

Proton beam therapy:

A rapid review of evidence

An Evidence Snapshot brokered by the Sax Institute for Cancer Australia
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Executive summary

Background and purpose

This rapid evidence review was commissioned by Cancer Australia and prepared by the Sax Institute. Note that it was completed within 3 weeks, to provide information for a Cancer Australia meeting on 3 May 2023, so while a rigorous process for searching was followed it is possible that some peer reviewed or grey literature may have been missed. We have highlighted the limitations throughout this report.

The purpose of the report is to conduct a rapid review of the recent evidence (since 2020) on proton beam therapy (PBT) for: paediatric cancers, central nervous system (CNS) tumours, head and neck cancer and prostate cancer. The report aims to provide a rapid summary of the current knowledge about PBT's effectiveness, safety, and potential advantages over conventional radiation therapy. The report includes evidence that has become available subsequent to the evidence submitted in the South Australian Health and Medical Research Institute (SAHMRI)'s Medical Services Advisory Committee (MSAC) application requesting Medicare Benefits Schedule (MBS) listing of PBT for paediatric and rare cancers (MSAC Application No. 1638). In addition, the report presents data on international benchmarking of PBT facilities per million population, and with consideration to Australia's population and numbers of people with cancers recommended for public funding for PBT by MSAC.

Review question

What is the strength of the evidence for PBT for cancers recommended for public funding for PBT by Medical Services Advisory Committee (MSAC)?

Methods

We searched MEDLINE, the Cochrane Collaboration Library, and Web of Science. We reviewed the title and abstracts of n=850 peer reviewed papers. In addition, we searched grey literature for health technology assessment (HTA) reports. We reviewed n=2 (HTA) reports. The searches were completed by 4th April 2023.

We report our full search criteria and results in Appendix 2-3.

Results

- We identified the following papers for full review: n=24 peer review papers: including n=4 meta-analyses, n=16 systematic reviews, n=3 narrative reviews, n=1 a randomised controlled trial (RCT); and n=2 publicly available health technology assessments (HTAs) in the grey literature.
- The overall quality of evidence in these reviews was limited due to factors such as small sample sizes, non-randomised study designs, heterogeneity in study designs, and short follow-up periods.
- Many reviews, including Underwood et al. (2022), Maillie et al. (2021), Jones et al. (2020), and Peterson and King (2022), noted that there is a need for well-designed randomised and model-based clinical trials to provide a stronger evidence base for PBT for particular cancer types.
- Overall, there is a need for more high-quality evidence to better understand the effectiveness, safety, and cost-effectiveness of PBT in various cancer types and populations.

Limitations

- Our search strategy focused on recent meta-analyses and systematic reviews, potentially excluding relevant primary studies, non-systematic reviews, or older publications, and limited to English language.
- The prioritisation of high-quality evidence may exclude informative studies with lower levels of evidence.
- The rapid review methodology may have led to less comprehensive searching, appraisal, and synthesis of literature, increasing susceptibility to bias and potentially missing relevant studies.
- The strength of the included evidence for proton beam therapy varied across cancer types and outcomes, with generally low quality due to retrospective case series, small cohorts, and lack of direct comparisons.
- Caution should be taken when interpreting findings from reviews that do not explicitly rate the quality of included evidence, such as Kiseleva et al. (2022).

Findings from peer reviewed meta-analyses and systematic reviews (since 2020)

Paediatric cancer

- The quality of evidence was limited and generally of low quality, suggesting further high-quality research is needed to fully understand the effectiveness and safety of PBT for paediatric patients, as well as addressing disparities in access to PBT.

However, we present the following findings from the evidence included in this review:

- One systematic review suggested that PBT may offer comparable or improved outcomes compared to conventional radiation therapy for paediatric patients, particularly in tumours near critical structures or radiation-sensitive tissues due to its precise targeting capabilities.
- Three systematic reviews reported that PBT may reduce acute and long-term toxicities in paediatric patients compared to conventional radiation therapy, helping to minimise treatment-related side effects and improve quality of life.
- Four systematic reviews noted that PBT's ability to spare healthy tissues from radiation may reduce the risk of late complications, such as secondary malignancies and growth disturbances, which can be especially significant in paediatric patients, potentially contributing to improved quality of life.
- Two systematic reviews observed that PBT treatment had been observed to cause less cognitive deficits compared with photon therapy for specific tumour types.

Central nervous system (CNS) tumours

- The quality of evidence in the studies included in this review was varied, with many studies having low certainty due to limitations such as heterogeneity of study designs, small number of studies, non-randomised nature of the studies, and lack of direct comparisons; more high-quality research is needed.

However, we present the following emerging findings from the evidence included in this review:

- One systematic review investigating the treatment of chordoma using PBT and photon therapy reported uncertainty regarding the effect of PBT compared to photon therapy on overall survival and progression-free survival, due to low certainty of evidence.
- One systematic review reported that proton CSI may provide safer palliation of symptoms and prolong survival in patients with leptomeningeal disease.
- One systematic review reported uncertainty regarding the effect of PBT compared to photon therapy on treatment-related toxicity.

Head and neck cancers

- The quality of evidence was limited and of low certainty due to limitations including heterogeneity of study designs, small number of studies and retrospective study designs; more prospective clinical trials are needed.

However, we present the following emerging findings from the evidence included in this review:

- One systematic review with 26 retrospective studies showed improved 2-year overall survival rates (33%-80%) in recurrent sinonasal (57%-76%), nasopharyngeal (33%-74%), and salivary gland (57%-80%) tumour patients treated with PBT compared to a range of 12%-68% for patients treated with IMRT.
- Only one study in one systematic review reported higher 5-year progression-free survival rates (34.9%) for PBT than IMRT (20.4%) in oesophageal cancer patients.
- Two reviews reported that PBT has potentially favourable toxicological profiles compared to photon irradiation. One of these reviews found that PBT can reduce acute toxicities and late xerostomia in head and neck squamous cell carcinomas patients compared to IMRT, with lower rates of higher-grade oral mucositis for nasopharyngeal cancer patients.
- One systematic review found proton therapy may cause late complications, with rates of late xerostomia grade ≥ 2 ranging from 3.9% to 47% in primary nasopharyngeal carcinoma patients.

Prostate cancer

- The quality of evidence was limited and of generally low quality; more high-quality evidence including RCTs and long-follow up studies are needed.

However, we present the emerging evidence from studies included in this review below.

- One systematic review suggested that PBT may offer higher overall survival rates compared to conventional and hypofractionated photon radiotherapy for prostate cancer patients.
- One systematic review found that PBT and CIRT were both associated with a lower incidence of grade 2 or greater acute and late genitourinary and gastrointestinal toxicity compared to photon radiotherapy.
- One systematic review of particle therapy toxicity outcomes reported gastrointestinal morbidities in prostate cancer patients treated with PBT compared to photon radiotherapy.
- One systematic review reported improved quality of life outcomes in prostate cancer patients treated with PBT compared to photon radiotherapy.

Emerging evidence for lung and breast cancer

This review found one randomised controlled trial that compared proton craniospinal irradiation (pCSI) with photon involved-field radiotherapy (IFRT) in patients with leptomeningeal metastasis solid tumor non-small cell lung cancer (NSCLC) and breast cancer. The authors found that pCSI significantly improved CNS progression-free survival (PFS) (7.5 months vs. 2.3 months, $p < .001$) and overall survival (OS) (9.9 months vs. 6.0 months, $p = .029$) without increasing high-grade adverse events. This trial provided high-quality evidence supporting the use of PBT for patients with NSCLC and breast cancer leptomeningeal metastasis.

Health technology assessments (HTAs)

- The Ontario Health HTA found that proton beam therapy may result in similar overall survival and progression-free survival, but fewer toxicity events, in various adult cancers, while evidence for paediatric cancers was insufficient or of low quality.
- The Belgian KCE HTA concluded that high-quality evidence on the effectiveness of proton treatment was lacking, making it impossible to determine if it was better or worse than photon-based radiotherapy for specific adult cancers.
- The Ontario Health HTA acknowledged that high-quality evidence remains scarce, but there is ongoing research, and the rapidly evolving technology of proton beam therapy may not be fully reflected in reviews of the research.

Effectiveness among specific populations

- There was no recent research on effectiveness among different age groups, culturally and linguistically diverse (CALD) backgrounds, or populations outside of populations with particular cancers.

Summary of findings

This section provides a summary of review papers identified with relevant findings relating to overall survival, progression-free survival, tumour or local control, toxicity or side effects, late complications, quality of life, patient experience, and effectiveness among specific populations by cancer type.

At its 80th Meeting (26-27 November 2020) MSAC supported the creation of new MBS items for PBT for specified rare cancers. MSAC recommended that PBT be restricted to:

- Paediatric, adolescent and young adult patients (under 25 years) with:
 - with a solid tumour located in:
 - the central nervous system; or
 - the orbit, including retinoblastoma; or
 - the axial skeleton or in close proximity to the axial skeleton, including bone or soft tissue sarcoma; or
 - craniopharyngioma
 - intracranial germ cell tumour
 - neuroblastoma
 - nephroblastoma.
- Adult patients with:
 - a tumour of the base of the skull, including meningioma, chordoma or chondrosarcoma; or
 - a tumour of the vertebral column or bony pelvis; or
 - an adenoid cystic carcinoma of the salivary or lacrimal gland.

