Health Policy Advisory Committee on Technology

Proton and Heavy Ion Therapy: An overview

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HealthPACT

emerging health technology

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Summary

HealthPACT recommends that the following is noted:

1. Conventional radiotherapy uses photon (x-ray) energy to damage or destroy cancerous cells. Particle therapy is employed in a similar manner to conventional radiotherapy, however uses particles (protons and heavy ions) instead of photons. Proton therapy is the most commonly applied form of particle therapy in use around the world, however the use of carbon ions is also growing internationally and being actively researched.

2. Proton beam therapy benefits over conventional radiotherapy include improved dose distribution to tumours, reduced radiation dose and damage to healthy tissue, and the ability to more accurately target and treat tumours located close to vital structures.

3. There is widespread international adoption and use of proton beam technology for the treatment of a range of difficult to treat paediatric tumours, and tumours of the skull base, head/neck and central nervous system, with considerable ongoing international research into effectiveness against other malignancies.

4. Although the use of carbon ion therapy has been described for radio-resistant tumours that are otherwise untreatable with conventional radiotherapy, or proton therapy, the use of heavy ions is still considered experimental, and further research is required into patient indications where therapeutic advantages are demonstrated.

5. Proton beam therapy is rapidly growing internationally, with 56 facilities in operation, 39 facilities under construction, and a further 18 facilities planned (as at January 2017). The majority of these are located in the Unites States, Japan, China and Europe. There are currently 10 carbon ion or combined carbon ion/proton facilities established in Japan, Germany, Italy and China, and four with additional facilities either under construction or planned in Austria, China, South Korea and the United States.

6. Publicly reported costs of building a proton facility range from approximately AU$34-260 million, depending on the scope of the facility, its planned service, and the number of treatment rooms. In addition, these facilities are associated with significant annual operational and maintenance costs.

7. There are no particle therapy facilities in Australia or New Zealand, although planning to introduce this technology has commenced in a number of Australian States. For example, Victoria has committed $50 million to the planning of a national proton beam facility at Parkville. Additionally, there are formalised agreements between proposed facilities in New South Wales, Queensland, and South Australian to construct an interstate network of proton-only facilities, and one facility capable of delivering both carbon ions and protons. Finally, there is also a private facility proposed for Queensland.

8. Currently, Australian patients who may benefit from this technology can be referred to the Australian Government's Medical Treatment Overseas Program (MTOP), which provides funding support for eligible Australians to access treatments not available in Australia. Not all patients requesting MTOP funding support for particle therapy overseas are granted approval, which is determined on a case by case basis in accordance with strict criteria endorsed by Cabinet, including consideration of whether effective alternative treatments to particle therapy will be available in Australia in time to benefit the applicant in question. Within the last five years, financial assistance for 24 patients was provided at a total cost of $3.4 million, equating to an average of four patients per year, with an average treatment cost of $142,800 per patient. Costs are decreasing in recent years as the number of international providers increases. At the request of the former Commonwealth Minister of Health, the Medical Services Advisory Committee (MSAC) is reviewing the evidence around the clinical indications for particle therapy, specifically protons, which have been previously granted approval through the MTOP. The New Zealand Ministry for Health maintains a similar overseas referral program, known as the High-Cost Treatment Pool (HCTP). Since 2005, there have been seven HCTP applications approved for the treatment of ocular (eye) melanoma, at an average treatment cost of NZ$35,000 per patient.

9. If an Australian facility is established, domestic demand for particle therapy will be highly dependent on the accepted clinical indications for referral. Conservative estimates for particle therapy services in Australia and New Zealand equate to 600 to 900 patients per year. Progressive estimates place demand at significantly higher numbers. The MSAC review of MTOP referral indications could potentially provide greater certainty in this regard.

10. Should planning processes occurring in some Australian States continue, consideration should be given to the formation of a high-level national reference group with appropriate government, clinical and scientific input. The role of this entity would be to oversee the potential introduction of this technology into the healthcare systems of Australia and New Zealand.

HealthPACT Advice

This overview was commissioned by HealthPACT in response to a number of Australian jurisdictions progressing with plans for the establishment of particle therapy facilities. Should current planning processes continue, it is possible that that at least one facility could be operating within 5-10 years.

The current clinical evidence-base supports the use of particle therapy in a limited range of clinical indications, with small numbers of Australian and New Zealand patients referred overseas to access this treatment. If a particle facility is established in Australia, patients clinically assessed as requiring this treatment modality will no longer have access to MTOP funding. Additionally, with no applicable Medical Benefits Scheme listing at present, funding for treatment would require that costs are borne entirely by the States and Territories, or by the patient themselves. This raises significant issues in relation to service funding, reimbursement, and equitable patient access to treatment.

HealthPACT recommends a national approach to the development of appropriate patient treatment criteria, investigation of the long-term affordability of particle therapy and consideration of equitable patient access. HealthPACT further recommends, at an appropriate time, the establishment a governance mechanism under the auspices of the Hospitals Principal Committee regarding the potential introduction of this technology in Australia.

Proton and Heavy Ion Therapy: An overview

This overview is provided due to the growing international diffusion of particle therapy technology, and increasing interest in the establishment of a particle therapy technology as a cancer treatment modality in Australia.

Introduction

Surgery, radiation therapy and chemotherapy are the standard methods of cancer treatment, with conventional radiotherapy utilising photons (x-rays) generated by linear accelerators (LINAC's). However, as part of continued research into improved radiotherapy precision and biological effectiveness, there is increasing international interest into the use of particle therapy (i.e. protons or heavy ions) in the treatment of solid tumours. The use of protons for the treatment of cancer is not a new technology, and has been undertaken internationally since the 1950's[1], with a marked increase within the past two decades. More recently, the clinical use of heavy ions (such as carbon, oxygen and fluorine) is being investigated. Although there are no particle therapy facilities in Australia or New Zealand at this time, there is considerable international investment in this technology. As at January 2017, there were 66 particle centres in operation (proton, carbon and combined proton/carbon), and 61 centres either planned or under construction (Table 1).

Table 1 **International particle therapy facilities and locations as at January 2017**[2, 3]

Particle Type	In operation		Under Construction		Planned		Total
	No. of Facilities	Locations	No. of Facilities	Locations	No. of Facilities	Locations	
Proton Beam Facilities	56	USA (24) Japan (10) Germany (4) Russia (3) France (2) Italy (2) Sth Korea (2) Canada (1) Czech Rep. (1) China (1) UK (1) Poland (1) Sth Africa (1) Sweden (1) Switzerland (1) Taiwan (1)	39	USA (11) China (6) UK (6) Japan (3) India (2) Netherlands (2) Russia (2) Denmark (1) Abu Dhabi (1) France (1) Saudi Arabia (1) Singapore (1) Slovak Rep. (1) Taiwan (1)	18	USA (3) China (2) Netherlands (2) Switzerland (3) Argentina (1) Belgium (1) India (1) Japan (1) Russia (1) Singapore (1) Slovak Rep. (1) Taiwan (1)	**113**
Carbon Ion Facilities	5	Japan (4) China (1)	1	China			**7**
Proton/Carbon Ion Facilities	5	Germany (2) China (1) Italy (1) Japan (1)	2	Austria (1) South Korea (1)	1	USA	**7**
Total	**66**		**42**		**19**		**127**

