Ontario Health

ONTARIO HEALTH TECHNOLOGY ASSESSMENT SERIES

Proton Beam Therapy for Cancer in Children and Adults: A Health Technology Assessment

Key Messages

What Is This Health Technology Assessment About?

Radiation therapy—a common type of cancer treatment—uses energy to kill cancer cells. Conventional radiation therapy uses photon (x-ray) beams, which can damage healthy cells near the tumour and lead to serious, long-term health problems. This is especially a concern for children, who are more sensitive to the effects of radiation and are likely to have many years of life ahead.

Proton beam therapy is an alternative type of radiation treatment that can reduce damage to healthy cells. It uses energized particles (protons) that release a burst of energy inside the tumour. The proton beam can also deliver radiation to the tumour more precisely than photon therapy. Proton beam therapy is not currently available in Ontario or anywhere in Canada. Patients can travel to the United States to receive it, but not all their costs are publicly covered and some people cannot undertake this travel.

This health technology assessment looked at safety, effectiveness, and cost-effectiveness of proton beam therapy, compared with photon therapy, for children and adults with various types of cancer. It also looked at the budget impact for the Ministry of Health to build and operate a proton beam therapy facility in Ontario, and at the experiences, preferences, and values of people affected by cancer.

What Did This Health Technology Assessment Find?

Proton beam therapy may be as effective as photon therapy, and it may cause fewer side effects, especially for children with brain tumours and for adults with certain types of cancer.

Based on previous studies, proton beam therapy may be cost-effective compared with photon therapy for children with brain tumours and adults with some types of cancer. We estimate that building and operating a proton beam therapy centre with four treatment rooms in Ontario would cost an additional $125 million over the next 5 years. The average cost per patient would be about $48,000 (including the initial construction and equipment costs), compared with about $327,000 per patient referred to a US hospital.

We interviewed 10 adults and parents of children with cancer who had received proton beam therapy or were exploring it as a treatment option. People who had received proton beam therapy spoke positively about it. But travelling for treatment, with weeks or months away from home, was often challenging logistically, emotionally, and financially. Overall, participants supported the idea of having proton beam therapy available in Ontario.

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Abstract

Background

Proton beam therapy has potential to reduce late toxicity in cancer treatment by reducing the risk of damage to surrounding healthy tissues. We conducted a health technology assessment of proton beam therapy, compared with photon therapy, for children and adults with cancer requiring radiotherapy. Our assessment included an evaluation of safety, effectiveness, cost-effectiveness, the budget impact of publicly funding the construction and use of proton beam therapy in Ontario, and patient preferences and values.

Methods

We performed a systematic literature search of the clinical evidence to retrieve systematic reviews and selected and reported results from one review that was recent, high quality, and relevant to our research question. We complemented the chosen systematic review (published in 2019) with a literature search to identify randomized controlled trials published after the review. We assessed the risk of bias of each included study using the Risk of Bias in Systematic Reviews (ROBIS) tool and the quality of the body of evidence according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group criteria. We performed a systematic economic literature search and also analyzed the budget impact of publicly funding proton beam therapy in cancer patients in Ontario. To contextualize the potential value of proton beam therapy, we spoke with 10 people with cancer (or their caregivers) who had either received or were considering proton beam therapy.

Results

We included one systematic review of the clinical evidence reporting on 215 publications on proton beam therapy in children and adults across 19 tumour categories/conditions. 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 pediatric tumours, as well as bladder cancer, bone cancer, lymphoma, and benign tumours in adults.

The economic evidence suggests that proton beam therapy may be cost-effective in pediatric populations with medulloblastoma; however, studies were based on limited clinical evidence. In other indications, the cost-effectiveness of proton beam therapy is unclear. The 5-year budget impact of funding a four-room proton beam therapy centre in Ontario would be $124.8 million, resulting in a cost per patient of $48,217, including both capital investment and operational costs, compared to the current average cost of $326,800 to send patients out of country. Funding a one-room proton beam therapy centre that would treat selected Ontario patients and patients from other Canadian provinces would have a lower budget impact of $15.2 million over the next 5 years. If we assume building proton beam therapy centres would substitute for new photon therapy centres, then the 5-year budget impact could be further reduced to approximately $13 million (one room) or $94.8 million (four rooms).

The people we interviewed who had received proton beam therapy reported positive responses to the treatment. They chose to have proton beam therapy because they believed it to be safer and to have fewer long-term side effects than photon therapy. However, accessing proton beam therapy in the United States was often challenging, with logistical and emotional burdens. Patients and families valued the opportunity to receive effective treatment close to family and other emotional supports.

Conclusions

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. Based on published economic evidence, proton beam therapy is likely cost-effective compared with photon therapy in children with medulloblastoma, but cost-effectiveness is unclear in children and adults with other clinical indications. We estimate that publicly funding a proton beam therapy centre in Ontario would result in additional costs of $124.8 million over the next 5 years, but with a six- to seven-fold reduction in the per-patient cost compared with current spending. People with cancer and caregivers with whom we spoke were generally supportive of having proton beam therapy available in Ontario.

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Objective

This health technology assessment evaluates the safety, effectiveness, and cost-effectiveness of proton beam therapy for children and adults with cancer. It also evaluates the budget impact of publicly funding the construction and use of proton beam therapy in Ontario, and the experiences, preferences, and values of people with cancer and their caregivers.

Background

Health Condition

Cancer is the leading cause of death in Canada. About one in two Canadians will develop some type of cancer in their lifetime and about one in four Canadians will die of cancer.[1] In 2019 alone, an estimated 220,400 Canadians were expected to be diagnosed with cancer and 82,100 were expected to die from the disease.[1] Cancer mostly affects Canadians aged 50 and older, but it can occur at any age.[1] Lung, breast, colorectal, and prostate cancer account for about half of all new cancer cases in adults, whereas half of all cancers in children aged 0 to 14 years are leukemia and cancer of the central nervous system.[1]

Clinical Need and Target Population

More than 50% of all cancer patients receive radiation therapy (also called radiotherapy) as part of their initial treatment, either alone or in combination with surgery, chemotherapy, or both. Radiation therapy is mostly delivered in the form of photon beams (energy in the form of x-rays or gamma rays) to irradiate and kill tumour cells. However, as the photons irradiate the tumour, they can also damage the surrounding healthy tissues and pose a risk of long-term side effects, known as late effects or toxicities, that may appear months or years after treatment.[2] Late effects include organ dysfunction, subsequent (secondary) malignant and benign neoplasms (abnormal growths), and psychological complications all of which place cancer survivors at risk of chronic health conditions later in life.[3] These late effects are especially problematic for children and young adults whose longer life expectancy increases both the risk of developing radiation-related late toxicity and the length of time they will live with these conditions.[4] In Ontario, 4,379 people under the age of 40 were estimated to be newly diagnosed with cancer in 2020.[5]

Children are more susceptible to the late effects of radiation because their developing, growing tissues are sensitive to radiation, they have more proliferating cells, and as noted above, their young bodies have a larger window of opportunity to express radiation damage over the long term.[3] In particular, radiation to the brain has been associated with later neurocognitive deficits, neuroendocrine dysfunction, and hearing loss; children treated before the age of 7 years are most affected.[6] According to the Childhood Cancer Survivor Study, the 30-year cumulative incidence for severe, disabling, or life-threatening conditions or death due to a chronic condition following cancer treatment was 42%.[7] From the same cohort, the leading cause of death in survivors of childhood cancer at 20 years following treatment was secondary malignancy.[8] Survivors of tumours of the central nervous system in childhood were at high risk of severe neurocognitive impairment in adulthood, and the greater the amount of cranial radiation, the larger the losses in function.[9]

Based on expert input and cancer activity data from Cancer Care Ontario (now part of Ontario Health; Cancer Activity Level Reporting dataset, prepared January 2019), in Ontario each year approximately 1,627 children and adults with 13 major types of cancer or tumour conditions may benefit from proton beam therapy, an alternative form of radiation therapy (described below, Health Technology Under

Review). These 13 conditions include breast, genitourinary, lung, gastrointestinal, skin, head and neck, gynecological, hematological, central nervous system, and endocrine cancer, along with sarcoma (cancer in connective tissue), benign neoplasm, and some tumours classified as "other/unknown." It is also estimated that 58 pediatric patients (aged 0–17 years) per year would significantly benefit from proton beam therapy when compared with photon therapy.[10]

Current Treatment Options

Treatment options for cancer vary depending on the type, location, and stage of the condition. Treatment may include radiation therapy, chemotherapy, targeted therapy, immunotherapy, and surgery, or combinations of these treatments.

In Ontario, radiation therapy is delivered using image-guided intensity-modulated photon (x-ray) beams generated by linear accelerators or by purpose-built precision radiotherapy platforms such as CyberKnife or Gamma Knife. These platforms for radiation treatment are coupled with advanced imaging and computerized treatment planning systems to deliver radiation as precisely and accurately as possible, directly to tumour cells (targets) while protecting normal structures and minimizing damage to healthy cells.[2] Despite this advanced technology, there are inherent limitations in the ability of therapy based on photon radiation to spare surrounding tissue. Due to their physical properties, photons gradually lose energy as they travel through the body. This means a photon beam will deliver a radiation dose and radiation effects to the tissues where it enters and exits the body as it moves through an area containing the cancer to be treated.

Health Technology Under Review

Proton beam therapy uses protons (positively charged particles) instead of photons as the source of radiation to treat cancer. It is an alternative to photon therapy. Unlike photons, protons have a defined range in tissue. As the proton beam enters the body, there is interaction with tissues on the entrance side of the beam path, but as the proton beam reaches a specific depth (determined by the specific energy of the proton beam), it releases a burst of energy and rapidly deposits radiation over a very narrow range of tissue, resulting in no further dose delivery beyond this depth. This physical quality of charged particles, termed the Bragg Peak, spares healthy cells beyond the cancer region being treated. This is particularly helpful in cancers where it is important to spare sensitive normal tissues near the tumour, such as in cancers of the brain in children.[11]

In recent years, proton beam therapy has undergone major technological advances, including:[4]

- Intensity-modulated pencil beam/spot scanning proton therapy, which enables shaping of the proton beam to match the contours of the tumour and sparing even more normal tissue
- Integration of image guidance using cone-beam computed tomography, which allows for real-time imaging of the patient in the treatment position at the treatment unit, enabling increased accuracy of treatment delivery

Modern proton beam delivery platforms couple the planning and delivery sophistication of photon-based radiation therapy with the physical advantages of the proton particle itself to enable enhanced targeting of cancer and sparing of normal tissue. Thus, the potential to reduce late effects (or escalate treatment dosage beyond limits that can be safely delivered with photons) exists with proton beam therapy (G. Bauman, MD, email communication, Oct 28, 2019).

Regulatory Information

The MEVION S250 and MEVION S250i Proton Beam Radiation Therapy Systems by Mevion Medical Systems (Littleton, MA) are licensed by Health Canada as Class III devices (licence number 94484). The S250 system shapes the radiation using technology known as double scatter beams. The S250i system shapes the radiation using pencil beams that are scanned throughout the target lesion.

According to Health Canada, the MEVION S250 and the MEVION S250i systems are medical devices indicated for the delivery of radiation for the treatment of patients with localized tumours or other conditions appropriate for treatment by radiation. Both are proton therapy treatment systems for use by therapists, physicians, dosimetrists, and medical physicists. The systems are designed to integrate with a hospital's oncology information system and recording and verification system, and both are single-room (also called single-vault) systems, meaning they are designed to treat one patient at a time.

Both the MEVION S250 and S250i proton beam therapy systems are based on the same proton therapy platform and clinical environment. The difference between the two systems is in the proton beam shaping technology. Pencil beam scanning is replacing double scattering as the beam shaping technology of choice for proton therapy due to its ability to deliver intensity-modulated proton therapy treatment with improved conformality (ability to conform to the shape of the target) (L. Bouchet, Mevion Medical Systems, email communication, November 19, 2019).

There are other manufacturers of proton beam therapy systems in clinical use worldwide that have been approved by the US Food and Drug Administration or other jurisdictions. These devices have not yet undergone the Health Canada approval process.

Health Canada has also licensed, as Class III devices, the treatment planning systems that design the proton beam therapy for each patient. These planning systems are outside the scope of this health technology assessment.

Ontario, Canadian, and International Context

As of the end of 2019, 222,425 people had been treated with proton beam therapy worldwide.[12] At present, hospital-based proton radiation centres are operational in 19 countries, including all the G7 countries with publicly funded health care systems, except Canada, although there are plans for construction of a private proton beam therapy facility in Quebec.[13] Six provinces—Ontario, Quebec, British Columbia, Saskatchewan, Manitoba, and Nova Scotia—currently refer patients to out-of-country hospitals for proton beam therapy.[14]

In Ontario, access to proton beam therapy in the United States is granted to cancer patients through the Ministry of Health Out-of-Country Prior Approval Program after expert review of individual cases facilitated by Ontario Health (Cancer Care Ontario). Clinical indications that have been approved by the program on a case-by-case basis include astrocytoma, adenoid cystic carcinoma, meningioma, craniopharyngioma, glioma, Hodgkin lymphoma, non-Hodgkin lymphoma, malignant myxoid lesion, medulloblastoma, thymic carcinoma, ependymoma, and sarcomas (e.g., Ewing's sarcoma, orbital sarcoma, osteosarcoma, rhabdomyosarcoma). Currently, proton beam therapy requires approximately 6 to 8 weeks of out-of-country treatment, depending on the diagnosis and the specific treatment plan. Ontario Health (Cancer Care Ontario) has worked with the Out-of-Country Program to establish arrangements with US providers.[4] Table 1 lists the preferred US providers. Prior to the implementation of preferred provider arrangements (PPAs), the average cost to the Ministry of Health to send a patient

for out-of-country proton beam therapy was $326,800 CAD ($250,000 USD; conversion rate: 1.31; email communication, July 2019). Although the medical cost is covered, the Out-of-Country Program does not fund patients' travel, food, or accommodations.

Table 1: Preferred US Providers of Proton Beam Therapy for Ontario's Out-of-Country Prior Approval Program

Pediatric Patients (< 18 Years of Age)	Adult Patients (≥ 18 Years of Age)
Cincinnati Children's Hospital, Liberty Township, Ohio	MD Anderson Cancer Center, Houston, Texas
Massachusetts General Hospital, Boston, Massachusetts	Northwestern Medicine Chicago Proton Center, Warrenville, Illinois
MD Anderson Cancer Center, Houston, Texas	University of Florida Health Proton Therapy Institute, Jacksonville, Florida
Northwestern Medicine Chicago Proton Center, Warrenville, Illinois	University of Pennsylvania Health System ("Penn Medicine"), Philadelphia, Pennsylvania
University of Florida Health Proton Therapy Institute, Jacksonville, Florida	

Source: Ontario Ministry of Health, 2019[15]

The Out-of-Country Prior Approval Program has approved 57 patients for proton beam therapy, and treatment for 89% has been billed to the Ministry of Health (Ontario Ministry of Health, email communication, July and September 2019). According to Ontario Health (Cancer Care Ontario), less than 30% of pediatric patients who may be eligible for proton beam therapy have been referred to the Out-of-Country Program; many patients are not referred because of nonmedical costs, the burden on their parents, and logistic difficulties of travel.[4] Many additional patients are unable to travel out of country due to postoperative complications, the need for intensive rehabilitation, or financial constraints. There are also costs to the patient and/or family during their time away from home, such as loss of work. Given the variability in patients' ability to afford the costs associated with out-of-country treatment, access to proton beam therapy solely through the Out-of-Country Program may contribute to inequity in the Ontario health care system if proton beam therapy leads to better outcomes.

In 2017, the Canadian Agency for Drugs and Technologies in Health published a health technology assessment, including an overview of systematic reviews, on proton beam therapy for the treatment of cancer in children and adults. They reported that the authors of the systematic reviews cautioned that the quality of the included primary studies was mostly low or insufficient to make definitive conclusions about the benefits or harms of proton beam therapy.[16]

Expert Consultation

We engaged with experts in the specialty areas of pediatric oncology, radiation oncology and medical physics to help inform our methodologies and our understanding of aspects of the health technology and to contextualize the evidence.

PROSPERO Registration

This health technology assessment has been submitted to PROSPERO, the international prospective register of systematic reviews (CRD registration number not yet received), available at https://www.crd.york.ac.uk/PROSPERO.

Clinical Evidence

Research Question

What are the effectiveness and safety of proton beam therapy compared with photon radiation therapy for children and adults with cancer?

Methods

Review Approach

To leverage existing evidence, we first systematically searched for a recent systematic review with high methodological quality that addressed our research question. Selection of the systematic review for final inclusion was based on the recency of the evidence, risk of bias assessment, comprehensiveness of outcomes reported, and quality of evidence assessment.

Second, we ran a systematic literature search starting from the end of the search of the selected systematic review to identify any relevant randomized controlled trials published since the previous search was conducted.

Clinical Literature Search

We performed a clinical literature search on July 24, 2019, using a methodological filter to retrieve systematic reviews, meta-analyses, and health technology assessments published from database inception until the search date. We used the Ovid interface in the following databases: MEDLINE, Embase, the Cochrane Database of Systematic Reviews, the Health Technology Assessment database, and the National Health Service Economic Evaluation Database (NHS EED).

Once a systematic review with low risk of bias was selected, we updated this study by using our same search strategy and applying a methodological filter to retrieve randomized controlled trials published from January 1, 2019, to September 9, 2019. We used the Ovid interface in the following databases: MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, and NHS EED.

A medical librarian developed the search strategies using controlled vocabulary (e.g., Medical Subject Headings) and relevant keywords. The final search strategy was peer-reviewed using the PRESS Checklist.[17]

For both searches, we created database auto-alerts in MEDLINE and Embase and monitored them for the duration of the assessment period. We also performed a targeted grey literature search of health technology assessment agency websites as well as clinical trial and systematic review registries. The grey literature search was updated on December 3–5, 2019. See Appendix 1 for our literature search strategies, including all search terms.

Eligibility Criteria

STUDY DESIGN—SYSTEMATIC REVIEWS

Inclusion Criteria

- English-language full-text publications
- Studies published from database inception until July 24, 2019
- Systematic reviews, meta-analyses, and health technology assessments that included a systematic review of any study designs and that:
  - Specified well-defined review questions and inclusion and exclusion criteria
  - Used a reproducible literature search strategy of two or more electronic databases and provided information on databases searched, search terms, and search dates
  - Assessed and reported the methodological quality of the included studies (e.g., risk of bias assessment)
- Studies that matched our research question and populations, interventions, comparators, and outcomes (see Participants, Interventions, Comparators, and Outcomes [PICO] below)

Exclusion Criteria

- Animal and in vitro studies
- Nonsystematic reviews, narrative reviews, abstracts, editorials, letters, case reports, and commentaries

STUDY DESIGN—PRIMARY STUDIES

Inclusion Criteria

- English-language full-text publications
- Studies published from January 1, 2019, until September 9, 2019
- Randomized controlled trials (RCT)
- Studies that matched our research question and populations, interventions, comparators, and outcomes (see Participants, Interventions, Comparators, and Outcomes [PICO] below)

Exclusion Criteria

- Animal and *in vitro* studies
- Observational studies, reviews, abstracts, editorials, letters, case reports, and commentaries
- Studies that are solely comparative planning studies without reported patient outcomes

PARTICIPANTS

- Children and adults with any type of cancer

INTERVENTIONS

- Proton beam therapy (alone or in combination with other treatment modalities)

COMPARATORS

- Photon therapy (alone or in combination with other treatment modalities), including image-guided intensity-modulated radiation therapy, stereotactic radiation techniques, other external beam therapies, or brachytherapy

OUTCOMES

- Late toxicities, including radiation-related cancer
- Overall survival
- Progression-free or relapse-free survival
- Acute toxicities

Literature Screening

A single reviewer conducted an initial screening of titles and abstracts using Covidence[18] and then obtained the full texts of studies that appeared eligible for review according to the inclusion criteria. A single reviewer then examined the full-text articles and selected studies eligible for inclusion.

Data Extraction

For systematic reviews, we extracted data on PICO (populations, interventions, comparators, outcomes), literature search information, and study types included to guide the selection of the best-quality systematic review. We extracted results on benefits and harms of proton beam therapy, risk of bias assessment, and assessment of the quality of the body of evidence, as reported directly in the selected systematic review. Because of the high risk of bias in case series studies, we extracted only the results of comparative studies but not those from case series of the selected systematic review.

Statistical Analysis

Since we did not identify any primary studies published after the selected systematic review, we did not perform a de novo (novel) synthesis. We report all statistical analyses as they were presented in the selected systematic review.

Critical Appraisal of Evidence

We used the Risk of Bias in Systematic Reviews (ROBIS) tool[19] to assess risk of bias of all identified systematic reviews. We report the risk of bias of studies and the quality of the body of evidence included in the selected systematic review as originally reported by the review authors (Appendix 4).

Results

Clinical Literature Search for Systematic Reviews

The database search for systematic reviews yielded 487 citations published from database inception until July 24, 2019. We identified 12 additional studies from other sources, for a total of 349 after removing duplicates. See Appendix 2, Table A1, for the list of studies excluded after full-text review. Figure 1 presents the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram for the clinical literature search for systematic reviews.

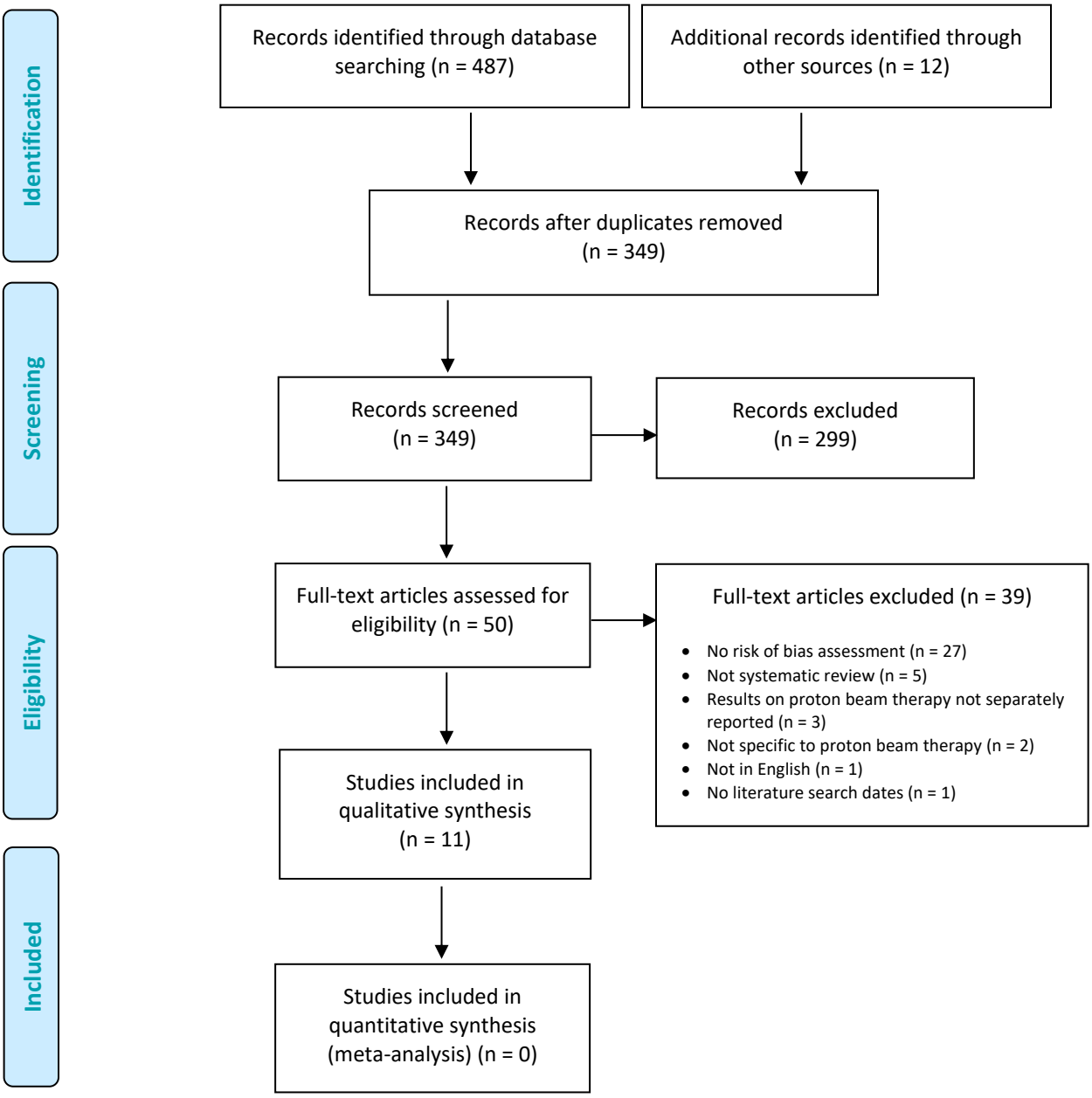

Figure 1: PRISMA Flow Diagram—Clinical Search Strategy for Systematic Reviews

Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.
Source: Adapted from Moher et al, 2009.[20]

Characteristics of Identified Reviews

SYSTEMATIC REVIEWS

Eleven systematic reviews initially met our eligibility criteria.[6,11,21-29] The reviews were published between 2007 and 2019, and all included selection criteria to capture studies that evaluated the use of

proton beam therapy in adults and/or children with cancer.[11] Appendix 3 summarizes details about the design and characteristics of all 11 systematic reviews. See Appendix 4 for their ROBIS risk of bias assessment.

Among the 10 reviews we excluded, four were excluded due to high risk of bias, with one or more of the following characteristics: unclear study selection criteria, limited description of literature search, limited description of data extraction, or inappropriate data synthesis.[22,24,27,29] Five reviews were published in or before 2017 and had an outdated literature search.[6,23,25,26,28] The health technology assessment by the Belgian Health Care Knowledge Centre, published in 2019, evaluated treatment for adults with a number of cancer types that have not been approved for reimbursement in Belgium.[21] This review included a validated risk of bias assessment as well as an assessment of the quality of the body of evidence for each outcome using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group criteria, but it did not review all cancer types.[21]

For our analysis, we ultimately selected the health technology assessment by the Washington State Health Care Authority[11] published in 2019 (search end date Dec 2018) because it included a comprehensive literature search of all cancer types in children and adults, and it provided detailed information on the included study designs, outcomes, and risk of bias assessment. Table 2 provides the inclusion criteria for the selected systematic review.

Table 2: Inclusion Criteria for Selected Systematic Review

Author, Year, *Search End Date*	Populations	Interventions	Comparators	Outcomes	Study Types
Washington State Health Care Authority, 2019[11] *December 2018*	Adults; children Primary or recurrent disease Cancer types (bone, brain, spinal, paraspinal tumours, breast, esophageal, gastrointestinal, gynecologic, head and neck, liver, lung, lymphomas, ocular, prostate, sarcomas, others) Noncancerous tumours	PBT (monotherapy, boost mechanism to conventional radiation, combination therapy with other treatment modalities)	Other radiation alternatives (IMRT, stereotactic radiation techniques and other external beam therapies and brachytherapy) Other treatment alternatives specific to each condition type treated (chemotherapy, immunotherapy, surgical procedures, and other devices)	Overall survival; disease-free survival Mortality Tumour regression, control, or recurrence Radiation-related harms Secondary malignancy risk due to radiation exposure	Comparative and noncomparative studies RCTs Quasi-RCTs Retrospective and prospective cohorts Case series

Abbreviations: IMRT, intensity-modulated radiation therapy; PBT, proton beam therapy; RCT, randomized controlled trial.

Clinical Literature Search for Primary Studies

The database search for randomized controlled trials yielded 453 citations published from January 1, 2019, until September 9, 2019. We identified no additional studies from other sources, for a total of 408 after removing duplicates. See Appendix 2, Table A2, for a list of studies excluded after full-text review. Figure 2 presents the PRISMA flow diagram for the clinical literature search for randomized controlled trials.

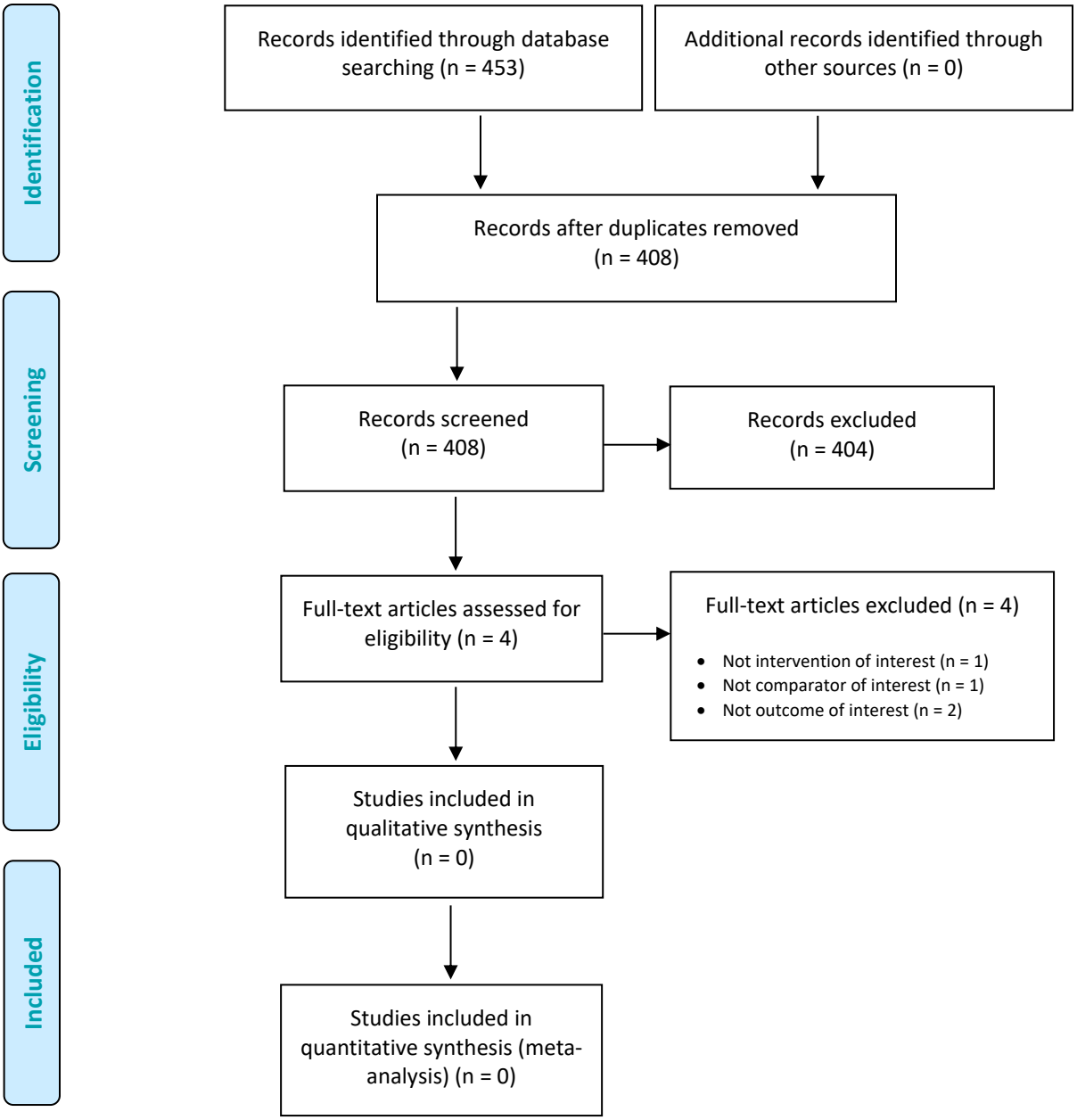

Figure 2: PRISMA Flow Diagram—Clinical Search Strategy for Primary Studies

Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.
Source: Adapted from Moher et al, 2009.[20]

PRIMARY STUDIES

No additional randomized controlled trials that met our inclusion criteria were identified from the search for primary studies published after the selected health technology assessment from Washington State Health Care Authority in 2019.[11]

Results from Selected Systematic Review

Proton beam therapy for cancer was originally reviewed by the Washington State Health Care Authority in 2014.[30] That review identified six RCTs (three on prostate cancer, two on uveal melanoma, and one on skull base chordoma and chondrosarcoma) and 37 nonrandomized comparative studies across 19 types of tumour and noncancer conditions. The authors concluded that the level of comparative evidence was extremely limited for certain conditions and entirely absent for others. Due to newly published evidence, proton beam therapy was re-reviewed in 2019.

The authors stated that the quality of comparative studies in the 2019 health technology assessment[11] appeared to be marginally better than in the 2014 review,[30] but this varied by tumour type. Many studies published after 2014 had larger sample sizes, made direct comparisons of treatment groups, and attempted to control confounding and potential selection bias. Due to changes in clinical practice over time, many comparators in the studies included in 2014 were not represented in the 2019 review as they were no longer being used.[11] These differences should be considered when comparing results between the two reports.

We report results as they were presented in the 2019 Washington State health technology assessment[11] because the authors systematically assessed the quality of evidence of individual studies and the overall strength of evidence for each primary outcome from comparative studies, based on criteria and methods established by the Cochrane Handbook for Systematic Reviews of Interventions,[31] the GRADE Working Group,[32] and recommendations by the Agency for Healthcare Research and Quality.[33]

The 2019 Washington State health technology assessment[11] included 215 publications (56 in pediatrics, 159 in adults). Among the 56 publications in pediatric tumours were 13 retrospective comparative cohort studies, 41 case series, and two cost-effectiveness studies. Most of these studies examined the use of proton beam therapy in various brain tumours. Among the 159 publications in adult tumours, there were two RCTs (one on liver cancer and one on lung cancer), one quasi-RCT (prostate cancer), 33 retrospective comparative cohort studies, 115 case series, four cost-effectiveness studies and four contextual studies. The majority of the evidence in adults was based on patients with esophageal cancer, head and neck cancer, brain cancer, lung cancer, ocular cancer, and prostate cancer.

QUALITY OF EVIDENCE FROM SELECTED SYSTEMATIC REVIEW

The 2019 Washington State health technology assessment used the GRADE criteria[32] to evaluate the quality of the body of evidence and concluded that the overall quality of the available evidence on proton beam therapy for children and adults with cancer was low to very low.[11]

According to the Washington State review authors, the large number of case series should be considered to have a high risk of bias.[11] The comparative evidence was predominantly from nonrandomized (observational) studies, which was considered to be at moderately high risk of bias. Most included studies were retrospective cohorts, which had a number of potential sources of bias. In the absence of high-quality RCTs, the Washington State review defined “best evidence” as prospective

comparative cohort studies that controlled for confounding variables and that had at least 80% follow-up and no more than a 10% difference in follow-up between treatment groups.

