Subject: Proton Beam Therapy for Prostate Cancer		Original Effective Date: 10/30/13
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PREFACE

This Medical Guidance is intended to facilitate the Utilization Management process. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (i.e., will be paid for by Molina) for a particular member. The member's benefit plan determines coverage. Each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their providers will need to consult the member's benefit plan to determine if there are any exclusions or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid members. CMS's Coverage Database can be found on the following website: http://www.cms.hhs.gov/center/coverage.asp.

FDA INDICATIONS

Proton beam therapy for prostate cancer is a procedure and, therefore, not subject to FDA regulation. Proton beam therapy systems are approved by the FDA as a 510(k) class II "medical device designed to produce and deliver a proton beam for the treatment of patients with localized tumors and other conditions susceptible to treatment by radiation". To view a general list of FDA 510(k)-approved proton beam devices use LHN as the Product Code in the form found at the FDA website. [1]

CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this Molina medical coverage guidance (MCG) document and provide the directive for all Medicare members. The directives from this MCG document may be followed if there are no available NCD or LCD documents available and outlined below.

No National Coverage Determination (NCD) for proton beam therapy for prostate cancer was identified on the CMS website. There are several Local Coverage Determinations (LCD) that outline coverage for proton beam therapy.[2]

INITIAL COVERAGE CRITERIA

Proton beam therapy (PBT) is considered not medically necessary and may not be authorized for the treatment of prostate cancer because clinical outcomes of this treatment have not been shown to be superior to other approaches such as intensity modulated radiation therapy (IMRT) or 3D-conformal radiation therapy.

CONTINUATION OF THERAPY

N/A

COVERAGE EXCLUSIONS

Proton beam therapy (PBT) is considered not medically necessary and may not be authorized for the treatment of prostate cancer because clinical outcomes of this treatment have not been shown to be superior to other approaches such as intensity modulated radiation therapy (IMRT) or 3D-conformal radiation therapy.

DESCRIPTION OF PROCEDURE/SERVICE/PHARMACEUTICAL

Proton Beam radiotherapy is a form of conformal external beam radiation treatment. Protons are positively charged atomic particles and have similar biological effects as conventional x-ray beams, but have very different energy disposition or physics profiles. Proton particles deliver a smaller amount of radiation energy as they enter the body (lower entrance dose) culminating in an intensity dose peak (e.g. Bragg Peak) therefore depositing 100% of the dosage at the targeted tissue. There is no further energy deposition beyond the Bragg peak (no exit dose). Proton beams typically deposit less radiation in normal non-targeted tissues than conventional radiation therapy and have been used to escalate the radiation dose to diseased tissues while minimizing damage to adjacent normal tissues. Proton beam therapy will typically have a significantly lower integral dose (dose to the whole body of the patient) compared to conventional x-ray therapy. In contrast, conventional external beam radiation therapy (EBRT) delivers radiation to all involved tissue, diseased and normal, and targeted tissue receives 60–70% of the intended dose.

Proton beam therapy is typically performed on an outpatient basis. For most tumor sites, a standard course of treatment is five to seven weeks, with treatments delivered five days per week. The length of each treatment will vary depending upon the tumor type and stage. The delivery of the proton beam to the patient lasts only a few minutes, although the total time spent in the treatment room will be longer (about 15 to 20 minutes) for positioning and adjustments to the equipment settings. [4]

GENERAL INFORMATION

Summary of Medical Evidence

There are numerous clinical trials underway studying proton beam therapy as a treatment for prostate cancer and to date no clinical trials have demonstrated that proton beam therapy has better outcomes than the conventional methods of radiation therapy. [22]

