

08.01.05 Proton Beam Radiation Therapy*

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Related Policies:

- [Stereotactic Radiosurgery \(SRS\) and Stereotactic Body Radiation Therapy \(SBRT\)](#)

Summary

Description

Proton beam radiation therapy (PBRT)/proton beam therapy (PBT) is a type of external beam radiotherapy that uses charged particles. Charged-particle beams consisting of protons or helium ions are a type of particulate radiotherapy. Treatment with charged-particle radiotherapy is proposed for a large number of tumors that would benefit from the delivery of a high dose of radiation with limited scatter, minimizing the radiation dose to surrounding normal tissues and critical structures.

Summary of Evidence

For individuals who have localized prostate cancer who receive proton beam radiation therapy (PBRT)/charged particle (proton or helium ion) radiotherapy, the evidence includes two randomized controlled trials (RCTs), systematic reviews, 3 single-arm studies, and a database analysis. Relevant outcomes are overall survival, disease-free survival, change in disease status, and treatment-related morbidity. A 2021 analysis of the National Cancer Database reported inferior survival outcomes with external beam radiation therapy (EBRT) compared to PBRT, but no significant survival difference when compared to brachytherapy. A retrospective analysis found similar rates of international prostate symptom scores and expanded prostate cancer index scores from 1 to 3 years follow-up between intensity modulated radiotherapy (IMRT) and PRBT. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have non-small cell lung cancer who receive PBRT/charged particle (proton or helium ion) radiotherapy, the evidence includes one RCT, nonrandomized studies, case series and systematic reviews. Relevant outcomes are overall survival, disease-free survival, change in disease status, and treatment-related morbidity. A more recent systematic review (2026) found no difference between PBRT and photon radiotherapy in overall survival and progression-free survival. A 2018 RCT failed to demonstrate superiority of passive scattering proton therapy (PSPT) to IMRT on the combined primary outcome of grade ≥ 3 radiation pneumonitis or local failure. A retrospective cohort study found PRBT was associated with reduced rates of grade 3 or greater lymphopenia and anemia, as well as a greater likelihood of having a worse performance status than IMRT. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have other neoplastic conditions who receive PBRT/charged particle (proton or helium ion) radiotherapy relevant outcomes are overall survival, disease-free survival, change in disease status, and treatment-related morbidity. High quality evidence in peer-reviewed medical literature evaluating PBRT for other neoplastic conditions is lacking. Numerous systematic reviews have been published that have evaluated the comparative effectiveness and safety of PBRT for the treatment of some, but not all, other neoplastic conditions, including but not limited to bladder cancer, bone cancer, brain, spinal and paraspinal cancer, breast cancer, esophageal cancer, gastrointestinal cancer, liver cancer, and head and neck cancers. However, none identified any high-quality RCTs in other neoplastic conditions that compared PBRT with other advanced conventional radiation therapies and found a survival benefit. Additional robust RCTs are warranted along with long-term outcomes to establish the safety and efficacy of this treatment in all other neoplastic conditions. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Additional Information

In response to requests while this policy was under review in 2019, clinical input on use of charged-particle (proton or helium ion) beam therapy for various tumor indications was received from 3 respondents, including 2 specialty society-level responses and 1 physician-level response identified by an academic health system. In addition, the specialty society responses included multiple physicians with academic medical center affiliations.

Clinical input and published guidelines support that the use of charged-particle beam therapy provides a clinically meaningful improvement in net health outcomes and is consistent with generally accepted medical practice in the following clinical scenarios, where treatment planning with conventional or advanced photon-based radiotherapy cannot meet dose-volume constraints for normal tissue radiation tolerance:

- Curative treatment of nonmetastatic primary non-small cell lung cancer.

Clinical input suggests a possible role of charged-particle beam therapy for the treatment of localized prostate cancer, but broad support for this use is pending until the results of an ongoing RCT comparing proton therapy to intensity-modulated radiotherapy (IMRT) become available.

Further details from clinical input are included in the [Appendix](#).

OBJECTIVE

The objective of this evidence review is to determine whether charged-particle irradiation with proton beam radiation therapy improves the net health outcome in individuals with neoplastic conditions.

PRIOR APPROVAL

Prior approval required.

Note: Refer to [Wellmark Authorization Table](#) for medical necessity clinical coverage criteria using InterQual® criteria related to proton beam radiation therapy.

POLICY

Clinical Trials and Clinical Registry Trials

Proton beam radiation therapy (PBRT) is considered a **non-covered benefit** when it is the experimental arm or subject of the clinical trial (refer to the member's benefit certificate language regarding clinical trials coverage)

When PBRT is studied as part of a clinical registry trial, Wellmark BCBS coverage criteria will be applied to determine the medical necessity of the PBRT services. When PBRT is part of a clinical registry trial and Wellmark BCBS criteria are not met, the PBRT will be considered **not medically necessary**.

Clinical registry trials are observational and lack the basic underpinning of clinical equipoise as there is inherent bias among both patients and investigators.

Proton Beam Radiation Therapy

PBRT not meeting Wellmark BCBS medical necessity criteria will be considered **not medically necessary** as PBRT has not been proven to be more effective than other radiotherapy modalities for this indication.

Prostate Cancer

PBRT is considered **not medically necessary** for the treatment of prostate cancer because it has not been proven to be more effective than other radiotherapy modalities for this indication.

Other Indications

PBRT is considered **not medically necessary**, including but not limited to the following indications in adults, ages > 21 years as PBRT has not been proven to be more effective than other radiotherapy modalities for these indications:

- When the medical necessity InterQual® criteria is not met, see [Prior Approval](#)
- Anal cancer
- Ampullary adenocarcinoma
- Basal cell skin cancer
- Bladder cancer/genitourinary cancers (upper tract tumors, urothelial carcinoma, primary carcinoma of urethra)
- Bone cancer (*except when the Wellmark BCBS coverage criteria are met for the following which will require medical review: chondrosarcoma; chordoma; and osteosarcoma unresectable or incompletely resectable*)
- Breast cancer (*except left side invasive breast cancer which will require medical review*)
- Central nervous system (CNS) cancers (*except when the Wellmark BCBS coverage criteria is met for the following which will require medical review: ependymoma by biopsy intracranial or spinal; glioma by biopsy; medulloblastoma by biopsy; primary spinal cord tumors, leptomeningeal metastases, and meningiomas*)
- Cervical cancer
- Colon cancer
- Cutaneous melanoma
- Dermatofibrosarcoma Protuberans
- Esophageal and esophagogastric junction cancers (*except when the Wellmark BCBS coverage criteria is met which will require medical review*)
- Gastric cancer
- Head and neck cancers (*except when the Wellmark BCBS coverage criteria is met for the following which will require a medical review: Cancers of the oropharynx; mucosal melanoma; nasopharyngeal cancer; occult primary when targeting the pharyngeal axis; paranasal sinus cancer [maxillary sinus tumor, ethmoid sinus tumor, frontal sinus tumor, sphenoid sinus tumor]; salivary gland cancer; supraglottic larynx cancer*)
- Hepatobiliary cancers (*except when the Wellmark BCBS coverage criteria is met for the following which will require medical review Hepatocellular carcinoma (HCC) and Intrahepatic cholangiocarcinoma*)
- Intracranial arteriovenous malformations (AVM) (*except when the Wellmark BCBS coverage criteria is met for the following which will require a medical review: intracranial arteriovenous malformations (AVM) not amenable to surgical excision, embolization, or standard stereotactic radiosurgery*)
- Kidney cancer
- Lung cancer (including non-small cell (*except when the Wellmark BCBS coverage criteria is met for non-small cell lung cancer (NSCLC) which will require a medical review: In the curative treatment of nonmetastatic primary NSCLC*) and small cell and other lung cancers)

- Lymphomas (Hodgkin's lymphoma, non-Hodgkin's lymphoma i.e., B-cell lymphomas, T-cell Lymphomas) *(except when the Wellmark BCBS coverage criteria is met which will require medical review)*
- Mesothelioma peritoneal/pleural
- Neuroendocrine and adrenal tumors
- Occult Primary – Cancer of Unknown Primary (CUP)
- Ovarian cancer including fallopian tube and primary peritoneal cancer
- Pancreatic cancer
- Penile cancer
- Rectal cancer *(except for rectal cancer when the Wellmark BCBS coverage criteria is met for the following which will require a medical review: locally recurrent disease after prior pelvic radiation therapy [re-irradiation])*
- Small bowel adenocarcinoma
- Soft tissue sarcomas *(except when the Wellmark BCBS coverage criteria is met for the following which will require a medical review: retroperitoneal/intrabdominal soft tissue sarcoma or extremity/body wall/head & neck soft tissue sarcomas)*
- Squamous cell skin cancer
- Testicular cancer *(except when the Wellmark BCBS coverage criteria is met for Pure Seminoma Stage IA/IB or Stage IIA/IIB which will require a medical review)*
- Thymomas and thymic carcinomas *(except when the Wellmark BCBS coverage criteria is met, which will require medical review)*
- Uterine neoplasm
- Vaginal cancer *(except when the Wellmark BCBS coverage criteria is met for the following which will require a medical review: recurrent disease and prior radiation therapy [re-irradiation])*
- Vulvar cancer

POLICY GUIDELINES

Required Documentation

The documentation requirements outlined below are used to assess whether the member meets the clinical criteria for coverage but does not guarantee coverage of the service requested.