However, few included studies met all these criteria. In most instances, patients were treated with photon therapy before switching to proton beam therapy when it became available. The use of historically consecutive controls resulted in differential length of follow-up by treatment groups, with historical groups who received photon therapy having longer follow-up than those receiving proton beam therapy. This differential length of follow-up imposed potential bias related to survivorship when comparing long-term benefits and harms. In addition, completeness of follow-up and differential loss to follow-up created a potential bias. There were also differences between treatment groups in patient characteristics, clinical presentation, tumour stage, comorbidities, prior or concurrent treatments, and surgical factors. Treatment selection bias was a concern with the included studies where patients with more advanced or aggressive tumours were more likely to receive more intensive treatments. In addition, results could be influenced by residual confounding or other biases. Quality of evidence was downgraded for risk of bias when included studies did not control for confounding and/or did not account for time at risk for survival outcomes. Studies that controlled for confounding via study design and/or statistical analyses (e.g., adequate randomization and concealing, matching, multivariate regression, propensity matching) were not downgraded.

Sample sizes varied and most included studies had fewer than 50 participants in each treatment arm. Small sample sizes likely impacted the ability to detect rare events and were reflected in potentially inflated estimates of percentages for certain outcomes. The review authors' finding of imprecision of effect estimate for an outcome was based on small sample size and/or confidence intervals that included both negligible effects and appreciable benefits or harms with the intervention. If sample size was likely too small to detect rare outcomes, they downgraded the evidence twice. If the estimate was statistically significant, it was considered imprecise if the confidence interval crossed the threshed for "mild/small" effects. Wide or unknown confidence interval and/or small sample size could also result in a downgrade. The majority of included studies had imprecise estimates; however, only some were downgraded for imprecision.

The review authors defined inconsistency as different estimates of effects across studies. If effect estimates across studies were in the same direction and did not vary substantially, or if heterogeneity could be explained, results were downgraded for inconsistency. Where evidence came from single studies, consistency was considered "unknown"; evidence from single studies was not downgraded. Consistency was also unknown if there was an overlap of study populations or if different treatment protocols and/or different treatment types were used, including co-intervention (e.g., chemotherapy).

Indirectness and publication bias were not specifically evaluated in the 2019 Washington State health technology assessment.[11]

PEDIATRIC TUMOURS

The 2014 Washington State review[30] did not identify any comparative studies on proton beam therapy for tumours in children; the authors generalized results from case series across all types of pediatric tumours. They concluded that the net health benefit for proton beam therapy could be considered incremental compared with other forms of radiation therapy, based on theoretical considerations that benefits would be comparable but harms would be lower. The 2019 Washington State review[11] identified no RCTs of proton beam therapy for pediatric tumours but did include 10 comparative cohort

studies in pediatric populations (eight on brain tumours, one on salivary gland tumours, and one on ocular tumours).

Brain, Spinal, and Paraspinal Tumours

The 2019 Washington State review[11] identified 25 case series (data not extracted) and eight comparative cohort studies (Table 3), which compared proton beam therapy with treatment alternatives in pediatric brain tumours, including ependymoma, medulloblastoma, and craniopharyngioma. All of these studies were at moderately high risk of bias.

Table 3 summarizes the effectiveness and safety findings of the eight comparative studies on pediatric brain tumours. There were no comparative studies on the effectiveness and safety of proton beam therapy in pediatric spinal or paraspinal tumours.

Across four studies, effectiveness in terms of overall survival, progression-free survival, and tumour recurrences at any time points were generally similar between patients who received proton beam therapy and alternative groups. Seven comparative studies reported on adverse events; across these studies, the risk of hypothyroidism, other endocrine-related toxicities, vision changes, and hypothalamic obesity tended to be lower with proton beam therapy than with other forms of radiotherapy. There was no significant difference between proton beam therapy and photon therapy on changes in intelligence quotient (IQ) scores, risk of vascular injury (damage to the circulation), hearing loss, and radiation necrosis (the death of healthy tissue caused by radiation therapy).[11] In a single study, the frequency of acute hematological toxicities (damage to blood cells or other blood components) was lower with proton beam therapy than with photon therapy.[11]

Based on the comparative studies reviewed, the Washington State authors assessed the quality of evidence of proton beam therapy in pediatric brain tumours as low for effectiveness and low to very low for safety, downgrading due to risk of bias.[11]

Table 3: Effectiveness and Safety of Proton Beam Therapy for Children With Brain Tumours

Outcomes	Tumour Type (No. of Studies)	Sample Size, N	Follow-Up Duration	Effect Estimates (95% CI), PBT vs. Photon RT or IMRT	GRADE[a]
Effectiveness					
Overall survival, probability	Ependymoma (n = 2)	79	3 y	*PBT vs. photon RT* 97% (83%–99%) vs. 81% (63%–90%), *P* = .08	⨁⨁ Low
		72	4 y	*PBT vs. photon RT* 87.5% (51.6%–97.3%) vs. 78.8% (60.6%–89.3%), *P* = .21	
			6 y	*PBT vs. photon RT* 88% vs. 70%, *P* = NR	
	Craniopharyngioma (n = 1)	52	3 y	*PBT vs. photon RT* 94.1% vs. 96.8%, *P* = .742	
	Medulloblastoma (n = 2)	783	5 y	*PBT vs. photon RT* HR 0.99 (0.41–2.4), *P* = .98	

Outcomes	Tumour Type (No. of Studies)	Sample Size, N	Follow-Up Duration	Effect Estimates (95% CI), PBT vs. Photon RT or IMRT	GRADE[a]
		88	6 y	*PBT vs. photon RT* 82.0% (65.4%–91.1%) vs. 87.6% (72.7%–94.7%), *P* = NR Adj. HR 2.17 (0.66–7.16)	
Progression-free survival probability	Ependymoma (n = 1)	79	3 y	*PBT vs. IMRT* 82% (64–92%) vs. 60% (42%–74%), *P* = NR HR 0.42 (0.16–1.10)	⨁⨁ Low
			6 y	*PBT vs. IMRT* PFS 82% vs. 38%, *P* = NR	
Relapse-free survival probability	Medulloblastoma (n = 1)	88	6 y	*PBT vs. photon RT* 78.8% (63%–89%) vs. 76.5% (60.6%–86.6%) Adj. HR 1.31 (0.5–3.41)	⨁⨁ Low
Adverse Events					
Hypothyroidism	Medulloblastoma (n = 2)	84	56.4 mo (PBT) vs. 121.2 mo (IMRT or CRT)	*PBT vs. IMRT or photon RT* Any hypothyroidism 19% vs. 46.3% Adj. HR (vs. IMRT or photon RT) 1.85 (0.8–4.2) Primary hypothyroidism 7.3% vs. 20.4% Adj. HR (vs. IMRT or photon RT) 2.1 (0.6–7.7) Central hypothyroidism 9.8% vs. 24.0% Adj. HR (vs. IMRT or photon RT) 2.2 (0.7–6.6)	⨁⨁ Low
		77	69.6 mo vs. 84 mo	Hypothyroidism 22.5% vs. 64.9% Adj. OR 0.13 (0.04–0.41)	
Change in IQ scores	Various brain tumours (n = 2)	150	32.4 mo vs. 64.8 mo	*PBT vs. photon RT* FSIQ (adj. β-coefficient): All patients −0.7 (−1.6, 0.2) vs. −1.1 (−1.8, −0.4), *P* = .51 CSI −0.8 vs. −0.9, *P* = .89 Focal irradiation 0.6 (−2.0, 0.8) vs. −1.6 (−3.0, −0.2), *P* = .34	⨁⨁ Low
		93	33.6 mo vs. 37.2 mo	*Focal PBT vs. surgery* No statistically significant difference on FSIQ or any subscales; scores remained stable for both groups over time *PBT vs. surgery* CSI (adj. β-coefficient) FSIQ −2.1 (−3.8, −0.3), *P* = .020 PSI −2.6 (−4.7, −0.3), *P* = .019	

Outcomes	Tumour Type (No. of Studies)	Sample Size, N	Follow-Up Duration	Effect Estimates (95% CI), PBT vs. Photon RT or IMRT	GRADE[a]
Other late toxicities or adverse events	Craniopharyngioma (n = 1)	52	33.1 mo vs. 106 mo	*PBT vs. photon RT* Vascular damage on imaging 10% vs. 10% Vision change 5% vs. 13%, RR 0.37 (0.04–3.07) Hypothalamic obesity 19% vs. 29%, RR 0.66 (0.23–1.9)	⨁⨁ Low
	Medulloblastoma (n = 1)	84	55.5 mo vs. 65.5 mo	*PBT vs. IMRT or photon RT* Grade 3 hearing loss 26.3% vs. 21.7% Grade 4 hearing loss 2.6% vs. 6.5% Grade 3 and 4 hearing loss 29.9% vs. 28.3%, *P* = 1.0	
	Ependymoma (n = 1)	79	31.2 mo vs. 58.8 mo	*PBT vs. IMRT* All events 7.3% vs. 13.2%, RR 0.56 (0.14–2.17) Radiation necrosis 7.3% vs. 7.9% Stroke 0% vs. 2.6% Cavernoma 0% vs. 2.6%	
Acute toxicities	Various tumours (n = 1)	43	Acute	*PBT vs. photon RT* <u>Leukopenia</u> Grade 3: 57% vs. 46% Grade 4: 7% vs. 31% Grade 3 or 4: RR 0.68 (0.44–1.08) <u>Anemia</u> Grade 3: 0% vs. 15%, *P* = .493 Grade 4: 0% vs. 0% <u>Thrombocytopenia</u> Grade 3: 20% vs. 31% Grade 4: 3% vs. 23% Grade 3 or 4: RR 0.43 (0.19–0.98)	⨁ Very low Risk of bias (−1)[b]

Abbreviations: Adj, adjusted; CI, confidence interval; CSI, craniospinal irradiation; FSIQ, full-scale intelligence quotient; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; HR, hazard ratio; IMRT, intensity-modulated radiation therapy; IQ, intelligence quotient; mo, month; no., number; NR, not reported; OR, odds ratio; PBT, proton beam therapy; PSI, processing speed index; RR, relative risk; RT, radiotherapy; y, year.

[a]Observational studies started with a low GRADE level because of inherent limitations in study design (e.g., lack of randomization, lack of blinding, loss to follow-up).

[b]Risk of bias was downgraded in the majority of studies, which did not control for confounding and/or did not account for time at risk for survival outcomes. Studies that controlled for confounding via study design and/or statistical analyses (e.g., adequate randomization and concealing, matching, multivariate regression, propensity matching) were not downgraded.

Adapted from Washington State Health Care Authority, 2019.[11]

Head and Neck Tumours

Within the category of head and neck tumours, the 2019 Washington State review[11] identified three case series (data not extracted) and one small retrospective cohort study in children with salivary gland tumours (n = 24; 11 treated with adjuvant proton beam therapy, 13 received adjuvant photon therapy).

This study reported only on acute toxicities but not on effectiveness outcomes. Mucositis was possibly less common in adjuvant proton beam therapy than in adjuvant photon therapy (relative risk 0.51 [95% confidence interval [CI] 0.27–0.94]). However, the risk of dysphagia and otitis externa was similar between groups.

Based on the one comparative study reviewed, the Washington State authors assessed the quality of evidence for safety of proton beam therapy in pediatric head and neck tumour as very low, downgrading due to serious imprecision and risk of bias.

There were no comparative studies evaluating the effectiveness of proton beam therapy in pediatric head and neck tumours.[11]

Lymphoma

The 2019 Washington State health technology assessment[11] identified two case series (data not extracted) but did not find any comparative studies on the effectiveness or safety of proton beam therapy in pediatric lymphoma.

Ocular Tumours

The 2019 Washington State health technology assessment[11] identified two case series (data not extracted) and one retrospective cohort study that evaluated the use of proton beam therapy as salvage treatment in children with retinoblastoma. (Salvage treatment is treatment given for recurrent disease or failure of initial therapy.) This small study included 16 eyes treated with proton beam therapy, 27 eyes treated with photon therapy, and 4 eyes treated with brachytherapy. Enucleation-free survival (meaning the eye did not need to be surgically removed) was lower in proton beam therapy (38.5%) compared with photon therapy (54.5%). Acute toxicity (mostly skin erythema) was similar between groups (93.8% for proton beam therapy vs. 74.1% for electron beam therapy, $P = .22$). Any event of late toxicity was also similar between groups (62.5% for proton beam therapy vs. 55.6% for electron beam therapy, $P = .275$).

Based on the comparative studies reviewed, the quality of evidence for effectiveness and safety of proton beam therapy in pediatric ocular tumour was very low, due to serious imprecision and risk of bias.[11]

Soft Tissue Sarcomas

The 2019 Washington State review[11] identified six case series (data not extracted) but did not find any comparative studies on the effectiveness or safety of proton beam therapy in pediatric soft tissue sarcomas.

Other Tumours

The 2019 Washington State review[11] identified one case series on Ewing sarcoma and one case series on various tumour types (data not extracted) but did not find any comparative studies on the effectiveness or safety of proton beam therapy in these pediatric populations.

ADULT TUMOURS

The 2014 Washington State health technology assessment[30] identified 38 comparative studies on all adult tumours, which included two RCTs (one on ocular cancer and one on prostate cancer), six prospective cohort studies, 22 retrospective cohort studies, and eight noncontemporaneous case series. The 2019 review[11] identified 36 comparative studies, which included two additional RCTs (one on liver cancer and one on lung cancer), one quasi-RCT on prostate cancer, and 33 retrospective cohort studies. The majority of evidence was in adults with esophageal, head and neck, brain, lung, ocular, and prostate cancers.

Bladder Cancer

The 2019 Washington State review[11] identified one case series (data not extracted) but did not find any comparative studies on the effectiveness or safety of proton beam therapy in adults with bladder cancer.

Bone Cancer

The 2019 Washington State review[11] identified one case series (data not extracted) but did not find any comparative studies on the effectiveness or safety of proton beam therapy in adults with bone cancer.

Brain, Spinal, and Paraspinal Cancer

The 2019 Washington State review[11] identified six case series (data not extracted) and five retrospective comparative cohort studies (Table 4) on the effectiveness or safety of proton beam therapy in adults with brain, spinal, or paraspinal cancer. Two of the five comparative studies reported effectiveness and/or safety outcomes of interest to our clinical evidence review.

Results on effectiveness were inconsistent across two retrospective case-matched cohorts evaluating adults with different types of brain tumours undergoing radiotherapy with curative intent. One study of patients with high-grade glioma showed that those who received proton beam therapy boost tended to have higher 1-to-2-year progression-free survival, but lower 1-to-3-year overall survival, than those who received photon therapy alone. Although this difference was not statistically significant, it may be clinically meaningful. In a large database study primarily of patients with high-grade glioma, 5-year overall survival was statistically higher following proton beam therapy than after photon therapy. In a small retrospective cohort study in patients with metastatic central nervous system disease undergoing radiotherapy as salvage treatment, proton beam therapy improved 1-year but not 6-month overall survival when compared with photon therapy.

In terms of safety, more patients with high-grade glioma who received photon therapy alone had acute grade 3 toxicity (e.g., increase in intracranial pressure, generalized seizures) than those who received proton beam therapy and photon therapy. However, the number of cases was small (0 vs. 5, respectively). There were no differences between groups in the proportion of patients experiencing either worsening of pre-existing symptoms or new symptoms following treatment.

The general trend in studies of patients with primary high-grade brain tumours was for improved survival with proton beam compared with photon therapy. Based on the comparative studies reviewed, the Washington State authors assessed the quality of evidence for effectiveness (for curative intent) and safety of proton beam therapy in adults with brain tumours as low.

Based on the comparative studies reviewed, the Washington State authors assessed the quality of evidence for effectiveness (as salvage treatment) and safety of proton beam therapy in adults with spinal or paraspinal tumours as very low, with downgrading due to serious imprecision and risk of bias, respectively.[11]

Table 4: Effectiveness and Safety of Proton Beam Therapy for Adults With Brain, Spinal, and Paraspinal Tumours

Outcomes	Tumour Type (No. of Studies)	Sample Size	Follow-Up Duration	Effect Estimates (95% CI), PBT vs. Photon RT	GRADE[a]
Effectiveness (for Curative Intent)					
Overall survival probability	High-grade glioma (n = 1)	132	1–3 y	*PBT + photon RT vs. photon RT alone* 1 y: 75% vs, 85% 2 y: 40% vs. 43% 3 y: 12% vs. 28% *P* = NS at all timepoints	⨁⨁ Low
	Glioma (n = 1)	170 (PBT) 49,405 (photon RT) 161:161 (propensity score matched)	5 y	*PBT vs. any photon RT* Entire cohort: adj. HR 0.66 (0.53–0.83) favours PBT Matched cohort: 46.1 vs. 35.5%, *P* = .009	
Progression-free survival probability	High-grade glioma (n = 1)	132	1–2 y	*PBT + photon RT vs. photon RT alone* 1 y: 31% vs, 21% 2 y: 8% vs. 2% *P* = NS at all timepoints	⨁⨁ Low
Effectiveness (as Salvage Treatment)					
Overall survival probability	Lymphoma or leukemia with CNS involvement (n = 1)	37	6 mo–1 y	*PBT vs. photon RT* 6 mo: 78.6% vs. 69.6%, *P* = .15 1 y: 70% vs. 38%, *P* = NR	⨁ Very low Serious imprecision (−1)[b]
Adverse Events					
Acute toxicity (≤ 3 months)	High-grade glioma (n = 1)	132	Median 15 mo	*PBT + photon RT vs. photon RT alone* Grade ≥ 2 toxicity 9% vs. 14%, *P* = NR Grade 3 toxicity 0% vs. 7.5%, *P* < .1	⨁⨁ Low
	Lymphoma or leukemia with CNS involvement (n = 1)	37	During CSI	*PBT vs. photon RT* Grade 3 mucositis 7% vs. 9%, *P* = .1 Any grade mucositis 7% vs. 44% RR 0.16 (0.02–1.15) Gastrointestinal 29% vs. 30%, *P* = 1.0 CNS 21% vs. 13%, *P* = .65	⨁ Very low Risk of bias (−1)[c]

Outcomes	Tumour Type (No. of Studies)	Sample Size	Follow-Up Duration	Effect Estimates (95% CI), PBT vs. Photon RT	GRADE[a]
			Late	*PBT vs. photon RT* Severe CNS neurotoxicity 7% vs. 0%, *P* = NS	
Radiation necrosis	High-grade glioma (n = 1)	132	Median 15 mo	*PBT + photon RT vs. photon RT alone* 0% vs. 0%	⨁⨁ Low
Change in symptomology	High-grade glioma n = 1)	132	Median 15 mo	*PBT + photon RT vs. photon RT alone* <u>Neurocognitive deficits</u> Worse than baseline 3% vs. 6%, *P* = NS New: 9% vs. 2%, *P* = NS <u>Sensorimotor deficits</u> Worse than baseline 3% vs. 5%, *P* = NS New 11% vs. 14%, *P* = NS <u>Seizures</u> Worse than baseline 0% vs. 0% New 2% vs. 6%, *P* = NS	⨁⨁ Low

Abbreviations: CI, confidence interval; CNS, central nervous system; CSI, craniospinal irradiation; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; HR, hazard ratio; mo, month; no., number; NR, not reported; NS, not statistically significant; PBT, proton beam therapy; RR, relative risk; RT, radiotherapy; y, year.

[a]Observational studies started with a low GRADE level because of inherent limitations in study design (e.g., lack of randomization, lack of blinding, loss to follow-up).

[b]Imprecision of effect estimate for an outcome was based on small sample size, and/or confidence interval that included both negligible effect and appreciable benefits or harms with the intervention. If sample size was likely too small to detect rare outcomes, evidence may be downgraded twice. If the estimate was statistically significant, it was imprecise if the confidence interval crossed the threshed for "mild/small" effects. Wide or unknown confidence interval and/or small sample size may result in downgrade.

[c]Risk of bias was downgraded in the majority of studies, which did not control for confounding and/or did not account for time at risk for survival outcomes. Studies that controlled for confounding via study design and/or statistical analyses (e.g., adequate randomization and concealing, matching, multivariate regression, propensity matching) were not downgraded.

Adapted from Washington State Health Care Authority, 2019.[11]

Breast Cancer

The 2019 Washington State review[11] identified four case series (data not extracted) and two comparative cohort studies that evaluated the effectiveness of proton beam therapy in adults with breast cancer. Of the two comparative studies, one reported the outcomes of interest to our clinical evidence review. This study was a large, retrospective comparative study using the US National Cancer Database. It evaluated patients with nonmetastatic breast cancer treated with adjuvant proton beam therapy (n = 871) versus photon therapy or photon plus electron boost (n = 723,621) following either breast-conserving surgery or mastectomy. There was no statistical difference in the overall survival probability at 5 years between patients who received proton beam therapy (91.9%) vs. photon with or without electron boost therapy (88.9%). The multivariable-adjusted hazard ratio was 0.85 (95% CI 0.68–1.07), *P* = .12.

The Washington State authors noted no clear trend of improved survival with proton beam therapy versus photon therapy in adults with breast cancer. Based on the comparative studies reviewed, they assessed the quality of evidence for effectiveness of proton beam therapy in adults with breast cancer as low.

There were no comparative studies on safety of proton beam therapy in adults with breast cancer.[11]

Esophageal Cancer

The 2019 Washington State review[11] identified two case series (data not extracted) and five comparative cohort studies (Table 5) that evaluated the use of proton beam therapy in adults with esophageal cancer. One of these five comparative studies reported safety outcomes only. Overall survival was similar between proton beam therapy and photon therapy at 1-year follow-up; however, in subsequent years, the survival probability appeared to favour proton beam therapy. At all time points up to 5 years following treatment, progression-free or disease-free survival was better with proton beam therapy than photon therapy.

For safety outcomes, the frequency of radiation pneumonitis was low in patients who received proton beam therapy or various forms of photon therapy (2 vs. 6 events, respectively). Radiation esophagitis and radiation-induced lymphopenia were less common following proton beam therapy than following various forms of photon therapy. Treatment-related toxicities (i.e., pulmonary, cardiac, and wound events) were similar between proton beam therapy and other photon therapy groups. Since all patients received concurrent or adjuvant chemotherapy, it was unclear to what extent proton beam therapy directly impacted these treatment-related toxicities.

The general trend across included studies was improved survival and reduced toxicity with proton beam therapy. Based on the comparative studies reviewed, the quality of evidence for effectiveness and safety of proton beam therapy in adults with esophageal cancer was low to very low, downgraded due to risk of bias.[11]

Table 5: Effectiveness and Safety of Proton Beam Therapy for Adults With Esophageal Cancer

Outcomes	Tumour Type (No. of Studies)	Sample Size, N	Follow-Up Duration	Effect Estimates (95% CI), PBT vs. Photon RT (Various)	GRADE[a]
Effectiveness					
Overall survival probability	Various stages of AC or SCC (n = 2)	343 (71% AC, 29% SCC; 34% stage I/II, 66% stage III)	1–5 y	*PBT vs. IMRT* 1 y: 88% vs. 85%, *P* = .01 2 y: 70% vs. 50%, *P* = .01 3 y: 55% vs. 39%, *P* = .01 4 y: 44% vs. 35%, *P* = .01 5 y: 41.6% vs. 31.6%, *P* = .01 Adj. HR at 5-year: 1.45 (1.09–1.94), *P* = .01 Stage III only: 35% vs. 25%, *P* = .04	⨁⨁ Low

Outcomes	Tumour Type (No. of Studies)	Sample Size, N	Follow-Up Duration	Effect Estimates (95% CI), PBT vs. Photon RT (Various)	GRADE[a]
		133 (74% AC, 26% SCC; stage III/IV only; retro-propensity score matched cohort at 5-year)		*PBT vs. IMRT* 1 y: 80% vs. 78%, *P* = .1 2 y: 66% vs. 49%, *P* = .1 3 y: 48% vs. 38%, *P* = .1 4 y: 42% vs. 30%, *P* = .1 5 y: 42% vs. 19%, *P* = .1 Matched: adj. HR at 5-year: 1.48 (0.93–2.35), *P* = .1 All: HR 0.82 (0.56–1.20), *P* = .30	
Progression-free survival probability	Various stages of AC or SCC (n = 1)	343 (71% AC, 29% SCC; 34% stage I/II, 66% stage III)	1–5 y	*PBT vs. IMRT* 1 y: 62% vs. 50%, *P* = .001 2 y: 50% vs. 33%, *P* = .001 3 y: 42% vs. 28%, *P* = .001 4 y: 39% vs. 24%, *P* = .001 5 y: 34.9% vs. 20.4%, *P* = .001 Adj. HR at 5-year: 1.56 (1.19–2.05), *P* = .001 Stage III only: 33.5% vs. 13.2%, *P* = .005	⨁⨁ Low
Disease-free survival probability	Stage III/IV AC or SCC (n = 1)	133 (74% AC, 26% SCC; retro-propensity score matched cohort)	1–5 y	*PBT vs. IMRT* 1 y: 55% vs. 45%, *P* = .11 2 y: 45% vs. 26%, *P* = .11 3 y: 41% vs. 23%, *P* = .11 4 y: 41% vs. 23%, *P* = .11 5 y: 41% vs. 18%; adj. HR at 5 y: 1.42 (0.92–2.19), *P* = .11	⨁⨁ Low
Mortality[c]	Various stages of AC or SCC (n = 1)	580 (92% AC, 8% SCC; stage III/IV 63%)	1–3 mo	*PBT vs. IMRT or 3D-CRT* 1 mo: 0% vs. 1.5%, *P* = .43 2 mo: 0.9% vs. 2.6%, *P* = .59 3 mo: 0.9% vs. 4.3%, *P* = .26	⨁ Very low Risk of bias (−1)[b]
	SCC (n = 1)	44 (52% stage III, 48% stage I/II)	Median 22 mo	*Passive scatter PBT vs. XRT* 20% vs. 31.6%, *P* = NR	
Adverse Events					
Radiation pneumonia, grade ≥ 3	Various stages of AC or SCC (n = 2)	343 (71% AC, 29% SCC; 34% stage I/II, 66% stage III)	NR	*PBT vs. IMRT* 1.5% vs. 2.8%, *P* = NS	⨁⨁ Low
	SCC (n = 1)	44 (52% stage III, 48% stage I/II)	late	*PBT vs. XRT* 0% vs. 5.3%, *P* = NS	

Outcomes	Tumour Type (No. of Studies)	Sample Size, N	Follow-Up Duration	Effect Estimates (95% CI), PBT vs. Photon RT (Various)	GRADE[a]
Radiation esophagitis, grade ≥ 3	Various stages of AC or SCC (n = 1)	343 (71% AC, 29% SCC; 34% stage I/II, 66% stage III)	NR	*PBT vs. IMRT* 11.4% vs. 14.2%, *P* = NS	⨁⨁ Low
Radiation induced lymphopenia, grade 4	Various stages of AC or SCC (n = 2)	220 (74% AC, 26% SCC; retro-propensity score matched cohort)	Acute	*PBT vs. IMRT* 31% vs. 47% Adj. OR 0.47 (0.26–0.84), *P* = .01	⨁⨁ Low
		272 (97% AC, 3% SCC; retro-propensity score matched cohort)	Acute	*PBT vs. IMRT* 17.6% vs. 40.4% Adj. OR 0.29 (0.16–0.52), *P* < .0001	

Abbreviations: 3D-CRT, 3-dimensional conformal radiation therapy; AC, adenocarcinoma; Adj, adjusted; CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; HR, hazard ratio; IMRT, intensity-modulated radiation therapy; mo, month; no., number; NR, not reported; NS, not statistically significant; OR, odds ratio; PBT, proton beam therapy; retro, retrospective; RT, radiotherapy; SCC, squamous cell carcinoma; XRT, x-ray radiation therapy; y, year.

[a]Observational studies started with a low GRADE level because of inherent limitations in study design (e.g., lack of randomization, lack of blinding, loss to follow-up).

[b]Risk of bias was downgraded in the majority of studies, which did not control for confounding and/or did not account for time at risk for survival outcomes. Studies that controlled for confounding via study design and/or statistical analyses (e.g., adequate randomization and concealing, matching, multivariate regression, propensity matching) were not downgraded.

[c]The review authors did not specify all-cause mortality or treatment-related mortality.

Adapted from Washington State Health Care Authority, 2019.[11]

Gastrointestinal Cancer

The 2019 Washington State review[11] identified two case series (data not extracted) and one comparative study (Table 6) on the use of proton beam therapy in adults with pancreatic cancer. Overall survival was similar between groups annually up to 3-year follow-up. There were no significant differences in disease control and local progression. Acute radiation-related toxicities, including hematological and nonhematological events, were not different between groups.

Based on the single comparative study reviewed, the quality of evidence for effectiveness and safety of proton beam therapy in adults with gastrointestinal cancer was very low, downgraded due to risk of bias.

Table 6: Effectiveness and Safety of Proton Beam Therapy for Adults With Gastrointestinal Cancer

Outcomes	Tumour Type (No. of Studies)	Sample Size	Follow-Up Duration	Effect Estimates (95% CI) PBT vs. HART	GRADE[a]
Effectiveness					
Overall survival probability	Pancreatic adenocarcinoma (n = 1)	25	1–3 y	1 y: 80% vs. 86.7% 2 y: 45% vs. 33.3% 3 y: 22.5% vs. 26.6% *P* = NS at all timepoints	⊕ Very low Risk of bias (−1)[b]
Disease control			NR	80% vs. 93%, *P* = NR RR 0.86 (0.61–1.20)	
Local progression			NR	40% vs. 60%, *P* = NR RR 0.60 (0.26–1.39)	
Adverse Events					
Acute toxicities	Pancreatic adenocarcinoma (n = 1)	25	≤ 3 mo	*Hematological toxicities* Leukopenia Grade 2: 10% vs. 13% Grade 3: 0% vs. 20% Thrombocytopenia Grade 2: 10% vs. 20% Grade 3: 0% vs. 6.7% Neutropenia/anemia Grade 2/3: 0% vs. 0% *Nonhematological toxicities* Ulcer Grade 2: 10% vs. 0% Grade 3: 10% vs. 0% Nausea Grade 2: 0% vs. 7% Grade 3: 0% vs. 0% Anorexia Grade 2: 0% vs. 20% Grade 3: 0% vs. 0% Malaise Grade 2/3: 0% vs. 0%	⊕ Very low Risk of bias (−1)[b]

Abbreviations: CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; HART, hyper-fractionated accelerated radiotherapy; mo, month; no., number; NR, not reported; NS, not statistically significant; PBT, proton beam therapy, RR, relative risk; y, year.

[a]Observational studies started with a low GRADE level because of inherent limitations in study design (e.g., lack of randomization, lack of blinding, loss to follow-up).

[b]Risk of bias was downgraded in the majority of studies, which did not control for confounding and/or did not account for time at risk for survival outcomes. Studies that controlled for confounding via study design and/or statistical analyses (e.g., adequate randomization and concealing, matching, multivariate regression, propensity matching) were not downgraded.

Adapted from Washington State Health Care Authority, 2019.[11]

Head and Neck Tumours

The 2019 Washington State review[11] identified 23 case series that evaluated proton beam therapy in a variety of cancer types involving the head and neck (data not extracted) and eight comparative studies that compared proton beam therapy with alternative treatments in adults with head and neck cancers. Among these eight studies, one was on skull base chondrosarcoma.

As shown in Table 7, across various head and neck cancer types, overall survival and progression-free survival (1 to 3 years) and all-cause mortality (24 months) were similar between patients receiving proton beam therapy versus intensity-modulated radiotherapy. For safety outcomes, there were no significant differences in the frequencies of acute or late toxicities (grade 3 or above) (Table 7). In addition, the incidence of emergency room visits or unplanned hospitalizations and of osteoradionecrosis (bone death due to radiation) was similar between treatment groups.

In a small cohort of 47 adults with skull base chondrosarcoma, the probability of progression-free survival at 10 years was better following surgery with adjuvant proton beam therapy versus surgery alone (87.5% [95% CI 64.6%–100%] vs. 58.2% [33.5%–82.8%], *P* = .006]. Disease-specific survival at 10 years was not significantly different (100% vs. 89.8% [95% CI 76.2%–100%], *P* = .138). Local control (total disappearance of the primary tumour with no local recurrence) was also better following surgery with adjuvant proton beam therapy (relative risk 0.13 [95% CI 0.02–0.96], *P* = .01). For safety outcomes, there were no differences in treatment-related death or toxicity (grade ≥ 3) between groups; however, those receiving adjuvant proton beam therapy had a higher risk of experiencing hearing loss or dizziness. The review authors cautioned on the uncertainty of these estimates because of wide confidence intervals.