Yu et al (2013) performed a retrospective study of all Medicare beneficiaries aged greater than or equal to 66 years who received PRT or IMRT for prostate cancer during 2008 and/or 2009. Multivariable logistic regression was used to identify factors associated with receipt of PRT. To assess toxicity, each PRT patient was matched with two IMRT patients with similar clinical and socio-demographic characteristics. The main outcome measures were receipt of PRT or IMRT, Medicare reimbursement for each treatment, and early genitourinary, gastrointestinal, and other toxicity. All statistical tests were two-sided. 27,647 men; 553 (2%) received PRT and 27,094 (98%) received IMRT. Patients receiving PRT were younger, healthier, and from more affluent areas than patients receiving IMRT. Median Medicare reimbursement was $32,428 for PRT and $18,575 for IMRT. Although PRT was associated with a statistically significant reduction in genitourinary toxicity at 6 months compared with IMRT (5.9% vs 9.5%; odds ratio [OR] = 0.60, 95% confidence interval [CI] = 0.38 to 0.96, P = .03), at 12 months post-treatment there was no difference in genitourinary toxicity (18.8% vs 17.5%; OR = 1.08,

95% CI = 0.76 to 1.54, P = .66). There was no statistically significant difference in gastrointestinal or other toxicity at 6 months or 12 months post-treatment. The authors concluded that although PRT is substantially more costly than IMRT, there was no difference in toxicity in a comprehensive cohort of Medicare beneficiaries with prostate cancer at 12 months post-treatment. [12]

Ohri at al. (2012) performed a review of published series that report late gastrointestinal (GI) and genitourinary (GU) toxicity rates following definitive RT for prostate cancer using the RTOG Late Radiation Morbidity Scoring Schema. Univariate analyses were performed to test RT technique, RT dose, pelvic irradiation, and androgen deprivation therapy (ADT) as predictors of moderate (grade ≥ 2) and severe (grade ≥ 3) GI and GU toxicity. To isolate the effect of radiotherapy dose on late toxicity a meta-analysis was restricted to randomized trials that tested RT dose escalation. Statistical analyses were repeated using the subset of studies that utilized escalated RT doses. Twenty published reports detailing the treatment techniques and toxicity outcomes of 35 patient series including a total of 11,835 patients were included in this analysis. Median rates of moderate late toxicity were 15% (GI) and 17% (GU). For severe effects, these values were 2% (GI) and 3% (GU). Meta-analysis of five randomized trials revealed that an 8-10 Gy increase in RT dose increases the rate of both moderate (OR = 1.63, 95% CI: [1.44 to 1.82], $p < 0.001$) and severe (OR = 2.03, 95% CI: [1.64 to 2.42], $p < 0.001$) late GI toxicity. Among 17 series where doses of at least 74 Gy were utilized, use of intensity-modulated radiotherapy (IMRT) or proton beam radiotherapy (PBRT) was associated with a significant decrease in the reported rate of severe GI toxicity compared to 3-D RT. The Meta-analysis of randomized dose escalation trials demonstrates that late toxicity rates increase with RT dose. Series where dose escalated RT is delivered using IMRT or PBRT have relatively short follow up but report lower late GI toxicity rates than those employing 3-D RT. [9]

Allen et al. (2012) conducted a systematic review to evaluate the state of the science of proton beam therapy (PBT) and arrive at a recommendation for the use of PBT. The emerging technology committee of the American Society of Radiation Oncology (ASTRO) routinely evaluates new modalities in radiotherapy and assesses the published evidence to determine recommendations for the society as a whole. In 2007, a Proton Task Force was assembled to evaluate the state of the art of PBT. This report reflects evidence collected up to November 2009. Data was reviewed for PBT in central nervous system tumors, gastrointestinal malignancies, lung, head and neck, prostate, and pediatric tumors. Current data do not provide sufficient evidence to recommend PBT in lung cancer, head and neck cancer, GI malignancies, and pediatric non-CNS malignancies. In hepatocellular carcinoma and prostate cancer and there is evidence for the efficacy of PBT but no suggestion that it is superior to photon based approaches. In pediatric CNS malignancies PBT appears superior to photon approaches but more data is needed. In large ocular melanomas and chordomas, we believe that there is evidence for a benefit of PBT over photon approaches. PBT is an important new technology in radiotherapy. Current evidence provides a limited indication for PBT. More robust prospective clinical trials are needed to determine the appropriate clinical setting for PBT. [10]

