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**Proton Beam Therapy for the treatment of
cancer**

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PRIORITISING SUMMARY

REGISTER ID: 000218

NAME OF TECHNOLOGY: PROTON BEAM THERAPY

PURPOSE AND TARGET GROUP: FOR THE TREATMENT OF CANCER

STAGE OF DEVELOPMENT (IN AUSTRALIA):

- | | |
|---|---|
| <input type="checkbox"/> Yet to emerge | <input type="checkbox"/> Established |
| <input type="checkbox"/> Experimental | <input type="checkbox"/> Established <i>but</i> changed indication or modification of technique |
| <input checked="" type="checkbox"/> Investigational | <input type="checkbox"/> Should be taken out of use |
| <input type="checkbox"/> Nearly established | |

AUSTRALIAN THERAPEUTIC GOODS ADMINISTRATION APPROVAL

- | | |
|---|-------------|
| <input type="checkbox"/> Yes | ARTG number |
| <input checked="" type="checkbox"/> No | |
| <input type="checkbox"/> Not applicable | |

INTERNATIONAL UTILISATION:

COUNTRY	LEVEL OF USE		
	Trials Underway or Completed	Limited Use	Widely Diffused
United States		✓	
Switzerland		✓	
United Kingdom		✓	
Japan		✓	
Italy		✓	
Germany		✓	
Canada		✓	
Russia		✓	
South Africa		✓	
Sweden		✓	
France		✓	

IMPACT SUMMARY:

A number of manufacturers produce either the complete proton beam therapy system or aspects of the system, such as the treatment planning software. Siemens AG, Varian Medical Systems, ACCEL Instruments GmbH, CMS Inc, Hitachi Ltd and Optivus Technology Inc all produce components of proton beam therapy systems. In addition, some of these systems have United States Food and Drug Administration approval, however none have TGA approval.

BACKGROUND

Conventional radiotherapy treatment for cancer patients utilises ionising radiation in the form of X-rays or gamma rays, both of which are photons. Radiation induces damage to the DNA of targeted tumour cells, ultimately causing tumour cell death. It is difficult to target radiation to tumour cells alone and the surrounding normal tissue is often damaged. This may be of concern especially in paediatric patients, as early exposure to high doses of ionising radiation may put them at risk of developing secondary, radiation induced malignancies later on in life. This may not be of such concern in adult patients as the median age of diagnosis is 70 and secondary malignancies tend to develop 10-15 years after radiation treatment. In addition, treatment of spinal and paraspinal tumours is complicated by the proximity of the spinal cord, which has a radiation tolerance of 45 Gy, well below that necessary to control most sarcomas (approximately 60 Gy) (Levin et al 2005).

To avoid secondary tissue damage, charged particle radiotherapy has been advocated. This technique utilises protons instead of photons, to achieve a superior dose distribution of radiation. Protons deposit very little energy in the surrounding tissue compared to X-rays, until the end of the proton energy range. The residual energy is lost over a very short distance, resulting in a steep rise in the absorbed dose known as the Bragg Peak (Figure 1). Therefore protons have a very rapid energy loss in the last few millimetres of tissue penetration. From this diagram it can be seen that the highest radiation dose of conventional X-rays is delivered to the normal tissue surrounding the tumour rather than at the tumour site itself. The Bragg Peak is considered too narrow for practical clinical applications, so for the irradiation of tumours, the proton beam energy is modulated by superimposing several Bragg Peaks of decreasing energies (ranges) and weights to create a region of uniform dose over the depth of the target tumour (DeLaney et al 2005). Proton beam therapy is not a new technology and was first carried out in 1954 (Chalmers 2003).

