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Health Technology Assessment

Proton Beam Therapy (PBT)

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Darren CHUA, LOW Yen Sia, ANG Shin Yuh, Jeremy LIM

For more information, please contact SingHealth CHSR at:
Web: http://www.singhealth.com.sg/research/hsr
Email: hsr@singhealth.com.sg
Fax: (65) 6323 2901
Mail: SingHealth Centre for Health Services Research
226 Outram Road
#03-01 Block A
Singapore 169030

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Summary

While Proton Beam Therapy (PBT) appears to be promising, the technology has not been fully tested, as comparative studies are few. PBT is also unlikely to be assessed in the near future in rigorously controlled trials to the best of the reviewers' knowledge. The high cost of PBT puts into doubt its cost-effectiveness for the treatment of most common cancers. PBT, as supported by current levels of evidence, may serve to benefit only selected patients with few other treatment options such as those with cancers of the eye, head and neck, central nervous system and paediatric cancers. As these cancers are relatively rare in Singapore, there may not be enough local patients to support a PBT facility (which would typically require an optimal load of 1000 patients each year). The catchment area will need to be enlarged to the region to include foreign patients with clinically appropriate cancers to support a PBT centre

Introduction

Objective

This paper aims to review existing literature for the safety, efficacy and cost-effectiveness of proton beam therapy (PBT).

Population	Patients with cancer
Intervention	Proton beam therapy (PBT)
Comparison	Conventional radiotherapy with or without stereotactic and/or image-guidance. Radiotherapy may be applied with externally (X-ray) or internally (e.g. brachytherapy)
Outcomes	Survival rate, complication rate, quality of life, cost-effectiveness

About the Technology

Proton beam therapy (PBT) involves irradiation of the tumour site with a beam of proton particles that are heavier and less prone to scattering unlike conventional radiotherapy which irradiates the tumour site with light. Thus, PBT is believed to achieve better precision and deeper penetration, sparing healthy tissue from unnecessary radiation damage. This makes PBT especially beneficial in cases where tumors are close to vital organs or in paediatric patients who may otherwise develop secondary radiation-induced malignancies later in life as a result of early exposure to high doses of radiation.

The relatively large size of protons (compared to photons or light) results in less scattering and less dispersion. All protons of a given energy have a certain range and no protons penetrate beyond that distance. It is therefore possible to focus the cell damage due to the proton beam at the very depth in the tissues where the tumor is situated (Bragg Peak). The goal is to bring particle dose exactly into the tumour.

Proton beams are generated using a particle accelerator, requiring large capital investment and space. The early PBT centres were often academic medical centres affiliated with the physics departments of universities (Loma Linda, CERN). In recent times, private investment has hastened the building of PBT centres dedicated to medical use and many are expected to come on-line over the next decade. Proposed in 1946 Robert Wilson, some 50,000 patients worldwide have undergone radiation treatment using this technology.

Burden of Disease

Cancer is the top killer in Singapore, accounting for 28% of deaths in 2006. In 2005, there were close to 9000 new cases of cancer, of which 80 were childhood cancer.
The following lists the local annual incidences of cancers that PBT is most commonly used for internationally:

- 4 new cases of eye tumours (ICD-9 190)
- 550 new cases of head and neck tumours (ICD-9 140-150)
- 70 new cases of brain and nervous system tumours (ICD-9 191-192)

PBT is also increasingly used for lung (1200 new cases/year) and prostate (260 new cases/year) cancers

Geographic Distribution

At present, there are no PBT centres in Singapore, Australia and New Zealand. Most of the PBT centres are concentrated in the US, Japan and Europe. China and Taiwan are also building their own PBT centres.

Methodology

Search terms: ‘proton beam cancer’; ‘proton therapy cancer’; ‘proton beam therapy cancer’
Databases: Pubmed, NHS Centre for Reviews and Dissemination Database (CRD) and the National Guidelines Clearinghouse
Search date: January 2008

Non-English papers and those without abstracts were excluded. Search results were also checked for clinical relevance.