Medical notes documenting **All** of the following:

- History of medical condition(s) requiring treatment;
- Documentation that sparing the surrounding normal tissues/organs at risk (OARs) cannot be achieved with standard radiation therapy techniques;
- Physicians' treatment plan.

Evidence is lacking on the definition of age parameters for the use of proton beam therapy in pediatric individuals. Some studies using proton beam therapy in pediatric central nervous system tumors have mostly included individuals younger than 3 years of age. However, experts cite the benefit of proton beam therapy in pediatric patients of all ages (<21 years of age).

Organs at risk (OAR) are defined as normal tissues whose radiation sensitivity may significantly influence treatment planning and/or prescribed radiation dose. These organs at risk may be particularly vulnerable to clinically important complications from radiation toxicity. For patients with radiation-sensitizing genetic

syndromes such as neurofibromatosis type 1 (NF-1) or retinoblastoma, clinical documentation of the condition may be used to demonstrate increased risk from exposure during treatment.

For charged-particle radiotherapy (proton or helium ion) therapy to provide outcomes superior to photon-based radiotherapy, there must be a clinically meaningful decrease in the radiation exposure to normal structures. There is no standard definition for a clinically meaningful decrease in radiation dose. In principle, a clinically meaningful decrease would signify a significant reduction in anticipated complications of radiation exposure. To document a clinically meaningful reduction in dose, dosimetry planning studies should demonstrate a significant decrease in the maximum dose of radiation delivered per unit of tissue, and/or a significant decrease in the volume of normal tissue exposed to potentially toxic radiation doses. While radiation tolerance dose levels for normal tissues are well-established, the decrease in the volume of tissue exposed that is needed to provide a clinically meaningful benefit has not been standardized. Therefore, precise parameters for a clinically meaningful decrease cannot be provided.

Definition

Curative Intent: Treatment provided with the main intent being to improve or eliminate symptoms that the individual is experiencing and to extend the individual's overall length of life.

Coding

See the [Codes](#) table for details.

BACKGROUND

Charged-particle beams consisting of protons or helium ions are a type of particulate radiotherapy. They have several unique properties that distinguish them from conventional electromagnetic (i.e., photon) radiotherapy, including minimal scatter as particulate beams pass through tissue, and deposition of ionizing energy at precise depths (i.e., the Bragg peak). Thus, radiation exposure of surrounding normal tissues and critical structures is minimized. The theoretical advantages of protons and other charged-particle beams may improve outcomes when the following conditions apply:

- Conventional treatment modalities do not provide adequate local tumor control;
- Evidence shows that local tumor response depends on the dose of radiation delivered; and
- Delivery of adequate radiation doses to the tumor is limited by the proximity of vital radiosensitive tissues or structures.

Regulatory Status

Radiotherapy is a procedure and, therefore, not subject to U.S. Food and Drug Administration (FDA) regulations. However, the accelerators and other equipment used to generate and deliver charged-particle radiation (including proton beam) are devices that require FDA oversight. The FDA's Center for Devices and Radiological Health has indicated that the proton beam facilities constructed in the United States prior to enactment of the 1976 Medical Device Amendments were cleared for use in the treatment of human diseases on a "grandfathered" basis, while at least one that was constructed subsequently received a 510(k)-marketing clearance. There are 510(k) clearances for devices used for delivery of proton beam therapy and devices considered to be accessory to treatment delivery systems, such as the Proton Therapy Multileaf Collimator (which was cleared in December 2009). Since 2001, several devices

classified as medical charged-particle radiation therapy systems have received 510(k) marketing clearance. FDA product code LHN.

RATIONALE

The evidence review was created in April 2001 and has been updated regularly with searches of the PubMed database. The most recent literature update was performed through August 2026.

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function, including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, two domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Proton Beam Radiation Therapy for Localized Prostate Cancer

Clinical Context and Therapy Purpose

The purpose of proton beam radiation therapy (PBRT) /charged particle (proton or helium ion) radiation therapy (RT) in individuals who have locally advanced prostate cancer is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals who have locally advanced prostate cancer (i.e., stages T3 or T4). These tumors may be associated with a high rate of local recurrence despite maximal doses of conventional RT.

Interventions

The therapy being considered is PBRT/charged particle RT. PBRT/Charged-particle therapy is administered in specially equipped treatment centers. PBRT can be administered with or without stereotactic techniques.

Comparators

The following practices are currently being used to make decisions about localized prostate cancer: other types of radiotherapy, surgical resection, and other types of therapy for localized tumor control.

Outcomes

The general outcomes of interest are OS, disease-free survival, change in disease status (local recurrence), and treatment-related morbidity. Local control and OS would be assessed at 1 and 5 years.

Review of Evidence

Systematic Reviews

Kim et al (2013), reported on an RCT of men with androgen-deprivation therapy-naïve stage T1, T2, and T3 prostate cancer that compared different protocols for administering hypofractionated PBT. However, without an alternative intervention, conclusions cannot be drawn about the efficacy and safety of PBT. The 5 proton beam protocols used were as follows: arm 1, 60 CGE in 20 fractions for 5 weeks; arm 2, 54 CGE in 15 fractions for 5 weeks; arm 3, 47 CGE in 10 fractions for 5 weeks; arm 4, 35 CGE in 5 fractions for 2.5 weeks; or arm 5, 35 CGE in 5 fractions for 5 weeks. Eighty-two patients were randomized, with a median follow-up of 42 months. Patients assigned to arm 3 had the lowest rate of acute genitourinary toxicity, and those assigned to arm 2 had the lowest rate of late gastrointestinal toxicity. However, without an alternative intervention, conclusions cannot be drawn about the efficacy and safety of PBT.

Sun et al (2014) assessed therapies for localized prostate cancer, for the Agency for Healthcare Research and Quality. Reviewers compared the risk and benefits of a number of treatments, including radical prostatectomy, EBRT (standard therapy as well as PBT, 3-dimensional conformal radiotherapy, IMRT, stereotactic body radiotherapy [SBRT]), interstitial brachytherapy, cryotherapy, watchful waiting, active surveillance, hormonal therapy, and high-intensity focused ultrasound. They concluded that the evidence for most treatment comparisons was inadequate to draw conclusions about comparative risks and benefits. Limited evidence appeared to favor surgery over surveillance or EBRT, and RT plus hormonal therapy over RT alone. Reviewers noted that advances in technologies for many of the treatment options for clinically localized prostate cancer (e.g., current RT protocols permit higher doses than those administered in many of the trials included in the report). Moreover, the patient population had changed since most of the studies were conducted. More recently, most patients with localized prostate cancer have been identified using prostate-specific antigen testing and may be younger and healthier than prostate cancer patients identified before such testing existed. Thus, reviewers recommended additional studies to validate the comparative effectiveness of emerging therapies such as PBT, robotic-assisted surgery, and SBRT.

From the published literature, it appears as if dose escalation is an accepted treatment strategy for organ-confined prostate cancer. PBT, using CRT planning or IMRT, is used to provide dose escalation to a more well-defined target volume. However, dose escalation is more commonly offered with conventional EBRT using 3-dimensional conformal radiotherapy or IMRT. Morbidity related to RT of the prostate is focused on the adjacent bladder and rectal tissues; therefore, dose escalation is only possible if these tissues are spared. Even if IMRT or 3-dimensional conformal radiotherapy permits improved delineation of the target volume, if the dose is not accurately delivered, perhaps due to movement artifact, the complications of dose escalation can be serious, because the bladder and rectal tissues are exposed to even higher doses. The accuracy of dose delivery applies to both conventional and PBT.