Sheets et al. (2012) conducted a retrospective population-based study using the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database to "determine the comparative morbidity and disease control of IMRT, proton therapy, and conformal radiation therapy for primary prostate cancer treatment". A total of 6666 men treated with IMRT, 6310 treated with conformal radiation therapy and 684 treated with PBT met inclusion criteria. Follow-ups occurred at 0.1–91.5 months for IMRT (median 44 months), 0.0–91.7 months for conformal (median 64 months), and 0.4–88.3 months (median 46 months) for PBT. Survival was not examined because death by prostate cancer was expected to occur within five years of diagnosis and not different based on the type of radiation treatment. Using adjusted analysis, men treated with IMRT compared to conformal therapy were significantly less likely to receive a diagnosis of gastrointestinal morbidity ($p<0.001$), have a hip fracture ($p=0.006$), and need additional cancer therapy ($p<0.001$) but more likely to experience erectile dysfunction ($p=0.006$). There were no significant differences between PBT and IMRT in urinary incontinence, erectile dysfunction, hip fracture, morbidly or additional cancer therapies. PBT patients were more likely to have gastrointestinal side effects and undergo gastrointestinal procedures. The authors concluded that the potential advantage of PBT over IMRT is "unclear" and these results do not "clearly demonstrate a clinical benefit to support the recent increase in" PBT for prostate cancer. Additionally, limitations of this study include: the use of the SEER-Medicare data which includes claims files that do not provide detailed clinical information; potential bias in patient and physician reporting of morbidity and additional cancer therapies; and it is unknown if these results are generalizable with respect to choice of treatments, disease severity and rates of outcomes. [5]

Coen et al. (2012) conducted a patient survey to assess long-term quality of life (QOL) outcome for men treated with conformal protons. QOL questionnaires were sent at specified intervals to 95 men who received proton radiation. Of these, 87 men reported 3- and/or 12-month outcomes, whereas 73 also reported long-term outcomes (minimum 2 years). Symptom scores were calculated at baseline, 3 months, 12 months, and long-term follow-up. Generalized estimating equation models were constructed to assess longitudinal outcomes while accounting for correlation among repeated measures in an individual patient. Men were stratified into functional groups from their baseline questionnaires (normal, intermediate, or poor function) for each symptom domain. Long-term QOL changes were assessed overall and within functional groups using the Wilcoxon signed-rank test. Statistically significant changes in all four symptom scores were observed in the longitudinal analysis. For the 73 men reporting long-term outcomes, there were significant change scores for incontinence (ID), bowel (BD) and sexual dysfunction (SD), but not obstructive/irritative voiding dysfunction (OID). When stratified by baseline functional category, only men with normal function had increased scores for ID and BD. For SD, there were significant changes in men with both normal and intermediate function, but not poor function. The authors concluded that patient reported outcomes are sensitive indicators of treatment-related morbidity. These results quantitate the long-term consequences of proton monotherapy for prostate cancer. Analysis by baseline functional category provides an individualized prediction of long-term QOL scores. High dose proton radiation was associated with small increases in bowel dysfunction and incontinence, with more pronounced changes in sexual dysfunction. [13]

Coen et al. (2011) conducted a case-match analysis (n=282) of two separate clinical trials to compare the outcomes of high-dose radiotherapy (i.e., photon with a proton boost) to brachytherapy. Outcomes of patients

who were randomized to the high-dose radiotherapy arm in one study were compared to patients who were treated with brachytherapy in a case series. Patients had stage T1c, T2a or T2b cancer. At eight years follow-up, there were no significant differences in overall survival (p=0.45), freedom from distant metastasis (p=0.21) and biochemical failure (p=0.42). The time to PSA nadir was similar in both groups and the number of patients with PSA nadir ≤ 0.5 nanograms per milliliter (ng/mL) was significantly higher after brachytherapy (p=0.0003). A well-designed randomized controlled trial comparing these two modalities is needed to validate the results of this retrospective comparison. [6]

