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THE FACULTY OF RADIATION ONCOLOGY, RANZCR, is the peak bi-national body advancing patient care and the specialty of Radiation Oncology through setting of quality standards, producing excellent Radiation Oncology specialists, and driving research, innovation and collaboration in the treatment of cancer.

VISION
To have an innovative, world class Radiation Oncology Specialty for Australia and New Zealand focused on patient needs and quality.

OUR VALUES
In undertaking our activities and in managing the way we interact with our Fellows, trainees, members, staff, stakeholders, the community and all others with whom we liaise, the Faculty of Radiation Oncology, RANZCR, will demonstrate the following values:

• Quality of Care - performing to and upholding high standards
• Integrity, honesty and propriety - upholding professional and ethical values
• Patient orientation - understanding and reflecting the views of Fellows and members and working with them to achieve the best outcomes
• Fiscal responsibility and efficiency - using the resources of the College prudently.

OUR PROMISE TO THE PATIENTS
We will advocate for the best possible care for individual patients in multidisciplinary meetings and for all patients with government.

OUR PROMISE TO TRAINEES
We ensure the highest standard of training in radiation oncology by combining a world-class curriculum with passionate and supportive supervisors. The voice of trainees is valued in Radiation Oncology.

OUR PROMISE TO OUR FELLOWS
We are a member based organisation that utilises its resources effectively and strategically to fulfil our vision, purpose and core objectives. We strive for best practice and facilitate life-long learning of our members.

OUR PROMISE TO OUR PARTNERS & STAKEHOLDERS
We are a transparent and collaborative organisation that strives to promote partnerships and participation of all relevant stakeholders to ensure that patients across Australia and New Zealand receive a high-quality, timely and appropriate level of care.
OBJECTIVES

This document aims to inform cancer professionals, health professionals, health administrators, consumers and interested individuals about the current status of particle therapy internationally, the evidence for their use and the target population. The document proposes a Royal Australian and New Zealand College of Radiologists endorsed process for assessing Australian and New Zealand patients for referral overseas for particle therapy.

METHOD

This position paper was drafted by a working group, circulated to College members and international experts for external review and feedback was incorporated into the final report. A systematic review of the literature was not undertaken as several current reviews exist [1][2]. Instead, individual working group members searched relevant literature and interpreted the evidence.

ABOUT RADIATION ONCOLOGY

Radiation Oncology is a medical specialty in which specialist doctors treat cancer with radiation. The vast majority of current radiation therapy uses X-Rays or electrons. Radiation therapy can be used to treat cancer anywhere in the body. Half of all cancer patients will need radiation therapy at least once during the course of their illness for cure, disease control or relief of symptoms [3]. The safe and accurate delivery of radiation therapy requires skills of a multidisciplinary team of radiation oncologists, radiation therapists, medical physicists as well as radiologists, cancer nurses, engineers and allied health staff.

Since inception, radiation treatment has focussed on maximising the radiation dose to cancer while keeping the dose in normal tissue as low as possible. This underlying tenet has driven all technological advances in radiation therapy. Radiation therapy is now delivered using highly sophisticated equipment and techniques to deliver a prescribed radiation dose to the target (tumour) while ensuring that the radiation dose to the surrounding normal tissues is as low as possible.

Radiation therapy techniques and technologies are evolving continually. Intensity modulated radiation therapy (IMRT), brachytherapy and stereotactic delivery techniques allow the radiation dose to critical normal tissues surrounding a tumour to be minimised [4].
ABOUT PROTON AND PARTICLE THERAPY

X-Rays are used to treat most cancer. Electrons are commonly used for treatment of skin and superficial tumours and are produced by the same linear accelerator equipment as photons [9].

Particle therapy is a form of external beam radiation therapy that uses heavier particles instead of X-rays (photons) or electrons. Hadron therapy is another term for particle beam therapy. Particles may be neutral (neutrons) or charged (protons, pions, or helium, neon, silicon, argon, and carbon ions). Proton beams and other heavy particles travel through tissue with minimal deposition of dose until the end of their paths, where a peak of energy is deposited. This is known as the Bragg peak (Figure 1). Beyond the Bragg peak, the dose for protons falls over an extremely short distance to zero. With heavier particles such as carbon ions, there is a small tail beyond the Bragg peak due to nuclear fragmentation. This means that normal tissues around the target (tumour) receive very little radiation dose, described as a low integral dose. Tumours in proximity to critical structures, such as the spinal cord and brain stem, can be treated potentially more safely with protons or carbon ions than photons.

Protons, photons and electrons in the energy range used in radiation therapy all have a low density of ionization events or linear energy transfer (LET) and therefore similar radiobiological properties and no difference in ability to control tumours. This assumption may not be correct at the end of the proton penetration range and there are small regions of higher LET (more cell kill) which may improve tumour control but cause more damage to normal tissues if higher LET regions fall in critical normal tissues. Other heavy particles have higher linear energy transfer so they behave in a biologically different manner to photons and protons.

Carbon ions are the most commonly used heavy particle in radiation therapy, other than protons. They have a narrower Bragg peak so a very detailed understanding of their behaviour in tissue is essential to prevent over-dose of radiation to critical surrounding normal tissues causing serious harm, and under-dose to the tumour. Their denser deposition of destructive energy means that there is little effect of fraction size so that few treatments, each of a higher dose, can be delivered so treatment courses are shorter. The ability to deliver shorter courses of treatment (hypofractionation) makes carbon ions an attractive treatment option. There remain uncertainties about the precise behaviour in tissues of protons, and more particularly with carbon ions, mandating their careful introduction and need for ongoing scientific investigation and clinical studies with long term outcome information.

Stereotactic body radiation therapy (SBRT) using photons (treating a very small tumour target in a very precise way) may well be as effective as particle therapy, and possibly even safer as photon beam characteristics are better understood. Clinical studies comparing SBRT and particle therapy are currently in development.

The physical characteristics of protons and physical as well as biological characteristics of carbon ions explain their potential benefits compared to photons, although these remain to be proven clinically. Potential benefits of particle therapy include:

- Fewer early and late side effects compared to photons.
  - This will depend on:
    - the nature of the photon therapy (IMRT, brachytherapy or SBRT, for example)
    - details of the proton treatment (intensity modulated or fixed beam, for example)
    - experience with the use of protons and carbon ions
    - the use of imaging verification of treatment set-up

- Reduction in risk of treatment induced benign or malignant tumours in tissues away from the tumour
- Reduction in the dose to surrounding normal tissues may allow:
  - an adequate dose to a tumour in close proximity to critical structures
  - dose escalation to a tumour to improve disease control
- Reduction in the number of required treatments
Passively scattered beam technology has been the traditional way of delivering proton therapy, typically using a fixed beam. Manual construction of compensators and collimators for each beam is required in an on-site workshop. The photon equivalent would be three-dimensional conformal therapy with manually constructed shielding blocks, although the construction of blocks for protons beams demands more engineering than for photons beams.

