Particle Therapy Toxicity Outcomes: A Systematic Review

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Abstract

Owing to its physical properties, particle therapy (PT), including proton beam therapy (PBT) and carbon ion therapy (CIT), can enhance the therapeutic ratio in radiation therapy. The major factor driving PT implementation is the reduction in exit and integral dose compared to photon plans, which is expected to translate to reduced toxicity and improved quality of life. This study extends the findings from a recent systematic review by the current authors which concentrated on tumour outcomes for PT, to now examine toxicity as a separate focus. Together, these reviews provide a comprehensive collation of the evidence relating to PT outcomes in clinical practice. 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 seventy-nine studies were included. Most demonstrated acceptable and favourable toxicity results. Comparative evidence reported reduced morbidities and improvement in quality of life in head and neck, paediatrics, sarcomas, adult central nervous system, gastrointestinal, ocular and prostate cancers compared to photon radiotherapy. This suggestion for reduced morbidity must be counterbalanced by the overall low quality of evidence. A concerted effort in the design of appropriate comparative clinical trials is needed which takes into account integration of PT's pace of technological advancements, including evolving delivery techniques, image guidance availability and sophistication of planning algorithms.

Five key words

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

Main text

Introduction

Owing to its physical properties, particle therapy (PT), including proton beam therapy (PBT) and carbon ion therapy (CIT) which also has additional biological advantages, is a means of enhancing the therapeutic ratio in radiation therapy (RT). Tumour outcomes for PT have not proven superior to current photon therapies so far. This is not unexpected, since it reflects the usual approach to using PT to prescribe to the same presumed biological equivalent radiation dose and coverage as comparative photon therapy, as well as the impact of sub-optimal clinical trial design and an under-representation thus far of evolving PT technologies. The major factor driving PT implementation is the reduction in exit and integral dose compared to photon plans¹, resulting in a reduction in dose to normal tissues. This should translate to reduced acute and long term toxicity² and improved post-therapy quality of life³. These dosimetry considerations, supported by specific clinical predictions from comparative dosimetric modelling and in-silico studies has been the main rationale for accepting PBT as the optimal radiotherapy for paediatric patients in many jurisdictions⁴, and the reason PT is being actively studied for various adult tumour types⁵.

This study extends the findings from a recent systematic review by the current authors which concentrated on tumour outcomes for PT⁶, to now examine toxicity as a separate focused outcome. Together, these reviews present a comprehensive review of the current evidence relating to the outcomes of PBT and CIT in clinical practice.

Methods

The systematic review was conducted in accordance with the 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses' (PRISMA) statement⁷. An initial search of previously published systematic reviews back to the year 2000 identified the 2012 De Ruyscher et al.⁸ review as thorough and also relevant to our research aim and this was used as a base from which to update. Therefore, the clinical evidence for PT covering the period February 2011 to March 2019 was retrieved, and studies investigating clinical toxicity outcomes were included (Table 1). Two researchers independently reviewed the 1326 non-duplicate titles and abstracts for eligibility and resolved discrepancies by consensus⁶. There were 62 articles which examined toxicity outcomes alone, and were excluded from our earlier systematic review⁶, on the basis that no tumour outcomes were reported. These 62 articles are included in the current systematic review, and added to the 127 studies which reported on both tumour and toxicity outcomes, included in the previous review⁶ regarding tumour outcomes. Dosimetry, planning, simulation or in-silico studies or studies which involved comparisons of treatment planning algorithms or modelled simulations of outcomes were excluded.

Grading level of evidence

Evidence quality was classified according to the National Health and Medical Research Council (NHMRC) evidence hierarchy⁹. 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.

Results

An initial search identified 1606 potentially relevant studies (1326 non-duplicate records), of which 133 were included in the previous systematic review of tumour outcomes⁶. Six of these did not report on toxicity outcomes, leaving 127 studies (Figure 1a) which reported on both tumour and toxicity outcomes. Of the original 1326 non-duplicate records, 62 reported 'toxicity outcomes only'. Twenty-eight of the 62 were excluded upon full text review, but a further 18 relevant articles were found from references of selected articles. Thus, 52 original investigations were found to have sufficient relevance to be incorporated into the current systematic review regarding toxicity outcomes (Figure 1b). Together with 127 studies from the earlier paper, there were a total of 179 studies included for the purposes of this review.

