PROTON BEAM THERAPY FOR PROSTATE CANCER

A Technology Assessment

INTRODUCTION

The California Technology Assessment Forum is requested to review the scientific evidence for the use of proton therapy for the treatment of localized prostate cancer. This is the first time that CTAF has addressed this topic.

BACKGROUND

Epidemiology of Prostate Cancer

Prostate cancer is the most commonly diagnosed cancer in U.S. men and is second only to lung cancer as a cause of cancer death in U.S. men. It is estimated that in the year 2012, there will be 241,170 new cases in the U.S. and that 28,170 men will die from prostate cancer.¹

Treatment options for prostate cancer depend on extent of disease at diagnosis. For men with clinically localized prostate cancer (cancer confined to the prostate), treatment
options focus on more local approaches, whereas systemic approaches, such as androgen deprivation therapy, are used in men with more distant disease. For men who have prostate cancer that extends beyond the prostatic capsule, into the seminal vesicles or the adjacent nodes, radical prostatectomy is sometimes combined with adjuvant radiation therapy.

A particular challenge in the treatment of prostate cancer is that because of the prolonged natural history of prostate cancer, many men will die WITH but not FROM prostate cancer, whereas some will develop metastatic and potentially fatal disease. Risk stratification helps identify which patients are low versus high risk and can be helpful in guiding therapy. Risk stratification for prostate cancer includes the following: clinical stage of disease, baseline serum prostate specific antigen (PSA) level, the Gleason score and the extent of prostatic involvement. The Gleason score is a grading scale (2-10) for prostate cancer tissue and indicates the likelihood that the cancer tumor will spread. Higher Gleason scores show greater differences between the cancer tissue and normal prostate tissue and indicates greater likelihood of the cancer tissue to metastasize.

Very low risk clinically localized prostate cancer is defined as disease detected by biopsy only (no abnormalities detected on rectal examination or imaging), Gleason score of 6 or less on biopsy and a serum PSA <10ng/ml. Within the prostate, the extent of disease must be limited (fewer than three positive biopsy cores with less than 50% involvement in any core and a PSA density of less than 0.15 ng/mL/gram).

Low risk, clinically localized prostate cancer is disease limited to one lobe of the prostate or with no apparent tumor (diagnosis based only on biopsy, serum PSA < 10 ng/ml and a Gleason score ≤ 6.
Men with low or very low risk prostate cancer are typically offered treatment options that include active surveillance, radiotherapy and radical prostatectomy.

Treatment of Localized Prostate Cancer

Standard treatment options for men diagnosed with localized prostate cancer include radiation therapy (external beam or brachytherapy), radical prostatectomy and for some patients, active surveillance. When disease has spread through the prostatic capsule, prostatectomy may be combined with adjuvant radiation therapy or androgen deprivation therapy may be added to radiation therapy.

1. Role of prostatectomy for treatment of localized prostate cancer

Radical prostatectomy is an established treatment option for localized prostate cancer. The entire prostate is removed. Prostatectomy has been associated with high rates of long term cancer control, but is also associated with significant complications including incontinence and impotence.

2. Role of external beam radiation therapy for localized prostate cancer

The overall goal of radiation therapy for prostate cancer is to deliver a therapeutic dose of radiation to the tumor while minimizing radiation of surrounding normal tissue. External beam radiotherapy uses an external radiation source to radiate the prostate and a small amount of surrounding tissue. The standard technique by which the radiation is administered is a three dimensional conformal radiation therapy technique (3D-CRT). This
technique has replaced the previously used two dimensional approaches, which are now considered outdated. Intensity modulated radiation therapy is an advanced type of 3D-CRT. The radiation beam varies in intensity with the goal of targeting a complex tumor more effectively and minimizing the impact on surrounding tissues.

In addition to recommending the use of 3D conformal techniques, the National Comprehensive Cancer Network (NCCN) Guidelines in Oncology recommends that a conventional dose of 70 Gy is not considered adequate and recommends doses between 75.6 and 79 Gy for individuals with low risk prostate cancer. For patients with intermediate or higher risk disease, they recommend that doses up to 81 Gy are appropriate.


Brachytherapy involves the implantation of a radioactive source directly into the prostate. Since the radiation source is within the tumor, the goal is to maximize the radiation to the tumor, while minimizing the effect on surrounding normal tissues. Treatment options include implanting a permanent radiation source, usually using iodine-125 or palladium-103 or a temporary radiation source such as iridium-192.

Technologic Advances in Prostate Cancer Treatment

Prostate cancer treatment is an area where there have been many recent technologic advances. These advances include minimally invasive radical prostatectomy, intensity modulated radiation therapy (IMRT) and proton therapy. Adoption of these technologies resulted in a $350 million increase in health care expenditures in 2005.
Proton beam therapy

Proton beam therapy is a type of external beam radiotherapy using ionizing radiation. The theoretic advantage of using protons for radiotherapy is that because of their relatively large mass, there is less scatter and therefore the radiation dose can be more concentrated on the tumor. As charged particles move through the tissue, they slow down and energy is transferred to adjacent tissues. Most of the energy gets deposited at the end of a “linear track.” known as the “Bragg Peak.” For protons, the dose of radiation beyond the Bragg peak drops quickly to zero (exit dose) thereby limiting the impact of the radiation on tissue beyond the Bragg peak. Thus, tissue that is beyond or distal to the tumor receive minimal radiation, whereas tissues that are closer to the body surface than the tumor will still receive some radiation.

The use of proton beams or particle therapy as an oncologic treatment was initially proposed in 1946 by Dr. Robert Wilson. During the 1950s, particle therapy use began at the Lawrence Berkeley Laboratory, the Harvard Cyclotron and in Uppsala, Sweden. Loma Linda University opened the first hospital based facility and started treating patients in the 1990s. Massachusetts General Hospital also has a proton facility.