Newer proton delivery systems use pencil scanning technology which allows intensity modulated proton therapy (IMPT). Pencil beams have a width of around 3.5mm which means they are very sensitive to movement of the target, for example by respiration. Gantry’s are available for the delivery of protons and carbon ions. Proton beam units are becoming more affordable and commercially available. But carbon ion therapy remains more expensive than protons because a larger accelerator and more shielding are required. Carbon ions are normally produced by a synchrotron but cyclotrons capable of producing more than one particle type are being developed.

While upfront costs of both protons and carbon ions are significant, this is offset by low depreciation levels compared to linear accelerators. A carbon ion unit with a gantry is a very recent development, although robotic rotating couches can assist in increasing the use of less expensive straight beam lines. Technology in this area will almost certainly drive down costs over the next several years.
FACULTY OF RADIATION ONCOLOGY POSITION

It is the Faculty position that patients in Australia and New Zealand must have access to particle therapy. Although the proportion of cancer patients that may benefit from particle therapy on current evidence is small, there are clear dosimetric advantages with particle therapy for some patients, particularly for children.

To date, there is a paucity of high level evidence to support the clinical benefits of particle therapy compared to modern photon therapy techniques and technologies. Clinical outcome data is accumulating worldwide, and is anticipated to demonstrate fewer long term effects of particle treatment which may prove to balance the initial cost of the treatment. The favourable biological interaction of carbon ions with tumour and normal tissues may lead to hypofractionated schedules of treatment leading to greater treatment efficiency, and also benefit patients with poor prognosis tumours who are not suitable at present for referral overseas for treatment.

The Faculty supports investigation of establishing a particle therapy facility or facilities in Australia and/or New Zealand which network with cancer centres nationally and internationally, and treat patients according to agreed clinical protocols which incorporate long term follow up.

THE INTERNATIONAL CONTEXT

Worldwide, more than 100,000 patients have been treated with protons and 13,000 with carbon ions since 1954. The high capital cost of building a proton facility has limited the number of facilities. However, capital costs are reducing and single treatment room facilities occupying a small footprint can now be constructed. The Children’s Oncology Group of North America currently has 72 open trials, 15 involve radiation treatment, and nine permit the use of protons. In the United States in 2012, 10% of paediatric patients who underwent radiation treatment did so by protons. At the end of 2013 there were 17 proton facilities in the United States, 19 in Europe, 13 in Japan and 4 in China. There were eight carbon ion facilities and only two were outside Japan and China (Italy and Germany). More than 30 particle therapy centres, with a total of about 80 treatment rooms, were under construction worldwide. Half of these centres are in the United States and one-third in Asia.

The National Health Service in the United Kingdom has committed to two proton facilities in London and Manchester as well as at least one research facility in Oxford, Denmark to a national facility in Aarhus, and the Netherlands to a national facility in Amsterdam. These facilities will become operational over the next five years. The UK, Denmark and the Netherlands, like Australia and New Zealand, have a public healthcare system predominantly financed through general taxes. Each of these jurisdictions has identified the importance of integrating clinical care at hospital-based proton national facilities with clinical research and technological development in order to build the evidence base for protons.
THE EVIDENCE

As recently as 2012, a systematic review identified no published randomised trials comparing photon to proton or carbon ion treatment (mixed proton/photon and other ions were excluded) \[2\]. Evidence of proven benefits and better long term patient outcomes from protons or carbon ions remains limited and based on retrospective and a few prospective series. Mostly these report small numbers of patients with inadequate follow-up to determine the long term consequences of particle treatment. There are currently a number of phase I-III trials recruiting in both proton and carbon ion therapy (Table 1).

Currently, the strongest and the most appropriate evidence is based on comparative treatment plans using different modalities of photons, protons or carbon ions. Methods of delivering proton treatment are evolving in the same way that photon treatments are evolving. For example, intensity modulated proton therapy is now an option instead of three dimensional proton therapy \[11\]. IMRT, arc and helical therapy and SBRT are now available in many centres in Australia and New Zealand \[12\]. Together with better tumour delineation by MRI and PET-CT imaging, and ability to track tumours in moving organs, higher doses of of radiation therapy to smaller targets can be achieved with better sparing of organs at risk (OAR). The main advantage to proton therapy over currently available sophisticated photon treatments is likely to be the reduction in dose to normal tissue which is particularly relevant for children, and the ability to deliver a tumoricidal radiation dose adjacent to normal structure. The main advantage of carbon ions may be the ability to deliver a higher biological dose to the tumour (while maximally sparing normal tissue) as well as the opportunity for hypofractionation. Robust clinical outcome data linked to photon and particle treatment planning information is an international priority.

The Trans Tasman Radiation Oncology Group (TROG) established the Assessment of New Radiation Oncology Technology and Treatments (ANROTAT) project “to develop a generic research Framework that would support the rapid production of the appropriate evidence on safety, effectiveness and cost-effectiveness of new technology to allow its timely introduction” in Australia \[13\]. This Framework and protocol templates are the logical vehicle for building the evidence, including comparative cost-effectiveness, for particle therapy in Australia and New Zealand. It has already been used to examine intensity modulated radiation therapy and image guided radiation therapy \[14\].

The following sections summarise the key evidence for particle treatment based on patient groups and tumour types.

**PAEDIATRIC PATIENTS**

Paediatric cancers are the only cancers defined by age (as a surrogate for growth and development) rather than tumour site. Most jurisdictions include patients up to the age of 16 years, but the United Kingdom has revised this recently to include teenagers and young adults up to their 25th birthday. The enhanced long term consequences of treating immature organs and tissues, together with the overall greater chance of surviving to experience second malignancies compared to adults, make particle therapy an attractive option when curative radiation therapy is required.

