TITLE: Proton Beam Therapy versus Photon Radiotherapy for Adult and Pediatric Oncology Patients: A Review of the Clinical and Cost-Effectiveness

DATE: 20 May 2016

CONTEXT AND POLICY ISSUES

Conventional external beam radiotherapy uses photons to irradiate and kill tumor cells. The photon dose is delivered to the tumor in a continuous beam that can damage surrounding tissues. New photon technologies such as intensity modulated radiotherapy (IMRT) and stereotactic radiotherapy aim to reduce collateral tissue damage through more comprehensive planning and advanced technology that enables more direct targeting of the tumor, but none of these techniques can completely prevent downstream damage caused by the exit dose of a photon beam.

An alternative to photon therapy — proton beam therapy (PBT) — uses protons, which deposit less energy before and after the tumor. This is due to a phenomenon called the Bragg peak, which allows the most energy to be released near the end of the proton path, effectively delivering the greatest dose to the exact tumor location. It has been estimated that there will be over 90 PBT centres operational worldwide by 2020. The number of sites in the US alone has grown four-fold over the past decade. Proton beam therapy was only recently approved for use in Canada. The first system (Mevion S250) received a medical device license in early 2015.

There is one operational site in Vancouver, British Columbia (TRIUMF Proton Treatment Facility), for the treatment of ocular tumors. Other hospitals and clinical centres are interested in acquiring this technology, but, in the meantime, patients must travel abroad to receive therapy with funding at the discretion of provincial health ministries.

Purported benefits of PBT include improved short and long-term clinical outcomes, and increased capacity to treat pediatric patients and those whose cancer would be untreatable with conventional therapy due to proximity to radiosensitive areas (e.g., central nervous system and ocular tumors). In addition to the clinical benefits, PBT could also hypothetically reduce healthcare spending on the extended care of previously untreatable patients and those experiencing complications resulting from conventional therapy. Pediatric cancer patients have an increased risk of experiencing secondary malignancies and other long-term consequences of treating immature tissues and organs. Exposure of critical structures, such as the brain, to low

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doses of radiation may increase the risk of long-term cognitive and behavioral defects as well as reduced growth, neuroendocrine and developmental function.\textsuperscript{5-12} For these reasons, but not based on high quality, comparative evidence, the Alberta Health Services Cancer Care Proton Therapy Guidelines working group has recommended that highest priority for PBT be for pediatric patients, as well as adults, with chondrosarcomas or chordomas of the skull base, large uveal and mucosal melanomas, large unresectable sarcomas, renal cell carcinoma, pancreatic and liver cancers.\textsuperscript{7,13,14} In Canada, patients must be prioritized according to greatest need and likelihood of benefit due to the limited availability of in-country and out-of-country treatment. With relatively low access to PBT in Canada, patients interested in this therapy may have to travel abroad to receive treatment. Guidance for referral to out-of-country treatment suggests that treatment should be delivered with curative intent, when overall survival is expected to reach or exceed five years, and when patients have sufficient self-care ability, and are willing and able to travel.\textsuperscript{14} The latter criteria often means that private funds must be accessible.

The potential clinical benefits of lower radiation exposure seem intuitive,\textsuperscript{15-19} but dosimetric superiority of PBT has not yet been demonstrated to achieve improved clinical outcomes.\textsuperscript{14} Comparative evidence is limited and it is unclear how PBT fits into the landscape of other available therapies, or what the most appropriate indications are. It has been suggested that tissue sparing benefits may not be as robust as initially suggested, and that the reduction in secondary malignancies may only be initially delayed.\textsuperscript{20-22} To address the lack of comparative evidence, indirect meta-analyses have been conducted on prostate, lung, and head and neck cancer populations.\textsuperscript{23,24} These reviews pool findings from non-comparative studies and conduct a comparative analysis, but they lack control groups, and the unknown distribution of potential confounders make their findings unreliable.

On top of concerns about the lack of comparative evidence, there are concerns regarding costs and barriers to implementation. Proton Beam Therapy is more expensive than conventional radiotherapy, with an estimated capital cost for new PBT centres of approximately $160 million USD, approximately six times the cost of a photon-only facility.\textsuperscript{25-27} One centre in the United States is expected to cost $235 million USD.\textsuperscript{28} Compact single-room cyclotron devices have significantly reduced capital costs to less than $50 million USD,\textsuperscript{7,29} but the overall costs of building and operating these facilities is still substantial. For example, the United Kingdom has committed £250 million towards developing and running two PBT facilities.\textsuperscript{28} The technology has a large physical footprint, and requires specialized construction to be safely housed.\textsuperscript{30} Staff require extensive training, and operational costs have been estimated at two to three times that of photon therapy. Cost-effectiveness assessment is complicated by wide variations in recent, context-specific costs and older economic evaluations on the resource implications of PBT may not be reliable.\textsuperscript{4,26,31} There are also concerns that the massive start-up expenses may precipitate inappropriate uses of PBT for other clinical conditions for which there is insufficient evidence to support its use, in order to recover costs.\textsuperscript{32} Given the limited availability of therapy in Canada, lengthy time-to-treatment may have an impact on the clinical benefit to patients, and the cost may be prohibitive for families seeking treatment abroad. Other practical considerations include an increased need to keep the patient stationary PBT during treatment. In some cases, general anesthesia or sedation may be required, with associated safety concerns.\textsuperscript{33,34} The precision of PBT means that any anatomical changes in a patient, caused by weight gain/loss or tumor growth/shrinkage may delay treatment as the proton therapy plan may need to be adjusted.
There is much interest in increasing the availability of PBT in Canada, but increased costs, implementation concerns, and unsubstantiated comparative clinical benefit and harms compared to other cancer radiotherapy treatments should be considered. This review will evaluate evidence on the comparative clinical and cost-effectiveness of PBT and photon radiotherapy in adult and pediatric patients requiring radiotherapy for the treatment of cancer.

RESEARCH QUESTIONS

1. What is the clinical effectiveness of proton beam therapy for the treatment of cancer patients?

2. What is the cost-effectiveness of proton beam therapy for the treatment of cancer patients?

KEY FINDINGS

Two systematic reviews of clinical evidence, two systematic reviews of economic evidence, and one primary economic evaluation were identified regarding the clinical and cost-effectiveness of proton beam therapy compared to photon radiotherapy for the treatment of cancer patients. There was limited comparative evidence, with insufficient evidence available for many indications, comparators, and outcomes. Comparable benefits and harms were demonstrated by most studies for the majority of outcomes in prostate, esophageal, lung, and breast cancer, as well as medulloblastoma, and pediatric brain tumours. An increased risk of patient harms was observed for some outcomes in breast, esophageal, prostate and lung cancer. As well, reduced survival was reported for spinal cord gliomas. Reduced harms were reported for some outcomes in patients with medulloblastoma, as well as lung, esophageal, and prostate cancer, and pediatric retinoblastoma. There was insufficient evidence to draw conclusions for recurrent liver and brain cancers, meningioma, head and neck cancers, uveal hemangioma, and for the outcome of secondary malignancies. The identified economic evidence is likely not generalizable to the Canadian context, and may not reflect accurate and up-to-date cost and benefit estimates. Most evaluations reported that PBT was not cost-effective; however, the technology was more likely to be cost-effective in pediatric populations, and under specific circumstances in younger adults, and patients with more advanced disease (e.g., high risk head and neck, lung cancer, and breast cancer patients). Overall, current comparative evidence does not suggest that PBT is superior to photon therapy from a clinical or cost perspective for the majority of indications. There are concerns regarding the quantity, quality and generalizability of the available evidence. Current ongoing studies and future investigation into differences in hard clinical endpoints and long-term outcomes may resolve some of this uncertainty.

METHODS

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments (HTA), systematic reviews (SRs), meta-analyses, randomized controlled trials (RCTs) and economic studies. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2013 and April 22, 2016.
The limited search timeframe reflects the availability of a comprehensive HTA with a search that was current to December of 2013.35 Rapid Response reports are organized so that the evidence for each research question is presented separately.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

<table>
<thead>
<tr>
<th>Population</th>
<th>Adult and pediatric oncology patients requiring radiation therapy</th>
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</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>Proton beam therapy (PBT) with or without adjunct surgery and/or chemotherapy</td>
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<tr>
<td>Comparator</td>
<td>Alternative radiotherapy (i.e., linear accelerator based treatment: intensity-modulated radiation therapy [IMRT], helical tomotherapy [TOMO], three-dimensional conformal radiation therapy [3C-CRT])</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Q1: Clinical effectiveness (e.g., disease-free survival, overall survival, local control, reduced tumor volume, quality of life); Harms (e.g., disease-specific adverse events, local or regional failure, distant metastases, mortality) Q2: Cost-effectiveness outcomes</td>
</tr>
<tr>
<td>Study Designs</td>
<td>Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, economic evaluations</td>
</tr>
</tbody>
</table>

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to September 2013, in acknowledgement of the 2014 HTA by the Institute for Clinical and Economic Review.35 Health technology assessments, SRs and meta-analyses were excluded if they were superseded by an update, or a more rigorous or recent review of the same studies. Primary clinical studies that were included within a SR of clinical evidence were excluded. Primary clinical studies and SRs that assessed dosimetry, dose planning, and simulated outcomes were excluded. In addition, studies that compared PBT to alternative therapies such as brachytherapy or other charged particle therapy were excluded. Systematic reviews with unique primary studies were excluded if the studies were non-comparative or did not meet the inclusion criteria. Economic studies that reported only on direct costs that were not cost-effectiveness, cost-utility, or cost-benefit analyses were excluded. Economic studies that were included within a SR of economic evidence were excluded.