Proton beam therapy can be given either by itself or as a boost to x-ray external beam radiotherapy. Proton beam therapy boost can be compared with either no boost or an x-ray boost. Proton beam therapy (alone or as a boost) can be compared with other prostate cancer treatments including brachytherapy, watchful waiting, radical prostatectomy or standard radiotherapy.
Radiation therapy dose is typically measured in Gray units (e.g., total dose was 70 Gy). The relative biological effectiveness (RBE) is the ratio of the photon dose to the particle dose required to produce the same biological effect. For proton beams, the relative biological effectiveness is 1.1. To measure the total radiation dose with proton beams, Gray equivalents (GyE) or cobalt Gray equivalents (CGE) are often used with protons. The CGE is the Gray multiplied by the RBE factor specific for the beam used.

Proton beam therapy has been used for the treatment of many cancers, including lung, hepatocellular, head and neck, cervical, renal cell, bone and soft tissue sarcomas, melanoma, chordoma and chondrosarcomas of the skull base, prostate cancer and pediatric malignancies. For some of these cancers, such as large uveal melanomas and selected pediatric malignancies, particle therapy is considered the standard of care, but for other cancers, the use of proton beam therapy has been more controversial. The use of proton beam therapy is increasing as more proton beam treatment centers are opening, and direct to consumer advertising is likely to lead to an increase in use.9,10 The goal of this assessment is to evaluate the evidence for the use of proton beam therapy in the treatment of localized prostate cancer.

TECHNOLOGY ASSESSMENT (TA)

TA Criterion 1: The technology must have final approval from the appropriate government regulatory bodies.
Proton beam therapy is a form of external radiotherapy using ionizing radiation. It is a procedure and therefore not under FDA regulations and oversight. The equipment used to create and deliver the proton beam (cyclotron, synchrotron, magnets, and other pieces of equipment to modify the range of protons and to shape/focus the beam) is considered a medical device and under FDA regulations and oversight.

TA Criterion 1 is met.

TA Criterion 2: The scientific evidence must permit conclusions concerning the effectiveness of the technology regarding health outcomes.

The Medline database, Cochrane clinical trials database, Cochrane reviews database and the Database of Abstracts of Reviews of Effects (DARE) were searched using the key words: “prostate cancer” and “proton therapy” or “protons.” The search was performed from database inception through August, 2012. The bibliographies of systematic reviews and key articles were manually searched for additional references. The abstracts of citations were reviewed for relevance and all potentially relevant articles were reviewed in full.

- Study had to evaluate proton beam therapy as a treatment for prostate cancer
- Study had to evaluate clinical outcomes
- Included only humans
- Published in English as a peer reviewed article
Our search revealed 250 potentially relevant articles. We reviewed all the titles and identified 22 potentially relevant abstracts. Abstracts were reviewed in full and we identified 13 studies as potentially relevant for inclusion. Reasons for exclusion included not focusing on clinically relevant outcomes, or being a duplicate of an earlier publication.

A total of 13 studies evaluated the use of proton beam therapy for the treatment of prostate cancer and assessed clinical outcomes. Seven of these studies were non-comparative studies and six were comparative (Table 3). Of the non-comparative studies, two were randomized and the remaining four were not.

Level of Evidence: 2,3,5

TA Criterion 2 is met
Table 1: Non-comparative studies of the use of Proton Beam Therapy for the Treatment of Prostate Cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>N</th>
<th>Location</th>
<th>Intervention</th>
<th>Inclusion Criteria</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mayahara, 2007</td>
<td>Retrospective cohort</td>
<td>287</td>
<td>Japan</td>
<td>Proton therapy 74GyE</td>
<td>T1-4NoMo prostate cancer and treated with proton therapy (Dose 76Gye)</td>
<td>Acute Genitourinary morbidity</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Acute Gastrointestinal Morbidity</td>
</tr>
<tr>
<td>Mendenhall, 2012</td>
<td>Retrospective cohort</td>
<td>211</td>
<td>Florida</td>
<td>78-82 CGE</td>
<td>Patients on e approved protocols with low risk, intermediate risk and high risk prostate cancer with at least 2 year follow up</td>
<td>Disease progression</td>
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<tr>
<td></td>
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<td>78 CGE for low risk disease</td>
<td></td>
<td>GI toxicity</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>78 CGE for intermediate risk disease</td>
<td></td>
<td>GU toxicity</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td>78 CGE for high risk with docetaxel and androgen deprivation</td>
<td></td>
<td></td>
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<tr>
<td>Nihei, 2005</td>
<td>Phase II</td>
<td>30</td>
<td>Japan</td>
<td>76 Gy XRT plus proton boost</td>
<td>T1-3N0M0</td>
<td>GI toxicities</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>GU toxicities</td>
</tr>
<tr>
<td>Nihei, 2011</td>
<td>Multi-institutional Phase II</td>
<td>151</td>
<td>Japan</td>
<td>74Gye proton therapy (included boost with intermediate risk patients)</td>
<td>T1-2 N0M0</td>
<td>Late Grade 2 or greater Rectal Toxicity at 2 years</td>
</tr>
<tr>
<td>Gardner, 2002</td>
<td>Subgroup analysis in long term survivors of Phase II study and experimental arm of RCT</td>
<td>39</td>
<td>Boston, MA</td>
<td>XRT plus photon boost 77.4Gy</td>
<td>T3-4 survivors of Phase II study and experimental arm of RCT [Duttenhaver, 1983; Shipley, 1979]</td>
<td>Late normal tissue sequelae</td>
</tr>
<tr>
<td>Slater, 2004</td>
<td>Retrospective Cohort</td>
<td>1255</td>
<td>Loma Linda, CA</td>
<td>XRT plus proton boost 75Gy</td>
<td>Localized prostate cancer (stages Ia-III)</td>
<td>Freedom from biochemical evidence of disease</td>
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<td></td>
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<td>Failure: 3 consecutive rises in PSA levels with the date of failure being midway between the nadir and the first rise</td>
</tr>
<tr>
<td>Johannson, 2012</td>
<td>Retrospective cohort</td>
<td>278</td>
<td>Sweden</td>
<td>XRT plus proton boost 70 Gy</td>
<td>Low, medium and high risk localized prostate cancer</td>
<td>5 year PSA progression free survival GI and GU toxicities</td>
</tr>
</tbody>
</table>