Currently the use of heavy ions, for example carbon, is considered highly experimental for children. The long term toxicities of greatest impact are neuro-cognitive, neuro-endocrine, cardiac, growth, organ function (renal, hepatic and lung) and induction of second malignant neoplasms (SMN). The paediatric cancers most likely to benefit from proton therapy are those that are in close proximity to the critical structures and require radiation doses of more than 20Gy, namely central nervous system and eye tumours, head and neck tumours, lymphomas, Ewing sarcoma and rhabdomyosarcoma. Tumours associated with an inherent risk of SMN such as known or suspected carriers of a retinoblastoma gene or P53 gene mutation, or
patients with NF1 may also be better treated by protons than photons in order to reduce the volume of normal tissue exposed to low dose irradiation, and therefore potential risk of SMN. SMN do occur following proton treatment, although insufficient clinical data exist to determine whether this is at a significantly lower rate than for photon treatments [15]-[17].

**Craniospinal irradiation (CSI):** Medulloblastoma is the most common paediatric tumour for which CSI is indicated. Late effects are considerable when the dose is 36Gy or higher, with neuro-cognitive deficits, pituitary failure and spinal growth failure more apparent by adulthood the younger the child at irradiation. These effects cause the greatest impact on quality of life, and cannot be minimised by the use of protons. The radiation dose prescribed does not differ between proton and photon therapy. Severity of long term effects of CSI is less but still significant when the dose can be lowered to 23.4Gy in combination with chemotherapy. Medulloblastomas arise in the posterior fossa and additional (boost) radiation dose must be directed to the tumour bed to maximise local control and therefore cure. Compared to three-dimensional conformal radiation therapy, IMRT and fractionated stereotactic radiation therapy boost techniques can minimise the dose to organs at risk particularly the pituitary and cochlea, depending on the position of the tumour bed for the individual patient. For some patients the dose received by the supratentorial brain as a consequence of the posterior fossa boost may be reduced by the use of protons. Hearing can also be impacted by adjuvant chemotherapy drugs used for medulloblastoma treatment, not simply by radiation therapy. Whether the risk of ototoxicity is less with protons than photons remains unclear, but minimising dose is essential if hearing is to be preserved [18][19]. Pituitary radiation dose may be no lower when protons are used rather than photons [20]. The incidence of SMN of the lung, pancreas and breast may be lower by the use of protons rather than conventional radiation therapy modalities, but although predicted by modelling studies there is as yet no clinical data to support these modelling studies [21]. While several jurisdictions consider medulloblastoma a diagnosis for which proton treatment is indicated, protons are not the only ethical form of radiation therapy [22]. Delay to commencement of CSI in a child with medulloblastoma beyond four to six weeks from tumour resection can be detrimental to survival [23]. Current treatment protocols are determined by the results of lumbar puncture and molecular biology of the tumour so the investigation pathway is complex and necessarily long. Many children are not sufficiently recovered from cranial surgery to travel overseas for proton therapy in a timely manner.

**Craniopharyngioma:** Children with this benign tumour often present with significant morbidity even prior to any treatment due to the tumour’s proximity to vital structures such as the pituitary gland, hypothalamus, optic chiasm and Circle of Willis [24]. With expected 5 year survival of over 80% minimising long-term morbidity for these patients is important. There remains debate regarding the optimal treatment strategy for this tumour in children. Immediate rather than delayed post-operative radiation therapy for residual disease is favoured, particularly in children who are already post-pubertal or are already on pituitary hormone replacement treatment. At least two published planning studies indicate reduced organ at risk radiation dose with the use of protons compared to photons [25][26], although this will not always be the case depending on the size of the target volume [27]. There is currently no clear evidence that proton therapy will improve survival or reduce morbidity including neuro-cognitive function for children with craniopharyngioma. However, proton therapy has the potential to reduce radiation dose to the Circle of Willis which may reduce the risk of future cerebrovascular complications.

**Ependymoma:** There is strong evidence that post-operative radiation therapy improves survival in this tumour [28]. Children as young as 12 months with posterior fossa tumours are now offered this treatment. No global decline in learning was demonstrated in a prospective study investigating post-operative conformal radiation therapy in this tumour [29]. A currently recruiting Children’s Oncology Group (COG) study permits the use of protons, but does not mandate it. Around 10% of children who received radiation therapy while enrolled on a clinical trial of the COG in 2012 did so by proton rather than photon therapy [30]. MacDonald et al published the first report on clinical outcomes for children treated for ependymoma by protons
in 2013, concluding that “Outcomes for children treated by Proton Radiation Therapy (PRT) compare favourably with the literature” [31]. No long term data exist to demonstrate whether children have fewer morbidities and better quality of life when treated by protons rather than photons.

**Intracranial germ cell tumours:** These tumours require treatment to the whole ventricles, albeit it to modest doses. Given the large target volume, a large volume of supratentorial brain is necessarily irradiated. Planning studies demonstrate that proton therapy reduces the volume of normal brain irradiated compared to photon therapy. However, no clinical data exist to demonstrate whether this translates to clinical benefit.

**Glioma:** Most gliomas in children are low grade and chemotherapy is often used to avoid radiation therapy. A small number of children do require radiation therapy to control their tumour. No general statement can be made regarding whether protons result in fewer long term effects than photons; a comparative radiation treatment plan will always be needed. The radiation dose is the same whether protons or photons are used, so there will be no difference in local control rates.

**Neuroblastoma:** These tumours typically arise in the adrenal gland of children under the age of three years, and present as large abdominal masses. Radiation therapy to the post-chemotherapy, pre-surgical volume including adjacent para-aortic lymph nodes to doses ranging from 21Gy to 36Gy is recommended for some patients. The target volume is challenging as the radiation dose to a solitary remaining, liver, bowel, and vertebrae must respect tolerance of these structures. In particular, the whole vertebral body must be irradiated to achieve growth symmetry. For some patients a conventional two dimensional anterior and posterior field arrangement may achieve a more favourable radiation treatment plan that IMRT [32]. For other patients, particularly those for whom a higher dose of radiation therapy is prescribed, protons may be the only method of meeting dose constraints [33]. Children with neuroblastoma who are referred for radiation therapy have undergone very intensive treatment and are often in poor general health whilst undergoing radiation therapy. These children have more advanced disease, and survival rates typically remain less than 50% at five years.

