



Australian Government

Department of Health

Application 1455:

Proton Beam Therapy (PBT)

PICO Confirmation

(to guide a new application to MSAC)

(Version 1.0)

This PICO Confirmation Template is to be completed to guide a new request for public funding for new or amended medical service(s) (including, but not limited to the Medicare Benefits Schedule (MBS)). It is relevant to proposals for both therapeutic and investigative medical services.

Please complete all questions that are applicable to the proposed service, providing relevant information only.

Should you require any further assistance, departmental staff are available through the Health Technology Assessment (HTA Team) on the contact number and email below to discuss the application form, or any other component of the Medical Services Advisory Committee process.

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Summary of PICO/PPICO criteria to define the question(s) to be addressed in an Assessment Report to the Medical Services Advisory Committee (MSAC)

Component	Description
Patients	<p>Patients who are currently eligible to access proton beam therapy (PBT) under the Medical Treatment Overseas (MTO) Program due to a diagnosis of one of the following conditions:</p> <ul style="list-style-type: none"> • Chordoma of the axial skeleton (defined as the skull, vertebral column and bony pelvis) • Sarcoma of the axial skeleton • Paediatric central nervous system (CNS) tumour • Ocular melanoma • Retinoblastoma • Soft tissue sarcoma in close proximity to the axial skeleton (to include rhabdomyosarcoma) • Adenoid cystic carcinoma of the lacrimal or salivary glands • Craniopharyngioma • Intracranial germ cell tumour • Neuroblastoma • Nephroblastoma
Intervention	<p>PBT with curative intent (primary treatment of the condition) or as salvage treatment (for recurrent disease or after failure of initial therapy):</p> <ul style="list-style-type: none"> • as monotherapy; • as a 'boost' mechanism to conventional radiation therapy; or • in combination with other modalities, such as chemotherapy and/or surgery.
Comparators	<p>Usual standard of care, which may include:</p> <ul style="list-style-type: none"> • radiation therapy alternatives, such as intensity modulated radiation therapy (IMRT), stereotactic radiation techniques or other external beam therapies, and also brachytherapy; • other treatment options specific to the clinical condition (e.g. surgery, chemotherapy, other devices such as laser therapy for ocular tumours); or • no treatment alternatives.
Outcomes	<p><i>Effectiveness:</i></p> <ul style="list-style-type: none"> • Disease-free and/or overall survival • Disease-related and/or all-cause mortality • Disease progression • Local tumour control (regression/remission) • Incidence of metastases • Health-related quality of life • Other patient-relevant outcomes (e.g. visual acuity for ocular tumours) <p><i>Safety:</i></p> <ul style="list-style-type: none"> • Acute radiation-related toxicities (i.e. within the first 90 days after treatment) • Late radiation-related toxicities (i.e. >90 days after treatment) • Systemic effects such as fatigue, erythema or hair loss

Component	Description
	<ul style="list-style-type: none"> • Toxicities specific to each cancer type (e.g. neurocognitive impairment in paediatric patients treated for brain cancers) • Secondary malignancy • Radiation dose <p><i>Healthcare resource use:</i></p> <ul style="list-style-type: none"> • Number of treatment sessions • Requirements for subsequent therapy • Resource use and cost of planning and treatment stages for delivery of PBT • Cost-effectiveness of PBT • Total Australian Government healthcare costs

Population

The proposed population includes patients who are currently eligible to receive proton beam therapy (PBT) under the Australian Government funded Medical Treatment Overseas (MTO) Program. Currently, there are very small numbers of patients in Australia who access PBT under the MTO Program, averaging just four patients per year.

The main group of patients are those suffering from chordoma or chondrosarcoma of the axial skeleton. The other main group is a small subpopulation of children with brain tumours. Formerly, the main treatment group was patients with eye malignancy, either retinoblastoma in children or melanoma in adults, but this patient population is now successfully treated with stereotactic radiosurgery within Australia.

In consultation with the Faculty of Radiation Oncology, the Department has agreed that the following clinical indications for PBT services are to be included in the assessment:

1. chordoma of the axial skeleton (defined as the skull, vertebral column and bony pelvis);
2. sarcoma of the axial skeleton;
3. paediatric CNS tumour;
4. ocular melanoma¹;
5. retinoblastoma¹;
6. soft tissue sarcoma in close proximity to the axial skeleton (to include rhabdomyosarcoma);
7. adenoid cystic carcinoma of the lacrimal or salivary glands;
8. craniopharyngioma;
9. intracranial germ cell tumour;
10. neuroblastoma; and
11. nephroblastoma.