Critical Appraisal of Individual Studies

The clinical and economic SRs were critically appraised using the AMSTAR checklist.36 The methods used when conducting the literature search, study selection, quality assessment, data
extraction, and for pooling and summarizing the data were assessed. Economic studies were assessed using the Drummond checklist. Study design, data collection, analysis, and interpretation of results were evaluated. Summary scores were not calculated for the included studies; rather, strengths and limitations of each included study were described narratively.

**SUMMARY OF EVIDENCE**

**Quantity of Research Available**

A total of 540 citations were identified in the literature search. Following screening of titles and abstracts, 515 citations were excluded and 25 potentially relevant reports from the electronic search were retrieved for full-text review. Five potentially relevant publications were retrieved from the grey literature search. Altogether 30 potentially relevant articles were obtained for full-text review.

**Excluded Studies**

Of the 30 potentially relevant articles, 25 publications were excluded for various reasons. Two reports were excluded as one was a non-systematic review and one was an evidence-based guideline. Two were included in a review of SRs. Two SRs were excluded as they were dosimetric or dose forecasting reviews. Four SRs were excluded as they included no comparative studies. Two SRs were excluded due to inappropriate interventions (e.g., combined photon and proton therapy) or comparators. One as it was superseded by a more recent review, and two due to a combination of the aforementioned reasons. Three RCTs were excluded as they were dosimetric or dose forecasting studies or due to an inappropriate comparator. One SR of economic evaluations was excluded as all studies were included in another SR. Five primary economic evaluations were excluded as they were included in a SR. One economic evaluation only reported direct costs and was excluded on that basis. Lastly, the ICER report was captured in a selected SR and is not reviewed separately.

**Included Studies**

Five publications, including two SRs, two SRs of economic evaluations, and one primary economic evaluation, met the inclusion criteria and were included in this report. The PRISMA flowchart of the study selection is presented in Appendix 1. Additional references of potential interest, including ongoing SRs and comparative clinical studies, are provided in Appendix 5.

**Summary of Study Characteristics**

A detailed summary of study characteristics is presented in Appendix 2.

**Clinical Evidence**

Two SRs were identified regarding the clinical effectiveness of PBT.

**Study Design**

Both SRs presented narrative summaries of the evidence rather than pooling results. The SR by Leroy et al., summarized 23 primary studies of which two were relevant to this report. The SR
by Peterson et al., summarized six SRs and 25 primary comparative studies of which 18 were relevant to this report. Primary clinical studies were retrospective non-randomized comparative studies, historically controlled studies, controlled before-and-after studies, and prospective non-randomized comparative studies. While both SRs included RCTs, none met the inclusion criteria of this report.

Country of Origin

One review was conducted by authors based in Belgium and the other by authors in the United States. One SR included primary studies conducted in the United States. The other included primary studies conducted in the United States, Germany, and Japan.

Patient Population

The SRs evaluated studies on pediatric cancer patients with craniopharyngioma and retinoblastoma and adult patients with newly diagnosed cancer or locally recurrent tumors after irradiation. The latter included breast, central nervous system, esophageal, head and neck, ocular, liver, lung, and prostate cancers.

Interventions and Comparators

Both reviews investigated PBT as an intervention. The intervention was compared to various photon-based radiotherapy techniques including IMRT, conventional radiation therapy (CRT), and 3D-CRT. These reviews included alternative comparators, but these findings are outside of the scope of this review. Primary studies varied in radiation dose and additional treatment (i.e., adjuvant chemotherapy or surgery). Some studies gave equivalent doses for the intervention and comparator, while others varied in the delivered dose across treatment groups.

Outcomes

The SR on pediatric patients assessed second malignancy, overall survival, disease-specific survival measures and symptoms, and quality of life over a variable follow-up period of one to 24 years. The SR on adult patients assessed benefits such as overall survival, progression-free survival, loco-regional failure, local recurrence rates, and quality of life, and harms such as post-operative complications, site-specific complications, pain, fracture, weight-loss, and acute and longer term systemic toxicity, over a variable follow-up period of approximately one to less than six years.

Economic Evidence

Two SRs of economic studies and one primary economic evaluation were identified regarding the cost-effectiveness of PBT.

Study Design

Both reviews used typical SR methods to identify economic evaluations and results were presented narratively. They included cost-effectiveness and direct-cost studies, but only the former were reviewed. The SR by Verma et al., included 18 evaluations of which 11 were relevant to this report. The SR by Amin et al., included 14 evaluations of which four were relevant to this report. Analyses were primarily cost-utility analyses. There was minor overlap...
in the studies included in the two SRs. Both SRs included a study on prostate cancer. The one primary evaluation was a cost-utility analysis.

Country of Origin and Perspective

Both SRs and the primary evaluation were conducted by study authors based in the United States. One review presented results from studies conducted in the United States from the payer perspective. One review presented results from studies conducted in Sweden, the United States, Holland, Belgium, and Japan. Perspectives were not reported. The primary study was conducted from the United States societal perspective.

Patient Population

The SRs addressed patients with various types of cancer including prostate, breast, lung, pediatric, and head and neck. The studies in one SR focused on older men (aged 60 to 70). One SR included studies on children, and adult populations. The adult populations were primarily middle-aged or older adults. The primary evaluation focused on adult breast cancer patients.

Interventions and Comparators

The cost-effectiveness of PBT was assessed against several alternative modalities, including CRT, IMRT, whole breast irradiation, and 3D-CRT. Both reviews included additional comparators that are outside of the scope of this review. Treatment doses and adjuvant therapies were not consistently reported by either review. The primary evaluation assessed PBT versus photon radiotherapy (specific technology unspecified) of varying treatment dose and no adjuvant cancer therapy.

Outcomes

Comparative cost-effectiveness was presented as an incremental cost-effectiveness ratio in cost per quality adjusted life years (QALYs) in both reviews and the primary evaluation. The willingness-to-pay (WTP) threshold varied within and between studies. The primary evaluation had a 100 year time horizon and assumed that coronary heart disease was managed medically in the base case analysis, no difference in tumor control between groups, different risk of major cardiac events depending on mean heart dose of radiation, higher risk of death in patients entering the model with coronary heart disease, and a WTP threshold of either 50,000 or 100,000 USD.

Summary of Critical Appraisal

A detailed summary of study strengths and limitations is presented in Appendix 3.

Clinical Evidence

Design and Conduct of Search

Neither SR provided reference to a published protocol or a priori objectives. One SR assessed the presence of a priori objectives in the SRs reviewed within the report as per AMSTAR criteria, and reported that only one SR had a priori design. Duplicate screening was
conducted for approximately a quarter of the identified articles in one SR, with the remaining titles and abstracts reviewed by a single author, who if unsure, discussed with a second author until consensus was reached.\textsuperscript{11} One author was involved in screening in the other SR and results were checked by a second author.\textsuperscript{24} In both cases, lack of duplicate screening may have increased the risk of overlooking relevant literature. Data in one SR was extracted by one reviewer and checked by another\textsuperscript{24} and the number of authors involved in data extraction was unclear in the other SR.\textsuperscript{11} Lack of duplicate extraction increases the likelihood of recording errors. Both SRs conducted comprehensive searches. One used multiple databases\textsuperscript{11} and one used a single database.\textsuperscript{24} Grey literature was searched in both cases\textsuperscript{11,24} and study authors of one SR contacted manufacturers for information.\textsuperscript{24} Both SRs restricted the search by language to English, French, German, and Dutch.\textsuperscript{11} One study restricted search dates to 2007 onward (search ended in 2014).\textsuperscript{11} Search dates were unclear for the other SR.\textsuperscript{24}

\textbf{Reporting}

Both SRs included a list of included studies. One SR gave information on reasons for exclusion for excluded SRs, but not primary studies.\textsuperscript{24} The other SR\textsuperscript{11} did not provide information on excluded studies. Study characteristics were provided in both cases. Leroy et al.,\textsuperscript{11} discussed study design, length of follow-up, adjuvant treatment, comparators, reported outcomes and conclusions. Peterson et al.,\textsuperscript{24} discussed the number and design of comparative studies for each type of cancer, sample size, study author names, intervention and comparator, but no further primary study characteristics. For SRs, they reported funding source, types of cancer, search end date, scope of review and relevant conclusions.\textsuperscript{24} Information about some relevant confounders such as tumor size, disease stage, use of imaging in treatment planning, and age were missing from some, but not all studies.

\textbf{Quality Assessment}

Both studies conducted a formal quality appraisal of studies.\textsuperscript{11,24} Cochrane Risk of Bias was used in both cases.\textsuperscript{11,24} One review also used the Drug Effectiveness Review Project methods for reviewing observational studies, and AMSTAR criteria\textsuperscript{36} to appraise SRs. This SR\textsuperscript{24} further considered the confidence in evidence based on quality using Guidance established for the Evidence-based Practice Centre program of the Agency for Healthcare Research and Quality. The other SR classified the quality of evidence and strength of recommendations using GRADE criteria.\textsuperscript{11} Both SRs\textsuperscript{11,24} considered study quality throughout presentation of the results and conclusions.