**Rhabdomyosarcoma (RMS):** These tumours may arise anywhere in the body. Primary sites in the head and neck region, including the orbit and para-meningeal sites prove challenging due to the many critical organs (pituitary, temporal lobes of brain including hippocampus, lens, lacrimal gland, teeth, salivary glands, developing skull and facial bones). Radiation doses are at least 45Gy and there are significant long term effects in young children. Two publications have driven opinion that children with orbital or head and neck RMS should be treated by proton therapy [34][35]. Childs et al reported the outcomes of 17 children with para-meningeal RMS treated by proton therapy, with 10 surviving patients. Late effects of proton therapy included growth retardation (3 patients), endocrinopathies (2 patients), mild facial hypoplasia (7 patients), failure of permanent tooth eruption (3 patients) and chronic nasal congestion (2 patients). The incidence of late effects was reported to be lower than published photon therapy studies. With a median follow-up of five years and age at diagnosis of 3 - 4 years it is probable that this patient cohort had not reached puberty when treatment effects most commonly declare. Furthermore, the comparative studies involved patients treated by photons prior to the availability of current techniques. Yock et al treated seven children with orbital RMS by proton therapy. Protons were able to deliver less dose to the brain, pituitary, hypothalamus, temporal lobes and orbital structures compared to four-field photon plans. All patients developed mild or moderate orbital bony asymmetry. IMRT may have resulted in more favourable radiation doses to the same structures, albeit with a larger volume of tissue irradiated with low dose risking an increase in treatment related malignancy. These studies highlight the need for comparative radiation plans (photons versus protons) as the position of the tumour in relation to critical structures in an individual patient is the only method of determining which radiation modality will result in the more favourable radiation treatment plan.
**Para-spinal tumours and sarcomas:** The management of spinal and para-spinal tumours is no different in children and adolescents compared to adults. Osteosarcomas of the vertebrae are typically inoperable and of poor prognosis, requiring a high dose of radiation to gain local control. Ewing sarcomas of this area are seldom operable with adequate margins, with the combination of surgery and radiation therapy recommended. While more radiation sensitive than osteosarcoma, respecting radiation tolerances of OAR including kidneys, liver, lung and heart, is typically challenging, even with treatment protocols which aim to minimise radiation dose through tumour down-staging by initial chemotherapy. Proton treatment may provide better target volume coverage and better sparing of critical normal structures but this can only be determined by comparing radiation therapy plans (photons and protons) for the individual patient.

**BASE OF SKULL OR CERVICAL SPINE CHORDOMA AND CHONDROSARCOMA**

Adjuvant radiation therapy for chordomas and chondrosarcomas poses difficulties due to the relative radioresistance of these tumours and proximity to critical structures including the optic nerves and chiasm and brain stem. Photon based treatment of up to 60Gy is associated with a 5 year progression free survival of less than 25% [36], whilst associated with risk to brainstem and cranial nerves at this dose [37]. A recent global consensus position paper regarding chordoma management recommends radiation therapy as post-surgical adjuvant treatment or following biopsy in inoperable patients, with doses of at least 74Gy using conventional fractionation (recommendation A) [38]. Proton beam irradiation allows dose to be escalated due to its sharp dose fall-off between tumour and critical organs. Five year local control rates of up to 81% for chordomas and 94% for chondrosarcomas of the skull base, with freedom from grade 3 or 4 toxicity of 94% at 5 years have been reported with proton therapy [39]. Two systematic reviews by Amichetti et al support this finding [40][41]. Highly conformal photon treatments (IMRT and stereotactic radiation therapy) allow dose escalation for some patients, particularly those with smaller tumours. No data comparing photon treatment to proton or carbon ion therapy exist. Patients with these tumours should be managed by an experienced multidisciplinary team.

**BRAIN TUMOURS (ADULTS)**

**Pituitary adenoma and gliomas:** The potential benefit for proton treatment of these tumours in adults is not as great as for children due to the maturity of the adult brain. The desire to increase radiation dose for more radiation resistant high grade gliomas has driven clinical trial interest in the use of particle therapy for these tumours, although dose escalation in glioblastoma multiforme has not shown a survival benefit [42][43]. The poor prognosis of high grade gliomas makes referral overseas for particle therapy an impractical proposition at present. The use of carbon therapy for high grade tumours is of research interest.

**NASAL CAVITY AND PARANASAL SINUS TUMOURS**

For head and neck tumours near the skull base and other critical structures, the delivery of radical doses can be challenging. Waldron et al reported that 41% of paranasal sinus patients suffered from blindness following conventional radiation therapy due to retinopathy or optic neuropathy in their retrospective series of 29 patients treated between 1976 and 1994 although current technologies make these risks rare [44]. High dose proton-photon combination therapy for locally advanced sinonasal cancer has been reported to be associated with a 5 year local control rate of 95%, 82% and 87% for complete resection, partial resection and biopsy only respectively [45]. A systematic review showed the overall survival to be significantly higher at 5 years for particle therapy than for photon therapy, whilst a subgroup analysis comparing particle therapy with intensity modulated radiation therapy showed a significantly higher disease free survival at 5 years and locoregional control [46].
**OCULAR TUMOURS (ADULTS)**

These are rare tumours which include choroidal haemangioma, uveal and conjunctival melanomas, metastases to the retina or whole eye, and retinoblastoma in infants and children. Photon radiation techniques include brachytherapy using plaques of different radio-isotopes (Ru-106, I-125), fractionated stereotactic radiation therapy and IMRT. The treatment volumes are typically very small, and close to critical structures such as the optic nerves and optic chiasm. All ocular tumours should be treated in dedicated centres by a multi-disciplinary team. More than 2,500 patients have undergone proton treatment for ocular tumours at Clatterbridge in the United Kingdom, and more than 5,000 at Nice in France. Proton therapy gained its favourable reputation in the treatment of ocular melanomas in particular, in the era prior to the availability of fractionated stereotactic radiation therapy. No data exist to determine the best radiation therapy option for an individual patient with ocular melanoma. Tumour control rates are very high irrespective of radiation modality used. One planning study comparing protons and photons for choroidal melanomas demonstrated no radiation dose to the contralateral eye with protons but more inhomogeneity within the Planning Target Volume, the significance of which is not known [47].

**GASTROINTESTINAL MALIGNANCIES (ADULTS)**

**Oesophagus:** Particle therapy has the potential to reduce lung volume irradiated. However, comparative studies have shown conflicting results on pulmonary toxicity. Evidence is inadequate to compare benefits or harms of particle therapy [48][49].

**Liver:** Proton treatment, carbon ions and stereotactic body radiation therapy are competing modalities for the treatment of hepatocellular cancer. There are a small number of prospective comparative studies in hepatocellular cancer demonstrating the potential benefit of particle therapy in both toxicity profile and tumour control [50]. A large retrospective review by Komatsu et al comparing proton and carbon ion therapy for liver malignancies showed no difference in outcome [51].

