| Subject: Proton Beam Therapy for Prostate Cancer | | Original Effective Date: 10/30/2013 |
|---|---|---|
| **Policy Number:** MCP-153 | **Revision Date(s):** 6/29/2016 | |
| **Review Date:** 12/16/2015, 6/29/2016, 6/22/2017, 3/8/2018 | | |
| **MCPC Approval Date:** 3/8/2018 | | |

## DISCLAIMER

*This Molina Clinical Policy (MCP) 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 exclusion(s) 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 CMS website. 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 Clinical Policy (MCP) document and provide the directive for all Medicare members.*

## 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]

## RECOMMENDATION

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.

## SUMMARY OF MEDICAL EVIDENCE [3 11-29]

The body of evidence related to proton beam therapy for prostate cancer is large and the best evidence includes a randomized study (n=82) [20] a prospective multicenter study (n=151) [21]; and 2 prospective comparison studies (n=1447 and n=291). [22 23] Additional evidence includes systematic reviews, prospective studies, comparison study, case series, and retrospective reviews. [3 11-29] 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. [19]

An AHRQ 2014 report called Therapies for Clinically Localized Prostate Cancer concluded that the body of evidence for treating prostate cancer continues to evolve, but the evidence for most treatment comparisons is largely inadequate to determine comparative risks and benefits. Although limited evidence appears to favor surgery over watchful waiting or external beam radiation therapy, or favors radiotherapy plus hormonal therapy over radiotherapy alone, the patients most likely to benefit and the applicability of these study findings to contemporary patients and practice remain uncertain. More randomized controlled trials and better-designed observational studies that reflect contemporary practice and can control for many of the known/unknown confounding factors that can affect long-term outcomes may be needed to evaluate comparative risks and benefits of therapies for clinically localized prostate cancer. [3]

A randomized controlled trial conducted by Kim et al (2014) investigated the feasibility of hypofractionated proton therapy (PT). Eighty-two patients with biopsy-proven T1-3N0M0 prostate adenocarcinoma and no history of androgen deprivation therapy were randomly assigned to five different dose schedules: Arm 1, 60 CGE (cobalt gray equivalent = proton dose in Gy x 1.1)/20 fractions/5 weeks; Arm 2, 54 CGE/15 fractions/5 weeks; Arm 3, 47 CGE/10 fractions/5 weeks; Arm 4, 35 CGE/5 fractions/2.5 weeks; or Arm 5, 35 CGE/5 fractions/5 weeks.The median follow-up duration was 42 months (11-52 months). The acute GI and GU grade > 2 toxicity rates were 0 and 5%, respectively. The late GI and GU grade > 2 toxicity rates were 16% and 7%, respectively. The best arm for acute GU toxicity was Arm 3, while that for late GI toxicity was Arm 2 in which none had grade > 2 toxicity. The four-year American Society for Therapeutic Radiology and Oncology and Nadir + 2ng/ml BCF free survival (BCFFS) rates were 85% and 86%, respectively. The authors concluded that hypofractionated PT for patients with prostate adenocarcinoma as used in this study is feasible with an acceptable toxicity profile. As the BCFFS rates do not seem to be inferior to those produced using conventional fractionation, the application of hypofractionated PT may save patients time and money. [20]

A Multi-institutional Phase II study of proton beam therapy for organ-confined prostate cancer focusing on the incidence of late rectal toxicities was conducted by Nihei et al. 151 patients were enrolled. Of the 151 patients, 75, 49, 9, 17, and 1 had Stage T1c, T2a, T2b, T2c, and T3a, respectively. The Gleason score was 4, 5, 6, and 7 in 5, 15, 80 and 51 patients, respectively. The initial prostate-specific antigen level was <10 or 10-20 ng/mL in 102 and 49 patients, respectively, and 42 patients had received hormonal therapy and 109 had not. The median follow-up period was 43.4 months. Acute Grade 2 rectal and bladder toxicity temporarily developed in 0.7%

and 12%, respectively. Of the 147 patients who had been followed up for >2 years, the incidence of late Grade 2 or greater rectal and bladder toxicity was 2.0% (95% confidence interval, 0-4.3%) and 4.1% (95% confidence interval, 0.9-7.3%) at 2 years, respectively. The results of the present prospective study have revealed a valuable piece of evidence that PBT for localized prostate cancer can achieve a low incidence of late Grade 2 or greater rectal toxicities. [21]

Hoppe et al. (2014) conducted a comparative effectiveness study of patient-reported outcomes after proton therapy or intensity-modulated radiotherapy for prostate cancer. A comparison was performed of prospectively collected QOL data using the Expanded Prostate Cancer Index Composite (EPIC) questionnaire. QOL data were collected during the first 2 years after treatment for men who received PT and IMRT. PT was delivered to 1243 men at a single center at doses from 76 grays (Gy) to 82 Gy. IMRT was delivered to 204 men who were included in the Prostate Cancer Outcomes and Satisfaction with Treatment Quality Assessment (PROSTQA) study in doses from 75.6 Gy to 79.4 Gy. The Wilcoxon rank-sum test was used to compare EPIC outcomes by modality using baseline-adjusted scores at different time points. Individual questions were assessed by converting to binary outcomes and testing with generalized estimating equations. No differences were observed in summary score changes for bowel, urinary incontinence, urinary irritative/obstructive, and sexual domains between the 2 cohorts. However, more men who received IMRT reported moderate/big problems with rectal urgency (P = 0.02) and frequent bowel movements (P = 0.05) than men who received PT. There were no differences in QOL summary scores between the IMRT and PT cohorts during early follow-up (up to 2-years). Response to individual questions suggests possible differences in specific bowel symptoms between the 2 cohorts. These outcomes highlight the need for further comparative studies of PT and IMRT. [22]