For these 179 studies, the indication and PT type is shown in Table 2. 'Mixed therapy' refers to studies reporting on patients treated with PBT or CIT at the same facility. Tables 3a, 3b and 3c present the types of studies identified and the strength of evidence for the included studies for PBT, CIT, and mixed therapy respectively. The vast majority of studies (81% PBT, 97% CIT and 95% mixed therapy) presented level IV evidence and most were retrospectively conducted. There were two randomised controlled trials (RCTs) reporting on toxicity outcomes.

Results according to tumour sites

A summary of the key findings according to each subsite is presented. Appendices I-VIII provide comprehensive information.

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

Thirty-two studies examined toxicity in H&N tumours (PBT=13, CIT=15, mixed therapy=4). All were of level IV evidence, except two comparative cohort studies (NHMRC level III), both examining oropharyngeal cancer patients. One compared osteoradionecrosis (ORN) outcomes in oropharyngeal cancer patients treated with intensity modulated radiation therapy (IMRT) (N=534) versus those treated with intensity modulated proton therapy (IMPT) (N=50)¹⁰. The minimum and mean doses to the mandible as well as the mandible V10-V70 were all significantly lower for patients treated with IMPT ($p<0.001$) but not the maximum dose ($p=0.503$). Osteoradionecrosis events were lower in the IMPT group (2%, N=1) versus the IMRT group (7.7%, N=41) and this was found significantly associated with higher dose irradiation to the mandible ($p<0.001$). Blanchard et al.¹¹ compared IMRT

(N=100) to IMPT (N=50) in oropharyngeal cancer patients, and found a trend toward a reduction in rate of gastrostomy tube use and grade 3 weight loss at 3 and 12 months¹¹.

Two systematic reviews were included^{12, 13}. Patel et al.¹² reviewed malignant tumours arising from the nasal cavity and paranasal sinuses treated with PT compared to those receiving photon RT. Forty-one non comparative observational studies were included with a median follow-up of 38 months. No difference in outcome was seen between the two modalities for eye, H&N, nasal, ear or haematological toxicities. However, there were significantly more neurological toxicities in the PT group than the photon therapy group ($p=0.0002$) including brain necrosis, neuropathy, epilepsy, and meningitis. This is in contrast to the systematic review by Ramaekers et al. who reviewed late toxicities for CIT, PBT and best available photon RT for a mix of H&N cancers¹³. Though availability of late toxicity data were limited, reduced toxicities with PT were suggested compared to photon RT in specific clinical scenarios including CIT in adenoid cystic carcinoma, and PBT in paranasal sinus tumours¹³.

Paediatric tumours (Appendix II)

The majority of PT toxicity studies were in relation to paediatric tumours (N=42, PBT=41, mixed therapy =1). Ten of these were of level III evidence, with the remainder level IV. All the included comparative cohort studies were for central nervous system (CNS) tumours, except for one examining rates of acute mucositis in salivary gland tumours¹⁴. Eaton et al. published two studies^{15, 16} in 2016 examining medulloblastoma treated with either PBT or photon RT delivered as three-dimensional conformal radiotherapy (3DCRT) or IMRT. One reported on secondary malignancy outcomes with an incidence of three of 43 patients treated with photon RT versus 0 of 45 patients treated with PBT with a median follow-up of 6.2 years¹⁶. The study was underpowered for significance. The other study examined endocrine effects in 77 children (PBT N=40, photon RT N=37) demonstrating a reduced risk of hypothyroidism ($p<0.001$), sex hormone deficiency ($p=0.025$) and requirement for endocrine replacement therapy ($p=0.03$) with PBT compared to photon RT¹⁶. Paulino et al.¹⁷ also reported on outcomes for patients with medulloblastoma, comparing PBT (n=38) to IMRT (N=46) and found mean cochlear doses to be lower in the PBT group, though this did not translate to a difference in grade 3-4 ototoxicity ($p=0.56$), with a median follow-up of 56 months.

