melanoma	994 patients (994 eyes)	Largest diameter ≤ 10mm: 183 patients 10.1-15.0mm: 444 patients >15.0mm: 299 patients Height < 5.0mm: 435 patients 5.0-8.0mm: 303 patients	5 fractions over 7 to 10 days **Dose:** 70 CGE (63.6 Gy)	At the time of analysis: 93.6% (median: 13 months) preservation 5-years: 90% preservation 5-years eye preservation according to risk groups: Low-risk: 99 ± 1% Moderate-risk: 92 ± 2% High-risk: 76 ± 7% Note: *high-risk* = tumour had 2 of more of the following characteristics: ciliary body involvement, height > 8mm and distance to fovea ≤ 2DD; *moderate-risk* = only one of the mentioned characteristics; *low-risk* = none of

			> 8.0mm: 189 patients		the mentioned characteristics.
Egger et al. (2001) <u>Follow-up</u> Median: 40 months	Uveal melanoma	2432 patients (2435 eyes)	Small (diameter ≤ 10mm, thickness ≤ 3mm): 126 patients Mid-sized (10mm < diameter ≤ 15mm and/or 3mm < thickness ≤ 5mm): 581 patients Large (15mm < diameter ≤ 20mm and/or 5mm < thickness ≤ 10mm): 1185 patients Extra-large (diameter > 20mm and/or thickness > 10mm): 543 patients	4 fractions in 4 consecutive days **Dose:** 54.5 Gy (60 CGE)	At the time of analysis: 98.6% preservation (enucleation due to recurrence only) *Data on eyes enucleated due to complications other than recurrence not presented*
Egger et al. (2003) <u>Follow-up</u> Median: 44 months	Uveal melanoma (large tumours or tumours located close to the optic disc or macula)	2645 patients (2648 eyes)	Mean diameter: 16.2 mm (4-27.5 mm) Mean height: 6.5 mm (0.9-15.6 mm)	4 fractions in 4 consecutive days. **Dose**: 54.5 Gy (60 CGE)	5-years: 88.9 ± 0.8% preservation 10-years: 86.2 ± 1.0% preservation 15-years: 83.7 ± 1.6% preservation Overall, 218/2648 eyes (8.2%) were enucleated.
Gragoudas et al. (1987) <u>Follow-up</u> Median: 5.4 years	Uveal melanoma	128 patients (128 eyes)	<u>Largest tumour diameter</u> Small: ≤ 10 mm Medium: 10.1-15 mm Large: ≥ 15.1 mm <u>Height</u> Small: ≤ 3 mm Medium: 3.1-5 mm Large ≥ 5.1 mm	5 fractions over 7 to 10 days **Dose:** 70 CGE (63.6 Gy)	At the time of analysis: 94% preservation *All due to complications not recurrence*
Gragoudas et al. (1992) <u>Follow-up</u> Mean: 4 years	Uveal melanoma	1077 patients (1077 eyes)	Mean diameter: 13.7 mm Mean height: 5.7 mm	Fractionated over 7 to 10 days **Dose:** 70 CGE	At the time of analysis: 99.1% preservation *Data on eyes enucleated due to complications other than recurrence not presented*
Höcht et al. (2004) <u>Follow-up</u> Median: 18.4 months	Uveal melanoma	245 patients (245 eyes)	Mean diameter: 10.3 mm Mean height: 3.5 mm	4 fractions over 4 consecutive days **Dose:** 60 CGE	At the time of analysis (median: 20 months): 92.6% preservation 3-years: 87.5% preservation
Kodjikian et al. (2004) <u>Follow-up</u> *Varies with outcome measured*	Uveal melanoma (ciliary and choroidal)	224 patients (224 eyes)	<u>Largest basal diameter</u> ≤ 10mm: 145 patients > 10 and ≤ 13mm: 64 patients >15mm: 15 patients <u>Apical height</u> ≤ 3mm: 40 patients >3 and ≤ 15mm:	Four fractions over 4 consecutive days **Dose:** 52 Gy (60 CGE)	<u>Enucleation free survival</u> Median 18 months: 90.2% 5-year: 69.6%

