

## Key Questions and Background

### Proton beam therapy – re-review

#### Background:

##### **Clinical need and target population**

Overall, it's estimated that 1.7 million new cases of cancer are diagnosed yearly and cancerous conditions are responsible for over half a million deaths per year. Treatment options for cancerous and noncancerous conditions vary depending on the type and stage of cancer and can include radiation therapy, chemotherapy, targeted therapy (e.g. inhibitor drugs), immunotherapy (including monoclonal antibodies) and surgery. In recent years the use of proton beam therapy (PBT) has expanded to include a variety of conditions including a number of cancer types, noncancerous brain tumors and cancerous conditions afflicting the central nervous system as well as eyes, lungs, liver, prostate, spine, and pelvis.

##### **Technology of interest**

The use of protons for radiotherapy has a history of over 60 years of clinical use. In conventional radiotherapy, photons deliver radiation across tissue depths on the way toward the target tumor and beyond. In contrast, PBT, which is a form of external beam radiotherapy, deposits peak radiation energy more precisely at or around the target followed by sharp decline in energy output to deeper tissues via a phenomenon known as the Bragg peak (Larsson, 1958). Because the proton beam is focused on a specific area, a greater dose of radiation may be delivered to the target neoplasm(s) while mitigating unwanted radiation delivered to surrounding tissue (Levin, 2005). PBT use was initially directed towards conditions where sparing sensitive adjacent normal tissues was considered to be of utmost importance (such as cancerous or noncancerous malformations of the brain stem, eye, or spinal cord) or for many pediatric tumors because of the particular risk of pronounced acute and long-term toxicity in pediatric patients (Thorp, 2010). PBT may be most promising for tumors in close proximity to organs at risk (OAR).

In the past two decades the number of centers offering PBT has increased to over 20, with more planned or under construction, even given the high cost of facility construction and operation. Despite increasing availability of PBT and its potential for precise delivery of radiation therapy, evidence of its effectiveness compared with other forms of therapy and with the emerging techniques, such as intensity modulated radiation therapy (IMRT) is evolving and currently not unclear for some conditions.

#### Policy context/reason for selection:

This topic was originally reviewed in 2014. It is being re-reviewed in 2018 due to newly available published evidence.

**Final**

## **Objectives**

The aim of this report is to update the 2014 HTA on proton beam therapy (PBT) by systematically reviewing, critically appraising and analyzing new research evidence on the safety and efficacy of PBT, as a primary or as a salvage therapy (i.e., for recurrent disease or failure of initial therapy), for the treatment of multiple cancer types as well as selected noncancerous conditions in adults and children.

## **Key questions (from previous report):**

1. What is the comparative impact of proton beam therapy (PBT) treatment with curative intent on survival, disease progression, health-related quality of life, and other patient outcomes versus radiation therapy alternatives and other cancer-specific treatment options (e.g., surgery, chemotherapy) for the following conditions:
  - a. Cancers
    - i. Bone tumors
    - ii. Brain, spinal, and paraspinal tumors
    - iii. Breast cancer
    - iv. Esophageal cancer
    - v. Gastrointestinal cancers
    - vi. Gynecologic cancers
    - vii. Head and neck cancers (including skull base tumors)
    - viii. Liver cancer
    - ix. Lung cancer
    - x. Lymphomas
    - xi. Ocular tumors
    - xii. Pediatric cancers (e.g., medulloblastoma, retinoblastoma, Ewing's sarcoma)
    - xiii. Prostate cancer
    - xiv. Soft tissue sarcomas
    - xv. Seminoma
    - xvi. Thymoma
    - xvii. Other cancers
  - b. Noncancerous Conditions
    - i. Arteriovenous malformations
    - ii. Hemangiomas
    - iii. Other benign tumors (e.g., acoustic neuromas, pituitary adenomas)
2. What is the comparative impact of salvage treatment (including treatment for recurrent disease) with proton beam therapy versus major alternatives on survival, disease progression, health-related quality of life, and other patient outcomes versus radiation therapy alternatives and other cancer-specific treatment options (e.g., surgery, chemotherapy) for the condition types listed in key question 1?
3. What are the comparative harms associated with the use of proton beam therapy relative to its major alternatives, including acute (i.e., within the first 90 days after treatment) and late (>90 days) toxicities, systemic effects such as fatigue and erythema, toxicities specific to each cancer type (e.g., bladder/bowel incontinence in prostate cancer, pneumonitis in lung or breast cancer), risks of secondary malignancy, and radiation dose?

4. What is the differential effectiveness and safety of proton beam therapy according to factors such as age, sex, race/ethnicity, disability, presence of comorbidities, tumor characteristics (e.g., tumor volume and location, proliferative status, genetic variation) and treatment protocol (e.g., dose, duration, timing of intervention, use of concomitant therapy)?
5. What is the comparative cost-effectiveness of proton beam therapy in the short- and long-term relative to other types of radiation therapy, radiation therapy alternatives or other cancer-specific treatment options (e.g., surgery, chemotherapy)?