General trends were reduced rates of toxicity among adults with head and neck cancers treated with proton beam therapy versus photon therapy. Based on the comparative studies reviewed, the Washington State authors assessed the quality of evidence for effectiveness of proton beam therapy in adults with head and neck (including skull base) cancer as low to very low, downgrading due to risk of bias. For safety, the quality of evidence was low.[11]

Table 7: Effectiveness and Safety of Proton Beam Therapy for Adults With Head and Neck Cancer

Outcomes	Tumour Type (No. of Studies)	Sample Size, N	Follow-Up Duration	Effect Estimates (95% CI), PBT vs. IMRT	GRADE[a]
Effectiveness					
Overall survival probability	Primary or metastatic salivary gland cancer (n = 1)	41	1 y	*Uniform scanning PBT beam vs. IMRT* 83.3% vs. 93.3%, *P* = .08	⊕ Very low Risk of bias (−1)[b]
	Oropharyngeal cancer (n = 1)	150	3 y	*Intensity-modulated spot scanning PBT vs. IMRT* 94.3% vs. 89.3% Adj. HR 0.55 (0.1–2.5), *P* = .44	⊕⊕ Low
Progression-free survival probability	Oropharyngeal cancer (n = 1)	150	3 y	*Intensity-modulated spot scanning PBT vs. IMRT* 86.4% vs. 85.8%	⊕⊕ Low

Outcomes	Tumour Type (No. of Studies)	Sample Size, N	Follow-Up Duration	Effect Estimates (95% CI), PBT vs. IMRT	GRADE[a]
				Adj. HR 1.0 (0.4–2.6), *P* = .99	
All-cause mortality	Nasopharyngeal cancer (n = 1)	30	Median 24 mo	*Intensity-modulated spot scanning PBT vs. IMRT* 10% vs. 5%, *P* = NS	⨁⨁ Low
Adverse Events					
Acute toxicities (grade ≥ 3)	Primary or metastatic salivary gland cancer (n = 1)	41	≤3 mo	*Uniform scanning PBT beam vs. IMRT* Dermatitis: 27.8% vs. 34.8% Mucositis: 0% vs. 8.7% No events on nausea, dysphagia, dysgeusia, fatigue and grade 4 toxicities in either group	⨁⨁ Low
	Oropharyngeal cancer (n = 1)	150	≤ 3 mo	*Intensity-modulated spot scanning PBT vs. IMRT* > 20% weight loss: 8.3% vs. 13.5%, adj. OR 0.64 (0.19– 2.11) Grade 2/3 fatigue: 40.8% vs. 36.2%, adj. OR 1.1 (0.53–2.27) Grade 2/3 xerostomia: 42% vs. 61.2%, adj. OR 0.38 (0.18–0.79)	⨁⨁ Low
	Nasopharyngeal cancer (n = 1)	30	≤ 3 mo	*Intensity-modulated spot scanning PBT vs. IMRT* Any grade 3 events: 50% vs. 90%, RR 0.56 (0.29–1.05) Grade 3 dermatitis: 40% vs. 25%, RR 1.6 (0.55–4.68) No grade 4 dermatitis in either group Swallowing dysfunction: 0% vs. 15%, *P* = .175 Weight loss (mean %, IQR): 5.7% (4.5%–11.2%) vs. 7.6% (6.1%–12.1%), *P* = .333	⨁⨁ Low
Late toxicities (grade ≥ 3)	Oropharyngeal cancer (n = 1)	150	1 y	*Intensity-modulated spot scanning PBT vs. IMRT* > 20% weight loss: 6.7% vs. 19.3%, adj. OR 0.28 (0.08– 1.05) Grade 2/3 fatigue 14.6% vs. 22.1%, adj. OR 0.5 (0.18–1.36) Grade 2/3 xerostomia: 42% vs. 47.2%, adj. OR 0.63 (0.30–1.33)	⨁⨁ Low
	Nasopharyngeal cancer (n = 1)	30	Median 24 mo	*Intensity-modulated spot scanning PBT vs. IMRT*	⨁⨁ Low

Outcomes	Tumour Type (No. of Studies)	Sample Size, N	Follow-Up Duration	Effect Estimates (95% CI), PBT vs. IMRT	GRADE[a]
				Any grade 3 event: 30% vs. 15%, RR 2.0 (0.49–8.18)	
Acute gastrostomy tube dependency	Oropharyngeal cancer (n = 1)	150	≤3 mo	*Intensity-modulated spot scanning PBT vs. IMRT* 12% vs. 23%, adj. OR 0.43 (0.16–1.17)	⨁⨁ Low
	Nasopharyngeal cancer (n = 1)	30	During and after RT	*Intensity-modulated spot scanning PBT vs. IMRT* 20% vs. 65%, *P* = .02 Adj. OR 9.33 (1.74–75.96), *P* = .008	⨁⨁ Low
	Nasopharynx, nasal cavity, or paranasal sinus cancer (n = 1)	40	End of RT 1 mo post-RT	*3D-conformal PBT vs. IMRT* Adj. OR 0.03 (<0.01–0.15), *P* < .001 Adj. OR 0.11 (<0.01–0.61), *P* = .028	⨁⨁ Low
	Primary or metastatic salivary gland cancer (n = 1)	41	≤ 3 mo	*Uniform scanning PBT beam vs. IMRT* 0% vs. 0%	⨁⨁ Low
Late gastrostomy tube dependency	Oropharyngeal cancer (n = 2)	150	1 y	*Intensity-modulated spot scanning PBT vs. IMRT* 2% vs. 7.8%, adj. OR 0.16 (0.02–1.37)	⨁⨁ Low
		64	6 mo	*Adjuvant pencil beam scanning PBT vs. IMRT* 0% vs. 0%	⨁⨁ Low

Abbreviations: Adj, adjusted; CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; HR, hazard ratio; IMRT, intensity-modulated radiation therapy; IQR, interquartile range; mo, month; no., number; NS, not statistically significance; OR, odds ratio; PBT, proton beam therapy; RT, radiotherapy; y, year.

[a]Observational studies started with a low GRADE level because of inherent limitations in study design (e.g., lack of randomization, lack of blinding, loss to follow-up).

[b]Risk of bias was downgraded in the majority of studies, which did not control for confounding and/or did not account for time at risk for survival outcomes. Studies that controlled for confounding via study design and/or statistical analyses (e.g., adequate randomization and concealing, matching, multivariate regression, propensity matching) were not downgraded.

Adapted from Washington State Health Care Authority, 2019.[11]

Liver Cancer

The 2019 Washington State review[11] identified one RCT and one retrospective comparative study (Table 8), as well as 12 case series (data not extracted), that evaluated proton beam therapy in adults with liver cancer.

In an interim analysis of an ongoing RCT of adult patients with unresectable (cancer that has spread and cannot be surgically removed) hepatocellular carcinoma, there was no significant difference in the 2-year overall survival between proton beam therapy and transarterial chemoembolization, although

progression-free survival and local control tended to be greater following proton beam therapy. The RCT provided limited information on acute toxicity. Significantly fewer patients who received proton beam therapy required hospitalization in the month following treatment compared with those who received transarterial chemoembolization.

In a small retrospective cohort study of adult patients with unresectable hepatocellular carcinoma, overall survival was significantly higher in patients receiving proton beam therapy compared with intensity-modulated radiation therapy; however, there was no significant difference in local and regional control between groups. For safety outcomes, proton beam therapy was associated with a lower risk of nonclassic radiation-induced liver disease and death due to liver failure than was intensity-modulated radiation therapy.

In direct comparison of proton- to photon-based treatment, proton beam therapy appeared to be associated with improved survival and reduced toxicity. Based on the comparative studies reviewed, the Washington State authors assessed the quality of evidence for effectiveness of proton beam therapy in adults with liver cancer as moderate to low, downgrading due to serious imprecision. For safety outcomes, the quality of evidence was moderate to very low, downgraded due to serious imprecision.[11]

Table 8: Effectiveness and Safety of Proton Beam Therapy for Adults With Liver Cancer

Outcomes	Tumour Type, (No. of Studies)	Sample Size, N	Follow-Up Duration	Effect Estimates (95% CI), PBT vs. TACE or IMRT	GRADE[a]
Effectiveness					
Randomized Controlled Trial					
Overall survival probability	Hepatocellular carcinoma (n = 1)	69	2 y	*Passive scatter PBT vs. TACE* All patients (PBT or TACE): 59%; no significant difference between treatment groups (data not reported, *P* = NS) Patients who received liver transplant post radiation treatment (n = 22): 82%; no significant difference between treatment groups (data not reported, *P* = NS)	⊕⊕⊕ Moderate Serious imprecision (−1)[b]
Progression-free survival probability	Hepatocellular carcinoma (n = 1)	69	2 y	*Passive scatter PBT vs. TACE* 48% vs. 32%, *P* = .06	
Local control probability	Hepatocellular carcinoma (n = 1)	69	2 y	*Passive scatter PBT vs. TACE* 88% vs. 45%, *P* = .06	
Observational Study					
Overall survival probability	Hepatocellular carcinoma (n = 1)	133	2 y	*Passive scatter PBT vs. IMRT* 59.1% vs. 28.6%, adj. HR 0.47 (0.27– 0.82)	⊕⊕ Low

Outcomes	Tumour Type, (No. of Studies)	Sample Size, N	Follow-Up Duration	Effect Estimates (95% CI), PBT vs. TACE or IMRT	GRADE[a]
Local control probability	Hepatocellular carcinoma (n = 1)	133	2 y	*Passive scatter PBT vs. IMRT* Cumulative incidence: 93% vs. 90%, HR 0.74 (0.18–3.01)	
Locoregional recurrence	Hepatocellular carcinoma (n = 1)	133	2 y	*Passive scatter PBT vs. IMRT* Cumulative incidence: 53% vs. 42%, HR 0.98 (0.54–1.75)	
Adverse Events					
Randomized Controlled Trial					
Acute toxicity	Hepatocellular carcinoma (n = 1)	69	≤ 3 mo	PBT: fatigue and radiation skin reaction TACE: abdominal pain and nausea (data not provided)	⊕⊕⊕ Moderate Serious imprecision (−1)[b]
Hospitalization from acute complications	Hepatocellular carcinoma (n = 1)	69	≤ 1 mo	*Passive scatter PBT vs. TACE* 6.1% (2/33) vs. 41.7% (15/36), *P* < .001	
Total days hospitalized	Hepatocellular carcinoma (n = 1)	69	≤ 1 mo	*Passive scatter PBT vs. TACE* 0.73 days/patient vs. 4.6 days/patient, *P* < .001	
Observational Study					
Incidence of nonclassic radiation-induced liver disease	Hepatocellular carcinoma (n = 1)	100	3 mo	*Passive scatter PBT vs. IMRT* Adj. OR 0.26 (0.08–0.86) (favours PBT)	⊕⊕ Low
Death due to liver failure	Hepatocellular carcinoma (n = 1)	36	Median 14 mo	*Passive scatter PBT vs. IMRT* 53% vs. 91%, RR 0.59 (0.36–0.97)	⊕ Very low Serious imprecision (−1)[b]

Abbreviations: Adj, adjusted; CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; HR, hazard ratio; IMRT, intensity-modulated radiation therapy; mo, month; no., number; NS, not statistically significant; OR, odds ratio; PBT, proton beam therapy; TACE, transarterial chemoembolization; y, year.

[a]Randomized controlled trials started with a high GRADE. Observational studies started with a low GRADE level because of inherent limitations in study design (e.g., lack of randomization, lack of blinding, loss to follow-up).

[b]Imprecision of effect estimate for an outcome was based on small sample size, and/or confidence interval that included both negligible effect and appreciable benefits or harms with the intervention. If sample size was likely too small to detect rare outcomes, evidence may be downgraded twice. If the estimate was statistically significant, it was imprecise if the confidence interval crossed the threshed for "mild/small" effects. Wide or unknown confidence interval and/or small sample size may result in downgrade.

Adapted from Washington State Health Care Authority, 2019.[11]

Lung Cancer

The 2019 Washington State review[11] identified one RCT and five retrospective comparative cohort studies (including the nonrandomized cohort of the RCT) that evaluated proton beam therapy for curative intent in adults with lung cancer (Table 9), as well as 11 case series (data not extracted).

In an RCT of adults with non-small cell lung cancer, the overall survival at any time point up to 5 years and the cumulative incidence of local failure (recurrence of the cancer) were not different between the proton beam therapy and intensity-modulated radiation therapy groups. However, there were biases of enrolment in this RCT. Of the 272 enrolled patients, only 149 were randomized. Among the randomized patients, target volumes were larger in the proton beam therapy group, with more patients receiving higher doses of radiation to their tumours, creating imbalance in intervention between the study arms.[34] Findings on effectiveness from the retrospective comparative cohort studies were consistent with those of the RCT.

In the RCT, the frequency of radiation pneumonitis (grade 3 or higher) in 1 to 5 years of follow-up was similar in patients receiving proton beam therapy versus intensity-modulated radiation therapy. In two retrospective cohort studies also comparing proton beam therapy and intensity-modulated radiation therapy, there were no significant differences in grade 3 or higher toxicities, including radiation pneumonitis, radiation esophagitis, and radiation dermatitis.

In general, trends were for similar effectiveness across treatment types for adults with lung cancer and for reduced toxicity with proton-based versus photon-based radiation therapy. Based on the comparative studies reviewed, the quality of evidence for effectiveness and safety of proton beam therapy in adults with lung cancer was moderate to very low, downgraded due to risk of bias or serious imprecision.[11]

Table 9: Effectiveness and Safety of Proton Beam Therapy for Adults With Lung Cancer

Outcomes	Tumour Type (No. of Studies)	Sample Size, N	Follow-Up Duration	Effect Estimates (95% CI), PBT vs. Photon RT (Various)	GRADE[a]
Effectiveness for Curative Intent					
Randomized Controlled Trial					
Overall survival probability	NSCLC (n = 1)	173	1–5 y	*Passive scatter PBT vs. IMRT* 1 y: 75% vs 82% 2 y: 56% vs. 60% 3 y: 26% vs. 37% 4 y: 38% vs. 32% 5 y: 24% vs. 32%, *P* = .3	⊕⊕⊕ Moderate Risk of bias (−1)[b]
Cumulative incidence of local failure				*Passive scatter PBT vs. IMRT* 1 y: 9% vs 10% 2 y: 27% vs. 26% 3 y: 37% vs. 37% 4 y: 37% vs. 32% 5 y: 37% vs. 39%, *P* = .99	

Outcomes	Tumour Type (No. of Studies)	Sample Size, N	Follow-Up Duration	Effect Estimates (95% CI), PBT vs. Photon RT (Various)	GRADE[a]
Observational Study					
Overall survival probability	NSCLC (n = 3)	39	1 y	*Passive scatter PBT vs. IMRT* 69% vs. 57%, *P* = .97	⨁⨁ Low
		61		*Double scatter or pencil beam PBT vs. IMRT* 85.2% (72.8%–99.7%) vs. 82.4% (70.5%– 96.2%), *P* = .65	
		1,850		*PBT vs. various photon radiation (external beam, 3D-conformal, IMRT)* 62.0% (56.2%–67.2%) vs. 54.2% (51.6%– 56.7%), *P* = NR	
	NSCLC (n = 3)	39	2 y	*Passive scatter PBT vs. IMRT* 43% vs. 43%, *P* = .97	
		61		*Double scatter or pencil beam PBT vs. IMRT* 77.8% (63.6%–95.2%) vs. 73.2% (59.6%– 89.9%), *P* = .65	
		468		*Pencil beam PBT vs. IMRT or 3D-CRT* 56% (40%–69%) PBT vs. 52% (45%–58%) IMRT, *P* = NS 56% (40%–69%) PBT vs. 39% (32%–46%) 3D-CRT, *P* = .015	
	NSCLC (n = 1)	39	3 y	*Passive scatter PBT vs. IMRT* 25% vs. 32.5%, *P* = .97	
	NSCLC (n = 1)	1,850	5 y	*PBT vs. various photon radiation (external beam, 3D-conformal, IMRT)* 5:1 matching 22.3% (16.3%–28.9%) vs. 15.7% (13.5%–18.1%) Adj. HR 1.18 (1.02–1.37)[d] A priori 1:1 matching Adj. HR 1.16 (0.97–1.39)	
Local recurrence-free survival probability	NSCLC (n = 1)	61	1–2 y	*Double scatter or pencil beam PBT vs. IMRT* 1 y: 92.3% (82.5%–100%) vs. 93.3% (84.8%–100%) 2 y: 93.1%–85.7%, *P* = .82	⨁ Very low Risk of bias (−1)[b]

Outcomes	Tumour Type (No. of Studies)	Sample Size, N	Follow-Up Duration	Effect Estimates (95% CI), PBT vs. Photon RT (Various)	GRADE[a]
Local failure	NSCLC (n = 1)	39	1–2 y	*Passive scatter PBT vs. IMRT* Cumulative incidence 1 y: 6% vs. 3% 2 y: 6% vs. 3% 3 y: 26% vs. 26%, *P* = .93	⊕ Very low Risk of bias (−1)[b]
	NSCLC (n = 1)	61	2 y	*Double scatter or pencil beam PBT vs. IMRT* 11.1% vs. 5.9%, *P* = NS[e]	
Adverse Events					
Randomized Controlled Trial					
Radiation pneumonitis, grade ≥3	NSCLC (n = 1)	173	1–5 y	*Passive scatter PBT vs. IMRT* At 1, 2, 3, 4, 5 years: 8% vs 7%, *P* = .58	⊕⊕⊕ Moderate Serious imprecision (−1)[c]
Observational Study					
Radiation esophagitis	NSCLC (n = 2)	61	NR	*Double scatter or pencil beam PBT vs. IMRT* Grade 2: 18.5% vs. 29.4%, *P* = NR Grade 3: 3.7% vs. 11.8%, *P* = NR	⊕ Very low Risk of bias (−1)[b]
		134	NR	*Passive scatter PBT vs. IMRT* Grade 2: 59.2% vs. 54.1%, *P* = NS Grade 3: 22.4% vs. 17.6% OR 1.4 (0.7–2.9), *P* = .37	
Radiation pneumonitis	NSCLC (n = 1)	61	NR	*Double scatter or pencil beam PBT vs. IMRT* Grade 2: 3.7% vs. 8.8%, *P* = NR Grade 3: 3.7% vs. 2.9%, *P* = NR	
Radiation dermatitis	NSCLC (n = 1)	61	NR	*Double scatter or pencil beam PBT vs. IMRT* Grade 2: 37% vs. 12%, *P* = NR Grade 3: 0% vs. 0%, *P* = NR	

Abbreviations: 3D-CRT, 3-dimension conformal radiation therapy; adj, adjusted; CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; IMRT, intensity-modulated radiation therapy; HR, hazard ratio; no., number; NR, not reported; NS, not significant; NSCLC, non-small cell lung cancer; OR, odds ratio; PBT, proton beam therapy; y, year.

[a]Randomized controlled trials started with a high GRADE. Observational studies started with a low GRADE level because of inherent limitations in study design (e.g., lack of randomization, lack of blinding, loss to follow-up).

[b]Risk of bias was downgraded in the majority of studies, which did not control for confounding and/or did not account for time at risk for survival outcomes. Studies that controlled for confounding via study design and/or statistical analyses (e.g., adequate randomization and concealing, matching, multivariate regression, propensity matching) were not downgraded.

Notes continued next page.

Table 9 notes continued.
[c]Imprecision of effect estimate for an outcome was based on small sample size, and/or confidence interval that included both negligible effect and appreciable benefits or harms with the intervention. If sample size was likely too small to detect rare outcomes, evidence may be downgraded twice. If the estimate was statistically significant, it was imprecise if the confidence interval crossed the threshed for "mild/small" effects. Wide or unknown confidence interval and/or small sample size may result in downgrade.
[d]Non-proton therapy was associated with a higher hazard for overall survival.
[e]More local failure in PBT than IMRT, but the difference was not statistically significant.
Adapted from Washington State Health Care Authority, 2019.[11]

Lymphoma

The 2019 Washington State review[11] identified three case series (data not extracted) but no comparative studies on the effectiveness or safety of proton beam therapy in adults with lymphoma.

Ocular Tumours

The 2019 Washington State review[11] identified 22 case series of proton beam therapy in adults with various types of ocular tumour (data not extracted) and three retrospective comparative cohort studies that compared proton beam therapy with other radiation therapies in adults with primary uveal melanoma or choroidal melanoma, two types of tumours of the eye (Table 10).

Across two retrospective cohort studies comparing proton beam therapy with brachytherapy or stereotactic radiosurgery for adults with ocular tumours, there were no significant differences in overall survival at 2 years and mortality at 3 years. In a larger database study of patients with choroid melanoma, proton beam therapy was associated with a higher risk of mortality when compared with brachytherapy at 5 years. At 10 years, proton beam therapy was associated with a lower frequency of local tumour recurrence than brachytherapy (both treatment arms also received transscleral resection, a surgery to remove the tumour). However, local recurrence was similar between proton beam therapy and stereotactic radiosurgery.

With the exception of optic neuropathy, which was lower following proton beam therapy (vs. stereotactic radiosurgery) in one retrospective study of uveal melanoma, the frequency of adverse events (i.e., radiation retinopathy, enucleation, rubeosis of the iris, neovascular glaucoma, rubeotic glaucoma) over 3 years was similar between proton beam therapy and brachytherapy or stereotactic radiosurgery.

Based on the comparative studies reviewed, the quality of evidence of proton beam therapy in adults with ocular tumours was low to very low for effectiveness, downgraded for risk of bias, and low for safety.[11]

Table 10: Effectiveness and Safety of Proton Beam Therapy for Adults With Ocular Tumours

Outcomes	Tumour Type (No. of Studies)	Sample Size, N	Follow-Up Duration	Effect Estimates (95% CI), PBT vs. Brachytherapy or Stereotactic Radiosurgery	GRADE[a]
Effectiveness					
Overall survival	Choroid melanoma (n = 1)	452	2, 5 y	*PBT vs. brachytherapy* 2 y: 93% vs. 97%, *P* = NS 5 y: 51% vs. 77%, *P* = NR Adj. HR for risk of mortality 1.89 (1.24– 2.95)	⨁⨁ Low
Mortality	Uveal melanoma (n = 1)	191	3 y	*PBT vs. stereotactic radiosurgery* 13% vs. 16%, *P* = NS	⨁⨁ Low
Local recurrence	Large uveal melanoma (n = 1)	140	3, 5, 10 y	*Neoadjuvant PBT + transscleral resection vs. adjuvant brachytherapy + transscleral resection* 3 y: 4% (1.2%–17.8%) vs. 24.6% (15.8% vs. 37.1%), *P* < .001 5 y: 9.1% (2.9%–27.3%) vs. 27.5% (17.8%–41.1%), *P* < .001 10 y: 9.1% (2.8%–27.3%) vs. 36.5% (20.7%–59.1%), adj. HR 7.69 (2.22–26.06)	⨁⨁ Low
	Uveal melanoma (n = 1)	191	Mean 3 y	*PBT vs. stereotactic radiosurgery* 2.8% vs. 0%, *P* = NS	⨁ Very low Risk of bias (−1)[b]
Adverse Events					
Late toxicities	Large uveal melanoma (n = 1)	140	Mean 3.3 y	*Neoadjuvant PBT + transscleral resection vs. adjuvant brachytherapy + transscleral resection* Enucleation: 8.5% vs. 15.7%, *P* = .196 Rubeosis of the iris: 1.4% vs. 0% (0/70), *P* = .316 Neovascular glaucoma: 1.4% vs. 1.4%, *P* = NS	⨁⨁ Low
	Uveal melanoma (n = 1)	191	Mean 3 y	*PBT vs. stereotactic radiosurgery* Enucleation: 1.9% vs. 2.4%, *P* = NS Rubeotic glaucoma: 4.7% vs. 11%, *P* = NS	

Outcomes	Tumour Type (No. of Studies)	Sample Size, N	Follow-Up Duration	Effect Estimates (95% CI), PBT vs. Brachytherapy or Stereotactic Radiosurgery	GRADE[a]
				Radiation retinopathy: 30% vs. 24%, *P* = NS Optic neuropathy: 13% vs. 28%, RR 0.49 (0.27–0.89)	

Abbreviations: Adj, adjusted; CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; HR, hazard ratio; no., number; NS, not significant; PBT, proton beam therapy; RR, relative risk; y, year.

[a]Observational studies started with a low GRADE level because of inherent limitations in study design (e.g., lack of randomization, lack of blinding, loss to follow-up).

[b]Risk of bias was downgraded in the majority of studies, which did not control for confounding and/or did not account for time at risk for survival outcomes. Studies that controlled for confounding via study design and/or statistical analyses (e.g., adequate randomization and concealing, matching, multivariate regression, propensity matching) were not downgraded.

Adapted from Washington State Health Care Authority, 2019.[11]

Prostate Cancer

The 2019 Washington State review[11] identified 11 case series (data not extracted), one quasi-RCT, and three retrospective comparative cohort studies (Table 11) that compared proton beam therapy with photon therapies for curative intent in adult men with prostate cancer.

In a quasi-RCT (i.e., patients were allocated but not truly randomized to treatment groups), 5-year and 10-year overall survival and biochemical relapse–free survival, as well as grade 3 or 4 toxicities, were similar between patients receiving photon therapy plus proton beam therapy versus photon therapy alone. However, acute and late grade 2 gastrointestinal toxicities, but not genitourinary, were less frequent in patients who received proton beam therapy boost than those who received photon therapy alone.

In two clinical studies, acute or late gastrointestinal and genitourinary toxicities were similar between proton beam therapy and intensity-modulated radiation therapy. However, in a large database study, proton beam therapy was associated with lower cumulative incidences of gastrointestinal and genitourinary toxicities (any grade) and erectile dysfunction, when compared with intensity-modulated radiation therapy.

The available evidence showed similar survival and generally reduced high-grade acute and late toxicity with proton beam therapy versus photon therapy. Based on the comparative studies reviewed, the quality of evidence of proton beam therapy in adults with prostate cancer was low for effectiveness and safety.[11]

Table 11: Effectiveness and Safety of Proton Beam Therapy for Adults With Prostate Cancer

Outcomes	Tumour Type (No. of Studies)	Sample Size, N	Follow-Up Duration	Effect Estimates (95% CI), PBT vs. Photon RT (Various)	GRADE[a]
Effectiveness					
Quasi-Randomized Controlled Trial					
Overall survival probability	Prostate cancer (n = 1)	289	5 y	*Photon RT + PBT boost vs. photon RT alone* 74% vs. 78.8%, *P* = NS	⨁⨁ Low
			10 y	*Photon RT + PBT boost vs. photon RT alone* 55.9% vs. 60.6%, *P* = NS	
Biochemical relapse-free survival probability			5 y	*Photon RT + PBT boost vs. photon RT alone* 60% vs. 61.9%, *P* = NS	
			10 y	*Photon RT + PBT boost vs. photon RT alone* 45.5% vs. 42.8%, *P* = NS	
Adverse Events					
Quasi-Randomized Controlled Trial					
GI toxicity	Prostate cancer (n = 1)	289	Acute	*Photon RT + PBT boost vs. photon RT alone* Grade 2: 54.4% vs. 69.2% ± , *P* < .01 Grade 3 or 4: 0% vs. 0%	⨁⨁ Low
			Late	*Photon RT + PBT boost vs. photon RT alone* Grade 2: 10.2% vs. 34.8% , *P* < .01 Grade 3 or 4: 0.9% ± 1.7%, vs. 1.3% ± 1.8%, *P* = NS	
GU toxicity			Acute	*Photon RT + PBT boost vs. photon RT alone* Grade 2: 33.3% vs. 36.1%, *P* = NS Grade 3 or 4: 0% vs. 1.9% %, *P* = NS	
			Late	*Photon RT + PBT boost vs. photon RT alone* Grade 2: 8.3% vs. 9.1% , *P* = NS Grade 3 or 4: 2.8 % vs. 3.8%, *P* = NS	
Actuarial frequency of GI and GU toxicities			10 y	*Photon Rt + PBT boost vs. photon RT alone* 1.7% vs. 8.7%, *P* = NR	

Outcomes	Tumour Type (No. of Studies)	Sample Size, N	Follow-Up Duration	Effect Estimates (95% CI), PBT vs. Photon RT (Various)	GRADE[a]
Observational Studies					
GI toxicity	Prostate cancer (n = 2)	58	Acute	*Passive scatter PBT vs. IMRT* Grade 1: 48% vs. 38%, RR 1.27 (0.70–2.32) Grade 2: 14% vs. 17%, RR 0.80 (0.24–2.68) Grade 3: 3% vs. 0%, *P* = .60	⨁⨁ Low
		188	Acute	*Passive scatter PBT vs. IMRT* Grade 0 or 1: 95.7% vs. 86.2% Grade 2 or 3: 4.3% vs. 13.8%; adj. OR 0.27 (0.06–1.24), *P* = .09	
	Prostate cancer (n = 3)	58	Late	*Passive scatter PBT vs. IMRT* Grade 1: 9% vs. 27%; RR 0.33 (0.08–1.47) Grade 2: 9% vs. 9% Grade 3: 5% vs. 0%, *P* = .32	
		188	Late	*Passive scatter PBT vs. IMRT* Grade 0 or 1: 87.2% vs. 88.3% Grade 2 or 3: 12.8% vs. 10.8%; adj. OR 1.24 (0.53–2.94), *P* = .62	
		4,158	Late	*PBT vs. IMRT* Cumulative incidence 6-month: 1.6% (n = 693) vs. 3.2% (n = 3,465) 12-month: 7.4% (n = 572) vs. 7.7% (n = 2,862) 24-month: 19.5% (n = 341) vs. 15.4% (n = 1,718) 36-month: 24.9% (n = 205) vs. 19.2% (n = 1,003) HR 1.27 (1.05–1.55), *P* = .02	
GU toxicity	Prostate cancer (n = 2)	58	Acute	*Passive scatter PBT vs. IMRT* Grade 1: 66% vs. 45%, RR 1.46 (0.90–2.37) Grade 2: 24% vs. 41%, RR 0.58 (0.27–1.27) Grade 3: 3% vs. 3%	⨁⨁ Low
		188	Acute	*Passive scatter PBT vs. IMRT* Grade 0 or 1: 78.7% vs. 71.3% Grade 2 or 3: 21.3% vs. 28.7% Adj. OR 0.69 (0.32–1.51), *P* = .36	

Outcomes	Tumour Type (No. of Studies)	Sample Size, N	Follow-Up Duration	Effect Estimates (95% CI), PBT vs. Photon RT (Various)	GRADE[a]
	Prostate cancer (n = 3)	58	Late	*Passive scatter PBT vs. IMRT* Grade 1: 23% vs. 32%; RR 0.71 (0.27–1.91) Grade 2: 23% vs. 27%, RR 0.83 (0.30–2.33) Grade 3: 0% vs. 5%, *P* = .32	
		188	Late	*Passive scatter PBT vs. IMRT* Grade 0 or 1: 87.2% vs. 80.9% Grade 2 or 3: 12.8% vs. 18.3% Adj. HR 0.56 (0.22–1.41), *P* = .22	
		4,158	Late	*PBT vs. IMRT* Cumulative incidence 6-month: 12.1% (n = 693) vs. 21.5% (n = 3,465) 12-month: 23.1% (n = 572) vs. 31.6% (n = 2,862) 24-month: 33.3% (n = 341) vs. 42.2% (n = 1,718) 36-month: 39.1% (n = 205) vs. 48.3% (n = 1,003) HR 0.72 (0.63–0.83), *P* < .001	
Erectile dysfunction	Prostate cancer (n = 1)	4,158	Late	*PBT vs. IMRT* Cumulative incidence 6-month: 5.0% (n = 693) vs. 9.7% (n = 3,465) 12-month: 10.6% (n = 572) vs. 18.1% (n = 2,862) 24-month: 20.7% (n = 341) vs. 27.8% (n = 1,718) 36-month: 28.6% (n = 205) vs. 34.3% (n = 1,003) HR 0.71 (0.59–0.84), *P* = .001	⨁⨁ Low

Abbreviations: adj, adjusted; CI, confidence interval; GI, gastrointestinal; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; GU, genitourinary; HR, hazard ratio; IMRT, intensity-modulated radiation therapy; no., number; NR, not reported; NS, not statistically significant; OR, odds ratio; PBT, proton beam therapy; RR, relative risk; RT, radiotherapy; y, year.

[a]Observational studies started with a low GRADE level because of inherent limitations in study design (e.g., lack of randomization, lack of blinding, loss to follow-up).

Adapted from Washington State Health Care Authority, 2019.[11]

Benign and Mixed Tumours

The 2019 Washington State review[11] identified two case series in hemangiomas, three case series in noncancerous tumours (i.e., meningioma, pituitary adenoma), and three case series in mixed tumour types (i.e., brain, spinal, and bone cancers, as well as tumours of the head and neck, lung, liver, ovaries, and more, with no particular conditions making up a majority) (data not extracted). There were no comparative studies on the effectiveness or safety of proton beam therapy in these adult populations.

Ongoing Studies

We are aware of two systematic reviews (Appendix 5, Table A5), 16 randomized clinical trials (Appendix 5, Table A6), and 10 nonrandomized comparative studies (Appendix 5, Table A7) that are underway and have potential relevance to the research question of this review. In addition, 12 nonrandomized noncomparative clinical studies in pediatric populations are potentially relevant, a majority of them on treatment for brain tumours (Appendix 5, Table A8).

The US National Cancer Institute and the US Patient-Centered Outcomes Research Institute have funded seven randomized clinical trials evaluating the benefits and harms of proton beam therapy for cancers of the breast, lung, prostate, liver, and esophagus, as well as glioblastoma and low-grade glioma. However, enrolment of these trials has been slower than expected.[35]

Discussion

In this clinical evidence review on proton beam therapy for children and adults with cancer, we based our evidence synthesis on data reported in the health technology assessment published by the Washington State Health Care Authority in April 2019.[11] That review included 215 publications: only two were randomized controlled trials, and the rest of the evidence came from retrospective cohort studies and case series. We excluded case series from our synthesis due to their high risk of bias.

While the magnitude of comparative effectiveness and the type of adverse events differed by type of tumour or cancer, proton beam therapy appeared to show similar overall survival and progression-free survival but cause fewer toxicity events than other forms of radiation therapy, especially in children with brain tumours and adults with certain malignancies. This is biologically plausible and of clinical importance as the potential value of proton beam therapy over photon therapy is to reduce long-term toxicity by reducing radiation of normal tissues surrounding the tumour.

The technology of proton beam therapy is evolving rapidly. The latest technology does not rely only on the Bragg Peak property of proton energy to reduce the radiation dose to normal tissue; it also uses modulation of the beam's intensity and multiple entrance points to distribute even more conformal doses of radiation. The literature we reviewed, including the few randomized controlled trials, does not necessarily reflect these advances. Emerging evidence has shown that, in adults with locally advanced cancer, proton chemoradiotherapy (radiation therapy combined with chemotherapy) was associated with a three-fold reduction of acute toxicity events resulting in unplanned hospitalization, compared with photon chemoradiotherapy.[36] The study authors said this was primarily attributable to the reduced dose of scattered radiation received by the surrounding normal tissues with the use of protons versus photons.[36]

There has been a surge of scientific publications on proton beam therapy in recent years. However, most of these new publications were dosimetry (radiation measurement), planning, or simulation studies. An array of case series reporting clinical outcomes has also been published, but the evidence

they provide would unlikely surpass that reported in randomized controlled trials or prospective cohort studies. High-quality evidence, especially from studies directly comparing photon and proton beam technology, remains scarce and potentially difficult to produce. Nevertheless, a considerable amount of relevant research is forthcoming (described above, Ongoing Studies). The timelines of these ongoing studies highlight that research in proton beam therapy, whether it be randomized controlled trials or prospective cohort studies, takes many years to conduct (see Appendix 5). This challenge is compounded by the fact that late toxicity and secondary tumours may take decades to develop. In pediatric populations and in rare tumour conditions, all ongoing studies are nonrandomized, noncomparative in design with acute and late toxicity as primary outcomes, suggesting evidence of an observational nature is probably more pragmatic for these populations.

The cost of proton beam therapy has slowed the dissemination of this technology and may also be creating inequity in access when patients are not able to afford the nonmedical costs associated with this treatment.[37] As a consequence, the number of patients treated with proton beam therapy is still relatively small, compared with photon therapy. This may impede enrolment in clinical trials and hence evidence development. Nevertheless, in coming years, ongoing studies should help to clarify whether the promise of proton beam therapy in limiting radiation of normal tissues will translate into improved clinical outcomes by reducing long-term toxicity and incidence of secondary tumours.

Strengths and Limitations

This clinical evidence review leveraged knowledge from existing systematic reviews to avoid duplication of prior work. Since we relied on work conducted by other review authors, there could be different interpretation of study results if we were to examine the included studies independently. We updated the chosen systematic review, limiting our search to randomized controlled trials (and found none); therefore, we did not capture new observational studies, which may have included patient-important outcomes. For example, a recently published longitudinal study showed favourable outcomes with potential downstream, positive impacts for children's growth and development: children with medulloblastoma who received proton beam therapy had superior intelligence outcomes than those who received photon therapy.[38] In addition, we did not review dosimetric studies on the effects of reduced radiation dose to normal tissues. Instead, we focused on clinical outcomes of long-term toxicity and survival.