Rationale

The MTO Program provides financial assistance for Australians with a life-threatening medical condition to receive proven life-saving medical treatment overseas where effective treatment is not available in Australia. Since the inception of the MTO Program in 1995, there have been 74 applicants for PBT from 1998 to 2016 (66 applications approved, four applications rejected, one application withdrawn, and three are currently under assessment).

To be eligible for the Program, the patient must meet the four mandatory medical criteria (as assessed by a panel of Departmental Medical Advisers) and their application must be supported by the treating Australian specialist and the Faculty of Radiation Oncology. It is the treating Australian specialist that nominates where their patient would be best treated. The assessment process takes a minimum of six weeks.

¹ Eye malignancies are now successfully treated with stereotactic radiosurgery within Australia and applications are no longer supported under the MTO Program.

A condition of the MTO Program eligibility is that alternative treatment is not available in Australia. Once a PBT facility is built in Australia, those assessed as requiring this treatment modality will no longer have access to MTO funding under current Program Guidelines.

Currently there are no PBT facilities in Australia; however, four states including New South Wales, South Australia, Queensland, and Victoria are considering investing in PBT facilities within the next three to five years. Given the prospect of up to four PBT centres opening in Australia, there is a risk that patients currently eligible for financial assistance under the MTO Program will no longer be eligible for reimbursement of their treatment costs as they will no longer meet the mandatory MTO eligibility criteria, if PBT is available in Australia. On 12th April 2016, the Minister for Health wrote to the Medical Services Advisory Committee (MSAC) Chair requesting MSAC to consider future public funding arrangements for PBT for the limited clinical indications supported by the MTO Program.

From 1st January 2012 to 31st December 2016, the Department provided financial assistance to 20 patients to access PBT overseas.² The indications for PBT under the MTO Program have included clival chordoma, spinal thoracic chordoma, atypical teratoid rhabdoid tumour, craniopharyngioma, pelvic osteosarcoma, supratentorial anaplastic ependymoma, skull base chondrosarcoma, chondrosarcoma of the cervical spine, perimeningeal rhabdomyosarcoma, adenoid cystic carcinoma on the lacrimal gland, ocular melanoma and choroidal melanoma.³ Patients who received PBT overseas ranged in age from 17 months to 63 years old.

There is also evidence for the use of PBT in the treatment of other conditions, including gastrointestinal malignancies (oesophagus, liver, pancreas), malignant lymphoma, breast cancer, lung cancer and prostate cancer. As there are competing treatment modalities for these indications, applications under the MTO Program would not be supported. Appendix A lists the radiation therapy options for various tumour types, taken from the Faculty of Radiation Oncology Position Paper on Particle Therapy (RANZCR, 2015).

Intervention

PBT is a form of external beam radiation therapy that uses heavier particles (protons) instead of X-rays (photons), which are used in conventional radiotherapy. PBT may be used as primary treatment or as salvage therapy (in the case of recurrent disease or after failure of initial therapy). It is typically delivered on an outpatient basis in daily fractions (Monday through Friday), with each treatment session taking 15-60 minutes depending on the type and location of the tumour (Washington State Health Care Authority, 2014). The total duration of the treatment course varies by type and location of the tumour, and may last up to eight weeks.

While PBT is often used as monotherapy, it is also used as a 'boost' mechanism to conventional radiation therapy, or in combination with other modalities such as chemotherapy and surgery (Washington State Health Care Authority, 2014). Traditionally, PBT has been delivered via passively scattered beam technology, typically using a fixed beam. However, newer proton delivery systems use pencil scanning technology which allows intensity modulated proton therapy (IMPT).

² Three patients in 2012, six patients in 2013, three patients in 2014, five patients in 2015, and three patients in 2016.

³ Ocular melanoma and choroidal melanoma are now successfully treated with stereotactic radiosurgery within Australia and applications are no longer supported under the MTO Program.

Radiation therapy requires a multidisciplinary team including radiation oncologists, medical physicists and radiation therapists. Some site-specific cancers may also involve a diagnostic radiologist and/or surgeon. The service is provided at PBT centres after referral from the radiation oncologist caring for the patient. Prior to PBT, patients will have undergone diagnostic imaging and pathology, and in some cases may have had surgery or other treatment such as chemotherapy.