GyE: Gray Equivalents  
CGE: Cobalt Gray Equivalents  
T_N_M_: A staging system for prostate cancer. T = measures the extent of the primary tumor, N = whether the cancer has spread to nearby lymph nodes, and M = absence or presence of metastases  
GI: Gastrointestinal  
GU: Genitourinary  
XRT: X-ray therapy  
PSA: Prostate Specific Antigen
Table 2: Outcomes of non-comparative studies of the use of proton beam therapy for the treatment of prostate cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>N</th>
<th>Duration of follow-up</th>
<th>Main Outcomes</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mayahara, 2007</td>
<td>Retrospective cohort</td>
<td>287</td>
<td></td>
<td>No grade 2 or higher GI morbidity</td>
<td>87% of patients with GU symptoms had relief with alpha blocker therapy</td>
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<td></td>
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<td></td>
<td></td>
<td>39% and 1% had Grade 2 and Grade 3 GU morbidities</td>
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<tr>
<td>Mendenall, 2012</td>
<td>Retrospective cohort</td>
<td>211</td>
<td>Minimum 2 years mean not reported</td>
<td>1/82 intermediate risk patients with disease progression</td>
<td>Early outcomes</td>
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<td>2/40 high risk patients with disease progression</td>
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<td>1.9% Grade 3 GU symptoms</td>
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<td></td>
<td></td>
<td>0.5% Grade 3 GI toxicities</td>
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<tr>
<td>Nihei, 2005</td>
<td>Phase II</td>
<td>30</td>
<td>30 months</td>
<td>No Grade 3 or greater acute or late toxicities</td>
<td>Feasibility study</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td>6 patients had biochemical relapse</td>
<td></td>
</tr>
<tr>
<td>Nihei, 2011</td>
<td>Multi-Institutional Phase II</td>
<td>151</td>
<td>43.4 months</td>
<td>At two years, incidence of late Grade 2 or greater: rectal toxicity 2% (95% C.I. 0-4.3%) and bladder toxicity 4.1% (95% C.I. 0.9-7.3%)</td>
<td>Long term follow up of patients already included in other studies</td>
</tr>
<tr>
<td></td>
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<td></td>
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<td></td>
<td>Few serious effects</td>
</tr>
<tr>
<td>Gardner, 2002</td>
<td>Subgroup analysis in long term survivors of Phase II study and experimental arm of RCT</td>
<td>39</td>
<td>13.1 years</td>
<td>Grade 2 or greater GU morbidity at 15 years: 59%</td>
<td></td>
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<tr>
<td></td>
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<td></td>
<td>Grade 2 or greater hematuria at 5 years: 21%; at 15 years: 47%</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Grade 2 or greater GI morbidity at 5 years: 13%; at 15 years: 13%</td>
<td></td>
</tr>
<tr>
<td>Slater, 2004</td>
<td>Retrospective cohort</td>
<td>1,255</td>
<td>63 months</td>
<td>Overall biochemical disease free survival 73%</td>
<td></td>
</tr>
<tr>
<td>Johansson, 2012</td>
<td>Retrospective cohort</td>
<td>278</td>
<td>57 months</td>
<td>5 year PSA progression free survival: 100%, 95% and 74% for low, intermediate and high risk</td>
<td>Bladder toxicities (not GI) were dose limiting</td>
</tr>
</tbody>
</table>

GI: Gastrointestinal
GU: Genitourinary
C.I.: Confidence Interval
RCT: Randomized Controlled Trial
PSA: Prostate Specific Antigen
Table 3: Description of Comparative Studies of the Use of Proton Beam Therapy for the Treatment of Prostate Cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>N</th>
<th>Location</th>
<th>Inclusion Criteria</th>
<th>Intervention</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROG/ACR 95-09, [Zietman, 2010; Zietman, 2005; Talcott, 2010]</td>
<td>RCT</td>
<td>393</td>
<td>Loma Linda University, CA and Massachusetts General, Boston MA</td>
<td>Stage T1b through T2b prostate cancer and PSA &lt;15 ng/ml</td>
<td>External radiation with a combination of conformal photon and proton beams to a total dose of 70.2Gy (conventional dose) or 79.2Gy (high dose)</td>
<td>Biochemical Failure (Increasing PSA level 5 years after treatment) Local Failure GI and GU morbidity Overall survival</td>
</tr>
<tr>
<td>Shipley, 1995</td>
<td>Phase III</td>
<td>202</td>
<td>Boston, MA</td>
<td>Stage T3-T4, N0-2, Mo</td>
<td>10-25 MV photons with conformal protons to total dose of CGE or XRT to dose of 67.2Gy</td>
<td>Overall survival (OS), disease specific survival (DSS) and total recurrence-free survival (TRFS) Local control (digital rectal and rebiopsy negative)</td>
</tr>
<tr>
<td>Sheets, 2012</td>
<td>Population based registry-propensity score matched comparison</td>
<td>1,368</td>
<td>U.S. 16 population based cancer registries</td>
<td>Patients with nonmetastatic prostate cancer</td>
<td>IMRT versus proton therapy</td>
<td>Rates of GI and urinary morbidity, erectile dysfunction, hip fractures and additional cancer therapy</td>
</tr>
<tr>
<td>Duttenhaver, 1983</td>
<td>Phase I/II comparison</td>
<td>180</td>
<td>Boston, MA</td>
<td>Localized prostate cancer (T1-4)</td>
<td>XRT 50Gy versus protons plus XRT50Gy plus 74 CGE proton boost</td>
<td>Survival, disease free survival and local recurrence free survival</td>
</tr>
<tr>
<td>Galbraith, 2001</td>
<td>Survey</td>
<td>185</td>
<td>Loma Linda,</td>
<td>Men with prostate cancer who had 1)watchful waiting, 2)surgery, 3) conventional</td>
<td>Quality of Life Index Medical Outcomes study General</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Type</td>
<td>N</td>
<td>Location</td>
<td>Inclusion Criteria</td>
<td>Intervention</td>
<td>Outcomes</td>
</tr>
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<td>---------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Coen, 2012</td>
<td>Case-matched analysis</td>
<td>282 (141 part of the PROG/ACR 95-09, trial)</td>
<td>Loma Linda and Boston</td>
<td>Localized Prostate cancer</td>
<td>141 patients in high dose proton/XRT arm of PROG/ACR95-09 matched with 141 patients who received brachytherapy</td>
<td>Biochemical Failure</td>
</tr>
</tbody>
</table>