Results

25 publications (4 systematic reviews, 18 case series, 3 economic evaluations) were reviewed. The systematic reviews generally considered all cancers while the case series focused on cancers of the eye (9), liver (3), central nervous system (3), bone (1), prostate (1), lung (1), connective tissue (1).

Systematic Reviews

Systematic reviews highlight the lack of evidence (current evidence mainly consists of case series) to support the use of PBT for most cancer types except in patients who stand to benefit the most from its tissue-sparing properties (i.e. eye, head and neck, central nervous system and paediatric cases). See Table 1.

Primary Studies

Most case series reported acceptable toxicity profiles with good local tumour control although they have not been rigorously compared with other forms of treatment. Evidence for the benefits of PBT remains scant for the indications (hepatocellular carcinoma (HCC), prostate, lung) not commonly recommended for PBT in the systematic reviews. The 3 studies on HCC described only the Japanese experience and did not compare against existing treatment methods. Similarly, there were only single studies on prostate cancer and on early stage lung cancer, which did not compare directly the many treatment alternatives for these 2 common cancers. See Table 3.

Economic Evaluations

All 3 economic evaluations found PBT to be not cost-effective for most cancers including those of the prostate and breast. See Table 4.

Clinical Guidelines

There is no special mention of PBT in current clinical guidelines. PBT is mentioned along with intensity-modulated radiotherapy (IMRT) and GammaKnife as examples of stereotactic radiosurgery for the possible treatment of pituitary adenomas, prostate cancer, intracranial arteriovenous malformations (AVM) and vestibular schwannomas. See Table 2.

Conclusion

There is a large body of low quality studies (mainly case series) examining the use of PBT with only a few comparative studies. Results range from the acceptable to promising (acceptable toxicity profiles, longer survival rates and good local tumour control) but have not been rigourously compared with existing treatment methods. PBT is not extensively covered in current clinical guidelines but is mentioned along with other examples of stereotactic radiotherapy. Economic evaluations performed thus far internationally, unanimously agree that PBT is not cost-effective for common cancers such as breast and prostate cancer and will cost at least 2-3 times more than conventional radiation therapy for cancer in general.

While PBT can be applied to all tumours, in view of the high costs and lack of facilities, systematic reviews have recommended usage in selected patients who stand to benefit the most from PBT. PBT is best used in cases to avoid damaging sensitive surrounding tissue such as the eye, head and neck, central nervous system and possibly prostate or in paediatric cases at risk of developing secondary tumours as a result of conventional radiotherapy.

The clinical need for PBT locally may be limited to a population of about 800 new cases of related cancers (eye, head and neck, CNS, paediatric) each year. The optimal load for a PBT facility is generally about 1000 patients each year (personal communication with vendors). There has been suggestion of increased usage of PBT for prostate cancer, but PBT should be compared against other modalities such as surgery and brachytherapy for safety, efficacy and cost-effectiveness.

The catchment area for a PBT facility may be extended to the region to benefit foreign patients with clinically relevant cancers.

PBT is expected to cost twice that of IMRT, an advanced form of stereotactic radiotherapy recently introduced and several times that of conventional radiotherapy. Assuming the existing framework of MediShield and Medisave limits, it is unlikely that the vast majority of local cancer patients will be able to afford PBT without significant subsidies.

Regulatory and Healthcare Financing Information

PBT has been approved by the US Food and Drug Administration (FDA) and the Australian Therapeutic Goods Administration (TGA)

In the US, Medicare/Medicaid covers PBT. Private insurers such as Aetna and Cigna considers PBT “medically necessary for some intracranial and skull base tumours, salivary glands tumours and prostate cancer” and is “experimental and investigational for all other cancers".