PBT can allow for radiation treatment plans that are highly conformal to the target volume. PBT planning defines the necessary field sizes, gantry angles, and beam energies needed to achieve the desired radiation dose distribution. PBT treatment planning is a multi-step process and shares functions common to other forms of external beam radiotherapy planning.

- (1) **Simulation and imaging:** Three-dimensional acquisition of the target region by simulation employing magnetic resonance imaging (MRI) or computed tomography (CT), with or without positron emission tomography (PET) is an essential prerequisite to PBT treatment planning.
- (2) **Contouring:** The radiation oncologist defines a margin around the Gross Tumour Volume (if there has not been previous treatment with surgery or chemotherapy), the Clinical Target Volume (which encompasses the areas at risk for microscopic disease) and nearby normal structures that could potentially be harmed by radiation.
- (3) **Radiation dose prescribing:** Specific dose coverage requirements are assigned by the radiation oncologist for the Clinical Target Volume to maximise the potential for disease control and minimise the risk of radiation injury to normal tissue.
- (4) **Dosimetric planning and calculations:** A qualified medical physicist or a supervised dosimetrist calculates a treatment plan to deliver the prescribed radiation dose to the Clinical Target Volume while simultaneously satisfying normal tissue constraints. The treatment plan specifies all delivery parameters and/or field specific hardware as well as the expected dose distribution. After completion of isodose planning, an independent verification of the radiation dose should be performed by a medical dosimetrist or physicist. As PBT dose distributions are sensitive to changes in target depth and shape, changes in patient anatomy during treatment may require repeat planning.

For every treatment fraction, imaging techniques such as stereotactic X-ray or CT scan (collectively referred to as Image Guided Radiation Therapy) are used to verify accurate and consistent patient and target setup.

From 1st January 2012 to 31st December 2016, the total treatment cost for PBT under the MTO Program (including travel reimbursement) was approximately \$AUD2.8m, which equates to an average cost of \$140,000 per patient. The cost of treatment with PBT depends on the regimen (the number of fractions per treatment ranged from 6 to 40) and whether PBT was performed as monotherapy or as multi-modal treatment (i.e. PBT plus adjuvant chemotherapy, or PBT plus surgery). Total treatment costs have ranged from \$AUD19,000 to \$270,000; however other costs (including accommodation, airfares and other treatment-related eligible expenses) bring the total cost to \$AUD27,000 to \$300,000.

The construction of cyclotrons at the core of proton beam facilities is very expensive; however, there is potential for considerable growth in patient numbers and reimbursement as the use of PBT expands in many settings to treat more common cancers, such as those of the prostate, breast, liver,

and lung. In recent years, the number of proton centres has grown substantially and proton beam units have become more affordable and commercially available (Washington State Health Care Authority, 2014). A number of alternative treatment facilities have emerged overseas that charge substantially lower costs with the same level of outcome. The Department does not have preferred provider arrangements with any PBT facility overseas.

Rationale

Protons are positively-charged subatomic particles that have been in clinical use as a form of external beam radiotherapy for over 60 years. As for all external beam radiotherapy, the goal is to deliver sufficient radiation to the target tumour while mitigating the effects on adjacent normal tissue. This has been a challenge for conventional photon therapy as radiation is delivered across tissue depths on the way toward the target tumour and to deeper tissue depths beyond the target (Washington State Health Care Authority, 2014).

In contrast, the physical profile of a beam of proton particles allows for the majority of its energy to be deposited over a very narrow range of tissue at a depth largely determined by the energy of the proton beam. Compared with a photon beam, a proton beam deposits relatively less radiation energy upon entering the body. The energy deposition of the proton beam then rapidly increases over a narrow range of tissue at the desired depth to produce an intense dose distribution pattern, which is known as the Bragg peak (Larsson et al, 1958). Beyond the Bragg peak, energy and dose deposition rapidly decrease, resulting in the absence of any significant exit dose deposited in normal tissue beyond the target.

