Particle Therapy Tumour Outcomes: An Updated Systematic Review

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Abstract

Particle therapy (PT) offers the potential for reduced normal tissue damage as well as escalation of target dose, thereby enhancing the therapeutic ratio in radiation therapy. Reflecting the building momentum of PT use worldwide, construction has recently commenced for The Australian Bragg Centre for Proton Therapy and Research in Adelaide - the first PT centre in Australia. This systematic review aims to update the clinical evidence base for PT, both proton beam and carbon ion therapy. The purpose is to inform clinical decision-making for referral of patients to PT centres in Australia as they become operational and overseas in the interim. Three major databases were searched by two independent researchers, and evidence quality was classified according to the National Health and Medical Research Council evidence hierarchy. One hundred and thirty six studies were included, two thirds related to proton beam therapy alone. PT at the very least provides equivalent tumour outcomes compared to photon controls with the possibility of improved control in the case of carbon ion therapy. There is suggestion of reduced morbidities in a range of tumour sites, supporting the predictions from dosimetric modelling and the wide international acceptance of PT for specific indications based on this. Though promising, this needs to be counterbalanced by the overall low quality of evidence found, with 90% of studies of level IV (case series) evidence. Prospective comparative clinical trials, supplemented by database derived outcome information, preferably conducted within international and national networks, are strongly recommended as PT is introduced into Australasia.

Five key words

Proton therapy, carbon ion therapy, particle therapy, hadron therapy, systematic review.

Main text

Introduction

Increasing the therapeutic ratio underpins all developments in radiation therapy (RT), specifically enhancing tumour control probability while minimising normal tissue damage. Owing to its physical properties, particle therapy (PT), including proton beam therapy (PBT) and carbon ion therapy (CIT) offers promise in achieving this objective¹. When compared to photon RT, PT delivers radiation dose at least as conformally to the target volume, but allows better sparing of nearby and more distant organs at risk, as well as allowing for dose escalation²⁻⁷.

As of the end of 2018, over 220,000 patients have been treated with PT worldwide⁸. Ninety-five PT centres (13 offering CIT alone or with PBT, the remainder PBT alone) are operational across Europe, Asia, the United States of America (USA) and Africa with another 66 centres under construction or in planning stages⁸. This includes the Australian Bragg Centre for Proton Therapy and Research (ABC) in Adelaide, for which construction is beginning at time of writing. With the increasing use of PT worldwide and the clear global need for collaboration to answer evidence gaps regarding PT application, Australia must be equipped at a networked national level to respond and contribute.

Radiation damages normal tissues and organs in a dose-dependent and volume-dependent way⁹, with even low doses of radiation increasing the probability of secondary malignancy and stroke¹⁰⁻¹². On the basis of comparative treatment planning studies, PBT could result in a two-thirds reduction of the integral radiation dose, as well as the mean and mid to low doses to critical structures compared with intensity modulated radiation therapy (IMRT) or other conformal photon-based techniques¹³. However, evidence of translation of theoretical benefits into clinically measurable benefits for patients through improved local control and survival as well as reduced toxicities is sparse¹⁴⁻¹⁶.

The aim of this systematic review is to update the clinical evidence base for PT. The purpose is to support clinical decision-making in Australia for referral of patients overseas now or to the ABC, or to other PT centres including the proposed National Particle Treatment and Research Centre with PBT and CIT proposed for the Westmead precinct in Sydney, as they become operational. To the best of our knowledge, no comprehensive systematic review on the clinical effectiveness of PBT and CIT across paediatric and adult tumour sites has been published since 2012. As our work was completing, a systematic review was published by Ofuya et al.¹⁷ which focused solely on proton studies from the point of view of assessing study methodologies.

Methods

The systematic review was conducted in accordance with the 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses' (PRISMA) statement¹⁸. An initial search of previously

published systematic reviews dating back to the year 2000 identified the 2012 review by De Ruyscher et al.¹⁹ as both thorough and relevant to our research aim and was used as a base from which to update. The review by De Ruyscher et al.¹⁹ covering the period 2006 to February 2011 was itself an update of an earlier systematic review conducted by Lodge et al.²⁰ covering the period from 1980's - 2006. Two search strategies were then employed to update this and were combined with summaries of the efficacy and toxicity outcomes from the De Ruyscher review.