In Singapore, MediShield insurance coverage for cancer is limited to $80-160 per day of radiotherapy and $1,000 per treatment of stereotactic radiotherapy. Medisave may be utilised to complement treatment fees and are subjected to withdrawal limits ranging from $30 per X-ray treatment to $2,800 per treatment of stereotactic radiotherapy. Both MediShield and Medisave limits will be insufficient to pay for PBT which is expected to cost twice that of other stereotactic radiotherapy such as IMRT or several times over conventional radiotherapy.

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1. National Cancer Centre, Singapore (NCCS) Department of Radiation Oncology
2. Sg2 (www.sg2.com)
3. Singapore General Hospital, Department of Diagnostic Radiology

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Tables

Table 1: Systematic reviews and health technology reports

Study	Organ	Methods	Conclusion
Olsen DR, Bruland OS, Frykholm G, Norderhaug IN. (2007) Proton therapy - a systematic review of clinical effectiveness Norway	All cancers	Systematic review of literature. Found 54 publications (4 RCTs, 5 comparative studies and 44 case series)	The evidence on clinical efficacy of proton therapy relies to a large extent on non-controlled studies, and thus is associated with low level of evidence according to standard heath technology assessment and evidence based medicine criteria.
Adelaide Health Technology Assessment (AHTA) on behalf of National Horizon Scanning Unit (2006) Australia	All cancers	Literature review of evidence regarding the use of PBT for the treatment of cancer. Comparators include radiotherapy and chemotherapy. Studies included were RCT, case series and economic evaluations between 1999 and 2006.	There is a large body of poor quality evidence indicating the successful use of PBT in a diverse patient base. PBT may be of great benefit to a group of vulnerable patients who either have untreatable cancers with conventional therapies or cancers where conventional therapies would put them at high-risk of future, secondary disease.
Al-Shahi R, Warlow CP (2006) Interventions for treating brain arteriovenous malformations in adults Cochrane	Brain arteriovenous malfunctions (AVM) in adults	Literature review of evidence regarding treatment interventions for brain AVM. Interventions include 1) neurosurgery, 2) radiotherapy (including PBT), 3) endovascular embolisation and 4) staged combinations of the above and 5) do nothing. Studies included were RCT, case series and economic evaluations between 1966 and 2004.	No evidence from RCTs with clear clinical outcomes, comparing different interventions. Did not find any RCTs to help decide whether and how to treat brain AVMs.
Khairi S, Ewend MG. (2002) US	Bone	Not stated	Proton beam radiation appears to have a distinct advantage over conventional external beam radiation in this disease because of the rapid fall-off of radiation beyond the target. Unfortunately, the data on efficacy and safety of treatments for chordoma is limited because of the rarity of disease. Current reports in the literature are exclusively case series and reports, limiting the strength of the conclusions that can be drawn.

