# Molina Clinical Policy
# Proton Beam Therapy for Prostate Cancer: Policy No. 153

**Last Approval: 10/13/2021**
**Next Review Due By: October 2022**

## DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. Policies are not a supplementation or recommendation for treatment; Providers are solely responsible for the diagnosis, treatment and clinical recommendations for the Member. 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 (e.g., 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 MCP and provide the directive for all Medicare members.[1] References included were accurate at the time of policy approval and publication.

## OVERVIEW

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.[4-6]

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 (15-20 minutes) for positioning and adjustments to the equipment settings.[9]

## COVERAGE POLICY

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.[7,8]

**DOCUMENTATION REQUIREMENTS.** Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

## SUMMARY OF MEDICAL EVIDENCE

According to 2020 Hayes Health Technology Assessment, available studies of PBT for localized or locally advanced prostate cancer (without evidence of distant metastases) have consistently found that most or nearly all patients remain free from cancer progression for 5 or more years following treatment. While the results are encouraging, none of the reviewed studies assessed the efficacy of PBT as the sole or primary radiation therapy for prostate cancer compared with the efficacy of other common methods of radiation therapy. Ten of the studies found that the safety of PBT as the sole or primary therapy was usually similar to or slightly better than the safety of other common radiation therapies. However, the studies are of low quality and retrospective. The 10 studies also lack sufficient evidence of

comparative safety as they were divided between evaluations of PBT compared with IMRT, SBRT, brachytherapy, and conformal XRT. Other studies lack evidence regarding the safety and efficacy of PBT for prostate cancer (studies evaluated it as an adjunct to XRT and/or did not compare it with another type of radiation therapy). Studies are needed to establish the clinical role of PBT relative to other therapies used for localized prostate cancer.[4]

**Professional Organizations**

The **American College of Radiology (ACR)-American Society of Radiation Oncology (ASTRO)** published the *Practice Parameter for the Performance of Proton Beam Radiation Therapy.* The publication states that this type of therapy is more expensive compared to other radiation-based treatments. Clinical benefits also need further study.[9]

In addition, **ASTRO** published the *Position Statement: Use of Proton Beam Therapy for Prostate Cancer.* It concludes that the comparative efficacy evidence of proton beam therapy with other prostate cancer treatments is still being developed.[10] ASTRO's Choosing Wisely guidelines for radiation oncology were developed to foster communication between the clinician and patient. It was suggested that clinicians refrain from routinely recommending PBT for prostate cancer unless therapy is provided as part of a prospective clinical trial or registry.[11]

The **American Urological Association (AUA), ASTRO,** and the **Society of Urologic Oncology (SUO)** guideline for *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). For prostate cancer, very limited information exists in relation to the comparative effectiveness of proton therapy compared to other radiation techniques or modalities of treatment.[12]

The **National Comprehensive Cancer Network (NCCN)** guidelines for prostate cancer indicate a lack of evidence supporting a benefit or decrement to proton therapy over IMRT for either treatment efficacy or long-term toxicity.[13]

**Peer Reviewed Literature**

The body of evidence related to proton beam therapy for prostate cancer is large and the best evidence includes a randomized study (n=82)[14]; a prospective multicenter study (n=151)[15]; and two prospective comparison studies (n=1447 and n=291).[16-17] Additional evidence includes systematic reviews, prospective studies, comparison study, case series, and retrospective reviews.[3] Numerous clinical trials continue the study of proton beam therapy as a treatment for prostate cancer; no clinical trials have demonstrated that proton beam therapy has better outcomes than the conventional methods of radiation therapy.[18]

The Agency for Healthcare Research and Quality (AHRQ) published *Therapies for Clinically Localized Prostate Cancer.* It 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. 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 (ASTRO) and Nadir + 2ng/ml BCF free survival (BCFFS) rates were 85% and 86%, respectively. It was concluded that hypofractionated PT for prostate adenocarcinoma as used in the 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.[14]

Nihei, et al. conducted a multi-institutional phase II study of proton beam therapy for organ-confined prostate cancer focusing on the incidence of late rectal toxicities. Of the 151 patients enrolled, 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.[15]

Hoppe, et al. 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. 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.[16]

Five-year outcomes from 3 prospective trials of image-guided proton therapy for prostate cancer were reported by Mendenhall, et 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.[17]

Allen, et al. 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.[18]
Sheets, et al. 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. 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 results are generalizable with respect to choice of treatments, disease severity and rates of outcomes.[19]