This review builds on the evidence for paediatric patients (≤ 18 years) with various tumours (including brain tumours, sarcomas, and other solid tumours) and adults with CNS cancers and head and neck cancers. New evidence is presented for prostate cancer, lung cancer and breast cancer which were not included in SAHMRI's application (MSAC Application No. 1638).

Strength of the evidence

Based on the papers identified in this review, the strength of evidence for proton beam therapy varied across different cancer types and outcomes. The quality of evidence was generally low, with most studies being retrospective case series, small patient cohorts, varied techniques, and a lack of direct comparison between photon and proton therapy. However, some studies suggest that proton therapy has promising outcomes and improved toxicity profiles compared to photon-based radiation, particularly in head and neck cancers such as nasopharyngeal cancer, recurrent sinonasal, and salivary gland tumours, and head and neck squamous cell carcinomas.

Overall, the evidence for PBT was limited by the small number of studies, retrospective nature, and heterogeneity among the included studies. Some papers, such as Beddok et al. (2020) and Doig et al. (2021), call for well-designed, randomised and model-based clinical trials to provide stronger evidence in the coming years. The quality of evidence was generally low, with most studies being

single institution retrospective case series (NHMRC level IV), and the certainty of the evidence was very low based on the meta-regression analysis in Li et al. (2021). The review by Halasz et al. (2022) also notes that there have been no RCTs comparing proton therapy to other radiation therapy techniques.

It is important to note that the review by Kiseleva et al. (2022) did not explicitly rate the quality of evidence, but rather summarised multiple clinical and experimental studies, indicating that the review is based on a wide range of existing research, meaning that caution should be taken in interpreting the findings of this paper.

Limitations

The limitations of this rapid evidence review should be considered when interpreting the findings.

1. The review prioritised systematic reviews, meta-analyses, and randomised controlled trials (RCTs). While these study designs provide high-quality evidence, they may not be as common in emerging fields such as PBT, which could lead to the exclusion of potentially informative studies with lower levels of evidence. Additionally, excluding primary studies may limit the ability to identify novel findings or trends in PBT effectiveness not yet covered in systematic reviews or meta-analyses.
2. The inclusion and exclusion criteria may limit the scope of the review, excluding studies on PBT for non-cancerous conditions, technical aspects of PBT, or studies not available in full-text. These criteria may overlook potentially relevant research that could provide additional insights into the effectiveness of PBT and its application in various patient populations.
3. The rapid review methodology is designed to quickly identify and synthesise relevant evidence, which may lead to less comprehensive searching, appraisal, and synthesis of the literature compared to a traditional systematic review. As a result, the rapid review may be more susceptible to bias and less likely to provide a complete overview of the available evidence on PBT effectiveness.
4. While the review includes a search for grey literature, it may not comprehensively cover all relevant health technology assessments (HTAs) or other unpublished studies, which could lead to publication bias and an incomplete picture of the evidence on PBT effectiveness.
5. Given that this rapid review was prepared in three weeks, our methodology may not allow for an extensive search, screening, and data extraction process due to time constraints. This limitation may increase the risk of missing relevant studies and decrease the comprehensiveness of the review.

Despite these limitations, this rapid evidence review aims to provide a timely and relevant overview of the current evidence on PBT effectiveness in treating specific cancer types.

Paediatric cancer

There was limited evidence available for the effectiveness of PBT for paediatric cancer patients. Moreover, the quality of the evidence in the studies reported in this review was limited by factors such as small sample sizes, inconsistent assessment methods, varying follow-up periods (Pahwa et al., 2022), and non-randomised study designs with variability in medical and sociodemographic factors between treatment groups (Peterson & King, 2022). These limitations suggest that more high-quality research is needed to fully understand the effectiveness and safety of PBT for paediatric cancer patients.

Notwithstanding these limitations, the available evidence suggests PBT may offer potential benefits in terms of reducing toxicities, minimising treatment-related side effects, and improving quality of life. However, further high-quality research is needed to better understand the long-term effectiveness and safety of PBT.

Six review papers were identified as relating to the effectiveness of proton beam therapy (PBT) for paediatric cancer patients; Pahwa et al. (2022), Doig et al. (2021), Yahya and Manan (2021), Peterson and King (2022), Upadhyay et al. (2022), and Thomas and Timmermann (2020). Four further papers included paediatric findings in their narrative review; Kiseleva et al. (2022) and Prasanna et al. (2021), Hwang et al. (2020) and Underwood et al. (2022) although not all directly reported on the following outcomes.

1. **Overall survival and progression-free survival:** The studies reviewed did not report specific overall survival or progression-free survival rates for paediatric cancer patients treated with PBT. However, Thomas and Timmermann (2020) noted that PBT may offer comparable or improved outcomes compared to conventional radiation therapy for medulloblastoma, ependymoma, low-grade glioma, rhabdomyosarcoma, and retinoblastoma.
2. **Tumour or local control:** Thomas and Timmermann (2020) reported good local control rates in various paediatric cancers, particularly in tumours such as CNS tumours, most rhabdomyosarcomas and retinoblastomas, which are located near critical structures or radiation-sensitive tissues where PBT's precise targeting capabilities can help reduce damage to healthy tissues.
3. **Toxicity and side effects:** Proton beam therapy has been shown to reduce acute and long-term toxicities compared to conventional radiation therapy (Thomas & Timmermann, 2020). This is particularly important for paediatric patients, as reducing toxicities can help minimise treatment-related side effects and improve their quality of life. Yahya and Manan (2021) reported that late endocrine abnormalities, radiogenic second cancers, and cardiac mortality were observed to be reduced with PBT. Hwang et al. (2020) reported that PBT demonstrated reduced toxicities compared to photon RT.
4. **Late complications:** Thomas and Timmermann (2020) suggested that PBT's ability to spare healthy tissues from radiation can potentially reduce the risk of late complications, such as secondary malignancies and growth disturbances, which can be especially significant in paediatric patients. Upadhyay et al. (2022) found a shorter latency to secondary cancers with PBT compared to photon therapy. Yahya and Manan (2021) reported that late endocrine abnormalities, radiogenic second cancers, and cardiac mortality were observed to be reduced with PBT. Hwang (2020) found reduced secondary malignancy rates in paediatric tumors treated

with PBT and uncommon late severe radiation morbidities in HCC treatment with PBT (2.3% rate of grade 3 or more late adverse events).

5. **Quality of life:** Doig et al. (2022) found that there is insufficient quality evidence to compare health-related quality of life (HRQoL) outcomes between photon (XRT) and PBT radiation therapy for childhood cancer survivors. Thomas and Timmermann (2020) reported that by reducing toxicities and late complications, proton therapy may contribute to improved quality of life for paediatric patients.
6. **Patient experience and effectiveness among specific populations:** Doig et al. (2022) suggested that PBT may offer certain advantages for patients with brain and CNS tumors, with improved HRQoL outcomes and fewer late toxicities. Pahwa et al. (2022) found a reduction in cognitive decline for paediatric brain tumour patients treated with proton therapy compared to photon therapy. While cognitive decline is evident, it was not profound for focal therapy at a median of 2- to 3-year follow-up following proton therapy. However, the study did note that neurocognitive impairments could impact the quality of life of paediatric brain tumour survivors. Yahya and Manan (2021) reported that the effectiveness of PBT among specific populations varied, with PBT observed to cause less cognitive deficits compared with photon therapy. Children who underwent focal therapy with PBT were consistently shown to have low risk of cognitive deficit, although patients treated with craniospinal irradiation and those with hydrocephalus had poorer cognitive outcomes. Peterson and King (2022) did not specifically discuss effectiveness among specific populations, but the paper did emphasise the sociodemographic disparities in access to PBT, suggesting that understanding the impact of PBT on different populations and patient experiences is essential for equitable access to treatment.

Central nervous system (CNS) tumours

The quality of evidence in the studies included in this review was varied, with many studies having low certainty due to various limitations such as heterogeneity of study designs, small number of studies, non-randomised nature of the studies, and lack of direct comparison between photon and proton therapy. Further research, including randomised controlled trials, is needed to strengthen the evidence behind PBT for CNS tumours.

While the evidence for the efficacy of PBT in CNS cancers is still limited, there are promising findings emerging related to improved HRQoL outcomes, reduced late toxicities, and better cognitive outcomes for specific populations, particularly those receiving PBT for brain tumours and CNS tumours. However, more high-quality research is needed.

Three papers were identified as being related to the review of CNS tumours; Halasz et al. (2022), El Sayed et al. (2021), and Maillie et al. (2021).

1. **Overall survival and progression-free survival:** El Sayed et al. (2021) investigated the treatment of chordoma using PBT and photon therapy. The authors reported uncertainty regarding the effect of PBT compared to photon therapy on overall survival and progression-free survival, with very low certainty of evidence due to the high risk of bias, imprecision, and inconsistency among studies. Maillie et al. (2021) reported a median overall survival of 5.3 months for patients treated with craniospinal irradiation for leptomeningeal disease. The authors

concluded that while leptomeningeal disease remains a devastating end-stage complication of some malignancies, in select patients marrow-sparing proton CSI may provide safer palliation of symptoms and prolong survival.