Particle therapy is of particular benefit in treating cancers that are difficult or dangerous to treat with surgery, and for tumours where conventional radiotherapy would damage surrounding tissue to an unacceptable level (e.g. optic nerve, spinal cord, central nervous system, and structures of the head and neck). In addition, protons are becoming increasingly accepted for the treatment of selected paediatric and young adult cancers, where the need to avoid secondary radiation-induced tumours is also important due to the potential long life span of the patient.[4, 5] Further, there is early evidence that heavy ions, including carbon, may be effective in treating radio-resistant tumours.[6-8]

Since the mid-1990's, there has been interest in the potential establishment of an Australian particle therapy centre.[9] In 2006 and 2007, HealthPACT reviewed the available evidence regarding proton beam therapy (PBT) for the treatment of specific cancers and concluded that further high quality research, demonstrating improved patient outcomes in comparison to conventional treatment, was required.[10-12] Since this time, the evidence base for both protons and heavy ions has progressed, particularly for PBT.

Currently, four Australia States have progressed planning towards establishing particle facilities. HealthPACT considers it timely to review the role of particle therapy in cancer treatment to inform broader discussion around its potential introduction in Australian and New Zealand. This paper aims to summarise the current state of play regarding protons and carbon ions in cancer treatment.

Particle Therapy Technology

The aims of particle therapy are similar to conventional radiotherapy, which is to induce an ionising effect within malignant cells, and create biological effects such as DNA disruption, and cell death.[1] However, instead of high-energy x-rays (photons) used in conventional radiotherapy, particle therapy involves directing a beam of accelerated subatomic, electrically charged particles to tumour targets. Different particles have been trialled, including neutrons, protons, pions, and various ions, however the most commonly used particles are protons, followed by carbon ions.[13]

The main potential benefits of particle therapy radiation (protons and carbon ions) primarily come from the physical distribution of its radiation dose. Conventional radiotherapy, utilising photon (x-ray) energy, deposits most of its energy near the skin surface, with a decreasing dose deposition along its path, including healthy tissue encountered before the target tumour, the tumour itself, and healthy tissue beyond the tumour (see Figure 1).[14]

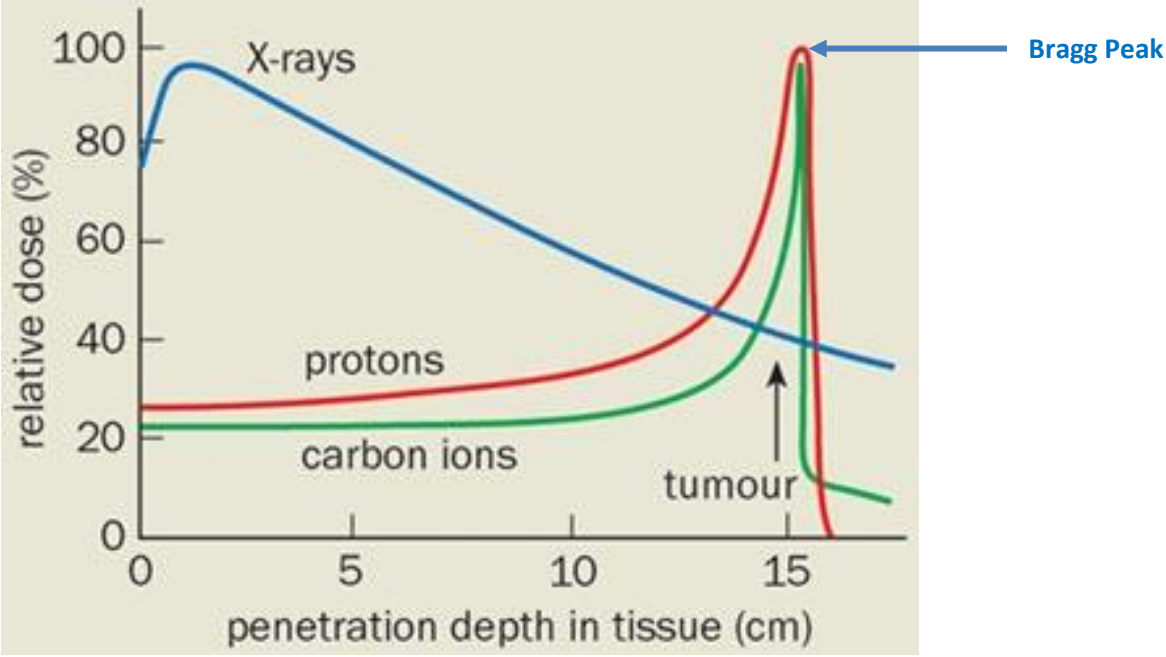

Figure 1 X-rays lose energy rapidly as they travel through the body. Protons and other ions deposit most of their energy at a specific depth depending on their energy (the Bragg Peak). Therefore, they can deliver a high radiation dose at a tumour site, sparing surrounding healthy tissue.[15]

In contrast, particle therapy radiation has a lower entrance dose and deposits most of its radiation energy to a small area at what is known as the Bragg Peak. The depth to which the protons or carbon ions penetrate, and at which the Bragg Peak occurs, is dependent on the energy of the beam, which is adjusted within the accelerator or beam transport system to correspond with the targeted tumour.[1] As particle therapy radiation is mostly absorbed at this point, there is little or no exit dose (i.e. irradiation of normal tissue beyond the target).[16] Therefore, particle therapy can reduce the radiation dose to healthy tissue around the tumour, reducing treatment side-effects. In addition, due to the difference in energy deposition between conventional radiotherapy and particle therapy radiation, there is an estimated reduction of approximately 60 per cent in the integral dose (the total energy absorbed by the human body).[17] Theoretically, this would lead to a reduction of radiation-induced secondary cancers; however there is limited clinical evidence to date to support this assertion, in part due to the limited number of *in vivo* clinical trials published.[18]

As a result of both its superior depth dose distribution and reduced integral dose, particle therapy technology is considered beneficial for paediatric and young adult patients, and in patients with tumours located near vital organs or tissues.[19] This includes tumours with adjacent nerves whose integrity could be compromised as a result of surgery or radiation, where a tumour cannot be resected with appropriate margins due to proximity to critical structures, and where, with conventional radiotherapy, there is an inability to irradiate to a curative dose without overdosing other local organs.[20] However, some uncertainties remain in particle therapy technology planning and delivery, including radiobiological effectiveness, planning calculations and costs, and further research is necessary to determine optimal treatment protocols.[21]

To produce protons, negatively charged electrons are split from hydrogen atoms leaving the positively charged protons, which are accelerated in a cyclotron or synchrotron to 40 to 70 per cent of the speed of light, then directed through a magnetic beam steering system to the treatment room.[1] Photons (used in conventional radiotherapy) and protons both have a low density of ionisation events or linear energy transfer (LET)[13], however protons are believed to have an increased 10 per cent relative biological effectiveness (i.e. RBE of 1.1) on both healthy and cancerous tissue.