Liu et al (2021) conducted an analysis of the National Cancer Database (NCDB) for cases of localized prostate cancer treated with definitive radiotherapy between 2004 and 2015. Patients with T1-T3, N0, M0 disease who received first-line treatment to the prostate and/or pelvis were included for analysis. Inclusion of individuals treated with EBRT or PBT was restricted to doses ≥ 60 Gy. The EBRT treatment cohort included individuals receiving 3D-CRT or IMRT and the brachytherapy (BT) treatment cohort allowed for monotherapy or a boost with EBRT. A total of 276,880 patients were identified with median age 68 years and median follow-up of 80.9 months. Patients treated with PBT generally had more favorable prognostic characteristics, including age, comorbidity score, tumor grade, risk group. Ten-year survival rates were 85.6%, 60.1%, and 74% for PBT, EBRT, and BT groups, respectively. In the multivariable analysis, the HR for death was 1.72 (95% CI, 1.51 to 1.96) for EBRT and 1.38 (95% CI, 1.21 to 1.58) for BT compared to PBT ($p < .001$ for all). Generalized propensity score matching of 1860 matched cases from each treatment cohort identified no statistically significant difference in OS between PBT and BT (HR, 1.18; 95% CI, 0.93 to 1.48; $p = .168$). However, EBRT continued to be associated with inferior OS (HR, 1.65; 95% CI, 1.32 to 2.04; $p < .001$) compared to PBT with propensity score matching. Ten-year survival rates in the matched samples were 80.2%, 71.3%, and 78.3% for PBT, EBRT, and BT groups, respectively. EBRT was also associated with inferior OS compared to BT. Older and higher-risk patients were associated with a decreased magnitude of improvement in OS with PBT. A sensitivity analysis determined that the observed difference in OS between PBT and EBRT cohorts was robust to an unmeasured confounder, with a $>400\%$ effect size needed to drive the estimate to nonsignificance. However, the authors note that unmeasured socioeconomic differences and other factors impacting access to proton centers are expected to underpin considerable selection biases. Additionally, the authors conclude that these findings support the rationale for ongoing studies comparing PBT to IMRT such as the PARTIQoL RCT and the COMPPARE prospective study (see clinicaltrials.gov.)

Nonrandomized Studies

Lukez et al (2023) conducted a retrospective analysis of 772 patients with localized prostate cancer treated with moderate-intensity IMRT ($n=287$) or PBT ($n=485$) between 2002 and 2018 at 4 centers in the United States. The median follow-up was 24 months for IMRT patients and 36 months for PBT patients, with overall outcome reporting rates of 62% and 50% at 1- and 3-years follow-up, respectively. Patients received daily fractions of 250 to 300 Gy to a total dose of 6000 to 7250 Gy. At baseline, treatment groups were not balanced. Patients treated with IMRT were more likely to be in an intermediate National Comprehensive Cancer Network (NCCN) risk group (81.2% vs. 68.2%; $p < .001$), to be diagnosed at an older age (70 vs. 67 years; $p < .001$), and to have a lower proportion of Gleason score 6 disease (38.8% vs. 32.1%; $p < .001$) compared to PBT. In both groups, the rate of toxicity was low through 3 years follow-up. Mean International Prostate Symptom Score (IPSS) at baseline was 7.0 for the IMRT cohort and 7.2 for the PBT cohort, with no significant differences between groups at 12, 24, or 36 months (OR, 1.01; 95% CI, 0.81 to 1.26; $p < .01$) follow-up. The Expanded Prostate Cancer Index Composite (EPIC) urinary pain score (OR, 6.88; 95% CI, 1.12 to 42.2; $p = .037$) favored the IMRT group at 1 year but did not differ between groups at 2- or 3-years follow-up. No between-group differences were observed in EPIC genitourinary frequency, problematic genitourinary stream, overall gastrointestinal, bowel pain/urgency, or bowel frequency at 1-, 2-, or 3-years follow-up.

Kubes et al (2023) conducted a retrospective analysis of 853 patients with low-, favorable intermediate-, and unfavorable intermediate-risk prostate cancer who received ultra-hypofractionated PBT at a single institution between January 2013 and June 2018. The study population had a mean age of 64.8 years, with 37.3%, 36.8%, and 25.9% of patients classified as low-, favorable intermediate-, and unfavorable intermediate-risk, respectively. The PBT regimen delivered a total dose of 36.25 Gy in 5 fractions. With a median follow-up of 62.7 months, the estimated 5-year biochemical disease-free survival rates were high across all risk groups: 96.5% for low-risk, 93.7% for favorable intermediate-risk, and 91.2% for unfavorable intermediate-risk patients. The study also reported low rates of adverse events. The

cumulative 5-year late gastrointestinal toxicity rates were 9.1% for grade 2 and 0.5% for grade 3, while the cumulative 5-year late genitourinary toxicity rates were 4.3% for grade 2, with no grade 3 toxicity observed. During the follow-up period, 58 patients (6.8%) experienced relapse, and 40 patients (4.7%) died due to causes unrelated to their prostate cancer diagnosis.

In 2019, Grewal et al published 4-year outcomes from a prospective phase 2 trial of moderately hypofractionated proton therapy (70 Gy in 28 fractions) for localized prostate cancer. A total of 184 men were followed for a median of 49.2 months. Four-year rates of biochemical-clinical failure-free survival were 93.5% (95% CI, 88 to 100) overall and 94.4% (95% CI, 89 to 100), 92.5% (95% CI, 86 to 100), and 93.8% (95% CI, 88 to 100) among subjects with low-risk, favorable intermediate-risk, and unfavorable, intermediate-risk, respectively. Overall survival was 95.8% (95% CI, 92 to 100) at 4 years, with no statistically significant differences by risk group (log-rank $p > .7$). Four-year cumulative incidence rates of late grade 2 or higher urologic or gastrointestinal toxicities were 7.6% (95% CI, 4 to 13) and 13.6% (95% CI, 9 to 20), respectively. One late grade 3 toxicity occurred, and all late toxicities were transient. Changes in urinary incontinence, irritation, and bowel function were minimal as reflected by International Prostate Symptom Score survey (IPSS) and Expanded Prostate Cancer Index Composite (EPIC) questionnaire scores. Patients receiving anticoagulation reported worse EPIC bowel scores over time ($p < .01$) and patients receiving androgen deprivation therapy reported worse International Index of Erectile Function (IIEF) ($p < .01$) and EPIC sexual ($p = .01$) and hormonal domain ($p = .05$) scores over time.

A similarly designed trial with 56 men enrolled published by Choo et al (2025) had similar 5-year results. Median follow-up was 62 months. Late grade 2 and 3 gastrointestinal adverse events were 16% and 4%, respectively, at 5 years. Late grade 2 and 3 genitourinary adverse events were 41% and 0%, respectively. No patients experienced a grade 4 or greater late adverse event. At 5-years, recurrence-free rate and disease-free survival were 90% and 89%, respectively.

Section Summary: Localized Prostate Cancer

The evidence on PBT for treating localized prostate cancer includes 2 RCTs, systematic reviews, 3 single-arm studies, and a comparative retrospective cohort study, and a comparative effectiveness analysis of the National Cancer Database (NCDB). A 2014 comparative effectiveness review concluded that the evidence on PBT for prostate cancer is insufficient. A 2021 comparative effectiveness analysis of the NCDB reported 10-year survival rates of 85.6%, 60.1%, and 74% for PBT, EBRT, and brachytherapy groups, respectively. With propensity score matching, EBRT was associated with inferior survival compared to PBT, and differences between PBT and brachytherapy were not significantly different. One retrospective analysis found similar rates of international prostate symptom scores and expanded prostate cancer index scores from 1 to 3 years follow-up between IMRT and PBRT. Limitations of the published evidence preclude determining the effects of the technology on net health outcome. Ongoing prospective studies comparing PBT to IMRT may alter the conclusions.

Proton Beam Radiation Therapy for Non-Small Cell Lung Cancer

Clinical Context and Therapy Purpose

The purpose of PBRT/charged particle (proton or helium ion) RT in individuals who have non-small-cell lung cancer (NSCLC) is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with NSCLC. NSCLC is the most common form of lung cancer, and RT is an essential component of treatment for many individuals. The potential benefit of PBRT is to reduce radiation toxicity to normal lung tissue and the heart.

Interventions

The therapy being considered is PBRT/charged particle (proton or helium ion) RT. PBRT/Charged-particle therapy is administered in specially equipped treatment centers. PBRT can be administered with or without stereotactic techniques.

Comparators

The following practices are currently being used to make decisions about NSCLCs: other types of radiotherapy, surgical resection, or other types of therapy for localized tumor control.

Outcomes

The general outcomes of interest are OS, disease-free survival, change in disease status (local recurrence), and treatment-related morbidity. Local control and OS would be assessed at 1 and 5 years.

Review of Evidence

Systematic Reviews

An indirect meta-analysis by Grutters et al (2010) found a nonsignificant difference of 9 percentage points between pooled 2-year OS estimates favoring SBRT over PBT for the treatment of NSCLC. The nonsignificant difference of 2.4% points at 5 years also favored SBRT over PBT. Based on separate groups of single-arm studies on SBRT and PBT, it is unclear whether this indirect meta-analysis adequately addressed the possible influence of confounding on the comparison of SBRT and PBT.