Conclusions

Effectiveness and Safety in Pediatric Cancer

- Compared with photon therapy, proton beam therapy may result in similar overall survival and progression-free survival in children with brain tumours (GRADE: Low)
- Compared with photon therapy, proton beam therapy may result in fewer events of hypothyroidism, but no significant difference in other toxicity events, in children with brain tumours (GRADE: Low to Very low)
- There was insufficient evidence to determine the relative effectiveness and safety of proton beam therapy, compared with photon therapy, in other pediatric tumours

Effectiveness and Safety in Adult Cancer

- Compared with photon therapy, proton beam therapy may result in similar overall survival and progression-free survival, but may result in fewer toxicity events, in adults with

esophageal cancer (GRADE: Low to Very low), head and neck cancer (GRADE: Low to Very low), and prostate cancer (GRADE: Low

- Compared with photon therapy, proton beam therapy may result in similar overall survival and progression-free survival, but results in fewer toxicity events in adults with liver cancer (GRADE: Moderate)
- Compared with photon therapy, 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 relative effectiveness and safety of proton beam therapy, compared with photon therapy, in adults with bladder cancer, bone cancer, lymphoma, and benign tumours

Economic Evidence

Research Question

What is the cost-effectiveness of proton beam therapy compared with photon radiation therapy for the treatment of children and adults with cancer?

Methods

Economic Literature Search

We performed an economic literature search on July 25, 2019, to retrieve studies published from database inception until the search date. To retrieve relevant studies, we developed a search using the clinical search strategy with an economic and costing filter applied. In addition to the databases used for the clinical search, we also used the Ovid interface in the Cochrane Central Register of Controlled Trials.

We created database auto-alerts in MEDLINE, Embase, and monitored them for the duration of the assessment period. We also performed a targeted grey literature search of health technology assessment agency websites, clinical trial and systematic review registries, and the Tufts Cost-Effectiveness Analysis Registry. The grey literature search was updated on December 5, 2019. See the Clinical Literature Search section, above, for further details on methods used. See Appendix 1 for our literature search strategies, including all search terms.

Eligibility Criteria

STUDIES

Inclusion Criteria

- English-language full-text publications
- Studies published from database inception until July 25, 2019
- Cost–benefit analyses, cost-effectiveness analyses, cost-minimization analyses, or cost–utility analyses

Exclusion Criteria

- Narrative reviews, letters/editorials, case reports, commentaries, abstracts, posters, unpublished studies

POPULATION

- Children and adults with cancer

INTERVENTIONS

- Proton beam therapy (alone or in combination with other treatment modalities)

COMPARATORS

- Conventional photon therapy (alone or in combination with other treatment modalities), including image-guided intensity-modulated radiation therapy (IMRT), stereotactic radiation techniques, other external beam therapies, or brachytherapy

OUTCOME MEASURES

- Costs
- Health outcomes (e.g., quality-adjusted life-years)
- Incremental costs
- Incremental effectiveness
- Incremental cost-effectiveness ratios

Literature Screening

A single reviewer conducted an initial screening of titles and abstracts using Covidence[18] and then obtained the full texts of studies that appeared eligible for review according to the inclusion criteria. A single reviewer then examined the full-text articles and selected studies eligible for inclusion.

Data Extraction

We extracted relevant data on study characteristics and outcomes to collect information about the following:

- Source (e.g., citation information, study type)
- Methods (e.g., study design, analytic technique, perspective, time horizon, population, intervention[s], comparator[s])
- Outcomes (e.g., health outcomes, costs, incremental cost-effectiveness ratios)

Study Applicability

We determined the usefulness of each identified study for decision-making by applying a modified quality appraisal checklist for economic evaluations originally developed by the National Institute for Health and Care Excellence (NICE) in the United Kingdom to inform the development of NICE's clinical guidelines.[39] We modified the wording of the questions to remove references to guidelines and to make it specific to Ontario. We assessed the applicability of each study to the research question (directly, partially, or not applicable).

Results

Economic Literature Search

The database search of the economic literature yielded 593 citations published from database inception until July 25, 2019. We identified 18 additional studies from other sources, for a total of 465 after removing duplicates. We identified 14 studies (all cost-effectiveness/cost-utility analyses) that met our inclusion criteria. We added two further citations (one cost-effectiveness study, one cost-utility study) that fit our inclusion criteria, identified through OVID alert, for a total of 16 studies. Figure 3 presents the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram for the economic literature search.

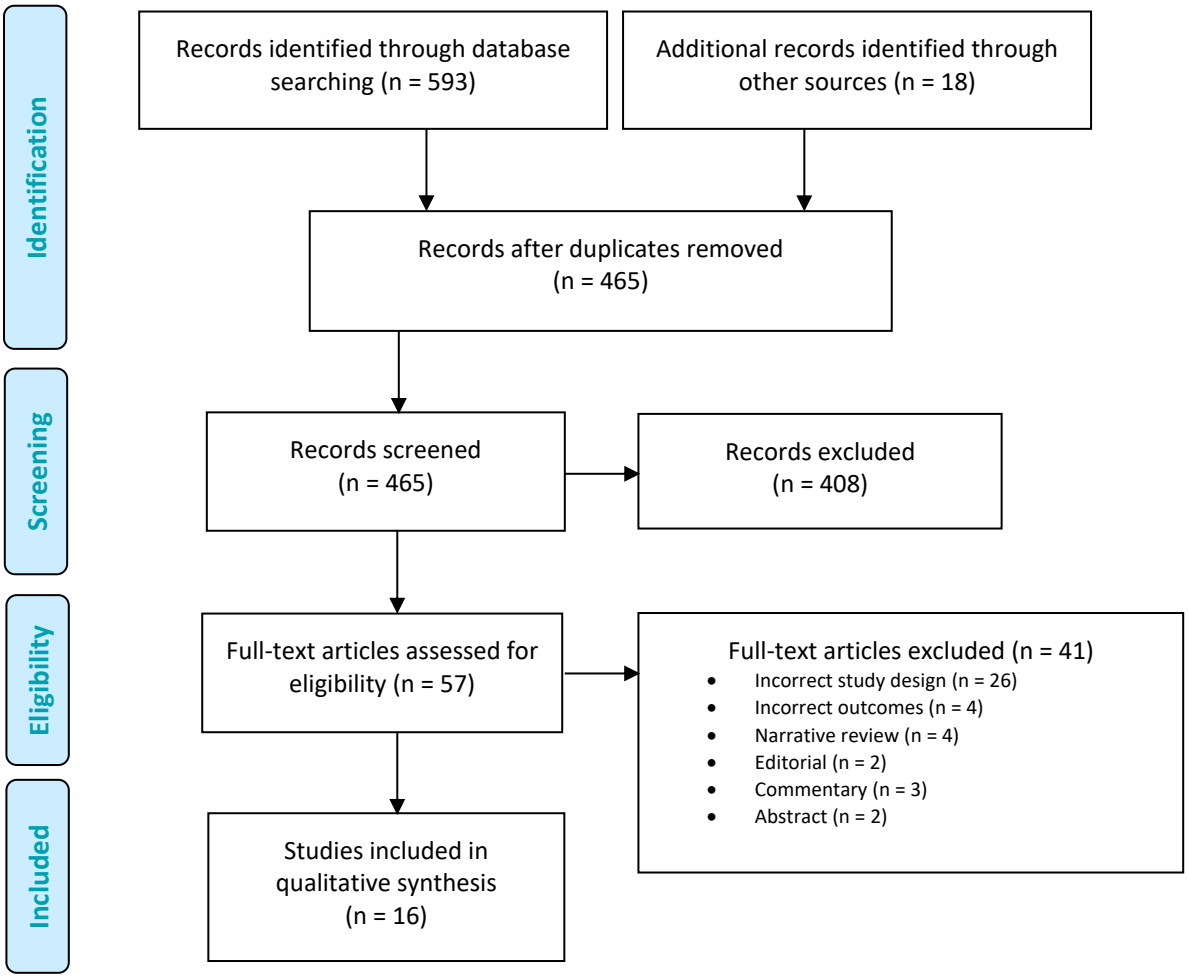

Figure 3: PRISMA Flow Diagram—Economic Search Strategy

Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.
Source: Adapted from Moher et al, 2009.[20]

Overview of Included Economic Studies

We summarize the evidence of the included economic studies below and in Table 12. The included publications assessed the cost-effectiveness of proton beam therapy, compared with conventional radiation therapy, in treating people with various cancers including pediatric medulloblastoma tumours and, in adults, cancers of the head and neck, lung, breast, liver, eye, base of the skull, and prostate. The incremental cost-effectiveness ratios (ICER), which we converted to Canadian dollars (CAD), varied by type of cancer. The majority of evidence supported consistent cost-effectiveness and cost savings in pediatric brain tumors. One study supported cost-effectiveness in adults with liver cancer,[40] and another study found cost-effectiveness in adults with skull base tumours.[41] The economic evidence also suggests that proton beam therapy may not be cost-effective in other clinical indications. In some instances, cost-effectiveness of proton beam therapy was observed in treating breast cancer and in people with increased risk of cardiac disease or with high-risk head and neck cancers; however, these results were mostly dependent on limited data. Overall, in populations other than children, the results were mixed or unclear or the studies did not find that proton beam therapy was cost-effective.

PEDIATRIC TUMORS

Medulloblastoma

Five economic evaluations explored the cost-effectiveness of proton beam therapy compared with conventional radiation therapy in children with medulloblastoma, using a societal and health system perspective in Sweden, the United States, and Brazil.[42-46] The ICERs ranged from proton beam therapy being the dominant strategy (more effective and less costly than the comparator treatment) to costing $28,883 CAD per quality-adjusted life-year (QALY) gained ($21,716 USD/QALY gained). Four studies found that proton beam therapy is likely to be cost-effective, mainly due to reduction in adverse events such as hearing loss, reductions in intelligence quotient scores, hypothyroidism, and growth hormone deficiency.[42-45] One study found that proton beam therapy was only likely to be cost-effective if more than 150 children are treated annually.[46] Table 12 summarizes the probabilistic sensitivity analyses (probability of being cost-effective) for chosen willingness-to-pay thresholds in these five studies.

ADULT CANCERS

Head and Neck Cancer

Two studies evaluated the cost-effectiveness of proton beam therapy,[47,48] compared with IMRT in adults with head and neck cancer, and a third study compared the cost-effectiveness of proton beam therapy with IMRT alongside chemotherapy.[49] In each study, proton beam therapy was more effective but more costly. The ICERs ranged from approximately $5,500 CAD per QALY gained (€3,811 EUR/QALY gained) to $924,300 CAD per QALY gained ($695,000 USD/QALY gained). These studies differed in terms of their study populations (type of head and neck cancer), and proton beam therapy was only found to be likely cost-effective when modelled in a population of patients aged 65 years old with head and neck cancers of all stages with an assumed risk reduction in adverse events.

Lung Cancer

We identified one study[50] evaluating the cost-effectiveness of stereotactic body radiation therapy (SBRT) compared with proton beam therapy, conventional radiation therapy, and carbon ion therapy (another alternative to photon therapy) in patients with inoperable and operable stage I non–small cell lung cancer. Proton beam therapy was dominated by SBRT: for inoperable non–small cell lung cancer, proton beam therapy was found to be both more expensive and less effective than either carbon ion or SBRT.

Breast Cancer

We identified three studies[48,51,52] that evaluated the cost-effectiveness of proton beam therapy in treating breast cancer. The ICERs ranged from approximately $50,000 CAD per QALY gained (€34,290 EUR/QALY) to over $191,152 CAD per QALY gained ($147,093 USD/QALY gained). Two evaluations found proton beam therapy was not cost-effective compared with conventional radiation therapy in breast cancer patients.[51,52] In the studies where proton beam therapy was deemed cost-effective (in the high risk population in the third study[48] and in sensitivity analyses of the other two studies[51,52]), the study populations were either younger or had a risk of cardiovascular disease.

Lundkvist et al[51] assessed the cost-effectiveness of proton beam therapy versus conventional radiation therapy in 55-year-old women with left-sided breast cancer over a lifetime horizon. In this study, proton beam therapy was much more costly and generated an ICER of approximately $97,200 CAD per QALY gained (€66,608/QALY gained). An additional study by Lundkvist et al[48] assessed the cost-effectiveness of proton beam therapy versus photon therapy in women with left-sided breast cancer, but the target population was focused on women at high risk of cardiac disease, which yielded an ICER of approximately $50,000 CAD per QALY gained (€34,290/QALY gained).

Liver Cancer

One study[40] evaluated the cost-effectiveness of proton beam therapy compared with SBRT in patients with inoperable, advanced, large hepatocellular carcinoma, over a 5-year time horizon. Proton beam therapy was found to be more costly than SBRT but led to an additional 2.61 QALYs and an ICER of $9,300 CAD per QALY gained ($213,354 New Taiwan dollar [NT]/QALY gained) and was therefore deemed cost-effective. The probabilistic sensitivity analysis indicated that proton beam therapy was 97% cost-effective at a willingness-to-pay threshold of $2,157,024 (NT), or approximately $100,000 CAD per QALY gained.

Intraocular Melanoma

One study[53] evaluated the cost-effectiveness of proton beam therapy versus enucleation (surgery to remove the eye) and plaque brachytherapy (radiation delivered via an implant) in 59-year-old patients with intraocular melanoma, over a 5-year time horizon. Base-case results showed that both proton beam therapy and brachytherapy were more costly than enucleation. The ICER for proton beam therapy versus enucleation was reported as approximately $141,000 CAD per QALY gained ($106,100 USD/QALY gained). The ICER for plaque brachytherapy was $103,000 CAD per QALY gained ($77,500 USD/QALY gained).

Base of Skull Cancer (Chordoma)

We identified one economic evaluation[41] comparing proton beam therapy and photon therapy in seven people with base of the skull cancers. The mean ICER in this study was approximately $1,700 CAD per QALY gained ($1,990/QALY gained, ranging from −$19,840 to $20,170/QALY gained in Australian dollars [AUD]). The study authors did not conduct a probabilistic sensitivity analysis to test for uncertainty in their cost-effectiveness estimates.

Prostate Cancer

Three evaluations[48,54,55] deemed proton beam therapy to be not cost-effective compared with photon therapy in men with prostate cancer. In all studies, proton beam therapy was more effective but more costly than IMRT, and in one study[55] proton beam therapy was less effective than SBRT but more effective than IMRT. The ICERs ranged from approximately $39,000 CAD per QALY gained (€26,776 EUR/QALY gained) to $1,317,500 CAD per QALY gained ($990,638 USD/QALY gained).

Table 12: Results of Economic Literature Review—Summary

Author, Year, Country of Publication	Analytic Technique, Study Design, Perspective, Time Horizon	Population	Intervention(s) and Comparator(s)	Results			
				Health Outcomes (Incremental QALYs)	Incremental Costs	Cost-Effectiveness	Probabilistic Sensitivity Analysis
Pediatric Cancers: Medulloblastoma							
Fernandes et al, 2019, Brazil[46]	CUA Microsimulation model Lifetime horizon Brazilian health system perspective	Children with medulloblastoma	PBT Photon RT	2.72	*Costs (USD/BZL, 3% discount rate)* $94,164 Capital costs included, attributed to each patient Unclear if training costs are included	*ICER (USD/BRL)* $34,590/QALY gained for 50 patients *WTP: $8,649/QALY*	Up to 96% for 150 patients, at a WTP of $31,746 USD/QALY
Hirano et al, 2014, Japan[45]	CUA Markov cohort-simulation model Lifetime horizon Health care payer perspective	Children (aged 6 y) with medulloblastoma	PBT Conventional XRT	EQ-5D: 0.98 HUI3: 1.82 SF-6D: 1.06	*Costs (USD, 3% discount rate)* $21,396 Capital and training costs not included	*ICER (USD)* HUI3: $11,773/QALY gained EQ-5D: $21,716/QALY gained SF-6D: $20,150/QALY gained *WTP: $46,729/QALY*	Probability of WTP: 99.51% 96.95% for EQ-5D, 100% for HUI3, and 98.72% for SF-6D, at a WTP of $46,729/QALY
Lundkvist et al, 2005, Sweden[42]	CUA Markov cohort-simulation model Lifetime horizon Societal perspective	Children (aged 5 y) with medulloblastoma	PBT IMRT	0.683	*Cost (EUR,3% discount)* −€23,646 Capital costs included (distributed evenly among patients)	*ICER (EUR)* PBT dominant or cost saving *WTP: not reported*	Not reported

Author, Year, Country of Publication	Analytic Technique, Study Design, Perspective, Time Horizon	Population	Intervention(s) and Comparator(s)	Results			
				Health Outcomes (Incremental QALYs)	Incremental Costs	Cost-Effectiveness	Probabilistic Sensitivity Analysis
					Training costs not included		
Mailhot Vega, 2013, USA[43]	CUA Monte Carlo Simulation Lifetime horizon Societal perspective	Patients aged 5 y treated for medulloblastoma	PBT Photon RT	3.46	*Cost (USD, 3% discount rate)* −$32,579 Capital and training costs included	*ICER (USD)* PBT dominant or cost saving *WTP: $50,000/QALY*	96.4% cost saving, at a WTP of $50,000/QALY
Mailhot Vega et al, 2015, USA[44]	CUA Markov cohort-simulation model 60-y time horizon Health care system perspective	Children (aged 4 and 12 y) with medulloblastoma	PBT Photon RT	Not reported	*Cost (USD, 3% discount rate)* Not reported Capital costs included Training costs not included	*ICER (USD)* Dose-dependent For example, $12,650/QALY gained for patients receiving 10 Gray (a radiation dose measure) PBT is dominant or cost-effective unless dosage is high (> 30 Gray)	Not reported
Adult Cancers: Head and Neck							
Lundkvist et al, 2005, Sweden[48]	Markov cohort-simulation model Lifetime horizon Societal perspective	Patients aged 65 y with head and neck cancer	PBT Photon RT	1.02	*Costs (EUR, 3% discount)* €3,887 Capital costs included Unclear if training costs included	*ICER (EUR)* €3,811/QALY gained *WTP: Not reported*	Not reported

Author, Year, Country of Publication	Analytic Technique, Study Design, Perspective, Time Horizon	Population	Intervention(s) and Comparator(s)	Results			
				Health Outcomes (Incremental QALYs)	Incremental Costs	Cost-Effectiveness	Probabilistic Sensitivity Analysis
Ramaemakers et al, 2013, Netherlands[47]	CUA Markov cohort-simulation model Lifetime horizon Health care perspective	Patients (average age 61 y) with locally advanced stage 3 or 4 oral cavity, laryngeal, pharyngeal cancer	IMPT (PBT) treatment (intervention) IMPT and IMRT treatment (intervention) IMRT treatment (comparator)	IMPT vs. IMRT: 0.057 IMPT/IMRT vs. IMRT: 0.043	*Costs (EUR, 4% discount)* IMPT vs. IMRT: €7,339 IMPT/IMRT vs. IMRT: €2,612 Unclear if capital and training costs included	*ICER (EUR)* IMPT vs. IMRT: €127,946/QALY gained IMPT/IMRT vs IMRT: €60,278/QALY gained *WTP: €80,000/QALY*	IMPT vs. IMRT: Approximately 7% IMPT/IMRT vs. IMRT: Approximately 60% at a WTP of €80,000/QALY
Sher et al, 2018, USA[49]	CUA Markov cohort model Lifetime time horizon Payer and societal perspective	Patients aged 65 y with stage III-IVB oropharyngeal squamous cell carcinoma	PBT IMRT	0.07 (HPV-positive) 0.04 (HPV-negative)	*Costs (USD, 3% discount)* Payer perspective: HPV-positive, $20,164 HPV-negative, $20,640 Societal perspective: HPV-positive, $27,311 HPV-negative, $27,787 Societal perspective included capital costs	*ICER (USD)* Payer perspective: HPV positive, $288,000/QALY gained HPV negative, $516,000/QALY gained Societal perspective: HPV positive, $390,000/QALY gained HPV negative, $695,000/QALY gained *WTP: $100,000/QALY*	0% in both perspectives at WTP of 100,000/QALY and 0.4% (payer) and 0% (societal) at a WTP of $150,000/QALY

Author, Year, Country of Publication	Analytic Technique, Study Design, Perspective, Time Horizon	Population	Intervention(s) and Comparator(s)	Results			
				Health Outcomes (Incremental QALYs)	Incremental Costs	Cost-Effectiveness	Probabilistic Sensitivity Analysis
Adult Cancers: Lung							
Grutters et al, 2010, Netherlands[50]	CUA Decision analysis 5-y time horizon Health care perspective	Patients with inoperable and operable stage I NSCLC	Intervention: SBRT Comparators: Photon RT PBT	In inoperable stage 1 NSCLC, SBRT vs. PBT: −0.26	*Costs (EUR, 4% discount)* €13,696 Capital and training costs not included	*ICER (EUR)* In inoperable stage 1 NSCLC, PBT dominated by SBRT *WTP: €80,000/QALY*	46% at a WTP threshold of €80,000/QALY
Adult Cancers: Breast							
Lundkvist et al, 2005, Sweden[48]	CUA Markov cohort-simulation model Lifetime horizon Societal Perspective	Women aged 55 y with left-sided breast cancer, at high risk of cardiac disease	PBT Photon RT	0.1726	*Cost (EUR, 3% discount)* €5,920 Capital costs included Unclear if training costs included	*ICER (EUR)* High risk: €34,290/QALY gained	Not reported
Lundkvist et al, 2005, Sweden[51]	CUA Decision analysis Time horizon: lifetime Societal perspective	Women aged 55 y with left-sided breast cancer	PBT Photon RT	0.0937	*Cost (EUR, 3% discount)* €6,243 Capital costs included (distributed per patient). Unclear if training costs included	*ICER (EUR)* €66,608/QALY	Not reported
Mailhot Vega et al, 2016, USA[52]	CUA Markov model Lifetime time horizon	Women aged 40, 50, or 60 y with breast cancer, with or without	PBT IMRT	Group means not reported 40 y, no CRF: 0.06[a]	*Cost (USD, 3% discount)* Group means not reported	*ICER (USD)* PBT not cost-effective in women without CRF	Not cost-effective in women without CRF, at a WTP of $50,000/QALY

Author, Year, Country of Publication	Analytic Technique, Study Design, Perspective, Time Horizon	Population	Intervention(s) and Comparator(s)	Results			
				Health Outcomes (Incremental QALYs)	Incremental Costs	Cost-Effectiveness	Probabilistic Sensitivity Analysis
	Societal Perspective	cardiac risk factors (CRF)		40 y, > 1 CRF: 0.15 50 y, no CRF: 0.07 50 y, > 1 CRF: 0.15 60 y, no CRF: 0.06 60 y, > 1 CRF: 0.06	40 y, no CRF: $7,790[a] 40-y, > 1 CRF: $7,028 50 y, no CRF: $7,628 50 y, > 1 CRF: $7,003 60 y, no CRF: $7,745 60 y, > 1 CRF: $7,825 Capital and operational costs included	PBT is cost-effective in women with or without CRF, but is dose dependent 40 y, no CRF: $129,005/QALY gained[a] 40 y, > 1 CRF: $47,595/QALY gained 50 y, no CRF: $100,048/QALY gained 50 y, > 1 CRF: $46,650/QALY gained 60 y, no CRF: $128,065/QALY gained 60 y, > 1 CRF: $147,093/QALY gained *WTP $50,000/QALY and $100,000/QALY*	Cost-effective in women of all ages with CRF, at a WTP of $100,000/QALY, if receiving at least 7 Gray doses of radiation
Adult Cancers: Liver							
Leung and Chan, 2017, Taiwan[40]	CUA Markov model 5-y time horizon Payer perspective	Inoperable advanced, large hepatocellular carcinoma PBT: age 70 y SBRT: age 69.4 y	PBT SBRT	2.61	*Costs (NT, 3% discount)* $557,907 Unclear if capital and training costs included	*ICER (NT dollar)* $213,354/QALY gained *WTP: NT$2,157,024*	97% at a WTP of NT$2,157,024

Author, Year, Country of Publication	Analytic Technique, Study Design, Perspective, Time Horizon	Population	Intervention(s) and Comparator(s)	Results			
				Health Outcomes (Incremental QALYs)	Incremental Costs	Cost-Effectiveness	Probabilistic Sensitivity Analysis
Adult Cancers: Ocular							
Moriarty et al., 2015, USA[53]	CUA Markov model 5-y time horizon Provider perspective	Patients aged 59 y with intraocular melanoma	PBT Brachytherapy Enucleation	0.02 (PBT vs. enucleation)	*Costs (USD, 3% discount)* $2,122 Capital costs not included	*ICER (USD)* $106,100/QALY gained (PBT vs. enucleation) $77,500/QALY gained (plaque brachytherapy vs. enucleation) ICER for PBT vs. brachytherapy not reported *WTP: $50,000/QALY*	Not reported
Adult Cancers: Skull							
Austin, 2019, Australia[41]	CEA Markov model	7 female patients aged 4 to 51 y with skull base cancer	PBT Photon RT	Group means not reported	*Costs (AUD, 3% discount)* Group means not reported Unclear if capital costs included	*ICER (AUD)* $1,990/QALY gained (mean) *WTP: AUD$36,000–54,000*	Not reported
Adult Cancers: Prostate							
Konski et al, 2007, USA[54]	CUA Decision analysis 15-y time horizon Payer Perspective	Men aged 70 y with intermediate prostate cancer	PBT IMRT	0.42	*Costs (USD, 3% discount)* $26,703 Capital costs not included/reported	*ICER (USD)* $63,578/QALY gained *WTP: $50,000/QALY*	49% for trials ending in 15 y at a WTP of $50,000/QALY for patients aged 70 y; 54% for patients aged 60 y

Author, Year, Country of Publication	Analytic Technique, Study Design, Perspective, Time Horizon	Population	Intervention(s) and Comparator(s)	Results			
				Health Outcomes (Incremental QALYs)	Incremental Costs	Cost-Effectiveness	Probabilistic Sensitivity Analysis
Lundkvist et al, 2005, Sweden[48]	Markov cohort-simulation model Lifetime horizon Societal perspective	Men aged 65 y with prostate cancer	PBT Photon RT	0.297	*Cost (EUR, 3% discount)* €7,952 Capital costs included	*ICER (EUR)* €26,776/QALY gained *WTP: Not reported*	Not reported
Parthan et al, 2012, USA[55]	CEA Decision analysis Lifetime time horizon Payer and societal perspective	Men aged 65 y with localized prostate cancer who declined or were ineligible for surgery but eligible for external radiation therapy	PBT SBRT	Payer perspective: −0.047 Societal perspective: −0.047	*Costs (USD, 3% discount)* Payer perspective $44,539 Societal perspective $46,560 Unclear if capital costs included	*ICER (USD)* PBT dominated by SBRT in both payer and societal perspectives *WTP: $50,000/QALY*	Approximately 4% at a WTP of $50,000/QALY for both perspectives

Abbreviations: AUD, Australian dollar; BRL, Brazilian real; CEA, cost-effectiveness analysis; CRF, cardiac risk factors; CUA, cost-utility analysis; EQ-5D, Euro Quality of Life 5-Dimension scale; EUR, Euro; HPV, human papillomavirus; HUI3, Health Utilities Index; ICER, incremental cost-effectiveness ratio; IMPT, intensity-modulated proton therapy; IMRT, intensity-modulated radiation therapy; NSCLC, non–small cell lung cancer; NT, New Taiwan dollar; PBT, proton beam therapy; RT, radiotherapy; SBRT, stereotactic body radiation therapy; SF-6D, Short Form 6-Dimension (quality of life scale); QALY, quality-adjusted life-year; USD, US dollar; WTP, willingness-to-pay value; XRT, x-radiation therapy; y, year.

Note: some studies do not state QALYs or costs used to calculate the ICER.

[a]Realistic examples of QALYs, cost, and ICER estimates retrieved from appendix.

Applicability and Limitations of the Included Studies

Appendix 6, Table A9, provides the results of the quality appraisal checklist for the applicability of economic evaluations applied to the included studies.

All 16 studies were deemed partially applicable to the research question. They presented their results from the US payer perspective, the Brazil and Netherlands health care system perspective, the Taiwan payer perspective, and the societal perspective of Sweden, the United States, Holland, and Japan. No studies were conducted using the Ontario or Canadian health care payer perspective. Therefore, it may be challenging to generalize findings to the Ontario context, due to possible variations in costs of both the intervention and comparator treatments. All studies looked at specific cancers, whereas our assessment looks at cancers as a whole.

Across all studies, we found limitations in both cost data and clinical effectiveness, including long-term outcomes and avoidance of late toxicities. This affects our confidence in the cost-effectiveness results. In terms of cost data, it was unclear whether studies that included capital costs were considering costs representative of a single-room or multi-room proton beam therapy centre. The number of rooms determines how many patients can be treated with proton beam therapy; therefore, the included studies may have either overestimated or underestimated the cost-effectiveness of proton beam therapy. We noted a number of other limitations among the included studies. For example, although Leung and Chan[40] found proton beam therapy to be cost-effective compared with stereotactic body radiation therapy, their study used two very different populations for the intervention and comparator treatments (i.e., patients differed by tumour size). Lundkvist et al[48] obtained clinical data from low quality studies, which can lead to uncertainty. In addition, some authors did not use appropriate utility scores for their study population (e.g., adult utilities for pediatric populations), limiting the applicability of these studies.

Discussion

Our economic evidence review identified 16 studies with different methodologies evaluating the cost-effectiveness of proton beam therapy for various indications of cancer. Findings were consistent that proton beam therapy may be cost-effective in treating pediatric medulloblastoma, even when capital costs—the largest single cost component—were included. However, for adult indications, findings were inconsistent or did not show cost-effectiveness. Overall, the available studies had limited relevance to the Ontario context.

Across the studies, the health economic models varied in their focus on short- or long-term health outcomes. While the studies of pediatric populations had overlap in their clinical adverse events, the health economic models in other studies used varying health outcomes and toxicities. This may be due to health outcomes being highly dependent on the type of cancer. The consistent finding of cost-effectiveness in children with medulloblastoma may be in part due to the consistency in the type of cancer and health outcomes modelled across studies. In contrast, studies of adults with head and neck, lung, breast, and prostate cancer considered different stages of disease, cancer subtypes, risk factors, or associated toxicities and adverse events.

We identified other costing studies that were not included in our review (they analyzed costs but not explicitly related to health outcomes).[56-58] One additional business case from the United Kingdom calculated the potential QALYs gained in using proton beam therapy to treat several types of cancer; applying the costs to develop a proton beam therapy site, they found that at least 610 patients would

need to be treated in two local centres for this to be a cost-effective strategy, compared to sending patients overseas for treatment.[59] The United Kingdom analysis did not compare incremental cost-effectiveness ratios for proton beam therapy and photon radiation therapy or other conventional treatments.

Conclusions

In summary, the cost-effectiveness of proton beam therapy depends on the patient population, but there are populations such as children with medulloblastoma where it may be cost-effective compared with photon therapy. It is unclear, however, whether these conclusions can be generalized to the Canadian context.

Primary Economic Evaluation

Our analysis seeks to understand the economic implications of building a proton beam therapy facility in Ontario. There is potential for proton beam therapy to be used to treat many types of cancer, and we are interested in the use of proton beam therapy to treat appropriate cancers as a whole. However, the clinical benefits and toxicities of cancer treatment vary by tumour type, stage, and patients' age group. Clinical studies comparing proton beam therapy with conventional radiation therapy are generally specific to certain cancer types. This makes it challenging to evaluate the cost-effectiveness of proton beam therapy in a broad cancer population.

Several economic evaluations suggest that proton beam therapy may be cost-effective compared with photon therapy for specific types of cancer (i.e., pediatric brain tumours). However, in other types of cancer, the cost-effectiveness of proton beam therapy is unclear. While it would be possible to evaluate a specific population from an Ontario Ministry of Health perspective, this would not fully answer our research question and the cost-effectiveness would likely be highly dependent on the population chosen. Based on the published evidence, proton beam therapy would likely be cost-effective in children with medulloblastoma but unlikely or uncertain in other populations.

Further, there is little evidence to support that proton beam therapy is more effective than photon therapy from a cancer control perspective, as long-term safety data are scarce. In addition, as seen in our clinical evidence review, the quality of the clinical evidence assessing adverse events is low or very low among the majority of studies that are available, although the prevention of long-term toxicities is where the main benefit of proton beam therapy is suspected. In addition, the existing literature may not capture the latest advances in proton beam therapy.

As a result, if we did conduct a cost-effectiveness analysis in a specific population (e.g., pediatric medulloblastoma), our findings may have a large amount of uncertainty. Generalizing the results of a cost-effectiveness analysis in one cancer to all indications would further increase our uncertainty. We therefore decided to forego a primary economic evaluation and focused on analyzing the budget impact of building a proton beam therapy centre in Ontario and publicly funding local delivery of this treatment.

Budget Impact Analysis

Research Question

From the perspective of the Ontario Ministry of Health, what is the potential budget impact of building a proton beam therapy centre in Ontario and publicly funding proton beam therapy for children and adults with cancer?

Methods

Target Population

The target population for this analysis is children (0 to 17 years of age) and adults (18 years and older) with cancer. Specifically, we include people who are currently receiving curative radiation therapy and may potentially benefit from proton beam therapy.

Research on proton beam therapy is emerging and ongoing for a variety of cancer types. Our reference case analysis included cancers as outlined in our clinical review and in a recent feasibility assessment by Cancer Care Ontario (now part of Ontario Health).[10] Based on these sources, we included patients with the following types of cancer: breast, genitourinary (including prostate), lung, gastrointestinal (including liver), skin, head and neck, gynecological, hematology, central nervous system, sarcoma, benign neoplasms, endocrine, and other/unknown cancers (including bone).

To estimate the eligible target population, we first used activity level reporting data from Cancer Care Ontario (Cancer Activity Level Reporting dataset, prepared January 2019) to obtain the number of people receiving curative radiation treatment per year, for each cancer type or group of types (Table 13). We define photon radiation treatment as either conventional radiation therapy, image-guided intensity-modulated radiation therapy, other external beam therapies or brachytherapy, either as monotherapy or combination therapy with other treatment modalities (Derek Tsang, MD, email communication, October 2019).