The physical characteristics of protons therefore offers potential benefits over photon X-ray therapy. These potential benefits, which remain to be proven clinically, are outlined in the Faculty of Radiation Oncology Position Paper on Particle Therapy (RANZCR, 2015):

- Fewer early and late side effects compared to photons, depending on the nature of the photon therapy (e.g. stereotactic body radiation therapy [SBRT], intensity modulated radiation therapy [IMRT]), the type of proton treatment (e.g. intensity modulated or fixed beam), clinical experience with the use of protons, and the use of imaging verification of treatment set-up.
- A reduction in risk of treatment-induced benign or malignant tumours in tissues away from the tumour.
- A reduction in the radiation dose to surrounding normal tissues, which may allow an adequate dose to a tumour in close proximity to critical structures and dose escalation to a tumour to improve disease control.
- A reduction in the number of required treatments.

While it is assumed that the biologic effects of protons are equivalent to photons, specific relative biological effectiveness (RBE) values of protons in relation to photons are not known with absolute certainty for all types of tissues and fractionation schemes (Paganetti et al, 2002).

Initial use of PBT focused on cancers or noncancerous malformations of the brain stem, eye, or spinal cord, where sparing very sensitive adjacent normal tissues was felt to be of utmost importance. PBT has also been advocated for many paediatric tumours due to long-standing concerns regarding radiation's potential to cause acute and long-term toxicity to normal tissues, secondary malignancy later in life, and other more nuanced effects in children, such as

neurocognitive impairment after radiotherapy for brain cancers (Washington State Health Care Authority, 2014).

Comparator

The comparator is usual standard care, which may include:

- radiation therapy alternatives, such as IMRT, SBRT or other external beam therapies, and also brachytherapy;
- other treatment options specific to the clinical condition (e.g. surgery, chemotherapy, other devices such as laser therapy for ocular tumours); or
- no treatment alternative.

Rationale

While PBT treatment planning and delivery have evolved, so too have other approaches to radiotherapy. In April 2015, MSAC supported public funding of IMRT for cancer treatment delivery on a cost neutral basis relative to three dimensional conformal radiotherapy (3D-CRT). The Public Summary Document noted that the intensity of the beams generated by IMRT is able to be modulated, resulting in a customisable radiation dose to target a tumour better, while sparing surrounding non-tumour tissues. This potentially improves treatment outcomes compared with 3D-CRT, including reduced incidence and severity of side effects such as acute and late toxicity. MSAC noted the capacity to sculpt the radiation around complex tumour volumes to avoid adjacent structures may provide a treatment advantage in some patients, such as those with small volume tumours located near critical organs. Both IMRT and 3D-CRT are delivered using a linear accelerator and are widespread throughout Australian radiation therapy departments.

Appendix A lists the treatment options for various tumour types, taken from the Faculty of Radiation Oncology Position Paper on Particle Therapy (RANZCR, 2015). IMRT has become standard of care for many of the clinical indications of interest and is funded on the Medical Benefits Schedule (MBS) using item 15275. IMRT simulation, preparation of a dosimetry plan, and treatment verification are available using MBS items 15555, 15565 and 15715. Stereotactic surgery (including all radiation oncology consultations, planning, simulation, dosimetry and treatment) is funded on the MBS using item 15600.

Other particle therapy, such as carbon ion therapy, is not as widely used around the world and remains more expensive than PBT because a larger accelerator and more shielding is required. Carbon ions are normally produced by a synchrotron; however, cyclotrons capable of producing more than one particle type are being developed (RANZCR, 2015).

Outcomes

The potential benefits of proton therapy are a consequence of normal tissues around the target (tumour) receiving very little radiation dose. This could result in fewer side effects compared with other forms of radiation therapy and a reduction in risk of secondary malignant tumours. A reduction in the radiation dose to surrounding normal tissues may also allow an adequate dose to be delivered to tumours in close proximity to critical structures, and dose escalation to improve disease control.

The outcomes of interest to the assessment are listed below.

Patient relevant

Effectiveness:

- Disease-free and/or overall survival
- Disease-related and/or all-cause mortality
- Disease progression
- Local tumour control (regression/remission)
- Incidence of metastases
- Health-related quality of life
- Other patient-relevant outcomes (e.g. visual acuity for ocular tumours)

Safety:

- Acute radiation-related toxicities (i.e. within the first 90 days after treatment)
- Late radiation-related toxicities (i.e. >90 days after treatment)
- Systemic effects such as fatigue, erythema or hair loss
- Toxicities specific to each cancer type (e.g. neurocognitive impairment in paediatric patients treated for brain cancers)
- Secondary malignancy
- Radiation dose