Jabbari et al. (2010) compared the outcomes of 249 patients treated with permanent prostate implant brachytherapy (PPI) to a matched cohort of 124 patients treated with 3D-CRT and published results of 195 patients, matched cohort treated with high-dose radiotherapy (photon with a proton boost). PPI patients had stages T1-T3a disease, 3D-CRT patients had stages T1-T2a, and radiotherapy patients had stages T1-T2b. Overall, the PPI group had a biochemical no evidence of disease (bNED) rate of 92% at five years and 86% at ten years. Patients treated with 3D-CRT had a 5-year bNED rate of 78% compared to 94% of a matched PPI subset. There was a significant difference in the five-year median PSA nadir for patients treated with PPI vs. 3D-CRT (p<0001). The five-year bNED rate following high-dose radiotherapy was 91% vs. 93% for a matched PPI subgroup. Also at five-years, a 0.5 ng/ml PSA nadir was reported in 91% of the PPI group vs. 59% in the high-dose radiotherapy group. The authors concluded that the results of this retrospective comparative study need to be validated in a well-designed randomized controlled trial comparing these modalities. [7]

Mayahara et al. (2007) reported one centers experience with proton therapy to investigate the incidence and influencing factors of acute genitourinary (GU) and gastrointestinal morbidities in patients with prostate cancer. A total of 287 patients with histologically proven Stage cT1-T4N0M0 prostate cancer were treated with proton therapy between 2003 and 2004. Of these, 204 (71%) received neoadjuvant androgen suppression therapy. The patients were treated with 190-230-MeV protons using lateral-opposed techniques to a dose of 74 GyE. Dose-volume histogram analyses were performed. The incidence of acute morbidity was evaluated using the National Cancer Institute Common Toxicity Criteria, version 2.0. Clinical factors, including age, clinical target volume, initial prostate-specific antigen level, T stage, presence of diabetes mellitus, and the use of androgen suppression therapy, were investigated to determine whether those affected the incidence of acute GU morbidity. None developed Grade 2 or higher acute gastrointestinal morbidity. In contrast, 111 (39%) and 4 (1%) patients experienced acute Grade 2 and Grade 3 GU morbidities, respectively. However, 87% of the patients were successfully relieved by the administration of a selective alpha-1 blocker. Multivariate analysis showed that a larger clinical target volume (p = 0.001) and the use of androgen suppression therapy (p = 0.017) were significant factors for the prediction of acute Grade 2-3 GU morbidity. The authors concluded that in our experience with proton therapy, a low incidence of acute gastrointestinal morbidity was observed. In contrast, the incidence of acute GU morbidity was similar to that in other reports of photon radiotherapy. Additional follow-up is warranted to elucidate the long-term safety and efficacy of proton therapy for prostate cancer. [14]

Hayes, Cochrane, UpToDate

Hayes does not have a Directory report on the topic of proton beam therapy for prostate cancer. There is a 2013 Search & Summary report. [3]

UpToDate has several reports on prostate cancer treatment and outlines that Proton Beam Therapy spares normal tissues better than IMRT in the low-to-mid dose range, although IMRT may offer a slight benefit in the high-dose range. To date, clinical studies have shown only limited improvement, if any, in toxicity profiles, although comparisons between nonrandomized series are inherently difficult. No randomized trials are currently underway and there are no randomized trials that compare proton beam therapy with photon beam therapy or brachytherapy in men with clinically localized prostate cancer. The most extensive data come from studies in which a combination of proton beam therapy and external beam RT was used. These studies have confirmed the value of high doses of RT. However, retrospective analyses have not established whether proton beam therapy (either alone or in combination with photon therapy) is either more effective or less toxic than photon therapy alone (especially IMRT) or brachytherapy. [17 18 19 20]