Pijls-Johannesma et al (2010) conducted a systematic literature review examining the use of particle therapy in lung cancer. Study selection criteria included having at least 20 patients and a follow-up of 24 months or more. Eleven studies, all dealing with NSCLC, were selected, 5 investigating protons (n=214) and 6 C-ions (n=210). The proton studies included 1 phase 2 study, 2 prospective studies, and 2 retrospective studies. The C-ion studies were all prospective and conducted at the same institution in Japan. No phase 3 studies were identified. Most patients had stage I disease, but because a wide variety of radiation schedules were used, comparisons of results were difficult, and local control rates were defined differently across studies. For proton therapy, 2-year local control rates were 74% and 85%, respectively, in the 2 studies reporting this outcome; 5-year local control rates ranged from 57% to 96% (4 studies). The 2-year OS rates ranged from 31% to 74%, and the 5-year OS rates ranged from 31% to 50% (2- and 5-year OS each reported in 4 studies). These local control and survival rates are equivalent or inferior to those achieved with SBRT. Radiation-induced pneumonitis was observed in about 10% of patients. For C-ion therapy, the overall local tumor control rate was 77%, and it was 95% when using a hypofractionated dosing schedule. The 5-year OS and cause-specific survival rates with C-ion therapy were 42% and 60%, respectively. Slightly better results were reported when using hypofractionation (50% and 76%, respectively). Reviewers concluded that, although the results with protons and heavier charged particles were promising, additional well-designed trials would be needed.

Fang et al (2026) published a systematic-review and meta-analysis comparing proton versus photon RT for NSCLC. Seven studies (N=244,604), including retrospective cohorts, multi-institutional datasets, and 1 RCT, were included. Authors found that PBT showed no significant superiority over photon RT for OS (HR, 0.91; 95% CI, 0.69 to 1.19; p=.483), PFS (HR, 1.09; 95% CI, 0.81 to 1.47; p=.572), or local PFS (HR, 0.89; 95% CI, 0.47 to 1.69; p=.732).

Randomized Controlled Studies

Liao et al (2018) conducted a RCT of PSPT versus IMRT in patients with inoperable NSCLC who were candidates for concurrent chemotherapy. Patients were eligible for randomization only if both treatment plans satisfied prespecified dose-volume constraints for organs at risk at the same tumor dose. The majority of enrolled patients were stage IIIA/B. The primary study endpoint was first occurrence of severe (grade ≥ 3) radiation pneumonitis or local failure. Compared to treatment with IMRT (n=92), patients treated with PSPT (n=57) had less lung tissue exposure to doses of 5-10 Gy (RBE [relative biological effectiveness]), increased lung tissue exposure to doses ≥ 20 Gy (RBE), and less heart tissue exposure at all dose levels between 5-80 Gy (RBE). Six patients in each group developed grade ≥ 3 radiation pneumonitis. At 1 year, rates of radiation pneumonitis were 6.5% and 10.5% in IMRT and PSPT groups, respectively (p=.537). Two patients in the IMRT group experienced grade 5 radiation pneumonitis, and no patients in the PSPT groups experienced grade 4 or 5 radiation pneumonitis. At 1 year, rates of local failure were 10.9% and 10.5% in IMRT and PSPT groups, respectively (p=1.0). Combined rates of radiation pneumonitis and local failure were not significantly different between groups (17.4% vs 21.1% for IMRT and PSPT groups, respectively; p=.175). Median OS was 29.5 months and 26.1 months for patients in IMRT and PSPT groups, respectively (p=.297), which is comparable to historical benchmarks. Considerably fewer events occurred in this trial than the 15% rate for radiation pneumonitis and 25% rate for local failure expected from historical data. In an exploratory analysis, the investigators evaluated whether a possible learning curve in the design or delivery of radiation with IMRT or PSPT over time influenced outcomes. Study participants enrolled before and after the trial midpoint in September 2011 were compared. No differences in clinical characteristics were noted for those treated with IMRT whereas the later PSPT group had a higher rate of adenocarcinoma and smaller gross tumor volumes. Combined rates of radiation pneumonitis and local failure at 12 months significantly differed according to time of enrollment in both IMRT (21.1% [early] vs 18.2% [late]) and PSPT groups (31.0% [early] vs 13.1% [late]). PSPT group radiation pneumonitis events occurred exclusively in the early cohort, whereas IMRT group radiation pneumonitis events occurred throughout the trial. Authors attributed the clinical effectiveness of IMRT in this trial to the introduction of an automated IMRT optimization system during the first year after trial activation. New treatment plans for the 6 patients who developed radiation pneumonitis in the PSPT group were generated post hoc and demonstrated lower mean lung doses for 3 individuals. The authors note that the importance of heart sparing for OS benefit is being elucidated in the ongoing Radiation Therapy Oncology Group (RTOG) 1308 RCT comparing photon versus proton chemoradiation see clinicaltrials.gov.

Nonrandomized Studies

Nakajima et al (2024) conducted a phase 2 study on image-guided proton therapy in patients with operable stage 1 non-small cell lung cancer (N=43). The patients included in the study had operable, histologically confirmed stage 1A or 1B NSCLC. The median age of the patients was 68 years, with a range of 47 to 79 years. Most patients (95%) had peripheral lesions, and 63% were stage 1A. The 3-year OS rate was 95% (95% CI: 83% to 99%), and the 7-year OS rate was 83% (95% CI: 66% to 92%). Local control rates were 95% (95% CI: 82% to 99%) at 3 years and 95% (95% CI: 82% to 99%) at 7 years. Progression-free survival (PFS) rates were 86% (95% CI: 72% to 94%) at 3 years and 77% (95% CI: 60% to 88%) at 7 years. Four patients (9%) developed grade 2 radiation pneumonitis, and one patient (2%)

developed grade 3 radiation pneumonitis. No other grade 3 or higher adverse events were observed. Global quality of life (QOL) remained favorable, although approximately 40% of patients reported dyspnea at 3 and 24 months. The authors concluded that image-guided proton therapy (IGPT) provides effective disease control and survival in operable stage 1 NSCLC, particularly for peripheral lesions. The toxicity associated with IGPT was minimal, and patients reported favorable QOL. Some limitations of the study were noted. The sample size of the study was small, and it was not a randomized comparison with surgery, which may introduce bias. Also, a high proportion (95%) of enrolled patients had peripheral tumors, which may not be representative of all patients with operable stage 1 NSCLC.

Yang et al (2024) conducted a single-arm, phase 2 study to investigate the outcomes of hypofractionated PBT in 27 patients with inoperable NSCLC treated at 2 centers between March 2018 and August 2020. The median age was 74 years, and two-thirds of patients had underlying lung diseases, including chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis, and combined pulmonary fibrosis and emphysema. Patients were treated with 64 Gy delivered in 8 fractions. With a median follow-up of 28.9 months, the 2-year local control rate was 73.5%. The 2-year OS rate was 76.5%. Grade ≥ 3 toxicities included radiation pneumonitis (3.7%) and dermatitis (3.7%). No grade 4-5 toxicities were observed. Quality of life assessed by the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire showed no significant change in global health status, but dyspnea worsened at 4 and 13 months post-PBT.

Cortiula et al (2024) reported on a retrospective analysis of prospectively collected data from 271 patients with stage III unresectable NSCLC treated with either intensity-modulated proton therapy (IMPT) (n=71) or IMRT (n=200) between June 2016 and December 2022 at 4 centers in the Netherlands and Italy. The primary endpoint was the incidence of lymphopenia grade ≥ 3 in patients who received IMPT versus IMRT. IMPT was associated with a lower incidence of lymphopenia grade ≥ 3 during treatment compared to IMRT (47% vs. 67%; OR, 2.2; 95% CI, 1.0 to 4.9; p=.032), which remained significant in multivariable analysis (adjusted OR, 2.6; 95% CI, 1.1 to 6.2; p=.029). IMPT was also associated with a lower incidence of anemia grade ≥ 3 (9% vs. 26%; OR, 4.9; 95% CI, 1.9 to 12.6; p=.001). Patients treated with IMPT had a lower rate of performance status ≥ 2 at day 21 (13% vs. 26%; p=.04) and day 42 (24% vs. 39%; p=.024) after treatment.

Nakamura et al. (2023) conducted a retrospective analysis of 34 patients with centrally located NSCLC treated with moderate hypofractionated PBT at a single center between 2006 and 2019. The median age was 77 years, and patients had tumors located within 2 cm of the proximal bronchial tree, mediastinal pleura, or pericardial pleura. Patients received either 72.6 Gy in 22 or 75 Gy in 25 fractions. With a median follow-up of 50.8 months, the 3-year OS, progression-free survival, and local control rates were 70.4%, 55.5%, and 80.5%, respectively. Grade 2 and 3 lung adverse events were observed in 14.7% of patients, with only 1 (2.9%) grade 3 radiation pneumonitis and 0 grade ≥ 4 adverse events. The mean lung dose showed a weak correlation with grade ≥ 2 lung adverse events (p=.035), while the clinical target volume had no significant correlation with lung adverse events.