Healthcare system

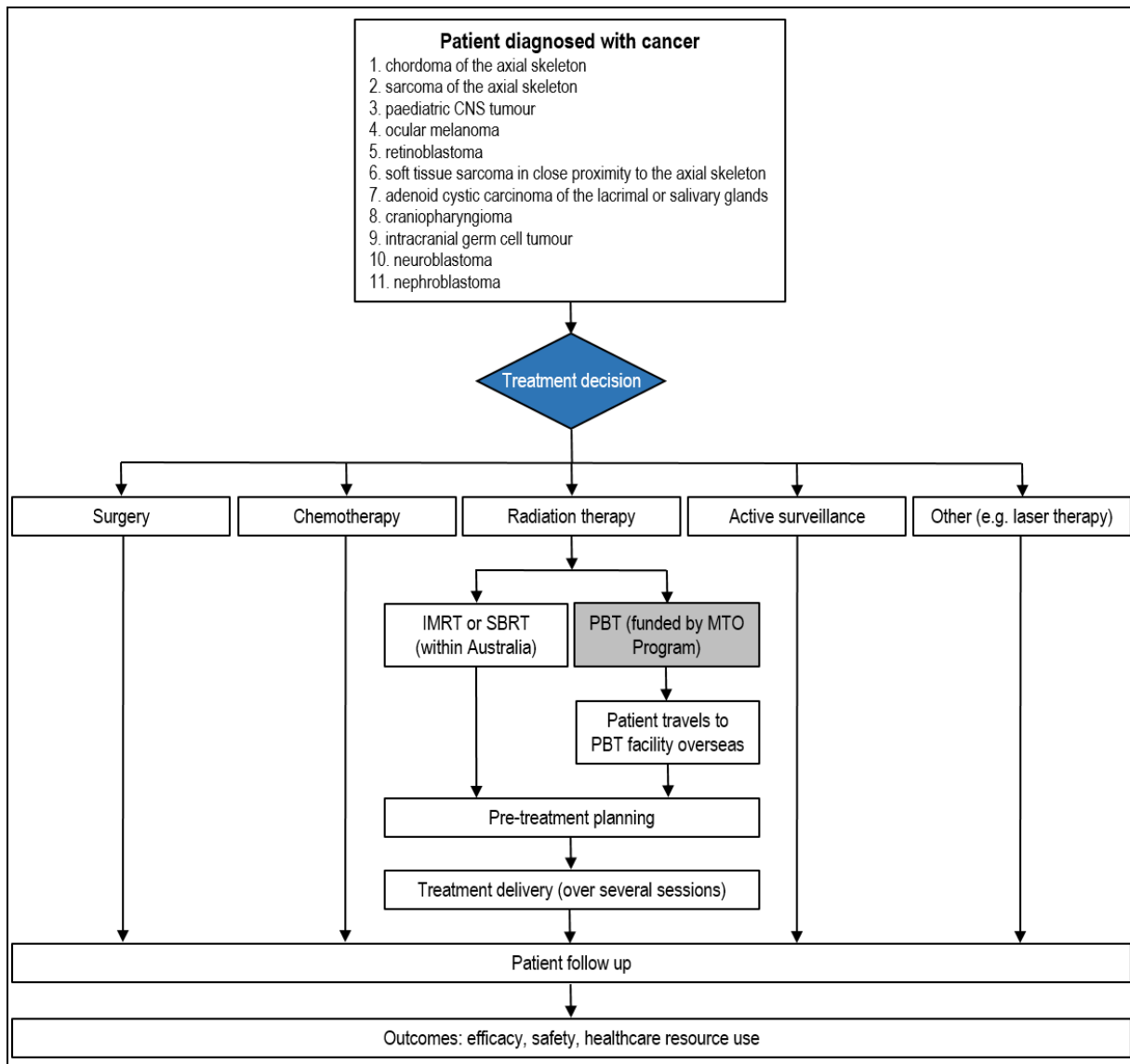
- Number of treatment sessions
- Requirements for subsequent therapy
- Resource use and cost of planning and treatment stages for delivery of PBT
- Cost-effectiveness of PBT
- Total Australian Government healthcare costs

If one or more PBT facilities become available in Australia, and PBT services are recommended by MSAC, costs will shift from the MTO Program to the MBS.