Professional Organizations

American College of Radiology (ACR) appropriateness criteria (2010) for irradiation for T1 and T2 prostate cancer state that "there are only limited data comparing proton beam therapy to other methods of irradiation or to radical prostatectomy for treating stage T1 and T2 prostate cancer. Further studies are needed to clearly define PBT's role for such treatment." ACR includes intensity modulated radiation therapy (IMRT) and 3-dimensional computed tomography (3D CT) along with PBT as the recommended forms of external beam radiation therapy. [8]

American College of Radiology (ACR) appropriateness criteria (2011) for external beam radiation therapy treatment planning for clinically localized prostate cancer rated proton beam therapy as a level seven therapy for the treatment of prostate cancer with IMRT being rated as a level eight. Regarding IMRT, ACR states that IMRT is most appropriate for patients treated with dose escalation. [15]

American Society of Radiation Oncology (ASTRO) 2010 technology evaluation of PBT concluded that outcomes for patients treated with PBT were similar to those treated with intensity modulated radiation therapy (IMRT). Based on the clinical data, there was no clear benefit from PBT over IMRT including disease control or prevention of late toxicity. In addition, careful attention must be paid to the role of dosimetric issues, including correction for organ motion in this disease. ASTRO stated that "further head to head clinical trials may be needed to determine the role of PBT in treating prostate cancer." [16]

National Comprehensive Cancer Network (NCCN) 2013 guidelines for prostate cancer state that proton beam therapy is not recommended in the routine use for the treatment of prostate cancer. Clinical trials have not reported data that "demonstrates superiority or equivalence of proton beam compared to conventional external beam for treatment of prostate cancer". [11]

American Urological Association (AUA) 2011 Guideline for the Management of Clinically Localized Prostate Cancer does not recommend proton beam therapy over other forms of radiation therapy. [21]

CODING INFORMATION

CPT	Description
77520	Proton treatment delivery; simple, without compensation
77522	Proton treatment delivery; simple, with compensation
77523	Proton treatment delivery; intermediate
77525	Proton treatment delivery; complex

HCPCS	Description
	N/A

ICD-9	Description
185	Malignant neoplasm of prostate
233.4	Carcinoma in situ of prostate

ICD-10	Description
C61	Malignant neoplasm of prostate
D70.5	Carcinoma in situ of prostate

RESOURCE REFERENCES

1. U.S. Food and Drug Administration. 510(k) Premarket Notification Data base. Accessed at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm
2. Centers for Medicare & Medicaid Services (CMS). Medicare National Coverage Database. Accessed at: http://www.cms.gov/mcd/index_list.asp?list_type=ncd
3. Hayes Search & Summary. Proton Beam Therapy for Prostate Cancer. Winifred Hayes Inc. Lansdale, PA. March 25, 2013.
4. American College of Radiology (ACR) website. Proton therapy. May 2012. Accessed at: http://www.radiologyinfo.org/en/info.cfm?PG=protonthera&bhcp=1
5. Sheets NC, Goldin GH, Meyer AM, et al. Intensity-modulated radiation therapy, proton therapy, or conformal radiation therapy and morbidity and disease control in localized prostate cancer. JAMA. 2012 Apr 18;307(15):1611-20.
6. Coen JJ, Zietman AL, Rossi CJ, Grocela JA, Efstathiou JA, Yan Y, Shipley WU. Comparison of High-Dose Proton Radiotherapy and Brachytherapy in Localized Prostate Cancer: A Case-Matched Analysis. Int J Radiat Oncol Biol Phys. 2011 Apr 4. [Epub ahead of print]