2. **Toxicity and side effects:** El Sayed et al. (2021) reported uncertainty regarding the effect of PBT compared to photon therapy on treatment-related toxicity. Halasz et al. (2022) reported acute side effects of radiation therapy for IDH-mutant grade 2 and grade 3 diffuse glioma, including fatigue, weight loss, headache, skin erythema, otitis, nausea/vomiting, and alopecia. Maillie et al. (2021) reported that hematologic and gastrointestinal toxicities were the most common side effects of craniospinal irradiation.
3. **Quality of life and patient experience:** Halasz et al. (2022) mentioned that late effects of radiation therapy and chemotherapy can be particularly devastating in patients with IDH-mutant grade 2 and grade 3 diffuse glioma, affecting their quality of life. In a study by Maillie et al. (2021), stable-to-improved neurological symptoms were noted in more than half of the cases treated with craniospinal irradiation for leptomeningeal disease.
4. **Effectiveness among specific populations:** Maillie et al. (2021) noted that younger patients may be better able to tolerate proton CSI and are more likely to be candidates for this treatment modality.

Head and neck cancers

The quality of evidence for the use of PBT in treating head and neck cancer patients in studies included in this review was limited due to the small number of studies, retrospective nature of the studies, and heterogeneity among the included studies. Further well-designed, prospective clinical trials are needed to establish a robust evidence base and identify the patients who will benefit the most from PBT.

While the evidence for the efficacy of PBT in treating head and neck cancer patients is limited, there are promising findings emerging in term of potential benefits in overall survival, progression-free survival, tumour or local control, and reduced toxicity compared to IMRT.

Six papers were identified as being related to the review of head and neck cancer; Yahya et al. (2023), Wang et al. (2021), Beddok et al. (2020), Gamez et al. (2021), Lee et al. (2021) and Nicholas et al. (2021). One further paper included head and neck findings in their narrative review; Jumaniyazova (2023).

1. **Overall survival:** A systematic review by Gamez et al. (2021) reported 2-year overall survival rates (33%-80%) in recurrent sinonasal (57%-76%), nasopharyngeal (33%-74%), and salivary gland (57%-80%) tumor patients compared to a range of 12%-68% for patients treated with IMRT. Another systematic review by Nicholas et al. (2021) reported a 5-year overall survival rate of 41.6% for PBT compared to 31.6% for IMRT in oesophageal cancer patients ($p=0.011$).
2. **Progression-free survival:** Only one study in Nicholas (2021) reported 5-year progression-free survival (PFS) rates of 34.9% for PBT and 20.4% for IMRT ($p=0.01$) in oesophageal cancer patients.

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3. **Tumour or local control:** Gamez et al. (2021) reported 2-year local control rates of 50%-86% for proton re-irradiation therapy and 41%-92% for carbon ion re-irradiation therapy in recurrent sinonasal, nasopharyngeal, and salivary gland tumours.
 4. **Toxicity and side effects:** Beddok et al. (2020) and Jumaniyazova (2023) both reported that PBT has potentially favorable toxicological profiles compared to photon irradiation. Beddok et al. (2020) found that proton therapy can reduce acute toxicities like mucositis, dysgeusia, dysphagia, and fatigue, as well as late xerostomia compared to IMRT in HNSCC patients. Gamez et al. (2021) reported rates for acute grade 3 toxicities ranging from 1% to 35%, with dysphagia, mucositis, and radiation dermatitis being the most frequent, and rates for late grade 3 toxicities ranged up to 37% for protons and up to 35% for carbons, with brain necrosis, ototoxicity, visual deficits, and bleeding being most commonly reported. Lee et al. (2021) reported lower rates of higher-grade oral mucositis (7%-11.1%) with PBT compared to IMRT for nasopharyngeal cancer patients. PBT has comparable or lower toxicity rates than photon techniques, except for Grade 4 lymphopenia in oesophageal cancer patients Nicholas et al. (2021).
 5. **Late complications:** Sixteen cases of grade 5 reported toxicities for all treated patients (n=16/1118, 1.4%) with fatal bleeding as the leading cause were reported by Gamez et al. (2021). Yahya et al. (2023) reported late xerostomia grade ≥ 2 in four studies affecting between 3.9% and 47% of primary nasopharyngeal carcinoma patients.
 6. **Quality of life and patient experience:** There is no explicit mention of quality of life or patient experience in the studies included in the reviews on head and neck cancers. However, lower toxicity levels are generally associated with better patient experiences, as suggested by the studies that discuss toxicity profiles (Yahya et al., 2023).
 7. **Effectiveness among specific populations:** PBT may have a greater impact on reducing cardiac toxicities in high-risk patients with underlying cardiac disease (Nicholas et al., 2021). A model-based approach to patient selection, considering individual patient characteristics and tumour location, may be more effective in determining which patients are more likely to benefit from proton therapy (Wang et al., 2021).

Prostate cancer

Two papers were identified as being related to the review of the treatment of prostate cancer; Du et al. (2022), and Li et al. (2021). Four further papers included prostate cancer findings in their review; Kiseleva et al. (2022) and Prasanna et al. (2021), Hwang et al. (2020) and Underwood et al. (2022) although not all directly reported on the following outcomes.

The quality of evidence in the studies included in this review for prostate cancer was generally low. Li et al. (2021) reported very low certainty of evidence according to the GRADE assessment¹. Hwang et al. (2020) reported that the quality of evidence in their systematic review was generally low. Of thirteen prostate cancer studies reviewed, nine were single institution retrospective case series (NHMRC level IV) and four were comparative studies (NHMRC level III).

¹ GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) is a systematic approach to rating the certainty of evidence in systematic reviews and other evidence syntheses and for making clinical practice recommendations.

The limited emerging evidence suggests that PBT may offer advantages for prostate cancer patients, including higher overall survival rates, improved local control rates, reduced toxicity, and better quality of life compared to conventional photon radiotherapy. However, the quality of the evidence was generally low, and more high-quality research, including randomised controlled trials and long-term follow-up studies is needed to provide a stronger evidence base for PBT in prostate cancer treatment.

1. **Overall survival:** Li et al. (2021) conducted a systematic review and meta-analysis comparing PBT and carbon ion radiotherapy (CIRT) to photon radiotherapy for prostate cancer treatment. PBT showed 3-, 4-, and 5-year overall survival (OS) rates of 97%, 87%, and 92%, respectively, while CIRT demonstrated 3-, 4-, and 5-year local control rates (LCR) of 98%, 97%, and 99%, respectively. The 5-year OS rate for conventional photon radiotherapy was 72%, and for hypofractionated photon radiotherapy 72.8%. These results suggest that PBT may offer higher overall survival rates compared to conventional and hypofractionated photon radiotherapy for prostate cancer patients.
2. **Tumour or local control:** Li et al. (2021) reported that CIRT showed higher local control rates compared to conventional and hypofractionated photon radiotherapy for prostate cancer patients.
3. **Toxicity or side effects:** Li et al. (2021) found that PBT and CIRT were both associated with a lower incidence of grade 2 or greater acute and late genitourinary and gastrointestinal toxicity compared to photon radiotherapy. Hwang et al. (2020) conducted a systematic review of particle therapy toxicity outcomes and reported reduced gastrointestinal morbidities in prostate cancer patients treated with PBT compared to photon radiotherapy.
4. **Quality of life:** Hwang et al. (2020) reported improved quality of life in prostate cancer patients treated with PBT compared to photon radiotherapy.
5. **Advantages of particle radiation:** Du et al. (2022) suggested potential advantages of PBT and CIRT over photon therapy for prostate cancer treatment, but the study was limited to in vitro data and did not examine clinical outcomes in humans.

Emerging cancers

The effectiveness of proton beam therapy (PBT) in the treatment of various cancers has gained increasing interest, particularly in cancers with an emerging evidence base for this type of therapy. Within our review of meta-analyses, systematic reviews and RCTs, we found five papers that explored the effectiveness of PBT outside of the four cancers above; Jumaniyazova (2023), Kiseleva (2022), Prasanna (2021), Hwang (2020) and Underwood (2022). We also identified one RCT on the effectiveness of PBT on lung and breast cancer; Yang (2022).

The quality of the evidence included in these reviews was generally low, suggesting that more high-quality studies, such as well-conducted randomised controlled trials, are needed to strengthen the evidence base for PBT and optimise its clinical application.

However, the limited emerging evidence included in this review suggests that PBT may offer improved outcomes in various cancer types, including breast cancer and lung cancer.

Leptomeningeal metastasis from breast cancer and lung cancer: Findings from a recent RCT

In a randomised phase II trial, Yang (2022) compared proton craniospinal irradiation (pCSI) with photon involved-field radiotherapy (IFRT) in patients with leptomeningeal metastasis solid tumour non-small cell lung cancer (NSCLC) and breast cancer. They found that pCSI significantly improved CNS progression-free survival (PFS) (7.5 months vs. 2.3 months, $p < .001$) and overall survival (OS) (9.9 months vs. 6.0 months, $p = .029$) without increasing high-grade adverse events. This trial provided high-quality evidence supporting the use of PBT for patients with NSCLC and breast cancer leptomeningeal metastasis.