Chang et al (2017) published final results from an open-label phase 2 study of 64 patients with stage III unresectable NSCLC treated with PBT plus concurrent chemotherapy (carboplatin and paclitaxel). Median OS was 26.5 months; at 5 years, the OS rate was 29% (95% CI, 18% to 41%). Median progression-free survival was 12.9 months; the 5-year progression-free survival rate was 22% (95% CI, 12% to 32%). At 5 years, 54% of patients had distant metastasis, 28% had locoregional recurrence, and 64% had a recurrence of any type. No grade 5 adverse events were observed, and grade 3 or 4 adverse events were rare. Poor OS was predicted by Karnofsky Performance Status score of 70 to 80, compared with of 90 to 100 (HR, 2.48; 95% CI, 1.33 to 4.65; p=.004). Other predictors of poor OS were stage III cancer (p=0.03), the presence of a tumor in the left lung or right lower lobe (p=.04), and a pretreatment tumor size greater than 7 cm (p=.03). The use of non-standardized induction and adjuvant

chemotherapy as well as the heterogeneity across study populations limit conclusions about treatment efficacy.

Ono et al (2017) published a retrospective case series of 20 patients with lung cancer treated with PBT at a single center between 2009 and 2015. In 14 (70%) patients, tumors were clinically inoperable; overall median tumor diameter was 39.5 mm (range, 24-81 mm). PBT was administered 3.2 Gy per fraction. Median follow-up was 27.5 months (range, 12-72 months), and the 1-year OS rate was 95.0% (95% CI, 87.7 to 100). At 2 years, the OS rate was 73.8% (95% CI, 53.9 to 93.7); no statistically significant difference was found between operable (n=6) and inoperable patients (n=14) for 2-year OS (p=.109), although operable patients had better survival rates. At 2 years, local control rate was 78.5% (95% CI, 59.5 to 97.5), and there were no reported toxicities of grade 3 or higher. The study was limited by small sample size and retrospective design.

Section Summary: Non-Small Cell Lung Cancer

A systematic review, also published in 2010, only identified case series. A more recent systematic review (2026) found no difference between PBT and photon RT in OS and PFS. Final results from a 2017 open-label phase 2 study included 5-year survival rates for patients who had PBRT with concurrent chemotherapy. A retrospective cohort study found that PBRT was associated with reduced rates of grade 3 or greater lymphopenia and anemia, as well as greater likelihood of having a worse performance status compared to IMRT. A 2018 RCT failed to demonstrate superiority of PSPT to IMRT on the combined primary outcome of grade ≥ 3 radiation pneumonitis or local failure. The ongoing RTOG 1308 RCT is expected to further elucidate the comparative safety and effectiveness of proton versus photon chemoradiation; this trial completed patient accrual October 2023.

Proton Beam Radiation Therapy for Other Neoplastic Conditions

Clinical Context and Therapy Purpose

The purpose of PBRT/charged particle (proton or helium ion) RT in individuals who have cancer is to provide a treatment option for neoplastic conditions, that is an alternative to or an improvement on existing therapies. The potential benefit of PBRT is to reduce radiation toxicity to organs at risk (OAR).

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with other neoplastic conditions.

Interventions

The therapy being considered is PBRT/charged particle (proton or helium ion) RT, which is administered in specially equipped treatment centers. PBRT can be administered with or without stereotactic techniques.

Comparators

The following practices are currently being used to make decisions about other neoplastic conditions: other types of radiotherapy, surgical resection, or other types of therapy (systemic therapy, immunotherapy, targeted therapy) for localized tumor control.

Outcomes

The general outcomes of interest are overall survival (OS), disease-free survival, change in disease status (local recurrence), and treatment-related morbidity. RT may be utilized as part of first-line treatment in various neoplastic conditions. Local control and OS would be assessed at 1 and 5 years.

Review of Evidence

High-quality evidence in peer-reviewed medical literature evaluating PBRT for other neoplastic conditions is lacking. Numerous systematic reviews have been published that have evaluated the comparative effectiveness and safety of PBRT for the treatment of some, but not all, other neoplastic conditions, including but not limited to bladder cancer, bone cancer, brain, spinal and paraspinal cancer, breast cancer, esophageal cancer, gastrointestinal cancer, liver cancer, and head and neck cancers. However, none identified any high-quality RCTs in other neoplastic conditions that compared PBRT with other advanced conventional radiation therapies and found a survival benefit. Additional robust RCTs are warranted along with long-term outcomes to establish the safety and efficacy of this treatment in all other neoplastic conditions.

SUPPLEMENTAL INFORMATION

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Clinical Input from Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

2019 Input

In response to requests while this policy was under review in 2019, clinical input on use of charged-particle (proton or helium ion) beam therapy for various tumor indications was received from 3 respondents, including 2 specialty society-level responses and 1 physician-level response identified by an academic health system. In addition, the specialty society responses included multiple physicians with academic medical center affiliations.

Clinical input and published guidelines support that the use of charged-particle beam therapy provides a clinically meaningful improvement in net health outcomes and is consistent with generally accepted medical practice in the following clinical scenarios, where treatment planning with conventional or

advanced photon-based radiotherapy cannot meet dose-volume constraints for normal tissue radiation tolerance:

- Curative treatment of nonmetastatic primary non-small cell lung cancer.

Clinical input suggests a possible role of charged-particle beam therapy for the treatment of localized prostate cancer but broad support for this use is pending until the results of an ongoing RCT comparing proton therapy to intensity-modulated radiotherapy (IMRT) are available.

Further details from clinical input are included in the Appendix.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American College of Radiology

The 2014 guidelines from the American College of Radiology on external-beam radiotherapy in stage T1 and T2 prostate cancer stated:

- "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.
- There are growing data to suggest that hypofractionation at dose per fraction <3.0 Gray (Gy) per fraction is reasonably safe and efficacious, and although the early results from hypofractionation/SBRT [stereotactic body radiation therapy] studies at dose per fraction >4.0 Gy seem promising, these approaches should continue to be used with caution until more mature, ongoing phase II and III randomized controlled studies have been completed."

American Society for Radiation Oncology

The American Society for Radiation Oncology (ASTRO) updated their Model Policy in 2022 on the medical necessity requirements for use of Proton Beam Therapy (PBT): ASTRO deemed disease sites for which evidence frequently supports the use of PBT.

"Indications and Limitations of Coverage and/or Medical Necessity

PBT is considered reasonable in instances where sparing the surrounding normal tissue is of added clinical benefit to the patient and cannot be adequately achieved with photon-based radiation therapy. Examples of such an advantage include, but not limited to:

- The target volume is new one or more critical structures and steep dose gradient outside the target must be achieved to avoid exceeding the tolerance dose to the critical structure(s), which portend a higher risk of toxicity.
- A proton-based technique would decrease the probability of clinically meaningful normal tissue toxicity by lowering an integral dose-based metric and/or organ at risk dose volume constraint associated with toxicity.

- The same or immediate adjacent area has been previously irradiated, and the dose distribution within the patient must be sculpted to avoid exceeding the cumulative tolerance dose of nearby normal tissue.”

“In addition to satisfying at least one of the three selection criteria noted above, the radiation oncologist’s decision to employ PBT requires an informed assessment of the benefits and risks including:

- Determination of patient suitability of PBT allowing for reproducible treatment delivery.
- Adequate definition of the target volumes and OARs.
- Equipment capability, including ability to account for organ motion when relevant.
- Physician, physicist and staff training.
- Adequate quality assurance and safety procedures.”

Group 1

“Based on the medical necessity requirements and published clinical data, disease sites that frequently support the use of PBT include the following:

General
Benign or malignant tumors or hematologic malignancies in children aged 21 years and younger treated with curative intent and occasionally palliative intent treatment of childhood tumors when at least one of the three criteria above under “indications for coverage” apply.
Benign or malignant tumors or hematologic malignancies in the adolescent/young adult (AYA) population aged 22 years to 39 years treated with curative intent when at least one of the three criteria above under “indications for coverage” apply.
Patients with genetic syndromes making total volume of radiation minimization crucial, such as but not limited to NF-1 patients, deleterious ATM mutations, Li-Fraumeni, retinoblastoma patients, and patients with known or suspected genetic mutations. In addition, patients with other genetic mutations who are at increased risk of developing second cancers at or near the same body location such as but not limited to BRCA 1 and 2, Lynch syndrome, etc.
Medically inoperable patients with a diagnosis of cancer typically treated with surgery where dose escalation is required due to the inability to receive surgery
Re-irradiation cases (where cumulative critical structure dose would exceed tolerance dose)
Primary malignant or benign bone tumors
Central Nervous System
Ocular tumors, including intraocular melanomas
Tumors that approach or are located at the skull base, including but not limited to: • Chordoma • Chondrosarcomas • Other histologies arising in this site
Malignant and benign primary CNS tumors excluding IDH wild-type GBM, that are treated with curative intent and with potential for long term prognosis
Primary spine cord tumors or metastatic tumors to the spine or spinal cord where organ at risk tolerance may be exceeded with photon treatments
Primary and metastatic tumors requiring craniospinal irradiation
Head and Neck
Cancers of the nasopharynx, nasal cavity, paranasal sinuses and other accessory sinuses
Advanced stage and unresectable head and neck cancers
Thoracic
Primary cancers of the esophagus
Primary tumors of the mediastinum, including thymic tumors, mediastinal tumors, mediastinal lymphomas and thoracic sarcomas
Malignant pleural mesothelioma
Abdominal
Hepatocellular cancer and intra-hepatic biliary cancers

Non-metastatic retroperitoneal sarcomas
Pelvic
Advanced and unresectable pelvic tumors with significant pelvic and/or peri-aortic nodal disease
Patient with a single kidney or transplanted pelvic kidney with treatment of an adjacent target volume and in whom maximal avoidance of the organ is critical"

Group 2

Note: Please refer to the member's benefit certificate language regarding clinical trials.