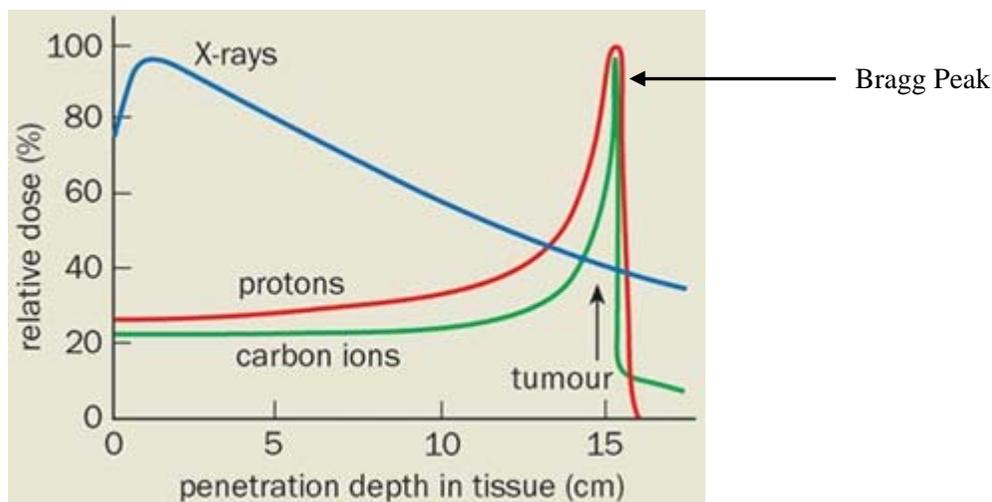


Figure 1 X-rays lose energy rapidly as they travel through the body. Protons deposit most of their energy at a specific depth depending on their energy (Bragg Peak), delivering a high radiation dose at the tumour site (printed with permission: Chalmers, Physics World 2003).

Patients undergoing proton beam therapy must be immobilised in the same position in respect to the radiation beam for each treatment. This is achieved with the use of a custom made foam whole-body mould, or in the case of tumours in the head or neck region, with the use of a

customised mask. Radiation planning is achieved by performing either a CT or PET scan on all patients to provide information about the position of the tumour and the density of the surrounding tissue. The treatment plan is produced using 3-D images created from the scans using specialised software, with the input from the clinician, medical physicist and a dosimetrist. The treatment plan includes target angle, energy of the proton beam and dose per treatment. Large gantries (90 tonnes), which can be rotated 360°, are used to deliver the proton beam at the precise angle prescribed by the treatment plan. The patient lies, immobilised, within the gantry and each treatment session lasts between 20-40 minutes. Most of this time is spent aligning the patient and the beam as the actual proton beam delivery takes approximately one minute (LLUMC 2006). The protons are generated in a linear accelerator, injected into a synchrotron where they are accelerated to higher energies. Once extracted they can be delivered down a beam line either via the gantry or to horizontal beam lines. Horizontal beam lines, where the patient is adjusted relative to the fixed proton beam, are primarily used for tumours of the head and neck, or to treat eye disease such as choroidal melanoma or macular degeneration (Jones 2006; LLUMC 2006).

CLINICAL NEED AND BURDEN OF DISEASE

Proton beam therapy is not suitable for all tumour types but may be of particular benefit treating superficial lesions (such as those of the eye), intermediate depth lesions (such as the head and neck), for cancers that are difficult or dangerous to treat with surgery and for tumours where conventional radiotherapy would damage surrounding tissue to an unacceptable level (optical nerve, spinal cord, central nervous system, head, neck and prostate). In addition, proton beam therapy may be ideal for use in paediatric patients where the need to avoid secondary tumours is important due to their potentially long life span after radiation treatment when they may develop radiation induced malignancies (Levin et al 2005; (National Cancer Institute 2004). The number of possible patients who may be eligible for treatment with proton beam therapy in Australia and New Zealand is indicated in Table 1. In New Zealand during 2002-2003, the prevalence of all cancers was 3.2% of the population (2.6-3.7%) and during that same period 47,715 patients received 201,445 chemotherapy and radiotherapy treatments for cancer (Ministry of Health 2004 and 2005).

Table 1 Possible clinical burden of disease

Principle diagnosis Malignant neoplasms	Number of new cases 2001, Australia	Number of public hospital separations 2001-2002, Australia	Number of public hospital separations 2001-2002, New Zealand
C01-C14 Head and neck	1,719	4,593	
C00-C14 Lip, oral cavity and pharynx			668
C61 Prostate	11,191	15,109	
C60-C63 Male genital organs			2,311
C69 Eye	233	590	
C70-C72 Brain and other central nervous system	1,421	4,879	
C69 – C72 Eye, brain and other central nervous system			889
Paediatric cases, all cancers (age 0-14 years)	603	11,000	2,266