Other emerging benefits

- Jumaniyazova (2023) highlighted the potential favourable toxicological profiles of PBT compared to photon irradiation due to the physical properties of protons. They found that proton therapy may have some advantages, such as causing more permanent DNA damage to tumour cells, modulating the expression of pro-inflammatory genes differently in head-and-neck squamous cell carcinoma (HNSCC). It may also hold advantages in treating hypoxic neoplasms such as breast cancer and pancreatic duct adenocarcinoma.
- Prasanna (2021) reviewed normal tissue injury induced by photon and proton therapies for various cancer types, including lung, prostate, breast, head and neck, and paediatric malignancies. They found that proton therapy has potential benefits such as lower radiation doses to healthy tissues and reduced acute and late toxicities.
- Underwood (2022) conducted a systematic review of clinical studies on variable proton Relative Biological Effectiveness (RBE) for various cancer types, including brain tumours, gliomas, breast cancer, head and neck tumours, prostate cancer, and paediatric cancers. Although the evidence for variable proton RBE was weak, the authors highlighted the need for larger, prospective datasets and better standardisation of follow-up timepoints, protocols, and statistical analysis methods.

Health Technology Assessments (HTAs)

Ontario Health (2021) published a health technology assessment (HTA) in 2021 which reported on the results as they were presented in the 2019 Washington State health technology assessment. The Ontario Health HTA systematically searched for a recent systematic review with high methodological quality to leverage existing evidence and identified the Washington State HTA. The authors also ran a systematic literature search to identify any relevant randomised controlled trials published since the Washington State HTA was conducted, however, none were identified that met their inclusion criteria.

The Ontario Health (2021) HTA reported that compared with photon therapy, proton beam therapy may result in similar overall survival and progression-free survival in children with brain tumours (GRADE: Low) and may result in fewer events of hypothyroidism (GRADE: Low to Very low). There was insufficient evidence to determine the effectiveness of proton beam therapy, compared with photon therapy, in other paediatric cancers. The authors also reported that proton beam therapy may result in similar overall survival and progression-free survival, but fewer toxicity events, in adults with

oesophageal cancer (GRADE: Low to Very low), head and neck cancer (GRADE: Low to Very low), prostate cancer (GRADE: Low) and liver cancer (GRADE: Moderate). Proton beam therapy may result in similar overall survival, progression-free survival, and toxicity events in adults with brain tumours (GRADE: Low), breast cancer (GRADE: Low), gastrointestinal cancer (GRADE: Very low), lung cancer (GRADE: Moderate to Very low), and ocular tumours (GRADE: Low). There was insufficient evidence to determine the effectiveness of proton beam therapy in adults with bladder cancer, bone cancer, lymphoma, and benign tumours.

The Belgian Health Care Knowledge (KCE) (Vlayen J, García Fernández Li, Boterberg T, & L., 2019), published a HTA in 2019 that evaluated PBT in adults with low-grade glioma, primary sinonasal tumours and recurrences of head and neck tumours, breast cancer in women, pancreatic cancer, hepatocellular cancer and locally recurrent rectal cancer. The KCE HTA found that high-quality evidence on the effectiveness of proton treatment was lacking, and it was impossible to conclude that proton treatment was better or worse than photon based radiotherapy.

The Ontario Health (2021) HTA noted that high-quality evidence remained scarce but that there was a considerable amount of research underway. The technology of PBT is evolving rapidly. The authors also noted that the literature reviewed did not necessarily reflect the advances of the latest technology.

Effectiveness among specific populations

Several studies have investigated the effectiveness of proton beam therapy (PBT) among specific patient populations. In their systematic review of PBT for CNS cancers and non-CNS cancers, including retinoblastoma, craniopharyngioma, chest wall sarcoma, rhabdomyosarcoma, and Hodgkin disease, Doig et al. (2021) observed a trend of improved health-related quality of life (HRQoL) for patients with brain tumours and CNS tumours who received PBT compared to photon therapy (Doig et al., 2022).

In a review of PBT for the management of nasopharyngeal cancer, the main findings suggest that PBT has comparable tumour control and survival outcomes to photon-based radiation, with a potential reduction in acute and late toxicities (Lee et al., 2021).

Overall, the effectiveness of PBT varies depending on the cancer type and individual patient factors, highlighting the need for personalised treatment planning and more research to determine the neuropsychological advantages of PBT (Kiseleva et al., 2022).

Appendix 1: Included publications

Research reviews and studies

1. Beddok, A., Vela, A., Calugaru, V., Tessonnier, T., Kubes, J., Dutheil, P., . . . Thariat, J. (2020). Proton therapy for head and neck squamous cell carcinomas: A review of the physical and clinical challenges. *Radiotherapy and Oncology*, 147, 30-39. doi:10.1016/j.radonc.2020.03.006
2. Doig, M., Bezak, E., Parange, N., Gorayski, P., Bedford, V., & Short, M. (2022). Can We Compare the Health-Related Quality of Life of Childhood Cancer Survivors Following Photon and Proton Radiation Therapy? A Systematic Review. *Cancers*, 14(16), 3937. doi:10.3390/cancers14163937
3. Du, T.-Q., Liu, R., Zhang, Q., Luo, H., Chen, Y., Tan, M., . . . Wang, X. (2022). Does particle radiation have superior radiobiological advantages for prostate cancer cells? A systematic review of in vitro studies. *European Journal of Medical Research*, 27(1). doi:10.1186/s40001-022-00942-2
4. El Sayed, I., Trifiletti, D. M., Lehrer, E. J., Showalter, T. N., & Dutta, S. W. (2021). Protons versus photons for the treatment of chordoma. *Cochrane Database of Systematic Reviews*, 2021(7). doi:10.1002/14651858.CD013224.pub2
5. Gamez, M. E., Patel, S. H., McGee, L. A., Sio, T. T., McDonald, M., Phan, J., . . . Rwigema, J.-C. M. (2021). A systematic review on re-irradiation with charged particle beam therapy in the management of locally recurrent skull base and head and neck tumors. *International Journal of Particle Therapy*, 8(1), 131-154. doi:10.14338/IJPT-20-00064.1
6. Halasz, L. M., Attia, A., Bradfield, L., Brat, D. J., Kirkpatrick, J. P., Laack, N. N., . . . Shih, H. A. (2022). Radiation Therapy for IDH-Mutant Grade 2 and Grade 3 Diffuse Glioma: An ASTRO Clinical Practice Guideline. *Practical Radiation Oncology*, 12(5), 370-386. doi:10.1016/j.prro.2022.05.004
7. Hwang, E. J., Gorayski, P., Le, H., Hanna, G. G., Kenny, L., Penniment, M., . . . Ahern, V. (2020). Particle therapy toxicity outcomes: A systematic review. *Journal of Medical Imaging and Radiation Oncology*, 64(5), 725-737. doi:10.1111/1754-9485.13036
8. Jumaniyazova, E., Smyk, D., Vishnyakova, P., Fatkhudinov, T., & Gordon, K. (2023). Photon- and Proton-Mediated Biological Effects: What Has Been Learned? *Life*, 13(1). doi:10.3390/life13010030
9. Kiseleva, V., Gordon, K., Vishnyakova, P., Gantsova, E., Elchaninov, A., & Fatkhudinov, T. (2022). Particle Therapy: Clinical Applications and Biological Effects. *Life*, 12(12). doi:10.3390/life12122071
10. Lee, A., Kitpanit, S., Chilov, M., Langendijk, J. A., Lu, J., & Lee, N. Y. (2021). A systematic review of proton therapy for the management of nasopharyngeal cancer. *International Journal of Particle Therapy*, 8(1), 119-130. doi:10.14338/IJPT-20-00082.1
11. Li, M., Li, X., Yao, L., Han, X., Yan, W., Liu, Y., . . . Yang, K. (2021). Clinical Efficacy and Safety of Proton and Carbon Ion Radiotherapy for Prostate Cancer: A Systematic Review and Meta-Analysis. *Frontiers in Oncology*, 11. doi:10.3389/fonc.2021.709530

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12. Maillie, L., Salgado, L. R., & Lazarev, S. (2021). A systematic review of craniospinal irradiation for leptomeningeal disease: past, present, and future. *Clinical and Translational Oncology*, 23(10), 2109-2119. doi:10.1007/s12094-021-02615-8
 13. Nicholas, O., Prosser, S., Mortensen, H. R., Radhakrishna, G., Hawkins, M. A., & Gwynne, S. H. (2021). The Promise of Proton Beam Therapy for Oesophageal Cancer: A Systematic Review of Dosimetric and Clinical Outcomes. *Clinical Oncology*, 33(8), e339-e358. doi:10.1016/j.clon.2021.04.003
 14. Pahwa, B., Medani, K., Lu, V. M., & Elarjani, T. (2022). Proton beam therapy for skull base chordomas: a systematic review of tumor control rates and survival rates. *Neurosurgical Review*, 45(6), 3551-3563. doi:10.1007/s10143-022-01880-7
 15. Peterson, R. K., & King, T. Z. (2022). A systematic review of pediatric neuropsychological outcomes with proton versus photon radiation therapy: A call for equity in access to treatment. *Journal of the International Neuropsychological Society*, 1-14. doi:10.1017/S1355617722000819
 16. Prasanna, P. G., Rawojc, K., Guha, C., Buchsbaum, J. C., Miszczyk, J. U., & Coleman, C. N. (2021). Normal Tissue Injury Induced by Photon and Proton Therapies: Gaps and Opportunities. *International Journal of Radiation Oncology Biology Physics*, 110(5), 1325-1340. doi:10.1016/j.ijrobp.2021.02.043
 17. Shaikh, F., Sodhi, S., Kale, L., Talib, Y., & Saleem, H. (2020). Implementation of meta-analysis approach, comparing conventional radiotherapy, and proton beam therapy treating head and neck cancer. *Journal of Cancer Research and Therapeutics*, 16(3), 594. doi:10.4103/jcrt.JCRT_111_19
 18. Thomas, H., & Timmermann, B. (2020). Paediatric proton therapy. *The British Journal of Radiology*, 93(1107), 20190601. doi:10.1259/bjr.20190601
 19. Underwood, T. S. A., McNamara, A. L., Appelt, A., Haviland, J. S., Sørensen, B. S., & Troost, E. G. C. (2022). A systematic review of clinical studies on variable proton Relative Biological Effectiveness (RBE). *Radiotherapy and Oncology*, 175, 79-92. doi:10.1016/j.radonc.2022.08.014
 20. Upadhyay, R., Yadav, D., Venkatesulu, B. P., Singh, R., Baliga, S., Raval, R. R., . . . Palmer, J. D. (2022). Risk of secondary malignant neoplasms in children following proton therapy vs. photon therapy for primary CNS tumors: A systematic review and meta-analysis. *Frontiers in Oncology*, 12. doi:10.3389/fonc.2022.893855
 21. Wang, X., Hobbs, B., Gandhi, S. J., Muijs, C. T., Langendijk, J. A., & Lin, S. H. (2021). Current status and application of proton therapy for esophageal cancer: Proton Therapy for Esophageal Cancer. *Radiotherapy and Oncology*, 164, 27-36. doi:10.1016/j.radonc.2021.09.004
 22. Yahya, N., & Manan, H. A. (2021). Neurocognitive impairment following proton therapy for paediatric brain tumour: a systematic review of post-therapy assessments. *Supportive Care in Cancer*, 29(6), 3035-3047. doi:10.1007/s00520-020-05808-z
 23. Yahya, N., Mohamad Salleh, S. A., Mohd Nasir, N. F., & Abdul Manan, H. (2023). Toxicity profile of patients treated with proton and carbon-ion therapy for primary nasopharyngeal carcinoma: A systematic review and meta-analysis. *Asia-Pacific Journal of Clinical Oncology*. doi:10.1111/ajco.13915