**Pancreas:** Particle therapy has the potential to reduce liver, kidney and small bowel radiation dose. A series of Japanese studies has evaluated the role of carbon ion therapy, particularly for resectable or locally advanced pancreatic cancer using progressively shorter courses of treatment, and excellent survival [52]. Information regarding toxicity from particle therapy is conflicting [53][54].

**PARA-SPINAL TUMOURS AND SARCOMAS (ADULTS)**

These are usually sarcomas and require high doses of radiation therapy for local control. The situation is similar to that for base of skull chondrosarcomas and chordomas. Most of the clinical experience has been with scattered proton beams at Massachusetts General Hospital (MGH) and with spot scanning at Paul Scherer Institute.

Several early studies showed improved dosimetry compared to standard radiation therapy. A more recent study shows that the conformity in the high dose region is similar for IMRT and IMPT but the lower dose to OAR’s allows safe dose escalation from 77Gy with IMRT up to 93 CGE with scanned protons [55]. The dose to most OARs is reduced by a factor varying from 1.3 to 25. Given the importance of dose in reducing local failure in what are often radioresistant tumours, this might be expected to translate into a clinical benefit. There are no randomised studies to confirm this benefit, but a Phase 2 study from MGH using 77 CGE scattered protons shows encouraging results with 5-year actuarial local control, recurrence-free survival, and overall survival being 78%, 63%, and 87% respectively [56].

Proton therapy should be considered in cases where an adequate dose cannot be delivered using photons without unacceptable dose to organs at risk. The presence of large metallic implants will perturb proton dose distributions more than for photons and may be a relative contraindication to proton therapy.
MALIGNANT LYMPHOMA, BREAST CANCER, LUNG CANCER (ADULTS)
Radiation planning studies and other reports are emerging in the literature regarding the use of proton treatment for these tumours, but without adequate follow-up at this stage to consider proton treatment a standard of care. A meta-analysis published in 2010 compared particle beam therapy with SBRT and found no significant differences in survival between SBRT and particle beam treatments in 74 patients with inoperable stage I Non-small cell lung cancer (NSCLC).

PROSTATE CANCER (ADULTS)
There are many options for the radiation treatment of localised prostate cancer with few comparative studies to guide choice. Most, but not all, studies have shown an advantage to dose escalation at the cost of increased toxicity. More precise treatment is hoped to reduce the toxicity at higher doses and this is particularly important for more advanced local disease. Proton dose distributions are similar to IMRT in the high dose region but have reduced areas of medium and low dose. These dosimetric advantages of protons have not been shown to affect clinical outcome.

Proton therapy has been shown to be an effective treatment for early stage prostate cancer with results comparable to other modalities such as surgery and brachytherapy. It may have advantages over other options in more advanced disease but this has not been proven in randomised trials. Randomised and registry studies are in progress to provide more evidence, but at this stage, there is no indication the proton therapy provides any local control, survival or quality of life benefit compared to conventional photon therapy options.
WHICH PATIENTS SHOULD BE TREATED BY PARTICLE THERAPY?

The fact that a patient has a diagnosis for which particle therapy is a recognised indication by some jurisdictions does not mean that particle therapy will necessarily or always be the preferred option. Many other factors must be taken into consideration, and these are particularly relevant when the patient must travel away from home to receive treatment. Important considerations are:

- Performance status and physical ability to travel
- Views of the patient, parent and family
- Timeliness of the start of the treatment
- Ability to integrate other treatments such as chemotherapy, without compromise
- Site of the tumour and its proximity to critical dose limiting structures
- Patient age
- Tumour stage and pathology
- The probability that overall survival will reach or exceed five years

The pros and cons of proton treatment compared with conventional radiation therapy and/or IMRT must be discussed in each case, and this almost always requires the generation of comparison plans. Individual cases need to be considered as it is not possible to consider all diagnoses and all situations generically. Re-irradiation of recurrent tumours, such as non-high grade gliomas is one example.

The Dutch used the Normal Tissue Complication Probability (NTCP) model and planning comparative studies to identify which tumours and patients will benefit from protons by the reduction of radiation dose to critical organs and therefore side effects both acutely and in the longer term[10]. Three groups of patients were identified – those who should receive protons and be enrolled on an observational study, those who should be enrolled on randomised trials of proton vs. photon treatment, and those who should receive photons (Figure 3). Standard indications for proton treatment (for which protons are an accepted form of treatment but not necessarily appropriate for all patients with these tumours) were identified as:

- Intraocular melanoma and other rare ocular conditions (choroidal haemangioma)
- Other intracranial and spinal / paraspinal tumours
- Paediatric tumours
  - Skull base tumours
  - Soft tissue sarcoma
  - Head and neck tumours, including craniopharyngioma and orbital rhabdomyosarcoma
  - Low grade gliomas
  - Meningioma
  - Other brain tumours – medulloblastoma, ependymoma
  - Neuroblastoma

The ASTRO Model Policy on Proton Beam Therapy defines two groups of tumours[62]. Based on medical necessity and published clinical data, Group 1 disease sites are those that frequently support the use of protons. Group 2 tumours are those for which clinical evidence needs to be developed and comparative effectiveness analyses performed. Group 1 includes:

- Ocular tumours
- Tumours that approach or are located at the base of skull
- Primary or metastatic tumours of the spine where spinal cord tolerance may be exceeded with conventional treatment
- Primary hepatocellular cancer treated by hypo-fractionation
- Paediatric tumours treated with curative intent

The Alberta Health Services in Canada, the National Health Service in the United Kingdom and Denmark have developed criteria for referral of patients for proton therapy abroad[63]. These are summarised in Table 2.
WHO TO REFER NOW

Combining the evidence, recommendations and referral guidelines of other jurisdictions, Table 3 categorises patients into three groups of Australian and New Zealand patients:

• those who should be considered for referral overseas for proton or carbon ion therapy now (vide infra),
• those who should be treated by photons now, and
• those who could be considered for particle therapy in clinical studies in the future.

There may be other individual patients for whom particle therapy may offer an advantage, especially if re-treatment is required. It is acknowledged that by the time a particle therapy facility is operational in Australia or New Zealand, the evidence base to inform decisions regarding who to treat with protons or carbon ions will be stronger.

REFERRAL PROCESS

A Particle Therapy Referral Committee will be established and convene by teleconference and email as required, under the direction of the RANZCR Secretariat. A radiation oncologist will chair the Committee.