"While PBT is not a new technology, there is a need for continued clinical evidence development and comparative effectiveness analysis for the appropriate use of PBT for various disease sites. All other indications not listed in Group 1 are suitable for Coverage with Evidence Development (CED). Radiation therapy for patients treated under CED paradigm should be covered by the insurance carrier as long as the patient is enrolled in either an IRB-approved (institution review board-approved) clinical trial or in a multi-institutional patient registry adhering to the Medicare requirements for CED. At this time, no indications are deemed inappropriate for CED and therefore Group 2 includes various systems such as, but not limited to, the following:

Head and Neck
All other head and neck cancers not included in Group 1 i.e., Periorbital tumors, primary tumors of the salivary glands, head and neck cancers with indications for concurrent systemic therapy
Cutaneous tumors with cranial nerve invasion to the base of skull, cavernous sinus and/or brainstem
Head and neck cancers requiring ipsilateral radiation treatments (e.g., oral cavity, salivary gland)
Mucosal melanoma
Occult primary of head and neck
Breast
Bilateral breast cancers requiring nodal treatment on at least one side
Locally advanced breast cancer requiring comprehensive nodal irradiation inclusive of the internal mammary lymph node chain
Breast cancer patients being treated with definitive intent and who have unfavorable anatomy (e.g., pectus excavatum) that would deliver unacceptably high doses to organs-at-risk
Breast cancer patients who have limited ipsilateral arm range of motion and require treatment in the arms down position
Early stage left sided breast cancer in which dose to the heart is unacceptably high with conventional photon or photon/electron using cardiac sparing techniques
Patients with clinically involved or suspicious internal mammary lymph nodes in whom dose escalation to the internal mammary chain is clinically indicated
Thoracic
Early-stage lung cancer in which a photon-based plan cannot meet the prespecified constraints or is associated with higher risk of toxicity
Locally advanced lung cancer
Abdominal
Abdominal malignancies, including non-metastatic primary pancreatic, kidney and adrenal cancers

Oligometastatic liver lesions being treated with curative intent in which a photon based plan cannot meet constraints
Genitourinary
Prostate cancer, not fitting pelvic and/or para-aortic lymph node coverage as per Group 1
Pelvic
Pelvic malignancies, including non-metastatic rectal, bladder and cervical cancers
Tumors of the pelvis, such as anal cancer, or proximal thigh where use of protons results in significant dose reduction to genitalia or reproductive organs"

"Coverage under CED requirements will help expedite more permanent coverage decisions for all indications. Due to the numerous studies under way, proton coverage policies need to be reviewed on a frequent basis. As additional clinical data published, this policy will be revised to reflect appropriate coverage."

American Urological Association and American Society for Radiation Oncology

In 2022, the American Urological Association (AUA) and American Society for Radiation Oncology (ASTRO) published evidence-based guidelines for the management of clinically localized prostate cancer. Part III of the guideline discusses principles of radiation therapy. Regarding the use of proton therapy, the guidelines state the following: "Clinicians may counsel patients with prostate cancer that proton therapy is a treatment option, but it has not been shown to be superior to other radiation modalities in terms of toxicity profile and cancer outcomes. (Conditional Recommendation; Evidence Level: Grade C)" The guidelines additionally note that while dosimetric planning studies have indicated that proton therapy can deliver lower integral and mean doses to normal tissues, it has not been established whether these dosimetric differences translate in fewer side effects or improvements in quality of life."

International Particle Therapy Co-operative Group

A 2016 consensus statement by the International Particle Therapy Co-operative Group (PTCOG) offered the following conclusion about proton therapy for non-small-cell lung cancer (NSCLC): "...Promising preliminary clinical outcomes have been reported for patients with early-stage or locally advanced NSCLC who receive proton therapy. However, the expense and technical challenges of proton therapy demand further technique optimization and more clinical studies...."

In 2021, PTCOG published consensus guidelines on particle therapy for the management of head and neck cancer. The following recommendations were made:

- Nasopharynx: "Consider proton therapy whenever feasible. Most advanced treatment, imaging, and adaptation techniques should be used to minimize risk of neurotoxicity, given anatomic location."
- Reirradiation: "Careful evaluation required for each patient to determine risks/benefits of reirradiation. Enrollment in clinical trial encouraged whenever possible."
- Sinonasal: "Consider proton therapy whenever feasible. Most advanced treatment, imaging, and adaptation techniques should be used to minimize risk of neurotoxicity, given anatomic location."
- Postoperative: "Consider proton therapy whenever feasible. Enrollment in clinical trial encouraged whenever possible."

- Oropharynx: "Consider proton therapy whenever feasible. Enrollment in clinical trial encouraged whenever possible."

In 2021, PTCOG published a consensus statement on proton therapy for prostate cancer.⁵⁷ Regarding localized prostate cancer, they made the following statement:

- "Several prospective cohort studies have documented the safety and efficacy of proton therapy in the management of localized prostate cancer...Overall, with follow-up extending out to 5 years, tumor control and toxicity outcomes appear to be at least on par with outcomes after delivery of IMRT. Additionally, outcomes appear to be consistent across multiple proton medical centers that span various regions, countries, decades, and patient ethnicities."

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN) is a nonprofit alliance of cancer centers throughout the United States. NCCN develops the Clinical Practice Guidelines in Oncology which are recommendations aimed to help health care professionals diagnose, treat, and manage patients with cancer. These [Clinical Practice Guidelines](#) update frequently; refer to the source document for most recent updates and for additional detail related to proton beam radiation therapy.

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review can be located at clinicaltrials.gov.

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2.2026. Also available at <https://www.nccn.org>
201. National Comprehensive Cancer Network (NCCN) Mesothelioma Pleural Version 3.2026.
Also available at <https://www.nccn.org>
202. National Comprehensive Cancer Network (NCCN) Melanoma Cutaneous Version 2.2026.
Also available at <https://www.nccn.org>
203. National Comprehensive Cancer Network (NCCN) Melanoma Uveal Version 2.2026. Also
available at <https://www.nccn.org>
204. National Comprehensive Cancer Network (NCCN) Multiple Myeloma Version 5.2026. Also
available at <https://www.nccn.org>
205. National Comprehensive Cancer Network (NCCN) Myelodysplastic Syndromes Version
3.2026. Also available at <https://www.nccn.org>
206. National Comprehensive Cancer Network (NCCN) Myeloid/Lymphoid Neoplasms with
Eosinophilia and Tyrosine Kinase Gene Fusions Version 3.2026. Also available at
<https://www.nccn.org>
207. National Comprehensive Cancer Network (NCCN) Myeloproliferative Neoplasms. Version
2.2026. Also available at <https://www.nccn.org>
208. National Comprehensive Cancer Network (NCCN) Neuroblastoma. Version 2.2026. Also
available at <https://www.nccn.org>
209. National Comprehensive Cancer Network (NCCN) Neuroendocrine and Adrenal Tumors
Version 1.2026. Also available at <https://www.nccn.org>
210. National Comprehensive Cancer Network (NCCN) Non-Small Cell Lung Cancer Version
7.2026. Also available at <https://www.nccn.org>
211. National Comprehensive Cancer Network Occult Primary (Cancer of Unknown Primary
[CUP]) Version 2.2026. Also available at <https://www.nccn.org>
212. National Comprehensive Cancer Network (NCCN) Ovarian Cancer Including Fallopian
Tube Cancer and Primary Peritoneal Cancer Version 4.2026. Also available at
<https://www.nccn.org>
213. National Comprehensive Cancer Network (NCCN) Pancreatic Adenocarcinoma Version
3.2026. Also available at <https://www.nccn.org>