PROG/ACR: Proton Radiation Oncology Group (PROG)/American College of Radiology (ACR) 95-09 (a randomized trial)
RCT: Randomized Controlled Trial
T_N_M: A staging system for prostate cancer. T = measures the extent of the primary tumor, N = whether the cancer has spread to nearby lymph nodes, and M = absence or presence of metastases
Gy: Gray
PSA: Prostate Specific Antigen
GI: Gastrointestinal
GU: Genitourinary
MV: Megavolts
XRT: X-ray Therapy
Table 4: Outcomes of Comparative Studies of Proton Beam Therapy for the Treatment of Prostate Cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Mean Age</th>
<th>Average Duration of Follow-Up</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PROG/ACR 95-09; Zeirman, 2010; Zeirman, 2005; Talcott, 2010]</td>
<td>67 in conventional group and 66 in high dose group</td>
<td>8.9 years</td>
<td>Proportion free from BF at 5 years: 61.4% for conventional dose versus 80.4% for high dose (p&lt;0.001) 10 year BF rates: 32.4% for conventional dose and 16.7% for high dose (p&lt;0.0001) No difference in overall survival at either time point GU toxicity ≥3: 2% in each arm GI toxicity ≥3: 1% in high dose arm</td>
<td>Mainly compared two doses of x-ray therapy. Both groups received proton therapy.</td>
</tr>
<tr>
<td>Shipley, 1995</td>
<td>70 in proton arm and 68.6 in conventional arm</td>
<td>61 months</td>
<td>No differences in OS, DSS, TRFS or local control Increase in local control only in patients with poorly differentiated tumors (5 year local control rate: 94% versus 64%: p&lt;0.01) Rectal bleeding higher in proton group (32% versus 12%; p=0.002) Urethral stricture nonsignificantly higher in proton group (19% versus 8%)</td>
<td></td>
</tr>
<tr>
<td>Nonrandomized Studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sheets, 2012</td>
<td>Not calculated-propensity matched</td>
<td>Propensity matched</td>
<td>GI morbidity: 12.2 per 100 person years for IMRT versus 17.8 per 100 person years for proton: RR 0.66 (95% C.I. 0.55-0.79) No differences in other morbidities</td>
<td>Proton therapy only available in few places so propensity matching</td>
</tr>
<tr>
<td>Duttenhaver, 1983</td>
<td>67.7</td>
<td>Not reported</td>
<td>No differences in survival, disease free survival and local recurrence free survival</td>
<td>Nonrandomized early study</td>
</tr>
<tr>
<td>Galbraith, 2001</td>
<td>68</td>
<td>18 months</td>
<td>No overall differences in health status or health related quality of life</td>
<td>Survey Patients not randomized</td>
</tr>
</tbody>
</table>
Coen, 2012

|        | 288 | 8.6 years for EBRT and 7.4 years for brachytherapy | No difference in 8 year biochemical failure rates ((7.7% for EBRT and 16.1% for brachytherapy (p=0.42)) |

PROG/ACR: Proton Radiation Oncology Group (PROG)/American College of Radiology (ACR) 95-09 (a randomized trial)
BF: Biochemical Failure
GI: Gastrointestinal
GU: Genitourinary
OS: Overall Survival
DSS: Disease Specific Survival
TRFS: Total Recurrence Free Survival
IMRT: Intensity Modulated Radiation Therapy
RR: Relative Risk
EBRT: External Beam Radiation Therapy
TA Criterion 3: The technology must improve the net health outcomes.

Health Outcomes

Ideally, studies of prostate cancer treatments would measure clinically significant long term outcomes such as total or prostate cancer mortality, and prostate cancer survival. Other clinically significant outcomes include quality of life and treatment related side effects. However, many of the studies of prostate cancer treatment measure intermediate outcomes, which are of less clear clinical significance, such as “biochemical failure.” Biochemical failure as defined by the Phoenix definition is a rise in the PSA of 2 ng/ml or more about the nadir after EBRT with or without hormonal therapy, with the date of failure being the date that failure is defined. An earlier, alternative definition is three consecutive increases in PSA. Biochemical failure has been defined as an “appropriate early endpoint for clinical trials,” but it is not equivalent to clinical failure.

Important outcomes in prostate cancer treatment are treatment related side effects. Toxicity is typically graded on a standard scale based on the RTOG Radiation Toxicity Grading Criteria. Toxicities are graded from level 1 (lowest severity) to level 4 (highest severity). Most studies use these criteria for grading toxicities and typically consider toxicities of Grade 2 or greater or Grade 3 or greater as clinically significant.