\textbf{Methods of Pooling and Publication Bias}

Neither study pooled results so no assessment of methods used to combine studies could be conducted. Neither review formally assessed publication bias, but both used search methods to reduce the risk of overlooking unpublished studies and manufacturers were contacted in one case.\textsuperscript{24} Conduct of publication bias assessment was evaluated for all SRs included in the Peterson et al., review as per AMSTAR criteria.\textsuperscript{24} Publication bias was assessed by one of the included SRs.\textsuperscript{24}
Conflict of Interest

Funding sources were provided in both reports.\textsuperscript{11,24} One SR\textsuperscript{24} further disclosed that there were no affiliations or financial involvements that could conflict with the material presented in the report. Affiliations were unclear for the other SR.\textsuperscript{11}

Economic Systematic Reviews

Design and Conduct of Search

Neither economic SR provided reference to a review protocol or a priori objectives.\textsuperscript{4,60} One review\textsuperscript{4} conducted screening in triplicate. The number of study authors involved in screening and data extraction was unclear for the Amin et al., review.\textsuperscript{60} Potential lack of duplicate screening and extraction increases the likelihood of overlooking relevant evidence and making recording errors, respectively. Both SRs\textsuperscript{4,60} conducted a comprehensive search using multiple databases (including the Cost-Effectiveness Analysis Registry) and grey literature strategies.\textsuperscript{4,60} Both SRs only included English language publications. One SR restricted the search to 2000 to June 2015.\textsuperscript{4} Given that PBT is a relatively new technology this may not be a concern. The other SR included studies from database inception to Dec 2013.\textsuperscript{60} Considering the rapid development of this technology overall cost-effectiveness observations from this review may be outdated.

Reporting

Both SRs provided a list of included studies, but neither provided a list of excluded studies. Characteristics of included studies were provided. One SR\textsuperscript{4} reported on methodology, key assumptions of the model, population characteristics, therapy comparisons, total costs, QALYs and ICER estimates, as well as conclusions and criticisms, but failed to disclose important information about country and currency as well as perspectives and time horizons. The other SR\textsuperscript{60} reported on the interventions, population characteristics, perspective, year of cost data, costs, QALYs, ICER, analysis methods and conclusions, but failed to disclose all assumptions (limited information presented in text), and time horizon for one\textsuperscript{62} of the studies. Omission of important study characteristics creates challenges for the interpretation of review findings, as the conclusions presented lack sufficient context.

Quality Assessment

Neither review did a formal quality assessment of the primary economic evaluations.\textsuperscript{4,60} Both SRs commented on strengths and limitations, but did not use a formal tool to consistently assess study quality. Quality was discussed generally in conclusions but in a limited and inconsistent way. Thus, the limitations of included studies were not always clear.

Method of Pooling and Publication Bias

As the primary study type evaluated by both SRs was economic studies, no pooling of results was conducted. No formal method of assessing publication bias was used.

Conflict of Interest

Both SRs\textsuperscript{4,60} disclosed funding sources and conflict of interest. One study had no concerning financial affiliations or other conflict of interest.\textsuperscript{60} The other\textsuperscript{4} did not disclose any specific funding.
for the project, but several study authors reported financial affiliations with clinical societies and industry. It is unclear whether any of these manufacturers have a current or future stake in the PBT market, or whether their involvement informed the design or conduct of the review.

Primary Economic Evaluation

The one economic evaluation clearly stated a research question, its economic importance, the analytical viewpoint, rationale for choosing comparators, and the type of evaluation, as well as how it addressed the research question. It did not provide rationale for the choice of the alternative intervention and did not provide sufficient description of the comparator. As such, it is unclear which specific photon therapies the results are applicable to. The authors disclosed their primary outcome measure, methods to value benefits, sources for estimates of unit costs, currency and price data, details of price adjustment, details of the economic model and sources to justify the choice of model and key parameters. The evaluation did not disclose the source of effectiveness estimates or details on design and results of the studies, and did not provide detail on subjects from which valuation information was derived. Quantities of resource use were not reported separately from unit costs. Further, the appropriateness of assuming equal effectiveness of the interventions, and using a QALY measure that did not consider cancer-related morbidity was unclear. The truncation of the healthy branch of the model to not include potential percutaneous coronary intervention as per the coronary heart disease branch was not explained. Regarding analysis and interpretation of results, the authors stated the time horizon (age 100 or participant death), discount rate (3%), approach sensitivity analysis, incremental analysis, and provided an answer to the study question with conclusions that properly reflected the data. They did not explain the choice of time horizon, discount rate, the choice of variables for sensitivity analysis, and did not provide disaggregated results.

Summary of Findings

A detailed summary of study findings is presented in Appendix 4.

What is the clinical effectiveness of proton beam therapy for the treatment of cancer patients?

All of the comparative evidence identified in the search was reviewed in two SRs. Both SRs were broad in scope, but only evidence that met the inclusion criteria of the report is presented.

Overall, none of the clinical evidence was suggestive of a substantial incremental benefit of PBT over photon radiotherapies. Clinical evidence from two SRs — which included a cumulative 20 comparative studies fitting the inclusion criteria of this report — suggests that there is insufficient evidence to support superiority of PBT versus photon therapy in pediatric patients with craniopharyngioma or retinoblastoma, and adult patients with breast cancer, head and neck cancer, uveal hemangioma, NSCLC, meningioma, and for the risk of secondary malignancies or benefit in recurrent cancers. Reductions in acute toxicity were observed in single trials for prostate cancer and medulloblastoma, for 30-day postoperative pulmonary complications in esophageal cancer, and for acute risk of severe esophagitis in NSCLC. These limited benefits were balanced by evidence of potential increased harm in breast cancer with regards to several 7-year skin toxicities, increased rate of death within five years in patients with spinal cord gliomas, increased risk of 3-month pneumonitis in patients with esophageal cancer, and increased risk of both acute and long-term gastrointestinal (GI) toxicity in patients with prostate cancer. Most of this evidence is from low quality retrospective studies and should be interpreted with caution. Further, it should be noted that evidence was limited to a single study
or few studies for each individual type of cancer, and not all trials assessed important clinical endpoints such as survival and recurrence measures, functional outcomes, long-term toxicity, and quality of life.

**Adults**

**Breast**

Based on a single non-randomized trial, treatment of breast cancer patients with PBT resulted in comparable seven-year cumulative recurrence rates, incidence of fat necrosis, moderate to severe fibrosis, seven-year moderate to severe breast pain and cosmetic outcomes. PBT was associated with higher rates of seven-year skin toxicities such as moderate to severe dyspigmentation and patchy or marked atrophy.

**Medulloblastoma**

Based on a single retrospective non-randomized study, assessed as “low-quality” by the review authors, overall and progression-free survival was comparable between patients treated with PBT versus IMRT. Acute toxicity and rates of several adverse effects were lower in the PBT group.

**Spinal Cord Glioma**

Based on a single retrospective non-randomized study, there were no differences in the rate of death at one year, or local recurrence. After multivariable adjustment PBT patients were more likely progress to death within five years.

**Esophageal**

Two retrospective non-randomized studies reported on comparative harms of PBT versus photon therapies. They suggested no difference in odds of post-operative pulmonary complications between patients who received PBT versus those that received IMRT, reduced odds of postoperative pulmonary complications in the 3D-CRT versus PBT group, and increased rates of acute pneumonitis in the PBT group versus either IMRT or 3D-CRT. There were no difference in the odds of GI complications between the PBT group and both IMRT and 3D-CRT groups.

**Meningioma**

One small (n=22) retrospective non-randomized study, assessed as “poor-quality” by the review authors, reported no differences in treatment side-effects, visual outcomes, and tumor control between patients who received PBT or CRT; however, results were deemed unreliable due to the confounding and absence of data and statistical tests on benefits and harms.

**Uveal Hemangioma**

One retrospective non-randomized study, assessed as “poor-quality” by the review authors, suggested no difference in stabilization of visual acuity, optic disc or nerve atrophy, retinopathy or grade 3 or 4 side effects, but the review authors thought that potential confounding due to
baseline imbalances and the limited scope of the evidence prevented confidence in these findings.

**Head and Neck**

Based on one small (n=6) “poor-quality” retrospective non-randomized study,\(^7^0\) there was insufficient evidence to support the use of PBT in head and neck cancer patients. Specifically, patients with malignant clival tumors showed increased rates of survival after PBT versus IMRT; however, different length of follow-up, and lack of baseline demographic information suggests that these results are unreliable. Further evidence from two non-comparative indirect meta-analyses, and one conference proceeding were presented, but the results were considered unreliable due to issues with methodology and reporting.\(^2^4\)

**Lung**

Based on two historically controlled non-randomized studies,\(^7^1,7^2\) there was no difference between PBT and 3D-CRT or IMRT in terms of overall survival.

PBT was superior to IMRT in terms of acute esophagitis at 6 months and grade 3 esophagitis at 15 to 17 months. Outcomes were similar between PBT and IMRT groups for grade 3 pneumonitis, grade 3 dermatitis and grade 3 fatigue.

PBT was superior to 3D-CRT for grade 3 esophagitis at 15 to 17 months, and grade 3 pneumonitis. Rates of grade 3 dermatitis were higher in the PBT group, and rates of acute esophagitis at 6 months and grade 3 fatigue were similar between groups.

**Prostate**

The review authors stated that the role of PBT in the context of other available therapies remains unclear.\(^2^4\)

Proton beam therapy and 3D-CRT were shown in one controlled before and after study,\(^7^3\) judged to be “poor-quality” by the review authors, to improve bowel and rectal quality of life, but differences between groups were not assessed. One retrospective study\(^7^4\) reported greater GI toxicity in patients who received PBT versus 3D-CRT.