Search Strategy I

Search Strategy I retrieved the clinical evidence for PT covering the period February 2011 to March 2019 (Table 1). Selection criteria were according to the Population, Intervention, Comparator and Outcome (PICO) framework (Table 2), with a more detailed breakdown in Appendix I. Studies must have reported a tumour outcome (e.g. local control [LC], overall survival [OS]); included at least 20 patients and have a minimum of two years median follow-up. Toxicity outcomes were desirable but not mandatory. Two researchers independently reviewed the first 1326 titles and abstracts for eligibility and resolved discrepancies by consensus. The principal researcher then reviewed the remaining full text studies and in cases of uncertainty, discussed these with a second researcher until consensus was reached. We excluded dosimetry, planning, simulation or in-silico studies or studies which involved comparisons of treatment planning algorithms or modelled simulations of outcomes. Studies were included only if actual patient outcomes were measured. This approach is in line with previous systematic reviews of PT^{14, 19}.

Search Strategy II

Search Strategy II covered the period from 2006 to February 2011, repeating the search conducted by De Ruyscher et al.¹⁹ but modified to capture any studies that assessed PT in combination with photon therapy which De Ruyscher et al. chose to exclude for their review. The scope of the present review (i.e. Search Strategy I) included all treatments involving PT.

Grading level of evidence

Evidence quality was classified according to the National Health and Medical Research Council (NHMRC) evidence hierarchy²¹. Observational case series whether retrospective or prospective were graded as level IV evidence, comparative cohort studies whether with concurrent or non-concurrent controls were considered level III and a randomised controlled trial (RCT) as level II. A systematic review was graded according to the cumulative strength of the studies it analysed. The number of RCTs within each systematic review was also reported.

Outcome measures

OS and progression-free survival were chosen as the outcome measures as they are most likely to be analysed by similar methods across all studies. On the other hand, the method of reporting LC rates

varies, making comparison between studies unreliable. LC rates as stated for each study are recorded in the Appendices but largely excluded from the body of the text.

Results

Search Strategy I

Search Strategy I identified 1606 potentially relevant studies, of which 133 were included in the current review (Figure 1). The search results for Search Strategy I presented by indication and PT type are shown in Table 3, with specific mention of included studies examining skull base tumours and those reporting on re-irradiation. Tables 4a-c present the types of studies identified and the strength of evidence for the included studies for PBT, CIT and mixed therapy, respectively. Patients in the mixed therapy group were treated in a facility where both treatment options were available and reports include outcomes by both forms of PT. The vast majority of studies (89%, 92% and 89% of PBT, CIT and mixed studies respectively) presented Level IV evidence and were mostly conducted retrospectively. There were only two RCTs of level II evidence found eligible for inclusion^{22, 23}, one of which compared PBT to IMRT²³. The other compared PBT to transarterial chemoembolization (TACE)²².

The reference list of the Lodge et al.²⁰ and De Ruyscher et al.¹⁹ systematic reviews identified that only four of the combined 106 studies were RCTs²⁴⁻²⁷, with the rest mostly level IV evidence through retrospective studies, case series or prospective cohort studies. The De Ruyscher et al. review was one of 17 systematic reviews identified totalling 538 studies collectively, of which 14 (2.6%) were of RCT design, dating back to 1988. Once repeated studies between systematic reviews were removed, nine RCTs remained. Only one of these compared PT to photon therapy in the context of prostate cancer dose escalation²⁵ using older (passive scattering) treatment delivery techniques and under-developed image guidance, the remaining were pure dose fractionation comparison studies²⁸⁻³¹, examined Helium ion therapy^{24, 26} or compared PT to another form of treatment such as TACE²² or transpupillary thermotherapy³².

Search Strategy II

Search Strategy II identified 2001 references, of which 443 were duplicates, and a further 1956 were excluded based on titles and abstracts. The remaining 45 full text references were reviewed, 42 of which were excluded, leaving three studies examining combination photon/proton therapy³³⁻³⁵ initially omitted in the De Ruyscher et al. study (Appendix IX).

Results according to tumour sites

A summary of the key findings of Search Strategy I according to each subsite is presented. Appendices II-IX provide comprehensive information.

Head and Neck (H&N) (Appendix II)

The largest group of the 133 studies involved H&N tumours (n=27 studies; PBT=11, CIT=12, mixed therapy=4). Eleven (41%) of the studies were for tumours of the sinonasal or olfactory region where proximity to critical structures translates to functionally morbid treatment effects. Another 10 (37%) related to treatment of historically radioresistant tumours such as adenoid cystic carcinoma or malignant mucosal melanoma. Only one comparative study (level III NHMRC evidence) was found, a retrospective cohort study assessing PBT and IMRT for oropharyngeal cancer, demonstrating no statistically significant difference in 3-year OS between PBT and IMRT (94% vs 89.3% respectively)³⁶.

All other H&N studies were of level IV evidence, mainly retrospective case series, overall demonstrating an equivalent OS compared to historical photon controls of equivalent patients, and acceptable levels of toxicities according to institution, though many with a limited follow-up period.