			65 patients > 5mm: 119 patients		
Marucci et al. (2006) <u>Follow-up</u> Mean: 50 months	Uveal melanoma (recurrent tumours re-treated with proton therapy)	31 patients (31 eyes)	Mean largest diameter: 14.6 mm (range: 4.5-24.1 mm) Mean height: 5.5mm (range: 2.0-8.2 mm)	5 fractions **Dose:** 70 CGE	At the time of analysis: 71% preservation 5-years: 55% preservation
Mosci et al. (2001) <u>Follow-up</u> Mean: 21 ± 5 months	Uveal melanoma (choroidal)	127 patients (127 eyes)	Diameter: N/A Height: 1.4-13.0 mm	4 fractions **Dose:** 60 CGE	At the time of analysis: 93.8% *4 enucleated for recurrence (3.1%)* *4 enucleated for neovascular glaucoma (3.1%)*
Munzenrider et al. (1988) <u>Follow-up</u> *Unclear*	Uveal melanoma	1006 patients (1006 eyes)	<u>Tumour dimensions</u> a) Small (height ≤3mm, diameter ≤10mm): 99 patients b) Intermediate (height 3.1-8mm, diameter 10.1-16mm): 566 patients c) Large (height >8mm, diameter >16mm): 341 patients	5 fractions over 7 to 10 days **Dose:** 70 CGE	At the time of analysis: 94.3% 5-years: 89.1 ± 3% 6-years: 89.1 ± 4.4%
Munzenrider et al. (1989) <u>Follow-up</u> Median: 16 months	Uveal melanoma (Ciliary and choroidal)	1006 patients (1007 eyes)	Not reported	5 fractions over 7 to 10 days **Dose:** 70 CGE	At the time of analysis: 98.1%
Wilson and Hungerford (1999) <u>Follow-up (mean ± SD)</u> ^{125}I: 47.3 ± 22 months ^{106}Ru: 45.3 ± 29.7 months Proton beam: 43 ± 20.6 months	Uveal melanoma (choroidal)	597 patients (597 eyes) **Proton group:** 267 patients **106Ru group:** 140 patients **125I group:** 190 patients	<u>Mean basal diameter</u> **Proton group:** 11.7 mm **106Ru group:** 9.7 mm **125I group:** 10.2 mm <u>Mean height</u> **Proton group:** 6.6 mm **106Ru group:** 4.2 mm **125I group:** 5.9 mm	**Proton group:** 60 CGE, 5 fractions over 7 days **106Ru group:** 100 CGE to tumour apex **125I group:** 100 CGE to tumour apex	At the time of analysis: **Overall:** 92.2% preservation **Proton group:** 89.1% preservation **106Ru group:** 95% preservation **125I group:** 94.2% preservation

Patients treated with proton beam therapy appeared to have a higher risk of enucleation compared to those treated with 106Ru or 125I brachytherapy. This was partly due to the fact that more patients developed neovascular glaucoma after proton beam therapy compared to other treatment modalities (Wilson and Hungerford 1999).

Potential Cost Impact

Cost Analysis

No studies analysing the specific cost effectiveness of proton beam therapy for uveal melanomas have been conducted.

The study by Goitein and Jermann (2003) in Switzerland analysed the relative costs of proton and X-ray radiation therapy and concluded that the construction costs of a two-gantry proton facility, complete with equipment, was estimated at €62,500,000 while a two-linac X-ray facility would cost €16,800,000. (One Euro = 1.67 Australian $ on 8/12/06.) The cost of operation of a proton therapy facility was found to be dominated by business costs (42%, primarily the cost of repaying the presumed loan for construction of the facility), personnel costs (28%) and the cost of servicing the equipment (21%). Meanwhile, the cost of operation for an X-ray facility was dominated by the personnel cost (51%) and the business cost (28%). The cost per fraction was estimated to be €1025 for proton therapy and €425 for X-ray therapy, which is a ratio of costs of 2.4 ± 0.35 (85% confidence). Goitein and Jermann suggested that they expect substantial opportunities for treatment cost reduction over the next 5 to 10 years. Based on a set criterion of assumptions[3], the authors estimated that the cost of proton and X-ray therapy can be reduced to €650 and €310 respectively, resulting in a ratio of costs of 2.1. If however the initial capital investments were ignored, which would mean that the operating costs need not repay the investment, the future costs for proton and X-ray therapy could be reduced to €370 and €230 respectively, for a cost-per-fraction ratio of 1.6. Overall, is it likely that proton beam therapy would continue to be more expensive compared to X-ray therapy; despite future assumptions of cost reductions (Goitein and Jermann 2003). The question is whether the greater cost of proton beam therapy is clinically worthwhile.

Ethical Considerations

Informed Consent

Clinicians have an ethical obligation to inform patients on the effectiveness of proton beam therapy for tumour control and to ensure that patients are aware of the risks and the ocular complications associated with this treatment modality. Patients should be informed in advance that during treatment it is necessary for the head and neck to be immobilised, and eyelids retracted to ensure accurate proton beam targeting.

[3] Reduction in equipment cost, nominal time per fraction, equipment service rate, and MD + PhD + dosimetrist effort (Table 6, Goitein and Jermann 2003).

Access Issues

Proton beam therapy is a complicated and technologically advanced treatment and therefore can only be performed in well-equipped medical institutions under the supervision of trained clinicians, medical physicists and dosimetrists. Therefore this treatment will only be available in major cities with adequate infrastructure and funding to purchase/maintain the equipment necessary for proton beam therapy.