Kahalley et al.¹⁸ examined change in IQ following PBT (N=90) versus photon RT (N=60), either 3DCRT and/or IMRT, in tumours including medulloblastoma (41%, N=62), glioma (19%, N=28) and ependymoma (11%, N=17). 51.7% of patients receiving photon RT and 56.7% of patients receiving PBT received craniospinal irradiation (CSI). Though the median follow-up was not stated, the mean interval from RT to last evaluation was 5.4 years for photon RT, and 2.7 years for PBT. Using multivariate modelling, no significant IQ decline was found in the PBT group ($p=0.130$) whereas in the photon RT group a statistically significant loss of 1.1 IQ points per year on average was seen ($p=0.004$). Despite this, there was no significant difference in the IQ change over time between the two RT modalities ($p=0.509$). A study by Sato et al.¹⁹ compared outcomes for children with localised

ependymoma treated with IMRT (N=38) or PBT (N=41). Six of the 79 patients (8%) developed radiation necrosis within the first 6 months after RT, three from each group. The same group published data describing MRI changes and radionecrosis in patients treated with IMRT and PBT²⁰ which demonstrated that post-radiation MRI changes were more common with PBT and in patients less than three years old at time of diagnosis and treatment. These changes were usually self-limiting, but some, especially those involving the brainstem, required medical intervention²⁰. A 2015 systematic review investigated PBT and CIT outcomes in the treatment of paediatric brain tumours between 1966 and March 2014²¹. Forty clinical studies were included (2760 patients, none of which used CIT), and cognitive impairments were reported to be lower with PBT, as were doses to the pituitary gland, auditory structures, visual structures and brainstem for infratentorial tumours²¹.

Six of the paediatric toxicity studies reported outcomes relating to secondary malignancies. One was a comparative cohort study by Sethi et al.²² regarding secondary malignancies in retinoblastoma patients, comparing PBT (N=55) with photon RT (N=31). The 10-year cumulative incidence of in-field second malignancies was lower in the PBT group than the photon RT group (0% versus 14%, p=0.015). The median follow-up was 6.9 years.

Sarcomas (Appendix III)

Twenty-three studies examined toxicity in patients with sarcoma (PBT =12, CIT=8, mixed therapy=3). All were of level IV evidence, except for one comparative cohort study comparing surgical treatment (N=24) to CIT (N=7) for chondrosarcoma of the pelvis²³. Post-treatment function was assessable in 21 of the 31 patients using the Musculoskeletal Tumour Society (MSTS) classification. Of the patients with periacetabular tumours, those who received CIT (N=7) had a more favourable mean MSTS score than those who underwent surgery (N= 10) (p=0.03) particularly in the functional scores pertaining to restrictions in daily activities, despite a higher complication rate in those treated by CIT²³.

All 22 of the remaining level IV case series studies concluded that PT was safe and well tolerated, with acute and late toxicities acceptable and comparable to their institutions' standards. This is in the context of doses up to 77.4GyRBE in 1.8-2Gy fractions in PBT studies²⁴, median doses of 70.5GyRBE/16# in CIT studies^{23, 25-27}, and in re-irradiation situations^{28, 29}. The majority of studies examined chondrosarcoma and/or chordoma in difficult to treat locations such as the spine/sacrum (n=14) and/or the skull base (n=7). Eight of the 23 studies reported on incidence of secondary malignancy in their cohorts (range N=24-222), and this ranged from 0% - 4%.

Adult Central Nervous System (CNS) (Appendix IV)

Eighteen studies examining CNS tumours (PBT = 16, mixed therapy = 2) were included in this review. Two were comparative cohort studies, both comparing PBT with photon RT. Brown et al.³⁰ reported patients with medulloblastoma who CSI with either PBT (N=19) or photon RT (N=21), with a median follow-up of 26 months. The photon RT used 3DCRT craniospinal fields, with a 3DCRT or IMRT posterior fossa or post-operative bed boost. PBT CSI patients experienced less bone marrow

suppression ($p=0.009$), less weight loss ($p=0.004$), less grade 2 nausea and vomiting ($p=0.004$) and were less likely to require medical management for esophagitis ($p<0.001$) than photon CSI patients³⁰. The other comparative cohort study investigated spinal cord gliomas and compared IMRT (N=22) to PBT (N=10). None of the patients, PBT or IMRT experienced significant long term toxicity and no cases of myelopathy were reported³¹.