De Ruysscher Findings

Six studies were included for H&N cancers including one prospective phase II trial investigating CIT in malignant mucosal melanoma demonstrating 5-year OS for those treated with CIT to be significantly higher as compared to conventional radiotherapy (44% versus 25% respectively, $p=0.007$)³⁷.

Paediatric tumours (Appendix III)

Twenty-five studies (PBT=24, CIT=0, mixed therapy=1) met inclusion criteria. The main tumour subsites were sarcoma (n=8 studies), ependymoma (n=7), medulloblastoma (n=2), and other central nervous system (CNS) tumours (n=3). The majority of studies were level IV evidence (n=17), with five level III evidence and three systematic reviews.

One of the five comparative cohort studies analysed paediatric salivary gland tumours, with the remaining four pertaining to CNS tumours. Sato et al.³⁸ reported 79 children with ependymoma and a median follow-up of 2.6 years. All underwent surgical resection followed by either post-operative IMRT (N=38 patients) or PBT (N=41). The 3-year progression free survival (PFS) was in favour of PBT over IMRT (82% versus 60%, $p=0.031$) although not significant on univariate analysis ($p=0.08$). In the retrospective study by Eaton et al.³⁹, no difference in relapse-free survival or OS was seen between PBT (N=45 patients) and photon therapy (N=43) for standard risk medulloblastoma, but more second malignancies were noted in the photon group (3 versus 0 patients), although follow-up duration was short.

One of the systematic reviews included PBT studies published between 2007 and 2015¹⁶. There were 23 studies and approximately 650 patients covering a broad range of paediatric tumours. The quality of the studies was low with none randomised and 20 of a retrospective nature. There was either insufficient or non-existent clinical evidence to support or refute the use of PBT in children in any of the indications surveyed. No CIT studies for any paediatric subsite were identified in our review.

De Ruysscher Findings

Eleven studies were included for paediatric tumours, only one using CIT in children with chordomas and chondrosarcomas with an OS rate of 100% after a median follow-up of 49 months. No severe long term toxicities were observed, but also with no evidence of lesser toxicity.

Sarcomas (Appendix IV)

The majority of studies (PBT=12, CIT=7, mixed therapy=3) were for chondrosarcomas or chordomas in difficult to treat locations (spine, sacrum and base of skull). All studies were of level IV evidence, mainly retrospective case series. All three of the Search Strategy II articles were in relation to sarcomas³³⁻³⁵, and all were retrospective case series. Doses for PBT were 70 to 77.4GyRBE delivered with definitive or adjuvant intent, and patients had a mix of primary or recurrent sarcomas. Five-year OS ranged from 67% to 94.9%. Acute and late toxicity was reported as generally low, acceptable and comparable to historical photon data which used generally lower doses. Late grade 3-4 toxicity was reported as up to 16% mainly relating to neurological dysfunction. Treatment related death was reported in five patients, four of which were a result of secondary malignancies⁴⁰⁻⁴², in a total of 935 patients included across the 12 PBT sarcoma studies.

A systematic review performed by Pennicooke et al.⁴³ reviewed the evidence for external beam radiation therapy overall for chordoma of the spine and sacrum. Of the 25 included studies (N=801 patients), seven were PBT and four were CIT. While OS was not significantly different between modalities, PBT and CIT both demonstrated higher LC rates compared to conventional IMRT.

De Ruysscher Findings

Two retrospective PBT studies were included (N=72 patients), with 5-year OS rates for both studies of 72% and 65%. No grade 3-4 toxicities were reported.

Central Nervous System (CNS) (Appendix V)

Sixteen CNS studies were included (PBT=12, CIT=1, mixed therapy=3). The overall level of evidence was low with no randomised trials, three retrospective comparative cohort studies, 12 case series and one systematic review. The majority of studies were for meningiomas (largely WHO grade I or II) (n=10 studies).

A recent systematic review by Lesueur et al.⁴⁴ examined PBT use in cervical spine or intracranial benign tumours and included 24 studies. Across the nine studies examining WHO grade 1 meningioma, fractionated PBT led to high 5-year LC rates ranging from 88 – 100%, with follow-up from 34 to 84 months. Other tumours included schwannomas (n=4 studies), pituitary adenomas (n=5), paragangliomas (n=5) and craniopharyngioma (n=1). Overall, a safe and acceptable level of toxicity was reported across the tumour types, though not in comparison to any specific photon data or any other intervention. Of the three comparative cohort studies in our review, two did not report on any

toxicity outcomes, while the remaining study comparing IMRT to PBT for spinal cord gliomas made no distinction in toxicity between treatment modalities⁴⁵.

De Ruysscher Findings

Eight studies (PBT=5, CIT=3) were included examining base of skull tumours and spinal chordoma and chondrosarcoma. Tumour and toxicity outcomes were deemed comparable with the best available photon series.