Training and Accreditation

Training

The administration of proton beam therapy appears to be similar to conventional radiotherapy. Medical specialists would need to familiarise themselves with the treatment planning software and the operation of the proton beam gantries. Details regarding formal training for proton beam therapy were not retrieved in our searches.

Clinical Guidelines

There are currently no clinical practice guidelines that include proton beam therapy in Australia and New Zealand. If proton beam therapy is approved by the TGA, clinical guidelines will need to be developed.

Limitations of the Assessment

Methodological issues and the relevance or currency of information provided over time are paramount in any assessment carried out in the early life of a technology. Horizon scanning forms an integral component of Health Technology Assessment. However, it is a specialised and quite distinct activity conducted for an entirely different purpose. The rapid evolution of technological advances can in some cases overtake the speed at which trials or other reviews are conducted. In many cases, by the time a study or review has been completed, the technology may have evolved to a higher level leaving the technology under investigation obsolete and replaced.
A Horizon Scanning Report maintains a predictive or speculative focus, often based on low level evidence, and is aimed at informing policy and decision makers. It is not a definitive assessment of the safety, effectiveness, ethical considerations and cost effectiveness of a technology.

In the context of a rapidly evolving technology, a Horizon Scanning Report is a ‘state of play’ assessment that presents a trade-off between the value of early, uncertain information, versus the value of certain, but late information that may be of limited relevance to policy and decision makers.

Search Strategy Used for Report

The sources utilised in this assessment are listed in Table 9. The medical literature was searched with the search terms outlined in Table 10 to identify relevant studies up to January 2007 in English only. In addition to this, major international health technology assessment databases and clinical trial registers were searched.

Table 9: Literature sources utilised in assessment

Source	Location
Electronic databases	
AustHealth	University of Adelaide library
Australian Medical Index	University of Adelaide library
CINAHL	University of Adelaide library
Cochrane Library – including Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, the Cochrane Central Register of Controlled Trials (CENTRAL), the Health Technology Assessment Databese, the NHS Economic Evaluation Database	University of Adelaide library
Current Contents	University of Adelaide library
Embase	Personal subscription
Pre-Medline and Medline	University of Adelaide library
PyscINFO	Personal subscription
RACS electronic library	Personal subscription
Internet	
Blue Cross and Blue Shield Association's Technology Evaluation Center	http://www.bcbs.com/tec/
Canadian Agency for Drugs and Technologies in Health	http://www.cadth.ca
Current Controlled Trials metaRegister	http://www.controlled-trials.com/
EuroScan	http://www.euroscan.bham.ac.uk/
Health Technology Assessment International	http://www.htai.org/
International Network for agencies for Health Technology Assessment	http://www.inahta.org
Medicines and Healthcare products Regulatory Agency (UK)	http://www.mhra.gov.uk/
US Food and Drug Administration, Center for Devices and Radiological Health	http://www.fda.gov/cdrh/index.html

US Food and Drug Administration, Manufacturer and User Facility Device Experience Database	http://www.fda.gov/cdrh/maude.html
UK National Research Register	http://www.nrr.nhs.uk/
Websites of specialty organisations	Dependent on technology assessed

Table 10: Search terms utilised

Search terms
MeSH Ionising radiation; radiotherapy; neoplasm; proton; radiation oncology; therapeutic radiology; radiation therapy; medical oncology; protons/therapeutic use; radiation Injuries/prevention and control. **Text words** proton beam therapy; proton therapy; proton radiation; radiotherapy; proton irradiation; heavy ions/therapeutic use; radiotherapy, high energy; ions/therapeutic use; protons/therapeutic use; particle accelerators; uveal melanoma. **Limits** English, human

Availability and Level of Evidence

A total of two randomised controlled trial (Level II intervention evidence), one comparative study (Level III-2 intervention evidence) and 22 peer reviewed case series studies (Level IV intervention evidence) reported safety and efficacy outcomes on the use of proton beam therapy for the treatment of patients uveal melanoma. In addition, one cost study was retrieved for assessment in this report. The profiles of the included case series studies are summarised in Appendix B.

Sources of Further Information

No ongoing or future clinical trials assessing the safety and efficacy of proton beam therapy for uveal melanomas were located within the Current-Controlled Trials or the UK National Research Register database.