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24. Yang, J. T., Wijetunga, N. A., Pentsova, E., Wolden, S., Young, R. J., Correa, D., . . . Boire, A. (2022). Randomized Phase II Trial of Proton Craniospinal Irradiation Versus Photon Involved-Field Radiotherapy for Patients with Solid Tumor Leptomeningeal Metastasis. *Journal of Clinical Oncology*, 40(33), 3858-3867. doi:10.1200/JCO.22.01148

Included Health Technology Assessments

1. Ontario Health. Proton beam therapy for cancer in children and adults: a health technology assessment. *Ont Health Technol Assess Ser* [Internet]. 2021 May;21(1):1–142. Available from: <https://www.hqontario.ca/evidence-to-improve-care/health-technology-assessment/reviews-andrecommendations/proton-beam-therapy-for-cancer-in-children-and-adults>
2. Vlayen J, García Fernández LI, Boterberg T, San Miguel L. Proton beam therapy in adults – a systematic review. *Health Technology Assessment (HTA) Brussels: Belgian Health Care Knowledge Centre (KCE)*. 2019. KCE Reports 307. D/2019/10.273/10.

Appendix 2: Search strategy

The search strategy was discussed and agreed with Cancer Australia, to achieve a rapid review of the evidence that could be completed within 3 weeks, and would be useful to support discussions for a meeting on 3 May 2023.

Timeframe

This review includes peer reviewed and grey literature published between 2020 and the date the search was completed: 4th April 2023.

Inclusion and exclusion criteria

We **included** studies examining proton beam therapy in the context of four types of cancer: head & neck, CNS, prostate, and paediatric. (However, we have noted some studies relating to the emerging use of proton beam therapy for other cancer types.) We **included** studies comparing proton beam therapy to other types of radiotherapy. We **included** meta-analyses, systematic reviews, randomised controlled trials, and a small number of narrative reviews.

We **included** studies written in English, and not in other languages.

We **excluded** studies that only examined photon radiotherapy and/or other types of particle beam therapy such as carbon ion radiotherapy, though if they compared these therapies to proton beam therapy we included them.

Because of the limited time available for the review, we **excluded** papers other than meta-analyses, systematic reviews and randomised controlled trials, though we did include a small number of narrative reviews where we judged that they would add to the substance of the review.

Sources

1. Medline

no.	terms	hits
3	(cancer or tumour or neoplasm or malignancy or carcinoma or oncology).tw. or (Neoplasms, Nerve Tissue/ or "Head and Neck Neoplasms"/ or Nervous System Neoplasms/ or Prostatic Neoplasms/) or (Child/ and Neoplasms/)	2838463
9	("proton beam therapy" or "proton therapy" or "protontherapy" or "charged particle therapy" or "particle therapy").tw. or Proton Therapy/	7912
10	limit 9 to (english language and humans and yr="2020 -Current")	1453
11	3 and 10	773
12	from 11 keep 1-768	768
13	limit 12 to (meta analysis or "review" or "systematic review" or "randomized controlled trial")	147

2. Web of Science

("proton beam" NEAR/3 therapy) or (proton NEAR/3 therapy) or (protontherapy) or (particle NEAR/3 therapy) or (proton NEAR/3 radiotherapy) or ("proton beam" NEAR/3 radiotherapy) or (particle NEAR/3 radiotherapy)

AND

cancer or tumour or neoplasm or malignancy or carcinoma or oncology

AND

pediatric or paediatric or CNS or "central nervous system" or "head and neck" or "neck" or "prostate" or lip OR tongue OR gum OR mouth OR palate OR "parotid gland" OR "salivary gland" OR tonsil OR pharynx OR oropharynx OR nasopharynx OR nasopharyngeal OR "piriform sinus" OR hypopharynx OR "oral cavity" OR "Nasal cavity" OR nose OR "middle ear" OR sinus OR sinuses OR larynx OR laryngeal

- Limited to 2020 to 2023
- Refined By: Languages: English. Document Types: Article or Review Article or Early Access. Document Types: Article or Early Access or Proceeding Paper or Correction or Data Paper

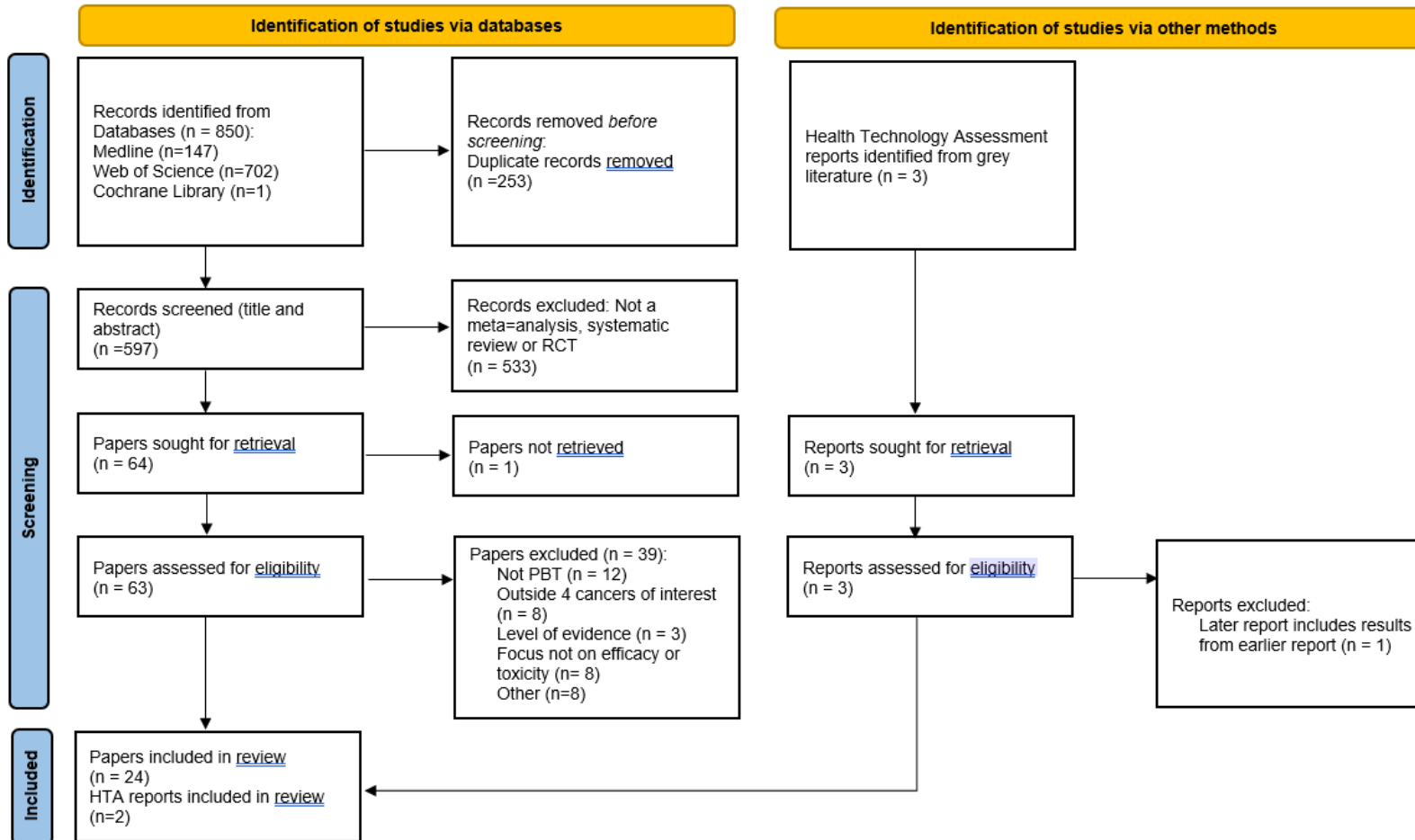
No. hits: 132 reviews and 570 other articles = 702 total

3. Cochrane Collaboration Library (reviews only)

Search terms: same as for MEDLINE above.