We then estimated the likely target population based on Cancer Care Ontario's feasibility assessment, in which clinical experts approximated the proportion of cancer patients who could benefit from proton beam therapy for each cancer type.[10] They estimated that, on average, 6% (lower limit 1.4% and upper limit 16.5%) of all cancer patients receiving curative radiation therapy are eligible for proton beam therapy. As the overall trend shows increasing numbers of patients are receiving curative radiation treatment, we applied this proportion to the most recent data available (fiscal year 2017/18) to estimate the total number of people eligible for proton beam therapy (N = 1,627, of which 58 are children; see Table 13). The lower bound of our estimate was 380 patients (1.4%) and the upper bound was 4,474 patients (16.5%).[10] While our target population is much larger than the number of patients currently going out of country, it represents the population of patients who are likely eligible for proton beam therapy but may not receive treatment due to travel costs, illness, potential loss of work, or other barriers (Derek Tsang, MD, phone communication, October 2019).

Table 13: Patient Volumes for Curative Radiation Treatment in Ontario, 2013/14 to 2017/18

	Number of Patients Treated				
Latest Clinical Practice Group	**2013/14**	**2014/15**	**2015/16**	**2016/17**	**2017/18**
Breast	7,810	8,139	8,228	8,351	8,459
Genitourinary	3,870	3,923	4,220	4,584	5,105
Lung	2,225	2,315	2,509	2,653	2,857
Gastrointestinal	2,203	2,362	2,206	2,292	2,362
Skin	2,590	2,461	2,382	2,413	2,236
Head and neck	1,658	1,668	1,683	1,687	1,680
Gynecological	1,310	1,395	1,565	1,601	1,610
Hematology	1,224	1,192	1,202	1,332	1,296
Central nervous system	741	728	730	703	756
Sarcoma	376	365	414	409	368
Benign neoplasms	238	249	304	264	272
Endocrine	65	70	71	77	60
Other/unknown	106	89	85	78	57
Total patients	**24,416**	**24,956**	**25,599**	**26,444**	**27,118**
Total eligible for PBT (6% of patients receiving radiation with curative intent)	**1,465**	**1,497**	**1,536**	**1,587**	**1,627**

Abbreviations: PBT, proton beam therapy.
Source: Cancer Activity Level Reporting data set, adapted from data prepared by System and Infrastructure Planning, Cancer Care Ontario (now part of Ontario Health), January 16, 2019.
Note: Treatment intent is linked to the last treatment in a radiation treatment course.

Patient Capacity

We calculated the patient capacity of various configurations for a proton beam therapy centre, to limit the number of people we assumed would be treated over the next 5 years in our budget impact.

A proton beam therapy centre can be constructed either as a single-room (also called single-vault) or multi-room (multi-vault) facility. Both types offer the same clinical benefits to patients; the only difference is that a multi-room centre has greater treatment capacity because more than one patient at a time can be preparing for or receiving treatment (Lionel G. Bouchet, Mevion Medical Systems, email communication, August 2019). A single-room centre operating 12 hours a day, with 1.7 treatments per hour, can treat approximately 270 patients a year (David Hodgson, MD, email communication, October 2019).[60] Theoretically, a multi-room centre with four independently functioning rooms could treat around 1,600 patients (4 x approximately 400 patients per room) per year (Lionel G. Bouchet, Mevion Medical Systems, email communication, October 2019). However, for this analysis, we assumed the annual capacity would be 270 patients per room, regardless of the type of facility (Table 14).

Analytic Framework

We estimated the 5-year budget impact of building a proton beam therapy centre and publicly funding proton beam therapy using the cost difference between two scenarios: (1) current clinical practice without a proton beam therapy centre in Ontario, where there is limited uptake of proton beam therapy through the Out-of-Country Prior Approval Program and many patients receive photon radiation therapy instead (the current scenario) and (2) and anticipated clinical practice with the construction of a four-room proton beam therapy centre (the new scenario). Figure 4 presents the budget impact model schematic.

We conducted a reference case analysis and sensitivity analyses. Our reference case analysis represents the analysis with the most likely set of input parameters and model assumptions. Based on the estimated clinical need in Ontario (1,627 patients annually), a single-room proton beam therapy centre does not have the capacity to treat the eligible population (Derek Tsang, MD, oral communication, October 2019). Therefore, in our reference case analysis, we assumed that a multi-room proton beam therapy centre, with four independent rooms, would be incorporated into an existing Ontario hospital. We assumed this facility would replace both out-of-country proton beam therapy and photon radiation treatment for patients eligible and able to receive proton beam therapy.

In our sensitivity analyses, we explored how the results are affected by varying input parameters and model assumptions. We also conducted a series of scenario analyses to explore the budget impact of different facility configurations and various public funding schemes.

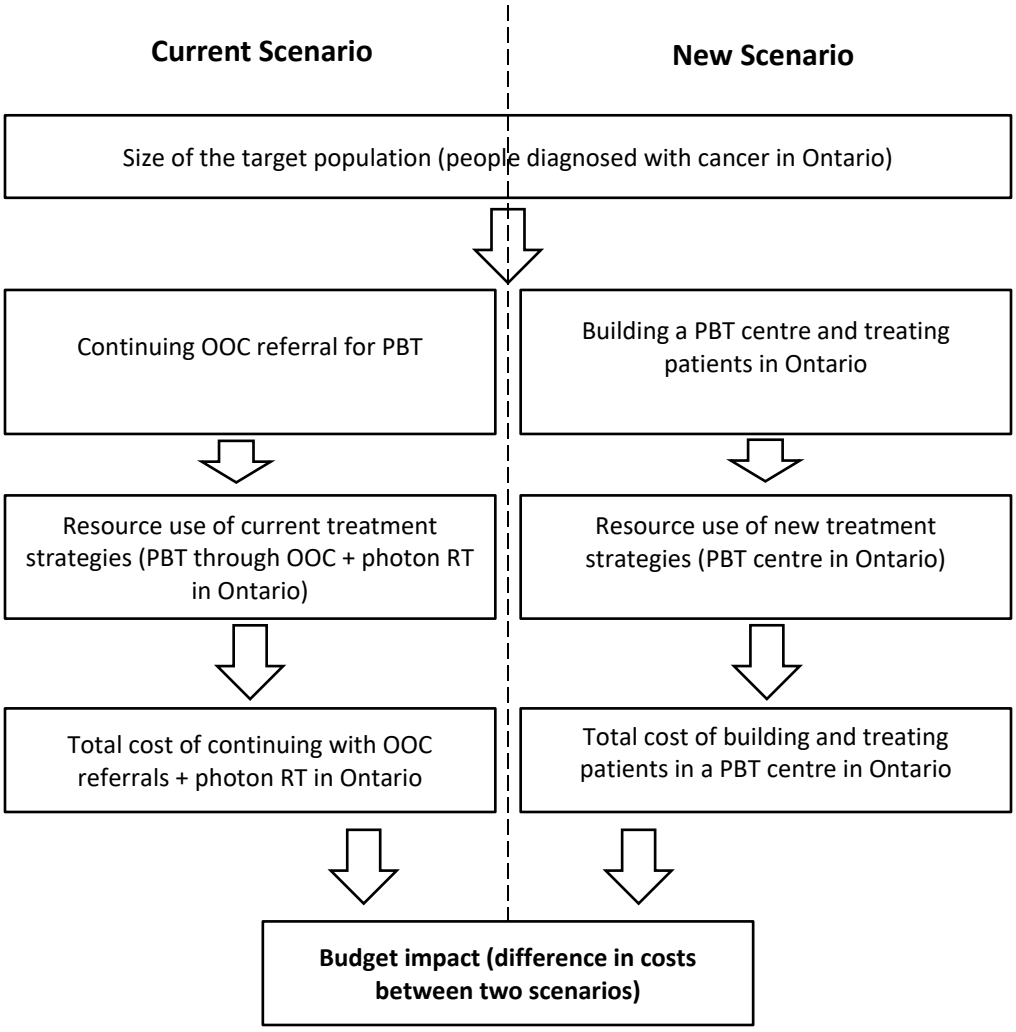

Figure 4: Schematic Model of Budget Impact

Abbreviations: OOC, Out-of-Country Prior Approval Program; PBT, proton beam therapy; RT, radiotherapy.

Key Assumptions, Reference Case Analysis

- In the current scenario, out-of-country referral estimates, based on prior patterns in uptake,[16] would increase 3% each year
- In the new scenario, we limited our target population to Ontario residents eligible for proton beam therapy (N = 1,627 patients, or 6% of all patients receiving radiation therapy with curative intent)[10]
- Cost estimates reflect a four-room proton beam therapy centre incorporated into an existing Ontario hospital
- Each year, one additional room will be filled, reaching full four-room capacity by year 4
- Annually, 270 patients can be treated per room
- The full capital costs will be incurred in the first year
- Operational costs will increase with the number of rooms filled
- Each room is fully functioning and independent
- Patients receiving proton beam therapy would not receive photon radiation treatment (i.e., this would be a cost-offset); we expect proton beam would reduce the need for some patients to receive radiation therapy and, therefore, we incorporated costs of avoided radiation therapy in the reference case analysis

Current Intervention Mix, Uptake of the New Intervention, and Future Intervention Mix

In our current scenario, we assumed that a small proportion of patients who may benefit from proton beam therapy receive it through Ontario's Out-of-Country Prior Approval Program. Although we estimated approximately 1,627 people may be eligible for proton beam therapy annually, the number who currently receive treatment through the Out-of-Country Program is much smaller. For example, an estimated 12 patients from Ontario received proton beam therapy in 2016,[16] and 57 patients in total have received proton beam therapy over the last 9 years (Ontario Ministry of Health, email communication, July 2019). Nationally, 45 patients received proton beam therapy outside Canada in 2016. As noted, we assumed in our analyses that the number going out of country will grow at 3% per year.[16]

Also in the current scenario, we assumed the remaining patients would receive photon radiation therapy. This could include image-guided intensity-modulated radiation therapy, other external beam therapies, or brachytherapy, either as monotherapy or in combination with other treatment modalities.

In our new scenario, we assumed a growing proportion of eligible patients would instead receive treatment in an Ontario proton beam therapy centre. We assumed that each year, one additional room will be operating, reaching a full four-room capacity in year 4 (i.e., in year 1, one room will be filled; in year 2, two rooms will be filled; etc.). Table 14 shows the number of patients treated per year in our reference case analysis.

Table 14: Number of Ontario Patients With Cancer Receiving Proton Beam Therapy, New vs. Current Scenarios

Procedure	Year 1	Year 2	Year 3	Year 4	Year 5	Total
New Scenario: Publicly Fund a 4-Room PBT Centre						
Operational rooms, N	1	2	3	4	4	4
Uptake of PBT, N patients	270	540	810	1080	1080	3,780
Theoretical maximum capacity, N patients[a]	400	800	1,200	1,600	1,600	5,600
Current Scenario: No PBT Centre in Ontario						
PBT via OOC, N patients	12	12	13	13	14	64
Photon RT, N patients	258	528	797	1067	1066	3,716

Abbreviations: OOC, Out-of-Country Prior Approval Program; PBT, proton beam therapy; RT, radiotherapy.

Note: Out-of-country numbers are based on estimates from the Canadian Agency for Drugs and Technologies in Health[16]; PBT patient counts were calculated based on estimates from Ontario Health (Cancer Care Ontario).[10]

[a]Rounded down from approximately 440 patients treated per year in centres operating 16 hours a day (to instead assume 12 hours a day).

Resources and Costs

In the current scenario of our reference case analysis, we included the average cost per patient for proton beam therapy delivered through the Out-of-Country Program (prior to PPAs): $326,800 CAD, paid by the Ministry of Health ($250,000 USD; conversion rate: 1.31; email communication, Ontario Ministry of Health, July 2019). We assumed that treatment-related costs other than those for proton beam therapy (such as for adjunct therapies) were negligible in our analyses.

Also in the current scenario, we included the cost of photon radiation therapy for patients who remain in Ontario for treatment. An Ontario study by Yong et al[61] estimated the unit costs of radiation therapy (intensity-modulated and conventional radiation therapy) for prostate, head and neck, and breast cancers, through a program and health system perspective. We used the program unit costs for head and neck cancer and assumed this would be the per-patient cost of radiation therapy for the cancers in our analysis (approximately $9,800 CAD). The program costs excluded physician fees, which we assumed would be similar for patients receiving proton beam therapy in our new scenario (i.e., these costs would cancel out). We inflated this unit cost to 2019 Canadian dollars and multiplied it by the number of patients expected to receive photon radiation therapy instead of proton beam therapy in our current scenario.

In the new scenario, we included costs related to building and maintaining a four-room proton beam therapy centre (Table 15). Specifically, we included capital costs of constructing a proton beam therapy facility in an existing hospital and annual operational costs which include electrical utilities, equipment servicing by the manufacturer (excluded in year 1, as the warranty covers this), other building costs, and staffing. Staff costs include salaries for a dosimetrist, nurse, radiation therapists, physicists, and administrative personnel.

In our additional scenario analyses, we varied the costs of our input parameters (capital and operational costs) to reflect the budget impact of building and operating a one-, two-, or three-room proton beam therapy centre in an existing hospital, as alternatives to the four-room centre in our reference case (see Table 15). Two other scenarios considered construction of one- and four-room proton beam therapy centres on a greenfield (i.e., a freestanding facility); for these scenarios, we assumed operational costs would be the same as in existing infrastructure.

Table 15: Capital and Operational Costs for One-, Two-, Three-, and Four-Room Proton Beam Therapy Centres

	1-Room		2-Room		3-Room		4-Room	
	Cost	Reference	Cost	Reference	Cost	Reference	Cost	Reference
Capital Costs, $[a]								
Device	26,600,000	Mevion[b]	53,200,000	Mevion[b]	79,800,000	Mevion[b]	106,400,000	Mevion[b]
Oncology information system	332,500	Mevion[b]	665,000	Mevion[b]	997,500	Mevion[b]	1,330,000	Mevion[b]
TPS	1,064,000	Mevion[b]	1,729,000	Mevion[b]	2,394,000	Mevion[b]	3,059,000	Mevion[b]
Dosimetry	399,000	Mevion[b]	598,500	Mevion[b]	798,000	Mevion[b]	997,500	Mevion[b]
Total device and installation	28,395,500	Calculation	56,192,500	Calculation	83,989,500	Calculation	111,786,500	Calculation
Construction	4,000,000	Mevion[b]	8,000,000	Assumption (1-room x 2)	12,000,000	Assumption (1-room x 3)	16,000,000	Assumption (1-room x 4)
Total capital costs	**32,395,500**		**64,192,500**		**95,989,500**		**127,786,500**	
Annual Operational Costs, $[a]								
Electrical	200,000	CADTH, Smith et al.[16,62]	400,000	Assumption (1-room x 2)	600,000	Assumption (1-room x 3)	800,000	Assumption (1-room x 4)
Staffing[c]	2,200,000	Mevion[b]	4,400,000	Assumption (1-room x 2)	6,600,000	Assumption (1-room x 3)	8,800,000	Assumption (1-room x 4)
Other building	13,300	Mevion[b]	19,950	Mevion[b]	26,600	Mevion[b]	33,250	Mevion[b]
Service with Mevion on site	2,394,000	Mevion[b]	3,724,000	Mevion[b]	5,054,000	Mevion[b]	5,985,000	Mevion[b]
Total operational costs	**4,807,300**		**8,543,950**		**12,280,600**		**15,618,250**	

Abbreviations: Canadian Agency for Drugs and Technologies in Health; TPS treatment planning systems.
[a]In 2019 Canadian dollars.
[b]Estimates provided by Lionel G. Bouchet, Mevion Medical Systems, email communication, November 2019.
[c]Includes salaries for a dosimetrist, nurse, radiation therapists, physicists, and administrative personnel.

Analysis

We estimated the required budget to publicly fund proton beam therapy in Ontario for people with cancer (children and adults combined). As described earlier, in the reference case analysis we assumed a four-room proton beam therapy centre would be incorporated into an existing hospital and would replace either out-of-country treatment or photon radiation therapy for eligible patients expected to receive proton beam therapy. To calculate the budget impact, we took the difference between the combined capital and operational costs of a four-room proton beam therapy centre in Ontario and the combined costs of out-of-country proton beam therapy and in-province photon radiation therapy.

We also carried out additional scenario analyses, described below. For each scenario, we estimated the budget impact for the target population. We calculated the cost per patient for each new scenario by dividing the total costs of proton beam therapy over 5 years by the number of patients expected to be treated. We also calculated the cost per patient, excluding capital costs, for each scenario by dividing the total operational costs over 5 years by the number of patients expected to be treated. All analyses were carried out in Microsoft Excel. Table 16 presents an overview of the parameters for all scenario analyses, along with the reference case analysis.

SCENARIO 1: PUBLICLY FUND A SINGLE-ROOM PROTON BEAM THERAPY CENTRE

This scenario models building a one-room proton beam therapy facility in an existing hospital, with an annual uptake of 270 patients per year, replacing out-of-country referrals for these patients. Many studies have concluded that proton beam therapy may be cost-effective in treating children with cancer, particularly brain tumours.[42-45,48] Therefore, we ran an analysis for a one-room centre, which would reflect the capacity needed to treat Ontario's pediatric population, with space to treat additional patients as well. Table 15 estimates the total capital ($32,395,500) and annual operational costs ($4,807,300) associated with building and treating patients in a single-room centre. In this scenario, we calculated the budget impact by taking the difference between the current scenario and the combined capital and operational costs for a one-room proton beam therapy centre.

SCENARIOS 2A AND 2B: PUBLICLY FUND A FOUR- OR ONE-ROOM PROTON BEAM THERAPY CENTRE THAT TREATS PATIENTS FROM ACROSS CANADA

For scenarios 2a and 2b, we assumed an Ontario proton beam therapy centre would receive referrals from other Canadian provinces. We assumed 33 patients would be referred from other provinces in year 1, with 3% growth per year (based on prior patterns of uptake in proton beam therapy through Ontario's Out-of-Country Program[16]). We assumed each referring province would pay Ontario the significantly lower cost per patient of $48,217 in a four-room centre (as calculated in our reference scenario) or $40,028 in a one-room centre (as calculated in scenario 1), compared with $326,800 per patient treated in the United States. For these scenarios, the budget impact was calculated using the new scenario minus the current scenario and subtracting the costs of treating patients from other Canadian provinces (e.g., 33 patents x $48,217) per year.

SCENARIO 3A AND 3B: PUBLICLY FUND A TWO- OR THREE-ROOM PROTON BEAM THERAPY CENTRE

For scenarios 3a and 3b, we explored the budget impact of building and funding a two-room or three-room proton beam therapy centre in Ontario.

Table 15 estimates the total capital ($64,192,500) and annual operational costs ($8,543,950) associated with building and treating patients in a two-room proton beam therapy centre. A three-room centre would incur total capital costs of $95,989,500 and annual operating costs of $12,280,600. Similar to the reference case analysis, we assumed that each year, one additional room would be filled. This is reflected in the operational costs (e.g., for a three-room centre, 270 patients would be treated in year 1, 540 in year 2, 810 in year 3, 810 in year 4, and 810 in year 5). To calculate the budget impact, we took the difference between the combined capital and operational costs for a two- or three-room proton beam therapy centre and the cost of sending these patients out-of-country for proton beam therapy or providing photon radiation therapy for them in Ontario.

SCENARIO 4: AMORTIZE CAPITAL COSTS OVER 20 YEARS

The service life of a proton beam therapy device is 20 years. As the capital costs are the largest costs incurred, we explored the 5-year budget impact of building and funding a proton beam therapy centre in Ontario with capital costs evenly distributed over a 20-year time horizon, instead of being fully incurred in year 1 as in our reference case.

SCENARIOS 5A AND 5B: PUBLICLY FUND A FOUR-ROOM OR ONE-ROOM PROTON BEAM CENTRE ON A GREENFIELD

We also calculated the budget impact of building and funding a four-room or one-room proton beam therapy centre on a greenfield (a new, freestanding facility), rather than as part of an existing hospital as in our reference case. We obtained costs of building a proton beam therapy centre on a greenfield from the device manufacturer (Mevion Medical Systems, personal communication, July 2019). Capital costs on a greenfield were assumed to be $134 million or $394 million for a one-room or a four-room proton beam therapy centre, respectively. We assumed operational costs on a greenfield would be the same as in existing infrastructure.

SCENARIOS 6A AND 6B: VARY THE COST OF PHOTON THERAPY

In scenario 6a, we used our reference case new scenario (build and publicly fund a four-room proton beam therapy centre within an existing hospital), but we increased the per-patient cost of photon radiation therapy ($9,800) to $12,150, based on a costing study by Smith et al[62] for Western Canada. That study estimated the cost of avoided standard radiation therapy for children and adults with cancers of the brain or other tumours in close proximity to the spinal cord. Scenario 6b explores the same change for a one-room proton beam therapy centre.

SCENARIOS 7A AND 7B: SUBSTITUTE A NUMBER OF PLANNED PHOTON THERAPY CENTRE(S) WITH PROTON BEAM THERAPY CENTRE(S)

Ontario Health (Cancer Care Ontario) currently has a strategic capital investment strategy to install 26 new photon linear accelerators machines across Ontario over the next 10 years.[60] In scenario 7A, we used the cost of purchasing four new photon linear accelerators (4 x $3,500,000), including the cost of construction and installation (4 x $4,000,000), and annual operating costs ($9,800 per patient) to calculate the budget impact of replacing four new, planned photon linear accelerators with a four-room proton beam therapy centre. We assumed the construction and installation cost would be the same for both technologies.

In scenario 7B, we used the cost of one new photon linear accelerator ($3,500,000), annual operating costs ($9,800), and the cost of construction and installation ($4,000,000) to calculate the budget impact of replacing one new, planned proton linear accelerator with a one-room proton beam therapy centre.

SCENARIO 8: EXCLUDE CAPITAL COSTS

In this scenario, we used only the operating costs to calculate the budget impact of publicly funding a four-room proton beam therapy centre in Ontario.

SCENARIO 9: BUILD SEVERAL ONE-ROOM CENTRES

Instead of a single four-room proton beam therapy centre, this scenario considers the costs of building and operating four one-room centres in different locations across Ontario.

SCENARIO 10: ASSUME LOWER STAFFING COSTS

Staffing costs for proton beam therapy may be lower than in our reference case analysis. This scenario considers the possibility that 6 radiation therapists, 0.3 radiation physicist, 0.5 nurse, 0.5 administrative personnel would be needed for each treatment room, for a total of $850,000 per room, per year (Derek Tsang, MD, email communication, December 2019).

Internal Validation

The secondary health economist conducted formal internal validation. This process included checking for errors and ensuring the accuracy of parameter inputs and equations in the budget impact analysis.

Table 16: Reference Case and Scenario (Sensitivity) Analyses, Budget Impact Analysis for Proton Beam Therapy

	Scenario Description	Costs, $[a]	Single- or Multi-Room PBT Centre	Comparator	Treat Out-of-Province Patients
Reference case, new scenario	(See Key Assumptions and Table 15)	Capital: 127,786,500 Operational: 15,618,250	4-room	OOC + photon RT	No
Scenario 1	Build a 1-room PBT facility in existing hospital, treating 270 patients/y (e.g., pediatric, others who could benefit most)	Capital: 32,395,500 Operational: 4,807,300	1-room	OOC + photon RT	No
Scenario 2a	Assume all patients from other Canadian provinces who would receive PBT out of country will instead receive it in Ontario (n = 33 in y 1, 3% growth/y)	Capital: 127,786,500 Operational: 15,618,250 (y 4+) Cost/patient from other provinces: 48,217	4-room	OOC + photon RT	Yes

	Scenario Description	Costs, $[a]	Single- or Multi-Room PBT Centre	Comparator	Treat Out-of-Province Patients
Scenario 2b	Same as 2a	Capital: 32,395,500 Operational: 4,807,300 Cost/patient from other provinces: 40,028	1-room	OOC + photon RT	Yes
Scenario 3a	Treat up to 540 patients/y by y 2	Capital: 64,192,500 Operational: 8,543,950 (y 2+)	2-room	OOC + photon RT	No
Scenario 3b	Treat up to 810 patients/y by y 3	Capital: 95,989,500 Operational: 12,280,600 (y 3+)	3-room	OOC + photon RT	No
Scenario 4	Amortize capital costs over 20 y	Capital: 127,786,500	4-room	OOC + photon RT	No
Scenario 5a	Build on a greenfield	Capital: 394,000,000 Operational same as ref case	4-room	OOC + photon RT	No
Scenario 5b	Build on a greenfield	Capital: 134,000,000 Operational same as scenario 1	1-room	OOC + photon RT	No
Scenario 6a	Assume higher cost for photon RT	Capital and operational same as reference case RT: 12,150	4-room	OOC + photon RT	No
Scenario 6b	Same as 6a	Capital: 32,395,500 Operational: 4,807,300 RT: 12,150	1-room	OOC + photon RT	No
Scenario 7a	Substitute 4 new photon RT machines with 4 PBT machines	Capital: 30,000,000 Operational: 9,800	4-room	OOC + new photon RT machines	No
Scenario 7b	Substitute 1 new photon RT machine with 1 PBT machine	Capital: 7,500,000	1-room	OOC + new photon RT machines	No
Scenario 8	Include only operational costs	Operational: 15,618,250 (y 4+)	4-room	OOC + photon RT	No
Scenario 9	Build multiple 1-room PBT centres	Capital: 32,395,500 (x 4) Operational: 4,807,300 (x 4)	1-room	OOC + photon RT	No
Scenario 10	Assume lower PBT staffing costs	Capital: 127,786,500 Operational: 10,218,250 (y 4+)	4-room	OOC + photon RT	No

Abbreviations: OOC, Out-of-Country Prior Approval Program; PBT, proton beam therapy; ref, reference; RT, radiotherapy; y, year.
[a]In 2019 Canadian dollars.

Results

Reference Case

In the current scenario, where proton beam therapy is funded for a small number of patients through the Out-of-Country Prior Approval Program and remaining patients receive photon therapy, the total cost ranged from $6.5 million in year 1 to $15.1 million in year 5 (Table 17). Over the 5-year period, the total costs were estimated at $57.5 million. In the new scenario, where a proton beam therapy is available in Ontario and replaces out-of-country referrals and photon therapy, the total cost ranged from $130.2 million in year 1 (when the total capital cost is incurred) to $15.6 million in year 5 (operational costs only). Over the 5-year period, the total costs were estimated as $182.3 million (Table 17).

The budget impact of building and publicly funding a four-room proton beam therapy centre would range from $123.7 million in year 1 to $0.56 million in year 5, with a total budget impact of $124.8 million over 5 years (Table 17). The cost per patient to fund proton beam therapy would be $48,217 ($182.3 million/3,780 patients), given the number of people we predicted would receive proton beam therapy in our reference case analysis. If only operational costs are considered, then the cost per patient would be $14,411 ($54.5 million/3,780 patients).

Table 17: Budget Impact Analysis Results, Reference Case for a Four-Room Proton Beam Therapy Centre in Ontario

	Budget Impact, $ Million[a]					
Scenario	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Total**
Current Scenario						
PBT funded through OOC	3.9	3.9	4.2	4.2	4.6	20.9
Photon RT in Ontario for remaining patients	2.5	5.2	7.8	10.5	10.5	36.5
Current scenario total	6.5	9.1	12.1	14.7	15.1	57.5
New Scenario[b]						
Capital	127.8	0	0	0	0	127.8
Operating	2.4	8.5	12.3	15.6	15.6	54.5
New scenario total	130.2	8.5	12.3	15.6	15.6	182.3
Budget impact (new scenario – current scenario)	**123.7**	**–0.57**	**0.19**	**0.88**	**0.56**	**124.8**
New scenario cost per patient, $[a]						**48,217[c]**

Abbreviations: OOC, Out-of-Country Prior Approval Program; PBT, proton beam therapy; RT, radiotherapy.
[a]In 2019 Canadian dollars.
[b]Construction and operation of a 4-room proton beam therapy centre that would replace publicly funded out-of-country PBT and in-province radiation therapy for eligible cancer patients.
[c]Not million.
Note: numbers may be inexact due to rounding.

Sensitivity Analysis

We group these results by facility configuration (number of treatment rooms), starting with scenarios for a four-room proton beam therapy centre.

Table 18 presents the budget impact of the additional scenarios that assume a four-room proton beam therapy centre will be built in Ontario. The largest budget impact was for a four-room centre built on a greenfield, rather than as part of part of an existing hospital (as in our reference case): the 5-year budget impact was over $391.0 million (scenario 5a). Offering proton beam therapy to patients from other provinces, at 33 patients per year and an annual growth rate of 3%, reduced the 5-year budget impact of building and operating a four-room proton beam therapy centre in an existing facility from $124.8 million (reference case) to $118.1 million (scenario 2a).

When we varied (increased) the cost of photon radiation therapy (scenario 6), this reduced the 5-year budget impact to $116.2 million (Appendix 7, Table A10). Reducing staffing costs also reduced the budget impact to $105.9 million over 5 years (scenario 10). Amortizing capital costs over the 20-year service life of the proton beam therapy technology (at approximately $6.4 million per year) would reduce the total budget impact to $29 million over 5 years (scenario 4, Table 18). When we considered substituting new photon radiation devices with proton beam therapy (scenario 7), this reduced the budget impact to approximately $94.8 million over the next 5 years (Appendix 8, Table A12).

Table 18: Budget Impact Analysis Results, Scenario Analyses for a Four-Room Proton Beam Therapy Centre

	Budget Impact, $ Million[a]					
	Year 1	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Total**
Current Scenario						
PBT funded through OOC	3.9	3.9	4.2	4.2	4.6	20.9
Photon RT in Ontario for remaining patients	2.5	5.2	7.8	10.5	10.5	36.5
Current scenario total	6.5	9.1	12.1	14.7	15.1	57.5
Scenario 2a: 4-Room PBT Centre, Patients From Ontario and Other Canadian Provinces						
Current scenario total[b]	6.1	8.8	11.7	14.4	14.7	55.7
New scenario (from reference case)	130.2	8.5	12.3	15.6	15.6	182.3
Savings from referrals from other Canadian provinces[c]	−1.6	−1.6	−1.7	−1.7	−1.7	−8.4
Total scenario 2a (with cashflow)	128.6	6.9	10.6	13.9	13.8	173.8
Budget impact	**122.5**	**−1.8**	**−1.1**	**−0.51**	**−0.86**	**118.1**
Cost per patient						**45,982[d]**
Scenario 4: 4-Room PBT Centre, 20-Year Amortization of Capital Costs						
Capital	6.4	6.4	6.4	6.4	6.4	31.9
Operating	2.4	8.5	12.3	15.6	15.6	54.5
Total scenario 4	8.8	14.9	18.7	22.0	22.0	86.4
Budget impact	**2.3**	**5.8**	**6.5**	**7.2**	**7.0**	**29.0**

	Budget Impact, $ Million[a]					
	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Scenario 5a: 4-Room PBT Centre, Greenfield						
Capital	394.0	0	0	0	0	394.0
Operating	2.4	8.5	12.3	15.6	15.6	54.5
Total scenario 5a	396.0	8.5	12.3	15.6	15.6	448.5
Budget impact	**390.0**	**−0.57**	**1.96**	**0.88**	**0.56**	**391.0**
Cost per patient						**118,644[d]**
Scenario 8: 4-Room PBT Centre, Operational Costs Only						
Capital	0	0	0	0	0	0
Operating	2.4	8.5	12.3	15.6	15.6	54.5
Total scenario 8	2.4	8.5	12.3	15.6	15.6	54.5
Budget impact	**−4.0**	**−0.57**	**0.19**	**0.88**	**0.56**	**−3.0**
Cost per patient						**14,411[d]**
Scenario 9: 4 1-Room PBT Centres						
Total scenario 9	139.2	19.2	19.2	19.2	19.2	216.2
Budget impact	**132.8**	**10.1**	**7.1**	**4.5**	**4.2**	**158.7**
Cost per patient						**57,183[d]**
Scenario 10: 4-Room PBT Centre, Lower Operational (Staffing) Costs						
Capital	127.8	0	0	0	0	127.8
Operating	1.1	5.8	8.2	10.2	10.2	35.5
Total scenario 10	128.8	5.8	8.2	10.2	10.2	163.4
Budget impact	**122.4**	**−3.2**	**−3.9**	**−4.5**	**−4.8**	**105.9**
Cost per patient						**43,217[d]**

Abbreviations: PBT, proton beam therapy; RT, radiotherapy.
[a]In 2019 Canadian dollars.
[b] Accounts for lower number of Ontario patients to accommodate patients from other province; room capacity is constant.
[c]($48,217 x 33 patients = $1.6 million)
[d]Not million.
Note: numbers may be inexact due to rounding.

Table 19 presents the budget impact of three scenarios that assume a one-room proton beam therapy centre will be built. The smallest budget impact in building and operating a one-room centre came from including patients from other Canadian provinces, assuming 33 people each year, with 3% annual growth (scenario 2b): this yielded a total budget impact of $15.2 million over 5 years and $34,839 cost per patient.

Appendix 8 outlines the budget impact of substituting new photon radiation devices with proton beam therapy technology. When we substituted one new photon radiation device with one proton beam therapy machine, this reduced the budget impact to approximately $13 million over the next 5 years (scenario 7b, Table A13).

Table 19: Budget Impact Analysis Results, Scenario Analyses for a One-Room Proton Beam Therapy Centre

	Budget Impact, $ Million[a]					
	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Current Scenario						
PBT funded through OOC	3.9	3.9	4.2	4.3	4.6	20.9
Photon RT in Ontario for remaining patients	2.5	2.5	2.5	2.5	2.5	12.6
Total current scenario	6.5	6.5	6.7	6.8	7.1	33.5
Scenario 1: 1-Room PBT Centre, Ontario patients only						
Capital costs	32.4	0	0	0	0	32.4
Operational costs	2.4	4.8	4.8	4.8	4.8	21.6
Total scenario 1	34.8	4.8	4.8	4.8	4.8	54.0
Budget impact	**28.4**	**−1.7**	**−2.0**	**−2.0**	**−2.2**	**20.5**
Cost per patient						**40,028[b]**
Scenario 2b: 1-Room PBT Centre, Patients From Other Canadian Provinces						
Total current scenario[c]	6.1	6.1	6.4	6.4	6.7	31.8
Total cost for 1 room (from scenario 1)	34.8	4.8	4.8	4.8	4.8	54.0
Savings from referrals from other Canadian provinces[d]	−1.3	−1.4	−1.4	−1.4	−1.5	−7.1
Total scenario 2b (with cashflow)	33.5	3.4	3.4	3.4	3.3	47.0
Budget impact	**27.3**	**−2.7**	**−3.0**	**−3.1**	**−3.4**	**15.2**
Cost per patient						**34,839[b]**
Scenario 5b: 1-Room PBT Centre, Greenfield						
Capital	134.0	0	0	0	0	134.0
Operational	2.4	4.8	4.8	4.8	4.8	21.6
Total scenario 5b	136.4	4.8	4.8	4.8	4.8	155.6
Budget impact	**130.0**	**−1.7**	**−2.0**	**−2.0**	**−2.3**	**122.0**
Cost per patient						**115,290[b]**

Abbreviations: OOC, Out-of-Country Prior Approval Program; PBT, proton beam therapy; RT, radiotherapy.
[a]In 2019 Canadian dollars.
[b]Not million.
[c]Accounts for lower number of Ontario patients to accommodate patients from other provinces; room capacity is constant.
[d]($40,572 x 33 patients = $1.3 million)
Note: numbers may be inexact due to rounding.