Five-year outcomes from 3 prospective trials of image-guided proton therapy for prostate cancer were reported by Mendenhallet al. A total of 211 prostate cancer patients (89 low-risk, 82 intermediate-risk, and 40 high-risk) were treated in institutional review board-approved trials of 78 cobalt gray equivalent (CGE) in 39 fractions for low-risk disease, 78 to 82 CGE for intermediate-risk disease, and 78 CGE with concomitant docetaxel therapy followed by androgen deprivation therapy for high-risk disease. Toxicities were graded according to Common Terminology Criteria for Adverse Events (CTCAE), version 3.0. Median follow-up was 5.2 years. Five-year rates of biochemical and clinical freedom from disease progression were 99%, 99%, and 76% in low-, intermediate-, and high-risk patients, respectively. Actuarial 5-year rates of late CTCAE, version 3.0 (or version 4.0) grade 3 gastrointestinal and urologic toxicity were 1.0% (0.5%) and 5.4% (1.0%), respectively. Median pretreatment scores and International Prostate Symptom Scores at >4 years posttreatment were 8 and 7, 6 and 6, and 9 and 8, respectively, among the low-, intermediate-, and high-risk patients. There were no significant changes between median pretreatment summary scores and Expanded Prostate Cancer Index Composite scores at >4 years for bowel, urinary irritative and/or obstructive, and urinary continence. Five-year clinical outcomes with image-guided proton therapy included extremely high efficacy, minimal physician-assessed toxicity, and excellent patient-reported outcomes. Further follow-up and a larger patient experience are necessary to confirm these favorable outcomes. [26]

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. [15]

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. [11]

Professional Organizations [4-10]

*American College of Radiology (ACR)* Appropriateness Criteria® guideline (Nguyen, 2014) on external beam irradiation in stage T1 and T2 prostate cancer states: 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 its role for such treatment. [5]

*American Society of Radiation Oncology (ASTRO)* 2013 position statement concludes that the comparative efficacy evidence of proton beam therapy with other prostate cancer treatments is still being developed.

*National Comprehensive Cancer Network* (NCCN) 2018 guidelines for prostate cancer state that there is no clear evidence supporting a benefit or decrement to proton therapy over IMRT for either treatment efficacy or long term toxicity. [6]

*American Urological Association* (AUA) The American Urological Association, ASTRO, and the Society of Urologic Oncology (SUO) (Sanda, 2017) guideline on clinically localized prostate cancer includes recommended approaches and details of specific care options for use of radiotherapy indicates that clinicians should inform localized prostate cancer patients who are considering proton beam therapy that it offers no clinical advantage over other forms of definitive treatment (Moderate Recommendation; Evidence Level: Grade C. In the specific context of prostate cancer, very limited information exists in relation to the comparative effectiveness of proton therapy compared to other radiation techniques or other modalities of treatment.[8]

**CODING INFORMATION:** THE CODES LISTED IN THIS POLICY ARE FOR REFERENCE PURPOSES ONLY. LISTING OF A SERVICE OR DEVICE CODE IN THIS POLICY DOES NOT IMPLY THAT THE SERVICE DESCRIBED BY THIS CODE IS COVERED OR NON-COVERED. COVERAGE IS DETERMINED BY THE BENEFIT DOCUMENT. THIS LIST OF CODES MAY NOT BE ALL INCLUSIVE.

| 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-10 | Description: [For dates of service on or after 10/01/2015] |
|---|---|
| C61 | Malignant neoplasm of prostate |
| D70.5 | Carcinoma in situ of prostate |

**RESOURCE REFERENCES**

**Government Agency**


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. Sun F, Oyesanmi O, Fontanarosa J, et al. Therapies for clinically localized prostate cancer: update of a 2008 systematic review. Comparative Effectiveness Review No. 146. (Prepared by the ECRI Institute–Penn Medicine Evidence-based Practice Center under Contract No. 290-2007- 10063.) AHRQ Publication No. 15-EHC004-EF. Rockville, MD: Agency for Healthcare Research and Quality;

December 2014. Available at: http://www.effectivehealthcare.ahrq.gov/ehc/products/521/2023/prostate-cancer-therapies-update-report-141216.pdf