Conclusions

Proton beam therapy has been utilised to treat uveal melanomas since the late 1980s. The procedure involves the placement of tantalum clips onto the sclera around the tumour base, followed by the construction of a precise 3D model of the patient's eye, including the lens, optic nerve and fovea utilising specialised treatment planning software (EYEPLAN). The tumour margins are drawn onto this model by the ophthalmologist and verified by the radiation oncologist. This information is then relayed to the proton beam accelerator (synchrotron) where the protons will be delivered into the targeted tumour. The procedure involves the use of high-tech equipment, requiring input from several medical and scientific specialists. At the time of writing, over 39,000 patients around the world have received proton therapy either alone or in conjunction with conventional radiotherapy (Levin et al. 2005), of which at least 8000 were treated for uveal melanomas (Blomquist et al. 2005).

Existing comparators for proton beam therapy includes other forms of external beam radiotherapy (photons, helium ions etc.), brachytherapy, laser photocoagulation, transpupillary thermotherapy, sclerouvectomy and endoresection. The key disadvantage of other radiotherapy treatments (photon beam therapy and brachytherapy) is the irradiation of healthy tissue located in close proximity to the target tumour. Research has revealed that protons have inherent dose-distribution characteristics that may confer substantial advantage over photon radiotherapy and brachytherapy (as illustrated in Figure 1).

The majority of studies included were low quality (level IV intervention evidence). The key measures of the effectiveness of proton beam therapy for the treatment of uveal melanoma were local tumour control, survival and retention of the treated eye. Meanwhile, the key complications assessed following proton beam therapy were the incidence of rubeosis, neovascular glaucoma, cataracts and vision loss.

Radiotherapeutic treatment of uveal melanomas is often associated with various complications, and proton beam therapy is of no exception. Two of the most severe complications after proton beam therapy are rubeosis and neovascular glaucoma, due to the high risk of enucleation associated with these conditions. There is substantial variation between studies with regards to the incidence of rubeosis (~8%) and neovascular glaucoma (9% to 29%). However, research has shown that both these conditions contribute significantly to secondary enucleation after proton beam therapy. The development of cataract is another common complication (ranging from 6% to 62%) following proton beam therapy, and contributes significantly to vision loss in the treated eye. In addition, the incidence of visual deterioration after treatment

with proton beam therapy is considerable and appears to be more severe compared to brachytherapy. However one study noted that despite experiencing substantial decrease of visual acuity, most patients retain useful vision (Seddon et al. 1987). Overall, the utilisation of proton beam therapy for the treatment of uveal melanomas appears to be associated with substantial complications. Several researchers have noted that most of these complications are highly dependent on tumour characteristics (size, location) as well as pre-treatment patient characteristics (e.g. pre-treatment visual acuity, glaucoma etc.). The lack of comparative studies severely limits the conclusions that can be drawn from the available evidence.

Local tumour control rates achieved with proton beam therapy was approximately 95%, indicating that this treatment is capable of preventing recurrence in most patients. Studies have shown that the possibility of recurrence is highly correlated to tumour size, in particular the height of the tumour. Nevertheless, the available literature is generally supportive that good local tumour control can be achieved with proton beam therapy. The incidence of metastasis appears to be comparable to other treatment modalities, with 5-year metastasis-free survival ranging from 73% to 80%. Overall patient survival after proton beam therapy ranged from 78% to 85% at 5-years post-treatment, which appears to be equivalent to patients treated with brachytherapy.

At the time of writing, there were no cost-effectiveness studies on the utilisation of proton beam therapy for the treatment of uveal melanomas. One study, by Goiten and Jermann (2003) reported that that proton beam therapy will continue to be more expensive compared to conventional X-ray/photon therapy despite future assumptions of cost reductions (Goitein and Jermann 2003).

There are substantial amount of studies on the utilisation of proton beam therapy for the treatment of uveal melanomas. However, these studies often varied in treatment doses, did not use a concurrent control, tumour characteristics (location and size) were markedly different, and treatment margins were not standardised. Despite the heterogeneity between the included studies, proton beam therapy appears to be capable of achieving high rates of local tumour control. Nevertheless, many issues remain with regards to the use of this technology. Studies need to be conducted to determine the optimal dose for various types of uveal melanomas (taking into account tumour size, distance from sensitive structures, involvement of the ciliary body etc.) and to refine the technique with the aim of reducing complication rates. In addition, long-term comparative studies with existing techniques of treating uveal melanomas are required to provide more definitive results as to whether proton beam therapy is indeed more effective in the treatment of uveal melanomas.