Based on results from several historically controlled\(^7^3,7^5\) and retrospective studies,\(^7^6-7^8\) compared to IMRT, PBT treatment resulted in comparable bowel, urinary, and sexual quality of life at 2 years, acute GI toxicity at 6 months, long-term GI complications, and long-term genitourinary (GU) complications. In the PBT group a reduction in acute GU complications at 6 months, but a significantly higher risk of GI toxicity at 4 to 5 years versus IMRT was observed.

**Various Cancers – Risk of Secondary Malignancies**

Based on a single retrospective study,\(^2^2\) it was reported that the risk for progressing to secondary cancer was reduced by half with PBT versus photon modalities, and that the rate of secondary malignancies was numerically lower after approximately 6 years. However no differences in the incidence of secondary malignancies per 1000 person years, or 10-year cumulative incidence rates were observed. Due to a large quantity of missing data and unclear
details of the comparator as well as ascertainment methods, the review authors deemed these findings unreliable.

**Recurrent Cancers**

Two retrospective non-randomized studies on recurrent cancer patients reported that there was insufficient evidence to allow conclusions regarding the comparative effectiveness of PBT and CRT in malignant brain tumor patients and liver cancer patients. Similar outcomes were observed between PBT and CRT groups, but both studies suffered from methodological limitations that reduced the reliability of findings.

**Pediatrics**

There were two retrospective non-randomized studies, summarized in one SR, regarding the clinical effectiveness of PBT versus photon therapy in pediatric patients.

**Craniopharyngioma**

Compared to IMRT, there were no differences in overall survival, cystic failure-free survival, nodular failure-free survival, early cyst growth, late cyst growth and quality of life following PBT treatment.

**Retinoblastoma**

Compared to CRT, there was no significant difference in the risk of secondary malignancy, but significantly lower rates of radiation therapy induced or in-field secondary malignancies in the PBT group.

**What is the cost-effectiveness of proton beam therapy for the treatment of cancer patients?**

The economic evidence suggested that based on the limited data available, PBT is unlikely to be cost-effective in prostate cancer and early stage NSCLC. Most evidence supported cost-effectiveness in pediatric brain tumors. Under some circumstances cost-effectiveness was demonstrated in well-selected breast cancers (younger patients and increased coronary heart disease risk), loco-regionally advanced NSCLC, and high-risk head and neck cancers, but these results were mostly borderline and dependent on unreliable assumptions. The review authors noted that emerging clinical evidence and cost reductions owing to improved technology would likely affect these conclusions. Further, variation in the approach to these analyses and perspectives assumed, as well as the patient populations assessed greatly limits the generalizability. Results should be interpreted accordingly.

**Adults**

**Prostate Cancer**

Based on results from four evaluations from the Swedish and United States perspective, PBT was not cost-effective versus photon modalities in older men with prostate cancer. The Swedish study reported borderline cost-effectiveness, but weaknesses in assumptions that result in unreliable findings.
Breast

Based on three evaluations\(^{59,83,84}\), PBT was not cost-effective versus whole breast irradiation and CRT in breast cancer patients of various ages without cardiac risk factors. In women with cardiac risk factors, PBT was more likely to be cost-effective, and in one study,\(^{59}\) PBT was more likely to be cost-effective in younger patients (aged 40 or 50, versus 60).

Lung

Based on one evaluation, PBT was not considered cost-effective for NSCLC from the Dutch perspective. Based on another evaluation presented in abstract format, PBT was reported to be “borderline cost-effective” (page 8)\(^{4}\) from the Belgian perspective when given with concurrent chemotherapy.\(^{85,86}\)

Head and Neck

From the Swedish perspective, PBT was considered cost-effective for head and neck cancers compared to CRT; however, this analysis did not consider long-term toxicity.\(^{83}\) Another study from the Dutch perspective reported that PBT was not cost-effective versus IMRT.\(^{57}\)

Pediatric Tumors

In patients with medulloblastoma, it was reported by four economic evaluations from the Swedish, American, and Japanese perspectives that treatment with PBT was cost-effective.\(^{53,54,83,87}\) However, it should be noted that there were issues with some of the evaluations. This included extrapolation of adult utility values to the pediatric population; assumption of reduced IQ loss, hearing loss and growth hormone deficiency with PBT use; lack of data for quality of life effects secondary to IQ and hearing loss; identical costs for growth hormone in adults and children; incomplete estimation of operational costs; and lack of accounting for productivity losses. One study in patients with brain tumors reported that PBT was considered cost-effective over a broad range of costs.\(^{55}\)

Limitations

Confounding

All clinical evidence was from non-randomized studies and few studies adjusted for all potential confounders. Factors such as older age, ethnicity, stage of clinical disease, tumor volume, adjuvant treatments, and time period of treatment (for historically controlled studies or studies with different recruitment time periods), and methods of motion control were not controlled for consistently across studies. This may have confounded the effect of PBT on clinical outcomes that were measured.

Generalizability

Evidence was only available for certain types of cancers, and for the types of cancer that were supported by evidence the number of comparative trials ranged from one to five. Potential indications such as renal cell carcinoma, liver cancers, GI cancers (i.e., pancreatic), lymphoma, bone cancers, and some pediatric cancers did not have any comparative evidence to support the use of PBT. The appropriateness of extrapolating evidence from different conditions to
support or refute the use of PBT is unclear, although the inconsistency in benefits and harms of PBT observed across conditions suggests that it would be unwarranted.

Equity of Access to Treatment

The evidence does not address potential issues such as the financial, geographical, and logistical barriers to accessing PBT and the impact of these factors on clinical outcomes and cost. In the current landscape, patients must go through an extensive review process to determine eligibility for treatment. This takes time and effort on behalf of the patient, healthcare provider, and health system, and may be less feasible for patients without proper social support systems or access to healthcare. In addition, the financial burden of travelling to receive treatment and the associated lost productivity costs may make treatment inaccessible for individuals of low socioeconomic status. Patients residing in rural and remote areas without proximity to large urban healthcare facilities may also be at a disadvantage if they cannot easily travel to receive treatment (e.g., due to poor proximity to major airports or PBT centres) and to undergo assessment for out-of-country treatment. Issues related to private financing of PBT therapy may be less of a concern if therapy centres are established within Canada, but, nevertheless, equity of access should be considered from all the perspectives discussed.

Dose and Delivery of Dose

Proton beam therapy can be delivered using passive scattering, uniform scanning, or spot scanning. Uniform scanning and spot scanning are pencil beam approaches. Passive scattering and uniform scanning require patient-specific collimators to shape the beam, which reduces efficiency. Spot scanning does not require a collimator and enables intensity modulated therapy and reduced neutron contamination. Neutron contamination can increase the risk of secondary malignancies. The majority of evidence has been generated based on technology that uses passive scattering. The potential benefits of pencil beam scanning, particularly for long-term avoidance of secondary malignancies should be considered. Thus, studies that use different PBT approaches may not be comparable.

Moving Tumours

The Veterans Affairs report inquired as to whether harms of proton versus photon therapies are different when treating mobile targets such as tumours of the lungs, esophagus, liver, pancreas, breast, prostate and kidneys, which are subject to respiratory motion. No studies were identified that assessed variation in clinical outcomes based on variability in tumor motion, imaging and planning methods used to account for respiratory motion, or quality assurance standards. They noted that several comparative studies describe imaging and planning methods used to account for respiratory motion, but not variability in methods. For instance, one study noted measures of managing motion of tumors used for IMRT and PBT patients, but not 3D-CRT patients with no difference in survival by treatment group; however, how the information from 4DCT scanning was used was unclear. The other studies did not assess clinical outcomes by method of radiation dose calculation, used the same respiratory-gated system, or used body casts in all patients preventing comparisons across modalities. As effectiveness and harms of PBT may be influenced to some extent by movement induced by respiration, this factor should be considered in future studies.
Primary or Adjuvant Treatment

Depending on the study and condition, PBT may have been provided alone, in addition to other radiotherapy techniques, or as adjuvant therapy alongside other cancer treatments like chemotherapy or surgery. It should be noted that outcomes observed in a specific context may not be generalizable to an alternative context. That is, a study that assessed adjuvant chemotherapy and PBT should not be assumed to have the same outcomes as PBT used in isolation, or in alternative contexts.

Appropriateness of Cost-Effectiveness Estimates

The ability to accurately assess the cost-effectiveness of PBT is greatly limited by the absence of high quality clinical evidence – particularly long-term outcomes – and the uncertainty about actual costs. Published evaluations largely rely on modeled outcomes from uncontrolled clinical studies. Also, it is suggested that current costs of implementing PBT programs and building facilities are substantially lower than earlier estimates. Single gantry facilities cost approximately one-third of multiple gantry facilities. The conclusions regarding cost-effectiveness of PBT discussed in this report may overestimate the ICERs for PBT in its current context. Conversely, overestimated effectiveness assumptions may make PBT appear more cost-effective than it is. More up to date evaluations are needed given changing costs and unclear effectiveness.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

There is very limited evidence on the comparative clinical effectiveness of PBT versus photon-based radiotherapy. On the whole, the published evidence fails to address all relevant types of cancer, all relevant comparisons, and to control for relevant confounders such as previous or adjuvant therapies, size and class of tumor, movement of the patient and tumor during the procedure, planning for dose and positioning, comorbidities, and other factors that can affect clinical outcomes and costs.

