

OVERVIEW

Proton Beam Therapy

Introduction

Protons are positively charged subatomic particles that feature particular characteristics of interest for clinical use. Specifically, proton beams are known to deposit the bulk of their radiation energy at the end of their range of penetration, or what is referred to as the Bragg peak. This feature allows for targeted dosing of proton radiation to a particular tumor site, with minimal dose delivery to the surrounding normal tissue, offering a theoretical advantage over the delivery of photons (i.e., gamma- or X-rays), which deposit their energy along a more disseminated distribution. This has led to an increase in the use of protons to treat clinically localized prostate cancer, in which the tradeoff between tumor control and perineal toxicity is an important consideration.

Clinical use of proton radiation, either alone or as a boost to photon therapy, was first employed at 2 major US centers (Loma Linda, CA and Boston, MA) in the 1970s, and has grown steadily over time; there are now approximately 25 operating or planned major proton therapy centers worldwide, and over 50,000 patients have received clinical proton beam therapy (PBT). Among patients with prostate cancer, protons have been used both in combination with conventional photon radiation (i.e., “boost” therapy) and alone. In either case, total dose to the patient currently ranges from 75-80 Gray (Gy) units. Given the significant expense involved in constructing proton treatment facilities (typically exceeding \$100 million for full-sized facilities), questions have been raised regarding whether the theoretical advantages of PBT have translated into objective improvements in local tumor control and survival.

Other questions remain, many of which this assessment seeks to address:

- 1) Impact of PBT on local toxicity, recurrence, and development of secondary cancers relative to existing standard therapy
- 2) Variation in treatment planning and delivery among proton centers
- 3) Cost, current reimbursement levels, and cost-effectiveness of PBT relative to existing standard therapy

Professional Organizations and Agency Recommendations:

- National Comprehensive Cancer Network (2007): The NCCN/ACS Prostate Cancer Panel groups PBT with all other forms of external beam radiation; panel consensus was that “modern radiotherapy and surgical series show similar progression-free survival in low-risk patients”, and that radiation therapy featuring use of conformal or intensity-modulated techniques should be considered a principle treatment option for clinically-localized disease.
- American Cancer Society (2006): The ACS concludes that early research results on PBT in prostate cancer are promising, but that long-term advantages over other forms of external beam radiation have not been proven.

- American College of Radiology (2006): Guidelines for external beam radiation therapy are currently being updated. The ACR appropriateness criteria for treatment planning consider PBT-, three-dimensional conformal radiation therapy (3D-CRT)-, and intensity-modulated radiation therapy (IMRT)-based plans appropriate for clinically-localized disease, although IMRT plans receive a slightly higher score on ACR's appropriateness rating system (8 vs. 7 on a 1-9 scale).
- American Urological Association (2007): The AUA has concluded that external beam radiotherapy is considered one of the viable monotherapy options for clinically-localized, low-risk prostate cancer, along with active surveillance, interstitial brachytherapy, and radical prostatectomy, and that "study outcomes data do not provide clear-cut evidence for the superiority of any one treatment"; no distinction is made by type of external beam.

Recent Technology Assessments & Systematic Reviews

Proton beam radiotherapy does not appear to have been extensively evaluated by HTA organizations for prostate cancer. Results of available systematic reviews are summarized below.

- California Technology Assessment Forum (CTAF, USA) (2007). While not an explicit topic for assessment, PBT was discussed at CTAF's recent roundtable on intensity-modulated radiation therapy (IMRT) for prostate cancer. The roundtable concluded that PBT was distinct form of radiotherapy based on differences in radiobiologic principles between protons and photons, and should be a future focus for data collection, clinical trials, and technology assessment.
- Center for Evaluation and Diffusion of Innovative Technologies (CEDIT, France) (2002): CEDIT's original guidance suggested that PBT has only shown proven effectiveness in melanomas of the eye and skull-based chordomas and chondrosarcomas. There has been no update to this guidance.
- Brada et al. (2007): A recent systematic review of clinical evidence sponsored by the Royal Marsden National Health Service Foundation (UK) concludes that "there are currently no studies demonstrating improved tumour control or survival" with PBT for localized prostate cancer compared to the best available photon therapy.
- Olsen et al. (2007): Another systematic review of clinical effectiveness, sponsored by the Norwegian Knowledge Centre for the Health Services, indicates that the available evidence is "largely inconclusive with respect to effectiveness of proton therapy of prostate cancer," in part because PBT patients in most of the comparative observational studies had less advanced disease than those receiving conventional radiotherapy.

Coverage Policies

- Medicare: There have been no National Coverage Decisions on PBT. Most Local Coverage Decisions allow for the use of PBT for prostate cancer only when there is documentation in the patient's record supporting its use over other treatment options and the following criteria are met:
 - For primary lesions, treatment intent must be curative; for metastatic lesions, there must be an expectation of long-term (>2y) benefit and complete eradication of metastases can only reasonably be expected through the dosimetric advantages of PBT;

AND at least one of the following conditions must be present:

 - Dose constraints to normal tissues limit the total dose of radiation safely deliverable to the tumor with other indicated methods; OR
 - There is reason to believe that doses generally thought to be above the level otherwise attainable with other methods might improve control rates; OR
 - Higher levels of precision associated with proton beam therapy as compared to other radiation methods are clinically relevant and necessary.
- Empire Blue Cross / Blue Shield (Wellpoint): PBT is considered medically necessary for the treatment of prostate cancer, but current data do not support any claims of superiority over IMRT or conformal radiation therapy.
- United Healthcare: PBT is considered equivalent, but not superior to, other forms of external radiation therapy for prostate cancer, and is covered as an in-network benefit only where other forms of external beam radiation are unavailable in the network.
- Humana: PBT is considered a covered benefit for the treatment of prostate cancer.
- Regence: Coverage of PBT is allowed as a primary therapy for clinically localized prostate cancer.
- Aetna: PBT is considered to be medically necessary for the treatment of prostate cancer; use of stereotactic techniques for administration of PBT is not covered, however.
- Cigna: PBT is considered equivalent, but not superior to, conventional external beam radiotherapy, and is not covered as an in-network benefit when conventional techniques are available in the network.
- PriorityHealth: PBT for prostate cancer is not covered, because "alternate equally effective forms of therapy which are more cost-effective exist."

Research in Progress

No comparative studies of PBT monotherapy are in progress (source: www.clintrials.gov). A small, open-label, single-center evaluation of salvage PBT is currently ongoing in 85 men, aged 18 years and older, with previously-treated prostate cancer that is stage T1c-T2b and Gleason ≥ 5 . Weekly doses of 82 Gy are being delivered; primary endpoints include both acute and late morbidity following PBT as well as level of cancer control. Patients are being followed for up to 5 years following 8 weeks of PBT.