AIHW 2006, New Zealand Ministry of Health

DIFFUSION

There is currently no proton beam therapy facility in Australia or New Zealand. In December 2001, the New South Wales Government announced funding for a feasibility study into the Australian National Proton Facility, with Hitachi Ltd as a key supporter (NSW Health 2001). It is envisaged that this facility would service cancer patients from Australia, New Zealand and the Asia Pacific region (PTCOG 2002). There are currently 23 proton beam therapy facilities operating world wide, with the majority situated in Japan (n=6) and the United States (n=4) (Levin et al (2005). By 2006 it was expected that this number would almost double with an additional 21 facilities planned (PTCOG 2002). Demand for proton beam therapy facilities is expected to be high in the near future with the United Kingdom predicting that they will require 7-8 facilities within the next 10-15 years (Jones 2006).

COMPARATORS

There is no one gold standard for the treatment of cancer. Treatment regimes may involve chemotherapy, conventional externally applied radiotherapy, or a combination of the two. Other new radiation based modalities also exist which may be used depending on the tumour type or the resources available to the treating physician and patient. Externally applied radiation is used to treat almost every type of solid tumours including those of the brain, breast, cervix, prostate, soft tissue sarcomas in addition to cancers of the blood forming cells (leukaemia, lymphoma). Intra-operative radiation is another form of external radiation that is applied during a surgical procedure, often for tumours which have high rates of recurrence such as breast cancer. After the majority of the tumour is removed surgically, the surrounding tissue is subjected to a high-energy dose of radiation. External radiation utilises photons as its energy source, either X-rays or gamma rays (National Cancer Institute 2004).

Internal radiation or brachytherapy utilises a radiation source that is sealed in an implant (catheter or capsule). This implant is then delivered close to, or inside the tumour. This technique may be used to treat prostate, cervical, ovarian, breast, oral, rectal, uterine and head and neck tumours. Internal radiation therapy utilises iodine 125, iodine 131, strontium 89, phosphorous, palladium, cesium, iridium, phosphate or cobalt (National Cancer Institute 2004).

Systemic radiation therapy, where materials such as iodine 131 or strontium 89 are taken orally or injected, may be used to treat cancer of the thyroid and non-Hodgkin's lymphoma. (National Cancer Institute 2004)

Other techniques include stereotactic radiosurgery for brain tumours (eg the gamma knife), 3-D conformal radiation therapy and intensity modulated radiation therapy (IMRT), which allows for the delivery of high doses of radiation to the tumour while sparing the surrounding normal tissue (National Cancer Institute 2004).

EFFECTIVENESS AND SAFETY ISSUES

There are currently no randomised trials comparing the use of proton beam therapy to conventional radiation for the treatment of cancer. "Dose searching" randomised trials have been conducted, using escalating doses of proton therapy to find an optimal value (Jones 2006).

A randomised controlled trial (level II intervention evidence) conducted by Zietman et al (2005) compared patients with prostate cancer who were treated with either conventional radiotherapy (70.2 Gy) (n=197) or conventional radiotherapy *combined* with proton beams to produce a higher energy dose (79.2 Gy) (n=195). Patients were stratified for prostate-specific antigen levels at

randomisation. There was no significant difference in overall survival rates for the two groups. Biochemical failure was defined as three successive increases in PSA. The proportion of men *free* from biochemical failure at 5-years was significantly higher in the high-dose therapy group (80.4%, 95%CI 74.7%, 86.1%) when compared to the conventional dose group (61.4%, 95%CI 54.6%, 68.3) ($p<0.001$). In addition, acute and late genitourinary (GU) and gastrointestinal (rectal) (GI) morbidity were scored using the Radiation Therapy Oncology Group criteria, on a scale 0 to 5, with lower scores indicating fewer symptoms. There was no significant difference between the two groups in GI or GU scores with 1% of conventional-dose and 2% of high-dose patients having an RTOG score of grade three or greater. There was no significant difference in grade 2 acute or late GU morbidity. There was a significant difference between the conventional dose and high-dose patients for both acute (41% vs 57%, $p=0.004$) and late (8% vs 17%, $p=0.005$) grade 2 GI morbidity.

Numerous case series have been published (level IV intervention evidence) describing the results of proton therapy in various patient groups and a sample of these are given below.