Table 2: Clinical Practice Guidelines

Issuing organization	Methodology	Recommendation
International RadioSurgery Association (IRSA). Stereotactic radiosurgery for patients with **vestibular schwannomas** May 2006	This radiosurgery guidelines group comprises neurosurgeons, neurotologists, and radiation oncologists	Stereotactic radiosurgery is defined as a single session, high-dose delivery of focused radiation precisely to the vestibular schwannoma, as identified by stereotactic imaging…The neurosurgeon and/or neurotologist are an integral part of the critical decision making steps and the target planning and dose approval within the brain for both LINAC and **proton beam** based systems (whether single session or stereotactically hypofractionated radiation therapy) regardless of head fixation system. The radiation delivery of the approved targeting and dosing plan (as designed and approved by the neurosurgeon/neurotologist and radiation oncologist together) may occur on subsequent days for LINAC or **proton beam** based single session or hypofractionated sessions under the direct supervision of a radiation oncologist without the neurosurgeon or neurotologist present. Should the original targeting plan require modification during the radiation delivery of the subsequent sessions, the neurosurgeon and/or neurotologist should review/design and approve the new targeting and dosing plan before the continuation of the radiation delivery by the radiation oncologist.
American College of Radiology (ACR) Locally advanced (high-risk) **prostate cancer** 2006	This radiosurgery guidelines group is comprised of neurosurgeons, intervention radiologist, medical physicist, and radiation oncologists	The available evidence supports the use of androgen deprivation therapy, pelvic lymph node irradiation, and prostate gland doses of greater than 70 Gy in men with high-risk locally advanced prostate cancer. Long-term androgen deprivation (at least 2 years) should be favored over shorter courses. *The optimal mechanism of boosting the prostate dose remains unknown, but HDR brachytherapy, LDR brachytherapy, and IMRT are all viable options, and it does not appear that a particular method of prostate boost (including **PBT**) is superior to another at this time.* Future research will be directed at optimizing combined radiation and hormonal therapies as well as incorporating systemic chemotherapeutics in the neoadjuvant, concurrent, and/or adjuvant settings.
International RadioSurgery Association (IRSA) **Stereotactic radiosurgery for patients with** pituitary adenomas	This radiosurgery guidelines group comprises neurosurgeons, endocrinologist, medical physicist, and radiation oncologists	Type I, II, and III evidence exists in support of stereotactic radiosurgery for pituitary adenomas. Current radiation delivery technologies for volumetric stereotactic conformal single session radiosurgery include Gamma Knife®, **proton beam** using Bragg Peak effect, and specially modified linear accelerators. Causes for failure of stereotactic radiosurgery include inadequate visualization of the tumor, lack of intraoperative stereotactic three-dimensional (3-D) (volumetric) imaging, and insufficient dose (due to proximity with optic apparatus) to achieve the growth control response.

Issuing organization	Methodology	Recommendation
April 2004		
International RadioSurgery Association (IRSA). Stereotactic radiosurgery for patients with **intracranial arteriovenous malformations (AVM)** Sep 2003	NA	Dose selection depends on location, volume, estimated adverse radiation risks, pre-existing neurological conditions, and prior bleeding history. Depending upon the technology used, the margin of the AVM dose is usually 50 to 70% of the central target dose within the AVM. Sharp fall-off of the radiation dose outside of the target volume is required. Current radiation delivery technologies for volumetric stereotactic conformal single fraction radiosurgery include Gamma Knife®, **proton beam** using Bragg Peak effect, and specially modified linear accelerators. Causes for failure of stereotactic radiosurgery have been identified and include inadequate visualization of the target nidus, lack of intraoperative stereotactic 3-D (volumetric axial plane imaging), insufficient dose to achieve the obliterative response, compression of the AVM nidus by a prior hematoma, or poor nidus visualization secondary to overlying vascular structures. In a few cases, selected radiobiological resistance of undetermined etiology may be the cause of obliteration failure. At present, technologies delivered to provide volumetric stereotactic radiosurgery are limited to Gamma Knife®, modified linear accelerators at centers supplemented by significant experience, and **proton beam** facilities in the United States.
American College of Radiology (ACR) External beam radiation therapy treatment planning for clinically localized **prostate cancer**. June 2000	Guidelines group comprised of mainly M.D.	Appropriateness of **PBT** for treatment planning: 7 (1=least appropriate, 9=most appropriate) Newer conformal radiation therapy methods, such as 3D conformal radiation therapy (3D CRT), intensity modulated radiation therapy (IMRT), and **proton beam** radiation therapy, have allowed radiation oncologists to improve the therapeutic ratio by lowering the dose to surrounding critical structures while simultaneously safely escalating the dose to the disease target.