Table 20 presents the budget impact of building a two-room (scenario 3a) or three-room (scenario 3b) proton beam therapy centre, instead of the four-room facility in our reference case. A two-room proton beam therapy centre would have a budget impact of $60.1 million in year 1, with cost savings starting in year 2 and reaching $1.2 million in year 5, for a total 5-year budget impact of $56.6 million. The cost per patient would be an estimated $41,473. A three-room proton beam therapy centre would have a budget impact ranging from $91.9 million in year 1 to −$0.12 million in year 5, with a total budget impact of $91.6 million over 5 years and a cost per patient of $44,379.

Table 20: Budget Impact Analysis Results, Scenario Analyses for a Two- or Three-Room Proton Beam Therapy Centre

	Budget Impact, $ Million[a]					
	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Current Scenario						
PBT through OOC	3.9	3.9	4.2	4.3	4.6	20.9
Photon RT (2 rooms)	2.5	5.2	5.2	5.2	5.2	23.3
Total cost of current scenario (2 rooms)	6.5	9.1	9.4	9.4	9.7	44.2
Photon RT (3 rooms)	2.5	5.2	7.8	7.8	7.8	31.2
Total cost of current scenario (3 rooms)	6.5	9.2	12.0	12.1	12.2	52.0
Scenario 3a: 2-Room PBT Centre						
Capital	64.2	0	0	0	0	64.2
Operational	2.4	8.5	8.5	8.5	8.5	36.6
Scenario 3a total	66.6	8.5	8.5	8.5	8.5	100.9
Budget impact	**60.1**	**−0.57**	**−0.89**	**−0.89**	**−1.2**	**56.6**
Cost per patient						**41,473[b]**
Scenario 3b: 3-Room PBT Centre						
Capital	96.0	0	0	0	0	96.0
Operational	2.4	8.5	12.3	12.3	12.3	47.8
Scenario 3b total	98.4	8.5	12.3	12.3	12.3	143.8
Budget impact	**91.9**	**−0.57**	**0.19**	**0.19**	**−0.12**	**91.6**
Cost per patient						**44,379[b]**

Abbreviations: OOC, Out-of-Country Prior Approval Program; PBT, proton beam therapy; RT, radiotherapy.
[a]In 2019 Canadian dollars.
[b]Not million.
Note: numbers may be inexact due to rounding.

Discussion

Our reference case analysis shows that constructing a four-room proton beam therapy centre incurs a construction cost of $127.8 million in the first year and ongoing costs of between $2.4 million and $15.6 million in subsequent years associated with utilities, service, and staffing. The budget impact would be significantly greater than the current access to photon therapy through the Out-of-Country Program, owing to the large capital costs in year 1. Providing proton beam therapy treatment to a small number of patients from other Canadian provinces would lower the budget impact by approximately $7 million over 5 years. Amortizing the capital costs over the 20-year service life of the technology would lower the upfront costs in the first year to $6.4 million per year, plus operational costs.

Still assuming a four-room centre, the cost per patient considering both capital and operational costs would be $48,217. This is approximately 6.7 times less than the cost of sending Ontario patients to the United States ($326,800). We also calculated the cost per patient excluding the capital cost ($14,411 per patient), as the initial capital investment masks the true cost of treatment. The per-patient cost is highly dependent on the number of patients treated, as well as which costs are included. For example, if rooms

operated at the theoretical maximum capacity (i.e., 400 treatments per year, per room), then the cost per patient would be $32,547 ($182.3 million/5,600 patients).

In addition, the current scenario does not ensure all patients who would benefit from proton beam therapy would receive it. We expect it will cost $182.3 million to build and operate a four-room proton beam therapy centre for 5 years in Ontario and that this would be able to treat an estimated 3,780 patients. If, instead, that money went to sending patients out of country, it would treat only 557 patients.

While our analysis considered operational costs for a 12-hour day, operating a proton beam therapy centre on a maximum 18-hour schedule may allow additional patients to be treated, similar to the operation of some magnetic resonance imaging systems.[63] This would lower the cost per patient, although it would increase overall operational costs.

As the number of patients referred through Ontario's Out-of-Country Prior Approval Program is low, it is possible the number of patients eligible for proton beam therapy may be smaller than the estimates in our analyses; some patients may be unable to receive treatment because they are not clinically indicated for proton beam therapy, are too ill to travel (within Ontario or from another province), or have other travel barriers. If actual demand is lower than we have estimated, this could indicate that a single-room proton beam therapy centre may be sufficient to meet the needs of Ontario patients. After an initial capital investment of $32 million plus incremental facility costs, building and operating a single-room proton beam therapy in Ontario would achieve cost savings in year 2 and beyond. This may present a more economically attractive scenario.

However, in our reference case analysis, we assumed 1,627 patients would be eligible for proton beam therapy annually, based on Ontario Health (Cancer Care Ontario) estimates, and this number of patients would require four rooms (four proton beam therapy machines). To build four single-room centres would cost a total of $216 million over 5 years (scenario 9), compared to $182 million for a four-room centre (the new scenario in our reference case). A consequence of building a single four-room centre is that some people within Ontario may still face travel barriers, and there may be fewer people receiving proton beam therapy than are eligible. Travel grants or other forms of travel reimbursement could be offered to people living in rural areas, but such programs and their costs to the Ministry of Health would depend on program implementation considerations.

Our analysis aligns with budget impact analyses by the Canadian Agency for Drugs and Technologies in Health (CADTH),[16] Cancer Care Ontario,[10] and Smith et al.[62] Similar to Smith et al, our scenario analyses exploring the impact of referrals from other Canadian provinces reduced the overall budget impact. However, it is uncertain how many patients are willing to travel from Western Canada to Ontario, as travel barriers may still exist for patients and caregivers. That is why we did not consider patients from other provinces in our reference case analysis and, instead, considered them in our sensitivity analyses. In their respective work, CADTH assumed fixed, annual operational costs and Cancer Care Ontario varied costs by the number of patients treated. Our approach, instead, made a conservative assumption that costs would increase by the number of rooms in operation, which is reflective of the number of patients treated. Our analysis could have accounted for inflation of these costs, which would reduce the cost of the new scenario. However, the cost of newer proton beam therapy technology has decreased over time, and the cost to send patients out of country is negotiated case by case.[62] Thus, it was uncertain if costs for both the current and new scenarios would increase or decrease over time.

Our estimates of the overall budget impact for both multi-room and single-room scenarios are lower than previous budget impact analyses[10,16] of proton beam therapy, as our work considers the cost offset from replacing photon therapy with proton beam therapy. In Ontario, it is estimated that 48% of cancer patients are eligible for photon therapy and 39% receive it.[64] Not only would a proton beam therapy centre lead to cost avoidance in photon radiation therapy, but it could potentially free up space for other patients requiring photon radiation therapy.

In our analysis, we assume all costs are paid immediately and no financing costs are incurred, whereas the actual construction of a proton beam therapy centre may involve an overall greater investment.

Strengths and Limitations

Our analysis includes a number of strengths. First, we used recent data from Ontario Health (Cancer Care Ontario): their Activity Level Reporting data set and estimates of the Out-of-Country Prior Approval Program. Second, our analyses considered both out-of-country and photon radiation therapy patients, which represents all patients who are theoretically eligible for proton beam therapy. To our knowledge, this is the first budget impact analysis of proton beam therapy to consider the cost of photon therapy that would be offset by building a proton beam therapy centre in Ontario. Our analysis also considered various scenarios to modify parameters in the reference case analysis. This included varying the capacity of the proton beam therapy centre and considering costs that could be rendered by other Canadian provinces.

There are limitations in our analysis as well. Proton beam therapy aims to reduce potential short- and long-term side effects of treatment. We did not consider costs potentially avoided through a reduction of adverse events associated with photon therapy. A limited number of Canadian studies have assessed the rates and costs of long-term toxicities of cancer treatment. However, the 5-year time horizon of our budget impact analyses is too short to capture long-term adverse events and, therefore, we omitted them from our analysis. If we had been able to consider this cost avoidance, the budget impact would likely be lower. The cost of delivering photon radiation therapy is also challenging to approximate for various cancers. While we used a range of costs assumed to be representative of the cancers included in our analysis, it may not be generalizable to all cancers.

Our model did not consider the possibility of building a facility with several rooms (such as four) but only operating some of them, leaving one to become operational in the future when the need expands. This would likely lower operational and device costs in the short term, while still meeting current demand. Also, our analyses considered the one manufacturer of proton beam therapy technology that is currently approved by Health Canada. Other models may have the ability to serve multiple rooms that share treatment equipment. We reached out to other vendors but did not receive costing information that could be published. These other manufacturers may also offer different variations of rooms and costs that we did not consider in this analysis.

While we also considered scenarios to build facilities on a greenfield, the costs of operating a new, stand-alone centre may be higher than if the same physical space were managed within an existing hospital network. Therefore, it is possible we have underestimated the cost of publicly funding a proton beam therapy centre as a stand-alone site.

Conclusions

Our budget impact analysis indicates that building a centre to provide proton beam therapy for cancers in Ontario and publicly funding this treatment over the next 5 years would result in net spending that varies by the number of rooms built. Some cost offsets would be found by not treating patients through the Out-of-Country Prior Approval Program, by avoiding photon therapy for these patients, and by treating patients from other Canadian provinces. Although a one-room centre had the lowest budget impact, a four-room centre could treat a higher number of patients.

Preferences and Values Evidence

Objective

The objective of this analysis was to explore the underlying values, needs, and priorities of those who have lived experience with proton beam therapy as a treatment for cancer, as well as their decision-making around seeking this treatment.

Background

Exploring patient preferences and values provides a unique source of information about people's experiences of a health condition and the health technologies or interventions used to manage or treat that health condition. It includes the impact of the condition and its treatment on the person with the health condition, their family and other caregivers, and the person's personal environment. Engagement also provides insights into how a health condition is managed by the province's health system.

Information shared from lived experience can also identify gaps or limitations in published research (e.g., outcomes important to those with lived experience that are not reflected in the literature).[65-67] Additionally, lived experience can provide information and perspectives on the ethical and social values implications of health technologies or interventions.

Because the needs, preferences, priorities, and values of those with lived experience in Ontario are important to consider to understand the impact of the technology in peoples lives, we may speak directly with people who live with a given health condition, including those with experience of the technology or intervention we are exploring.

For this analysis, we used direct patient engagement to examine the preferences and values of people with cancer who may have sought proton beam therapy for treatment or may wish to seek this treatment in the future.

Direct Patient Engagement

Methods

PARTNERSHIP PLAN

The partnership plan for this health technology assessment focused on consultation to examine the experiences of those with lived experience with proton beam therapy as a treatment for cancer and those of their families and other caregivers. We engaged people via phone interviews and, for one person, by email.

We used a qualitative interview, as this method of engagement allowed us to explore the meaning of central themes in the experiences of participants.[68] The sensitive nature of exploring people's experiences of a health condition and their quality of life are other factors that support our choice of an interview methodology.

PARTICIPANT OUTREACH

We used an approach called purposive sampling,[69-72] which involves actively reaching out to people with direct experience of the health condition and health technology or intervention being reviewed. We

approached a variety of health system organizations to spread the word about this engagement activity and to contact people with cancer, and their family members or caregivers, including those with experience of proton beam therapy.

Inclusion Criteria

We sought to speak with people with lived experience surrounding proton beam therapy as a treatment for cancer. Participants did not need to have direct experience with proton beam therapy to participate, but may have been in the process of seeking out more information or accessing this treatment option.

Exclusion Criteria

We did not set exclusion criteria.

Participants

For this project, we spoke with five people with cancer living in Ontario, as well as five family members and caregivers of those with cancer. All participants were familiar with proton beam therapy and indicated that they had sought this treatment. Participants included:

- Two adult patients who sought and received proton beam therapy for themselves in the United States
- Two adult patients who, as youth, received proton beam therapy in the United States through Ontario's Out-of-Country Prior Approval Program
- Three caregivers of young children who received proton beam therapy in the United-States through the Out-of-Country Program
- Three adults (two caregivers, one patient) who are exploring the potential of receiving proton beam therapy in the future

APPROACH

At the beginning of the interview, we explained the role of Ontario Health, the purpose of this health technology assessment, the risks of participation, and how participants' personal health information would be protected. We gave this information to participants both verbally and in a letter of information (Appendix 9) if requested. We then obtained participants' verbal consent before starting the interview. With participants' consent, we audio-recorded and then transcribed the interviews.

Interviews lasted approximately 20 to 60 minutes. The interview was loosely structured and consisted of a series of open-ended questions. Questions were based on a list developed by the Health Technology Assessment International Interest Group on Patient and Citizen Involvement in Health Technology Assessment.[73] Questions focused on the impact of the diagnosis of cancer, on the quality of life of people with cancer, their experiences with treatments to manage or treat their condition, their decision-making about proton beam therapy, their perceptions of the benefits or limitations of proton beam therapy, and the potential impact of having this technology available on Ontario. For family members and caregivers, questions focused on their perceptions of the impact of cancer diagnosis and treatments on the quality of life of the person with cancer, as well as the impact of the person's health condition and treatments on the family members and caregivers themselves. See Appendix 10 for our interview guide.

DATA EXTRACTION AND ANALYSIS

We used a modified version of a grounded-theory methodology to analyze interview transcripts. The grounded-theory approach allowed us to organize and compare information on experiences across participants. This method consists of a repetitive process of obtaining, documenting, and analyzing responses while simultaneously collecting, analyzing, and comparing information.[74,75] We used the qualitative data analysis software program NVivo[6] to identify and interpret patterns in the data. The patterns we identified allowed us to highlight the impact of a cancer diagnosis, decision-making around proton beam therapy, and the impact of treatment on the people with cancer, family members, and caregivers we interviewed.

Results

DIAGNOSIS OF CANCER

Participants reported experiencing a variety of health issues prior to receiving a diagnosis of cancer. Often the symptoms would appear suddenly and escalate quickly. Some participants said they dismissed or ignored the symptoms until they became more severe. Participants reported eventually sensing something was wrong and urgently seeking care and advice from a variety of health care practitioners:

After presenting their symptoms at a hospital, participants reported they eventually received medical imaging to examine potential causes of the symptoms. This process could involve a great deal of waiting, causing anxiety and fear. Usually, it was after the medical imaging that participants were informed a tumour had been discovered. All participants reported their surprise and dismay at this news:

> *Waiting for imaging, it was kind of driving him nuts, because he would like to know [what was happening].*
>
> *We go wait to do the MRI, maybe five hours later, and what they had told us is, "If someone that's more high risk comes up, then [your daughter is] going to get bumped." And we're, like, "Okay, we have no other choice" because ... we've been going back and forth for two weeks [to get this test done].*
>
> *He had been throwing up and he had headaches, and so he had a CT scan in the middle of the night, and the next morning we had the head of neurosurgery in our room explaining that he had a tumour.*
>
> *Okay, so I was 49 years old and healthy. I was doing—I was doing yoga. I was in very good shape. I was doing a lot of things to stay in shape, and the last thing I ever thought that I would get into the—diagnosed with cancer.*

Many patients and caregivers spoke of the overwhelming nature of the diagnosis and the emotional toll it could take, especially when it was a young child receiving the diagnosis:

> *It takes such an emotional strain on everybody that is involved with the child's health.*
>
> *And then it was just a whirlwind. But it was crazy; from seven days prior, I had a perfectly healthy four-year-old, and then a week passes and he has cancer.*

Participants also commented on the vast amount of information coming at once. Some participants emphasized that there can be a delay prior to receiving specific details about the type and severity of the discovered cancer and the additional burden this delay can cause:

> *They told us earlier they were going to do biopsies to find out if [the cancer is] going to be malignant or benign, [to] look at the tumor. I kid you not, those five days were the longest five days of my life because we're just there in the hospital waiting, saying, "You know what, it's not even over yet."*
>
> *I was getting so anxious, wanting to know what was happening.*
>
> *It was the worst because—I know they're just doing their job, but— ... it doesn't matter what type of support they try and provide—the social services aspect—you get all these doctors ... when they're telling you everything, it's just like "why are you guys explaining [this] to me? I haven't gone to medical school ... I haven't been in this profession."*

INFORMATION ABOUT TREATMENT OPTIONS

Following the diagnosis of a tumour, participants reported they immediately sought information about next steps and treatment options. For this information, participants relied on the expertise of their health care teams. Depending on the type of tumour and its location, participants said their initial treatment could involve surgery, chemotherapy, radiation, or some combination of the three. Some participants underwent immediate surgery to remove the growth and/or obtain a biopsy sample to determine the precise type and severity of the cancer:

> *The next day, they're like, "Okay, her surgery may be another week." And then ... the surgeon, he said, "You know what? I'm going to do it [tomorrow]." So, the next day, they woke up at 6:00 and were going to do surgery right away. [And we said], "Okay, do what you have to do."*
>
> *So, by the time this was all caught, his small little four-year-old bladder was almost to the point of bursting, so they rushed him into surgery to get a catheter inserted and a biopsy of the tumour.*

Specific surgeries mentioned during interviews included those intended to remove tumours from the brain, spinal cord, and prostate. For some participants, surgery was not their preferred option due to fears of surgical complications and side effects. They sought information about alternative treatments which could include brachytherapy, photon therapy, or proton beam therapy:

> *The surgery—let's talk about surgery for a moment. The surgery not only causes impotence, okay, it also causes incontinence in a lot of cases. So, a lot of people are also having big urology problems and they can't control their bowels. They really have a lot of problems, not to mention other things that the surgery may damage ... But, you know, for a young guy that's devastating. So, I said, "Well, wait a minute, what's our alternatives? What are the alternatives to this?"*
>
> *So, I did fly down to New York and I said, "Well, okay, tell me brachytherapy," and they did: "Well, let's see, we take about 100 needles and stick them into the prostate, bigger than a walnut, that are radioactive." So, let's just put it this way: after I assessed that, I said, "Well, I'm not too thrilled about that."*

Other participants said their health care team recommended radiation treatment as the next step, rather than surgery, and gave them some information about why radiation was needed:

> *It was a meningioma, so it was on top of the brain, and I understand that it can come back, and [it] was explained to me that ... instead of having about an 85% chance of it coming back within 10 years ... with radiation I could reverse that to about 85% chance it would* not *come back.*

DECIDING ABOUT TREATMENT OPTIONS

During interviews, participants reported receiving different amounts of information about types of radiation treatment and the potential difference between photon therapy and proton beam therapy. Typically, for adult patients, health care providers did not present proton therapy as a viable option, even when the patient specifically inquired about it. Some participants were currently inquiring about proton beam therapy for future treatment, and they reported having to push for more information from their health care providers:

> *I never even heard about [proton beam therapy]. When asking about it at the hospital, I was told it is not available in Canada and [they] said it wasn't an option.*

> *Nobody is talking about proton. No one mentioned it to me at [the hospital] and when I mentioned it, they seem surprised that I knew about it. They didn't have a lot of knowledge about it.*

> *The first thing that somebody should have done with me [was to] hand me a piece of paper that said, "There are two options: photon, which we have in Canada, and proton, which we do not have in Canada. Here is some information on proton. Here's some people you can talk to. It's expensive. It might be worth it in your case." Just give people that information. Just disclose that to them, let them make their own decision. [It's] like it's a deep, dark secret.*

Some of these patients reported receiving information about proton therapy from colleagues in the United States or friends who urged them to seek out information about this type of treatment:

> *He was a best friend of a friend, who told me about [a US centre for proton beam therapy] and he said, "You know, he had this treatment and he can't say anything but good about it. You got to come out and check it out."*

> *So, within a half-hour of learning the word "medulloblastoma," the response from the surgeon at [a US hospital] was, "Well, the next step is proton."*

For adult patients who researched and sought proton beam therapy on their own, a key factor in their decision-making was the desire to avoid side effects and potential long-term health consequences from photon therapy:

> *I'm 74. I could live another 15 years, maybe a bit longer, but the quality of that 15 years is what concerns me. Who wants to live 15 years if he can't remember last week? ... But, you know, if you have a choice, if you have the resources, and I do, why wouldn't you go to Boston or MD Anderson or Mayo Clinic, or wherever and get this treatment?*

> *In a personal sense ... being able to enjoy your family, remember what your kids are doing and where they're struggling in their lives and how you helped them before and maybe how we can help them in the future, and things you've talked about. Your grandkids, enjoying your grandkids, enjoying your spouse—these are all things that get pretty badly impact[ed] by the loss of short-term memory, by the loss of an ability to think rationally, make decisions, and even physical disabilities that occur like balance and coordination, that kind of thing. So, when I started to study proton [beam therapy] ... it took me probably three or four days to come to the conclusion that was what I should have.*

> *The problem with photon radiation is that photon radiation delivers 100% impact equally throughout the body. And it's like a gun, you know, you aim it—or a ray gun if you want to call it that ... Just imagine a beam that fires out equally. It doesn't distinguish. I know they have the IMRTs [intensity-modulated radiation therapy], which they say is [a] narrow beam, focused beam. That just means it's either wider or broader.*

For young adults or caregivers of children newly diagnosed with a cancerous tumour, proton therapy was more commonly discussed. Health care providers would bring it up as a treatment option immediately or seemed more open when participants mentioned it:

> *When I was told about [the treatment] protocol, proton was what we were told it was—that was what was happening. It wasn't an option to go with the photon [therapy] that's available in Canada. Proton was the best option for him [their child].*

> *I'd never heard of proton radiation. I asked what it was ... he [the doctor] gave me a whole bunch of resources to decide if that's what I wanted to do. And after reading it all, it was clear that that's what I wanted to do.*

> *So, by the time I saw the medical oncologist ... it was a very, very brief meeting, but I said I would be asking for proton therapy and she said she'll bring it up to the radiation oncologist. But by the time I saw the radiation oncologist, I had a full annotated bibliography and I knew that for a pediatric indication and for, like we were looking at, there was no good reason not to refer [to the Out-of-Country Prior Approval Program for proton beam therapy] so I kind of didn't give them a choice.*

However, one interview participant mentioned that this readiness to refer families for out-of-country proton beam therapy may not be a common part of typical treatment pathways. Rather, it may reflect selection bias in those who volunteered to be interviewed:

> *I've spoken to other families who have subsequently gone through the same diagnosis here in Ottawa and it's not even raised or raised only peripherally.*

Typically, participants reported having thorough discussions with trusted health care providers about the differences between photon therapy and proton beam therapy, and these discussions helped make them more comfortable with the treatment decision-making. Naturally, parents of children described wanting the most effective treatment with fewest long-term consequences or side effects:

> *Well, the key difference, you know, for a pediatric brain tumour, the deficits are 15 or 20 years from now. Yes, so it's the preserving of cognitive function and the reducing the impacts on that, and so, it's really his ability to ... to have a job and [be] a productive citizen when he's older.*
>
> *So, when it was all being told to us, they actually had one of the radiation oncologists from the adult hospital here come over and speak to us and tell me the difference between photon versus proton, the benefits versus the concerns and everything. So, I was definitely well-informed ... and it seemed to be the clear-cut decision for us.*
>
> *So, how do we get the best type of radiation for her that's going to cause the least side effects of her growing up because we want her to have a normal life. Despite her having whatever she has. She's still deserves a regular life.*
>
> *You don't get those serious side effects during the treatment or after, for that matter, but there's some necrosis on occasion. But now that they're better at it and they've been doing it for over 20 years, that doesn't happen so much. So, there's a good argument for proton in that you do not have those serious side effects during the treatment.*

Some people we interviewed expressed surprise that a treatment presented by their physicians as the best option was simply not available in Canada. They felt, from the information they received and found on their own, that proton beam was a safer and more effective form of radiation therapy and were surprised it wasn't available without travelling to the United States:

> *Well, it did seem odd. I thought it was strange that we would have to go out of country to receive this treatment.*
>
> *And I'm like, "How can we ... if we know of technology to limit the side effects on what a developing child has to go through. Why not invest in that type of therapy?" For me, when they were explaining it to me, I couldn't understand ... why we didn't have this technology when it's known.*

ACCESSING PROTON BEAM THERAPY

Among the people we interviewed were caregivers of children who accessed proton beam therapy treatment in the United States through coordination with the Ontario Ministry of Health's Out-of-Country Prior Approval Program. While participants expressed gratitude and appreciation that this access exists, they also spoke about the challenge of absorbing the details, filling out paperwork, waiting for final approval, and preparing for time away from home. Given that they had just recently received the diagnosis of cancer and were told their child urgently needed treatment, this complicated process became even more stressful:

> *Because we don't know what's happening. We don't know. They didn't know and we didn't know. So it's just like, there has to be a better process for people that are going through this, for us to understand what we're getting ourselves into. You can't expect someone to just drop everything they're doing and just relocate right away without having a plan.*
>
> *As soon as it was told to us, I ... also had my mind at ease because they told us all of the options that are available to us to help us in that. But it's still daunting. You're still leaving the country for two full months. I couldn't—it was almost impossible for us to get traveller's insurance*

> *because my—I have a Stage 4 cancer kid. Who's going to cover him? So, as much as they eased my mind, it was still a lot of pressure and a lot of stress to get there.*

Some of theses participants expressed concern that their application would be rejected and commented on the anxiety this caused:

> *You know, the scary thing is the unknown, right? We can throw out all these papers, hope for the best, but you don't know what's going to happen three weeks from now ... One person can review [the application] and say, "No, I'm not going to do it. I'm not going to approve it." Or "Yeah, I can approve it." So it was just hard.*

Travelling away from home for an extended time also impacted patients and families. Participants described the challenges with coordinating schoolwork, employment, and the emotional burden of being away from friends and family. They expressed concerns they had, prior to leaving, about the overall cost of treatment and their secondary expenses. Often, it was not clear which costs they would have to bear and which would be covered by the Out-of-Country Program:

> *So, that was really scary. Originally, when I was told, I was like, "Oh, my God, I'm going to the States for a procedure for two months. It's going to be a ridiculous amount of money." I was told that it likely would have cost more than a quarter of a million dollars for us to go, had OHIP [the Ontario Health Insurance Plan] not covered it.*
>
> *I knew I would be gone for three months. I was in university, so that knocked off a whole semester for me and threw off my graduation.*
>
> *You know, honestly, so we were lucky in terms of our employers [who] were very flexible. We're both professionally employed, had lots of flexibility, and they provided us lots of room, so again, we were very lucky. We were going—we only had one child, so that made it easier.*

Adding to the complications, participants who accessed proton beam therapy through the Out-of-Country Program often mentioned they were unaware which US hospital they would be travelling to for treatment. They wouldn't find out until relatively close to treatment time, requiring some last-minute logistical arrangements:

> *We were told that we were going to be going. We didn't know where, whether it was between—we were given the option between Boston and then Florida. And we were told that all of the information had to be kind of sent to both places, upon approval we would know. And it was about two weeks, maybe not even two weeks, before we were set to leave when we were told, "Okay, this is where you're going. This is what's going to happen." And it was —it was very much a last-minute throw it all together ... to make sure that the hospital that we were going to and all of the travel and all that stuff was okay before we left. So, it was definitely last minute.*
>
> *And then it was approved I think on the Friday. So, the hospital found out that it was approved, that the hospital that approved it called us and said "Hey, you know what, you've been approved for the proton therapy. We need you to get on plane tomorrow."*
>
> *I think they had ... it was narrowed to Boston, St. Jude, and I think Jacksonville were the three that were kind of at the top of the list. I think those were the three.*

We also interviewed two adult patients who had the financial means and ability to travel to the United States and access proton beam therapy on their own, without needing the Out-of-Country Program to cover costs or arrange logistical details. These participants identified treatment centres based on their own criteria and sought the treatment on a schedule that was most convenient for them:

> *But the idea was to go to an academic centre where they had proton for at least 15 or 20 years and those were the two that came up. So I decided I'd rather go to Boston than Houston and contacted the hospital.*

RECEIVING PROTON BEAM THERAPY

Among the interviews we conducted, there was consensus that the experience of receiving proton beam therapy in the United States was relatively positive. Treatment sessions were typically five days per week and each session lasted less than an hour:

> *Honestly, it was like, once we got there it was so much easier ... the hospital picked us up from the airport. They took us straight to the hospital. We started going ahead and filled out the paperwork ... I guess because they go through this process so many times it was, it was just like we were going to a regular doctor checkup.*

Typically, participants described the treatment as painless, though they reported side effects such redness or burns, in some cases severe, and some mentioned loss of appetite and hair loss:

> *There is no sensation. There's no burning. There's no ... and I guess and that's the same here, I don't know, but over a period of a couple of weeks, I started to get some reddish splotchy kind of marks on my forehead.*

Most participants reported staying in the United States for a little over a month to complete the course of treatment. A few reported having to stay for rehabilitation services following treatment. For those who accessed treatment through the Out-of-Country Program, the program covered medical costs but family members incurred secondary costs such as meals outside the hospital, car rentals, or costs associated with activities when not in treatment:

> *There was material ... to support some of the living expenses, but you know, there were costs and we covered the travel, but again, we had the flexibility and the support of our employers, so the financial impact was not as great as it might have been, kind of uprooting yourself for 12 weeks or so.*

> *We were luckily able to come home, like the day after he finished treatment. They may have wanted us to stay a little bit longer just to follow-up with him, but OHIP was like, "Nope. You're done. That's all we're covering."*

> *But luckily all of our medical costs were covered, but just the cost of living ... luckily, there was food provided to us somewhat, but you still have to—you're eating out a lot. You're having to live life for two months away from all of the stuff that you have at home. So, you have to buy all this new stuff and you have to rent a car and you have to entertain yourself, so ... we often were, on the weekends when we didn't have to do treatment, we'd go off and do different things, so you're spending more money than you usually would at home just to entertain yourselves.*

Additionally, some participants commented on the emotional toll of being away from friends and family and the discomfort of being in an unknown city for weeks or months. Others reported that they tried to put a positive spin on the situation, using the necessity of being in a foreign city as an opportunity to explore and enjoy the time outside of treatment hours:

> *As soon as treatment started, though, that's kind of when real life it, after the two weeks of fun time, it was like, every day intense, it was overwhelming and [the patient] was definitely ready to be home and he was feeling it and it was hard to have to go through all of this stuff and then not go home to sleep in your own bed, you have to go into a Ronald McDonald House bed.*

> *It was such a simple treatment. I was in and out in 20 minutes ... I'd go in, they'd pin me down to the machine, wheel me in, I'd listen to some Beatles music or something they had playing. Then they'd say, "Alright, we're turning it on," and then they'd come back out two minutes later and move it around and do it again. And then they'd be helping me off to the bed, and I had the rest of the day to walk around and have lunch and dinner and shop and just have a great time in Boston.*

> *So, we were super anxious to get home, so the chances of us sticking around were not very likely. But we were able to come home and kind of follow-up with our home team and they were able to monitor him.*

PERSPECTIVES ON PROVIDING PROTON BEAM THERAPY IN ONTARIO

We asked interview participants for their thoughts about the potential impact if proton beam therapy were available in Canada, particularly in Ontario. Both adult patients who accessed proton beam therapy in the United States on their own provided their thoughts, as did parents of children who accessed proton beam therapy through the Out-of-Country Program. Generally, both types of participants were highly supportive of having this treatment provided in Ontario. They cited multiple reasons why it would be beneficial to have this technology locally available; some participants focused on their belief that proton beam therapy is more effective and has fewer long-term health concerns than photon therapy and, therefore, should be available to as many people as possible in Ontario:

> *So [with photon radiation], now you've created a patient. You may have cured the cancer for the prostate in particular in this case, but you've created other major issues. You put a guy into the system where the system is going to pay for a long time. Proton eliminates a lot [of] that, from what I've seen.*

> *I think the precision of pencil beam proton versus photon, which affects such a larger area in the body, could be huge. Even in future avoiding additional cancer, because the cancers that you can potentially get from the radiation that you're trying to treat your initially cancer from is unreal. So, if we can reduce the future side effects or future effects of the treatment that's trying to save your life, that would be ideal, in my opinion.*

> *An argument that says that ... for children, certainly, but in for adults as well, because of the lack of side effects and the fact that is not so necessary to treat these people for the next 5, 10, 15, 20 years for these other side effects that come about from photon, that our health care system saves money over the long term.*

Similarly, some participants were aware that proton beam therapy is currently not available to those without the financial means to pay for it in the United States or who do not meet the criteria for Ontario's out-of-country coverage. Having a proton beam facility in Ontario would increase access to this treatment:

> *Yes, I would be such a supporter of having a proton beam centre in Ontario, just the fact of having it not available to the people who might need it and maybe there's other cases, or people with adult cancer who might maybe not get that government approval to go to another country to get this treatment that might be life-saving to them.*

Other participants focused on how having proton beam therapy available in Ontario would ease the challenges—the emotional burdens, costs, and logistical issues—of travel to the United States and a lengthy stay for treatment far from home:

> *To be honest, I think it would make people's lives within Ontario so much easier because ... when you're going through the whole process and then you have to pick up and go somewhere, you don't have your family so no one's there. It was just us. We didn't have everybody that could provide that moral support.*
>
> *So it would have been so much easier. It would have to if it was in Ontario, it would have taken [the] financial burden off us because you know there's less things that we have to worry about ... Just because we're going away and they're accommodating us while we're there doesn't mean that we forget everything that we had; we still had bills that we had to pay. We had rent. We had car insurance, we wasted groceries ...*
>
> *I just say that we should have—the option should be there for Canadians. If I had any of my family [needing proton beam therapy], I mean I would figure out how to write that cheque.[to pay for it]*

Despite the general consensus about the value of having proton beam therapy available in Ontario, some participants also provided reasons why it could be less beneficial. One participant said travelling from their home for treatment would be just as difficult if proton beam therapy were available in Toronto as it would be in Boston. The location of a proton beam treatment facility in Ontario would therefore be a factor in its overall benefit in this case:

> *And if I think about it, it wouldn't be any different, honestly, going to Boston or going to Toronto from Ottawa.*

Another participant mentioned a concern about the expertise of medical professionals who would be providing proton beam therapy in Canada. Given the volume of patients using the treatment in the United States, they felt that perhaps the expertise that US professionals have attained would not be available here:

> *I'm of two minds. It would be very helpful if more kids can get access to it at a high level here, that would be excellent. But having seen the facilities in the US and the fact is that my son's doctor wrote the book, literally. So, I'm sure Canadian doctors would do well, but there's also something to be said about having access to the doctors who have, you know, the depth and breadth of experience with the patients.*

Despite these potential concerns, participants overall supported the idea of having proton beam therapy available to more Ontario patients by being provided locally.