Gastrointestinal tract (GIT) (Appendix VI)

Fifteen studies were included (PBT=8, CIT=3, mixed therapy=4), including one of the two RCTs in our systematic review. There was also one level III retrospective comparative cohort study and all other studies were of level IV evidence.

Hepatocellular carcinoma (HCC) was the most prevalent tumour (8 studies, including the RCT). Bush et al.⁴⁶ examined 69 patients, randomised to receive PBT (N=33 patients) or TACE (N=36). PFS at two years was superior for those who received PBT as compared to TACE (48% versus 31%), though this was not statistically significant. The total number of hospitalisation days, used as a surrogate for toxicity, was significantly shorter in the PBT arm compared to TACE (24 vs 166 days, $p < 0.001$).

De Ruysscher Findings

Six studies (PBT=4, CIT=2) were included, four for HCC. The LC rate with CIT for HCC was between 70-97% depending on the delivered tumour dose and proximity to porta hepatis. All PBT studies were from the same centre in Japan and the 3-year OS for HCC was 62-87%. Toxicities were all less than grade 2 and favourably comparable with radical surgery.

Ocular (Appendix VII)

Fourteen studies for ocular tumours were included (PBT=12, CIT=1, mixed therapy=1). The overall level of evidence was low, with no RCTs, three retrospective comparative cohort studies, nine retrospective case series and two systematic reviews. All studies reported on ocular melanomas, except one PBT study examining ocular epithelial tumours⁴⁷.

The more recent systematic review by Verma & Mehta included a total of 15,069 patients across 14 original investigations examining the use of PBT in uveal melanomas⁴⁸. PBT demonstrated LC rates of >90% sustained over 10 to 15 years and a 5-year OS rate consistently between 70-85%. The other systematic review⁴⁹ compared pooled rates of local recurrence and toxicities experienced by patients receiving PT to those experienced by plaque brachytherapy patients, data of which were obtained from a large randomised study of ocular melanoma patients comparing brachytherapy or enucleation⁵⁰. It reported a significant reduction of local tumour recurrence with PT, as well as lower rates of retinopathy and cataract formation as compared to plaque brachytherapy⁴⁹.

De Ruyscher Findings

Nine studies (PBT=8, CIT=1) were reviewed, including one prospective CIT study which treated large choroidal melanomas. Forty percent developed neovascular glaucoma. The Lodge et al. systematic review included a RCT by Char et al.²⁴ which randomised uveal melanoma patients to helium ions versus Iodine-125 brachytherapy. There was a significantly increased local recurrence and enucleation rate following brachytherapy compared to helium ion therapy.

Other tumour sites (Appendix VIII)

There were four studies for lung cancers, three for prostate cancers, two for breast cancers, one for skin and one for re-irradiation for a mix of tumour sites. Three systematic reviews covered a mix of tumour sites. Though the majority of studies for these miscellaneous tumour sites were of level IV evidence (case series), there was one RCT identified²³. This study by Liao et al. examined 149 patients with locally advanced non-small cell lung cancer (NSCLC) randomised to IMRT (N=92 patients) or PBT (N=57)²³. The study hypothesised a 10% reduction in grade 3 or more radiation pneumonitis for PBT compared with IMRT without compromise of local tumour control. Despite a significant reduction in low dose volume in the dosimetric histogram, the PBT group experienced 10.5% grade 3 or more radiation pneumonitis compared with only 6.5% in the IMRT group. There was no difference in local failure between treatment arms.

Seven studies examining re-irradiation for recurrent disease were identified across five different subsites⁵¹⁻⁵⁷, including a recent systematic review⁵⁸ of 16 studies across broad indications. The level and quality of evidence was low as the majority of studies are retrospective, with small sample size, limited follow-up duration and do not directly compare results to photon-based re-irradiation.

Discussion

This systematic review has not demonstrated any strengthening of evidence for PT with the addition of 136 new studies, including 17 other included previous systematic reviews. Most evidence remains of low quality, mostly single institution retrospective case series (NHMRC level IV), with a high risk of bias and probability of confounding results across the studies. Nevertheless, there is a unifying conclusion that PT at the very least is equivalent in survival outcomes compared to photon RT controls. The review supports the potential for reduction of morbidity with PT for H&N tumours³⁶,

paediatric tumours³⁹, sarcomas⁵⁹, GIT tumours²² and ocular tumours^{48, 49}. Specifically, the review supports the use of PBT for paediatrics, base of skull chordoma and chondrosarcoma, spinal/para-spinal sarcoma, ocular tumours, meningioma and paranasal sinus tumours, in line with current international recommendations^{60, 61}. It also supports the use of CIT for mucosal and ocular melanoma and base of skull and pelvic chordoma and chondrosarcoma, in terms of both survival and local control^{37, 48}.