Table 3: Primary Studies

Author	Organ	Study Type	Title	Method	Conclusion
Noël G, (2001) France	Bone	Prospective case series (n=44)	Combination of photon and proton radiation therapy for chordomas and chondrosarcomas of the skull base: the Centre de Protonthérapie D'Orsay experience	Prospective analysis of local tumor control, survival, and treatment complications in 44 consecutive patients treated with fractionated photon and proton radiation for a chordoma or chondrosarcoma of the skull base.	For skull-base chordomas and chondrosarcomas, the combination of photons with a proton boost of one-third the total dose offers an excellent chance of cure at the price of an acceptable toxicity. These results should be confirmed with a longer follow-up.
Weber DC, Swiss Proton Users Group. (2004) Switzerland	Central Nervous System (CNS) Brain	Prospective case series (n=16)	Spot-scanning proton radiation therapy for recurrent, residual or untreated intracranial meningiomas.	To assess the safety and efficacy of spot scanning PBT in the treatment of intracranial meningiomas	Spot-scanning PBT is an effective treatment for patient with untreated, recurrent or incompletely resected intracranial meningiomas. It offers highly conformal irradiation for complex-shaped intracranial meningiomas, while delivering minimal non-target dose. Observed ophthalmologic toxicity is dose-related.
St Clair WH, (2004) US	CNS (Brain)	Case report (n=1)	Advantage of protons compared to conventional X-ray or IMRT in the treatment of a pediatric patient with medulloblastoma.	To compare treatment plans from standard photon therapy to intensity modulated X-rays (IMRT) and protons for craniospinal axis irradiation and posterior fossa boost in a patient with medulloblastoma	The present study clearly demonstrates the advantage of conformal radiation methods for the treatment of posterior fossa and spinal column in children with medulloblastoma, when compared to conventional X-rays. Of the two conformal treatment methods evaluated, protons were found to be superior to IMRT.
Noel G, (2003) France	CNS	Prospective case series (n=17)	Proton beam therapy in the management of central nervous system tumors in childhood: the preliminary experience of the Centre de Protonthérapie d'Orsay.	The purpose of the study was to evaluate clinical results and complications of a combination of proton and photon irradiation administered to 17 children with selected central nervous system (CNS) tumors	With a mean 27 months follow-up, PBT was well tolerated for doses up to 69 CGE and with an excellent local control rate
Weber DC, (2007) Switzerland	Connective tissue	Retrospective case series (n=16)	Spot scanning proton therapy in the curative treatment of adult patients with sarcoma: the Paul Scherrer institute experience.	To assess the safety and efficacy of spot scanning proton beam therapy (PT) in the curative treatment of soft-tissue sarcoma (STS) in adults patients	Spot scanning PBT is an effective and safe treatment for patient with STS in critical locations. The observed toxicity rate was acceptable

