

Final Key Questions and Background

Proton Beam Therapy

Background

It is estimated that nearly 14 million Americans are cancer survivors and that 1.7 million new cases will be diagnosed in 2013. Among the treatment options for cancer, radiation therapy is commonly employed; an estimated 50% of patients receive radiation therapy at some point during the course of their illness.

The use of external beam radiation therapy (EBRT) for the treatment of cancer dates back more than 100 years. Conventional EBRT is comprised of photon (X-ray) beams and is targeted directly at solid tumors to destroy cancerous cells. While photons are an effective means of eliminating malignant cells, these high-energy x-rays also cause damage to normal tissue along the beam path as they enter and exit the body. Toxicities associated with injury to normal tissue include those specific to the anatomic location being treated (e.g., urinary or bowel dysfunction in patients treated for prostate or gynecological cancers) as well as general effects such as nausea and fatigue. Exposure of normal tissues to radiation also may increase the future risk of secondary malignancies.

To address these concerns, advanced techniques in the application of X-rays to reduce toxicity and more accurately target the cancer have been developed, including CT-based 3D-conformational radiation therapy (3D-CRT), intensity-modulated radiation therapy (IMRT), and stereotactic radiation therapy. An alternate approach to the use of photons is the use of heavy particles such as electrons, neutrons and protons as agents of radiation energy deposition. Of particular interest is proton beam therapy (PBT), as the physical properties of protons permit dose delivery at specific tissue depths. Protons deliver the bulk of their radiation energy at the end of their range of penetration, a phenomenon known as the “Bragg peak.” By focusing delivery of radiation to the target tumor, it is believed that PBT may reduce toxicity associated with normal tissue damage. However, because of its physical properties, PBT also has more uncertainties in delivery than photon radiation, which may also affect clinical outcomes.

Policy Context

PBT has the potential to be an important therapeutic option for specific cancers. Interest in its use for a variety of clinical applications has grown substantially in recent years. There are 12 operating PBT facilities in the U.S., with the most recent facility opening in Seattle, WA in March 2013. Fifteen additional centers are currently under construction or in development in the U.S.

However, there are significant uncertainties with the use of PBT. Some of these are technical. For example, treatment planning and delivery is more complex with protons and the location of the Bragg peak may be affected by organ motion, anatomical variation, and other factors. In addition, there are questions regarding how the more targeted treatment delivery with PBT translates into comparative effects on cancer control, toxicity, and health-related quality of life relative to other treatment approaches. These uncertainties have led to variability in coverage policy for PBT among public and private payers.

In addition, the cost of treatment with PBT may be substantially higher than for other EBRT modalities such as IMRT and 3D-CRT. Proton facilities must be able to house large cyclotrons to effectively accelerate protons for treatment delivery, and can cost anywhere from \$25 million to over \$200 million to construct. In addition, Medicare payments per dose fraction of PBT are 1.5-2 times higher than those for IMRT.

With the recent availability of PBT in Washington State, it is timely to assess the evidence on its clinical benefits, potential harms, and costs in comparison to alternative treatment options for a variety of cancers.

Project Scope

This project will involve a systematic review of the published literature on the use of PBT and its relevant comparators in the conditions for which PBT has been tested or is being promoted (note that PBT is also used for arteriovenous malformations and other noncancerous conditions). Specific details on the proposed scope (Population, Intervention, Comparators, and Outcomes, or PICO) are detailed in the following sections.

Population

The target population for this review will be adults and children undergoing treatment for a variety of cancer types as well as noncancerous conditions (see Key Question 1). All specific conditions within the broad categories presented in Key Question 1 will be considered. All levels of disease within these categories also will be considered.

Intervention

We will evaluate the use of PBT as an independent therapeutic approach as well as in combination with other treatment such as chemotherapy or surgery. Additionally, studies that evaluate the use of PBT as a “boost” therapy in combination with conventional photon therapy will be considered. Analyses will focus on use of PBT as initial treatment with curative intent as well as for “salvage” treatment (i.e., after failure of initial therapy or disease recurrence).