Carbon ions are of particular interest due a high rate of energy loss towards the end of the particle range, resulting in a larger increase of the LET at the Bragg Peak.[22] For carbon ion production, newer facilities utilise carbon dioxide gas as an ion source. Heavier than protons, carbon ions undergo a two-stage acceleration process: initial acceleration in a linear accelerator up to 10 per cent of light speed; followed by further acceleration in a synchrotron up to 75 per cent of light speed.[23] Carbon ions are considered to have as good or better distribution of absorbed dose as protons, are superior to photons[22], and with a higher RBE (between 1.5 and 3.4) may prove to be a more effective treatment option.[24] High-LET ions such as carbon have a reported range of radiobiological advantages compared with photons or protons for treating tumours resistant to low-LET irradiation, such as adenocarcinomas, adenoid cystic carcinomas, malignant melanomas and sarcomas.[25] Additionally, due to the physical and biological properties of carbon ions, there is potential for increased use of treatment hypo-fractionation (delivery of radiation by larger doses over a shorter timeframe)[24], which can reduce patient treatment times and improve cost-effectiveness. However, as there are only a limited number of carbon ion facilities in operation internationally, further investigations are needed, especially in the area of dose-distribution of carbon ions during treatment,[20] and translation into radiobiological and clinical effects.

A summary of the advantages and disadvantages of protons and carbon ions, compared to traditional photons, are presented below in Table 2.

Table 2 Biological advantages and disadvantages of conventional radiotherapy and particle therapy

Treatment	Advantages	Disadvantages
Photon (X-rays) Radiotherapy	Established treatment modality and protocols	High integral radiation dose High risk for tumours located near vital organs or tissues Low LET reduces effectiveness for tumours resistant to low LET irradiation
Proton Beam Therapy	Lower integral radiation dose compared to conventional radiotherapy Believed increased relative biological effectiveness compared to x-rays Use in tumours located near vital organs or tissues	Low LET reduces effectiveness for tumours resistant to low LET irradiation Some uncertainties in relation to radiobiological effectiveness, treatment protocols, and effectiveness in range of tumour types Higher establishment and running costs compared to conventional radiotherapy Limited cost-effectiveness evidence
Carbon Ion Beam Therapy	Lowest integral radiation dose High relative biological effectiveness Use in tumours located near vital organs or tissues High LET for use in tumours resistant to low LET irradiation Potential for hypo-fractionation (reduced number of treatments in a course of treatment)	Emerging treatment Limited effectiveness evidence Uncertainties in relation to radiobiological effectiveness, treatment protocols, and effectiveness in range of tumour types Unknown cost-effectiveness Higher establishment and running costs compared to conventional radiotherapy and proton therapy

Particle Therapy Facilities

In relation to particle beam generation, cyclotrons and synchrotrons are used to generate proton and carbon/heavy ion particles. Proton beams are generated either in a cyclotron which uses a single-stage acceleration process (i.e. the cyclotron alone can accelerate the protons to the required energies), or a synchrotron, with subsequent delivery through high vacuum 'beamline' structures to treatment rooms.

Synchrotrons are necessary for the generation of heavy ion beams due to the increased energies required in accelerating heavy particles to clinical therapy velocities. However, as synchrotrons are unable to accelerate particles from zero kinetic energy, they require a two-stage acceleration processes (i.e. a pre-accelerator structure that injects the particle beam into the synchrotron for further acceleration). Therefore, facilities that utilise a synchrotron accelerator typically require a larger footprint than a cyclotron installation.

A cyclotron is only able to accelerate to a set maximum energy, which then requires an energy degrader to reduce the energy at the expense of some beam current and "sharpness" of the Bragg peak. A synchrotron can accelerate the particle to a given energy before extraction which can then be delivered to the patient, allowing beam current and the sharpness of the Bragg peak to be optimally maintained.

Figures 2 and 3 demonstrate a typical layout of a conventional large-scale proton or combination proton/carbon ion-beam facility utilising a synchrotron. The beams are produced at position 1, with hydrogen gas used to obtain protons and carbon dioxide used for carbon ions. The two-stage linear accelerator is situated at position 2, where protons or carbon ions are accelerated in high-frequency structures to up to 10 per cent of the speed of light. The protons or carbon ions are then sent into the synchrotron (position 3), where six 60° magnets bend the beams into a circular path. The protons or carbon ions are accelerated to up to 75 per cent of the speed of light orbit by orbiting the synchrotron approximately a million times.[26]

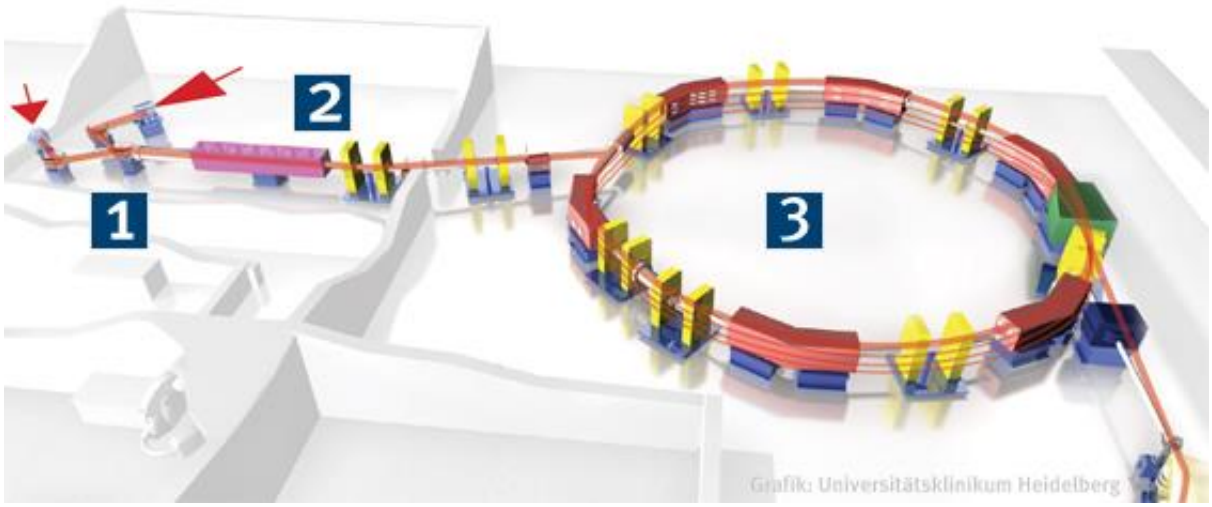

Figure 2 Diagram demonstrating the ion sources, the 2-stage linear accelerator and the synchrotron[26]