Current clinical management algorithm for identified population

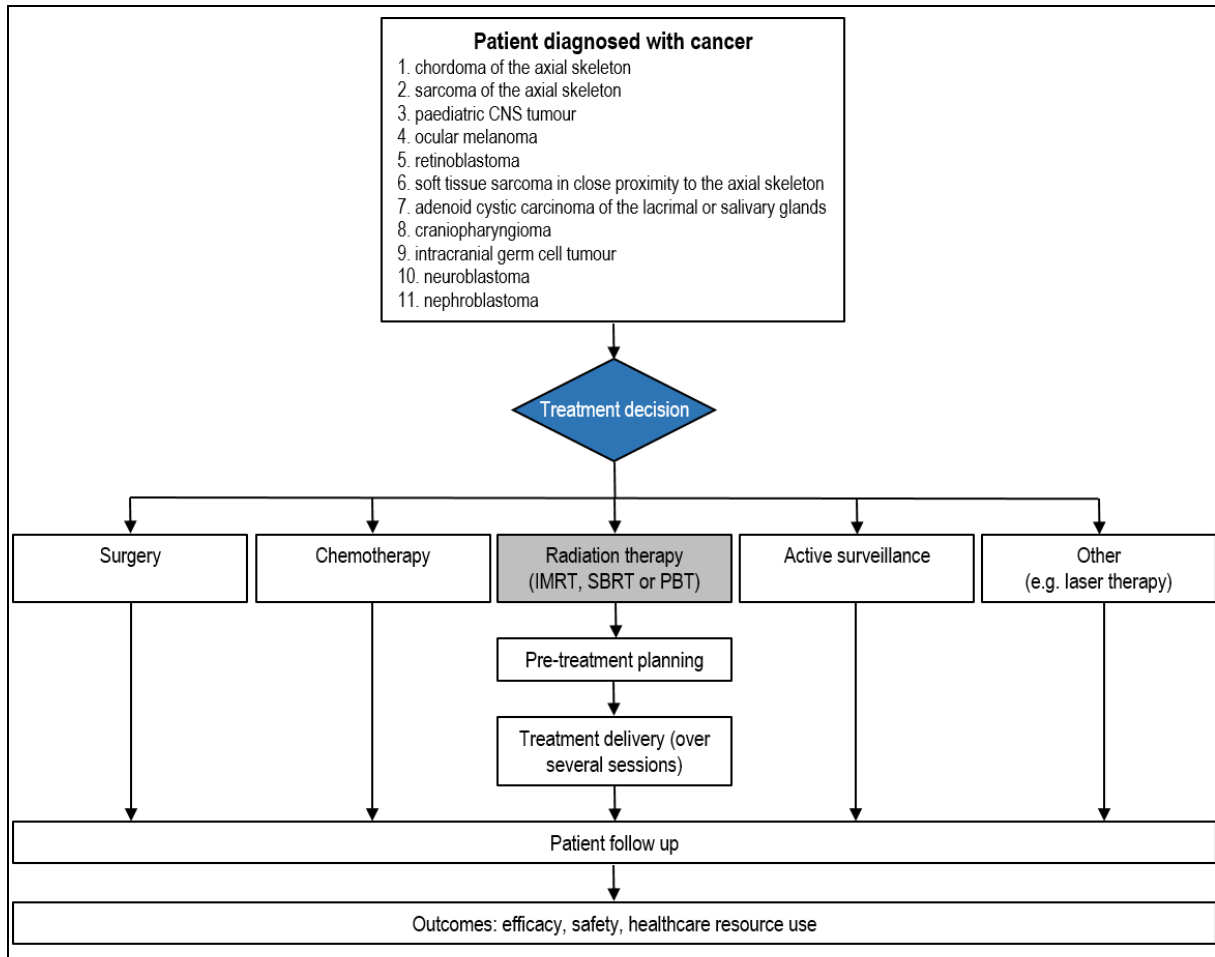
PBT is an alternative treatment delivery method to existing forms of radiation therapy. Currently, there are no PBT facilities within Australia and patients must travel overseas for treatment. While not all patients will require PBT, there are circumstances where this treatment would be preferred over other techniques such as IMRT or SBRT. The decision to pursue PBT would be based on the treating physicians' consideration of individual patient circumstances and assessment of superiority of PBT over alternative treatment options. When considering an application for PBT, all diagnostic, imaging, operation and pathology reports are necessary for the Committee to review the case. A planning CT scan with photon plan should also be provided if possible.

The clinical algorithm below is a generalised representation of PBT with curative intent. In practice, treatment of the cancers of interest may be multi-modal (e.g. radiation therapy may be used in combination with surgery).