Based on the two clinical SRs reviewed there are few conditions for which there was sufficient evidence to draw conclusions regarding the comparative effectiveness of PBT and photon radiotherapy. Where evidence was available it was usually from a single or few small poor-quality retrospective studies. There was insufficient evidence, or evidence was of insufficient quality, to draw conclusions for giant cell tumor of the bone, head and neck cancers, uveal hemangioma, early-stage NSCLC, meningioma, recurrent cancers, and the risk of secondary malignancies in various cancers. The majority of evidence indicates comparable effectiveness of PBT and photon therapies (i.e., IMRT, 3D-CRT or CRT) for various outcomes in adult cancers including prostate, esophageal, lung, and breast cancer, as well as medulloblastoma and pediatric cancers including craniopharyngioma and retinoblastoma. A minority of evidence supports reduced harms, and conversely, increased harms of PBT. Evidence of increased harms was observed for breast cancer (i.e., increased skin toxicities), esophageal cancer (i.e., risk of pneumonitis at 3 months), prostate cancer (i.e., increased long-term GI toxicity), and lung cancer (i.e., grade 3 dermatitis). Risk of progression to death was increased in spinal cord glioma patients. Evidence of reduced harms were observed for medulloblastoma (i.e., acute toxicity), lung cancer (i.e., acute and early esophagitis, early pneumonitis; depending on comparator), esophageal cancer (i.e., postoperative pulmonary complications) prostate cancer (i.e., acute genitourinary toxicity), and pediatric retinoblastoma (i.e., in-field secondary malignancies). Most evidence was deemed 'low-strength', meaning it is unlikely to allow for definitive conclusions.
Keeping in mind the limitations of potentially inappropriate assumptions regarding clinical effectiveness and costs, and the poor generalizability of evidence to the Canadian context, the majority of economic evidence suggested that PBT would not be cost-effective compared to alternative photon radiotherapy offerings. Notable exceptions are the pediatric population - where cost-effectiveness was demonstrated consistently under the assumption that long-term benefits would be realized - and younger adults and those with greater risk of radiation-attributed morbidity (e.g., breast cancer patients with cardiovascular risk factors), as these factors were associated with an increased likelihood of cost-effectiveness. The potential decline in cost of PBT facilities with the advent of compact units, increased experience in implementation and operation, and more accurate clinical and cost estimates from ongoing trials should be considered and accounted for in future analyses.

The body of non-comparative trials on PBT is much larger than for comparative evidence. While this information is valuable, particularly to inform safety of the technology, it does not address whether the increased costs associated with developing PBT therapy centres and providing treatment are warranted. Non-comparative data has been used in many economic evaluations to inform clinical assumptions, which reduces the reliability of these analyses. To justify substantial spending, it would be preferable to have good quality comparative evidence to inform strategic planning. More studies are needed in order to clarify the relative benefits and harms of available radiation therapies in all types of cancer and contexts in which they will be used. There are gaps in the literature regarding the long-term safety and effectiveness of PBT, and there is limited evidence to speak to shorter-term outcomes, all relevant comparators, and all treatment contexts. These outstanding uncertainties should be addressed in future research. This may be challenging due to increased patient perceptions that PBT is a superior technology, which may complicate patient recruitment, and debate as to whether randomizing patients to proton or photon therapy would be unethical, given concrete evidence to support reduced radiation exposure. It has been proposed that mandatory registries of data on patients treated with PBT, and the conduct of prospective studies may aid in reducing uncertainty. Several ongoing comparative studies and SRs may provide answers for the identified knowledge gaps (Appendix 5).

In conclusion, the evidence assessed in this review suggests that the benefit, harms and cost-effectiveness of PBT versus photon radiotherapy alternatives remain largely unclear. Furthermore, though not evaluated in this report, resource implications and feasibility of implementation are uncertain. From a dose reduction standpoint, pediatric patients theoretically stand to reap to greatest benefits, but further research is needed to address long-term outcomes in this patient group. While there is great interest in increasing the availability of this treatment due to reduced radiation exposure, the evidence based on clinical endpoints does not appear to support the claims of greater benefit, though ongoing research may provide further clarity.
REFERENCES


89. Kunkler IH. Randomised controlled trials of proton beam therapy are needed. BMJ. 2012;344:e3193.


APPENDIX 1: SELECTION OF INCLUDED STUDIES

540 citations identified from electronic literature search and screened

515 citations excluded

25 potentially relevant articles retrieved for scrutiny (full text, if available)

5 potentially relevant reports retrieved from other sources (grey literature, hand search)

30 potentially relevant reports

25 reports excluded:
- irrelevant or no comparator (4)
- irrelevant intervention or comparator, or no comparator (4)
- already included in at least one of the selected systematic reviews (8)
- evidence-based guideline (1)
- other (review articles, editorials) (1)
- dosimetric or dose-planning (4)
- superseded by more recent systematic review (2)
- only reported direct costs (1)

5 reports included in review
n = 2 systematic reviews
n = 2 systematic reviews of economic evidence
n = 1 economic evaluation
### APPENDIX 2: Characteristics of Included Publications

<table>
<thead>
<tr>
<th>First Author, Publication Year, Country, Databases and Search Dates</th>
<th>Types and numbers of primary studies included</th>
<th>Population Characteristics</th>
<th>Intervention, Irradiation Dose</th>
<th>Comparator(s), Irradiation Dose</th>
<th>Additional treatment</th>
<th>Clinical Outcomes, Length of Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leroy, 2016, Belgium; (^{11}) Medline, Embase, Cochrane Library 2007 to 2014, updated June 25(^{th}), 2015 (\text{Restricted based on previous report on Hadron therapy by Belgian Healthcare Knowledge Centre search dates})</td>
<td>(n = 23) non-randomized studies ((n = 2) comparative studies)</td>
<td>Pediatric cancer patients(^{a})</td>
<td>PBT</td>
<td>Photon radiotherapy (IMRT, conventional RT)</td>
<td>Variable provision of chemotherapy or surgery</td>
<td>Retinoblastoma: Second malignancy, Craniopharyngioma: overall survival, cystic failure-free survival, nodular failure-free survival, early cyst growth, late cyst growth, quality of life, Follow-up: 1 to 24.4 years</td>
</tr>
<tr>
<td>Peterson, 2015, United States, Department of Veterans Affairs; (^{24}) Medline, Cochrane Clinical Register of Controlled Trials, ClinicalTrials.gov, search dates unclear</td>
<td>(n = 6) systematic reviews; (n = 25) primary comparative studies (retrospective cohorts, cohorts with historical controls, controlled before/after studies, and prospective cohorts) (n = 18) primary studies with relevant to this report</td>
<td>Adult patients newly diagnosed with cancer or those with locally recurrent tumours after irradiation</td>
<td>PBT(^{c})</td>
<td>IMRT ((n = 12) studies), 3D-CRT ((n = 6) studies), Conventional RT ((n = 5) studies)</td>
<td>Variable provision of chemotherapy</td>
<td>Benefits: Overall survival, progression-free survival, locoregional failure, local recurrence rates, quality of life Harms: Post-operative complications, site-specific complications (e.g., genitourinary toxicity in prostate cancer), pain, fracture, acute and long-term systemic toxicity, weight loss Follow-up: (~1) year to 6.7 years(^{a})</td>
</tr>
</tbody>
</table>

\(^{a}\) Reporting on follow-up time was inconsistent

PBT = proton beam therapy
### Table A2: Characteristics of Included Economic Systematic Reviews

<table>
<thead>
<tr>
<th>Study Author, Publication Year, Country; Databases and Search Dates</th>
<th>Types and number of studies</th>
<th>Population Characteristics</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Countries of Conduct and Perspectives; Time Horizon</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verma, 2016, United States; PubMed, EMBASE, Cost-Effectiveness Analysis Registry 2000 to June 31st, 2015</td>
<td>Economic evaluations(^d): n = 18 primary studies (3 abstracts, 15 articles) Of these studies 11 economic evaluations met the inclusion criteria of this report</td>
<td>Patients with various types of cancer(^a)</td>
<td>PBT</td>
<td>CRT (n = 5 studies); IMRT (n = 7 studies); Whole breast irradiation (n = 1 study); 3D-CRT (n = 1 study)</td>
<td>Perspectives and time horizon of primary studies not reported; Studies conducted from the perspective of Sweden, the United States, Holland, Belgium, and Japan</td>
</tr>
<tr>
<td>Amin, 2014, United States(^b) PubMed, Cost-Effectiveness Analysis Registry Inception to December 4th, 2013</td>
<td>Economic evaluations n = 14 primary studies (n = 4 on PBT)</td>
<td>Patients with prostate cancer</td>
<td>PBT(^c)</td>
<td>IMRT(^g)</td>
<td>United States, Canada, or United Kingdom payer or societal perspective; Only studies from the United States payer perspective fit the inclusion criteria of this report Cost data from 2002 to 2012</td>
</tr>
</tbody>
</table>

\(^a\) Including skull base chondrosarcoma, skull base and (para)spinal chordoma, craniopharyngioma, ependymoma, esthesioneuroblastoma, Ewing sarcoma, central nervous system germinoma, low-grade glioma, medulloblastoma/primitive neuroectodermal tumours, nonresectable osteosarcoma, pelvic sarcoma, pineal parenchymal tumors, retinoblastoma, rhabdomyosarcoma, and (para)spinal “adult-type” soft tissue sarcoma

\(^b\) Also assessed a combination of photon and proton therapy, these results are not discussed in this report as they are out of scope

\(^c\) Also assessed the comparator of brachytherapy, these results are not discussed in this report as they are out of scope

\(^d\) Systematic review included studies that only reported direct costs and were not cost-effectiveness analyses – the results of these studies are not presented in this report

\(^e\) Prostate, breast, non-small cell lung cancer, head and neck, pediatric cancers, esophageal, skull base cancers, uveal melanoma

\(^f\) Included studies on the cost-effectiveness of alternative radiotherapy

\(^g\) Other comparators including active surveillance, brachytherapy and radical prostatectomy were evaluated in this review but the results are not presented as they are out of scope.