CIT studies were a minority in this systematic review, simply because there were only 11 facilities operational worldwide before 2019. Six facilities are in Japan, three in Europe and two in China. Only English language publications were included in our systematic review and important studies may have been excluded. Our conclusions regarding CIT concur with Goetz et al.⁶² that though CIT is a promising cancer treatment, neither superiority or inferiority can be claimed when compared to conventional treatment options. The unique biological as well as physical properties of carbon ions mean that CIT needs to be integrated into translational treatment programs in novel ways in order to exploit their maximum potential such as eliciting an enhanced immune response^{1, 63, 64}.

There are more study reports of PT across a number of indications as a result of increasing experience and the number of PT centres operating worldwide. However, data remain limited in terms of high-quality comparative evidence. Two RCTs met our inclusion criteria^{22, 23}. One study compared TACE to PBT in HCC²². The other RCT was the only study which assessed PT compared to photon therapy (PBT versus IMRT for NSCLC)⁶⁵. A reduction in radiation pneumonitis was anticipated but not demonstrated. Several proposed reasons for this include flaws in the method of randomisation, the likelihood of a steep learning curve with PBT based planning, a mis-modelled biologic effect from greater uncertainty in factors included in the dose computation model, greater setup uncertainty, or incorrect choice of end point definitions⁶⁵. These factors need to be addressed in the design of future PT studies.

What evidence is needed?

While randomised phase III trials provide the most robust clinical evidence of comparative efficacy, there are recognised barriers to this for PT particularly if international collaboration is not pursued. The debate between the advocates in favour of level I evidence in all circumstances, and those who consider this to be unfeasible or even unethical in some cases, continues⁶⁵⁻⁷². Tumours set to benefit most from PT are paediatric and other rare tumours. Paediatric solid tumours are regarded as a special category by many jurisdictions. The lifetime sequelae of photon RT along with compelling dosimetric planning comparisons provide support for PT. The reduced incidence of late toxicities such as secondary malignancies resulting from lower integral doses from PT compared to photon RT is virtually impossible to test in a randomised trial due to the relatively low absolute incidence and latency of these cancers⁷³. The feasibility of a conventional RCT should be evaluated for each tumour type¹⁶ and consideration given to other options such as registry-based randomised clinical trials⁷⁴. Recently, a prospective, multi-centre, high quality database derived study was published which for the

first time compared intellectual trajectories between paediatric patients treated with PBT versus those treated with photon RT and demonstrated a translation of theoretical dosimetric advantages into clinically measurable outcomes⁷⁵.

RCTs are challenging to perform when testing new radiotherapy technologies^{1, 73}. This has been recognised by the Trans Tasman Radiation Oncology Group (TROG) group and the Assessment of New Radiation Oncology Technologies and Treatment (ANROTAT) Project was developed to address these complexities⁷⁶. Process measures and operational characteristics have been proposed as the means of assessing new technologies given that the sensitivity and specificity of clinical outcome is low for detecting quality improvement⁷³. Technological advancements, for example, introduction of IMRT and stereotactic ablative radiotherapy (SABR), took place without randomised clinical trials^{65, 69, 73}. In the case of PT, the significant capital cost investment and the relatively small number of facilities are key factors contributing to the demand for high quality evidence to support its use, but also explains why high-quality evidence has been slow and difficult to obtain.

In place of the lack of comparative clinical evidence, users of PT call for consideration of modelled dose distributions as a vital and ubiquitously utilised tool for predicting radiotherapy outcomes in both conventional radiotherapy and PT^{73, 77, 78}, and historically often form the basis for the introduction of novel and advanced technology in radiotherapy. Randomised trials for all patients are unlikely to be feasible or produce meaningful results, while randomised trials where patients are selected using biomarkers such as hypoxia, dosimetry, or normal tissue complication probability (NTCP) models are considered more sensitive and appropriate¹. The NTCP model-based approach uses normal tissue effect thresholds to categorise patients into those deemed likely to benefit from PBT, those who will not and a selection of patients where there is uncertainty for whom RCTs would be used to compare the two treatment modalities^{65, 77, 78}.

Countries offering PT are conducting or planning clinical trials^{15, 72}. However, a waning of clinical trial initiation was noted by Odei et al.⁷⁹ in 2016 with funding barriers one cited cause. There is however currently increasing support from insurers in the USA to fund PBT treatment in clinical trials^{69, 72}. This, along with the recent operation of PBT facilities in nationally funded health care systems such as Denmark, the United Kingdom and the Netherlands with prospective patient databases and defined groups of patients for funded PBT, is likely to lead to a new generation of evidence becoming available. It is not too late for Australia to contribute patients to international efforts in generating further evidence through registries, and prospective databases for both PBT and CIT, helping to shape and expand indications for PT over time. As evidence accumulates, indications for PT will evolve. In the meanwhile, consensus conferences are convened to establish PT use recommendations such as those provided by ASTRO⁸⁰.