Comparators

Primary comparators of interest will include radiation therapy alternatives such as brachytherapy (radioactive seed implants), IMRT and 3D-CRT. For some cancers and other conditions, the most relevant alternative treatments may be non-radiation-based, however (e.g., chemotherapy, surgery). In these instances, we will consider the most common treatment employed to represent PBT's primary comparator.

Outcomes

Outcomes of interest will include overall and disease-free survival, all-cause and disease-related mortality, local and/or regional tumor control, incidence of metastases, cancer recurrence, requirements for subsequent treatment, and health-related quality of life. Other outcomes specific to each condition will also be reported (e.g., visual acuity in uveal melanoma, shunt requirements for arteriovenous malformations).

Acute (i.e., within the first 90 days after treatment) and late (>90 days) toxicities associated with PBT also will be assessed. These will include systemic effects such as fatigue and erythema as well as toxicities specific to each cancer type (e.g., urinary incontinence in prostate cancer, pulmonary toxicity in lung or breast cancer).

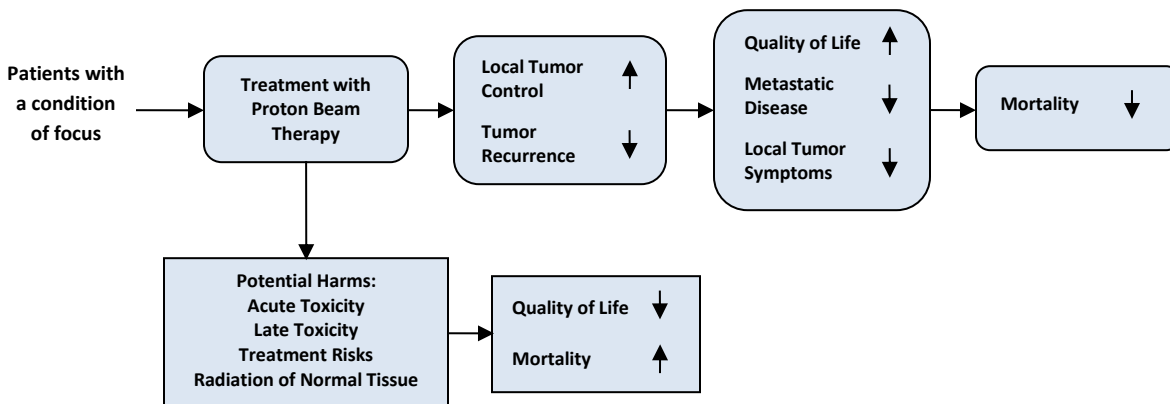
Importantly, while information from treatment planning and dosimetry studies will be used to set a context for risks of secondary malignancy and other harms from radiation of normal tissue, abstraction of outcomes data will be limited to direct measures of clinical benefit and harm as described above.

Information on the costs and cost-effectiveness of PBT relative to treatment alternatives also will be collected from available studies, including initial costs of treatment as well as downstream costs such as management of toxicity and long-term morbidity, requirements for subsequent therapy, and work or productivity loss.

Analytic Framework

The proposed analytic framework for this project is depicted below. Because it is expected that there will be little data directly linking treatment with PBT to patient survival and mortality, judgments about the effectiveness of this intervention will likely rest predominantly upon consideration of the strength of intermediate endpoints and evaluation of treatment-associated risks.

Analytic Framework: Proton Beam Therapy



Key Questions

- 1) What is the comparative impact of proton beam therapy 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. Brain, spinal, and paraspinal tumors
 - ii. Breast cancer
 - iii. Esophageal cancer
 - iv. Gastrointestinal cancers
 - v. Gynecologic cancers
 - vi. Head and neck cancers (including skull base tumors)
 - vii. Liver cancer
 - viii. Lung cancer
 - ix. Lymphomas
 - x. Ocular tumors
 - xi. Pediatric cancers (e.g., medulloblastoma, retinoblastoma, Ewing's sarcoma)
 - xii. Prostate cancer
 - xiii. Sarcomas
 - xiv. Seminoma
 - xv. Thymoma

- 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 age, race/ethnicity, 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 are the costs and cost-effectiveness of proton beam therapy relative to radiation therapy alternatives and other condition-specific treatment options (e.g., surgery, chemotherapy)?

Public Comment & Response

See [*Draft Key Questions: Public Comments & Response*](#) document published separately.