A January 2019 systematic review reported clinical outcomes of adult patients with benign intracranial or cervical tumours treated with PBT, and included 24 studies with 1123 patients in total³². Safe and acceptable levels of toxicity across CNS tumour types, with a potential for reduced secondary malignancy were found for PBT. This supports the findings of the remaining 16 level IV evidence studies, the majority of which examined meningiomas ($n=9$) and reported acceptable and expected levels of toxicity according to their institutions' historical photon controls.

Gastrointestinal tract (GIT) (Appendix V)

Of the 18 studies examining toxicity in GIT tumours, one was of level II RCT evidence³³ and two were comparative cohort studies^{34, 35}. The RCT by Bush et al.³³ compared PBT (N=33) with transarterial chemoembolization (TACE) (N=36) for hepatocellular carcinoma (HCC). Hospitalisation secondary to treatment related complications was significantly increased in the TACE group (4.6 vs 0.73 days, $p<0.001$)³³, demonstrating that PBT could be a safer alternative to TACE for HCC.

Two comparative cohort studies in GIT tumours examined oesophageal cancer patients. One retrospectively analysed patients who received definitive chemoradiation with either PBT (N=132) or IMRT (N=211)³⁴. Grade 3-4 toxicities occurred more frequently in patients treated with IMRT than PBT (45% vs. 37.9%, $p=0.192$), as did grade 5 toxicities (4 versus 1 patient, $p=0.653$). A greater proportion of elderly patients (≥ 67 years) received PBT than IMRT (70.5% vs. 38.4%, $p<0.001$) which may have been a confounding factor for treatment tolerability.

Lin et al.³⁵ assessed the effect of radiotherapy modality on postoperative outcomes in a cohort of 580 patients, comparing 3DCRT (N=214), IMRT (N=255) and PBT (N=111) delivering neoadjuvant chemoradiation to oesophageal cancer patients. The incidence of pulmonary and wound complications was lowest for PBT (16.2% and 4.5%) versus 24.2-39.5% for 3DCRT and 14.1-15.3% for IMRT, as was the 90 day post-operative mortality rate (0.9% versus 4.2-4.3%)³⁵. The average length of hospital stay was significantly different between the 3 groups ($p<0.001$), shortest for PBT (9.3 days, compared to 11.8-13.2 days).

Three systematic reviews examining treatment of HCC³⁶⁻³⁸ were included, the most recent of which was published by Igaki et al. in June 2018. This reviewed clinical studies ($n=11$, N=787) on PT for HCC with late radiation morbidities as one primary outcome³⁸. Late severe radiation morbidities were uncommon, with a 2.3% (N=18) rate of grade 3 or more late adverse events. Overall the safety of PT was affirmed for HCC treatment³⁸.

Ocular (Appendix VI)

Fifteen articles were included in this review, of which 13 were level IV case series evidence, and two were of level III comparative cohort study evidence, both examining ocular melanoma. Sikuade et al.³⁹ compared single fraction stereotactic radiosurgery (SRS) (N=85) to PBT (N=106) in treatment of posterior uveal melanoma with a median follow-up of 29 months. Significant visual acuity loss was worse for SRS (65%) compared to PBT (N=45%). There was no significant difference between the two therapies for tumours beneath or touching the fovea ($p=0.271$). However, patients whose melanomas touched the optic nerve head were significantly more likely to suffer severe visual loss when treated with SRS compared to PBT ($p=0.008$), as well as for those with tumours located more than 3mm from the fovea ($p=0.04$). In the study by Mosci et al.⁴⁰, PBT (N=70) was compared to enucleation (N=62) for large T3-T4 uveal melanomas. PBT resulted in an eye retention rate of 74% at 5 years, and about one third of patients preserved useful vision.