Takagi, Demizu, et al. reported on a retrospective observational study of 2021 patients from 2003 to 2014 at a single institution. The purpose was to examine the long-term efficacy and toxicity of proton therapy for localized prostate cancer. Patients were classified using the risk groups defined by the National Comprehensive Cancer Network (NCCN) guidelines from 2019. Of the patients, 98% received 74 Gy (relative biological effectiveness) in 37 fractions; 51% and 6% of the patients received neoadjuvant and adjuvant androgen deprivation therapy, respectively. The outcomes were the time of freedom from biochemical relapse and the time to late toxicity by the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0). Outcomes were estimated using the Kaplan-Meier method and were analyzed using multivariable Cox proportional hazards models. The study demonstrates the favorable biochemical controls of proton therapy even in advanced localized prostate cancer patients with a low incidence of late toxicities, supporting the feasibility of conducting prospective clinical trials. The risk groups defined by the NCCN guidelines can aid in classifying patients with localized prostate cancer.[20]

Liu, Patel, et al. queried the National Cancer Data Base (NCDB) from 2004-2015 to examine the therapeutic delivery of proton beam therapy (PBT) versus the more utilized photon-based external-beam radiation (EBRT) and brachytherapy (BT). The impact of PBT on overall survival (OS) was evaluated and compared to EBRT or BT on patients with localized prostate cancer. The study included men with clinical stage T1-3, N0, M0 prostate cancer treated with radiation, without surgery or chemotherapy. The primary clinical outcome – OS – was fit by the Cox proportional hazard model. Propensity score matching was implemented for covariate balance. Of 276,880 eligible patients, the median follow-up was 80.9 months. A total of 4900 (1.8%) received PBT; 158,111 (57.1%) received EBRT; and 113,869 (41.1%) received BT. Compared to EBRT and BT, PBT patients were younger and were less likely to be in the high-risk group. On multivariable analysis, compared to PBT, men had worse OS after EBRT (adjusted hazard ratio [HR] = 1.72; 95% confidence interval [CI], 1.51-1.96) or BT (adjusted HR = 1.38; 95% CI, 1.21-1.58). After propensity score matching, the OS benefit of PBT remained significant compared to EBRT (HR = 1.64; 95% CI, 1.32-2.04) but not BT (adjusted HR = 1.18; 95% CI, 0.93-1.48). The improvement in OS with PBT was most prominent in men ≤ 65 years old with low-risk disease compared to other subgroups (interaction $P < .001$). PBT was associated with a significant OS benefit compared to EBRT, and with outcomes similar to BT. These results remain to be validated by ongoing prospective trials.[21]

## SUPPLEMENTAL INFORMATION

None.

## CODING & BILLING INFORMATION

**Non-Covered CPT Codes**

| 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 |

## Non-Covered HCPCS Codes – N/A

**CODING DISCLAIMER.** Codes listed in this policy are for reference purposes only and may not be all-inclusive. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement. Listing of a service or device code in this policy does guarantee coverage. Coverage is determined by the benefit document. Molina adheres to Current Procedural Terminology (CPT®), a registered trademark of the American Medical Association (AMA). All CPT codes and descriptions are copyrighted by the AMA; this information is included for informational purposes only. Providers and facilities are expected to utilize industry standard coding practices for all submissions. When improper billing and coding is not followed, Molina has the right to reject/deny the claim and recover claim payment(s). Due to changing industry practices, Molina reserves the right to revise this policy as needed.

## APPROVAL HISTORY

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|---|---|
| **10/13/2021** | Policy reviewed, no changes to criteria, included 3 new articles from 2021, and updated references. |
| **9/16/2020** | Policy reviewed, no changes to clinical criteria, technology remains experimental, investigational and unproven. Added Hayes information. References updated. |
| **9/18/2019** | Policy reviewed, no changes to clinical criteria, updated references. Published literature has not demonstrated that clinical outcomes are superior to other approaches such as intensity modulated radiation therapy (IMRT) or 3D-conformal radiation therapy. |
| **12/16/2015, 6/29/2016, 6/22/2017, 3/8/2018** | Policy reviewed, no changes to clinical criteria, updated references. |
| **10/30/2013** | New policy. |

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## APPENDIX

***Reserved for State specific information*** *(to be provided by the individual States, not Corporate). Information includes, but is not limited to, State contract language, Medicaid criteria and other mandated criteria.*