Table 5: RTOG Radiation Toxicity Grading Criteria

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Genitourinary Tract</th>
<th>Gastrointestinal System</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Frequency of urination or nocturia twice pretreatment</td>
<td>Increased frequency or change in quality of bowel habits not</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Frequency of urination or nocturia that is less frequent than every hour. Dysuria, urgency, bladder spasm requiring local anesthetic (e.g. Pyridium);</td>
<td>Diarrhea requiring parasympatholytic drugs (e.g. Lomotil), mucous discharge not necessitating sanitary pads or rectal or abdominal pain requiring analgesics</td>
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<tr>
<td>Grade 3</td>
<td>Frequency with urgency and nocturia hourly or more frequently/dysuria, pelvis pain or bladder spasm requiring regular, frequent narcotic/gross hematuria with or without clot passage</td>
<td>Diarrhea requiring parenteral support, severe mucous or blood discharge necessitating sanitary pads, abdominal distention (flat plate radiograph demonstrates distended bowel loops)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Hematuria requiring transfusion/acute bladder obstruction not secondary to clot passage, ulceration or necrosis</td>
<td>Acute or subacute obstruction, fistula or perforation: GI bleeding requiring transfusion: abdominal pain or tenesmus requiring tube decompression or bowel diversion.</td>
</tr>
</tbody>
</table>

Potential Benefits

The goal of proton beam therapy is to prolong overall and disease specific survival, to delay progression of disease and to improve quality of life. Because proton beams can theoretically be more concentrated on the tumor and less concentrated on the surrounding normal tissues, theoretically it could be a treatment option for patients with localized prostate cancer that maximizes the effect on the tissue while limiting effects on adjacent tissue.
Potential Harms

The main harms associated with radiotherapy of the prostate are toxicities to the genitourinary and gastrointestinal systems. Genitourinary toxicities include urethral stricture, urinary incontinence or retention, frequency, hematuria or impotence. Toxicities of the gastrointestinal system include diarrhea, proctitis and rectal bleeding or pain. Hip fractures have also been associated with radiotherapy for prostate cancer.

Outcomes of Non-comparative studies

A total of seven non-comparative studies evaluated proton therapy for the treatment of prostate cancer. The description of these studies is included in Table 1 and the main study outcomes are described in Table 2. Study size ranged from 30 to 1,255 participants. Three studies were done in Japan,

11,13,14
one in Sweden17 and the remaining three in the U.S.12,15,16 Two of the studies used proton therapy alone11,12, four used proton therapy with a boost13,15-17 and one used a boost in intermediate risk but not low risk patients.14 All used radiation doses ranging from 70 to 82 Gy or CGE. The most common outcomes evaluated were GI and GU toxicities, biochemical failure (defined by rises in PSA levels) and progression free survival.

The largest non-comparative study of proton beam therapy is a retrospective cohort from Loma Linda University, where proton beam therapy for localized prostate cancer has
been used since 1991. They evaluated all patients treated between 1991 and 1997 at Loma Linda. The main outcomes were toxicities and biochemical relapse. Patients were treated with both photons and protons. Initially, the treatment was a conformal boost of 30 CGE in 15 fractions and was then followed by 45 Gy of photon radiation therapy. Later during the study period, participants were divided into low or high risk categories. Those considered high risk continued to receive the combined proton-photon treatment and those considered low risk were treated with protons alone. Biochemical failure was defined using the consensus definition in place at the time by the American Society for Therapeutic Radiology (ASTRO), which was defined as three consecutive rises in PSA levels, with the date of failure being midway between the nadir and the first rise.

Participants were followed for an average of 62 months. Seven hundred thirty one patients received a combination of protons and photos and 524 received all their treatments with protons to the prostate and seminal vesicle(s) only. Biochemical disease free survival was measured at five and eight years and were 75% and 73% respectively. For both GI and GU toxicities, the rate of RTOG Grade 3 or greater toxicities was <1%. Late GI toxicity was relatively rare but there was one small bowel obstruction requiring a diverting colostomy and two episodes of bleeding and pain. GU toxicity late in the treatment course was more common. A total of 14 patients developed late GU toxicity, including eight urethral strictures, four with hematuria and two with dysuria. One patient developed necrosis of the symphisis pubis. There were no differences in toxicity between those treated with photons and protons versus those treated with protons alone.

Johansson and colleagues recently reported on five year outcomes from a cohort of patients in Sweden treated with proton boost therapy. A total of 278 patients with localized prostate cancer received XRT plus a proton boost to a total of 70 Gy. Five year survival for the cohort was 89% and eight year survival was 71%. Patients were divided into
three risk categories based on the NCCN guidelines and were classified as low, intermediate or high risk. They analyzed survival and PSA relapse separately by risk group. There were no significant differences in overall survival by risk group. They also evaluated the likelihood of PSA relapse by risk group. Five year actuarial relapse was 0%, 5% and 26% for low, intermediate and high risk groups (p<0.001).

In all of the non-comparative studies, GI and GU toxicities were assessed. Except for the one study that measured late outcomes in long term survivors, GI and GU toxicities were generally less than 5%. In the one study that measured GU and GI morbidity, at five and 15 years, rates were higher. They found that the incidence of Grade 2 or greater GU morbidity at 15 years was 59% but that the symptoms persisted to the time of interview in only 18% of patients. The actuarial incidence of Grade 2 or greater hematuria at 15 years was 47%, but the incidence of Grade 3 or greater hematuria was 8%. The actuarial incidence of Grade 2 or greater GI morbidity was 13% at five and 15 years, although Grade 1 rectal bleeding occurred in 41% of men. Thus, although there were long term sequelae after proton beam treatment, most of the toxicities were not severe.