Planning and dosimetric evidence

Although the systematic review excluded planning and dosimetric studies, these are worthy of comment. There is a substantial body of evidence from in-silico comparative planning studies across a broad range of tumour sites comparing dose distributions between photon RT and PT demonstrating superiority in regard to normal tissue sparing^{2-7, 44, 81-83}. Proponents of PT view these data as indicating that PT will become the treatment of choice for specific indications once its availability is wide enough, in part for its compliance with the generally agreed As Low As Reasonably Achievable (ALARA) principle.

The arguments in favour of PT's dosimetric superiority however depend on the accuracy of the predicted dose distribution and sound estimates of the relative biological effectiveness (RBE) values for the cancer and for each normal tissue. This however remains contentious particularly for CIT. Other limitations and uncertainties that necessitate further investigation are the magnitude of lateral penumbra, range inaccuracies and uncertainties related to tumour location and organs at risk (OAR)⁸⁴⁻⁸⁶. Small shifts of the tumour or the OARs in areas with high density gradients, may directly result in large changes and errors in dose distribution. Adaptive radiotherapy techniques and use of 'robust' approaches thus become even more crucial for PT than for photon RT, and is an area of recent rapid development⁸⁷⁻⁸⁹. With growing knowledge of the dose-volume effects of PT on OARs, it is possible to more precisely measure the trade-offs between the investment in PT and risk of side effects such as those resulting from uncertainties relative to the RBE in the Bragg peak¹⁶.

Limitations of the systematic review

There are several limitations to our study. First, the search was limited to studies from 2011 onwards given that an appropriate and relevant past systematic review by De Ruyscher et al.¹⁹ was identified covering evidence to that date. The findings of that systematic review were largely assumed and accepted as a thorough summary of evidence from 1980's to 2011. Furthermore, though a variety of databases were searched, and two researchers used to screen all titles and abstracts, it is still possible that important studies may have been missed. We aimed to mitigate the risk by ensuring that any systematic review captured in our Search Strategy I was used as a crosscheck and any studies not initially retrieved included as grey literature.

There were over 60 studies pertaining to toxicity outcomes alone that were excluded from this systematic review. Inclusion and analysis of these studies may have presented a more comprehensive representation of the proposed benefits of PT use. Though beyond the scope of this review, these studies will form the basis of future analysis.

The Way Forward

There is an increasing global enthusiasm and sense of urgency to correct the lack of robust clinical data regarding PT, and Australia has an opportunity to respond, collaborate and contribute to these efforts. The paucity of high-quality evidence has led many jurisdictions to develop empiric indication lists for PT and there are some commonalities between these lists worldwide. Randomised phase III

trials of PT are needed for relevant indications and patient sub-groups to investigate whether modelled benefits translates to clear clinical benefit for patient outcomes and their cost-effectiveness^{15, 65}. In turn, indications will change and evolve as facilities treating with PT better understand the clinical translation of PT's dosimetric properties. Promoting high enrolment and retention rates onto RCTs is imperative⁷². Prospective data suggest that there is a high public willingness to participate in trials comparing PBT with photon RT⁹⁰.

PT studies should be integrated into large international clinical research networks, including prospective databases⁹¹. The European Particle Therapy Network (EPTN) is one example⁹². The preliminary results of the US Pediatric Proton Consortium Registry are promising⁹³ and plans are underway to launch an International Pediatric Proton Therapy Consortium⁹⁴. New PT centres such as the Christie Proton Therapy Centre in the United Kingdom exemplify the model of embedding clinical operations within a network of research and clinical trial units, supported by funding bodies that will allow for properly conducted trials and radiotherapy quality assurance⁶⁹.

A collaborative networked approach to introduce PT to Australia has been developing through a national steering committee involving relevant professional bodies, clinical and academic organisations and centres. This network will establish a national PT registry, and the planning and delivery of PT with associated research partnerships with TROG and the RANZCR. This systematic review is a product of that collaboration.

Conclusion

There is currently no conclusive estimate of the incremental clinical effectiveness of PT in comparison with conventional photon RT. There is the promise of decreased morbidities in a range of sites, supporting the predictions from dosimetric modelling and the wide international acceptance of this rationale for PT use for specific indications. Prospective comparative clinical trials will address specific clinical questions and knowledge gaps but evidence must be supplemented by detailed database-derived outcome information. Such practices will be facilitated and strengthened when conducted within international and national networks.