No. hits: 1 systematic review.

Appendix 3: Search results: PRISMA diagram



Appendix 4: Data extraction tables

Table 4.1 Peer reviewed meta-analyses and systematic reviews – Paediatric cancer

Author, Year, Title	Summary	Main findings	Quality of the evidence
<p>Doig et al. (2021) Can We Compare the Health-Related Quality of Life of Childhood Cancer Survivors Following Photon and Proton Radiation Therapy? A Systematic Review</p>	<p>The paper is a systematic review comparing the Health-Related Quality of Life (HRQoL) of childhood cancer survivors treated with photon (XRT) and proton (PRT) radiation therapy. It concludes that based on the current evidence, no significant difference can be identified in HRQoL during or after RT, between XRT and PRT. This finding is likely due to the variability in patient characteristics, diagnoses, treatment regimens, and length of follow-up in the included studies of both modalities.</p>	<p>There is no significant difference in HRQoL during or after radiation therapy between XRT and PRT. HRQoL scores appear to improve with increased time from treatment.</p>	<p>The authors assessed the quality of evidence in the review and found it to be low due to various limitations including the heterogeneity of study designs, the small number of studies, the non-randomised nature of the studies, and a lack of direct comparison between photon and proton therapy in the studies they examined. They noted that there is a need for international efforts to increase quality data collection following both XRT and PRT, and to promote data sharing to aid comparisons</p>

Author, Year, Title	Summary	Main findings	Quality of the evidence
<p>Yahya and Manan (2021) Neurocognitive impairment following proton therapy for paediatric brain tumour: a systematic review of post-therapy assessments</p>	<p>Systematic review of post-therapy assessments of neurocognitive impairment following proton therapy for paediatric brain tumours.</p>	<p>While neurocognitive decline is evident following proton therapy, it is not profound for focal therapy at about a median of 2- to 3-year follow-up. Patients treated with proton therapy performed better in all cognitive measures where differences were significant. Furthermore, patients treated with craniospinal irradiation and those with hydrocephalus had poorer cognitive outcomes. The reduction of cognitive decline for patients treated with proton compared with photon was also observed.</p>	<p>The included studies had a reasonable quality, but most reported a lower accrual rate than the pool of eligible persons due to the lack of neurocognitive assessment available.</p>

Author, Year, Title	Summary	Main findings	Quality of the evidence
<p>Peterson and King (2022) A systemic review of pediatric neuropsychological outcomes with proton versus photon radiation therapy: A call for equity in access to treatment</p>	<p>This systematic review aimed to compare neuropsychological outcomes in pediatric patients treated with proton radiation therapy (PRT) versus conventional photon radiation therapy (XRT). The study highlights the sociodemographic disparities in access to PRT and emphasises the need for more research to objectively determine the neuropsychological advantages of PRT.</p>	<p>PRT demonstrated better neuropsychological outcomes compared to XRT in overall intellectual functioning, and verbal and perceptual reasoning. However, results for visual-motor integration, attention, academic achievement, and parent-reported adaptive skills are limited and inconclusive for processing speed and working memory. Longitudinal studies showed stable neuropsychological skills with PRT, except for working memory and processing speed, which showed variable outcomes.</p>	<p>The quality of the evidence is limited due to the non-randomized nature of the studies and the variability in medical and sociodemographic factors between the treatment groups. More research is needed to control for these factors and determine the effectiveness of PRT</p>

Author, Year, Title	Summary	Main findings	Quality of the evidence
<p>Upadhyay et al. (2022) Risk of secondary malignant neoplasms in children following proton therapy vs. photon therapy for primary CNS tumors: A systematic review and meta-analysis</p>	<p>This systematic review and meta-analysis investigates the risk of secondary malignant neoplasms (SMNs) in children following proton therapy (PBT) compared to photon therapy for primary central nervous system (CNS) tumors.</p>	<ul style="list-style-type: none"> • Pooled incidence of SMNs was 1.8% for photon therapy and 1.5% for proton therapy. • No statistically significant difference between the two groups regarding SMNs or any secondary neoplasms. • Shorter latency to secondary cancers with proton therapy compared to photon-based radiation. 	<p>While the evidence presented in the review is strong, there are limitations, including high heterogeneity among the included studies, different patient populations across the studies, heterogeneity in treatment regimens, shorter overall follow-up for proton therapy, and different time periods of comparison. These factors could impact the conclusions drawn from the review.</p>

Author, Year, Title	Summary	Main findings	Quality of the evidence
Thomas & Timmermann (2020) Paediatric proton therapy	Proton beam therapy is an important therapeutic component in multidisciplinary management in pediatric oncology.	<p>The authors highlight the advantages of proton therapy for pediatric patients, such as its ability to precisely target tumors and minimise damage to surrounding healthy tissues. They also discuss the growing evidence supporting the use of proton therapy for pediatric cancers and the challenges of implementing proton therapy in clinical practice, including the need for collaboration between multidisciplinary teams and the importance of long-term follow-up to monitor for potential late effects.</p> <ul style="list-style-type: none"> • Proton beam therapy is a highly conformal form of radiation therapy, which offers significant advantages over conventional photon-based radiotherapy. • Clinical results of irradiating childhood tumours with high-precision proton therapy are promising with regard to tumour cure and the reduction of adverse events. • Modern proton therapy techniques such as pencil beam scanning and intensity modulation are increasingly established modern facilities. 	Not reported

Table 4.2 Peer reviewed meta-analyses and systematic reviews – CNS tumours

Author, Year, Title	Summary	Main findings	Quality of the evidence
<p>El Sayed et al. (2021) Protons versus photons for the treatment of chordoma.</p>	<p>The systematic review investigates the differences in outcomes between proton and photon therapy for the treatment of chordoma. It aimed to determine if there is an advantage for either therapy in terms of local control, overall survival, progression-free survival, and treatment-related toxicity</p>	<p>Insufficient data to show an advantage for proton or photon therapy in terms of local control, overall survival, progression-free survival, and treatment-related toxicity. No difference between interventions in the outcomes measured. The review did not identify any randomized studies; all included studies were retrospective or observational.</p>	<p>The level of evidence for all outcomes was downgraded to very low due to high risk of bias in included studies, very serious imprecision, and inconsistency among studies.</p>

Author, Year, Title	Summary	Main findings	Quality of the evidence
<p>Halasz et al. (2022) Radiation Therapy for IDH-Mutant Grade 2 and Grade 3 Diffuse Glioma: An ASTRO Clinical Practice Guideline.</p>	<p>The paper provides an overview and guidelines for the use of radiation therapy (RT) in the treatment of IDH-mutant grade 2 and grade 3 diffuse glioma, discussing the benefits and adverse effects of RT, the optimal timing of treatment, and the potential of combining RT with chemotherapy.</p>	<p>RT after surgery remains a cornerstone for improving progression-free survival (PFS). The optimal timing of RT remains controversial. Sequential chemotherapy combined with RT improves overall survival (OS). Long-term effects of RT and chemotherapy can be devastating in this patient population.</p>	<ul style="list-style-type: none"> • No RCTs have been performed comparing 3-D conformal RT to intensity-modulated radiation therapy/volumetric modulated arc therapy or proton therapy. • Retrospective studies report outcomes after intensity-modulated radiation therapy (IMRT), which is currently being used as the control arm of NRG BN005 (NCT03180502), an RCT evaluating neurocognitive outcomes for patients with IDH-mutant grade 2 glioma after proton therapy versus IMRT. • Proton therapy has been examined in dosimetric and retrospective studies, as well as in a small prospective nonrandomised trial. • Overall, the strength of evidence for PBT is relatively limited, as there have been no RCTs comparing it to other radiation therapy techniques. The evidence comes from retrospective studies, dosimetric studies, and a small prospective nonrandomised trial

Author, Year, Title	Summary	Main findings	Quality of the evidence
<p>Maillie et al. (2021) A systematic review of craniospinal irradiation for leptomeningeal disease: past, present, and future</p>	<p>This systematic review analyses the use of craniospinal irradiation (CSI) for leptomeningeal disease (LMD), a condition caused by the spread of cancer to the membranes covering the brain and spinal cord. The paper covers data from 13 studies, with a focus on adult patients with LMD from solid and hematologic malignancies treated with CSI.</p>	<p>The median overall survival (OS) was 5.3 months, with proton beam therapy showing potential for improved survival in select patients. More than half of the patients with reported neurological response showed improvement or stabilization of symptoms.</p>	<p>The quality of the evidence in the review is primarily based on retrospective and prospective data from 13 studies. While this is the largest analysis of its kind, the overall evidence base is limited. The recent prospective study by Yang et al. provides the most promising data on proton CSI, with a median overall survival of 8 months in their cohort. However, more research is needed to strengthen the evidence behind PBT.</p>

Table 4.3 Peer reviewed meta-analyses and systematic reviews – Head and neck cancer