Appendix A: Levels of Evidence

Designation of levels of evidence according to type of research question

Level	Intervention	Diagnosis	Prognosis	Aetiology	Screening
I	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies
II	A randomised controlled trial	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, §§among non-consecutive patients with a defined clinical presentation††	A prospective cohort study ***	A prospective cohort study ***	A randomised controlled trial
III-1	A pseudorandomised controlled trial (i.e. alternate allocation or some other method)	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, §§among non-consecutive patients with a defined clinical presentation††	All or none§§§	All or none§§§	A pseudorandomised controlled trial (i.e. alternate allocation or some other method)
III-2	A comparative study with concurrent controls: Non-randomised, experimental trial† Cohort study Case-control study Interrupted time series with a control group	A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	Analysis of prognosis factors amongst unrelated control patients in a randomised controlled trial	A retrospective cohort study	A comparative study with concurrent controls: Non-randomised, experimental trial Cohort study Case-control study
III-3	A comparative study with concurrent controls: Historical control study Two or more single arm study‡ Interrupted time series without a parallel control group	Diagnostic case-control study††	A retrospective cohort study	A case-control study	A comparative study without concurrent controls: Historical control study Two or more single arm study
IV	Case series with either post-test or pre-test/post-test outcomes	Study of diagnostic yield (no reference standard) ⌗	Case series, or cohort study of patients at different stages of disease	A cross-sectional study	Case series

Tablenotes

[*] A systematic review will only be assigned a level of evidence as high as the studies it contains, excepting where those studies are of level II evidence.

[§] Definitions of these study designs are provided on pages 7 – 8 *How to use the evidence: assessment and application of scientific evidence* (NHMRC 2000b).

[†] This also includes controlled before-and-after (pre-test/post-test) studies, as well as indirect comparisons (i.e. utilise A vs B and B vs C, to determine A vs C).

[‡] Comparing single arm studies i.e. case series from two studies.

[**] The dimensions of evidence apply only to studies of diagnostic accuracy. To assess the effectiveness of a diagnostic test there also needs to be a consideration of the impact of the test on patient management and health outcomes. See *MSAC (2004) Guidelines for the assessment of diagnostic technologies.* Available at: www.msac.gov.au

[§§] The validity of the reference standard should be determined in the context of the disease under review. Criteria for determining the validity of the reference standard should be pre-specified. This can include the choice of the reference standard(s) and its timing in relation to the index test. The validity of the reference standard can be determined through quality appraisal of the study. See Whiting P, Rutjes AWS, Reitsma JB, Bossuyt PMM, Kleijnen J. The development of QADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews, *BMC Medical Research Methodology*, 2003, 3: 25.

[††] Well-designed population based case-control studies (e.g. population based screening studies where test accuracy is assessed on all cases, with a random sample of controls) do capture a population with a representative spectrum of disease and thus fulfil the requirements for a valid assembly of patients. These types of studies should be considered as Level II evidence. However, in some cases the population assembled is not representative of the use of the test in practice. In diagnostic case-controlled studies a selected sample of patients already known to have the disease are compared with a separate group of normal/healthy people known to be free of the disease. In this situation patients with borderline or mild expressions of the disease, and conditions mimicking the disease are excluded, which can lead to exaggeration of both sensitivity and specificity. This is called spectrum bias because the spectrum of study participants will not be representative of patients seen in practice.

[‡‡] Studies of diagnostic yield provide the yield of diseased patients, as determined by an index test, without confirmation of accuracy by a reference standard. These may be the only alternative when there is no reliable reference standard.

[***] At study inception the cohort is either non-diseased or all at the same stage of the disease.

[§§§] All or none of the people with the risk factor(s) experience the outcome. For example, no smallpox develops in the absence of the specific virus; and clear proof of the causal link has come deom the disappearance of small-pox after large-scale vaccination.

[†††] If it is possible and/or ethical to determine a causal relationship using experimental evidence, then the 'Intervention' hierarchy of evidence should be utilised. If it is only possible and/or ethical to determine a causal relationship using observational evidence (i.e. cannot allocate groups to a potential harmful exposure, such as nuclear radiation), then the 'Aetiology' hierarchy of evidence should be utilised.

Note 1: Assessment of comparative harms/safety should occur according to the hierarchy presented for each of the research questions, with the proviso that this assessment occurs within the context of the topic being assessed. Some harms are rare and cannot be feasibly captures within randomised controlled trials; physical harms and psychological harms may need to be addressed by different study designs; harms from diagnostic testing include likelihood of false positive and false negative results; harms from screening include the likelihood of false alarm and dales reassurance results.

Note 2: When a level of evidence is attributed in the text of a document, it should also be framed according to its corresponding research question e.g. level II intervention evidence; level IV diagnostic evidence; level III-2 prognostic evidence etc.