Before a referral is made, the case must have been considered by a multi-disciplinary team (MDT) whenever possible and a written record of the MDT opinion provided to the referral Committee. Referrals will only be accepted from a radiation oncologist who then remains the primary contact with the family and local MDT. The referring radiation oncologist should liaise carefully with the family to manage expectations in the event that referral is not supported. It is imperative that patients and their families as well as their treating team understand that consideration for referral overseas for particle treatment does not mean that referral will be approved. All referrals to the Committee should be made prior to the patient travelling to a particle centre for treatment. No cases will be considered retrospectively.

A completed referral form (to be made available on the RANZCR website), all diagnostic imaging, operation and pathology reports are necessary for the Committee to review the case. A planning CT scan with photon plan should be provided if at all possible. The Committee will comprise a multi-disciplinary team including medical physicist, a radiation therapist, a medical or paediatric oncologist, and a suitably specialised surgeon, pathologist and radiologist when appropriate. The Chair will provide a written reply on behalf of the Committee. The Committee will aim to meet a target of providing a written assessment to the referrer within 10 working days of receipt of referral. The Committee expects this information will be available to the Australian Medical Treatment Overseas Programme to support a funding application for treatment overseas. The Committee may suggest which particle therapy centre the patient might be referred to, and a contact person at that centre.

THE CLINICAL CARE PATHWAY

<table>
<thead>
<tr>
<th>POTENTIAL CANDIDATE FOR PARTICLE THERAPY</th>
<th>PARTICLE THERAPY REFERRAL COMMITTEE</th>
<th>APPLY FOR FUNDING IF APPROVED</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Local MDT must consider the case prior to referral</td>
<td>• RANZCR convenes teleconference</td>
<td>• Written report from Particle Therapy Referral Committee sent to referrer</td>
</tr>
<tr>
<td>• Referring radiation oncologist contacts RANZCR Secretariat and forwards relevant de-identified patient information, including planning CT scan and photon plan</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
THE PARTICLE THERAPY REFERRAL COMMITTEE

The Committee will comprise:

- A radiation oncologist appointed by the RANZCR Faculty of Radiation Oncology Council to Chair the Committee
- At least one, and no more than two other radiation oncologists, appointed by the Faculty from a panel of radiation oncologists.
- At least one radiation oncologist, other than the treating radiation oncologist, should practice in New Zealand at the time of appointment to the Committee if the patient is a New Zealand citizen
- The radiation oncologist caring for the patient may attend the Committee meeting to provide further background if so desired, but will not be present for the discussion which results in the decision of the Committee
- When the patient is a child (<16 years), either the Chair or a radiation oncologist un-involved with the patient should have experience of prescribing radiation treatment for children within the last five years
- A medical or paediatric oncologist, as appropriate
- A medical physicist appointed by the Australasian College of Physical Scientists and Engineers in Medicine (ACPSEM)
- A radiation therapist appointed by the Australian Institute of Radiography (AIR)
- A surgeon relevant to the case(s) to be considered, appointed by the relevant specialist College

PARTICLE FACILITIES IN AUSTRALIA AND NEW ZEALAND

The small population of Australia and New Zealand spread over a large geographical area is a challenge to making an expensive resource available to all. As the cost of establishing and running a proton facility decreases, it is likely more than one proton centre will become available in Australasia, particularly single room commercial solutions, but not likely that there will be more than one heavy ion facility. In order to develop the evidence to support the expansion of indications for protons and heavier ions for treatment, it is imperative that facilities work as a network nationally and internationally to treat and follow up patients according to protocols agreed by Australasian clinical trials groups including TROG, Cooperative Trials Group for Neuro-Oncology (COGNO), Australian and New Zealand Children’s Haematology/Oncology Group (ANZCHOG) and Australasian Gastro-Intestinal Trials Group (AGIT).

Furthermore, additional training in particle therapy will be required for the radiation oncologists, medical physicists and radiation therapists through formal credentialing processes agreed by the relevant Australasian Colleges.

ACKNOWLEDGEMENT

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No Funding or conflicts of interest are declared.
TABLE 1: CURRENTLY RECRUITING TRIALS IN PROTON AND CARBON ION THERAPY

*Final development phase (Professor BD Minsky, MD Anderson Cancer Center. Personal communication 22 September 2015)