The studies did not assess the impact on prostate cancer mortality or total mortality, although three studies assessed the impact on survival, progression free survival or freedom from biochemical evidence of disease. At Loma Linda, Slater and colleagues found that the five and eight year biochemical disease free survival rates were 75% and 73%. Mendenhall and colleagues at the University of Florida, found that at two year follow up, the overall survival rate for treated patients was 96%, and that progression free survival was 99% at two years. Finally, Johansson and colleagues reported a five year progression free survival of 100% for low risk patients, 95% for intermediate risk patients and 74% for high risk patients. Although there are no comparison groups in these
studies, these outcomes are similar to those see for IMRT treatment of prostate cancer.\textsuperscript{30}

Summary

In summary, seven non-comparative studies have evaluated the use of proton beam therapy for the treatment of localized prostate cancer. Rates of disease free progression seem to be relatively high, and comparable to rates seen with other treatments of localized prostate cancer. Although low grade toxicities are somewhat common, rates of higher grade toxicities are relatively low. Overall, the net benefits appear to outweigh the risks such that there is a net benefit for the use of proton beam therapy to treat prostate cancer.

TA Criterion 3 is met

TA Criterion 4: The technology must be as beneficial as any established alternatives.

A total of six studies have compared proton beam therapy to an alternative (Table 3). Two of these studies were randomized.\textsuperscript{18,21} The other four studies were not randomized.\textsuperscript{22-25} In the earliest randomized study, published by Talbot and colleagues in 1995, a Phase III trial was conducted where patients with Stages T3-T4, Nx0-2 prostate cancer received a treatment combining 10-25 MV photons with conformal protons to a total dose of 75.6
CGE or conventional external beam radiation therapy t a total dose of 67.2 Gy. There were 103 patients in the proton arm and 99 patients in the conventional therapy arm. Patients were followed for an average of 61 months. There were no differences in overall survival, disease free survival or total recurrence-free survival. The rates of local control at five and eight years for the proton group was 94% and 84% and 80% and 60% for those receiving proton therapy (p=0.090). There were higher rates of Grade 2 or less rectal bleeding in the proton group [32% versus 12%; p=0.002) and a nonsignificant increase in urethral stricture [19% versus 8%).

The other randomized trial, PROG-95-09, actually compared “low dose” and “high dose” conformal radiation therapy that used a combination of proton and photon beams. The PROG-95-09 study randomized 393 patients to receive either 70.2 Gy of combined photons plus protons versus 79.2 Gy of combined photons plus protons. All received conformal photon therapy at a dose of 50.4 Gy. The boost dose was protons and was either 19.8 Gy or 28.8 Gy. The main measured outcome was “biochemical failure” as measured by an increased PSA level at five years after treatment. At five years, there were more men in the high dose group free from biochemical failure than there were in the conventional dose group, resulting in a 49% reduction in the risk of failure in the high dose group. There was no difference in overall survival between the two treatment groups. Only 1% of patients in the conventional group and 2% in the high dose group experienced acute urinary or rectal morbidity of RTOG Grade 3 or greater. The authors subsequently reported on longer term follow-up. After a median of 8.9 years of follow-up, those receiving the high dose treatment had a significantly lower likelihood of local failure (HR 0.57). The ten year rates of biochemical failure were 32.4% for the conventional dose group versus 16.7% for the high dose group. There was no difference in overall survival when comparing the two treatment groups.
Finally, the PROG 9509 Group also reported on long term patient reported outcomes of combined proton and photon therapy. They conducted a survey of 280 of the surviving 337 patients enrolled in this protocol. The main outcomes were Prostate Cancer Symptom Indices, a validated measure of urinary incontinence, urinary obstruction and irritation, bowel problems and sexual dysfunction, and other quality of life measures. The study was conducted a median of 9.4 years after treatment. Rates of symptoms were not statistically different between treatment groups. These symptoms included urinary obstruction and irritation, urinary incontinence, bowel problems, and sexual dysfunction.

In summary, the results of this randomized trial showed that higher dose combined proton and photon therapy is associated with improved rates of biochemical survival, with no significant difference in treatment related side effects including long term patient reported outcomes between treatment group. Thus, higher dose combined proton and photon therapy leads to improved outcomes compared with lower dose. However, since participants in both study arms received proton therapy, this study did not compare proton therapy with photon therapy alone, which limits conclusions.

Four nonrandomized studies have compared proton beam therapy to another treatment in the earliest study. Duttenhaver and colleagues compared outcomes among patients with localized prostate cancer receiving either 50 Gy of conventional therapy alone versus receiving a proton boost to reach a total dose of 74 CGE. There were no significant differences in patient survival, disease free survival or local recurrence free survival. However, the doses used in this study are much lower than currently used doses and the techniques used in that study are now outmoded and so not relevant to current practice.
In a recent case-matched analysis, high dose external beam proton and photon XRT (79.2 GYE) was compared with brachytherapy for treatment of localized prostate cancer. The 199 participants who received high dose proton and photon therapy were those in the PROG 95-09 high dose arm, all recruited from Loma Linda University and Massachusetts General Hospital (MGH) during 1996-1999 were eligible for inclusion. After excluding those with a Gleason Score of >7, there were 177 left for case matching. A total of 203 similar patients were treated at MGH with brachytherapy from 1997-2002 by one brachytherapist. Case matching, which included T stage, Gleason Score, PSA and age resulted in 141 matched cases. Median follow up was 8.6 years for EBRT and 7.4 years for brachytherapy. The primary endpoint was biochemical failure. Median age was 67 years old. The eight year rates of biochemical failure were not significantly different between the two groups (7.7% for EBRT versus 16.1% for brachytherapy: p=0.42). There was also no difference in overall survival at eight years (93% versus 96%; p=0.45). Analysis by subgroup (low versus intermediate risk: there were no high risk patients) also showed no significant differences between groups. The results suggest that outcomes are similar for men treated with proton therapy or with brachytherapy, although this was a case matched, non-randomized analysis among patients treated at different time periods.