Author, Year, Title	Summary	Main findings	Quality of the evidence
<p>Wang et al. (2021) Current status and application of proton therapy for esophageal cancer</p>	<p>The paper discusses the current status and application of proton therapy for treating esophageal cancer, highlighting its potential advantages, clinical benefits, limitations, challenges, and future directions. It covers the dosimetric superiority of proton therapy compared to photon-based approaches, the need for further research and large randomised trials, and the potential benefits of combining proton therapy with immunotherapy.</p>	<p>The paper reports that proton therapy has dosimetric advantages over photon therapy, with potential emerging clinical benefits observed in retrospective and prospective studies. However, definitive large randomized trials are needed to prove the benefits</p>	<p>The paper does not explicitly discuss the quality of the evidence included but comments on the need for further research and large randomized trials to confirm the emerging clinical benefits observed in retrospective and prospective studies</p>

Author, Year, Title	Summary	Main findings	Quality of the evidence
<p>Beddok et al. (2020) Proton therapy for head and neck squamous cell carcinomas: A review of the physical and clinical challenges</p>	<p>Provides an overview of the challenges and benefits of using proton beam therapy (PBT) for head and neck squamous cell carcinomas (HNSCC). It compares PBT with intensity-modulated radiation therapy (IMRT) in terms of dosimetry, treatment planning, and clinical outcomes. The paper also discusses the limitations and uncertainties surrounding PBT in HNSCC treatment and highlights the need for further clinical trials.</p>	<ul style="list-style-type: none"> • Proton-based plans can produce similar or better target coverage and conformity than IMRT. • PBT can offer better sparing of organs at risk (OARs) compared to IMRT. • There is a lack of valid data comparing clinical outcomes after IMRT and IMPT in HNSCC. • Uncertainties surrounding IMPT may lead to poor quality radiation therapy and misinterpretation of clinical trial results. 	<p>The quality of evidence varies across the studies discussed in the paper. Some studies have small patient cohorts and varied techniques, which limit the strength of the evidence. The paper calls for well-designed randomised and model-based clinical trials to provide stronger evidence in the coming years.</p>

Author, Year, Title	Summary	Main findings	Quality of the evidence
Lee et al. (2021) A Systematic Review of Proton Therapy for the Management of Nasopharyngeal Cancer	The systematic review aims to evaluate the effectiveness and safety of proton beam therapy (PBT) in the management of nasopharyngeal cancer (NPC) by analysing published literature and investigating the outcomes and toxicity profiles of nasopharyngeal cancer patients treated with proton therapy, highlighting the improved toxicity profile and comparable outcomes to photon-based radiation	<ul style="list-style-type: none"> • PBT demonstrated comparable tumor control and survival outcomes with photon-based radiation. • PBT showed a potential reduction in acute and late toxicities • Proton therapy minimises dose to normal structures, reducing acute toxicities such as mucositis and feeding tube requirements. • Lower integral dose offers potential advantages, such as lowering the incidence of radiation-induced tumors and allowing for reirradiation. • Late toxicities showed varying rates, potentially due to differences in treatment planning, physician grading, and patient heterogeneity. 	<ul style="list-style-type: none"> • The strength of evidence is limited by the small number of studies, their retrospective nature, and the heterogeneity among the included studies and the lack of prospective studies or randomised trials. • There is also a relatively short follow-up duration, limiting understanding of late effects. • The existing evidence does suggest that proton therapy has promising outcomes and improved toxicity profiles compared to photon-based radiation. • Heterogeneity among the included studies with respect to proton technique, utilisation of systemic therapy, and inclusion of proton boost following photon-based radiation, which makes aggregated interpretation of the data difficult. • The review highlights the need for further research to better evaluate the efficacy and toxicity of proton therapy in NPC and to better understand the clinical implications of these findings for PBT.

Author, Year, Title	Summary	Main findings	Quality of the evidence
<p>Nicholas (2021) The Promise of Proton Beam Therapy for Oesophageal Cancer: A Systematic Review of Dosimetric and Clinical Outcomes</p>	<p>This systematic review evaluates the dosimetric and clinical outcomes of proton beam therapy (PBT) for oesophageal cancer, comparing them to photon radiotherapy techniques and discussing the potential benefits and limitations of PBT</p>	<p>Toxicity rates: PBT has comparable or lower toxicity rates than photon techniques, except for Grade 4 (G4) lymphopenia, which is lower in PBT.</p> <p>Survival outcomes: PBT shows at least comparable or superior survival outcomes to photon radiotherapy.</p> <p>Cardiac toxicity: PBT may reduce medium-term cardiac toxicities (3 months - 2 years post-RT), especially for high-risk patients with underlying cardiac disease. However, it may not have an impact on immediate post-operative cardiac complications.</p> <p>G4 lymphopenia: PBT reduces the incidence of G4 lymphopenia, an emerging predictive biomarker negatively correlated with survival and local control rates post-radiotherapy.</p> <p>Technical considerations: There is uncertainty in dose delivery due to various factors, and newer technologies may help improve the certainty of delivered dose in the future.</p>	<p>The strength of evidence for PBT in oesophageal cancer treatment is limited by the paucity of randomised, prospective data. Most of the evidence comes from single-centre retrospective cohorts, and only one prospective trial has been published to date. While the clinical outcomes suggest potential benefits of PBT in toxicity reduction and survival, the quality of evidence is low. More well-designed, prospective clinical trials are needed to establish a robust evidence base and identify the patients who will benefit the most from PBT.</p>

Author, Year, Title	Summary	Main findings	Quality of the evidence
<p>Yahya (2023) Toxicity profile of patients treated with proton and carbon-ion therapy for primary nasopharyngeal carcinoma: A systematic review and meta-analysis</p>	<p>This systematic review and meta-analysis aimed to evaluate the toxicity profile of patients treated with proton and carbon-ion therapy for primary nasopharyngeal carcinoma (NPC). The study found lower toxicity rates for patients treated with particle-based therapy (PBT) compared to photon-based therapy, with the exception of acute dermatitis. The reduced toxicity rates were likely due to the improved dose distribution for PBT.</p>	<p>Pooled event rates of acute toxicities grade ≥ 2 ranged from 16% (xerostomia) to 47% (dermatitis). PBT showed better outcomes for most toxicity endpoints compared to photon-based therapies, except for acute dermatitis.</p>	<p>No study reported the sample size justification, only four studies reported the effect of dose, and only four determined the effects of clinical and treatment factors.</p>

Author, Year, Title	Summary	Main findings	Quality of the evidence
Shaikh et al. (2020) Implementation of meta-analysis approach, comparing conventional radiotherapy, and proton beam therapy treating head and neck cancer.	An evaluation of the efficacy of conventional photon radiotherapy and proton beam therapy (PBT) in the treatment of HNC	<ul style="list-style-type: none"> • Although adaptive IMRT reduced dose to several normal structures compared with standard IMRT, nonadaptive proton therapy had a more favorable dosimetric profile than IMRT or adaptive IMRT and may obviate the need for adaptive planning • Protons allowed significant sparing of the spinal cord, parotid glands, larynx, and brainstem and should be considered for SCCHN to decrease normal tissue toxicity while still providing optimal tumor coverage • A reduction in mean dose to OARs was achieved using particle therapy compared to photons in the re-irradiation of HNSCC 	Low-to-moderate quality of evidence cited (only 5 papers included)

Author, Year, Title	Summary	Main findings	Quality of the evidence
<p>Gamez et al (2021) A Systematic Review on Re-irradiation with Charged Particle Beam Therapy in the Management of Locally Recurrent Skull Base and Head and Neck Tumors</p>	<p>This systematic review analyses the use of charged particle re-irradiation therapy in the management of recurrent skull base and head and neck tumors. The review includes 26 retrospective single-institution studies involving 1,118 patients treated with curative-intent charged particle re-irradiation therapy. The results suggest that proton and carbon ion re-irradiation therapy may achieve favorable local control and overall survival rates with a limited risk of severe late toxicities compared to photon radiotherapy re-irradiation.</p>	<p>2-year local control rates ranged from 50% to 86% for proton reRT, and 41% to 92% for carbon ion reRT. 2-year overall survival rates for proton and carbon ion reRT ranged from 33% to 80% and 50% to 86%, respectively. Rates for acute grade 3 toxicities ranged from 1% to 35%, with dysphagia, mucositis, and radiation dermatitis being the most frequent, and rates for late grade 3 toxicities ranged up to 37% for protons and up to 35% for carbons, with brain necrosis, ototoxicity, visual deficits, and bleeding being most commonly reported. Sixteen cases of grade 5 reported toxicities for all treated patients (n=16/1118, 1.4%) with fatal bleeding as the leading cause.</p>	<p>This review suggests that charged particle therapy, including proton and carbon ion therapy, may offer potentially more favourable local control and toxicity outcomes in properly selected patients. However, there are limitations to the evaluated series, such as significant variability in patient selection, recurrent disease sites, histologies, treatment technique, doses and fractionation employed, and the reported toxicities and outcomes. Further studies, including randomized controlled trials, are needed to better understand the benefits of charged particle therapy for recurrent or secondary skull base and head and neck malignancies.</p>