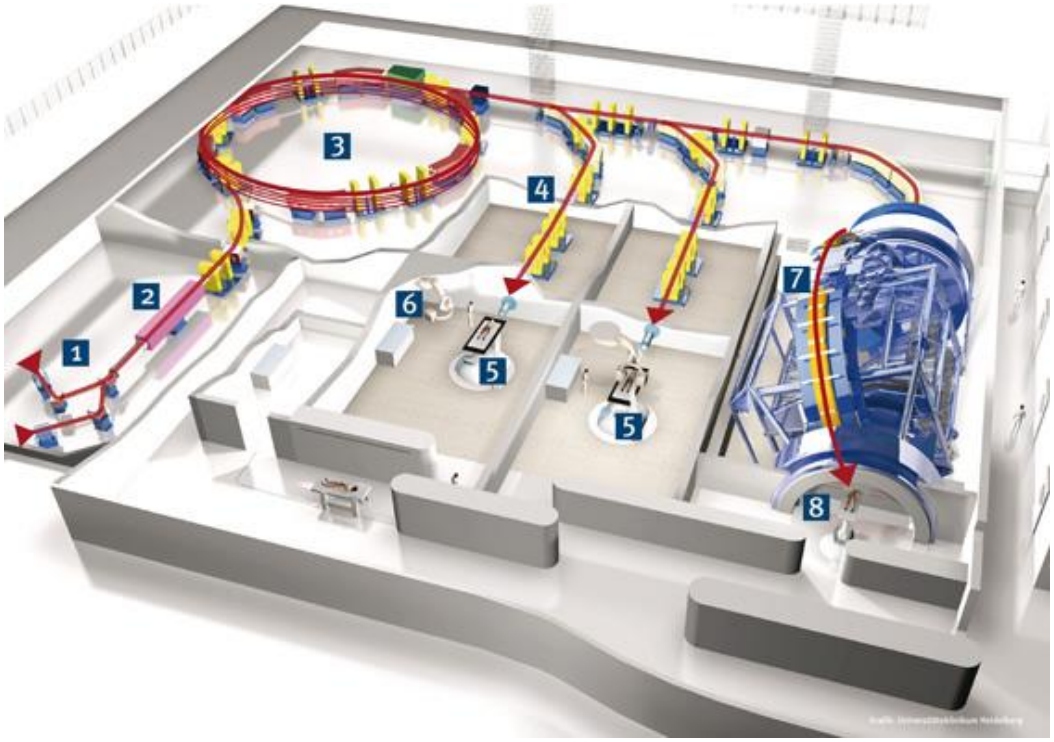

Figure 3 **Diagram demonstrating a typical ion-beam facility with two fixed beam treatment rooms (#5), where the treatment beam enters the room and is targeted at a particular site and one treatment room within a gantry (#8)[26]**

The accelerated protons or carbon ions are then directed towards the treatment rooms, with magnets guiding and focusing the beam within high vacuum 'beamline' structures. In the treatment rooms (position 5, Figure 3), the proton or carbon ion beam enters via a window and is directed by computer-control to the required treatment site in the patient, who is positioned on a robotics-based treatment couch. The patient's position is controlled by a high precision image-guidance system (position 6, Figure 3), using digital X-rays taken prior to irradiation, to match those taken at the treatment planning stage to accurately align and adjust the position of the patient. Different treatment protocols may require the use of a gantry (position 7, Figure 3), which rotates around the patient to deliver therapy beams toward the patient at the optimal combination of angles. The patient lies within the gantry (position 8, Figure 3).[26]

As one example, Germany's Heidelberg combined proton and carbon ion-beam facility took five years to construct at a total cost of €119 (AU$187 million). The facility is 5,027 m^2 and three stories high (two of which are underground) to accommodate the size of the rotating gantry. The facility has three sections: above-ground glass structure with the staff offices; underground particle therapy area; and the copper block with the heavy ion rotating gantry, which weighs 670 tons and is 13 meters in diameter that extends through all three stories. It is expected that in the long term this facility will treat up to approximately 10 per cent of cancer patients whose tumour growth cannot be readily controlled with conventional radiation therapy, that is, those patients with tumours that are located deep in the body; those with tumours that are resistant to conventional radiation; and those with tumours that are surrounded by radiation-sensitive healthy tissue, such as the optic nerve, brain stem, spinal cord or the intestines.[26]

Since this facility started operating in November 2009, over 1,000 patients have received particle therapy in the two horizontal irradiation sites. Once the gantry, commissioned in late 2012, is running at full capacity, it is estimated 750 patients will be treated per year. The facility operates 24-hours a day, with the particle beam used around the clock, either for therapeutic or for research purposes. It is used for patient radiation six days a week for an estimated 12 to 14 hours a day. The accelerators are also in use 24 hours a day and are operated in shifts. The entire facility consumes a maximum of three megawatts, equivalent to the energy required for a small town with a population of approximately 3,000 people.[26] However, it should be noted that developments in technology over the relatively few years since this system was installed, particularly in gantry design and superconducting magnets, has significantly reduced the size and weight of gantries. Japan's National Institute of Radiological Sciences (NIRS) Heavy Ion Medical Accelerator in Chiba (HIMAC) recently installed a smaller and lighter superconducting magnet gantry for carbon ions that weighs less than half the weight of the Heidelberg gantry. A second superconducting gantry is also currently planned for installation at Yamagata University.

Additionally, there are particle therapy systems in development utilising alternative acceleration technologies. Laser-driven proton accelerators have been proposed which have potential to reduce equipment costs to a fraction of current accelerators;[27, 28] however this approach is still theoretical with challenges in controlled beam production, efficient beam guidance, and radiation protection.[27, 29]

Advanced Oncotherapy (London, United Kingdom) is developing a series of cavity LINAC modules, which are anticipated to be able to accelerate protons to therapeutic speeds. There are claims that this system, planned for commercialisation in 2017, will vastly reduce facility costs through savings in space, equipment, shielding, maintenance and operating costs.[30, 31] However, at present, this technology is unproven.

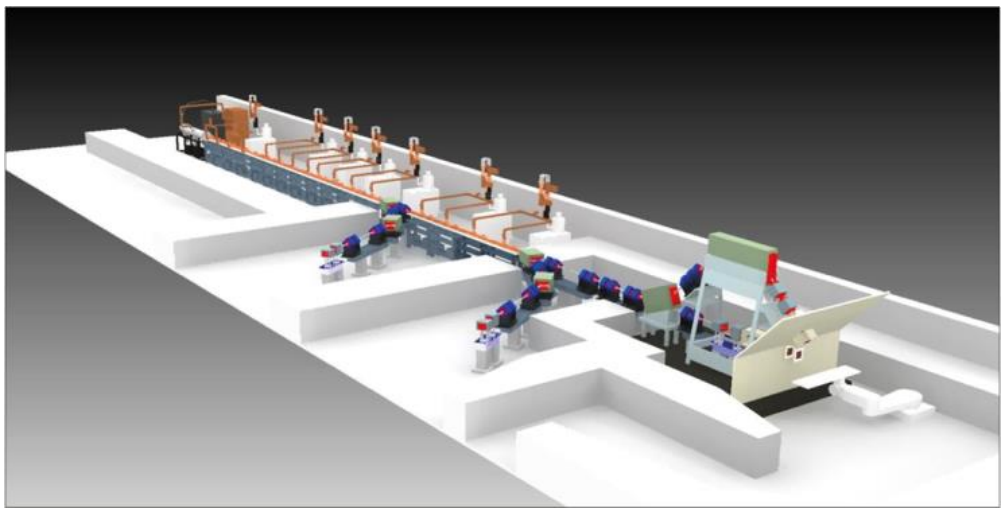

Figure 4 Advanced Oncotherapy LINAC Image-Guided Hadron Technology (under development) [32]

Furthermore, Ion Beam Applications (IBA, Belgium) and the Joint Institute for Nuclear Research (JINR, Dubna, Russia) are developing a cyclotron with superconducting coils that can produce 400 MeV energy, allowing for acceleration of both protons and carbon ions.[24] This hybrid system is yet to be demonstrated, however may offer a compact and cost-effective solution for particle therapy.