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Tables

Table 1: Search Strategy I

	Date	Results	Included after duplicates	Included
PubMed				
(Heavy Ion Radiotherapy[MeSH Terms]) OR proton therapy[MeSH Terms]) OR charged particle*[Title/Abstract] OR hadron therap*[Title/Abstract]) OR particle therap*[Title/Abstract])) AND (((radiation oncology[MeSH] OR Paediatrics[MeSH Terms] OR Sarcoma[MeSH Terms] OR Central Nervous System Neoplasms[MeSH Terms] OR Head and Neck Neoplasms[MeSH Terms] OR Systematic Review [Publication Type] OR Pancreatic Neoplasms[MeSH Terms]))) AND English[Language]) AND ("2000"[Date - Publication] : "3000"[Date - Publication])	07/03/2019	1015	1015	95
Ovid MEDLINE				
(Heavy Ion Radiotherapy or proton therapy).sh. or charged particle*.tw. or carbon-ion.tw. or hadron therap*.tw. or particle therap*.af. AND (radiation oncology or Paediatrics or Sarcoma or Central Nervous System Neoplasms or (Head and Neck Neoplasms) or Pancreatic Neoplasms.sh.	01/03/2019	258	12	1
Ovid EMBASE				
(Heavy Ion Radiotherapy or proton therapy).sh. or charged particle*.tw. or carbon-ion.tw. or hadron therap*.tw. or particle therap*.af. AND (radiation oncology or Paediatrics or Sarcoma or Central Nervous System Neoplasms or (Head and Neck Neoplasms) or Pancreatic Neoplasms.sh.	01/03/2019	228	195	1
Grey literature				
Hand searching through current clinical trials database, recent conference abstracts and articles suggested by leading clinicians in proton therapy or in relevant major review articles.	01/04/2019	105	103	36

Table 2: PICO table and selection criteria for Search Strategy I

Selection criteria	Inclusion criteria	Exclusion criteria
Population	Rare tumours, difficult to treat tumours, paediatric tumours, adult tumours, neoplasms, sarcomas, central nervous system tumours, skull base tumours,	Pathologic conditions not listed under inclusion criteria

	head and neck tumours, pancreatic tumours, ocular tumours	
Intervention	Particle therapy, carbon ion therapy, proton therapy, heavy ion radiotherapy	Photon therapy Helium ion therapy
Comparator	Photon therapy	
Outcomes	Clinical efficacy, benefits of therapy, survival outcomes, local control, complications, acute toxicities, late toxicities, patient reported outcomes, secondary tumours	Cost effectiveness, dose escalation outcomes, fractionation outcomes, technical or dosimetric outcomes, toxicity outcomes alone
Study Design	Systematic reviews, meta-analyses, randomised controlled trials, non-randomised trials, cohort studies, case series, retrospective studies, prospective studies	Animal study, case reports, comparative in-silico studies, review articles (non-systematic reviews), consensus articles, feasibility studies, preliminary studies, in-vitro studies, no full text publication, published before February 2011, less than 2 years median follow-up, less than 20 patients
Language	English	Non-English

Table 3: Number of studies according to tumour subsite and type of particle therapy

Subsite	Total	Proton	Carbon	Mixed
H&N [†] (1 Skull base, 1 re-irradiation)	27	11	12	4
Paediatrics (1 re-irradiation)	25	24	0	1
Sarcoma (6 Skull base, 2 re-irradiation)	22	12	7	3
CNS [‡] (1 Skull base, 1 re-irradiation)	16	12	1	3
GIT [§] (1 re-irradiation)	15	8	3	4
Ocular (1 re-irradiation)	14	12	1	1
Thoracic	4	2	0	2
Prostate	3	3	0	0
Breast	2	2	0	0
Skin	1	0	1	0
Re-irradiation (mix of tumour types)	1	1	0	0
Mix of tumour types	3	1	1	1
Total	133	88	26	19

[†]Head and neck; [‡]Central nervous system; [§]Gastrointestinal tract

Table 4a: Strength of evidence- proton therapy studies

Subsite	Proton studies	Level II <i>RCT[¶]</i>	Level III <i>Comparative cohort study</i>	Level IV <i>Case series</i>	Systematic review (<i>RCT[¶]=n</i>)
H&N [†]	11	-	1	10	-
Paediatrics	24	-	5	17	2
Sarcoma	12	-	-	11	1
CNS [‡]	12	-	1	10	1
GIT [§]	8	1	1	5	1 (<i>RCT[¶]=1</i>)
Ocular	12	-	3	8	1
Re-irradiation	1	-	-	-	1
Thoracic	2	1	-	1	-
Prostate	3	-	1	2	-
Breast	2	-	-	2	-
Skin	0	-	-	-	-
Mix of tumour types	1	-	-	-	1 (<i>RCT[¶]=6</i>)
Total	88	2	12	66	8