Two systematic reviews on ocular tumours were included in the review^{41, 42}. Verma & Mehta⁴¹ provide a comprehensive review of all available patient outcomes of PBT for uveal melanoma from 2000 to June 2015. Visual acuity data was limited. When low-volume outliers were removed, rates of loss of vision to <20/200 were 30-40%, with a further 30-40% of patients experiencing stabilisation or improvement of visual acuity following PBT. Acknowledging the lack of large-volume comparative data between plaque brachytherapy and PBT, complication rates appeared to be lower for PBT than historical brachytherapy controls.

Other tumour sites (Appendix VII)

There were 13 studies for prostate cancer, seven for lung cancer, four for breast cancer, one for skin, one for re-irradiation across a variety of body sites and five covering a mix of tumour sites. Though the majority of studies were of level IV case series evidence, seven were comparative cohort studies⁴³⁻⁴⁸ and there was one RCT identified⁴⁹. This was a study by Liao et al. which examined locally advanced non-small cell lung cancer (NSCLC) patients randomised to IMRT (N=92) or PBT (N=57). Despite a significant reduction in low dose volume in the dose-volume histogram, albeit also an increase in high dose lung volume, the PBT group experienced 10.5% grade 3 or more radiation pneumonitis compared with only 6.5% in the IMRT group⁴⁹ though this difference was not statistically significant ($p=0.537$). While no patients in the PBT group suffered grade 4 or 5 radiation pneumonitis, two patients in the IMRT group died from grade 5 radiation pneumonitis.

Four comparative studies in prostate cancer compared photon RT to PBT treatment related toxicities. Hoppe et al.⁴⁴ compared patient reported quality of life (QoL) outcomes after PBT (N=1243) and IMRT (N=204), using the EPIC-26 questionnaire examining five domains of urinary incontinence, urinary irritative/obstructive, bowel function, sexual function and hormonal function. No difference in changes in summary scores for these five domains were seen between the two cohorts, however men treated with IMRT were more likely to report moderate to major problems with rectal urgency ($p=0.02$)

and frequent bowel movement ($p=0.05$) than those treated with PBT. Gray et al. similarly compared QoL outcomes in men with prostate cancer treated with PBT ($N=95$), IMRT ($N=153$) or 3DCRT ($N=123$)⁴⁵. At the first post-treatment follow up, 3DCRT and IMRT patients reported a clinically meaningful decrement in bowel QoL but not patients treated with PBT. However, by 12 and 24 months, all three cohorts reported comparable decrements in bowel QoL. Two studies from an earlier era using the linked Surveillance, Epidemiology, and End Results (SEER) and Medicare database demonstrated increased gastrointestinal toxicity with PBT compared to IMRT^{47, 48}.

Another study using the SEER registry, performed a comparative analysis of second cancer incidence rates for patients treated by photon RT ($N=558$) or PBT ($N=558$)⁵⁰ with a median follow-up of 6.7 years. Patients treated with PBT were case-matched according to number of paediatric patients ($N=44$ each), median age at diagnosis (59 years), sex (70% male) and primary tumour site (33% genitourinary, 32% CNS, 24% H&N, 7.7% musculoskeletal, 2.7% GIT). Second malignancies occurred in 29 patients (5.2%) treated with PBT versus 42 patients (7.5%) with photon therapy, which translated to 6.9 cancers per 1000 person-years for patients treated with PBT, and 10.3 per 1000 person-years for the patients treated with photons. This demonstrated that PBT was not associated with an increased risk of second malignancy (adjusted hazard ratio 0.52, $p=0.009$) although longer follow-up is needed⁵⁰.

A systematic review of 17 studies across a broad range of tumour sites assessed QoL and patient reported outcomes (PROs) in patients treated with PBT³. Acknowledging the limited data, PBT provided improved PROs than photon-based RT for H&N and lung cancer. QoL did not deteriorate during PBT for skull base tumours, nor following PBT for brain tumours. Outcomes for prostate and breast cancer showed comparable results to other modalities³.