Author	Organ	Study Type	Title	Method	Conclusion
Zambarakji HJ, (2006) US	Eye	RCT (2 doses) (n=166)	Proton beam irradiation for neovascular age-related macular degeneration.	To evaluate safety and visual outcomes after proton therapy for subfoveal neovascular age-related macular degeneration (AMD)	No significant differences in rates of visual loss were found between the 2 dose groups. Proton radiation may be useful as an adjuvant therapy or as an alternative for patients who decline or are not appropriate for approved therapies.
Dendale R,. (2006) France	Eye	Retrospective case series (n=1406)	Proton beam radiotherapy for uveal melanoma: results of Curie Institut-Orsay proton therapy center (ICPO).	This study reports the results of proton beam radiotherapy based on a retrospective series of patients treated for uveal melanoma at the Orsay Center	This retrospective study confirms that proton beam radiotherapy ensures an excellent local control rate. Further clinical studies are required to decrease the incidence of postirradiation ocular complications.
Lumbroso-Le Rouic L, (2006) France	Eye	Retrospective case series (n=15)	Proton beam therapy for iris melanomas.	To describe the results in terms of local control, eye preservation and systemic evolution of iris melanomas treated by proton beam irradiation	Proton beam therapy shows potential utility for selected cases of localised iris melanomas allowing excellent local tumour control and eye preservation. Further follow-up on larger series is needed to confirm these results.
Damato B, (2005)	Eye	Prospective case series (n=349)	Proton beam radiotherapy of choroidal melanoma: the Liverpool-Clatterbridge experience	To report on outcomes after proton beam radiotherapy of choroidal melanoma using a 62-MeV cyclotron in patients considered unsuitable for other forms of conservative therapy	PBT with a 62 MeV cyclotron achieves high rates of local tumor control and ocular conservation, with visual outcome depending on tumor size and location.
Höcht S, (2005) Germany	Eye	Prospective case series (n=10)	Proton or stereotactic photon irradiation for posterior uveal melanoma? A planning intercomparison	Proton and stereotactic radiotherapy with photons (SRT) are both used to treat choroidal melanomas in proximity to optic disk and fovea centralis	When dose deposition to those structures most important for the preservation of vision is taken into account, under the conditions examined proton therapy offers an advantage in the majority of the patients evaluated.
Frau E, (2004) France	Eye	Retrospective case series (n=17)	Low-dose proton beam therapy for circumscribed choroidal hemangiomas.	To evaluate the efficacy and safety of proton beam therapy for complicated circumscribed choroidal hemangiomas	Proton beam therapy for choroidal hemangiomas seems to be an effective and safe alternative option. A total dose of 20 CGEs delivered in 4 daily 15-second fractions of 5 CGEs seems adequate for local control of both the tumor and serous retinal detachment

Author	Organ	Study Type	Title	Method	Conclusion
Spatola C, (2003) Italy	Eye	Prospective case series (n=30)	Clinical application of proton beams in the treatment of uveal melanoma: the first therapies carried out in Italy and preliminary results (CATANA Project).	With its energy (62 MeV proton beam), it is ideal for the treatment of shallow tumors like those of the ocular region: uveal melanoma, first of all (the most common primary intraocular malignancy of adults) and other less frequent lesions like choroidal hemangioma, conjunctiva melanoma, and eyelid tumors.	The literature data show that charged particle therapy has allowed an optimal local control in the treatment of uveal melanomas (about 96% in the different series, superior to that obtained with plaquetherapy [between 83% and 92%]), a metastatic rate slightly better than enucleation reports, and a survival rate of almost 90% at 5 years. Our preliminary results show a tumor response in almost all cases, with no major acute or subacute side effects. We thus plan to continue with our treatment procedures and our dose prescription.
Egger E, (2001) Switzerland	Eye	Retrospective case series (n=2435)	Maximizing local tumor control and survival after proton beam radiotherapy of uveal melanoma.	This study reports local tumor control and survival after proton beam radiotherapy (PBRT) of uveal melanoma. It identifies the risk factors for local tumor-control failure and for ocular tumor-related death	Reduced safety margins, large ciliary body tumors, eyelids within the treatment field, inadequate positioning of tantalum clips, and male gender were identified to be the main factors impairing local tumor control. The improvement of local tumor control rate after 1993 is attributed to changes implemented in the treatment procedure. Our data strongly support that the rate of death by metastases is influenced by local tumor control failure: improvement of the local tumor control rate results in a better survival rate.
Flaxel CJ, (2000) US	Eye	Prospective case series (n=14)	Proton beam irradiation of subfoveal choroidal neovascularisation in age-related macular degeneration	To assess the safety and potential toxicity of proton beam radiation in the treatment of subfoveal choroidal neovascular membrane (CNVM) due to age-related manner degeneration (ARMD) in a prospective, non-randomised study	To date, 14 CGE (Cobalt Gray Equivalent) has suggested a favourable influence on visual function and growth inhibition of CNVM. Proton beam irradiation appears to inhibit CNVM growth. The 14 CGE dose regimen appears to have a longer effect of CNVM growth than does 8 CGE, with overall stabilisation of visual function and growth inhibition. Radiation retinopathy has developed over time, but severe visual loss has been limited. On the basis of the incidence of radiation retinopathy, adjustments in the total radiation dosage and/or fractionation of the dosage should be considered