<table>
<thead>
<tr>
<th>TRIAL</th>
<th>SPONSOR</th>
<th>TITLE</th>
<th>STUDY PHASE</th>
<th>PRIMARY OUTCOME MEASURE</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT01586767</td>
<td>Massachusetts General Hospital</td>
<td>Intensity modulated or proton radiation therapy for sinonosal malignancy</td>
<td>Phase II</td>
<td>Local control at 2 years</td>
</tr>
<tr>
<td>NCT01893307</td>
<td>M.D. Anderson Cancer Center</td>
<td>Intensity modulated proton beam therapy (IMPT) versus intensity modulated photon therapy (IMRT) in head and neck cancer</td>
<td>Phase III</td>
<td>Rates and severity of late grade 3-5 toxicity</td>
</tr>
<tr>
<td>NCT0177048</td>
<td>Proton Collaboration Group</td>
<td>Phase I/II study of hypofractionated proton therapy for Stage II-III non-small cell lung cancer</td>
<td>Phase I/II</td>
<td>Maximum tolerated dose, number of patients surviving one year</td>
</tr>
<tr>
<td>NCT01076231</td>
<td>Abramson Cancer Center, University of Pennsylvania</td>
<td>Proton beam radiation therapy and chemotherapy in treating patients with Stage III non-small cell lung cancer that can be removed by surgery</td>
<td>Phase II</td>
<td>Feasibility, radiation planning study</td>
</tr>
<tr>
<td>NCT01993810</td>
<td>RTOG</td>
<td>Comparing photon therapy to proton therapy for treating patients with lung cancer</td>
<td>Phase III</td>
<td>Overall survival</td>
</tr>
<tr>
<td>NCT01182779</td>
<td>Heidelberg University Hospital</td>
<td>Trial of proton versus carbon ion radiation therapy in patients with chordoma of skull base (HIT-1)</td>
<td>Phase III</td>
<td>Local progression free survival</td>
</tr>
<tr>
<td>NCT01182753</td>
<td>Heidelberg University Hospital</td>
<td>Trial of proton versus carbon ion radiation therapy in patients with low and intermediate grade chondrosarcoma of the skull base</td>
<td>Phase III</td>
<td>Local progression free survival</td>
</tr>
<tr>
<td>NCT01963429</td>
<td>National Cancer Centre, Korea</td>
<td>Comparison between radiofrequency ablation and hypofractionated proton beam radiation for recurrent / residual hepatocellular carcinoma</td>
<td>Phase III</td>
<td>Local progression free survival</td>
</tr>
<tr>
<td>NCT01492972</td>
<td>Proton Collaboration Group</td>
<td>Hypofractionated proton radiation therapy with or without androgen suppression for intermediate risk prostate cancer</td>
<td>Phase III</td>
<td>Morbidity outcomes</td>
</tr>
<tr>
<td>NCT01230866</td>
<td>Proton Collaboration group</td>
<td>Study of hypo-fractionated proton radiation for low risk prostate cancer</td>
<td>Phase III</td>
<td>Freedom from failure</td>
</tr>
<tr>
<td>NCT01230866</td>
<td>Proton Collaboration Group</td>
<td>Proton beam therapy (PBT) versus intensity modulated radiation therapy (IMRT) trial in esophageal cancer</td>
<td>Phase III</td>
<td>Progression free survival, total toxicity burden</td>
</tr>
<tr>
<td>NCT01617161</td>
<td>Massachusetts General Hospital</td>
<td>Proton therapy versus intensity modulated radiation therapy for low or intermediate risk prostate cancer (PARTIQoL)</td>
<td>Phase III</td>
<td>Efficacy, reduction in EPIC bowel scores</td>
</tr>
<tr>
<td>NCT01683422</td>
<td>Loma Linda University</td>
<td>Chemotherapy plus proton-chemotherapy for locally advanced pancreatic cancer</td>
<td>Phase II</td>
<td>One year survival</td>
</tr>
<tr>
<td>NCT01220752</td>
<td>Heidelberg University Hospital</td>
<td>Treatment of malignant sinonasal tumours with intensity modulated radiotherapy and carbon ion boost</td>
<td>Phase II</td>
<td>Mucositis grade 3</td>
</tr>
<tr>
<td>NCT</td>
<td>Institution</td>
<td>Treatment Description</td>
<td>Phase</td>
<td>Primary Outcome</td>
</tr>
<tr>
<td>-----</td>
<td>-------------</td>
<td>------------------------</td>
<td>-------</td>
<td>----------------</td>
</tr>
<tr>
<td>NCT01811394</td>
<td>Heidelberg University Hospital</td>
<td>Ion irradiation of sacrococcygeal chordoma</td>
<td>Phase I</td>
<td>Safety and feasibility</td>
</tr>
<tr>
<td>NCT01166321</td>
<td>Heidelberg University Hospital</td>
<td>Carbon ion radiotherapy for atypical meningioma (MARCIE) Recruitment status unknown</td>
<td>Phase II</td>
<td>Progression free survival</td>
</tr>
<tr>
<td>NCT01167374</td>
<td>Heidelberg University Hospital</td>
<td>Carbon ion radiotherapy for hepatocellular carcinoma (PROMETHEUS-01) Recruitment status unknown</td>
<td>Phase I</td>
<td>Overall survival</td>
</tr>
<tr>
<td>NCT01166308</td>
<td>Heidelberg University Hospital</td>
<td>Carbon ion radiotherapy for recurrent gliomas (CINDERELLA). Recruitment status unknown</td>
<td>Phase II/III</td>
<td>Overall survival</td>
</tr>
<tr>
<td>NCT01528683</td>
<td>Heidelberg University Hospital</td>
<td>Phase III trial evaluating carbon ion radiotherapy for the treatment of recurrent rectal cancer (PANDORA)</td>
<td>Phase III</td>
<td>Safety and efficacy</td>
</tr>
<tr>
<td>NCT01192087</td>
<td>Heidelberg University Hospital</td>
<td>Adenoid cystic carcinoma, Erbitux, and particle therapy</td>
<td>Phase III</td>
<td>Acute adverse toxicity</td>
</tr>
<tr>
<td>NCT02242916</td>
<td>Maastricht Radiation Oncology</td>
<td>State of the art photon therapy versus particle therapy for recurrent head and neck tumours: a planning study</td>
<td>Observational</td>
<td>Radiation exposure for organs at risk</td>
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<tr>
<td>NCT01758445</td>
<td>Proton Collaboration Group</td>
<td>Proton radiation for Stage II/III breast cancer</td>
<td>Phase II</td>
<td>Rates of acute and late toxicity</td>
</tr>
<tr>
<td>NCT02172846</td>
<td>Washington University School of Medicine</td>
<td>Hypofractionated proton beam radiation therapy, paclitaxel, and carboplatin in treating patients with Stage II-III non-small cell lung cancer</td>
<td>Phase I</td>
<td>Maximum tolerated dose</td>
</tr>
<tr>
<td>NCT01629498</td>
<td>MD Anderson Hospital</td>
<td>Intensity modulated scanning beam proton therapy (IMPT) with simultaneous integrated boost (lung cancer)</td>
<td>Phase I/II</td>
<td>Maximum tolerated dose</td>
</tr>
<tr>
<td>NCT01684904</td>
<td>Loma Linda University</td>
<td>Proton therapy in treating liver metastases</td>
<td>Phase II</td>
<td>Safety and tolerability, local control</td>
</tr>
<tr>
<td>NCT01697371</td>
<td>Loma Linda University</td>
<td>Proton therapy for esophageal cancer</td>
<td>Phase II</td>
<td>Overall survival</td>
</tr>
<tr>
<td>Final development phase; MD Anderson and Massachusetts General Hospitals*</td>
<td>RTOG / NRG</td>
<td>Low grade glioma</td>
<td>Phase II/III</td>
<td>Cognitive function, patient reported outcomes</td>
</tr>
<tr>
<td>Final development phase; MD Anderson and Massachusetts General Hospitals*</td>
<td>RTOG / NRG</td>
<td>Oesophagus</td>
<td>Phase III</td>
<td>Grade 3+ toxicity, patient reported outcomes, progression free survival</td>
</tr>
<tr>
<td>Final development phase; MD Anderson and Massachusetts General Hospitals</td>
<td>RTOG / NRG</td>
<td>Oropharynx</td>
<td>Phase III</td>
<td>Grade 3+ toxicity</td>
</tr>
<tr>
<td>Final development phase; MD Anderson and Massachusetts General Hospitals*</td>
<td>RTOG / NRG</td>
<td>Hepatocellular</td>
<td>Phase II</td>
<td>2-year local control</td>
</tr>
<tr>
<td>Final development phase; MD Anderson and Massachusetts General Hospitals*</td>
<td>RTOG / NRG</td>
<td>Nasopharynx</td>
<td>Phase III</td>
<td>Patient reported outcomes</td>
</tr>
<tr>
<td>Condition</td>
<td>Danish (9)</td>
<td>UK NHS</td>
<td>Alberta (60)</td>
<td></td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>------------</td>
<td>--------</td>
<td>--------------</td>
<td></td>
</tr>
<tr>
<td>Chordoma base of skull / spinal</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chondrosarcoma base of skull</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spinal / paraspinal bone and soft tissue sarcomas (non-Ewing)</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intraocular melanoma</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intradural arterio-venous malformation</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pituitary adenoma</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medulloblastoma</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benign meningioma</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Craniopharyngioma</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low grade glioma</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphoma (&lt;30 years of age)</td>
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<td></td>
<td></td>
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<tr>
<td>Neurorsanomas</td>
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<td></td>
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<tr>
<td>Sarcomas</td>
<td>√</td>
<td>Spinal and para-spinal</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>Paranasal sinus / nasal cavity tumours</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Re-irradiation</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paediatric</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>up to age 16 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Includes teenage and young adult, up to 25th birthday</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>up to age 16 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chordoma base of skull / spinal</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chondrosarcoma base of skull</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intraocular melanoma</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spinal / paraspinal ‘adult type’ bone and soft tissue sarcomas</td>
<td>√</td>
<td></td>
<td></td>
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<tr>
<td>Medulloblastoma</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primitive neuroectodermal tumours</td>
<td>√</td>
<td></td>
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<td>Rhabdomyosarcoma</td>
<td>√</td>
<td>√ up to age 10 years (not extremity primaries)</td>
<td>√</td>
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<tr>
<td>Ependymoma</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ewing sarcoma</td>
<td>√</td>
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<tr>
<td>Retinoblastoma</td>
<td>√</td>
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</tr>
<tr>
<td>Pelvic sarcoma</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Optic pathway and other selected low grade glioma</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Craniopharyngioma</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pineal parenchymal tumours (not pineoblastoma)</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphoma</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intracranial germinoma / germ cell tumour</td>
<td>√</td>
<td>√ (non-germinomas treated by focal RT)</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>Nasopharyngeal carcinoma</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intracranial arterio-venous malformation</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Esthesioneuroblastoma</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nephroblastoma</td>
<td>√</td>
<td></td>
<td></td>
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<tr>
<td>Children with NF1 and any other cancer predisposition syndrome requiring RT for any of the above indications</td>
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<td></td>
<td></td>
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</tbody>
</table>
TABLE 3: EVIDENCE