Hierarchies adapted and modified from: NHMRC 1999; (Lijmer et al 1999; Phillips et al 2001; Bandolier editorial 1999)

Appendix B: Profile of Studies

Study	Location	Study design	Study population	Study details	Outcomes assessed	Length of follow-up
Brovkina AF, Zarubei GD. (1986)	Moscow, Russia	Case series Level IV intervention evidence Proton beam therapy	63 patients with uveal melanoma (ciliochoroidal)	1500 rad per session at intervals of 1-2 days for 4/5 sessions Dose: 10,000 to 12,500 rad	Ocular complications, tumour control / resorption, survival.	Mean: 33.8 months
Damato B, Kacperek A, Chopra M, Campbell IR, Errington RD. (2005a)	United Kingdom	Case series Level IV intervention evidence Proton beam therapy	349 patients with uveal melanoma	4 fractions Dose: 53.1 Gy Adjunctive transpupillary thermotherapy in 11 patients	Local tumour control, eye preservation, metastasis, visual acuity	Median: 3.1 years
Damato B, Kacperek A, Chopra M, Sheen MA, Campbell IR, Errington RD. (2005b)	United Kingdom	Case series Level IV intervention evidence Proton beam therapy	88 patients with uveal melanoma (iris)	4 fractions Dose: 53.1 Gy	Visual acuity, ocular complications, eye preservation, metastasis	Median: 2.7 years
Dendale R, Rouic LL, Noel G, Feuvret L, Levy C, Delacroix S, Meyer A, Mauraye C, Mazal A, Mammar H, Garcia P, D'Hermies F, Frau E, Plancher C, Aseelain B, Schlienger P, Mazeron JJ, Desjardins L. (2006)	Orsay, France	Retrospective case series Level IV intervention evidence Proton beam therapy	1406 patients with uveal melanoma	4 fractions over 4 consecutive days Dose: 60 CGE	Local control, overall survival, metastasis-free survival, ocular complications, visual acuity.	Median: 73 months
Desjardins L, Lumbroso-Le Rouic L, Levy-Gabriel C, Dendale R, Delacroix S, mauraye C, Esteve M, Plancher C, Asselain B. (2006)	Paris, France	Randomised controlled trial Level II intervention evidence Proton beam therapy + transpupillary thermotherapy (TTT)	151 patients with uveal melanoma Proton beam alone: 75 patients Proton beam + TTT: 76 patients	4 fractions over 4 days Dose: 60 Gy	Ocular complications (cataract, maculopathy, papillopathy, glaucoma)	Median: 38 months
Egan KM, Gragoudas ES, Seddon JM, Glynn RJ, Munzenrider JE, Goitein M, Verhey L, Urie	Cambridge, United States	Case series Level IV intervention evidence Proton beam	1006 patients (1007 eyes) with uveal melanoma	5 fractions over 7 to 10 days Dose: 70 CGE	Eye preservation	Median: 2.7 years

M, Koehler A. (1989)		therapy				
Egger E, Schalenbourg A, Zografos L, Bercher L, Boehringer T, Chamot L, Goitein G. (2001)	Switzerland	Case series Level IV intervention evidence Proton beam therapy	2432 patients (2435 eyes) with uveal melanoma	4 fractions in 4 consecutive days Dose: 54.5 Gy (60 CGE)	Local tumour control, reduction of tumour size, survival	Median: 40 months
Egger E, Zografos L, Schalenbourg A, Beati D, Bohringer T, Chamot L, Goitein G. (2003)	Switzerland	Case series Level IV intervention evidence Proton beam therapy	2645 patients (2648 eyes) with uveal melanoma	4 fractions in 4 consecutive days Dose: 54.5 Gy (60 CGE)	Eye preservation	Median: 44 months
Foss AJE, Hungerford JL, Anderson DF, Errington RD, Kacperek A, Restori M, Kongerud J, Sheen M. (1997)	United Kingdom	Retrospective case series Level IV intervention evidence Proton beam therapy	127 patients with uveal melanoma	4 fractions over 4 days Dose: 52 CGE	Rubeosis incidence	Unclear
Gragoudas ES, Seddon JM, Egan K, Glynn R, Munzenrider J, Austin-Seymour M, Goitein M, Verhey L, Urie M, Koehler A. (1987)	Cambridge, United States	Case series Level IV intervention evidence Proton beam therapy	128 patients with uveal melanoma	5 fractions over 7 to 10 days Dose: 70 CGE (63.6 Gy)	Local tumour control, visual acuity, ocular complications, metastasis	Median: 5.4 years
Gragoudas ES, Egan KM, Seddon JM, Walsh SM, Munzenrider JE. (1992)	Cambridge, United States	Case series Level IV intervention evidence Proton beam therapy	1077 patients with uveal melanoma	Fractionated over 7 to 10 days Dose: 70 CGE	Local tumour control, survival	Mean: 4 years
Gragoudas ES, Egan KM, Walsh SM, Regan S, Munzenrider JE, Taratuta V. (1995)	Cambridge, United States	Case series Level IV intervention evidence Proton beam therapy	383 patients with uveal melanoma	5 fractions over approximately 8 days Dose: 70 CGE	Lens opacification	Mean: 37 months
Gragoudas ES, Lane AM, Regan S, Wenjun MS, Judge HE, Munzenrider JE, Seddon JM, Egan KM. (2000)	Cambridge, United States	Randomised controlled trial Level II intervention evidence Proton beam therapy	188 patients with small/medium uveal melanoma (choroidal) 50 CGE group: 94 patients 70 CGE group: 94 patients	5 fractions delivered over 7 days Dose: 50CGE/70CGE (depending on group randomisation)	Visual acuity, visual field, ocular complications, local tumour control	5 years
Gragoudas	Cambridge,	Case series	1922	5 fractions	Local tumour	Median:

ES, Lane AM, Munzenrider J, Egan KM, Li WJ. (2002)	United States	Level IV intervention evidence Proton beam therapy	patients with uveal melanoma	over 7 to 10 days. Dose: 70 Gy	control	5.2 years
Höcht S, Bechrakis NE, Nausner M, Kreusel KM, Kluge H, Heese J, Heufelder J, Cordini D, Homeyer H, Fuchs H, Martus P, Foerster MH, Wiegel T, Hinkelbein W. (2004)	Berlin, Germany	Case series Level IV intervention evidence Proton beam therapy	245 patients with uveal melanoma	4 fractions over 4 consecutive days Dose: 60 CGE	Local tumour control, eye preservation, ocular complications, visual acuity	Median: 18.4 months
Kodjikian L, Roy P, Rouberol F, Garweg G, Chauvel P, Manon L, Jean-Louis B, Little RE, Sasco AJ, Grange JD. (2004)	Nice, France	Case series Level IV intervention evidence Proton beam therapy	224 patients with uveal melanoma	Four fractions over 4 consecutive days Dose: 52 Gy (60 CGE)	Overall survival, metastasis-free survival, local recurrence-free survival, enucleation-free survival	*Varies with outcome measured*
Li W, Gragoudas ED, Egan KM. (2000)	Cambridge, United States	Case series Level IV intervention evidence Proton beam therapy	1848 patients with uveal melanoma (choroidal / ciliary)	5 fractions Dose: 70CGE	Metastatic death	Median: 9.5 years
Li W, Gragoudas ES, Egan KM. (2003)	Cambridge, United States	Case series Level IV intervention evidence Proton beam therapy	1204 patients with uveal melanoma (choroidal)	5 fractions Dose: 70CGE	Metastatic death	Median: 7.9 years
Marucci L, Lane AM, Li W, Egan KM, Gragoudas ES, Adams JA, Collier JM, Munzenrider JE. (2006)	Cambridge, United States	Case series Level IV intervention evidence Proton beam therapy	31 patients with *recurrent* uveal melanoma	5 fractions Dose: 70 CGE	Local tumour control, ocular complications, eye preservation, metastasis	Mean: 50 months
Mosci C, Polizzi A, Squarcia S, Mascialino B, Chauvel P, Zingirian M. (2001)	Nice, France	Case series Level IV intervention evidence Proton beam therapy	127 patients with uveal melanoma (choroidal)	4 fractions Dose: 60 CGE	Local tumour control, eye preservation, ocular complications, metastasis	Mean: 21 ± 5 months
Munzenrider JE, Gragoudas ES, Seddon JM, Sisterson	Cambridge, United States	Case series Level IV intervention evidence	1006 patients (1007 eyes) with uveal melanoma	5 fractions over 7 to 10 days Dose: 70 CGE	Eye preservation	Unclear

J, MaNulty P, Birnbaum S, Johnson K, Austin-Seymour M, Slater J, Goitein MM, Verhey LJ, Urie M, Ruotolo DM, Egan K, Osuna F. (1988)		Proton beam therapy	(ciliary and choroidal)			
Munzenrider JE, Verhey LJ, Gragoudas ES, Seddon JM, Urie M, Gentry R, Birnbaum S, Ruotolo DM, Crowell C, McManus P, Finn S, Sisterson J, ohnson K, Egan K, Lento D, Bassin P. (1989)	Cambridge, United States	Case series Level IV intervention evidence Proton beam therapy	1006 patients (1007 eyes) with uveal melanoma (ciliary and choroidal)	5 fractions over 7 to 10 days Dose: 70 CGE	Local tumour control, visual acuity	Median: 16 months
Park SS, Walsh SM, Gragoudas ES. (1996)	Cambridge, United States	Case series Level IV intervention evidence Proton beam therapy	59 patients with uveal melanoma (parapapillary chroidal)	Overall dose note reported	Visual field	At least 18 months post-treatment
Seddon JM, Gragoudas ES, Egan KM, Glynn RJ, Munzenrider JE, Austin-Seymour, Goitein M, Verhey L, Urie M, Koehler A. (1987)	Cambridge, United States	Case series Level IV intervention evidence Proton beam therapy	666 patients (667 eyes) with uveal melanoma	5 fractions over 7 to 10 days Dose: 70 CGE	Visual acuity	Median: 20.4 months
Wilson MW, Hungerford JL. (1999)	London, England	Retrospective comparative study Level III-2 intervention evidence Proton beam therapy	597 patients Proton group: 267 patients 106Ru group: 140 patients 125I group: 190 patients	Proton group: 60 CGE, 5 fractions over 7 days 106Ru group: 100 CGE to tumour apex 125I group: 100 CGE to tumour apex	Local tumour control, visual acuity, ocular complications, survival, metastasis	(mean ± SD) ^{125}I: 47.3 ± 22 months ^{106}Ru: 45.3 ± 29.7 months Proton beam: 43 ± 20.6 months