Particle Therapy Facility Costs

It is well recognised that high equipment and facility costs, with long construction times, are a major obstacle in the adoption of particle therapy.[1] Although costs are decreasing with the introduction of newer compact designs, a particle therapy facility represents a significant investment, with costs directly relating to facility size. Publicly reported PBT facility costs range from approximately $34 million for a compact, single-room facility to approximately $260 million for a larger, e.g. five-room facility; and up to approximately AU$290 million for a heavy ion facility (see Appendix A and B).

Although particle therapy installation costs are be considered high, it should be recognised that particle accelerators and treatment gantries have an intended lifespan of 30 years,[33, 34] compared to 10 years for linear accelerators utilised in conventional radiotherapy.[35] Therefore, direct comparison of initial construction costs may be misleading, as linear accelerators may require multiple replacements over the typical lifetime of a particle accelerator.

Additionally, proton therapy facilities have high annual maintenance and service costs, which are reported as approximately one-tenth of the purchase price.[1] Further additional annual costs would include medical personnel and staff involved in service delivery, associated equipment (medical imaging and treatment planning facilities), administration and running costs (e.g. energy).

If an Australian particle therapy facility were to be established, there will be a requirement for formal particle therapy training and credentialing for radiation oncologists, medical physicists and radiation therapists, which should be undertaken by relevant Australasian colleges (e.g. the Royal Australasian College of Radiologists; RANZCR).[13] This training will likely involve the international exchange of personnel through fellowships, which will necessitate recognition of international credentialing for visiting experts to supply local training.

It is also noted that where patients are required to travel to access such a facility, there will be travel and accommodation costs incurred.

These high overheads result in particle therapy being more expensive than conventional radiotherapy treatments. When compared to conventional radiotherapy facilities, a PBT facility has a reported treatment fraction cost ratio of 3.2, and 4.8 for a combined proton/carbon ion facility.[36] However, research is emerging that reports PBT may be more cost-effective than conventional radiotherapy when quality adjusted life years are taken into account in calculations.[34] A recent systematic review concluded that PBT offers promising cost-effectiveness for paediatric brain tumours, well-selected breast cancers, advanced non-small cell lung cancer, and high-risk head/neck cancers. However, cost-effectiveness was not demonstrated for prostate cancer or early stage non-small cell lung cancer.[37]

It is proposed that particle equipment and operating costs will decline as the technology continues to mature and delivery efficiencies are improved (e.g. pencil-beam scanning, intensity-modulated particle therapy, image guidance, hypofractionation, and compact units),[34] however particle therapy facilities will still represent significant expenditure in terms of construction, maintenance, staffing, and running costs. A comparison of conventional radiotherapy and particle facilities is presented below in Table 3.

Table 3 Comparison of conventional radiotherapy and particle facilities

	Conventional Radiotherapy	Proton Beam	Carbon Ion Beam
Accelerator	LINAC	Cyclotron or Synchrotron	Synchrotron
Typical beam energy range	4-25 MeV	60–250 MeV	120–430 MeV
Treatment rooms	One room per LINAC	Single to five rooms	Typically three treatment rooms and research room
Publicly reported costs (likely equipment only)	$5 million (per LINAC and gantry)	$34 million-$260 million (single to multi-room facility)	$180 million-$290 million (multi-room facility)
Operational costs (utilities, maintenance, cleaning, administration)	$4.51 million (2 room facility)	$8.8 million (3 room facility)	$17.9 million (3 room facility)
Staffing costs	$4.25 million (2 room facility)	$10.4 million (3 room facility)	$10.4 million (3 room facility)
Treatment Fraction Cost Ratio	1	3.2	4.8
Equipment lifespan	10 years	30 years or more	30 years or more

Note: all prices are adjusted for inflation and presented in 2016 AU$
Publicly reported facility costs are presented in Appendix A and B
Operational, staffing costs and treatment fraction costs adapted from Peeters et al. (2010)[36]

Particle Therapy Evidence Overview

Proton Beam Therapy

PBT is being employed increasingly for the treatment of a range of paediatric tumours; skull base, hepatocellular, head/neck, and central nervous system tumours; and cancers of the breast, lung, prostate, and pancreas.[37]

There is debate as to what constitutes a reasonable level of accepted evidence for proton therapy. Commentators note a lack of randomised control trial (RCT) evidence, which would provide clear evidence of proton superiority and safety over conventional radiotherapy treatment in many instances, and propose that further studies are needed.[21] However, proponents of proton therapy have pointed out that implementation of some radiation procedures (e.g. intensity modulated radiation therapy) has occurred without robust RCT data, and that issues of informed consent and equipoise[a] arise.[34] These issues were recently considered in the United Kingdom (UK), with recommendations for further studies on particle therapy, including well-defined and conducted phase III studies. However RCTs were considered to be neither necessary nor appropriate where improved dose distribution and clinically significant superiority has been clearly demonstrated.[38]

In terms of evidence to date, this paper does not intend to provide a systematic review of the literature but will summarise the most recent evidence available.

A recent systematic review conducted by the Washington State Health Care Authority identified limited comparative evidence regarding the effectiveness of PBT for the treatment of specific cancers.[39] The majority of studies identified were case series, which can inform on important safety outcomes of treatment with PBT, but not on the clinical effectiveness of the treatment. It was acknowledged that comparative studies are unlikely to be conducted for paediatric cancers despite uncertainty over long-term outcomes, nor for rare cancers, however it is not unreasonable to expect comparative studies for the treatment of prostate or breast cancer.

A total of six RCTs were identified for inclusion. Four of these RCTs were dose/fractionation comparisons in prostate cancer published in 2011 (n= 82) and 2010 (n=391), uveal melanoma (n=188) published in 2000, and skull-base chordoma and chondrosarcoma (n=96) published in 1998). The remaining two RCTs compared treatment modalities. In 2006, PBT was compared to PBT plus tomotherapy in 151 patients with uveal melanoma, and in 1995 a total of 202 patients with prostate cancer were enrolled in an RCT that compared PBT plus conventional radiotherapy to conventional radiotherapy alone. Despite being RCTs, these studies give limited information as to the effectiveness of PBT as five of the six RCTs involved different treatment protocols for PBT and had no other comparison groups. Of the six RCTs, 5 were considered to be fair or poor quality. In addition, a total of 37 non-randomised comparative studies across 19 different conditions were identified, however the majority of these were retrospective with additional concerns over quality, with only one study being considered good quality.[39]

[a] an ethical consideration of assigning a patient to a trial arm where it is anticipated that they will receive a reduced outcome compared to other trial arms.