IMRT = intensity modulated radiation therapy; PBT = proton beam therapy; RT = radiation therapy
### Table A3: Characteristics of Included Economic Evaluations

<table>
<thead>
<tr>
<th>First author, Publication Year, Country</th>
<th>Type of Analysis, Perspective</th>
<th>Intervention, Comparator</th>
<th>Study Population</th>
<th>Time Horizon</th>
<th>Main Assumptions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mailhot Vega, 2016, United States⁹⁹</td>
<td>Cost-utility analysis with probabilistic sensitivity analysis; Societal perspective</td>
<td>PBT, Photon RT</td>
<td>Breast Cancer Patients</td>
<td>Model cycles equivalent to 1 year, 100 years</td>
<td>CHD managed medically, No difference in tumor control between arms, Differential mean heart doses would result in different rates of major cardiac events Patients entering model with CHD were at increased risk of death versus healthy counterparts, Participants entered the model at age 40, 50 or 60 with or without CRFs Discounted at 3% rate Assumed WTP threshold of 50 or 100 thousand USD</td>
</tr>
</tbody>
</table>

CHD = coronary heart disease; CRF = cardiac risk factor; PBT = proton beam therapy; RT = radiotherapy
### Table A4: Strengths and Limitations of Systematic Reviews and Meta-Analyses using the AMSTAR checklist

<table>
<thead>
<tr>
<th>AMSTAR Item</th>
<th>Clinical</th>
<th>Economic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was a priori design provided?</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Was there duplicate study selection and data extraction?</td>
<td>Selection ⊕</td>
<td>X</td>
</tr>
<tr>
<td>Extraction ⊗</td>
<td>⊗</td>
<td>⊗</td>
</tr>
<tr>
<td>Was a comprehensive literature search performed?</td>
<td>⊗</td>
<td>X</td>
</tr>
<tr>
<td>Was the status of publication used as an inclusion criterion?</td>
<td>X</td>
<td>⊗</td>
</tr>
<tr>
<td>Was a list of studies (included and excluded) provided?</td>
<td>Included ⊗</td>
<td>X</td>
</tr>
<tr>
<td>Excluded ⊗</td>
<td>⊗</td>
<td>X</td>
</tr>
<tr>
<td>Were the characteristics of the included studies provided?</td>
<td>⊗</td>
<td>⊗</td>
</tr>
<tr>
<td>Was the scientific quality of the included studies assessed and documented?</td>
<td>⊗</td>
<td>⊗</td>
</tr>
<tr>
<td>Was the scientific quality of the included studies used appropriately in formulating conclusions?</td>
<td>⊗</td>
<td>X</td>
</tr>
<tr>
<td>Were the methods used to combine the findings of studies appropriate?</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Was the likelihood of publication bias assessed?</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Was the conflict of interest included?</td>
<td>X</td>
<td>⊗</td>
</tr>
</tbody>
</table>

Legend: ⊗ = Yes, X = No, ? = Unclear
N/A = not applicable

### Table A5: Strengths and Limitations of Primary Economic Studies using Drummond

#### Strengths

**Mailhot Vega 2016**

- **Study Design**
  - Research question and economic importance of question stated (for which patients and under what dosimetric conditions is proton therapy potentially cost-effective in comparison with photon therapy due to differences in mean heart dose)
  - Viewpoint (societal) clearly stated
  - Rational given for choosing alternative interventions
  - The choice of type of economic evaluation (cost-utility analysis using Markov modeling and probabilistic sensitivity analysis) properly addresses the type of questions asked

- **Data Collection**
  - Primary outcome measure (ICER) stated
  - Methods to value benefits clearly stated
  - Details not provided on subjects from whom the valuation was obtained
  - Sources for estimation of unit costs provided
  - Currency (USD) and price data recorded
  - Details of price adjustments (adjusted to 2012 USD) provided
  - Details of economic model presented in text and visually
  - Sources were given to justify the choice of model and key parameters

#### Limitations

- **Study Design**
  - Insufficient rationale provided for the choice of alternative intervention (only stated that mean heart dose is different)
  - The alternative therapy was described generally as photon therapy – the specific type of photon radiotherapy was unclear

- **Data Collection**
  - The source of effectiveness estimates are not stated
  - Details on the design and results of effectiveness studies are not provided
  - Interventions are assumed to be equally effective – appropriateness of this is unclear as this assumption is not cited
  - Pooled efficacy estimates are not provided – no information given
  - QALYs determined for CHD – disregards other cancer-related concerns
  - Productivity changes not reported or discussed despite societal viewpoint stated
  - Quantities of resource use not reported separately from unit costs
  - Sources for estimation of quantities not
### Table A5: Strengths and Limitations of Primary Economic Studies using Drummond"d"

<table>
<thead>
<tr>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mailhot Vega 2016**</td>
<td>Reason for truncation of healthy branch of model to not include potential for percutaneous coronary intervention unclear</td>
</tr>
<tr>
<td>Time horizon (up to 100 years or life) stated</td>
<td>Analysis and Interpretation of Results</td>
</tr>
<tr>
<td>Discount rate (3%) stated</td>
<td>Citation for discount rate provided, but reason choice of discount rate not discussed</td>
</tr>
<tr>
<td>Approach to sensitivity analysis is stated</td>
<td>Reasons for choice of variables for sensitivity analysis (different risk of PCT and inpatient treatment, and different WTP thresholds) not provided</td>
</tr>
<tr>
<td>Relevant alternative compared</td>
<td>Specifics about alternative stated not provided (i.e., type of photon therapy, dose)</td>
</tr>
<tr>
<td>Incremental analysis reported</td>
<td>Disaggregated results not presented</td>
</tr>
<tr>
<td>Answer to the study question is given</td>
<td></td>
</tr>
<tr>
<td>Conclusions follow that data as reported and consider relevant caveats</td>
<td></td>
</tr>
</tbody>
</table>

ICER = incremental cost-effectiveness ratio; USD = United States Dollars
### Table A6: Study Findings and Author’s Conclusions for Clinical Systematic Reviews and Meta-Analyses

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Intervention Group</th>
<th>Control Group</th>
<th>Effect Estimate</th>
<th>Interpretation or Author’s Conclusions</th>
</tr>
</thead>
</table>
| Leroy, 2016<sup>16</sup>  
Craniopharyngioma  
(n = 1 study)<sup>62</sup> | PBT | IMRT | | |
| Overall survival at 3 years | 94.1% | 96.8% | p = 0.742 | No significant differences in clinical outcomes between patients treated with PBT versus IMRT |
| CFFS at 3 years | 67.0% | 76.8% | p = 0.994 | |
| NFFS at 3 years | 91.7% | 96.4% | p = 0.546 | |
| Early cyst growth | 4/21 (19%) | 13/31 (42%) | p = 0.082 | |
| Late cyst growth | 4/21 (19%) | 10/31 (32%) | p = 0.353 | |
| Quality of life | Satisfactory | Satisfactory | NR | |
| Retinoblastoma<sup>54</sup> (n = 1 study) | PBT | RT | | |
| Second malignancy  
(10 year cumulative incidence) | 5% (0 to 21) | 14% (2 to 31) | 0.12 | Very limited evidence to suggest potential reduced risk of developing RT-induced in-field secondary malignancies |
| Second malignancy  
(10 year cumulative incidence, radiation-therapy-induced or in-field) | 0% (NR) | 14% (3 to 31) | 0.015 | |

### Type of Cancer; Number of studies | Intervention<sup>*</sup> | Comparator<sup>*</sup> | Findings | Interpretation, Observations, or Author’s Conclusions |
|-----------------|-----------------|-----------------|-----------------|----------------------------------------|
| Peterson, 2015<sup>44</sup>  
Breast Cancer, n = 1<sup>63</sup> | PBT (passive double scattering system) | Photon Therapy | | |
<p>| | PBT (passive double scattering system) | 3D-CRT (twice daily over 4 consecutive days, dose = 32 Gy in 8 fractions) | Comparative 7-year cumulative recurrence rates (11% in PBT group, 4% in 3D-CRT group; p = 0.22); Higher rates of moderate to severe dyspigmentation (90% in PBT group, 27% in 3D-CRT group; p &lt;0.0001) and patchy/marked atrophy (54% in PBT group, 15% in 3D-CRT group, p &lt;0.0001); No difference in fat necrosis (10% in PBT group, 12% in 3D CRT group, p = 0.73), moderate to severe fibrosis (51% in PBT group, 32% in 3D-CRT group, p = 0.15), 7-year moderate to severe breast pain (21% in PBT group, 17% in 3D-CRT group; p = 0.46), rib-fracture | Low strength evidence of comparable efficacy between PBT and 3D-CRT, apart from higher rates of some skin toxicities with PBT |</p>
<table>
<thead>
<tr>
<th>Table A6: Study Findings and Author’s Conclusions for Clinical Systematic Reviews and Meta-Analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medulloblastoma, n = 1&lt;sup&gt;64&lt;/sup&gt;</strong></td>
</tr>
<tr>
<td><strong>Spinal Cord Glioma, n = 1&lt;sup&gt;65&lt;/sup&gt;</strong></td>
</tr>
<tr>
<td><strong>Recurrent Malignant Brain Tumor (patients received previous irradiation treatment), n = 1 study&lt;sup&gt;70&lt;/sup&gt;</strong></td>
</tr>
</tbody>
</table>
Table A6: Study Findings and Author's Conclusions for Clinical Systematic Reviews and Meta-Analyses