Author	Organ	Study Type	Title	Method	Conclusion
Kawashima M, (2005) Japan	Liver (HCC)	Phase II (n=30)	Phase II study of radiotherapy employing proton beam for hepatocellular carcinoma	To evaluate the safety and efficacy of proton beam radiotherapy (PRT) for hepatocellular carcinoma	PBT showed excellent control of the primary tumor, with minimal acute toxicity. Further study is warranted to scrutinize adequate patient selection in order to maximize survival benefit of this promising modality.
Mizumoto M, (2008) Japan	Liver (HCC)	Prospective case series (n=22)	Proton Beam Therapy for Hepatocellular Carcinoma Adjacent to the Porta Hepatis.	To evaluate the efficacy and safety of proton beam therapy (PBT) for patients with hepatocellular carcinoma (HCC) located adjacent to the porta hepatis	The PBT delivering 72.6 GyE in 22 fractions appears to be effective and safe for HCC adjacent to the porta hepatis.
Hashimoto T, (2006) Japan	Liver (HCC)	Retrospective case series (n=225)	Repeated proton beam therapy for hepatocellular carcinoma	To retrospectively evaluate the safety and effectiveness of repeated proton beam therapy for newly developed or recurrent hepatocellular carcinoma (HCC	Repeated proton beam therapy for HCC is safe when the patient has a target in the peripheral region of the liver and liver function is Child-Pugh class A.
Shioyama Y, (2003) Japan	Lung (NSCLC)	Prospective case series (n=25)	Clinical evaluation of proton radiotherapy for non-small-cell lung cancer.	evaluate the clinical results of proton radiotherapy for patients with non-small-cell lung cancer (NSCLC).	Proton therapy is a very safe and effective treatment for patients with NSCLC, especially for those with early stages. The relative merit of proton therapy in comparison with stereotactic photon radiotherapy or three-dimensional conformal photon radiotherapy remains to be defined through future clinical trials
Nihei K, (2005) Japan	Prostate	Phase II (n=30)	Phase II feasibility study of high-dose radiotherapy for prostate cancer using proton boost therapy: first clinical trial of proton beam therapy for prostate cancer in Japan.	To assess the feasibility of high-dose radiotherapy for prostate cancer using proton boost therapy following photon radiotherapy	Proton boost therapy following photon radiotherapy for prostate cancer is feasible. To evaluate the efficacy and safety of proton beam therapy, a multi-institutional phase II trial is in progress in Japan.

Table 4: Economic Evaluations

Study	Methodology	Results	Remarks
Konski A, (2007) J Clinical Oncology 25: 3603-3608 US	Markov model simulation of cost-effectiveness of PBT vs IMRT for a prostate cancer patient (60-70 years old).	PBT costs US$63,500-US$65,000 to give 8.54-9.91QALY. IMRT costs US$36,800-US$39,400 to give 8.12-9.45 QALY. ICER: International Centre for Economic Research PBT costs US$63,578 per QALY gained (60 year old) PBT costs US$55,726 per QALY gained (70 year old)	An intervention is generally considered cost-effective if it costs less than US$50,000 per QALY. In both 60-year olds and 70-year olds with prostate cancer, PBT is not cost-effective.
Lundkvist (2005) Acta Oncol 44:850-861 Sweden	Markov model simulation of cost-effectiveness of PBT vs conventional radiotherapy for a 55-year old breast cancer patient.	PBT costs €67,000 per QALY gained.	An intervention is considered cost-effective if it costs less than €50,000 per QALY. In 55-year old breast cancer patients, PBT is not cost-effective.
Goitein (2003) Clin Oncol (R Coll Radiol) 15:S37-S50 Switzerland	Compare cost of treatment for a cancer patient including capital costs	PBT costs €25,600 while conventional RT costs €10,600.	