<table>
<thead>
<tr>
<th>Tumour type</th>
<th>Target population</th>
<th>Particle treatment currently used abroad</th>
<th>Treatment options</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chordoma / chondrosarcoma base of skull or spine</td>
<td>Paediatric Adult</td>
<td>Yes</td>
<td>IMRT, stereotactic techniques</td>
<td></td>
</tr>
<tr>
<td>Intra-ocular melanoma</td>
<td>Paediatric Adult</td>
<td>Yes</td>
<td>IMRT, stereotactic techniques</td>
<td></td>
</tr>
<tr>
<td>Medulloblastoma</td>
<td>Paediatric</td>
<td>Yes</td>
<td>IMRT, photon/electron spinal fields</td>
<td></td>
</tr>
<tr>
<td>Ependymoma</td>
<td>Paediatric</td>
<td>Yes</td>
<td>IMRT, stereotactic techniques</td>
<td></td>
</tr>
<tr>
<td>Craniopharyngioma</td>
<td>Paediatric</td>
<td>Yes</td>
<td>IMRT, stereotactic techniques</td>
<td></td>
</tr>
<tr>
<td>Low grade gliomas, including optic pathway</td>
<td>Paediatric</td>
<td>Yes</td>
<td>IMRT, stereotactic techniques</td>
<td></td>
</tr>
<tr>
<td>Intracranial germ cell tumour</td>
<td>Paediatric</td>
<td>Yes</td>
<td>IMRT</td>
<td></td>
</tr>
<tr>
<td>Ewing sarcoma</td>
<td>Paediatric Adult</td>
<td>Yes</td>
<td>IMRT</td>
<td></td>
</tr>
<tr>
<td>Spinal / paraspinal bone and soft tissue sarcoma (non-Ewing)</td>
<td>Paediatric Adult</td>
<td>Yes</td>
<td>IMRT</td>
<td></td>
</tr>
<tr>
<td>Rhabdomyosarcoma: orbit, parameningeal/ head and neck, pelvis</td>
<td>Paediatric</td>
<td>Yes</td>
<td>IMRT</td>
<td></td>
</tr>
<tr>
<td>Retinoblastoma</td>
<td>Paediatric</td>
<td>Yes</td>
<td>IMRT, stereotactic techniques</td>
<td></td>
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<tr>
<td>Hepatocellular cancer</td>
<td>Adult</td>
<td>Yes, both protons and carbons ions</td>
<td>Stereotactic techniques</td>
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<tr>
<td>Oesophageal cancer</td>
<td>Adult</td>
<td>Yes</td>
<td>IMRT, 3D conformal</td>
<td></td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>Adult</td>
<td>Yes, both protons and carbon ions</td>
<td>IMRT, 3D conformal</td>
<td></td>
</tr>
<tr>
<td>Lymphoma</td>
<td>Paediatric</td>
<td>Yes, photons</td>
<td>IMRT, 3D conformal</td>
<td></td>
</tr>
<tr>
<td>Re-irradiation</td>
<td>Paediatric Adult</td>
<td>Yes, both protons and carbon ions</td>
<td>IMRT, 3D conformal, stereotactic techniques, brachytherapy</td>
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<tr>
<td>Prostate cancer</td>
<td>Adult</td>
<td>Yes</td>
<td>IMRT, 3D conformal, brachytherapy</td>
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</tr>
<tr>
<td>Lung</td>
<td>Adult</td>
<td>Yes</td>
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<td></td>
</tr>
<tr>
<td>Breast</td>
<td>Adult</td>
<td>Yes</td>
<td>IMRT, 3D conformal, stereotactic techniques</td>
<td></td>
</tr>
</tbody>
</table>

May be suitable for particle therapy. Review by the Particle Therapy Referral Committee is an option
May become suitable for particle therapy in future
Treat with photons
REFERENCES


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FIGURE 1 (FROM REFERENCE 64)

![Graph showing dose distribution for different beam types and a target depth comparison](image)

FIGURE 2 (FROM REFERENCE 6)

![Chart showing patients treated with protons and C-ions in North America, Asia, and Europe](image)

FIGURE 3 (FROM REFERENCE 10)

![Diagram illustrating the comparison of treatment planning with photons and protons](image)