Although the strength of evidence was low or moderate, the evaluators concluded that PBT had a superior net health benefit for ocular tumours, and an incremental net health benefit for adult brain/spinal tumours and paediatric cancers. PBT was found to be comparable to alternative treatment options for patients with liver, lung, and prostate cancer as well as one noncancerous condition (haemangiomas). The evidence base for all other cancers, including those of the breast, gastrointestinal, gynaecological and prostate, was found to be insufficient to determine net health benefit (Table 4).[39]

Table 4 Summary of the evidence indicating the strength of the evidence and direction of benefit[39]

Condition	Net health benefit vs comparators	Type of net health benefit	Strength of the evidence
Cancer			
Ocular	Superior	Benefit ↑ Harm ↓	++
Brain/spinal	Incremental	Benefit = Harm ↓	+
Paediatric	Incremental	Benefit = Harm ↓	++
Liver	Comparable	Benefit = Harm =	+
Lung	Comparable	Benefit = Harm =	++
Prostate	Comparable	Benefit = Harm =	++
Bone	Insufficient		+
Breast	Insufficient		0
Oesophageal	Insufficient		0
Gastrointestinal	Insufficient		0
Gynaecological	Insufficient		0
Head/neck	Insufficient		+
Lymphomas	Insufficient		0
Sarcomas	Insufficient		0
Seminoma	Insufficient		0
Thymoma	Insufficient		0
Non-cancerous			
Haemangiomas	Comparable	Benefit = Harm =	+
Arteriovenous malformations	Insufficient		0
Other	Insufficient		0

Strength of the evidence: Low = +, moderate = ++, high = +++, no evidence = 0

Subsequently, in 2015 the RANZCR produced a position paper on particle therapy. Within that overview of evidence, the RANCR concluded that:

- hepatocellular (liver) cancer and Ewing sarcoma (a bone or soft tissue cancer) may also form an indication for PBT referral, in addition to the Washington State Health Care Authority findings;
- further evidence is required for cancers of the oesophagus, pancreas, and lymphatic system;
- prostate, lung and breast cancer should be treated with conventional radiotherapy.[13]

Other potential applications of PBT are being actively investigated internationally, with 75 phase I-III studies currently listed in the United States (US) National Institutes of Health Clinical Trials Registry.

Carbon Ion Therapy

In comparison to protons, there is relatively little clinical literature describing the use of carbon ion treatment, mainly due to fewer operating facilities (10 in operation internationally, three under construction).[2, 40] The countries that have most heavily invested in this technology include Japan (five facilities), China (two facilities, with one under construction) and Germany (two facilities). Additionally, Stanford University has recently announced plans to construct a combined proton/heavy ion installation. This will be the first US heavy ion facility.[3]

Studies published to date have been undertaken in the treatment of a range of head and neck, thoracic, abdominal and pelvic malignancies, and generally demonstrate improved local control in comparison to standard of care, with comparable toxicity ranges (Table 5).[20] Carbon ion therapy shows promising results in the treatment of bone and soft-tissue sarcomas, recurrent rectal cancer, pancreatic cancer; tumours of the salivary gland, paranasal sinus and nasal cavity; adenoid cystic carcinomas, malignant mucosal melanomas, and hepatocellular carcinomas.[24, 41] However, further research into the use carbon ions is required to demonstrate both clinical and cost effectiveness.

As at December 2016, there are 24 planned or ongoing studies currently listed in the US National Institutes of Health Clinical Trials Registry. These studies incorporate the effects of carbon ion therapy on a range of malignancies including: hepatocellular carcinoma (3), meningioma's (2), sinonasal tumours (3), pancreatic cancer (1), prostate cancer (3), rectal cancer (1), gliomas (2), radio-resistant tumours (1), chondrosarcoma (1), sacrococcygeal chordoma (1), skull base chordoma (1), salivary gland tumours (1), nasopharyngeal carcinoma (3), and adenoid cystic carcinoma (1). With a growing number of international carbon ion centres, it is anticipated that there will be increasing evidence into the effectiveness of carbon ions in oncology treatment.

Table 5 Carbon ion treatment compared to standard of care [20]

Site	5 year LC range		Toxicity range (late ≥ GIII injury)	
	SOC	Carbon	SOC	Carbon
Head and Neck				
Adenoid cystic	27-72%	26-96%	0-12.9%	0-17%
Bone/soft tissue sarcoma	43-70%	24-73%	0%	2-18.5%
Skull base	46-73%	82-88%	0-7%	0-5%
Thorax				
NSCLC	80-97%	90-95%	0-15%	3% (pneumonitis)
Abdomen and Pelvis				
HCC	75-96%	81-96%	7-22%	3-4%
Pancreas	10-20%	66-100%	1.8-20%	7.7%
Prostate	80-95%**	87-99%*	4-28%	0.1-25%
Rectal cancer	24-28%	95%	14-27%	-
Cervix cancer	20%	53%	0-10.6%	9.6-18.2%
Sacral chordoma	55-72%	88%	17.6%	5.9%-17.9%
Chondrosarcoma	20-40%	60%	-	-

Abbreviations: SOC Standard of Care, *LC* Local Control, *HCC* Hepatocellular carcinoma, *GIII* Grade III toxicity, *OS (Overall survival); **bPFS (biochemical progression free survival).

Although the use of carbon ion particle therapy appears to be a promising treatment, particularly for highly aggressive and radio-resistant tumours, until such time as sufficient evidence of clinical superiority and cost-effectiveness exists, this modality should be treated as experimental, and its use within Australia or New Zealand should be restricted to clinical research.

Demand for Particle Therapy Services

Since 1995, the Commonwealth Department of Health has administered the Medical Treatment Overseas Program (MTOP), which provides financial assistance for Australians with a life-threatening medical condition to receive proven life-saving medical treatment overseas where:

- the proposed overseas treatment or an effective alternative treatment must not be available in Australia in time to benefit the applicant in question
- the proposed treatment must be significantly life extending and potentially curative
- there must be a real prospect of success for the applicant, and
- the treatment must be accepted by the Australian medical profession as standard form of treatment for the medical condition.

The MTOP supports individuals applying for PBT who have met all four of the above criteria. Historically, approved clinical indications for PBT have been limited to chordoma or chondrosarcoma of the axial skeleton, and some paediatric brain tumours where conventional radiotherapy treatment was considered suboptimal. Patients with eye malignancy were previously accepted for MTOP funding, however these conditions are now treated with stereotactic radiosurgery within Australia, which has demonstrated similar efficacy against cancerous tumours. There is some evidence that stereotactic radiosurgery may lead to an increased incidence of radiation induced blindness in comparison to PBT,[42] however, study results were not obtained from randomised controlled trial evidence. Patients with ocular tumours treated with PBT may also experience optical trauma, therefore high-level comparative evidence is required before a definitive conclusion can be made.

Since the inception of the MTOP, 68 applicants have been approved for overseas PBT access, and four applications were rejected. From 1 July 2010 to 31 December 2015, financial assistance for 24 patients was provided at a total cost of $3,427,469 (treatment costs only). This equates to an average of four patients per year, at an average treatment cost of $142,800 per patient. Within recent years, the costs for treatment have reduced as the number of overseas service providers has increased. The Medical Services Advisory Committee (MSAC) is currently reviewing the evidence around the clinical indications for PBT that have been previously approved by the MTOP.