214. National Comprehensive Cancer Network (NCCN) Pediatric Acute Lymphoblastic Leukemia Version 1.2026. Also available at <https://www.nccn.org>
215. National Comprehensive Cancer Network (NCCN) Pediatric Aggressive Mature B-Cell Lymphoma Version 1.2026. Also available at <https://www.nccn.org>
216. National Comprehensive Cancer Network (NCCN) Pediatric Central Nervous System Cancers Version 1.2026. Also available at <https://www.nccn.org>
217. National Comprehensive Cancer Network (NCCN) Pediatric Hodgkin Lymphoma Version 1.2026. Also available at <https://www.nccn.org>
218. National Comprehensive Cancer Network (NCCN) Pediatric Soft Tissue Sarcoma Version 1.2026. Also available at <https://www.nccn.org>
219. National Comprehensive Cancer Network (NCCN) Primary Cutaneous Lymphomas Version 3.2025. Also available at <https://www.nccn.org>
220. National Comprehensive Cancer Network (NCCN) Penile Cancer Version 2.2026. Also available at <https://www.nccn.org>
221. National Comprehensive Cancer Network (NCCN) Prostate Cancer Version 6.2026. Also available at <https://www.nccn.org>
222. National Comprehensive Cancer Network (NCCN) Rectal Cancer Version 2.2026. Also available at <https://www.nccn.org>
223. National Comprehensive Cancer Network (NCCN) Small Bowel Adenocarcinoma Version 2.2026. Also available at <https://www.nccn.org>
224. National Comprehensive Cancer Network (NCCN) Small Cell Lung Cancer Version 1.2027. Also available at <https://www.nccn.org>
225. National Comprehensive Cancer Network (NCCN) Soft Tissue Sarcoma Version 5.2026. Also available at <https://www.nccn.org>
226. National Comprehensive Cancer Network (NCCN) Squamous Cell Skin Cancer Version 2.2026. Also available at <https://www.nccn.org>
227. National Comprehensive Cancer Network (NCCN) Systemic Light Chain Amyloidosis Version 2.2026. Also available at <https://www.nccn.org>
228. National Comprehensive Cancer Network (NCCN) Systemic Mastocytosis Version 3.2026. Also available at <https://www.nccn.org>
229. National Comprehensive Cancer Network (NCCN) T-cell Lymphomas Version 2.2026. Also available at <https://www.nccn.org>
230. National Comprehensive Cancer Network (NCCN) Testicular Cancer Version 2.2026. Also available at <https://www.nccn.org>
231. National Comprehensive Cancer Network (NCCN) Thymomas and Thymic Carcinomas Version 2.2026. Also available at <https://www.nccn.org>
232. National Comprehensive Cancer Network (NCCN) Thyroid Carcinoma Version 2.2026. Also available at <https://www.nccn.org>
233. National Comprehensive Cancer Network (NCCN) Uterine Neoplasm Version 3.2026. Also available at <https://www.nccn.org>
234. National Comprehensive Cancer Network (NCCN) Vaginal Cancer Version 2.2026. Also available at <https://www.nccn.org>

235. National Comprehensive Cancer Network (NCCN) Vulvar Cancer Version 2.2026. Also available at <https://www.nccn.org>
236. National Comprehensive Cancer Network (NCCN) Waldenstrom Macroglobulinemia/Lymphoplasmacytic Lymphoma. Version 1.2027. Also available at <https://www.nccn.org>
237. National Comprehensive Cancer Network (NCCN) Wilms Tumor (Nephroblastoma) Version 1.2026 Also available at <https://www.nccn.org>
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CODES

To report provider services, use appropriate CPT codes, HCPCS codes, Revenue codes, and/or ICD diagnosis codes.

Codes	Number	Description
CPT		
	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		
	None	
Type of Service	Therapy	
Place of Service	Outpatient/Inpatient	

POLICY HISTORY

Date	Reason	Action
August 2026	Annual Review	Policy Revised
October 2025	Annual Review	Policy Renewed
September 2024	Annual Review	Policy Revised
September 2023	Annual Review	Policy Revised
January 2023	Interim Review	Policy Revised
August 2022	Annual Review	Policy Renewed
August 2021	Annual Review	Policy Revised
August 2020	Annual Review	Policy Revised
August 2019	Annual Review	Policy Revised
November 2018	Interim Review	Policy Revised
August 2018	Annual Review	Policy Revised
August 2017	Annual Review	Policy Renewed
May 2017	Interim Review	Policy Revised
August 2016	Annual Review	Policy Revised
September 2015	Annual Review	Policy Revised
May 2015	Interim Review	Policy Revised
January 2015	Annual Review	Policy Revised
October 2014	Annual Review	Policy Renewed
January 2014	Annual Review	Policy Revised
January 2013	Annual Review	Policy Renewed
January 2012	Annual Review	Policy Renewed
January 2011	Annual Review	Policy Revised

Appendix

2019 Clinical Input

Respondent Profile

Specialty Society						
#	Name of Organization			Clinical Specialty		
1	American Society for Radiation Oncology (ASTRO)			Radiation Oncology		
2	Massachusetts Society of Clinical Oncology (MSCO)			Radiation Oncology, Clinical Oncology		
	Physician					
#	Name	Degree	Institutional Affiliation	Clinical Specialty	Board Certification and Fellowship Training	
Identified by Academic Medical Center						
3	Anonymous	MD	Academic Medical Center	Radiation Oncology		

Respondent Conflict of Interest Disclosure

#	1) Research support related to the topic where clinical input is beingsought	2) Positions, paid or unpaid, related to the topic where clinical input is beingsought	3) Reportable, more than \$1,000, health care–related assets or sources of income for myself, my spouse, or my dependent children related to the topic where clinical input is beingsought	4) Reportable, more than \$350, gifts or travel reimbursements for myself, my spouse, or my dependent children related to the topic where clinical input is beingsought				
	YES/NO	Explanation	YES/NO	Explanation	YES/NO	Explanation	YES/NO	Explanation
3	No	Not applicable, as this response is from health system, and not from individual physicians	No	Not applicable, as this response is from health system, and not from individual physicians	No	Not applicable, as this response is from health system, and not from individual physicians	No	Not applicable, as this response is from health system, and not from

								individual physicians
#	Conflict of Interest Policy Statement							
1	ASTRO's Payer Relations Committee provided feedback. Regarding COI: "If there is any material information that raises potential conflict of interest issues for a Committee member at any time throughout the course of our work, it should be brought to the attention of the Committee Chair." No Committee members reported any conflicts of interest.							
2	No conflicts of interest reported.							

Individual physician respondents answered at individual level. Specialty Society respondents provided aggregate information that may be relevant to the group of clinicians who provided input to the Society-level response.

Clinical Input Responses

Clinical Input Background

Charged-particle beams consisting of protons or helium ions are a type of particulate radiotherapy. Treatment with charged-particle radiotherapy is proposed for a large number of indications, often for tumors that would benefit from the delivery of a high dose of radiation with limited scatter.

Clinical Input Objective

Clinical input is sought to help determine whether the use of charged-particle (proton or helium ion) beam therapy for various tumor indications would provide a clinically meaningful improvement in net health outcome and whether the use is consistent with generally accepted medical practice

Responses

1. We are seeking your opinion regarding whether and when clinical scenarios using charged-particle (proton or helium ion) therapy (PBT) for the tumor types highlighted below provide a clinically meaningful improvement in net health outcome that is **superior** to advanced conformal, fractionated photon-based radiotherapy including intensity modulated radiotherapy (IMRT), volume-modulated arc therapy (VMAT), stereotactic radiosurgery (SRS), or stereotactic body radiation therapy (SBRT). Please respond based on the evidence and your clinical experience. Please address these points in your narrative rationale:
 - Relevant patient inclusion/exclusion criteria or clinical context important to consider when PBT may offer superior improvement in net health outcome;
 - Relevant critical organs at risk for each clinical indication and associated thresholds for radiation dose limits; and
 - Supporting evidence from the authoritative scientific literature (please include PMID).
 - a) Non-small cell lung cancer (curative treatment)

#	Rationale:
1	· Akita K, Iwata H, Ogino H, et al. A phase II trial of S-1 plus cisplatin with concurrent proton-beam therapy for locally advanced non-small cell lung cancer. J Clin Oncol. 2017;35(15):e20070 · Bush DA, Cheek G, Zaheer S, et al. High-dose hypofractionated proton beam radiation therapy is safe and effective for central and peripheral early-stage non-small cell lung cancer: results of a 12-year experience at Loma Linda University Medical Center. Int J Radiat Oncol Biol Phys. 2013;86(5):964-968.