Galbraith and colleagues assessed the impact of different prostate cancer treatments on health outcomes in five different treatment groups. They conducted a longitudinal survey of 185 men treated for prostate cancer at one tertiary care medical center (Loma Linda University). There were a total of 185 men, all of whom had received different treatments for prostate cancer. These treatments included watchful waiting (n=30), surgery (n=59), conventional external beam radiotherapy (n=25), proton beam radiotherapy (n=24) or mixed beam radiation (n=47). At six months, 163 of the patients
completed another survey and at 12 months, 154 completed another survey and at 18 months, 153 completed a survey. The main outcomes were health related quality of life, health status and prostate treatment specific symptoms and sex role identity. Health related quality of life was measured using the Quality of Life Index (QLI), a measure to assess health related quality of life that was designed specifically for patients with cancer. Overall, the five groups did not differ in measures of health related quality of life during the 18 months following prostate cancer treatment. Post hoc analyses showed that at 12 months, the mixed beam radiation group and the proton beam radiation group reported better health related quality of life than those in the watchful waiting group ($p=0.02$ and $p=0.05$ respectively). Health status was measured with the Medical Outcomes Study General Health Survey. At 18 months, there were no overall differences in health status among the five groups. Prostate treatment related symptoms were measured using the Southwest Oncology Group Prostate Treatment Specific Symptoms Measure (PTSS). The PTSS is a 19 item scale which was developed to measure and compare treatment related symptoms that can occur after any treatment for prostate cancer. Symptoms are related to bowel, bladder and sexual functioning. At 18 month follow-up, there were differences among the five treatment groups in prostate treatment specific symptoms. Each group was compared to every other group at multiple time periods. At 18 months, there were differences in sexual and GI symptoms among groups, but no differences in urinary symptoms. Multiple post hoc analyses were done at different time points (6 months and 12 months). Of note, at 12 months, the men who had mixed beam radiation reported more symptoms than those who received watchful waiting ($p=0.005$), but there were still no differences in urinary symptoms among groups. In summary, in this study of 185 patients who had received various treatments, there was no difference in health related quality of life or health status at 18 month follow-up. There were more GI symptoms with radiation treatment.
Finally, a recent study evaluated the comparative efficacy of IMRT, proton therapy and conformal radiation therapy for primary treatment of prostate cancer. This was a population based study using data from the Surveillance, Epidemiology, and End Results (SEER) Medicare-linked data from 2000-2009 for patients with non-metastatic prostate cancer. SEER-Medicare links the registry data to Medicare claims data. The main outcomes were rates of GI and GU morbidity, erectile dysfunction, hip fractures and need for additional cancer therapy. Overall, they identified 6,666 patient treated with IMRT and 6,310 treated with conformal radiation therapy. For the proton versus IMRT comparison, they identified 684 men treated with proton therapy from 2002 to 2007. Because there were so few institutions that offered proton therapy, baseline characteristics between proton therapy and IMRT patients were very different, primarily because of two variables - SEER region and institutional affiliation with the RTOG. To overcome this, they used propensity score matching to compare the patients who received proton therapy with those who received IMRT. Median follow-up for this comparison was 46 months for IMRT and 50 months for proton therapy. Comparing those who received proton therapy with the propensity matched IMRT patients, there was a lower rate of GI morbidity in those who received IMRT (absolute risk 12.2 versus 17.8 per 100 person-years: RR 0.66: 95%; C.I. 0.55-0.79). There were no significant differences in rates of other morbidities or need for additional therapies between IMRT and proton therapy. Proton therapy was not compared with conformal radiation therapy in this analysis.

In summary, six studies have compared proton beam therapy for prostate cancer to another treatment. Only two of these have been randomized. The first of the two randomized studies included 202 patients was done 15 years ago and found no evidence of differences in survival although there were higher rates of rectal bleeding in the proton
beam treated group. The second study actually compared low to high dose photons plus protons. Although they found that high dose combined therapy was better, there was no comparison group that did not receive proton therapy. The one study that compared proton beam therapy to brachytherapy was a non-randomized case matched study and the study that compared proton beam therapy to IMRT was a case matched propensity analysis among patients treated at different time periods, thus limiting the conclusions that can be drawn from these studies.

TA Criterion 4 is not met.

TA Criterion 5: The improvement must be attainable outside the investigational settings.

Despite limited evidence of efficacy, the use of new technologies for prostate cancer treatment, proton therapy has spread widely. Proton therapy is widely used in specialized centers. However, since an improvement has not been shown in the investigational setting, improvement cannot be attained outside the investigational setting.

TA Criterion 5 is not met
CONCLUSION

In summary, proton beam therapy has been widely used for the treatment of localized prostate cancer. In nonrandomized studies, rates of disease free progression appear to be favorable and although side effects are common, rates of significant toxicity are relatively low. However, there is limited evidence of comparative efficacy with other prostate cancer treatments. The main recent RCT evaluating proton beam therapy actually compared low dose with high dose proton beam therapy and did not include a group that did not receive proton beam therapy. The comparisons with other treatments (brachytherapy, IMRT) have been limited by being retrospective case matched analyses and have included patients treated during different time periods. Thus the role of proton beam therapy for localized prostate cancer within the current list of treatment options remains unclear.

RECOMMENDATION

It is recommended that proton beam therapy for localized prostate cancer does not meet CTAF criteria 4 or 5 for safety, efficacy and improvement in health outcomes.

This is the first review of this technology by CTAF.
RECOMMENDATIONS OF OTHERS

Blue Cross Blue Shield Association Technology Evaluation Center (BCBSA TEC)

BCBSA TEC performed an assessment on this technology in June 2011. The assessment noted that “Good comparative studies are lacking for...comparisons addressed in the Assessment”, that “There is inadequate evidence from comparative studies to permit conclusions....” and therefore the technology did not meet BCBSA TEC criteria. The assessment can be found at http://www.bcbs.com/blueresources/tec/vols/25/proton-beam-therapy-for-1.html

Canadian Agency for Drugs and Technologies in Health (CADTH)

In 2008, CADTH published a limited literature search to address the following four questions:

1. What is the clinical effectiveness of proton beam therapy for various indications including different types of cancer?
2. Is there evidence that proton beam therapy is clinically more effective for specific indications when compared with conventional treatment options?
3. What is the cost effectiveness of proton beam therapy?
4. What are the guidelines for use of proton beam therapy?