Discussion

Through interviews with people with lived experience of proton beam therapy, we were able to explore the preferences, values, and decision-making around this treatment for cancer. We spoke with adult patients who have used proton beam therapy, parents of children who have used this treatment, as well as those who are still considering proton beam therapy for their cancer. This robust engagement allowed us to include and consider multiple perspectives on this technology.

Despite the emotional toll of receiving a cancer diagnosis and the multiple challenges of applying for and accessing proton beam therapy in the United States, all participants were supportive of and grateful for this treatment option. There was a consistent belief that proton beam therapy was more effective and had fewer long-term side effects than photon therapy. Additionally, while there were costs associated with travelling to the United States and the process could be complicated, participants expressed gratitude for the opportunity and potential funding to receive this treatment. However, this consensus may be due to a selection bias in those we were able to interview; we did not hear from any patients or families who may have halted the process of seeking proton beam therapy due to access or financial issues. Additionally, we did not hear from patients who were approved for proton beam therapy but did not receive it due to other circumstances.

Without proton beam therapy in Ontario, participants were only able to hypothesize about the potential impact of a local treatment centre. They provided perceptions of multiple benefits as well as several areas of concern, while overall supporting the concept of having this technology available in Ontario.

Conclusions

The discovery of a tumour and diagnosis of cancer can have a large, negative impact on patients and families. Participants who had received proton beam therapy expressed positive responses to the treatment, believing it safer and with fewer long-term side effects than photon therapy. Accessing proton beam therapy in the United States was often challenging, with logistical and emotional burdens. Overall, participants were supportive of having proton beam therapy available in Ontario.

Conclusions of the Health Technology Assessment

We reviewed recent evidence on the clinical effectiveness and safety of proton beam therapy to treat cancer in children and adults, compared with photon therapy. The apparent relative effectiveness and safety of proton beam therapy appeared to vary by the cancer or tumour type.

- Based on evidence of low to very low quality from predominantly observational studies, proton beam therapy may result in fewer toxicity events, but may result in similar overall survival and progression-free survival, when compared with photon therapy in children with brain tumours, and adults with esophageal cancer, head and neck cancer, and prostate cancer.
- Based on evidence of low to very low quality from predominantly observational studies and one randomized controlled trial, proton beam therapy may result in similar overall survival, progression-free survival, and toxicity events when compared with photon therapy in adults with brain tumours, breast cancer, gastrointestinal cancer, lung cancer, and ocular tumours.
- Based on evidence of moderate quality from one randomized controlled trial, proton beam therapy likely results in similar overall survival and progression-free survival, but fewer toxicity events, when compared with photon therapy in adults with liver cancer.

Several economic evaluations suggest that proton beam therapy may be cost-effective compared to photon therapy for specific types of cancer (i.e., pediatric brain tumours). However, in other types of cancer, the cost-effectiveness of proton beam therapy is unclear. We did not conduct a primary economic evaluation because of three limitations in the existing clinical evidence: it is available only for specific populations, not the full range of cancers we would want our model to represent; the quality of the evidence is generally low or very low, which would make our cost-effectiveness estimates very uncertain; and it does not reflect recent advances in proton beam technology.

Publicly funding proton beam therapy for cancers in Ontario over the next 5 years would result in net spending that varies by the number of rooms built. For example, the total budget impact of building and operating a four-room centre would be about $124.8 million over the next 5 years ($48,217 per patient), compared with current spending. This includes the cost avoided by not treating patients through the Out-of-Country Prior Approval Program (currently about $326,800 per patient) and by not using photon therapy for these patients. Additional offsets could be found by treating patients from other Canadian provinces. Although a one-room centre had the lowest budget impact, a four-room centre could treat more patients.

The discovery of a tumour and diagnosis of cancer can have a large, negative impact on patients and families. We interviewed 10 people affected by cancer who had received or were considering proton beam therapy. Participants who had received proton beam therapy felt positively about it and had pursued this treatment because they believe it to be safer than photon therapy. Accessing proton beam therapy in the United States was often challenging, with logistical and emotional burdens. Overall, participants were supportive of having proton beam therapy available in Ontario.

Abbreviations

CADTH	Canadian Agency for Drugs and Technologies in Health
CI	Confidence interval
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
ICER	Incremental cost-effectiveness ratio
IMRT	Intensity-modulated radiation therapy
IQ	Intelligence quotient
NICE	National Institute for Health and Care Excellence
OOC	Out-of-country
OR	Odds ratio
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
QALY	Quality-adjusted life-year
RCT	Randomized controlled trial
ROBIS	Risk of Bias in Systematic Reviews
RR	Relative risk
SBRT	Stereotactic body radiation therapy
SD	Standard deviation

Glossary

Adjuvant therapy	Additional cancer treatment given after the primary treatment to lower the risk that the cancer will come back.
Adverse event	An unexpected medical problem that happens during treatment for a health condition. In cancer care, adverse events may include late effects (see definition), also called toxicities.
Boost radiation	Additional treatment to increase the amount of radiation given to a specific area, to reduce the risk that the tumour will recur.
Brachytherapy	A type of radiation therapy in which radioactive material sealed in needles, seeds, wires, or catheters is placed directly into or near a tumor. Also called implant radiation therapy, internal radiation therapy, and radiation brachytherapy.
Curative intent	In cancer treatment, the intent to eliminate all cancerous cells and cure the disease.
Grade	This report uses *grade* in two ways, to classify (1) the severity of a cancer: low-grade cancers tend to grow and spread more slowly than high-grade cancer; and (2) the severity of an adverse event (also called late effect or toxicity): according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, adverse events are graded 1 (mild), 2 (moderate), 3 (severe), 4 (life-threatening), or 5 (death related to the adverse event).
Late effect	A health problem that occurs months or years after treatment has ended but may be caused by the cancer or cancer treatment. Late effects may include physical or mental health problems and secondary cancers.
Local control	Total disappearance of the primary tumour (the place where the cancer began) with no recurrence.
Local failure	Persistence or recurrence of the cancer in the primary tumour.
Radiation therapy	Also called radiotherapy, the use of high-energy radiation from x-rays, gamma rays, neutrons, protons, and other sources to kill cancer cells and shrink tumours. The radiation may come from a machine outside the body (external-beam radiation therapy) or from radioactive material placed in the body near the cancer cells (internal radiation therapy or brachytherapy).
Salvage therapy	Treatment given after the cancer has not responded to other treatments.
Stereotactic body radiation therapy	A type of external radiation therapy that uses special equipment to position the patient and precisely deliver radiation to a tumor. It is mostly used to treat brain tumors. The total dose of radiation is divided into several smaller doses given over several days.

Stereotactic radiosurgery	Using equipment similar to stereotactic radiotherapy, this treatment gives a single large dose of radiation to a tumor. It is used to treat brain tumors and other brain disorders that cannot be treated by regular surgery, and it is being studied for treatment of other types of cancer.

Appendices

Appendix 1: Literature Search Strategies

Clinical Evidence Search

Clinical Literature Search for Systematic Reviews
Search date: July 24, 2019
Databases searched: Ovid MEDLINE, Embase, Cochrane Database of Systematic Reviews, Health Technology Assessment Database, and NHS Economic Evaluation Database

Database: EBM Reviews - Cochrane Database of Systematic Reviews <2005 to July 18, 2019>, EBM Reviews - Health Technology Assessment <4th Quarter 2016>, EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>, Embase <1980 to 2019 Week 29>, Ovid MEDLINE(R) ALL <1946 to July 23, 2019>
Search Strategy:
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1 exp Neoplasms/ (7202062)
2 (cancer* or neoplas* or tumo?r* or carcinoma* or malignan* or metastatic* or metastas?s or oncolog*).ti,ab,kf. (7222150)
3 or/1-2 (9080770)
4 Proton Therapy/ (10440)
5 (proton therap* or protontherap*).ti,ab,kf. (7678)
6 (proton* adj2 (beam* or minibeam* or radiation* or irradiation* or radiotherap* or radio-therap* or chemoradiation* or chemoradiotherap*)).ti,ab,kf. (12838)
7 (hadron therap* or hadrontherap* or particle therap*).ti,ab,kf. (2668)
8 radiotherapy.fs. (489213)
9 Protons/ or proton*.ti. (114913)
10 and/8-9 (5113)
11 or/4-7,10 (21091)
12 3 and 11 (14444)
13 (Systematic Reviews or Meta Analysis).pt. (103064)
14 Systematic Review/ or Systematic Reviews as Topic/ or Meta-Analysis/ or exp Meta-Analysis as Topic/ or exp Technology Assessment, Biomedical/ (541540)
15 ((systematic* or methodologic*) adj3 (review* or overview*)).ti,ab,kf. (370239)
16 (meta analy* or metaanaly* or met analy* or metanaly* or meta review* or metareview* or health technolog* assess* or HTA or HTAs or (technolog* adj (assessment* or overview* or appraisal*))).ti,ab,kf. (376247)
17 (evidence adj (review* or overview* or synthes#s)).ti,ab,kf. (14203)
18 (review of reviews or overview of reviews).ti,ab,kf. (1303)
19 umbrella review*.ti,ab,kf. (540)
20 GRADE Approach/ (185)
21 ((pool* adj3 analy*) or published studies or published literature or hand search* or handsearch* or manual search* or ((database* or systematic*) adj2 search*) or reference list* or bibliograph* or relevant journals or data synthes* or data extraction* or data abstraction*).ti,ab,kf. (405647)
22 (medline or pubmed or medlars or embase or cinahl or web of science or ovid or ebsco* or scopus).ab. (419751)
23 cochrane.ti,ab,kf. (176998)
24 (meta regress* or metaregress*).ti,ab,kf. (17219)

25 (((integrative or collaborative or quantitative) adj3 (review* or overview* or synthes*)) or (research adj3 overview*)).ti,ab,kf. (23557)
26 (cochrane or (health adj2 technology assessment) or evidence report or systematic review*).jw. (61209)
27 ((comparative adj3 (efficacy or effectiveness)) or relative effectiveness or ((indirect or indirect treatment or mixed-treatment) adj comparison*)).ti,ab,kf. (41006)
28 or/13-27 (1115948)
29 12 and 28 (555)
30 29 use medall (174)
31 12 use coch,clhta,cleed (30)
32 or/30-31 (204)
33 exp Animals/ not Humans/ (17259097)
34 32 not 33 (203)
35 Case Reports/ or Comment.pt. or Editorial.pt. or Congress.pt. (3829162)
36 34 not 35 (198)
37 limit 36 to english language [Limit not valid in CDSR; records were retained] (185)
38 exp neoplasm/ (7196828)
39 (cancer* or neoplas* or tumo?r* or carcinoma* or malignan* or metastatic* or metastas?s or oncolog*).tw,kw. (7228692)
40 or/38-39 (9099975)
41 proton therapy/ (10440)
42 proton therapy system/ (159)
43 proton radiation/ (3970)
44 fast proton radiation/ (349)
45 *particle radiation/ (353)
46 (proton therap* or protontherap*).tw,kw,dv. (8044)
47 (proton* adj2 (beam* or minibeam* or radiation* or irradiation* or radiotherap* or radio-therap* or chemoradiation* or chemoradiotherap*)).tw,kw,dv. (13074)
48 (hadron therap* or hadrontherap* or particle therap*).tw,kw,dv. (2860)
49 radiotherapy.fs. (489213)
50 proton/ or proton*.ti. (116420)
51 and/49-50 (5124)
52 or/41-48,51 (22680)
53 40 and 52 (14899)
54 Systematic review/ or "systematic review (topic)"/ or exp Meta Analysis/ or "Meta Analysis (Topic)"/ or Biomedical Technology Assessment/ (535029)
55 (meta analy* or metaanaly* or health technolog* assess* or systematic review*).hw. (529620)
56 ((systematic* or methodologic*) adj3 (review* or overview*)).tw,kw. (381754)
57 (meta analy* or metaanaly* or met analy* or metanaly* or meta review* or metareview* or health technolog* assess* or HTA or HTAs or (technolog* adj (assessment* or overview* or appraisal*))).tw,kw. (403156)
58 (evidence adj (review* or overview* or synthes#s)).tw,kw. (14589)
59 (review of reviews or overview of reviews).tw,kw. (1491)
60 umbrella review*.tw,kw. (579)
61 ((pool* adj3 analy*) or published studies or published literature or hand search* or handsearch* or manual search* or ((database* or systematic*) adj2 search*) or reference list* or bibliograph* or relevant journals or data synthes* or data extraction* or data abstraction*).tw,kw. (430895)

62 (medline or pubmed or medlars or embase or cinahl or web of science or ovid or ebsco* or scopus).ab. (419751)
63 cochrane.tw,kw. (180588)
64 (meta regress* or metaregress*).tw,kw. (18126)
65 (((integrative or collaborative or quantitative) adj3 (review* or overview* or synthes*)) or (research adj3 overview*)).tw,kw. (24437)
66 (cochrane or (health adj2 technology assessment) or evidence report or systematic review*).jw. (61209)
67 ((comparative adj3 (efficacy or effectiveness)) or relative effectiveness or ((indirect or indirect treatment or mixed-treatment) adj comparison*)).tw,kw. (42651)
68 or/54-67 (1142962)
69 53 and 68 (619)
70 (exp animal/ or nonhuman/) not exp human/ (10363988)
71 69 not 70 (616)
72 Case Report/ or Comment/ or Editorial/ or conference abstract.pt. (9346597)
73 71 not 72 (510)
74 limit 73 to english language [Limit not valid in CDSR; records were retained] (486)
75 74 use emez (302)
76 37 or 75 (487)
77 76 use medall (160)
78 76 use coch (2)
79 76 use clhta (15)
80 76 use cleed (8)
81 76 use emez (302)
82 remove duplicates from 76 (344)

Clinical Literature Search for Randomized Controlled Trials
Search date: September 9, 2019
Databases searched: Ovid MEDLINE, Embase, Cochrane Central Register of Controlled Trials, and National Health Service (NHS) Economic Evaluation Database

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <August 2019>, EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>, Embase <1980 to 2019 Week 36>, Ovid MEDLINE(R) ALL <1946 to September 06, 2019>
Search Strategy:

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1 exp Neoplasms/ (7339672)
2 (cancer* or neoplas* or tumo?r* or carcinoma* or malignan* or metastatic* or metastas?s or oncolog*).ti,ab,kf. (7486676)
3 or/1-2 (9370852)
4 Proton Therapy/ (11016)
5 (proton therap* or protontherap*).ti,ab,kf. (8324)
6 (proton* adj2 (beam* or minibeam* or radiation* or irradiation* or radiotherap* or radio-therap* or chemoradiation* or chemoradiotherap*)).ti,ab,kf. (13488)
7 (hadron therap* or hadrontherap* or particle therap*).ti,ab,kf. (2776)
8 radiotherapy.fs. (492520)
9 Protons/ or proton*.ti. (117963)

10 and/8-9 (5188)
11 or/4-7,10 (22209)
12 3 and 11 (15290)
13 Clinical Trials as Topic/ (296550)
14 controlled clinical trials as topic/ (14611)
15 exp Randomized Controlled Trials as Topic/ (304554)
16 controlled clinical trial.pt. (184355)
17 randomized controlled trial.pt. (966547)
18 Pragmatic Clinical Trial.pt. (2248)
19 Random Allocation/ (201157)
20 Single-Blind Method/ (81511)
21 Double-Blind Method/ (415006)
22 Placebos/ (328649)
23 trial.ti. (766396)
24 (random* or sham or placebo* or RCT*1).ti,ab,kf. (3800683)
25 ((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,kf. (638983)
26 ((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,kf. (3502)
27 or/13-26 (4818932)
28 12 and 27 (1732)
29 12 use cctr (360)
30 28 use medall,cleed (489)
31 or/29-30 (849)
32 exp Animals/ not Humans/ (17517049)
33 31 not 32 (843)
34 Case Reports/ or Comment.pt. or Editorial.pt. or Congress.pt. (3860143)
35 33 not 34 (803)
36 limit 35 to english language (671)
37 limit 36 to yr="2019 -Current" (45)
38 exp neoplasm/ (7336970)
39 (cancer* or neoplas* or tumo?r* or carcinoma* or malignan* or metastatic* or metastas?s or oncolog*).tw,kw. (7498961)
40 or/38-39 (9396001)
41 proton therapy/ (11016)
42 proton therapy system/ (199)
43 proton radiation/ (4050)
44 fast proton radiation/ (349)
45 *particle radiation/ (357)
46 (proton therap* or protontherap*).tw,kw,dv. (8733)
47 (proton* adj2 (beam* or minibeam* or radiation* or irradiation* or radiotherap* or radio-therap* or chemoradiation* or chemoradiotherap*)).tw,kw,dv. (13767)
48 (hadron therap* or hadrontherap* or particle therap*).tw,kw,dv. (2966)
49 radiotherapy.fs. (492520)
50 proton/ or proton*.ti. (119411)
51 and/49-50 (5200)
52 or/41-48,51 (23821)
53 40 and 52 (15774)
54 53 use emez (10111)
55 (exp animal/ or nonhuman/) not exp human/ (10427000)

56 54 not 55 (9783)
57 Case Report/ or Comment/ or Editorial/ or conference abstract.pt. (9487552)
58 56 not 57 (5707)
59 limit 58 to english language (5274)
60 limit 59 to yr="2019 -Current" (408)
61 37 or 60 (453)
62 61 use medall (32)
63 61 use emez (408)
64 61 use cctr (13)
65 61 use cleed (0)
66 remove duplicates from 61 (415)

Economic Evidence Search

Economic Evaluation and Cost-Effectiveness Search
Search date: July 25, 2019
Databases searched: Ovid MEDLINE, Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Centre for Reviews and Dissemination (CRD) Health Technology Assessment Database, and National Health Service (NHS) Economic Evaluation Database

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <June 2019>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to July 24, 2019>, EBM Reviews - Health Technology Assessment <4th Quarter 2016>, EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>, Embase <1980 to 2019 Week 29>, Ovid MEDLINE(R) ALL <1946 to July 23, 2019>
Search Strategy:
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1 exp Neoplasms/ (7271778)
2 (cancer* or neoplas* or tumo?r* or carcinoma* or malignan* or metastatic* or metastas?s or oncolog*).ti,ab,kf. (7409604)
3 or/1-2 (9282657)
4 Proton Therapy/ (10482)
5 (proton therap* or protontherap*).ti,ab,kf. (7892)
6 (proton* adj2 (beam* or minibeam* or radiation* or irradiation* or radiotherap* or radio-therap* or chemoradiation* or chemoradiotherap*)).ti,ab,kf. (13115)
7 (hadron therap* or hadrontherap* or particle therap*).ti,ab,kf. (2709)
8 radiotherapy.fs. (489213)
9 Protons/ or proton*.ti. (116473)
10 and/8-9 (5113)
11 or/4-7,10 (21500)
12 3 and 11 (14795)
13 economics/ (252855)
14 economics, medical/ or economics, pharmaceutical/ or exp economics, hospital/ or economics, nursing/ or economics, dental/ (829651)

15 economics.fs. (421671)
16 (econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmacoeconomic* or pharmaco-economic*).ti,ab,kf. (885794)
17 exp "costs and cost analysis"/ (578844)
18 (cost or costs or costing or costly).ti. (263817)
19 cost effective*.ti,ab,kf. (325134)
20 (cost* adj2 (util* or efficacy* or benefit* or minimi* or analy* or saving* or estimate* or allocation or control or sharing or instrument* or technolog*)).ab,kf. (213623)
21 models, economic/ (12731)
22 markov chains/ (19796)
23 (decision adj1 (tree* or analy* or model*)).ti,ab,kf. (42283)
24 (markov or markow).ti,ab,kf. (47659)
25 quality-adjusted life years/ (39775)
26 (QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs).ti,ab,kf. (73438)
27 ((adjusted adj1 (quality or life)) or (willing* adj2 pay) or sensitivity analys*s).ti,ab,kf. (119676)
28 or/13-27 (2453441)
29 12 and 28 (1023)
30 29 use medall,cctr (333)
31 12 use coch,clhta,cleed (30)
32 or/30-31 (363)
33 exp Animals/ not Humans/ (17259105)
34 32 not 33 (362)
35 Congress.pt. (65598)
36 34 not 35 (357)
37 limit 36 to english language [Limit not valid in CDSR; records were retained] (329)
38 exp neoplasm/ (7266544)
39 (cancer* or neoplas* or tumo?r* or carcinoma* or malignan* or metastatic* or metastas?s or oncolog*).tw,kw. (7424623)
40 or/38-39 (9310025)
41 proton therapy/ (10482)
42 proton therapy system/ (159)
43 proton radiation/ (3970)
44 fast proton radiation/ (349)
45 *particle radiation/ (353)
46 (proton therap* or protontherap*).tw,kw,dv. (8301)
47 (proton* adj2 (beam* or minibeam* or radiation* or irradiation* or radiotherap* or radio-therap* or chemoradiation* or chemoradiotherap*)).tw,kw,dv. (13393)
48 (hadron therap* or hadrontherap* or particle therap*).tw,kw,dv. (2901)
49 radiotherapy.fs. (489213)
50 proton/ or proton*.ti. (117919)
51 and/49-50 (5124)
52 or/41-48,51 (23100)

53 40 and 52 (15278)
54 Economics/ (252855)
55 Health Economics/ or Pharmacoeconomics/ or Drug Cost/ or Drug Formulary/ (128672)
56 Economic Aspect/ or exp Economic Evaluation/ (453843)
57 (econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmacoeconomic* or pharmaco-economic*).tw,kw. (911523)
58 exp "Cost"/ (578844)
59 (cost or costs or costing or costly).ti. (263817)
60 cost effective*.tw,kw. (337455)
61 (cost* adj2 (util* or efficac* or benefit* or minimi* or analy* or saving* or estimate* or allocation or control or sharing or instrument* or technolog*)).ab,kw. (224684)
62 (decision adj1 (tree* or analy* or model*)).tw,kw. (46091)
63 (markov or markow).tw,kw. (51087)
64 Quality-Adjusted Life Years/ (39775)
65 (QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs).tw,kw. (77275)
66 ((adjusted adj1 (quality or life)) or (willing* adj2 pay) or sensitivity analys*s).tw,kw. (140385)
67 or/54-56 (741689)
68 53 and 67 (388)
69 (exp animal/ or nonhuman/) not exp human/ (10364002)
70 68 not 69 (387)
71 conference abstract.pt. (3489656)
72 70 not 71 (338)
73 limit 72 to english language [Limit not valid in CDSR; records were retained] (330)
74 73 use emez (264)
75 37 or 74 (593)
76 75 use medall (279)
77 75 use coch (2)
78 75 use cctr (25)
79 75 use clhta (15)
80 75 use cleed (8)
81 75 use emez (264)
82 remove duplicates from 75 (456)

Grey Literature Search

Systematic review and health technology assessment search performed on: July 18–24, 2019
Randomized controlled trials search performed on: September 10, 2019
Searches updated: December 3–5, 2019

Websites searched: HTA Database Canadian Repository, Alberta Health Evidence Reviews, BC Health Technology Assessments, Canadian Agency for Drugs and Technologies in Health (CADTH), Institut national d'excellence en santé et en services sociaux (INESSS), Institute of Health Economics (IHE), McGill University Health Centre Health Technology Assessment Unit,

Centre Hospitalier de l'Universite de Quebec-Universite Laval, Health Technology Assessment Database, Epistemonikos, National Institute for Health and Care Excellence (NICE), Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Centers, Australian Government Medical Services Advisory Committee, Council of Australian Governments Health Technologies, Centers for Medicare & Medicaid Services Technology Assessments, Institute for Clinical and Economic Review, Ireland Health Information and Quality Authority Health Technology Assessments, Washington State Health Care Authority Health Technology Reviews, Health Technology Wales, Oregon Health Authority Health Evidence Review Commission, Veterans Affairs Health Services Research and Development, Italian National Agency for Regional Health Services (AGENAS), Australian Safety and Efficacy Register of New Interventional Procedures -Surgical (ASERNIP-S), Belgian Health Care Knowledge Centre, Ludwig Boltzmann Institute for Health Technology Assessment, Ministry of Health Malaysia Health Technology Assessment Section, Swedish Agency for Health Technology Assessment and Assessment of Social Services, PROSPERO, EUnetHTA, Tufts Cost-Effectiveness Analysis Registry, SickKids Paediatric Economic Database Evaluation (PEDE) database, ClinicalTrials.gov

Keywords used:
proton beam, proton therapy, proton radiotherapy, proton radiation, hadron, particle therapy, proton, protons

Clinical results (included in PRISMA): 12
Economic results (included in PRISMA): 15
Ongoing health technology assessments (PROSPERO/EUnetHTA/MSAC): 5
Ongoing randomized controlled trials (ClinicalTrials.gov): 8

Appendix 2: Excluded Studies—Clinical Evidence

For transparency, we provide a list of systematic reviews that did not meet our inclusion criteria, along with the primary reason for exclusion.

Table A1: Excluded Systematic Reviews—Clinical Evidence

Citation	Primary Reason for Exclusion
Kamran SC, Light JO, Efstathiou JA. Proton versus photon-based radiation therapy for prostate cancer: emerging evidence and considerations in the era of value-based cancer care. Prostate Cancer Prostatic Dis. 2019.	Not systematic review
Lesueur P, Calugaru V, Nauraye C, Stefan D, Cao K, Emery E, et al. Proton therapy for treatment of intracranial benign tumours in adults: a systematic review. Cancer Treat Rev. 2019;72:56-64.	No risk of bias assessment
Mercado CE, Holtzman AL, Rotondo R, Rutenberg MS, Mendenhall WM. Proton therapy for skull base tumors: a review of clinical outcomes for chordomas and chondrosarcomas. Head Neck. 2019;41(2):536-41.	No risk of bias assessment
Spychalski P, Kobiela J, Antoszewska M, Blazynska-Spychalska A, Jereczek-Fossa BA, Hoyer M. Patient specific outcomes of charged particle therapy for hepatocellular carcinoma - a systematic review and quantitative analysis. Radiother Oncol. 2019;132:127-34.	No risk of bias assessment
Wu A, Jin MC, Meola A, Wong HN, Chang SD. Efficacy and toxicity of particle radiotherapy in WHO grade II and grade III meningiomas: a systematic review. Neurosurg Focus. 2019;46(6):E12.	PBT results not reported separately
Chan TY, Tang JI, Tan PW, Roberts N. Dosimetric evaluation and systematic review of radiation therapy techniques for early stage node-negative breast cancer treatment. Cancer Manag Res. 2018;10:4853-70.	No risk of bias assessment
Deshpande TS, Blanchard P, Wang L, Foote RL, Zhang X, Frank SJ. Radiation-related alterations of taste function in patients with head and neck cancer: a systematic review. Curr Treat Options Oncol. 2018;19(12):72.	Not specific to PBT
Goetz, G, Mitic, M. Carbon ion beam radiotherapy (CIRT) for cancer treatment: a systematic review of effectiveness and safety for 12 oncologic indications. HTA Project Report No. 101; 2018. Vienna: Ludwig Boltzmann Institute for Health Technology Assessment.	Not specific to PBT
Huynh M, Marcu LG, Giles E, Short M, Matthews D, Bezak E. Current status of proton therapy outcome for paediatric cancers of the central nervous system - analysis of the published literature. Cancer Treat Rev. 2018;70:272-88.	No risk of bias assessment
Igaki H, Mizumoto M, Okumura T, Hasegawa K, Kokudo N, Sakurai H. A systematic review of publications on charged particle therapy for hepatocellular carcinoma. Int J Clin Oncol. 2018;23(3):423-33.	No risk of bias assessment
Kammerer E, Guevelou JL, Chaikh A, Danhier S, Geffrelot J, Levy C, et al. Proton therapy for locally advanced breast cancer: a systematic review of the literature. Cancer Treat Rev. 2018;63:19-27.	No risk of bias assessment
Thurin E, Nystrom PW, Smits A, Werlenius K, Back A, Liljegren A, et al. Proton therapy for low-grade gliomas in adults: a systematic review. Clin Neurol Neurosurg. 2018;174:233-8.	No risk of bias assessment

Citation	Primary Reason for Exclusion
Verma V, Simone CB, 2nd, Mishra MV. Quality of life and patient-reported outcomes following proton radiation therapy: a systematic review. J Natl Cancer Inst. 2018;110(4):01.	No risk of bias assessment
Tseng YD, Cutter DJ, Plastaras JP, Parikh RR, Cahlon O, Chuong MD, et al. Evidence-based review on the use of proton therapy in lymphoma from the Particle Therapy Cooperative Group (PTCOG) Lymphoma Subcommittee. Int J Radiat Oncol Biol Phys. 2017;99(4):825-42.	Not systematic review
Verma V, Rwigema JM, Malyapa RS, Regine WF, Simone CB, 2nd. Systematic assessment of clinical outcomes and toxicities of proton radiotherapy for reirradiation. Radiother Oncol. 2017;125(1):21-30.	No risk of bias assessment
Doyen J, Bondiau PY, Benezery K, Thariat J, Vidal M, Gerard A, et al. Indications and results for protontherapy in cancer treatments. Cancer/Radiotherapie. 2016;20(6-7):513-8.	Not in English
Doyen J, Falk AT, Floquet V, Herault J, Hannoun-Levi JM. Proton beams in cancer treatments: clinical outcomes and dosimetric comparisons with photon therapy. Cancer Treat Rev. 2016;43:104-12.	Not systematic review
Husak AI, Bridge P. Proton therapy in craniospinal irradiation: a systematic review. J Radiother Pract. 2016;15(2):196-202.	No literature search dates
Matloob SA, Nasir HA, Choi D. Proton beam therapy in the management of skull base chordomas: systematic review of indications, outcomes, and implications for neurosurgeons. Br J Neurosurg. 2016;30(4):382-7.	No risk of bias assessment
Pennicooke B, Laufer I, Sahgal A, Varga PP, Gokaslan ZL, Bilsky MH, et al. Safety and local control of radiation therapy for chordoma of the spine and sacrum: a systematic review. Spine (Phila Pa 1976). 2016;41 Suppl 20:S186-S92.	No risk of bias assessment
Verma V, Lin SH, Simone CB, 2nd, Mehta MP. Clinical outcomes and toxicities of proton radiotherapy for gastrointestinal neoplasms: a systematic review. J Gastrointest Oncol. 2016;7(4):644-64.	No risk of bias assessment
Verma V, Mehta MP. Clinical outcomes of proton radiotherapy for uveal melanoma. Clin Oncol (R Coll Radiol). 2016;28(8):e17-27.	No risk of bias assessment
Verma V, Simone CB, 2nd, Wahl AO, Beriwal S, Mehta MP. Proton radiotherapy for gynecologic neoplasms. Acta Oncol. 2016;55(11):1257-65.	No risk of bias assessment
Verma V, Shah C, Mehta MP. Clinical outcomes and toxicity of proton radiotherapy for breast cancer. Clin Breast Cancer. 2016;16(3):145-54.	No risk of bias assessment
Qi WX, Fu S, Zhang Q, Guo XM. Charged particle therapy versus photon therapy for patients with hepatocellular carcinoma: a systematic review and meta-analysis. Radiother Oncol. 2015;114(3):289-95.	PBT results not reported separately
Dionisi F, Widesott L, Lorentini S, Amichetti M. Is there a role for proton therapy in the treatment of hepatocellular carcinoma? a systematic review. Radiother Oncol. 2014;111(1):1-10.	No risk of bias assessment
Wink KC, Roelofs E, Solberg T, Lin L, Simone CB, 2nd, Jakobi A, et al. Particle therapy for non-small cell lung tumors: where do we stand? a systematic review of the literature. Front Oncol. 2014;4:292.	No risk of bias assessment

Citation	Primary Reason for Exclusion
De Ruysscher D, Mark Lodge M, Jones B, Brada M, Munro A, Jefferson T, et al. Charged particles in radiotherapy: a 5-year update of a systematic review. Radiother Oncol. 2012;103(1):5-7.	Not systematic review
Wang Z, Nabhan M, Schild SE, Stafford SL, Petersen IA, Foote RL, et al. Charged particle radiation therapy for uveal melanoma: a systematic review and meta-analysis. Int J Radiat Oncol Biol Phys. 2013;86(1):18-26.	PBT results not reported separately
Ramaekers BL, Pijls-Johannesma M, Joore MA, van den Ende P, Langendijk JA, Lambin P, et al. Systematic review and meta-analysis of radiotherapy in various head and neck cancers: comparing photons, carbon-ions and protons. Cancer Treat Rev. 2011;37(3):185-201.	No risk of bias assessment
van de Water TA, Bijl HP, Schilstra C, Pijls-Johannesma M, Langendijk JA. The potential benefit of radiotherapy with protons in head and neck cancer with respect to normal tissue sparing: a systematic review of literature. Oncologist. 2011;16(3):366-77.	No risk of bias assessment
Amichetti M, Amelio D, Cianchetti M, Enrici RM, Minniti G. A systematic review of proton therapy in the treatment of chondrosarcoma of the skull base. Neurosurg Rev. 2010;33(2):155-65.	No risk of bias assessment
Grutters JP, Kessels AG, Pijls-Johannesma M, De Ruysscher D, Joore MA, Lambin P. Comparison of the effectiveness of radiotherapy with photons, protons and carbon-ions for non-small cell lung cancer: a meta-analysis. Radiother Oncol. 2010;95(1):32-40.	No risk of bias assessment
Pijls-Johannesma M, Grutters JP, Verhaegen F, Lambin P, De Ruysscher D. Do we have enough evidence to implement particle therapy as standard treatment in lung cancer? A systematic literature review. Oncologist. 2010;15(1):93-103.	No risk of bias assessment
Amichetti M, Cianchetti M, Amelio D, Enrici RM, Minniti G. Proton therapy in chordoma of the base of the skull: a systematic review. Neurosurg Rev. 2009;32(4):403-16.	No risk of bias assessment
Terasawa T, Dvorak T, Ip S, Raman G, Lau J, Trikalinos TA. Systematic review: charged-particle radiation therapy for cancer. Ann Intern Med. 2009;151(8):556-65.	No risk of bias assessment
Trikalinos TA, Terasawa T, Ip S, Raman G, Lau J. Particle beam radiation therapies for cancer. Technical Brief No. 1. (Prepared by Tufts Medical Center Evidence-based Practice Center under Contract No. HHSA-290-07-10055.) Rockville (MD): Agency for Healthcare Research and Quality. Revised November 2009. Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm.	Not systematic review
Pijls-Johannesma M, Grutters JP, Lambin P, Ruysscher DD. Particle therapy in lung cancer: where do we stand? Cancer Treat Rev. 2008;34(3):259-67.	No risk of bias assessment
Widesott L, Amichetti M, Schwarz M. Proton therapy in lung cancer: clinical outcomes and technical issues: a systematic review. Radiother Oncol. 2008;86(2):154-64.	No risk of bias assessment

Abbreviations: PBT, proton beam therapy.