The New Zealand Ministry for Health maintains a similar program known as the High-Cost Treatment Pool (HCTP). Since 2005, there have been seven HCTP applications approved for PBT, and two applications declined. All approved applications were to treat ocular (eye) melanoma in the UK, with average treatment cost of NZ$35,000 per patient. The New Zealand Ministry of Health has advised that New Zealand does not currently have any plans to introduce proton beam facilities.

It should be noted that if a proton facility is built in Australia, those assessed as requiring this treatment modality will no longer have access to MTOP funding. Additionally, with no applicable Medical Benefits Scheme listing at this time, funding for treatment would require that costs are borne entirely by States and Territories, or by the patient themselves.

International modelling of PBT demand was recently undertaken within the United Kingdom (UK). As at 2012, with a population of 64 million,[43] the UK Department of Health modelled a PBT demand of 1,487 patients (including 252 paediatric cases) per annum, utilising a conservative list of predominantly complex craniospinal indications. As a PBT facility (comprised of three gantry treatment rooms and a research room) was anticipated to achieve a maximum throughput of 750 patients per year, the UK Government funded construction of two PBT facilities (currently underway), with the potential development of a third facility in the longer term.[44] Subsequent to this announcement, some private PBT facilities were announced for the UK,[45-48] however the range of clinical indications that will be treated at these is not known.

The economic analysis of an Australian proton beam facility would need to consider current and future patient demand. Current patient demand within Australia and New Zealand is entirely dependent on the accepted range of clinical indications where PBT would be considered superior to other potential treatments. Until dedicated modelling is undertaken, the potential domestic demand for this treatment modality is difficult to estimate. As stated previously, the current indications where the evidence base supports the use of PBT include ocular tumours, tumours located proximal to the base of skull, including chordoma and chondrosarcomas, primary or metastatic tumours of the spine where spinal cord tolerance may be exceeded with conventional treatment, and selected paediatric tumours. The number of Australian and New Zealand patients with these indications, who would require PBT, remains small. Future patient demand would increase dramatically if the clinical indications for PBT were widened to include prostate cancer, however the results of an RCT comparing the use of PBT to photon therapy for prostate cancer will not be available until at least late 2018. In addition, an economic analysis should consider the redundancy cost to the health system of existing linear accelerators (LINACs), which may be underutilised if patients are shifted to treatment with PBT.

Nevertheless, there have been some attempts by ANTSO to ascertain the number of patients eligible for particle therapy, which are provided for indicative purposes only. [49]

The first approach used 2009 Australian cancer incidence data, obtained from the Australian Cancer Database, adjusted to the 2014 population. Using Australian recommendations on optimal radiotherapy utilisation rates,[50] and assumed eligibility rates for particle therapy substitution, potential demand was calculated for nine malignancy indications (Table 6).

This approach estimated that the total number of patients who would be potentially eligible for particle therapy is estimated to be 3,878 persons, including 203 paediatric patients. At the time, this patient number was considered by ANTSO as a very high end estimate, due to the challenges of calculating particle therapy eligibility rates, which would be based on the strength of clinical evidence, patient clinical need, and the caseload capacity of local facilities. However, it was provided as a guide to potential demand, and an indicator for longer term future planning.

This modelling suggests Australian particle therapy demand for brain/CNS and ocular malignancy (as clinical conditions where evidence most supports particle therapy effectiveness) would be 899 patients, including 133 paediatric patients.

Table 6 2014 ANTSO estimation of Australian patients eligible for particle therapy using nine indicators

Indication	Incidence in 2014		Candidates for Conventional Radiotherapy		Candidates for particle therapy	
	All patients	Paediatric patients	All patients	Paediatric patients	All patients	Paediatric patients
Brain/CNS	1,773	138	1,418	110	709	110
Head and neck/skull	2,609	16	1,931	12	913	13
Ocular	271	23	271	23	190	23
Lung	6,883	2	5,506	2	619	2
Prostate	20,914	0	12,130	0	837	0
Liver	1,402	19	0	0	70	10
Bone	199	43	0	0	100	43
Uterine Cervix	830	1	589	1	166	1
Pancreas	2,739	1	1,342	0	274	1
Total	**37,620**	**243**	**23,187**	**148**	**3,878**	**203**

The second ANTSO approach was to adopt the projected UK PBT caseload estimates, and apply demand on a population basis to the 2012 Australian population. In Table 7, a similar demand has also been calculated for the New Zealand population.

Through this method, ANTSO estimated 534 Australian patients (444 adults and 91 paediatric cases) as being potential candidates for PBT. A similar calculation for New Zealand results in an estimated 104 patients (86 adults and 18 children), resulting in a total potential demand of 638 patients for both countries. It should be noted that the UK case mix is viewed as a conservative list of clinical indications that reflects the UK's cancer epidemiology and clinical needs. However, ANTSO considers that they retain a reasonable applicability to Australia, and therefore these patients would be considered highly eligible for particle therapy when first made locally available.

Table 7 Adaptation of caseload estimates by the UK's National Proton Beam Therapy Service Development Programme to the 2012 Australian and New Zealand populations

Country	Estimated Population in 2012 (millions)	Estimated PBT Patients		Total
		Adult	Paediatric	
UK	63.2	1,235	252	1,487
Australia	22.7	444	91	534
New Zealand	4.4	86	18	104
Total AUS/NZ		**530**	**109**	**638**

NB: all figures rounded to nearest whole number

More recently, based on evidence arising from Japanese clinical experiences, ANSTO has estimated that 0.02 to 0.04 per cent of the Australian population would benefit from access to particle therapy each year. This equates to approximately 4,800-9,600 patients.

As previously stated, greater certainty of domestic patient demand would require an accepted list of particle therapy clinical indications, and subsequent modelling from current and projected Australian and New Zealand cancer incidence and radiotherapy referral rates. This would allow for more accurate determination of facilities required to meet both current and projected demand.

Proposed Particle Therapy Facilities in Australia

Within Australia, several jurisdictions have indicated interest in establishing PBT and carbon ion facilities, including:

- Victoria – as part of the 2015-2016 state budget, the State Government announced $2 million funding to progress planning and development of a National Centre for Proton Beam Therapy as part of the Victorian Comprehensive Cancer Centre (VCCC), undertaken in conjunction with the University of Melbourne and Peter MacCallum Cancer Centre.[51] Subsequently, in August 2016, the Victorian Government announced $50 million for further planning activity, with Parkville nominated as a potential PBT location[52]

- New South Wales - Westmead Hospital, in conjunction with the University of Sydney and the University of Wollongong have developed a business case for a National Particle Therapy and Research Centre (using carbon ions and protons) to be located at the Westmead Hospital precinct[53]

- South Australia – South Australia is actively seeking to establish a proton therapy treatment and research centre based at the South Australian Health and Biomedical Precinct

- Queensland (public) – the Queensland Metro North Hospital and Health Service have developed a business plan for the potential introduction of a PBT facility at the Royal Brisbane and Women's Hospital. It is proposed that this facility will be developed in partnership with the University of Queensland, the Queensland Institute of Technology, and Children's Health Queensland, and

- Queensland (private) - in September 2014, Mater Health Services announced an alliance with Proton Therapy Australia Pty Ltd to construct a $170 million proton beam facility,[54] and as at October 2016 were seeking equity for land purchase near the Lady Cilento Children's Hospital, South Brisbane.[55]

Currently, relevant entities involved in the proposed NSW, QLD and SA facilities have formalised Memoranda of Understanding to network and integrate their planning activities. This clinician-led collaboration has established links with ANSTO and RANZCR; and internationally with the New Zealand government, the Queen's Medical Research Institute (UK), the European Organization for Nuclear Research (CERN), and with particle centres in the USA, Germany, Denmark, Italy and Japan. The collaboration is additionally seeking to undertake the development of standardised protocols for particle therapy patient selection, treatment, physics, research, education and training as a national collaborative effort, with professional representation through the tripartite committee, the RANZCR, universities, and other relevant bodies, including the State public health systems where appropriate.