The list of documents can be found at http://www.cadth.ca/media/pdf/htis/Proton%20Beam%20Therapy%20Clinical%20and%20Cost-Effectiveness%20and%20Guidelines%20for%20Use.pdf

National Institute for Health and Clinical Excellence (NICE)

Agency for Healthcare Research and Quality (AHRQ)


AHRQ funded a systematic review and guide, Comparative Effectiveness of Therapies for Clinically Localized Prostate Cancer (2008), that was prepared by the Minnesota Evidence-Based Practice Center. Findings relevant to this assessment include:

- “Radiation therapy with protons may improve dose distribution with higher doses delivered locally to the tumor preserving surrounding healthy tissues. However, no randomized trials have evaluated the comparative effectiveness of protons vs. photons in men with localized prostate cancer.

- “No randomized trials were found that compared clinical outcomes of proton beam radiation therapy versus other therapies.”

The review can be found at
National Comprehensive Cancer Network (NCCN)

The NCCN Clinical Practice Guidelines In Oncology: Guideline Version 3.2012: Prostate Cancer states the following regarding proton beam therapy:

“Proton beams can be used as an alternative radiation source. Theoretically, protons may reach deeply-located tumors with less damage to surrounding tissues. However, proton therapy is not recommended for routine use at this time, since clinical trials have not yet yielded data that demonstrates superiority to, or equivalence of, proton beam and conventional external beam for treatment of prostate cancer.”

The NCCN guideline can be found at

American Cancer Society (ACS)

The ACS website shows the following information about proton beam therapy:

“Proton beam therapy is related to 3D-CRT and uses a similar approach. But instead of using x-rays, this technique focuses proton beams on the cancer. Protons are positive parts of atoms. Unlike x-rays, which release energy both before and after they hit their target, protons cause little damage to tissues they pass through and then release their energy after traveling a certain distance. This means that proton beam radiation may be able to deliver more radiation to the prostate and do less damage to nearby normal tissues. Although early results are promising, studies are needed to see if
proton beam therapy is better in the long-run than other types of external beam radiation. Right now, proton beam therapy is not widely available. The machines needed to make protons are expensive, and there are only a handful of them in use in the United States. Proton beam radiation may not be covered by all insurance companies at this time.”


Centers for Medicare and Medicaid Services (CMS)

There is no National Coverage Determination (NCD) for proton beam therapy for prostate cancer. Coverage for the procedure is determined under Local Coverage Determination (LCD).

American College of Radiology (ACR)

ACR was invited to provide an opinion on this technology and to send a representative to the CTAF public meeting.

American College of Radiation Oncology (ACRO)

ACRO was invited to provide an opinion on this technology and to send a representative to the CTAF public meeting.

American Society for Radiation Oncology (ASTRO)

ASTRO was invited to provide an opinion on this technology and to send a representative to the CTAF public meeting.
American Urological Association (AUA)

In its guideline: *Prostate Cancer Guideline for the Management of Clinically Localized Prostate Cancer: 2007 (reviewed and validity confirmed in 2011)*, the AUA states that "External beam radiotherapy is indicated as a curative treatment for prostate cancer in men who do not have a history of inflammatory bowel disease such as Crohn’s disease, ulcerative colitis, or a history of prior pelvic radiotherapy….techniques include a CT scan for treatment planning and either a multileaf collimator, IMRT, or proton radiotherapy....” The AUA guideline can be found at [http://www.auanet.org/content/clinical-practice-guidelines/clinical-guidelines/main-reports/proscan07/content.pdf](http://www.auanet.org/content/clinical-practice-guidelines/clinical-guidelines/main-reports/proscan07/content.pdf)

Association of Northern CA Oncologists (ANCO)

ANCO was invited to provide an opinion on this technology and to send a representative to the CTAF public meeting.

California Radiological Society (CRS)

CRS was invited to provide an opinion on this technology and to send a representative to the CTAF public meeting.

California Urological Association (CUA)

CUA was invited to provide an opinion on this technology and to send a representative to the CTAF public meeting.

The National Association For Proton Therapy

The National Association for Proton Therapy was invited to provide an opinion on this technology and to send a representative to the CTAF public meeting.
ABBREVIATIONS USED IN THIS ASSESSMENT:

NG: Nanograms
PSA: Prostate Specific Antigen
3D-CRT: Three Dimensional Conformal Radiation Therapy
NCCN: National Comprehensive Cancer Network
Gy: Gray
RBE: Relative Biological Effectiveness
GyE: Gray Equivalents (GyE)
CGE: Cobalt Gray equivalents
DARE: Database of Abstracts of Reviews of Effects
EBRT: External Beam Radiation Therapy
GI: Gastrointestinal
GU: Genitourinary
XRT: X-ray Therapy
RTOG: Radiation Therapy Oncology Group
OS: Overall Survival
DSS: Disease Specific Survival
TRFS: Total Recurrence-Free Survival
MV: Megavolts
BF: Biochemical Failure
ASTRO: American Society for Therapeutic Oncology
IMRT: Intensity Modulated Radiation Therapy
PROG-95-09: Proton Radiation Oncology Group (PROG)/American College of Radiology (ACR) 95-09 (a randomized trial)
QLI: Quality of Life Index
PTSS: Southwest Oncology Group Prostate Treatment Specific Symptoms Measure
SEER: Surveillance, Epidemiology, and End Results
RR: Relative Risk
C.I.: Confidence Interval
H.R.: Hazard Ratio

REFERENCES