Discussion

This systematic review focused on the clinical evidence regarding toxicity outcomes for PT in adult and paediatric tumours. Overall, the quality of evidence was low, with the majority of included studies derived from single institution retrospective case series (NHMRC level IV). Nevertheless, the majority of included studies demonstrate acceptable toxicity results, with comparative evidence reporting reduced morbidities in H&N tumours (lower rates of ORN¹⁰, gastrostomy insertions and weight loss¹¹), paediatric tumours (lower rates of secondary malignancy^{16, 21, 22}, endocrine effects¹⁶, IQ decline¹⁸), sarcomas²³, CNS tumours requiring CSI³⁰, GIT tumours (reduced hospitalisation days³³ and toxicities^{34, 35}), ocular tumours (less visual acuity loss³⁹ and toxicities⁴¹), prostate cancer (reduced rectal toxicity⁴⁴) and improved QoL³ compared to photon RT.

Some level III studies demonstrating reduced toxicities with PT compared to IMRT were not eligible for, and hence not included in this systematic review due to insufficient follow-up⁵¹. The included level III studies providing comparative evidence were limited in the fact they compared their PT cohort with non-concurrent photon RT controls which lends itself to inherent biases⁴. Furthermore, recent advances in PT delivery techniques such as the widespread implementation of IMPT, the increasing availability of on-board three-dimensional image guidance, with potential for reduced margins and adaptive approaches, and the use of Monte Carlo based planning could substantially impact the results of future toxicity analyses^{52, 53}. Comparison of forward planned passively scattered PBT for example (compromising a large proportion of the studies included in this review) is most analogous to photon 3DCRT, not IMRT. Therefore literature comparing advanced photon techniques with first generation PT might be inherently biased against PT. When technology is rapidly evolving, such as in the field of image guidance, there can be a misalignment of pace of technology adoption which can impact on the conduct of studies and trials⁴. This is a challenge not exclusive to PT, but to trial development in RT in general.

While there are many PBT centres globally, only a few treat with CIT, resulting in limited information regarding its treatment toxicity, and further complicated by the greater variety of fractionation schedules used and the impact of this on the comparability of toxicity outcomes. There was a suggestion of reduced toxicity with CIT in H&N adenoid cystic carcinoma¹³, as well as periacetabular sarcoma²³ but the exclusion of non –English literature in this systematic review may have missed relevant and important information. The National Institute of Radiological Sciences (NIRS) Chiba, Japan is a pioneer in CIT, with long-term follow-up of thousands of its patients demonstrating no evidence of increased secondary malignancy risk⁵⁴. There is recognition by NIRS of the need to better collect toxicity and quality of life assessments which are universally comparable⁵⁴. This, together with the NIRS radiobiology programme, strengthening international collaborations, clinical trial activity in CIT in Heidelberg and more recently the Italian (CNAO) and Austrian (MedAustron) centres⁵⁵, heralds promise of more robust data from a worldwide effort to understand CIT's unique biological effects including interaction with immune therapies⁵⁴.

Two RCTs were included in this review^{33, 49}. That by Liao et al.⁴⁹ is unique in being the first published randomised comparison of PT with standard of care photon therapy⁵⁶. The rationale of the RCT was to observe for potentially decreased toxicity, with no anticipation of improved tumour control. This was a negative study and it has been criticised for several reasons including a biased method of randomisation, a mis-modelled biologic effect, and an incorrect choice of end points⁵⁷. Furthermore image guidance for PBT in this study was not as well-developed for the PBT-treated patients who had larger tumour margins than those treated by photons^{52, 53}. These issues must be addressed in the design of future PT studies⁵⁸. More recently initiated PT RCTs, which are based on IMPT, use reduced margins⁵². Finally, this study highlights that learning curves exist with the implementation of any new technology. Combined rates of local failure and radiation pneumonitis in the PBT group were

31% in the first half of patients recruited versus 13.1% in the latter half ($p=0.027$)⁵⁸. Both PBT and IMRT plan quality improved as the trial progressed, supporting the downstream benefits of a concurrent PT service and a focus on quality assurance⁵⁹.

The implications of a learning curve with experience, or other improvements in planning and delivery techniques occurring through the trial duration, mean extra caution needs to be taken in implementation, quality assurance and verification of the latest technology in radiation oncology, and expertise needs to be acquired before its use can be compared to existing interventions. Two studies examining prostate cancer toxicity demonstrated increased gastrointestinal toxicity with PBT compared to IMRT^{47, 48}. In one study, lower gastrointestinal toxicity was seen less often among patients treated during the last two years of their cohort accrual with PBT⁴⁷. Both studies derived radiotherapy complication rates from billing claims linked to Medicare codes which were a coarse measure of treatment complications not reflecting patient symptom severity and prone to misclassification and confounders⁴⁵. There was also no information regarding RT dose, target volumes, margins or dose-volume histograms.