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Treatment 1</th>
<th>Treatment 2</th>
<th>Findings and Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PBT (50.4 Gy)</td>
<td>3D-CRT (50.4 Gy)</td>
<td>No differences in rate of local recurrence between groups (25% in PBT group, 25% in conventional photon group, p &gt; 0.99)</td>
</tr>
<tr>
<td><strong>Esophageal Cancer</strong></td>
<td>PBT (50.4 Gy)</td>
<td>IMRT (50.4 Gy)</td>
<td>Reduced odds of post-operative pulmonary complications (3D-CRT versus PBT, OR = 1.83 [95% CI = 1.83 to 45.42]) or gastrointestinal complications (3D-CRT versus PBT, OR = 2.31 [95% CI = 0.69 to 7.74]) between groups</td>
</tr>
<tr>
<td></td>
<td>PBT (50.4 Gy)</td>
<td>3D-CRT or IMRT (50.4 Gy)</td>
<td>The odds of post-operative pulmonary complications were comparable between PBT patients and those who received 3D-CRT or IMRT treatment (36)</td>
</tr>
<tr>
<td><strong>Optic nerve sheath meningioma, n = 1 study</strong></td>
<td>PBT (51.1 GyE)</td>
<td>CRT (51.4 GyE)</td>
<td>No significant differences in general treatment side effects, visual outcomes, or tumor control between groups (no data presented)</td>
</tr>
<tr>
<td><strong>Head and Neck, n = 1 study, n = 1 abstract</strong></td>
<td>PBT</td>
<td>IMRT</td>
<td>Overall survival numerically higher in the PBT group (100% in PBT group, 67% in IMRT group) at 16 to 24 months in patients with malignant clival tumours; Potential for reduced toxicity (no data presented) in patients with major salivary gland cancer or cutaneous squamous cell carcinoma metastases</td>
</tr>
<tr>
<td><strong>Ocular (Uveal Hemangioma), n = 1 study (38)</strong></td>
<td>PBT (20 to 22.5 CGE)</td>
<td>Photon therapy (16 to 30 Gy)</td>
<td>No significant difference in stabilization of visual acuity (p = 0.43), optic disc or nerve atrophy (p = 0.27), retinopathy (p = 0.98), or grade 3 (p = 0.77) or 4 (p = 0.38) side-effects between Baseline differences in uveal hemangioma, poor quality studies, reliability of findings unclear</td>
</tr>
<tr>
<td>Table A6: Study Findings and Author’s Conclusions for Clinical Systematic Reviews and Meta-Analyses</td>
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<tr>
<td><strong>Recurrence liver cancer, n = 1 study (18)</strong></td>
<td>PBT (68.8 to 84.5 Gy)</td>
<td>CRT (60 or 70 Gy)</td>
<td>Similar number of deaths between groups (80% in proton, 100% in photon, ( p = 0.62 )); Median survival time 18 months in PBT group and 15.5 months in photon group (unclear statistical significance)</td>
</tr>
<tr>
<td></td>
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<td>Better prognosis in the proton group at baseline not accounted for in analysis; insufficient evidence to make conclusions about comparative efficacy of PBT and CRT in recurrent liver cancer; study did not adjust for potential confounding of lower age in proton group and smaller average tumor size</td>
</tr>
<tr>
<td><strong>Lung (NSCLC)</strong></td>
<td>PBT, n = 2 studies (74 Gy)</td>
<td>3D-CRT (63 Gy)</td>
<td>No difference in median survival times survival between groups (PBT = 24.4 months; 3D-CRT = 17.7 months); No difference in acute risk of esophagitis at 6 months (PBT = 6%; 3D-CRT = 8%; ( p = 0.42 )), or grade 3 fatigue (PBT = 19%; 3D-CRT = 29%; ( p = 0.09 ))</td>
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<td>Lower risk of grade 3 esophagitis (PBT = 5%, 3D-CRT = 18%; ( p = 0.02 )) and grade 3 pneumonitis at 15 to 17 months in PBT group (PBT = 2%, 3D-CRT = 30%; ( p &lt; 0.0001 )) (in subgroup that received concurrent chemotherapy); Significantly higher risk of grade 3 dermatitis in PBT group (PBT = 24%; 3D-CRT = 5%; ( p = 0.005 ));</td>
</tr>
<tr>
<td></td>
<td>PBT, n = 2 studies (74 Gy)</td>
<td>IMRT (63 Gy)</td>
<td>No significant difference in median survival times between groups (PBT = 24.4 months; IMRT = 17.6 months); Significantly lower risk of acute severe esophagitis at 6 months (PBT = 6%, IMRT = 28%; ( p &lt; 0.0001 )) and risk of grade 3 esophagitis at 15 to 17 months (PBT = 5%, IMRT = 39%; ( p &lt; 0.001 ));</td>
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<td></td>
<td></td>
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<td>No significant differences between groups in risk of</td>
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</table>
Table A6: Study Findings and Author’s Conclusions for Clinical Systematic Reviews and Meta-Analyses

<table>
<thead>
<tr>
<th></th>
<th>Study Findings and Author’s Conclusions</th>
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<tbody>
<tr>
<td><strong>Prostate</strong></td>
<td></td>
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<tr>
<td>PBT, n = 2 studies</td>
<td>3D-CRT</td>
</tr>
<tr>
<td>IMRT, n = 6 studies</td>
<td></td>
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</tbody>
</table>
Table A6: Study Findings and Author’s Conclusions for Clinical Systematic Reviews and Meta-Analyses

<table>
<thead>
<tr>
<th>Various Cancers, n = 1 study(^\text{22})</th>
<th>PBT</th>
<th>Photon modalities</th>
<th>In a retrospective cohort, the risk for progressing to secondary cancer of PBT patients was half that of photon patients controlling for age, sex, tumor site, and year of diagnosis, HR = 0.52 (95% CI = 0.32 to 0.85) after adjustment for potential confounders;(^\text{22})</th>
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<tbody>
<tr>
<td></td>
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<td>Secondary malignancies: PBT = 5.2%, photon = 7.5% (after median follow-up of approximately 6 years);</td>
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<td>No significant differences in the incidence of secondary malignancies per 1000 person years or 10-year cumulative incidence rates, between groups (p = 0.085 for both);</td>
</tr>
</tbody>
</table>

Proton therapy patients may have received 20% of total dose from photon radiation, very few patients received IMRT in photon group, substantial missing data, unknown field size and dose, and variation in ascertainment methods.

\(^\text{aHR} = \text{adjusted hazard ratio}; 3\text{D-CRT} = \text{3-dimensional conformal radiation therapy}; \text{CRT} = \text{conventional radiotherapy}; \text{IMRT} = \text{intensity-modulated radiation therapy}; \text{NR} = \text{not reported}; \text{NSCLC} = \text{non-small-cell lung cancer}; \text{PBT} = \text{proton beam therapy}\)

Toxicity (24 months) (HR = 1.24 [95% CI = 0.53 to 2.94])
- Clinician reported late GU toxicity (24 months) (HR = 0.56 [95% CI = 0.22 to 1.41])
- Reduced acute genitourinary complications at 6 months in PBT group (OR = 0.60 [95% CI = 0.38 to 0.96]);\(^\text{76}\)