[†]Head and neck; [‡]Central nervous system; [§]Gastrointestinal tract; [¶]Randomised controlled trial

Table 4b: Strength of evidence- carbon ion studies

Subsite	Carbon	Level II <i>RCT[¶]</i>	Level III <i>Comparative cohort study</i>	Level IV <i>Case series</i>	Systematic review (<i>RCT[¶]=n</i>)
H&N [†]	12	-	-	12	-
Paediatrics	0	-	-	-	-
Sarcoma	7	-	1	6	-
CNS [‡]	1	-	1	-	-
GIT [§]	3	-	-	3	-
Ocular	1	-	-	1	-
Re-irradiation	0	-	-	-	-
Thoracic	0	-	-	-	-
Prostate	0	-	-	-	-
Breast	0	-	-	-	-
Skin	1	-	-	1	-
Mix of tumour types	1	-	-	-	1
Total	26	0	2	23	1

[†]Head and neck; [‡]Central nervous system; [§]Gastrointestinal tract; [¶]Randomised controlled trial

Table 4c: Strength of evidence- mixed therapy studies

Subsite	Mixed therapy	Level II <i>RCT[¶]</i>	Level III <i>Comparative cohort study</i>	Level IV <i>Case series</i>	Systematic review (<i>RCT[¶]=n</i>)
H&N [†]	4	-	-	2	2

Paediatrics	1	-	-	-	1
Sarcoma	3	-	-	2	1
CNS[‡]	3	-	1	2	-
GIT[§]	4	-	-	2	2
Ocular	1	-	-	-	1 (RCT [¶] =3)
Re-irradiation	0	-	-	-	-
Thoracic	2	-	1	1	-
Prostate	0	-	-	-	-
Breast	0	-	-	-	-
Skin	0	-	-	-	-
Mix of tumour types	1	-	-	-	1 (RCT [¶] =4)
Total	19	0	2	9	8

[†]Head and neck; [‡]Central nervous system; [§]Gastrointestinal tract; [¶]Randomised controlled trial

Appendix

Appendix I: Detailed reasons for exclusion of studies

Supplementary Material: Further Appendices (online only)

Legend for appendices

Appendix II: Head and Neck tumours (studies as per PT type)

Appendix III: Paediatric tumours (studies as per PT type)

Appendix IV: Sarcomas (studies as per PT type)

Appendix V: Central nervous system tumours (studies as per PT type)

Appendix VI: Gastrointestinal tumours (studies as per PT type)

Appendix VII: Ocular tumours (studies as per PT type)

Appendix VIII: Other tumour sites (studies as per subsite)

Appendix IX: Search Strategy II studies summary

Appendix I: Detailed reasons for exclusion of articles (Search Strategy I)

	Database			Grey literature	Total
	PubMed	MEDLINE	Embase		
Number of citations retrieved by Search I	1015	258	228	105	1606
Number of duplicates	0	246	33	1	280
Reason for exclusion					
Animal study	9	0	0	0	9
Before February 2011	92	4	2	1	99
Case report	77	0	1	7	85
Comparative plan papers	40	0	0	5	45
Consensus paper	50	0	38	0	88
Cost	12	0	7	0	19
Dose escalation study	6	0	0	0	6
Dosimetric study	15	2	0	0	17
Feasibility study	13	0	1	0	14
Fractionation study	3	0	0	0	3
Full text unavailable	0	0	50	0	50
Inadequate follow-up (<2 years)	28	0	4	15	47
In vitro study	33	1	2	0	36
Irrelevant to study	169	2	50	4	225

question (e.g. clinical trial strategies, socioeconomic papers)					
Low patient numbers (<20)	39	0	0	5	44
Not in English	0	0	10	1	11
Review study (not a systematic review)	105	2	14	16	137
Technical aspects of planning	181	0	12	4	197
Toxicity outcomes only	49	0	3	10	62
Total excluded	920	11	194	68	1193
Number of citations included in systematic review Search Strategy I					

844

Figure 1. PRISMA flow chart of study selection.

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Author/s:

Hwang, EJ;Gorayski, P;Le, H;Hanna, GG;Kenny, L;Penniment, M;Buck, J;Thwaites, D;Ahern, V

Title:

Particle therapy tumour outcomes: An updated systematic review

Date:

2020-04-08

Citation:

Hwang, E. J., Gorayski, P., Le, H., Hanna, G. G., Kenny, L., Penniment, M., Buck, J., Thwaites, D. & Ahern, V. (2020). Particle therapy tumour outcomes: An updated systematic review. JOURNAL OF MEDICAL IMAGING AND RADIATION ONCOLOGY, 64 (5), pp.711-724. <https://doi.org/10.1111/1754-9485.13021>.

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