Should more than one of these proposals progress to construction, there is great risk of considerable expenditure and a potential oversupply of PBT facilities in Australia. It would be considered preferable to have a coordinated, national approach to the introduction of particle therapy to Australia, similar to the process recently undertaken within the UK where planning was commenced in 2008 by the National Health Service. Following development of a strategic outline case,[44] and hospital-led business cases, in 2013 the UK Health Secretary announced £250 million (AU$396) funding for construction of two new PBT facilities in Manchester and London. Facility construction commenced in 2015, with planned completion in 2018 and 2019, respectively.

If the current planning within Australia continues in the present manner, PBT is unlikely to be introduced in a coordinated and controlled manner. The establishment of a formal bi-national high-level reference group would provide an appropriate entity to consider and oversee the potential introduction of this technology, with due respect to State and Territory rights. This reference group could include appropriate representatives from the Commonwealth Government, Australian and New Zealand jurisdictions; and relevant scientific, clinical and health consumer entities.

The role of this group could include developing an Australasian Particle Therapy Business Case, including establishment of an agreed list of clinical indications for particle therapy and research as per the UK and Danish approaches, informed by a comparative dose planning approach as recommended in the RANZCR position paper. Other deliverables could also include determination of current and projected service demand, evaluation of economic considerations and treatment cost disbursement, preferred infrastructure requirements, and investigation of workforce and training issues. Additionally, development of a bi-national data registry, to provide quantitative data for evaluation of particle therapy clinical efficacy, cost effectiveness and safety, would likely inform future planning of additional facilities.

Whether the reference group makes recommendations regarding the number of proton facilities needed, or specific preferred locations or centres for construction, would form part of the Terms of Reference of the group. Such recommendations would need to be informed by demand modelling and stakeholder input. Nevertheless, a centralised planned approach might provide a single body of expertise and investigation to assist national planning and introduction of PBT.

However, it should also be noted that such activity could lead to *post hoc* private sector investment in PBT, which would increase PBT capacity, as has occurred in the UK following the NHS announcement to build two public PBT facilities.

Appendix A – Selected Proton Beam Facility Manufacturers: Facilities and Reported Costs

Accelerator Manufacturer	Model and Treatment Room Capacity	Faculties built or under construction	Facility Treatment Rooms	Reported costs* ($AUD)
Hitachi Ltd (Japan)	PROBEAT™-RT (Single treatment room)	Hokkaido University Hospital, Japan (opened 2016)	One	NA
	PROBEAT™-V (Two to five treatment rooms)	Sibley Memorial Hospital, USA (opening 2021)	Four	$182M[56]
		Mayo Clinic, USA (opening 2016)	Five	$254M[57]
IBA (Belgium)	Proteus ONE™ (Single treatment room)	Beaumont Hospital, USA (opening 2017)	One	$52M[58]
	Proteus PLUS (two to five treatment rooms)	UMCG, Netherlands (opening 2017)	Two	$72M[59]
		Irving's Texas Center For Proton Therapy, USA (opened 2015)	Three	$141M[60]
Mitsubishi Electric Corporation (Japan)	Proton Type	Tsuyama Chuo Hospital Proton Beam Cancer Center (opening 2016)	One	NA
Optivus Proton Therapy Inc. (USA)	Conforma 3000® (one to seven rooms)	James M. Slater, MD, Proton Treatment and Research Center (opened 1990)	Five	$262M[61]
Sumitomo Heavy Industries (Japan)	Proton Therapy System	Samsung Medical Center, South Korea (opened 2016)	Three	NA
ProNova Solutions LLC (USA)	SC360 (single to four rooms)	Scott Hamilton Proton Therapy Center, USA (opening 2018)	Three	$131M[62]
Varian Medical Systems Inc. (USA)	Probeam® Compact (Single room)	Biopolis Oncology Center, Singapore (opening NA)	One	NA
	Probeam® (multi-room)	Cincinnati Children's/UC Health Proton Therapy Center (opened 2015)	Three	$158M[63]
Mevion Medical Systems (USA)	S250™ (single room)	S. Lee Kling Proton Therapy Center, USA (opened 2013)	One	$34M[64]
	S250i™ (Single room with Intensity Modulated Proton Therapy)	Zuidoost Nederland Protonen Therapie Centrum, Netherlands (opening 2018)	One	$34M[65]
	S250mx™ (two to four rooms)	Los Angeles Proton Center (opening 2017)	Three	NA
Protom International (USA)	Radiance 330® (one to four rooms)	Massachusetts General Hospital (opening 2017)	One	NA

NA = not available

* International costs adjusted for inflation and converted into 2016 AUD$ using current conversion rate and reported costs may represent particle equipment costs only, and are not inclusive of total facility costs

Appendix B – Selected Carbon Ion Facility Manufacturers: Facilities and Reported Costs

Accelerator Manufacturer	Particles	Faculties built or under construction	Facility Treatment Rooms	Reported costs ($AUD)
IBA (C400 prototype)	Carbon ions, protons	Advanced Resource Center for HADrontherapy in Europe, France (opening 2018)	Three	$186M[66]
Korea Institute of Radiological and Medical Science	Carbon ions, protons	Korea Heavy Ion Medical Accelerator, South Korea (opening 2017)	Three	$226M[67]
European Organization for Nuclear Research (CERN)	Carbon ions, protons	Med-AUSTRON, Austria (opened 2016)	Three	$288M[68]
Lanzhou Institute of Modern Physics	Carbon ions	Lanzhou Heavy-Ion Beam Cancer Treatment Center, China (opening 2016)	Three	$215M[69]
Danfysik A/S	Carbon ions, protons	MIT, Marburg, Germany (opened 2015)	Four	$202M[70]
Toshiba Corporation	Carbon ions	i-Rock Kanagawa Cancer Center, Japan (opened 2015)	Four	NA
Danfysik A/S	Carbon ions, protons	Shanghai Proton and Heavy Ion Center, China (opened 2014)	Three	$203M[70]
Mitsubishi Electric Corporation	Carbon ions	SAGA Heavy Ion Medical Accelerator in Tosu, Japan (opened 2013)	Three	$189M[71]
GSI Helmholtz Centre for Heavy Ion Research	Carbon ions, oxygen ions, protons	Heidelberg Ion-Beam Therapy Center, Austria (opened 2012)	Three	$187M[70]

NA = not available
* International costs adjusted for inflation and converted into 2016 AUD$ using current conversion rate and reported costs may represent particle equipment costs only, and are not inclusive of total facility costs

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