**Professional Society Guidelines**

4. American College of Radiology (ACR) website. Proton therapy. 2017. Accessed at: http://www.radiologyinfo.org/en/info.cfm?PG=protonthera&bhcp=1
5. Nguyen PL, Aizer A, Assimos DG, 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). Am J Clin Oncol. 2014; 37(3):278-288.
6. National Comprehensive Cancer Network® (NCCN®). NCCN Clinical Practice Guidelines in Oncology™. Prostate cancer. V1.2018. Accessed at: https://www.nccn.org/
7. 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. Accessed at: https://acsearch.acr.org/docs/69396/Narrative/
8. American Urological Association (AUA): Sanda MG, Cadeddu JA, Kirkby E, et al. Clinically localized prostate cancer: AUA/ASTRO/SUO Guideline. Part I: Risk stratification, shared decision making, and care options. J Urol. 2017 Dec 14.
9. American Society for Radiation Oncology (ASTRO). Position Statement. Use of proton beam therapy for prostate cancer. February 2013. Available at: https://www.astro.org/uploadedFiles/Main_Site/Practice_Management/Reimbursement/ProtonProstateStatement.pdf.
10. American Society for Therapeutic Radiology and Oncology (ASTRO). Model Policies. Proton Beam Therapy Model Policy. June 2017. For additional information visit the ASTRO website: https://www.astro.org/uploadedFiles/_MAIN_SITE/Daily_Practice/Reimbursement/Model_Policies/Content_Pieces/ASTROPBTModelPolicy.pdf

**Peer Reviewed Publications**

11. 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.
12. 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]
13. 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.
14. 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.

15. 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.
16. 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.
17. 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.
18. 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.
19. National Institutes of Health. Clinical Trials.gov. Accessed at: http://clinicaltrials.gov/ct2/results?term=proton+beam+therapy+prostate+cancer&Search=Search
20. Kim YJ; Cho KH; Pyo HR; Lee KH et al. A phase II study of hypofractionated proton therapy for prostate cancer. Acta Oncologica. 52(3):477-85, 2013 Apr.
21. Nihei K; Ogino T; Onozawa M et al. Multi-institutional Phase II study of proton beam therapy for organ-confined prostate cancer focusing on the incidence of late rectal toxicities. International Journal of Radiation Oncology, Biology, Physics. 81(2):390-6, 2011 Oct 1.
22. Hoppe BS; Michalski JM; Mendenhall NP et al. Comparative effectiveness study of patient-reported outcomes after proton therapy or intensity-modulated radiotherapy for prostate cancer. Cancer. 120(7):1076-82, 2014 Apr 1
23. Pugh TJ; Munsell MF; Choi S et al. Quality of life and toxicity from passively scattered and spot-scanning proton beam therapy for localized prostate cancer. International Journal of Radiation Oncology, Biology, Physics. 87(5):946-53, 2013 Dec 1.
24. Cuaron JJ(1), Harris AA, Chon B et al. Anterior-oriented proton beams for prostate cancer: A multi-institutional experience. Acta Oncol. 2015 Jun; 54(6):868-74. doi: 10.3109/0284186X.2014.986288. Epub 2015 Jan 16.
25. Fang P., Mick R., Deville C. et al. A case-matched study of toxicity outcomes after proton therapy and intensity-modulated radiation therapy for prostate cancer. Cancer. 121 (7) (pp 1118-1127), 2015.
26. Mendenhall NP; Hoppe BS; Nichols RC et al. Five-year outcomes from 3 prospective trials of image-guided proton therapy for prostate cancer. International Journal of Radiation Oncology, Biology, Physics. 88(3):596-602, 2014 Mar 1.
27. Schiller KC, Habl G, Combs SE. Protons, photons, and the prostate - is there emerging evidence in the ongoing discussion on particle therapy for the treatment of prostate cancer? Front Oncol. 2016;6:8.
28. Vargas CE, Hartsell WF, Dunn M, et al. Hypofractionated versus standard fractionated proton-beam therapy for low-risk prostate cancer: interim results of a randomized trial PCG GU 002. Am J Clin Oncol. 2015. Epub ahead of print. October 29, 2015.
29. Walsh S, Roelofs E, Kuess P, et al. A validated tumor control probability model based on a meta-analysis of low, intermediate, and high-risk prostate cancer patients treated by photon, proton, or carbon-ion radiotherapy. Med Phys. 2016;43(2):734-747.

**Other Resources**

30. Hayes. Winifred Hayes Inc. Lansdale, PA:
    - Search & Summary: Proton Beam Therapy for Prostate Cancer. May, 2015.
    - Medical Technology Directory: Proton Beam Therapy for Prostate Cancer. June, 2016. Updated May, 2017.
31. UpToDate: [website]: Waltham, MA: Walters Kluwer Health; 2018.
    - Ward J, Volgelzang N, Davis B. Initial management of regionally localized intermediate and high-risk prostate cancer. Updated review 2018.
    - Klein R. Initial approach to low-risk clinically localized prostate cancer. Updated review 2018.
    - Dibiase S, Roach M. External beam radiation therapy for localized prostate cancer. Updated review 2018.
32. Advanced Medical Review (AMR): Policy reviewed by a practicing MD Board certified in Urology. September 22, 2013.

**Revision/Review History:** 3/8/18: Policy reviewed, clinical criteria has not changed.