Table A2: Excluded Primary Studies—Clinical Evidence

Citation	Primary Reason for Exclusion
Eekers DBP, Roelofs E, Cubillos-Mesias M, Niel C, Smeenk RJ, Hoeben A, et al. Intensity-modulated proton therapy decreases dose to organs at risk in low-grade glioma patients: results of a multicentric in silico ROCOCO trial. Acta Oncol. 2019;58(1):57-65.	Not outcome of interest
Ha B, Cho KH, Lee KH, Joung JY, Kim YJ, Lee SU, et al. Long-term results of a phase II study of hypofractionated proton therapy for prostate cancer: moderate versus extreme hypofractionation. Radiation Oncology. 2019;14(1):4.	Not comparator of interest
Jayadevappa R, Chhatre S, Gallo JJ, Wittink M, Morales KH, Lee DI, et al. Patient-centered preference assessment to improve satisfaction with care among patients with localized prostate cancer: a randomized controlled trial. J Clin Oncol. 2019;37(12):964-73.	Not intervention of interest
Palma G, Monti S, Xu T, Scifoni E, Yang P, Hahn SM, et al. Spatial dose patterns associated with radiation pneumonitis in a randomized trial comparing intensity-modulated photon therapy with passive scattering proton therapy for locally advanced non-small cell lung cancer. Int J Radiat Oncol Biol Phys. 2019;104(5):1124-32.	Not outcome of interest

Appendix 3. Summary of Identified Systematic Reviews and Health Technology Assessments Meeting Study Selection Criteria

Table A3: Characteristics of Systematic Reviews and Health Technology Assessments Considered for Inclusion

Author, Year, *Search End Date*	Population	Intervention	Comparator(s)	Outcomes	Study Types Included
Belgian Health Care Knowledge Centre, 2019[21] *July 2018*	Adults Low-grade glioma Primary sinonasal tumours Recurrent head and neck tumours Breast cancer in women Hepatocellular cancer Locally recurrent rectal cancer	PBT	Photon therapy (whether or not in combination with chemotherapy and/or surgery)	Overall survival Recurrence or progression-free survival Quality of life Local tumour control Secondary tumours Complications, side effects	SRs HTAs Single-arm studies
Washington State Health Care Authority, 2019[11] *December 2018*	Children and adults Primary or recurrent disease Cancer types (bone, brain, spinal, paraspinal tumours, breast, esophageal, gastrointestinal, gynecologic, head and neck, liver, lung, lymphomas, ocular, prostate, sarcomas, seminoma, thymoma, others) Noncancerous tumours	PBT (monotherapy, boost mechanism to conventional radiation, combination therapy with other treatment modalities)	Other radiation alternatives (IMRT, stereotactic radiation techniques, other external beam therapies, brachytherapy) Other treatment alternatives specific to each condition type treated (chemotherapy, immunotherapy, surgical procedures, other devices)	Overall survival/ disease-free survival All-cause and/or disease-related mortality Direct measures of tumour regression, control or recurrence Incidence of metastases Treatment-related harms Secondary malignancy risk due to radiation exposure	Comparative and noncomparative studies RCTs Quasi-RCTs Retrospective and prospective cohorts Case series

Author, Year, *Search End Date*	Population	Intervention	Comparator(s)	Outcomes	Study Types Included
Zhou et al, 2018[22] *May 2017*	Chordoma	Particle therapy (i.e., proton, carbon ion)	Photon therapy	3-year overall survival 5-year overall survival 10-year overall survival	Single-arm studies
Kim et al (CADTH), 2017[16] *June 2017*	Children and adults Any non-skin malignancies	PBT, in any form, alone or in combination with one or more concurrent or neoadjuvant non-PBT radiotherapy	External radiotherapy, of any type other than PBT Internal radiotherapy in all dosimetric methods alone or in combination with one or more concurrent or neoadjuvant non-PBT radiotherapy and/or radiation-free therapy	Tumour or cancer control or response Overall survival or mortality Recurrence- or progression-free survival Quality of life Acute and long-term toxicity Secondary malignancies	SRs
Malaysia Ministry of Health, 2017[24] *October 2017*	Patients with cancer	PBT	Conventional radiation therapy	Survival rate Reduction in progression of cancer Adverse events Complications	SRs RCTs HTAs
Leroy et al, 2016[25] *June 2015*	Children Skull base chondrosarcoma Skull base and (para) spinal chordoma Craniopharyngioma Ependymoma Esthesioneuroblastoma Ewing sarcoma CNS germinoma Low-grade glioma	PBT	Photon therapy Carbon ion therapy Surgery Chemotherapy	Clinical effectiveness Complications Side effects Secondary tumours	SRs RCTs Comparative studies Case series At least 5 patients received PBT

Author, Year, *Search End Date*	Population	Intervention	Comparator(s)	Outcomes	Study Types Included
	Medulloblastoma/primitive neuroectodermal tumours Nonresectable osteosarcoma Pelvic sarcoma (i.e., nonrhabdomyosarcoma, non-Ewing sarcoma) Pineal parenchymal tumours Retinoblastoma Rhabdomyosarcoma (Para) spinal "adult-type" soft tissue sarcoma				
US Department of Veteran Affairs, 2015[26] *December 2014*	Adults with any cancer type (except ocular)	PBT	Photon therapy Other treatment modalities	Survival Quality of life Functional capacity Local tumour control Delivery of planned chemotherapy and radiation regimens Toxicity Secondary malignancies	All study designs except letters, comments, and reviews
Patel et al, 2014[27] *April 2014*	Patients with malignant disease of either the paranasal sinuses (i.e., frontal, sphenoid, ethmoid, or maxillary) or the nasal cavity	Charged particle therapy (PBT reported as ad hoc subgroup analysis)	Photon therapy Other treatment modalities	Overall survival Disease-free survival Locoregional control Toxic effects Functional status Quality of life	All study designs except case studies

Author, Year, *Search End Date*	Population	Intervention	Comparator(s)	Outcomes	Study Types Included
Lodge et al, 2007[28] *January 2007*	Patients with cancer	Hadron therapy (PBT reported separately)	Conventional radiotherapy	Overall survival Cause-specific survival Local control Acute and late toxicities	All study designs with at least 20 patients and with a follow-up of at least 2 years
Olsen et al, 2007[29] *March 2006*	Patients with malign or benign tumour	PBT or in combination with surgery or external beam irradiation	Other treatment modalities	Overall survival Cancer-free survival Local control Acute and late adverse effects Functional measures Quality of life Biochemical markers Endocrine status	RCTs Cohort studies Case-control studies Cross-sectional studies Case series > 50 patients (except for papers in children)

Abbreviations: CADTH, Canadian Agency for Drugs and Technologies in Health; CNS, central nervous system; HTA, health technology assessment; PBT, proton beam therapy; RCT, randomized controlled trial; SR, systematic review.

Appendix 4: Critical Appraisal of Clinical Evidence

Table A4: Risk of Bias[a] Among Systematic Reviews (ROBIS Tool)

	Phase 2				Phase 3
Author, Year	Study Eligibility Criteria	Identification and Selection of Studies	Data Collection and Study Appraisal	Synthesis and Findings	Risk of Bias in the Review
Belgian Health Care Knowledge Centre, 2019[21]	Low	Low	Low	Low	Low
Washington State Health Care Authority, 2019[11]	Low	Low	Low	Low	Low
Zhou et al, 2018[22]	Low	High[b]	Low	Low	High
Kim et al (CADTH), 2017[16]	Low	Low	Low	Low	Low
Malaysian Ministry of Health, 2017[24]	Low	High[c]	High[d]	Low	High
Leroy et al, 2016[25]	Low	Low	Low	Low	Low
Belgian Health Care Knowledge Centre, 2015[6]	Low	Low	Low	Low	Low
US Department of Veteran Affairs, 2015[26]	Low	Low	Low	Low	Low
Patel et al, 2014[27]	Low	Low	Low	High[e]	High
Lodge et al, 2007[28]	Low	Low	Low	Low	Low
Olsen et el, 2007[29]	Low	High[f]	High[g]	Low	High

Abbreviations: CADTH, Canadian Agency for Drugs and Technologies in Health; ROBIS, Risk of Bias in Systematic Reviews.

[a]Possible risk of bias levels: low, high, unclear.

[b]Limited databases searched.

[c]Limited description on literature search and study selection.

[d]Unclear data extraction process.

[e]Data on harms were grouped as charged particle therapy and not specific to proton beam therapy.

[f]No description on exclusion and inclusion criteria.

[g]No description on data extraction process.

Appendix 5: Ongoing Studies—Clinical Evidence

Table A5: Ongoing Systematic Reviews on Proton Beam Therapy for Cancer

ID (Registry)	Title	Review Status	Expected Completion
CRD42019125202 (PROSPERO)	Effectiveness of proton therapy in comparison with standard and other types of radiation therapy in prostate cancer: an umbrella review	Review ongoing	July 2019
CRD42019146192 (PROSPERO)	Particles versus photons for the treatment of chordoma [Cochrane protocol]	Review ongoing	November 2020

Table A6: Ongoing Randomized Clinical Trials on Proton Beam Therapy for Cancer

ID (Registry)	Title	Outcomes	Expected Enrolment	Start Date – Expected Completion
NCT01629498 (Clinicaltrial.gov)	Image-guided intensity-modulated photon or proton beam radiation therapy in treating patients with stage II-IIIB non-small cell lung cancer	*Primary* Maximum tolerated dose Survival-free of grade 3 or greater toxicity Local progression-free survival *Secondary* Time to local failure Progression-free survival Overall survival Posterior probability of dose-limiting toxicity Change in selected biomarkers Change in symptom burden	100	September 2012 – September 2019
NCT00915005 (Clinicaltrial.gov)		*Primary* Time to treatment-related pneumonitis or local failure (whichever comes first)	250	June 2009 – June 2020

ID (Registry)	Title	Outcomes	Expected Enrolment	Start Date – Expected Completion
		Time to development CTCAE v 3.0 grade > 3 treatment-related pneumonitis		
NCT01512589 (Clinicaltrial.gov)	Phase IIB randomized trial of proton beam therapy versus intensity-modulated radiation therapy for the treatment of esophageal cancer	*Primary* Progressive-free survival Total toxicity burden (1 year)	180	April 2012 – April 2021
NCT02923570 (Clinicaltrial.gov)	A phase II randomized study of proton vs. photon beam radiotherapy in the treatment of unilateral head and neck cancer	*Primary* Number of patients with grade 2 or greater acute mucositis	132	October 2016 – October 2021
NCT01795300 (Clinicaltrial.gov)	Comparison of proton and carbon ion radiotherapy with advanced photon radiotherapy in skull base meningiomas: the PINOCCHIO trial	*Primary* Toxicity graded according to CTCAE *Secondary* Overall survival Progression-free survival Quality of life	80	May 2019 – May 2022
NCT03164460 (Clinicaltrial.gov)	A phase II randomized trial of stereotactic onco-ablative reirradiation versus conventionally fractionated conformal radiotherapy for patients with small inoperable head and neck tumours (SOAR-HN)	*Primary* Incidence of grade 3 or higher toxicity *Secondary* Local control Local failure-free survival Incidence of acute grade 3 or higher toxicity Incidence of late grade 3 or higher toxicity Progressive-free survival Overall survival Patient-reported outcomes	100	May 2017 – May 2023

ID (Registry)	Title	Outcomes	Expected Enrolment	Start Date – Expected Completion
NCT01893307 (Clinicaltrial.gov)	Randomized trial of intensity-modulated proton beam therapy (IMPT) versus intensity-modulated photon therapy (IMRT) for the treatment of oropharyngeal cancer of the head and neck	*Primary* Rates and severity of late grade 3–5 toxicity *Secondary* Progression-free survival	360	August 2013 – August 2024
NCT02731001 (Clinicaltrial.gov)	Proton therapy to reduce acute normal tissue toxicity in locally advanced non-small-cell lung cancer (PRONTOX)	*Primary* Occurrence of acute and intermediate radiation induced side effects	98	August 2016 - Oct 2024
NCT01993810 (Clinicaltrial.gov)	Comparing photon therapy to proton therapy to treat patients with lung cancer	*Primary* Overall survival *Secondary* Progressive-free survival Adverse events	330	February 2014 – December 2025
NCT02179086 (Clinicaltrial.gov)	Dose-escalated photon IMRT or proton beam radiation therapy versus standard-dose radiation therapy and temozolomide in treating patients with newly diagnosed glioblastoma	*Primary* Overall survival *Secondary* Progression-free survival Change in perceived cognitive function Change in neurocognitive function Incidence of treatment-related toxicity Change in CD4 lymphopenia count Differentiation between tumor progression and pseudo-progression	606	October 2014 – May 2026
NCT01617161 (Clinicaltrial.gov)	Proton therapy vs. image-modulated radiation therapy for low or intermediate risk prostate cancer (PARTIQOL)	*Primary* Reduction in mean EPIC bowel scores *Secondary* Disease-specific quality of life	400	July 2012 – December 2026

ID (Registry)	Title	Outcomes	Expected Enrolment	Start Date – Expected Completion
		Cost-effectiveness Association between radiation dose and bowel, urinary, and erectile function Biomarkers of prostate cancer behaviour in response to radiotherapy Long-term (10-year) survival and development of late effects		
NCT03186898 (Clinicaltrial.gov)	Radiation therapy with protons or photons in treating patients with liver cancer	*Primary* Overall survival *Secondary* Progression-free survival Local progression Incidence of adverse events Fatigue Correlation of hepatocyte growth factor biomarker with overall survival, progression-free survival and fatigue Quality-adjusted survival Overall quality of life	186	June 2017 – August 2027
NCT03829033 (Clinicaltrial.gov)	Photon therapy versus proton therapy in early tonsil cancer (ARTSCAN V)	*Primary* Acute side effects Late side effects (5 years)	100	January 2019 – January 2028
NCT03180502 (Clinicaltrial.gov)	Proton beam or intensity-modulated radiation therapy in preserving brain function in patients with IDH mutant grade II or III glioma	*Primary* Change in cognition *Secondary* Change in quality of life Change in symptoms	120	August 2017 – January 2030

ID (Registry)	Title	Outcomes	Expected Enrolment	Start Date – Expected Completion
		Cognition Incidence of adverse events Local control Overall survival Progression-free survival		
NCT03801876 (Clinicaltrial.gov)	Phase III randomized trial of proton beam therapy versus intensity modulated photon radiotherapy for the treatment of esophageal cancer (NRG GI 006)	*Primary* Overall survival Cardiopulmonary adverse events *Secondary* Pathologic response rate Grade 4 lymphopenia during chemoradiation Lymphocyte count Locoregional failure Distant metastatic free survival (8 years) Progression-free survival (8 years) Quality-adjusted life years Cost-benefit economic analysis of treatment	300	March 2019 – February 2032
NCT02603341 (Clinicaltrial.gov)	Pragmatic randomized trial of proton vs. photon therapy for patients with non-metastatic breast cancer: a Radiotherapy Comparative Effectiveness (RADCOMP) Consortium Trial	*Primary* Major cardiovascular events *Secondary* Disease control Quality of life Radiation dose and cardiac toxicity Long-term survival (15 years)	1,278	February 2016 – November 2032

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; EPIC, Expanded Prostate Cancer Index Composite; IMRT, intensity modulated radiation therapy.

Table A7: Ongoing Nonrandomized Comparative Clinical Studies on Proton Beam Therapy for Cancer

ID (Registry)	Title	Outcomes	Expected Enrolment	Started Date – Expected Completion
NCT01659203 (Clinicaltrial.gov)	Proton or photon radiotherapy for retroperitoneal sarcomas	*Primary* Maximum tolerated dose Local control rate *Secondary* Overall survival Pathologic response Tumour response Progress-free survival	80	December 2012 – August 2020
NCT01494155 (Clinicaltrial.gov)	Short course radiation therapy with proton or photon beam, capecitabine and hydroxychloroquine for resectable pancreatic cancer	*Primary* Progression-free survival *Secondary* Pathologic response rate Overall survival Toxicity/adverse events Surgical morbidity Postoperative mortality Biomarkers Pathologic down staging Local control Quality of life Utilization of health services	50	December 2011 – December 2020
NCT02725840 (Clinicaltrial.gov)	Breast cancer lung late effects (BELLE)	*Primary* Lower dose limit for measurable change in number of small blood vessels Vessel number change dose response relationship Recovery of number of small blood vessels	55	May 2016 – April 2021

ID (Registry)	Title	Outcomes	Expected Enrolment	Started Date – Expected Completion
		Temporal patterns of blood cytokines following radiation exposure Correlate change in number of small blood vessels *Secondary* Incidence of long-term clinical grade 2 and higher radiation toxicity to the lung Overall survival		
NCT03561220 (Clinicaltrial.gov)	A prospective comparative study of outcomes with proton and photon radiation in prostate cancer	*Primary* Bowel, urinary and sexual dysfunction EPIC domains *Secondary* Grade 2 or higher for each adverse event assessed by CTCAE Grade 2 or higher for each adverse event assessed by PRO-CTCAE Freedom from biochemical progression using PSA results	3,000	July 2018 – April 2023
NCT02766686 (Clinicaltrial.gov)	Preference-based comparative study on definitive radiotherapy of prostate cancer with protons (PROTOCHOICE-P)	*Primary* Cumulative incidence of moderate/severe (grade 2 or higher by CTCAE combined for genitourinary and gastrointestinal) side effects	146	September 2016 – August 2023
NCT04066465 (Clinicaltrial.gov)	Neurocognitive function after proton therapy in children and adolescents (ELBE-PROKIDS) Comparators: no radiotherapy; healthy children	*Primary* Neurophysiological correlates of cognitive control Quality of life parameters *Secondary* Dose-volume parameters to normal tissues	90	September 2019 – March 2024

ID (Registry)	Title	Outcomes	Expected Enrolment	Started Date – Expected Completion
NCT01586767 (Clinicaltrial.gov)	Intensity-modulated or proton radiation therapy for sinonasal malignancy	*Primary* Local control rates *Secondary* Vision preservation Regional control Survival Quality of life Patterns of tumour relapse Local control Neurocognitive function	90	July 2011 – July 2024
NCT01352429 (Clinicaltrial.gov)	Mild hypofractionation with proton therapy or intensity-modulated radiation therapy for intermediate risk prostate cancer	*Primary* Number of participants with adverse events Acute toxicity *Secondary* Late toxicity Biochemical/clinical progression-free survival	200	August 2009 – December 2025
NCT02824731 (Clinicaltrial.gov)	Comparison of proton and photon radiotherapy of brain tumours (ProtoChoice-Hirn)	*Primary* Late toxicity (1-year) *Secondary* Local tumour control Overall survival Acute toxicity Late toxicity (2-year)	346	July 2016 – July 2026

ID (Registry)	Title	Outcomes	Expected Enrolment	Started Date – Expected Completion
NCT03270072 (Clinicaltrial.gov)	The differential impact of proton beam irradiation versus conventional radiation on organ-at-risk in stage II-III breast cancer patients	*Primary* Change in global longitudinal strain *Secondary* Change in left ventricular ejection fraction Radiation-induced lung parenchymal changes Incidence of thyroid dysfunction Incidence of ipsilateral arm lymphedema Severity of ipsilateral arm lymphedema Ipsilateral breast/chest wall cosmesis	100	October 2017 – July 2027

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; EPIC, Expanded Prostate Cancer Index Composite; PSA, prostate specific antigen.

Table A8: Ongoing Nonrandomized Noncomparative Clinical Studies on Proton Beam Therapy in Children With Cancer

ID (Registry)	Title	Outcomes	Expected Enrolment	Started Date – Expected Completion
NCT01180881 (Clinicaltrial.gov)	Neurobehavioral functioning in pediatric brain tumour patients after proton beam radiation treatment	*Primary* Executive functions Behaviour functions Adaptive skills	150	October 2009 – August 2019
NCT00592592 (Clinicaltrial.gov)	Proton radiation for the treatment of pediatric rhabdomyosarcoma	*Primary* Late toxicity *Secondary* Acute toxicity Dosimetric comparison Local control	110	October 2004 – June 2020

ID (Registry)	Title	Outcomes	Expected Enrolment	Started Date – Expected Completion
NCT02842723 (Clinicaltrial.gov)	Management of pediatric craniopharyngioma by a combination of partial surgical resection and proton therapy	*Primary* Local control *Secondary* Visual pathway tolerance	33	March 2010 – December 2020
NCT01502150 (Clinicaltrial.gov)	Data collection of normal tissue toxicity for proton therapy for pediatrics	*Primary* Acute toxicity Late toxicity	798	June 2005 – June 2021
NCT00592293 (Clinicaltrial.gov)	Proton radiation for the treatment of pediatric bone and non-rhabdomyosarcoma soft tissue sarcomas	*Primary* Acute and late toxicities Local control *Secondary* Dosimetric comparison	70	September 2006 – September 2021
NCT00105560 (Clinicaltrial.gov)	Proton beam radiation therapy in treating young patients who have undergone biopsy or surgery for medulloblastoma or pineoblastoma	*Primary* Ototoxicity *Secondary* Endocrine dysfunction Change in neurocognitive outcomes Progression-free survival Overall survival	59	May 2002 – December 2021
NCT01067196 (Clinicaltrial.gov)	Outcomes study of late effects after proton radiation for pediatric tumors of the brain, head and neck (CN01)	*Primary* Late effects *Secondary* Local control Progression-free survival Overall survival Cause-specific survival	500	February 2010 – May 2022

ID (Registry)	Title	Outcomes	Expected Enrolment	Started Date – Expected Completion
NCT01288235 (Clinicaltrial.gov)	Proton radiotherapy for pediatric brain tumors requiring partial brain irradiation	*Primary* Endocrine dysfunction Neurocognitive sequalae *Secondary* Disease control Acute effects Auditory function	100	January 2011 – September 2022
NCT02608762 (Clinicaltrial.gov)	Neurobehavioral outcomes and quality of life in pediatric patients with brain or head/neck tumours receiving proton or photon radiotherapy	*Primary* Change in intellectual function *Secondary* Neurobehavioural function Psychosocial adjustment	72	September 2014 – December 2022
NCT02644993 (Clinicaltrial.gov)	Registry for analysis of quality of life, normal organ toxicity and survival of pediatric patients treated with proton therapy	*Primary* Quality of life *Secondary* Adverse events	400	November 2015 – November 2025
NCT01696721 (Clinicaltrial.gov)	Proton and photon consortium registry (PPCR): a multi-centre registry of pediatric patients treated with radiation therapy	*Primary* Establish registry *Secondary* Describe patterns of care Describe patterns of follow-up Acute effects Late effects Establish a cohort of photon-treated patients (as controls)	5,000	July 2012 – December 2025
NCT03223766 (Clinicaltrial.gov)	Evaluation of proton therapy in pediatric cancer patients	*Primary* Incidence of radiation-associated nonhematologic toxicities	1,000	August 2017 – July 2037

Appendix 6: Results of Applicability Checklist for Studies Included in the Economic Literature Review

Table A9: Assessment of the Applicability of Studies Evaluating the Cost-Effectiveness of Proton Beam Therapy

Author, Year, Country of Publication	Is the study population similar to the question?	Are the interventions similar to the question?	Is the health care system studied sufficiently similar to Ontario?	Were the perspectives clearly stated? If yes, what were they?	Are all direct effects included? Are all other effects included where they are material?[a]	Are all future costs and outcomes discounted? If yes, at what rate?	Is the value of health effects expressed in terms of quality-adjusted life-years?	Are costs and outcomes from other sectors fully and appropriately measured and valued?[b]	Overall Judgment[c]
Austin et al, 2019, Australia[41]	Yes	Yes	No	Unclear	Yes	Yes, 3%	Yes	No	Partially applicable
Fernandes et al, 2019, Brazil[46]	Yes	Yes	No	Yes, health system	Yes	Yes, 3%	Yes	No	Partially applicable
Grutters et al, 2010, Netherlands[50]	Yes	Yes	No	Yes, health care	Partially	Yes, 4%;1.5%	Yes	No	Partially applicable
Hirano et al, 2014, Japan[45]	Yes	Yes	No	Yes, health care payer	Yes	Yes, 3%	Yes	No	Partially applicable
Konski et al, 2007, USA[54]	Yes	Yes	No	Yes, payer (Medicare)	Yes	Yes, 3%	Yes	No	Partially applicable
Leung and Chan, 2017, Taiwan[40]	Yes	Yes	No	Yes, payer (health care system)	Yes	Yes, 3%	Yes	No	Partially applicable
Lundkvist et al, 2005, Sweden[42]	Yes	Yes	No	Yes, societal	Yes	Yes, 3%	Yes	Yes	Partially applicable
Lundkvist et al, 2005, Sweden[48]	Yes	Yes	No	Yes, societal	Yes	Yes, 3%	Yes	Yes	Partially applicable

Author, Year, Country of Publication	Is the study population similar to the question?	Are the interventions similar to the question?	Is the health care system studied sufficiently similar to Ontario?	Were the perspectives clearly stated? If yes, what were they?	Are all direct effects included? Are all other effects included where they are material?[a]	Are all future costs and outcomes discounted? If yes, at what rate?	Is the value of health effects expressed in terms of quality-adjusted life-years?	Are costs and outcomes from other sectors fully and appropriately measured and valued?[b]	Overall Judgment[c]
Lundkvist et al, 2005, Sweden[51]	Yes	Yes	No	Yes, societal	Partially	Yes, 3%	Yes	Yes	Partially applicable
Mailhot Vega et al, 2013, USA[43]	Yes	Yes	No	Yes, societal	Yes	Yes, 3%	Yes	No	Partially applicable
Mailhot Vega et al, 2015, USA[44]	Yes	Yes	No	Yes, health care payer	Partially	Yes, 3%	Yes	No	Partially applicable
Mailhot Vega et al, 2016, USA[52]	Yes	Yes	No	Yes, societal	Partially	Yes, 3%	Yes	Yes	Partially applicable
Moriarty et al, 2015, USA[53]	Yes	Yes	No	Yes, provider	Partially	Yes, 3%	Yes	No	Partially applicable
Parthan et al, 2012, USA[55]	Yes	Yes	No	Yes, payer and societal	Yes	Yes, 3%	Yes	Yes	Partially applicable
Ramaemakers et al, 2013, Netherlands[47]	Yes	Yes	No	Yes, health care system	Partially	Yes, 4%;1.5%	Yes	No	Partially applicable
Sher et al, 2018, USA[49]	Yes	Yes	No	Yes, payer and societal	Partially	Yes, 3%	Yes	Yes	Partially applicable

Note: Response options for all items were "yes," "partially," "no," "unclear," and "NA" (not applicable).

[a]"No" or "partially" were selected if other direct effects that may be expected were not included

[b]"Yes" was chosen if a societal perspective was chosen. "No" or "partially" were selected if costs that may be expected were not assessed

[c]Overall judgment may be "directly applicable," "partially applicable," or "not applicable."

Appendix 7: Budget Impact Analysis Results, Scenarios With Higher Costs for Photon Therapy

Table A10: Budget Impact Analysis Results, Scenario Analysis for a Four-Room Proton Beam Therapy Centre, Varying the Cost of Photon Therapy

	Budget Impact, $ Million[a]					
Scenario	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Total**
Current Scenario						
PBT funded through OOC	3.9	3.9	4.2	4.2	4.6	20.9
Photon RT in Ontario for remaining patients[b]	3.1	6.4	9.6	13.0	13.0	45.1
Current scenario total	7.1	10.3	13.9	17.2	17.5	66.1
Scenario 6a (4-Room PBT Centre vs. Current Scenario With Higher Photon RT Costs)						
Capital	127.8	0	0	0	0	127.8
Operating	2.4	8.5	12.3	15.6	15.6	54.5
Scenario 6a total	130.2	8.5	12.3	15.6	15.6	182.3
Budget impact	**123.1**	**−1.8**	**−1.7**	**−1.6**	**−1.9**	**116.2**
Cost per patient						**48,217[c]**

Abbreviations: OOC, Out-of-Country Prior Approval Program; PBT, proton beam therapy; RT, radiotherapy.
[a]In 2019 Canadian dollars.
[b]Assumes RT cost is higher than in our reference case.
[c]Not million.
Note: numbers may be inexact due to rounding.

Table A11: Budget Impact Analysis Results, Scenario Analysis for a One-Room Proton Beam Therapy Centre, Varying the Cost of Photon Therapy

	Budget Impact, $ Million[a]					
	Year 1	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Total**
Current Scenario						
PBT funded through OOC	3.9	3.9	4.2	4.3	4.6	20.9
Photon RT in Ontario for remaining patients[b]	3.1	3.1	3.1	3.1	3.1	15.6
Total current scenario	7.1	7.1	7.4	7.4	7.7	36.5
Scenario 6b (1-Room PBT Centre vs. Current Scenario With Higher Photon RT Costs)						
Capital costs	32.4	0	0	0	0	32.4
Operational costs	2.4	4.8	4.8	4.8	4.8	21.6
Total scenario 6b	34.8	4.8	4.8	4.8	4.8	54.0
Budget impact	**27.8**	**−2.2**	**−2.6**	**−2.6**	**−2.9**	**17.5**
Cost per patient						**40,028[c]**

Abbreviations: OOC, Out-of-Country Prior Approval Program; PBT, proton beam therapy; RT, radiotherapy.
[a]In 2019 Canadian dollars.
[b]Assumes proton therapy cost is higher than in our reference case.
[c]Not million.
Note: numbers may be inexact due to rounding.

Appendix 8: Budget Impact Analysis Results, Scenarios Substituting New Photon Linear Accelerators With Proton Beam Therapy Centres

Table A12: Budget Impact of Substituting Four New, Planned Photon Linear Accelerators With a Four-Room Proton Beam Therapy Centre

	Budget Impact, $ Million[a]					
	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Current Scenario						
PBT funded through OOC	3.9	3.9	4.2	4.2	4.6	20.9
Photon RT in Ontario for remaining patients	2.5	5.2	7.8	10.5	10.5	36.5
Capital investment of new photon linear accelerators	30.0	0	0	0	0	30.0
Current scenario total	36.5	9.1	12.1	14.7	15.1	87.5
Scenario 7a: 4-Room PBT Centre, Replacing 4 New Photon Linear Accelerators						
Capital	127.8	0	0	0	0	127.8
Operating	2.4	8.5	12.3	15.6	15.6	54.5
Total scenario 7a	130.2	8.5	12.3	15.6	15.6	182.3
Budget impact	**93.7**	**–0.57**	**0.19**	**0.88**	**0.56**	**94.8**
Cost per patient						**48,217[b]**

Abbreviations: OOC, Out-of-Country; PBT, proton beam therapy; RT, radiotherapy.
[a]In 2019 Canadian dollars.
Note: numbers may be inexact due to rounding.

Table A13: Budget Impact of Substituting One New, Planned Photon Linear Accelerator With a One-Room Proton Beam Therapy Centre

	Budget Impact, $ Million[a]					
	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Current Scenario						
PBT through OOC	3.9	3.9	4.27	4.3	4.6	20.9
Photon RT in Ontario for remaining patients	2.5	2.5	2.5	2.5	2.5	12.6
Capital investment, new photon linear accelerators	7.5	0	0	0	0	7.5
Total current scenario	14.0	6.5	6.8	6.8	7.1	41.1
Scenario 7b: 1-Room PBT Centre, Replacing 1 New Photon Linear Accelerator						
Capital	32.4	0	0	0	0	32.4
Operating	2.4	4.8	4.8	4.8	4.8	21.6
Total scenario 7b	34.8	4.8	4.8	4.8	4.8	54.0
Budget impact	**20.9**	**–1.7**	**–2.0**	**–2.0**	**–2.2**	**13.0**
Cost per patient						**40,028**

Abbreviations: OOC, Out-of-Country; PBT, proton beam therapy; RT, radiotherapy.
[a]In 2019 Canadian dollars.
Note: numbers may be inexact due to rounding.

Appendix 9: Letter of Information

LETTER OF INFORMATION

Health Quality Ontario* is conducting a review of **Proton Beam Therapy (PBT),** a type of radiotherapy for the treatment of certain cancers. The purpose is to understand whether this therapy should be more broadly funded in Ontario.

An important part of this review involves speaking to patients and family members of those who may have experience with Proton Beam Therapy, or who may have attempted to access it. Our goal is always to make sure the lived experience of individuals and families are considered in the funding recommendations for this test.

WHAT DO YOU NEED FROM PARTICIPANTS?

- ✓ 20–30 minutes of time for a phone or in-person interview to hear about their experiences
- ✓ Permission to audio- (not video-) record the interview

WHAT PARTICIPATION INVOLVES

If a participant agrees to share their experiences, they will be asked to have an interview with Health Quality Ontario staff. The interview will likely last 20–30 minutes. It will be held in a private location or over the telephone. With consent, the interview will be audio-recorded. The interviewer will ask questions about perspectives of radiotherapy treatments, decision-making and more general thoughts about the potential use of Proton Beam Therapy in Ontario.

Participation is voluntary. Those who volunteer may decide not to participate, refuse to answer any questions or withdraw before the interview. Withdrawal will in no way affect the care received.

CONFIDENTIALITY

All information collected for the review will be kept confidential and privacy will be protected except as required by law. The results of this review will be published, however no identifying information will be released or published. Any records containing information from the interview will be stored securely.

RISKS TO PARTICIPATION:

There are no known physical risks to participating. Some participants may experience discomfort or anxiety after speaking about their lived experience. If this is the case, participants can speak to our staff.

If you have any questions, please contact Health Quality Ontario staff:

* Health Quality Ontario is now part of Ontario Health.

Appendix 10: Interview Guide

Introduction
Explain purpose of Health Quality Ontario,* health technology assessment process, and purpose of interview

Lived Experience With Cancer and Diagnosis
How was diagnosis of cancer made?
Was there a change in day-to-day routine or impact on quality of life?
What is the impact on family?

Therapies
What are your experiences with other therapies and cancer services?
Process of decision-making in choosing therapies? Was it difficult to weigh potential benefits and risks when deciding which therapies to choose?
Availability of information surrounding services – was there enough?
Barriers to accessing therapies?

Proton Beam Therapy
Information around proton beam therapy
What was the process and factors in the decision-making around seeking out proton beam therapy?
Expectations, barriers, benefits, drawbacks of proton beam therapy?
What was the process for accessing proton beam therapy: determining cost, location of services, travel, treatment itself, etc.?

Was cost a barrier to accessing proton beam therapy? Were there other barriers?

General thoughts on making proton beam therapy available in Ontario/Canada?

* Health Quality Ontario is now part of Ontario Health.

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Ontario Health is an agency of the Government of Ontario. Our mandate is to connect and coordinate our province's health care system in ways that have not been done before to help ensure that Ontarians receive the best possible care. We work to support better health outcomes, patient experiences, provider experiences and value for money spent.

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