Several clinical reports on the harms of PT have been published previously^{60, 61}, including the possibility of increased acute brain injury with use of PBT in children⁶² with a high (31%) incidence of rates of radiation necrosis occurring in multiple areas in the brain remote to the initial tumour site and with a short time to onset⁶⁰. Gunther et al. reported more frequent MRI changes with PBT compared to IMRT for paediatric ependymoma²⁰. There were higher rates of neurological adverse effects in the systematic review by Patel et al.¹² in patients with paranasal sinus tumours. This could reflect a reporting bias as toxicity was more commonly reported in PT studies (92%) than photon RT studies (57%, $p=0.03$), or referral bias whereby anatomically challenging cases were referred to PT institutions. Higher toxicity with PBT might also reflect the greater relative biological effectiveness of PT which was not accounted for in some cases¹².

The results of studies demonstrating either no reduction of, or at times increased frequency or severity of toxicities, runs counter to the opinion that PT is inherently superior to photon RT and therefore it is unethical to conduct randomised trials⁵⁷. Randomised trials are underway and early reports are emerging. Most of the more recent RCTs are IMPT based and use more advanced technology, e.g. in planning and image guidance, now more widely available. The results of a phase IIB randomised trial for PBT vs IMRT in patients with oesophageal cancer was presented at the 2019 ASTRO Annual Meeting⁶³. This reported that the dosimetric superiority of PBT translates to clinically significant reductions in severe adverse events following chemoradiation performed at a single institution. The total toxicity burden was significantly less for PBT than IMRT by 2.3-2.5 times, while the progression-free survival, overall survival and tumour pathological response were comparable between groups for a median follow-up period of 44.1 weeks⁶⁴. The preliminary results of this study have prompted the launch of a Phase III trial equivalent by the same investigators (NRG-G1006). As

of November 2019, there are 120 recruiting phase II trials examining PT registered on ClinicalTrials.gov⁵⁵.

More robust data are required. This could be through implementation of well-designed and conducted randomised trials, as well as formation of a national and international PT registry incorporating outcomes including acute and long term toxicity, on which strategies such as the model-based approach for patient selection^{65, 66} could be used to feed back into optimal clinical trial design. Furthermore, photon patient outcomes data would also be collected in the registry for patients considered for PT but assigned to photon RT to develop a comparative outcome group. Prospective, high-quality, database-derived toxicity data are emerging such as the recently published study by Kahalley et al.⁶⁷ demonstrating for the first time more favourable intellectual outcomes with PBT compared with photon RT for paediatric patients with medulloblastoma treated on a comparable contemporary protocol. Even more recently, a large non-randomised comparative effectiveness study from the University of Pennsylvania Health System reported on 1483 adult patients with locally advanced cancer of 11 different types comparing photon RT to PBT, both with concurrent chemotherapy, using prospectively collected adverse event data⁶⁸. It found PBT to be associated with a nearly two-thirds reduction in 90-day severe adverse events, unplanned hospitalisations and lower risk of performance status decline⁶⁸. Indications for PT will evolve as clinical trials and well-curated databases and registries provide data about toxicity, quality of life and patient reported measures. Through a nationally unified approach across Australia and New Zealand, a meaningful contribution to this growing international effort can be made.

Conclusion

The majority of studies included in this systematic review reported equal or improved toxicity outcomes with PT as evaluated against photon RT, in comparison with either historical controls or non-concurrent cohorts. This demonstration of potentially decreased toxicities in a range of sites supports the predictions from dosimetric modelling and the wide international acceptance of this rationale for PT use in specific indications. The review supports the use of PBT for H&N tumours^{10, 11}, paediatrics^{15, 18, 21, 22}, CNS³⁰, GIT^{33, 34} and ocular tumours^{39, 41}, and CIT for sarcoma²³, in line with international recommendations^{69,70} and consistent with our earlier review⁶. Future clinical trials must take into account technological advancement in PT including its evolving delivery techniques, image guidance availability and sophistication of planning algorithms⁷¹. Collection of detailed outcome data particularly acute and late toxicity and patient reported measures is paramount, and optimally collected through well-orchestrated national and international registries.