Proposed clinical management algorithm for identified population

The proposed clinical management algorithm assumes that PBT will be included on the MBS after facilities become operational in Australia, and will provide patients with an alternative to the existing treatments available in Australia.



Proposed economic evaluation

The clinical claim is that PBT is superior in clinical effectiveness and either non-inferior or superior in safety to usual standard of care (which includes radiation therapy alternatives, other treatment options specific to the clinical condition, or no treatment alternative). According to the *Technical Guidelines for Preparing Assessment Reports for the Medical Services Advisory Committee – Service Type: Therapeutic*, the required economic analysis is therefore a cost-utility or a cost-effectiveness analysis.

Proposed item descriptor

Although PBT is not yet available in Australia, it is expected that one or more proton beam facilities may be operational within three to five years. If public funding is sought through the MBS for the specific clinical indications currently funded under the MTO Program, the relevant MBS item will be located in Category 3, Group T2 – Radiation Oncology. Separate items may be necessary for pre-treatment planning and simulation, and for treatment delivery with imaging guidance.

References

Larsson B, Leksell L, Rexed B, Sourander P, Mair W, Andersson B (1958). The high-energy proton beam as a neurosurgical tool. *Nature*. 182:1222-1223.

Paganetti H, Niemierko A, Ancukiewicz M, Gerweck LE, Goitein M, Loeffler JS, Suit HD (2002). Relative biological effectiveness (RBE) values for proton beam therapy. *Int J Radiat Oncol Biol Phys*. 53:407-421.

The Royal Australian and New Zealand College of Radiologists. Faculty of Radiation Oncology Position Paper on Particle Therapy, October 2015.

Washington State Health Care Authority (2014). Proton beam therapy: final evidence report. Olympia, Washington.

Appendix A

Tumour type	Target population	Particle treatment currently used abroad	Treatment options	Category
Chordoma/ chondrosarcoma base of skull or spine	Paediatric Adult	Yes Yes	IMRT, stereotactic techniques	May be suitable for particle therapy
Intra-ocular melanoma	Paediatric	Yes	IMRT, stereotactic techniques	May be suitable for particle therapy
Medulloblastoma	Paediatric	Yes	IMRT, photon/electron spinal fields	May be suitable for particle therapy
Ependymoma	Paediatric	Yes	IMRT, stereotactic techniques	May be suitable for particle therapy
Craniopharyngioma	Paediatric	Yes	IMRT, stereotactic techniques	May be suitable for particle therapy
Low grade gliomas, including optic pathway	Paediatric	Yes	IMRT, stereotactic techniques	May be suitable for particle therapy
Intracranial germ cell tumour	Paediatric	Yes	IMRT	May be suitable for particle therapy
Ewing sarcoma	Paediatric Adult	Yes	IMRT	May be suitable for particle therapy
Spinal/paraspinal bone and soft tissue sarcoma (non-Ewing)	Paediatric Adult	Yes	IMRT	May be suitable for particle therapy
Rhabdomyosarcoma: orbit, parameningeal/ head and neck, pelvis	Paediatric	Yes	IMRT	May be suitable for particle therapy
Retinoblastoma	Paediatric	Yes	IMRT, stereotactic techniques	May be suitable for particle therapy
Hepatocellular cancer	Adult	Yes, both protons and carbon ions	Stereotactic techniques	May be suitable for particle therapy
Oesophageal cancer	Adult	Yes	IMRT, 3D-CRT	May become suitable for particle therapy in the future
Pancreatic cancer	Adult	Yes, both protons and carbon ions	IMRT, 3D-CRT	May become suitable for particle therapy in the future
Lymphoma	Paediatric	Yes, photons	IMRT, 3D-CRT	May become suitable for particle therapy in the future
Re-irradiation	Paediatric Adult	Yes, both protons and carbon ions	IMRT, 3D-CRT, stereotactic techniques, brachytherapy	May become suitable for particle therapy in the future
Prostate cancer	Adult	Yes	IMRT, 3D-CRT, brachytherapy	Treat with photons
Lung	Adult		IMRT, 3D-CRT, stereotactic techniques	Treat with photons
Breast	Adult	Yes	IMRT, 3D-CRT	Treat with photons

Source: RANZCR, 2015 (Table 3, page 19)

Abbreviations: 3D-CRT, three dimensional conformal radiotherapy; IMRT, intensity modulated radiation therapy.