Significantly higher risk of GI toxicity at 4 to 5 years \(^\text{43,78}\)
- Increased risk of progression to gastrointestinal toxicity in PBT group (HR = 3.32 [95% CI = 2.12 to 5.20])
- Increased risk of procedures (including colonoscopy) in PBT group (IMRT versus PBT, RR = 0.82 [95% CI = 0.70 to 0.97])
- Diagnoses at 46 to 50 months (IMRT versus PBT, RR = 0.66 [95% CI = 0.55 to 0.79])
<table>
<thead>
<tr>
<th>Type of Cancer, Primary Studies</th>
<th>Intervention</th>
<th>Comparator</th>
<th>ICER or Cost per Outcome</th>
<th>Interpretation or Author’s conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prostate</strong></td>
<td></td>
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</tr>
<tr>
<td>Konski, 2005, USA (2002 costs)</td>
<td>PBT</td>
<td>IMRT</td>
<td>63, 579 USD/QALY</td>
<td>PBT not likely not cost-effective versus IMRT for most prostate cancer patients, but reduced ICER in younger patients</td>
</tr>
<tr>
<td>Lundkvist, 2005, Sweden (2002)</td>
<td>PBT</td>
<td>CRT</td>
<td>$30,001 USD/QALY</td>
<td>PBT may be cost-effective from the Swedish perspective in men aged 65 given appropriate patient selection; however, estimates of incremental cost were likely underestimated, and the estimate of clinical benefit may have been overstated</td>
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<tr>
<td><strong>Breast</strong></td>
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<tr>
<td>Lundkvist, 2005, Sweden (2002)</td>
<td>PBT</td>
<td>Whole breast radiation</td>
<td>General population: $80,596 USD/QALY Women with double cardiac disease risk: $41,491 USD/QALY</td>
<td>PBT not cost-effective in women aged 55 with left-sided breast cancer, but may be “economically beneficial“ in women at higher cardiac disease risk; however, simulated patients were younger than average breast cancer patients and arbitrary assumptions about risk of pneumonitis and sick leave were made</td>
</tr>
<tr>
<td>Lundkvist, 2005, Sweden (2002)</td>
<td>PBT</td>
<td>CRT</td>
<td>#30,551 USD/WALY</td>
<td>PBT not cost-effective versus conventional radiation in women aged 55 years with left-sided breast cancer</td>
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<tr>
<td><strong>Lung</strong></td>
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<tr>
<td>Grutters, 2010, Holland (2012 costs)</td>
<td>PBT</td>
<td>CRT (also carbon ion and SBRT)</td>
<td>Protons and CRT were dominated by alternative therapies</td>
<td>PBT was associated with increased costs at all examined levels – not cost-effective in inoperable stage 1 NSCLC versus alternative therapies; authors suggested interpreting results with caution given uncertainty observed in sensitivity analysis</td>
</tr>
<tr>
<td>Lievens, 2013, Belgium (2012 costs) 10 year time horizon (Abstract)</td>
<td>PBT</td>
<td>IMRT or 3D-CRT</td>
<td>$35,309 USD/QALY versus IMRT $38,505 USD/QALY versus 3D-CRT</td>
<td>In Belgian context, PBT is borderline cost-effective for NSCLC when provided with concurrent chemotherapy, not considering capital investment labor, or operational costs</td>
</tr>
<tr>
<td><strong>Head and Neck</strong></td>
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<tr>
<td>Lundkvist, 2005, Sweden (2002 costs)</td>
<td>PBT</td>
<td>CRT</td>
<td>$4,254 USD/QALY</td>
<td>PBT potentially cost-effective in patients aged 65 y with head and neck cancer compared to CRT; interpret with caution due to lack of long-term toxicity and quality of life data</td>
</tr>
</tbody>
</table>
| Raemakers, 2013, Holland (2010 costs) | PBT (intensity modulated) | IMRT | Costs were higher for PBT versus IMRT ($61,697) | PBT was associated with increased costs at all examined levels and does not appear to be
<table>
<thead>
<tr>
<th>Type of Cancer, Primary Studies</th>
<th>Intervention</th>
<th>Comparator</th>
<th>ICER or Cost per Outcome</th>
<th>Interpretation or Author’s conclusions</th>
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<tbody>
<tr>
<td>Pediatric Tumors</td>
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<tr>
<td>Lundvist 2005, Sweden (2002 costs), Medulloblastoma</td>
<td>PBT</td>
<td>IMRT</td>
<td>NR</td>
<td>PBT superior in children aged 5 y due to less IQ loss, hearing loss, and growth hormone deficiency; however the same utility values were used for pediatric and adult life; quality of life secondary to IQ and hearing loss not considered</td>
</tr>
<tr>
<td>Lundkvist 2005, Sweden (2002 costs), Medulloblastoma</td>
<td>PBT</td>
<td>CRT</td>
<td>-$26,419 USD/QALY</td>
<td>PBT was superior in children aged 5 y compared to CRT; however, did not account for QOL secondary to IQ and hearing loss</td>
</tr>
<tr>
<td>Mailhot-Vega 2013, US (2012 costs), Medulloblastoma</td>
<td>PBT</td>
<td>IMRT</td>
<td>NR (PBT $80,211/17.37; IMRT $112,790/13.91)</td>
<td>PBT superior in children aged 5 y owing to reduction in adverse effects; however did not consider quality of life</td>
</tr>
<tr>
<td>Hirano, 2014, Japan (2012 costs), Medulloblastoma</td>
<td>PBT</td>
<td>IMRT</td>
<td>$11,773 USD/QALY or $21,719 USD/QALY (depending on QOL scale used)</td>
<td>PBT may be cost effective in children aged 6 y; however, IQ and productivity/wage loss were not considered, operational costs may not have been appropriate, and there was high variability in sensitivity analysis</td>
</tr>
<tr>
<td>Mailhot-Vega, 2015, US (2012 costs), Brain tumours requiring hypothalamus RT dose</td>
<td>PBT</td>
<td>IMRT</td>
<td>NR</td>
<td>PBT more cost-effective unless costs exceed $580,000 in children aged 12 y or $725,000 in children aged 4 y additional costs over IMRT; however did not consider IQ or productivity loss, long-term toxicity not considered</td>
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<tr>
<td>Amin, 2014</td>
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<td>Prostate</td>
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<tr>
<td>Prostate, Konski, 2007</td>
<td>PBT (91.8 CGE)</td>
<td>IMRT (81 Gy)</td>
<td>70 year old man 63, 579 USD/QALY 60 year old man 55, 726 USD/QALY</td>
<td>From the US private payer perspective, PBT therapy was not cost-effective compared to IMRT at a WTP threshold of 50 thousand USD</td>
</tr>
<tr>
<td>Prostate, Parthan, 2012</td>
<td>PBT</td>
<td>IMRT</td>
<td>PBT = $69,412 per 8.05 QALY IMRT = $33,069 per 8.11 QALY</td>
<td>From the US payer perspective, assuming equivalent long-term efficacy and a WTP threshold of $50 thousand USD, SBRT was more cost-effective than IMRT or PBT in 65 year old men. While there was no direct comparison reported between PBT and IMRT – costs were higher in the PBT group and QALYs gained were similar between groups.</td>
</tr>
<tr>
<td>Prostate, Ollendorf, 2009</td>
<td>Open prostatectomy</td>
<td>PBT, IMRT and other</td>
<td>PBT $169,867/QALY</td>
<td>From the US private payer perspective using 2009 cost data,</td>
</tr>
<tr>
<td>Type of Cancer, Primary Studies</td>
<td>Intervention</td>
<td>Comparator</td>
<td>ICER or Cost per Outcome</td>
<td>Interpretation or Author's conclusions</td>
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<tr>
<td>Comparators</td>
<td>IMRT</td>
<td>$35,233/QALY</td>
<td>PBT was not cost-effective versus IMRT and considered to have low comparative value in low risk men aged 65 or 55; While QALY's gained were similar, costs were substantially different – PBT had the highest cost and was the least cost-effective overall</td>
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</table>

CFFS = cystic failure-free survival; CRT = conventional radiotherapy; ICER = incremental cost-effectiveness ratio; IMRT = intensity modulated radiation therapy; IQ = intelligence quotient; NR = not reported; PBT = proton beam therapy; QALY = quality adjusted life year; QOL = quality of life; RT = radiation therapy (conventional); SBRT = stereotactic body radiation therapy; US = United States; USD = United States Dollars; WTP = willingness to pay; y = years
### Table A8: Study Findings and Author’s Conclusions for Primary Economic Studies

<table>
<thead>
<tr>
<th>Clinical Population</th>
<th>ICER Threshold</th>
<th>WTP Threshold</th>
<th>Mean Heart Dose (Gy) at which PBT is preferable to photon therapy</th>
<th>Sensitivity Analysisa</th>
<th>Interpretation or Author’s Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mailhot Vega, 2016, Left-Sided Breast Cancer</td>
<td>NR</td>
<td>$50,000 USD</td>
<td>40 y = &gt;10 Gy 50 y = 9 Gy 60 y = 10 Gy</td>
<td>40 y = 9 Gy 50 y = 7 Gy 60 y = 8 Gy</td>
<td>PBT more likely to be cost-effective at WTP thresholds of $50 to 100 thousand USD in patients with a higher risk of CHD, and in women 40 and 50 compared to 60 year old women; In sensitivity analysis accounting for subsequent percutaneous coronary intervention, PBT was more likely to be cost-effective at lower doses than the base-case analysis</td>
</tr>
<tr>
<td>50 year old females with left sided breast cancer and ≥ 1 cardiac risk factor</td>
<td>NR</td>
<td>$50,000 USD</td>
<td>40 y = 6 Gy 50 y = 5 Gy 60 y = 6 Gy</td>
<td>40 y = 5 Gy 50 y = 4 Gy 60 y = 5 Gy</td>
<td></td>
</tr>
<tr>
<td>50 year old females with left sided breast cancer (otherwise healthy)</td>
<td>NR</td>
<td>$50,000 USD</td>
<td>PBT not cost-effective at 40, 50, or 60 years of age at any MHD ≤10 Gy</td>
<td>PBT not cost-effective at 40, 50, or 60 years of age at any MHD ≤10 Gy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$100,000 USD</td>
<td>40 y = &gt;10 Gy 50 y = 9 Gy 60 y = 10 Gy</td>
<td>40 y = 9 Gy 50 y = 7 Gy 60 y = 9 Gy</td>
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</tbody>
</table>

3D-CRT = three dimensional conformal radiotherapy; CHD = coronary heart disease; Gy = Gray; MHD = mean heart dose; NR = not reported; PBT = proton beam therapy; QALY = quality adjusted life years; USD = United States Dollars; WTP = willingness to pay

*aConsidering percutaneous coronary intervention subsequent to coronary heart disease*
APPENDIX 5: Additional References of Potential Interest

**CADTH Rapid Responses related to Proton Beam Therapy**


**Ongoing Primary Studies**

**Breast Cancer**


**Lung Cancer**


Prostate Cancer


Quality of Life in Pediatric Patients


Esophageal Cancer


Glioblastoma


Head and Neck Cancer


Clinical Systematic Reviews

Prostate Cancer


Craniopharyngioma


Safety in Patients with Implanted Cardioverter Defibrillators

Economic Systematic Reviews

Pediatric Central Nervous System Tumors