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Tables

Table 1: Search strategy and number of included articles

	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	07/03/2019	1015	1015	122

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])				
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	3
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	53

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Table 2: Number of articles according to tumour subsite and type of particle therapy

Subsite	Total	Proton	Carbon	Mixed
H&N [†]	32	13	15	4
Paediatrics	42	41	0	1
Sarcoma	23	12	8	3
CNS [‡]	18	16	0	2
GIT [§]	18	11	3	4
Ocular	15	13	1	1
Thoracic	7	5	0	2
Prostate	13	13	0	0
Breast	4	4	0	0
Skin	1	0	1	0
Re-irradiation (mix of tumour types)	1	1	0	0
Mix of tumour types	5	3	1	1
Total	179	132	29	18

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

Table 3a: Strength of evidence- proton therapy studies

Subsite	Proton	Level II <i>RCT</i> [†]	Level III <i>Comparative cohort study</i>	Level IV <i>Case series</i>	Systematic review
H&N [†]	13	0	2	11	0
Paediatrics	41	0	10	30	1
Sarcoma	12	0	0	12	0
CNS [‡]	16	0	2	13	1
GIT [§]	11	1	2	7	1 (RCT=1)
Ocular	13	0	2	10	1
Re-irradiation	1	0	0	0	1
Thoracic	5	1	0	4	0
Prostate	13	0	4	9	0
Breast	4	0	1	3	0
Skin	0	0	0	0	0
Mix	3	0	1	0	2 (RCT=6)
Total	132	2	24	99	7

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

Table 3b: Strength of evidence- carbon ion studies

Subsite	Carbon ion	Level II <i>RCT</i> [†]	Level III <i>Comparative cohort study</i>	Level IV <i>Case series</i>	Systematic review
H&N [†]	15	0	0	15	0
Paediatrics	0	0	0	0	0
Sarcoma	8	0	1	7	0
CNS [‡]	0	0	0	0	0
GIT [§]	3	0	0	3	0
Ocular	1	0	0	1	0

Re-irradiation	0	0	0	0	0
Thoracic	0	0	0	0	0
Prostate	0	0	0	0	0
Breast	1	0	0	0	0
Skin	0	0	0	1	0
Mix	1	0	0	0	1
Total	29	0	1	27	1

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

Table 3c: Strength of evidence- mixed therapy studies					
Subsite	Mixed therapy	Level II RCT[†]	Level III Comparative cohort study	Level IV Case series	Systematic review
H&N [†]	4	-	-	2	2
Paediatrics	1	-	-	-	1
Sarcoma	3	-	-	2	1
CNS [‡]	3	-	0	2	-
GIT [§]	4	-	-	2	2
Ocular	1	-	-	-	1 (RCT=3)
Re-irradiation	0	-	-	-	-
Thoracic	2	-	1	1	-
Prostate	0	-	-	-	-
Breast	0	-	-	-	-
Skin	0	-	-	-	-
Mix	1	-	-	-	1 (RCT=4)
Total	18	0	1	9	8

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

Supplementary Material: Further Appendices (online only)

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

- 721 Appendix II: Paediatric tumours (studies as per PT type)
- 722 Appendix III: Sarcomas (studies as per PT type)
- 723 Appendix IV: Central nervous system tumours (studies as per PT type)
- 724 Appendix V: Gastrointestinal tumours (studies as per PT type)
- 725 Appendix VI: Ocular tumours (studies as per PT type)
- 726 Appendix VII: Other tumour sites (studies as per subsite)
- 727 Appendix VIII: Included studies from Tumour Outcomes systematic review⁶ (studies as per subsite
- 728 and PT type)

Figure 1a: PRISMA flow chart of study selection for 'tumour and toxicity outcomes' studies

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Figure 1b: PRISMA flow chart of study selection for 'toxicity outcomes only' studies

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