One of the largest case series by Egger et al (2003) treated 2645 patients (2648 eyes) with proton beam therapy for uveal melanoma. The median follow-up time was 44 months. The overall eye retention rates at 5, 10 and 15 years after treatment were 89, 86 and 84%, respectively. In total, 218 eyes had to be enucleated (surgically removed) and this was related to tumour size. After optimisation of the treatment protocol the 5-year eye retention rate increased from 97% to 100%, 87% to 100%, and from 71% to 90% for small, medium and large tumours, respectively. No data were provided for eye retention rates using other therapies.

Munzenrider and Liebsch (1999) reported on a case series of 169 patients with chordoma and 165 patients with chondrosarcoma. Ten-year local control rates for skull based tumours was highest for chondrosarcomas (94%), intermediate for male chordomas (65%) and low for female chordoma (42%). For cervical spine tumours, 10-year local control rates for chordoma and chondrosarcomas were 54% and 48%, respectively. No data were provided for other therapy modalities used to treat these conditions.

Hug et al (2002) evaluated proton beam therapy in the treatment of 27 paediatric patients with intracranial low-grade astrocytoma (progressive, unresectable or residual disease following subtotal resection). Mean follow-up was 3.3 years (range 0.6-6.8 years). Four out of 27 patients died (14.8%) and 6/27 (22.2%) experienced local failure. Local control and survival were 87% and 93%, respectively for centrally located tumours, 71% and 86% for hemispheric tumours, and 60% and 60% for tumours of the brainstem. No data were provided for survival or local failure rates using other treatment modalities, however these patients are likely to have few treatment options available to them.

COST IMPACT

Lundkvist et al (2005) conducted a cost-effectiveness study comparing proton beam therapy to conventional radiotherapy for the treatment of a 55-year old woman with breast cancer. A Markov cohort simulation model was used to simulate the life of patients diagnosed with breast cancers and then treated with radiation. The treatment cost of proton beam therapy is initially much higher than for conventional radiation due to the large initial investment cost of building a proton beam therapy facility. The treatment benefits must therefore be high to justify these high costs. The study found that a cost per quality adjusted life year gained of €7,000 for an average breast cancer patient. (Lundkvist et al 2005). It is generally agreed that an intervention that delivers a cost per quality adjusted life year gained of €50,000 or less delivers value for money

(Lievens and Van den Bogaert 2005). The cost-effectiveness analysis may alter for cancers where fewer treatment options are available. A study by Goitein and Jermann in Switzerland estimated the cost of radiation treatment per patient as €25,600 and €10,600 for proton beam therapy and conventional X-ray radiation, respectively, including capital costs. Excluding capital costs, the costs per patient were €14,700 and €7,600 for proton beam therapy and conventional X-ray radiation, respectively (Lundkvist et al 2005).

In 2001, the New South Wales Government estimated the cost to establish a National Proton Facility to be \$160 million (NSW Health 2001).

ETHICAL, CULTURAL OR RELIGIOUS CONSIDERATIONS

The high cost of developing a proton therapy facility would mean that it is likely that only one central facility in New South Wales will be constructed to service the whole of Australia and New Zealand. This may present access and issues for patients living in areas other than NSW and may add to the high cost of treatment.

OTHER ISSUES

The Loma Linda Medical Center in the United States recently received a referral through the Department of Health and Ageing to treat an Australian patient with proton therapy (personal communication, LLUMC May 2006).

CONCLUSION:

It appears unlikely that comparative studies of the gold standard radiotherapy and proton beam therapy will be conducted. There is a large body of poor quality evidence indicating the successful use of proton beam therapy in a diverse patient base. Proton beam therapy may be of great benefit to a group of vulnerable patients who either have untreatable cancers with conventional therapies, or conventional therapies would put them at high-risk of future, secondary disease.

HEALTHPACT ACTION:

Decision held over until the next HealthPACT meeting; however it is likely that an horizon scanning report will be commissioned.

SOURCES OF FURTHER INFORMATION:

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LIST OF STUDIES INCLUDED

Total number of studies

Level II Intervention evidence 1

Level IV Intervention evidence 3

SEARCH CRITERIA TO BE USED:

Heavy Ions/therapeutic use

Neoplasms

Particle Accelerators

Radiotherapy Dosage

Radiotherapy, High-Energy

Protons/*therapeutic use

Radiation Injuries

Radiometry

Radiotherapy

*Cyclotrons

Ions/therapeutic use

Medical Oncology/*instrumentation