**Final scope:** (based on previous report and consideration of public comment)

**Inclusion and exclusion**

Study Component	Inclusion	Exclusion
<b>Population</b>	Adults and children undergoing treatment of primary or recurrent disease to include: <ul style="list-style-type: none"> <li>• Cancers (bone, brain/spinal/paraspinal, breast, esophageal, gastrointestinal, gynecologic, head and neck, liver, lung, ocular, pediatric, and prostate cancers; lymphomas, sarcomas, seminomas, thymomas, other cancers)</li> <li>• Noncancerous conditions (arteriovenous malformations, hemangiomas, other benign tumors).</li> </ul>	<ul style="list-style-type: none"> <li>• Conditions not amenable to proton-beam therapy or for which proton beam therapy would be contra-indicated.</li> </ul>
<b>Interventions</b>	<ul style="list-style-type: none"> <li>• Proton beam therapy (PBT) use as a</li> <li>• Curative therapy</li> <li>• Primary or monotherapy</li> <li>• “Salvage” treatment (e.g. following failure of initial therapy or disease recurrence)</li> <li>• “Boost” mechanism to conventional radiation</li> <li>• Combination therapy with other treatments (e.g., chemotherapy, surgery).</li> </ul>	<ul style="list-style-type: none"> <li>• Devices or therapies that are not FDA approved or cleared</li> </ul>
<b>Comparator</b>	<ul style="list-style-type: none"> <li>• Other radiation therapy alternatives (e.g., intensity-modulated radiation therapy (IMRT), stereotactic radiation techniques, other external beam therapies, and brachytherapy)</li> <li>• Other treatment alternatives specific to each condition type treated; may include chemotherapy, immunotherapy, surgical procedures, and other devices (e.g., laser therapy for ocular tumors).</li> <li>• Dose/fractionation comparison (will be included for completeness as was done in prior report) but not formally evaluated as evidence</li> </ul>	<ul style="list-style-type: none"> <li>• Technologies or treatments that are not widely available or are no longer routinely used</li> <li>• Devices or therapies that are not FDA approved or cleared</li> </ul>

Study Component	Inclusion	Exclusion
<b>Outcomes</b>	<p><b>Clinical outcomes:</b></p> <p><u>Primary</u></p> <ul style="list-style-type: none"> <li>• Overall survival/disease-free survival</li> <li>• All-cause and/or disease-related mortality</li> <li>• Direct measures of tumor regression, control or recurrence</li> <li>• Incidence of metastases</li> </ul> <p><u>Secondary or indirect (intermediate) measures</u></p> <ul style="list-style-type: none"> <li>• Patient reported outcomes, including health-related quality of life (HrQoL), based on validated instruments</li> <li>• Requirements for subsequent therapy</li> <li>• Other outcomes specific to particular conditions (e.g., visual acuity for ocular tumors, shunt requirements for arteriovenous malformations)</li> <li>• Intermediate measures of tumor recurrence such as biochemical measures</li> </ul> <p><b>Safety outcomes:</b></p> <ul style="list-style-type: none"> <li>• Treatment-related harms, with a focus on adverse effects requiring medical attention, to include:                             <ul style="list-style-type: none"> <li>◆ Generalized effects (e.g., fatigue, erythema)</li> <li>◆ Localized toxicities specific to each condition (e.g., urinary incontinence in prostate cancer, pulmonary toxicity in lung or breast cancer) to include consideration of:                                     <ul style="list-style-type: none"> <li>▪ Early (≤90 days post-treatment)</li> <li>▪ Late (&gt;90 days post-treatment)</li> </ul> </li> </ul> </li> <li>• Secondary malignancy risk due to radiation exposure</li> </ul> <p><b>Economic outcomes:</b></p> <ul style="list-style-type: none"> <li>• Long term and short term comparative cost-effectiveness measures (e.g. ICER)</li> </ul>	<ul style="list-style-type: none"> <li>• Non-clinical outcomes</li> </ul>
<b>Study Design</b>	<ul style="list-style-type: none"> <li>• Focus will be on highest quality (lowest risk of bias) comparative studies (e.g., randomized controlled trials, comparative cohort studies with concurrent controls) for questions 1-4.</li> <li>• Case series will be considered but will not be the primary focus of evaluation for each key question.</li> <li>• Case series in children with &lt;10 patients will be considered if no comparative studies are available.</li> <li>• Case series designed specifically to evaluate safety may be included</li> <li>• Dosimetry and planning studies may be included for context. To the extent that they specifically answer the key questions, information will be included as part of the evidence base.</li> </ul>	<ul style="list-style-type: none"> <li>• Simulation studies</li> <li>• Studies of low quality (high risk of bias)</li> <li>• Comparative studies with fewer than 10 per treatment arm</li> <li>• Case reports</li> <li>• Case series in adults with &lt;30 patients; Case series of ≥ 10 patients may be considered for very rare conditions.</li> <li>• Studies comparing modes of therapy; dose comparisons may be included for completeness/context per previous report</li> </ul>

Study Component	Inclusion	Exclusion
<b>Publication</b>	<ul style="list-style-type: none"> <li>Formal, full economic studies will be sought for question 5. Studies using modeling may be used to determine cost-effectiveness.</li> <li>Studies published in English in peer reviewed journals, technology assessments or publically available FDA reports</li> <li>Studies published subsequent to the 2014 report (previous report search date through February 2014)</li> <li>For question 5, comparative, full formal economic analyses (e.g., cost-effectiveness, cost-utility studies) published in English in a peer reviewed journal</li> </ul>	<ul style="list-style-type: none"> <li>Abstracts, editorials, letters</li> <li>Duplicate publications of the same study that do not report different outcomes or follow-up times</li> <li>Single reports from multicenter trials</li> <li>White papers</li> <li>Narrative reviews</li> <li>Articles identified as preliminary reports when full results are published in later versions</li> <li>Incomplete economic evaluations such as costing studies</li> </ul>

Figure 1. Analytic framework