Appendix C: HTA Internet Sites

AUSTRALIA

- Centre for Clinical Effectiveness, Monash University
  http://www.med.monash.edu.au/healthservices/cce/evidence/

- Health Economics Unit, Monash University
  http://chpe.buseco.monash.edu.au

AUSTRIA

- Institute of Technology Assessment / HTA unit
  http://www.oeaw.ac.at/ita/welcome.htm

CANADA

- Agence d'Evaluation des Technologies et des Modes d'Intervention en Santé (AETMIS) http://www.aetmis.gouv.qc.ca/en/

- Alberta Heritage Foundation for Medical Research (AHFMR)
  http://www.ahfmr.ab.ca/publications.html

- Canadian Coordinating Office for Health Technology Assessment (CCOHTA)
  http://www.cadth.ca/index.php/en/

- Canadian Health Economics Research Association (CHERA/ACRES) – Cabot database http://www.mycabot.ca

- Centre for Health Economics and Policy Analysis (CHEPA), McMaster University http://www.chepa.org

- Centre for Health Services and Policy Research (CHSPR), University of British Columbia http://www.chspr.ubc.ca

- Health Utilities Index (HUI) http://www.fhs.mcmaster.ca/hug/index.htm

- Institute for Clinical and Evaluative Studies (ICES) http://www.ices.on.ca

DENMARK

- Danish Institute for Health Technology Assessment (DIHTA)
  http://www.dihta.dk/publikationer/index_uk.asp

- Danish Institute for Health Services Research (DSI)
  http://www.dsi.dk/engelsk.html

FINLAND

- Finnish Office for Health Technology Assessment (FINOHTA)
  http://finohta.stakes.fi/FI/index.htm

FRANCE

- L'Agence Nationale d'Accréditation et d'Evaluation en Santé (ANAES)
  http://www.anaes.fr/

GERMANY

- German Institute for Medical Documentation and Information (DIMDI) / HTA
  http://www.dimdi.de/dynamic/en/

THE NETHERLANDS

- Health Council of the Netherlands Gezondheidsraad
  http://www.gr.nl/adviezen.php

NEW ZEALAND

- New Zealand Health Technology Assessment (NZHTA)
  http://nzhta.chmeds.ac.nz/

NORWAY

- Norwegian Centre for Health Technology Assessment (SMM)
  http://www.kunnskapssenteret.no/

SPAIN

- Agencia de Evaluación de Tecnologias Sanitarias, Instituto de Salud "Carlos III" / Health Technology Assessment Agency (AETS)
  http://www.isciii.es/htdocs/investigacion/Agencia_quees.jsp

- Catalan Agency for Health Technology Assessment (CAHTA)
  http://www.aatrm.net/html/en/dir394/index.html

SWEDEN

- Swedish Council on Technology Assessment in Health Care (SBU)
  http://www.sbu.se/www/index.asp

- Center for Medical Health Technology Assessment
  http://www.cmt.liu.se/

SWITZERLAND

- Swiss Network on Health Technology Assessment (SNHTA)
  http://www.snhta.ch/

UNITED KINGDOM

- NHS Quality Improvement Scotland
  http://www.nhshealthquality.org

- National Health Service Health Technology Assessment (UK) / National Coordinating Centre for health Technology Assessment (NCCHTA)
  http://www.hta.nhsweb.nhs.uk/

- University of York NHS Centre for Reviews and Dissemination (NHS CRD)
  http://www.your.ac.uk/inst/crd/

- National Institute for Clinical Excellence (NICE)
  http://www.nice.org.uk/

UNITED STATES

- Agency for Healthcare Research and Quality (AHRQ)
  http://www.ahrq.gov/clinic/techix.htm

- Harvard School of Public Health – Cost-Utility Analysis Registry
  http://www.tufts-nemc.org/cearegistry/index.html

- U.S. Blue Cross / Blue Shield Association Technology Evaluation Center (TEC)
  http://www.bcbs.com/tec/index.html

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