Table 4.4 Peer reviewed meta-analyses and systematic reviews – Prostate cancer

Author, Year, Title	Summary	Main findings	Quality of the evidence
<p>Li et al (2021) Clinical Efficacy and Safety of Proton and Carbon Ion Radiotherapy for Prostate Cancer: A Systematic Review and Meta-Analysis</p>	<p>The efficacy and safety of Proton Beam Therapy and CIRT for prostate cancer were similar.</p>	<p>The review found that both PBT and CIRT demonstrated higher overall survival (OS) and local control rates (LCR) for prostate cancer patients compared to conventional and hypofractionated photon radiotherapy. However, the quality of the included studies was generally low, limiting the strength of the conclusions.</p> <ul style="list-style-type: none"> • CIRT and PBT have favorable efficacy and safety, with similar 5-year overall survival (OS) and lower incidence of grade 2 or greater acute and late genitourinary and gastrointestinal toxicity compared to photon radiotherapy. • The 3-, 4-, and 5-year local control rate (LCR) of CIRT for prostate cancer was 98, 97, and 99%; the 3-, 4-, 5-, and 8-year biochemical relapse-free rate (BRF) was 92, 91, 89, and 79%. • Meta-regression results did not show a significant relationship based on the variables studied (P<0.05). 	<p>The quality of the included studies was generally low, limiting the strength of the conclusions. GRADE assessment results indicated that the certainty of the evidence was very low. Meta-regression results did not show a significant relationship based on the variables studied (P<0.05).</p>

Author, Year, Title	Summary	Main findings	Quality of the evidence
<p>Du et al. (2022) Does particle radiation have superior radiobiological advantages for prostate cancer cells? A systematic review of in vitro studies</p>	<p>The paper is a systematic review of in vitro studies investigating the radiobiological advantages of particle radiation for treating prostate cancer cells. The review compares particle radiation therapy to photon radiation therapy, focusing on their biological effectiveness, tumor control, and side effects.</p>	<ul style="list-style-type: none"> • Carbon ion irradiation showed higher RBE values (1.67-3.7) than proton irradiation (0.94-1.52). • Carbon ion irradiation was more effective in clonogenic survival than X-rays or protons. Particle irradiation, alone or combined with drugs, induced cell cycle arrest and apoptosis, and affected DNA damage and repair, cell motility, and migration in prostate cancer cells. • The combination of particle irradiation with certain drugs enhanced the therapy's efficacy (SER values). • The oxygen enhancement ratio (OER) was lower for carbon ions than for photon irradiation. 	<p>Not reported</p>

Table 4.5 Narrative reviews and the RCT – Various cancer types

Author, Year, Title	Summary	Main findings	Quality of the evidence
Hwang et al. (2020) Particle therapy toxicity outcomes: A systematic review	The paper systematically reviews clinical evidence regarding toxicity outcomes for particle therapy (PT) in adult and pediatric tumors. It aims to compare the toxicity results of PT with photon radiation therapy and assess its safety and efficacy in various cancer types.	The majority of included studies demonstrate acceptable toxicity results for PT. Compared to photon RT, PT showed reduced morbidities in H&N tumors, pediatric tumors, sarcomas, CNS tumors, GIT tumors, ocular tumors, and prostate cancer, as well as improved QoL	The quality of evidence is generally low, with most studies being single institution retrospective case series (NHMRC level IV)
Jumaniyazova et al. (2023) Photon- and Proton-Mediated Biological Effects: What Has Been Learned?	The paper discusses the biological effects of photon and proton irradiation on tumour cells and the surrounding environment, as well as their immunomodulatory potential in cancer treatment	Irradiation, both photon and proton, can damage tumour vasculature, induce immune responses, and cause DNA damage in tumor cells. Proton therapy may have some advantages over photon therapy, such as causing more permanent DNA damage and modulating the expression of pro-inflammatory genes differently.	No quality assessment was conducted on the papers included in this study

Author, Year, Title	Summary	Main findings	Quality of the evidence
Kiseleva et al. (2022) Particle Therapy: Clinical Applications and Biological Effects	The paper reviews clinical applications and biological effects of particle therapy, a promising field in cancer treatment. It focuses on clinical evidence, biological mechanisms, and molecular responses to particle therapy, discussing its benefits, limitations, and future developments.	Particle therapy shows promise in treating different types of cancer with better tumor control and fewer side effects than conventional radiation therapy. However, more research is needed to fully understand its biological mechanisms and molecular responses, as well as to optimise its clinical application	The quality of the evidence in the review is not explicitly discussed or rated but it does cite multiple clinical and experimental studies, indicating that the review is based on a wide range of existing research, however this means that caution should be taken in interpreting the findings of this paper
Prasanna et al. (2021) Normal Tissue Injury Induced by Photon and Proton Therapies: Gaps and Opportunities.	The review paper compares normal tissue injuries caused by photon and proton radiation therapies. It identifies gaps in knowledge and highlights areas for future research in order to optimise and personalise these treatments.	The review highlights the potential benefits of proton therapy, such as lower radiation doses to healthy tissues, and reduced acute and late toxicities. However, it also notes the need for more research to better understand the biological differences between photon and proton therapies, and to optimize dose distribution and treatment planning for individual patients.	The quality of the evidence in the review varies, as it includes randomized controlled trials, non-randomized comparative studies, and single-arm studies. Some of the studies have limitations due to small sample sizes, short follow-up periods, or other methodological issues. Therefore, the overall quality of evidence should be interpreted with caution.

Author, Year, Title	Summary	Main findings	Quality of the evidence
<p>Underwood et al. (2022) A systematic review of clinical studies on variable proton Relative Biological Effectiveness (RBE).</p>	<p>This paper presents a systematic review of clinical studies investigating variable proton RBE in various cancer types. The main findings show mixed results, with some studies finding evidence for variable proton RBE, while others did not. Outcomes such as imaging changes, toxicities, and complications were observed in some studies.</p>	<p>This systematic review analysed 22 clinical studies investigating variable proton RBE. Six studies found evidence for variable proton RBE, four studies found no evidence, and the remaining 12 studies presented more nuanced conclusions. The majority of studies involved fewer than 20 proton patients for their outcome under consideration. Studies were classified into two groups: 'Group A' (voxelised) studies and 'Group B' studies comparing proton and photon cohorts.</p>	<p>The quality of the evidence in the review is reported to be weak, primarily due to small sample sizes, which limit the ability to draw conclusions. The maximum sample size in the studies reviewed is 50, which leads to imprecise estimates from regression models and low statistical power for significance testing. The authors identify several limitations in the statistical methods and models linking LET to biological effect, as well as clinical limitations.</p>

Table 4.6 Health Technology Assessments

Author, year, country and title	Study design (e.g. RCT, cohort, review)	Study population	For SR, how many studies were included?	Cancer type	Effectiveness of PBT	Patient outcomes (survival, side effects)
<p>Ontario Health, 2021, Canada</p> <p>Proton beam therapy for cancer in children and adults: a health technology assessment.</p>	<p>HTA-systematic reviews and RCTs only</p>	<p>Adults and children</p>	<p>Included one systematic review reporting on 215 publications on proton beam therapy in children and adults across 19 tumour categories/conditions.</p>	<p>19 tumour categories</p>	<p>Proton beam therapy may be as effective as conventional radiation therapy, and it may cause fewer side effects, especially for children with brain tumours and for adults with certain types of cancer</p>	<p>Compared with photon therapy, proton beam therapy may result in fewer adverse events but similar overall survival and progression-free survival in children with brain tumours (GRADE: Low), adults with esophageal cancer (GRADE: Low to Very low), head and neck cancer (GRADE: Low to Very low), and prostate cancer (GRADE: Low). Proton beam therapy may result in similar adverse events, overall survival, and progression-free survival in adults with brain tumours (GRADE: Low), breast cancer (GRADE: Low), gastrointestinal cancer (GRADE: Very low), liver cancer (GRADE: Moderate to Very low), lung cancer (GRADE: Moderate to Very low), and ocular tumours (GRADE: Low). There was insufficient evidence to evaluate the effectiveness and safety of proton beam therapy in other paediatric tumours, as well as bladder cancer, bone cancer, lymphoma, and benign tumours in adults</p>

Author, year, country and title	Study design (e.g. RCT, cohort, review)	Study population	For SR, how many studies were included?	Cancer type	Effectiveness of PBT	Patient outcomes (survival, side effects)
Belgian Health Care Knowledge, 2019, Belgium	Systematic review	Adults	11 systematic reviews / HTA reports	Low-grade glioma, primary sinonasal tumours and recurrences of head & neck tumours, breast cancer in women, pancreatic cancer, hepatocellular cancer and locally recurrent rectal cancer.	High-quality evidence on the effectiveness of proton treatment is lacking for the studied indications. With the available evidence, it is impossible to conclude that proton treatment is better or worse than photonbased radiotherapy. However, there are some concerns in patients with primary intramedullary spinal cord gliomas (survival) and stage I breast cancer (cosmesis).	There is evidence of very low level (1 study, 32 patients) that proton treatment is associated with a worse survival than photon radiotherapy in patients with primary intramedullary spinal cord gliomas. The data on recurrence are too imprecise to draw a firm conclusion. o There is evidence of very low level (1 study, 98 patients) that proton treatment is associated with worse physician-rated cosmetic results at 5 years than photon radiotherapy in patients with stage I breast cancer. No significant difference was found for patient-rated cosmetic results. The data on local failure rate are too imprecise to draw a firm conclusion. o There is evidence of very low level (1 study, 25 patients) that proton treatment and hyperfractionated acceleration radiotherapy with concomitant S-1 do not differ significantly in their effect on survival and disease control in patients with locally advanced and unresectable pancreatic cancer,

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