7. Jabbari S, Weinberg VK, Shinohara K, Speight JL, et al. Equivalent biochemical control and improved prostate-specific antigen nadir after permanent prostate seed implant brachytherapy versus high-dose three-dimensional conformal radiotherapy and high-dose conformal proton beam radiotherapy boost. Int J Radiat Oncol Biol Phys. 2010 Jan 1;76(1):36-42.
8. Moran BJ, DeRose P, Merrick G, Hsu IC, et al. Expert Panel on Radiation Oncology-Prostate. ACR Appropriateness Criteria® definitive external beam irradiation in stage T1 and T2 prostate cancer. [online publication]. Reston (VA): American College of Radiology (ACR); 2010. 20 p. Accessed at: http://www.guideline.gov/content.aspx?id=32635&search=proton+beam+and+prostate
9. Ohri N. Dicker AP. Showalter TN. Late toxicity rates following definitive radiotherapy for prostate cancer. Canadian Journal of Urology. 19(4):6373-80, 2012 Aug.
10. Allen AM, Pawlicki T, Dong L, Fourkal E, Buyyounouski M, et al. An evidence based review of proton beam therapy: the report of ASTRO's emerging technology committee. Radiother Oncol. 2012 Apr;103(1):8-11. doi: 10.1016/j.radonc.2012.02.001. Epub 2012 Mar 9.
11. National Comprehensive Cancer Network® (NCCN®). NCCN Clinical Practice Guidelines in Oncology™. Prostate cancer. V4.2013. Accessed at: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#site
12. Yu JB, Soulos PR, Herrin J, et al. Proton versus intensity-modulated radiotherapy for prostate cancer: patterns of care and early toxicity. J Natl Cancer Inst. 2013 Jan 2;105(1):25-32. doi: 10.1093/jnci/djs463. Epub 2012 Dec 14.
13. Coen JJ, Paly JJ, Niemierko A, et al. Long-term quality of life outcome after proton beam monotherapy for localized prostate cancer. Int J Radiat Oncol Biol Phys. 2012 Feb 1;82(2):e201-9. doi: 10.1016/j.ijrobp.2011.03.048. Epub 2011 May 27.
14. Mayahara H, Murakami M, Kagawa K, et al. Acute morbidity of proton therapy for prostate cancer: the Hyogo Ion Beam Medical Center experience. Int J Radiat Oncol Biol Phys. 2007 Oct 1;69(2):434-43. Epub 2007 May 7.
15. Abdel-Wahab M, Mahmoud O, Merrick G, Hsu IC, et al. Expert Panel on Radiation Oncology-Prostate. ACR Appropriateness Criteria® external beam radiation therapy treatment planning for clinically localized prostate cancer. [online publication]. Reston (VA): American College of Radiology (ACR); 2011. 13 p. Accessed at: http://www.guideline.gov/content.aspx?id=35164&search=proton+beam+and+prostate
16. American Society of Radiation Oncology (ASTRO). Emerging technology. Proton beam radiation therapy. 2010. Accessed at: https://www.astro.org/Clinical-Practice/Emerging-Technology-Reports.aspx
17. UpToDate: [website]: Ward J, Volgelzang N, Davis B. Initial management of regionally localized intermediate and high-risk prostate cancer. August, 2013
18. UpToDate: [website]: Klein R. Initial approach to low-risk clinically localized prostate cancer. August, 2013.
19. UpToDate: [website]: Meyer J, Lee A, DelaneyT. Proton and ion beams in cancer therapy. August 2013.
20. UpToDate: [website]: Dibiase S, Roach M. External beam radiation therapy for localized prostate cancer. August, 2013.
21. American Urological Association (AUA) Guideline for the Management of Clinically Localized Prostate Cancer. 2007 reaffirmed 2011. Accessed at: http://www.auanet.org/education/guidelines/prostate-cancer.cfm

22. National Institutes of Health. Clinical Trials.gov. Accessed at: http://clinicaltrials.gov/ct2/results?term=proton+beam+therapy+prostate+cancer&Search=Search
23. Advanced Medical Review (AMR): Policy reviewed by a practicing MD Board certified in Urology. September 22, 2013.