#	Rationale: · Chang JY, Jabbour SK, De Ruyscher D, et al. Consensus statement on proton therapy in early-stage and locally advanced non-small cell lung cancer. <i>Int J Radiat Oncol Biol Phys.</i> 2016 May; 95(1):505-16. · Cooper BT, Mah D, Chen CC, et al. Hypofractionated Proton Therapy for Early Stage Non-small Cell Lung Cancer: Clinical Outcomes and Comparative Dosimetric Analysis. <i>Int J Radiat Oncol Biol Phys.</i> 2017; 99(2): E449. · Gomez DR, Li H, Chang JY. Proton therapy for early-stage non-small cell lung cancer (NSCLC). <i>Transl Lung Cancer Res.</i> 2018;7(2):199-204. · Jeter MD, Gomez D, Nguyen Q, et al. Simultaneous Integrated Boost for Radiation Dose Escalation to the Gross Tumor Volume with Intensity-Modulated (Photon) Radiation Therapy or Intensity-Modulated Proton Therapy and Concurrent Chemotherapy for Stage II-III Non-Small Cell Lung Cancer: A Phase I Study. <i>Int J Radiat Oncol Biol Phys.</i> 2017; https://doi.org/10.1016/j.ijrobp.2017.10.042. · Nakajima K, Iwata H, Ogino H, et al. Clinical Outcomes of Image-Guided Proton Therapy for Stage I Non-small Cell Lung Cancer. <i>Int J Radiat Oncol Biol Phys.</i> 2017;99(2S):E483. · Yang P, Xu T, Gomez DR, Deng W, et al. Patterns of local-regional failure after intensity-modulated radiation therapy or passive scattering proton therapy with concurrent chemotherapy for non-small cell lung cancer. <i>Int J Radiat Oncol Biol Phys.</i> 2018.
2	Vyfhuis et al "Advances in Proton Therapy in Lung Cancer" (<i>Ther Adv Respir Dis</i> 2018;12:1-16) provides a comprehensive review of this subject. There are a number of papers reporting on institutional experiences with PBT for non-small cell lung cancer. The evidence is not sufficiently robust to support PBT. PBT is being evaluated in comparison to photon therapy in a number of clinical trials
3	Radiation therapy is a vital component of the curative management for patient advanced lung cancer. Unfortunately, it has become quite clear morbidity and mortality following standard treatment can limit outcomes specifically related to injuries to the esophagus, lung and heart (Bradley 2015, Khalil 2015, Graham 1999). Several large single and multi-institutional studies have demonstrated critical dosimetric cut points for each of these normal tissues. If these critical dosimetric parameters which are described below can't be achieved, Proton Beam Radiation can reduce these parameters to a safer level. Esophageal dose: Bradley et. al. (Bradley 2015) from RTOG 0617 demonstrated the development of grade 3 esophagitis was one of the variables that predicted for a detriment in survival on multivariate analysis with a hazard ratio of 1.54 (p=0.01). Based on the work by Palma et. al (Palma 2013), the volume of esophagus that receives 60 Gy was critical in predicting grade 3 or higher events where the major cut points to achieve were 0.07 and 17 %. This correspond to risks of grade 3 esophagitis of 4% (< 0.07%), 10% (0.07-17%) and 22% (>17%). Heart dose: The results of RTOG 0617 (Bradley 2015) demonstrate that a higher heart dose predicted for a lower rate in survival presumably related to an increase in non-cancer related deaths. Several authors have demonstrated the importance of mean heart as the most important predictor of major/symptomatic cardiac events that are likely the cause of this decrease in survival. Chun et. al. demonstrated that an important cut point was a mean dose to the heart > 20 Gy has a 40% rate of cardiac events which can be decrease to 10%. In addition, Darby (NEJM 2013) demonstrated major coronary events continue to occur as there was no apparent threshold and that for every 1 Gy increase in dose to the heart the relative risk of major coronary events increases 7.4%. Lung Dose: The initial experience at Washington University (Graham 1999) demonstrated all of the cases of fatal pneumonitis occurred when the V20 > 35%, so this patient has substantial risks. Palma (Palma 2013) describes an odd ratio of 1.09 in fatal pneumonitis per every 1% increase in V20. · Palma, David A., et al. "Predicting radiation pneumonitis after chemoradiation therapy for lung cancer: an international individual patient data meta-analysis." <i>International Journal of Radiation Oncology* Biology* Physics</i> 85.2 (2013): 444-450. · Palma, David A., et al. "Predicting esophagitis after chemoradiation therapy for non-small cell lung cancer: an individual patient data meta-analysis." <i>International Journal of Radiation Oncology* Biology* Physics</i> 87.4 (2013): 690-696. · Khalil, Azza A., et al. "New dose constraint reduces radiation-induced fatal pneumonitis in locally advanced non-small cell lung cancer patients treated with intensity-modulated radiotherapy." <i>Acta oncologica</i> 54.9 (2015): 1343-1349.

#	Rationale:
	- Bradley, Jeffrey D., et al. "Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study." <i>The lancet oncology</i> 16.2 (2015): 187-199. - Graham, Mary V., et al. "Clinical dose–volume histogram analysis for pneumonitis after 3D treatment for non-small cell lung cancer (NSCLC)." <i>International Journal of Radiation Oncology* Biology* Physics</i> 45.2 (1999): 323-329. - Darby, Sarah C., et al. "Risk of ischemic heart disease in women after radiotherapy for breast cancer." <i>New England Journal of Medicine</i> 368.11 (2013): 987-998. - Speirs, Christina K., et al. "Heart dose is an independent dosimetric predictor of overall survival in locally advanced non–small cell lung cancer." <i>Journal of Thoracic Oncology</i> 12.2 (2017): 293-301. - Wang, Kyle, et al. "Cardiac toxicity after radiotherapy for stage III non–small-cell lung cancer: pooled analysis of dose-escalation trials delivering 70 to 90 Gy." <i>Journal of Clinical Oncology</i> 35.13 (2017): 1387. - Dess, Robert T., et al. "Cardiac events after radiation therapy: combined analysis of prospective multicenter trials for locally advanced non–small-cell lung cancer." <i>Journal of Clinical Oncology</i> 35.13 (2017): 1395.

NR = not reported

Rating Questions:	#	YES / NO	Low Confidence	Intermediate Confidence	High Confidence
			1	2 3	4 5
Does the evidence show that PBT provides a clinically meaningful improvement in net health outcome that is superior to other advanced conformal, fractionated photon-based radiotherapy techniques ¹ for most patients with this indication?	1	No		X	
	2	No	Rating not provided		
	3	No		X	
Does PBT provide a clinically meaningful improvement in net health outcome that is superior ONLY when radiation dose constraints for critical organs at risk (i.e., surrounding normal tissue) cannot be met by other conformal, fractionated photon-based radiotherapy techniques ¹ for patients with this indication?	1	Yes		X	
	2	No	Rating not provided		
	3	Yes			X
Is use of PBT for this indication consistent with generally accepted medical practice?	1	No		X	
	2	No	Rating not provided		
	3	Yes		X	

NR = not reported

b) Prostate Cancer

#	Rationale:
1	- Arimura T, Kondo N, Matsukawa K, et al. The role of proton beam therapy for patients with intermediate- and high-risk prostate cancer. <i>J Clin Oncol.</i> 2018;36(6):97. - Bryant C, Smith TL, Henderson RH, et al. Five-year biochemical results, toxicity, and patient-reported quality of life following delivery of dose-escalated image-guided proton therapy for prostate cancer. <i>Int J Radiat Oncol Biol Phys.</i> 2016;95(1):422-434. - Choi S, Blanchard P, Ye R, et al. Outcomes Following Proton Therapy for the Treatment of Prostate Cancer: Efficacy and Toxicity Results from 2 Prospective Single Institution Cohorts. <i>Int J Radiat Oncol Biol Phys.</i> 2017;99(2S):E221.

#	Rationale:
	- Ho CK, Bryant CM, Mendenhall NP, et al. Long-term outcomes following proton therapy for prostate cancer in young men with a focus on sexual health. Acta Oncol. 2018. https://doi.org/10.1080/0284186X.2018.1427886. - Jain et al. Acute and late toxicity report of post-prostatectomy proton therapy for prostate cancer patients undergoing adjuvant or salvage radiotherapy. Int J Radiat Oncol Biol Phys. 2017;98(2):e25. - Mendenhall NP, Wong W, Bryant C et al. Comparison of clinical outcomes with IMRT and proton therapy for prostate cancer. J Clin Oncol. 2017; e16555-e16555. - Walsh S, Roelofs E, Kuss P, et al. Towards a Clinical Decision Support System for External Beam Radiation Oncology Prostate Cancer Patients: Proton vs. Photon Radiotherapy? A Radiobiological Study of Robustness and Stability. Cancers. 2018;10(55):1-16.
2	NR
3	The definitive randomized trial for localized prostate cancer (NCT01617161) is near completion of enrollment and should report in a few years.

NR = not reported

Rating Questions:	#	YES / NO	Low Confidence	Intermediate Confidence	High Confidence
			1	2 3	4 5
Does the evidence show that PBT provides a clinically meaningful improvement in net health outcome that is superior to other advanced conformal, fractionated photon-based radiotherapy techniques ¹ for most patients with this indication?	1	No			X
	2	No	Rating not provided		
	3	No			X
Does PBT provide a clinically meaningful improvement in net health outcome that is superior ONLY when radiation dose constraints for critical organs at risk (i.e., surrounding normal tissue) cannot be met by other conformal, fractionated photon-based radiotherapy techniques ¹ for patients with this indication?	1	Yes			X
	2	No	Rating not provided		
	3	No			X
Is use of PBT for this indication consistent with generally accepted medical practice?	1	Yes		X	
	2	No	Rating not provided		
	3	Yes			X

NR = not reported

2. Additional narrative rationale or comments regarding the clinical context or specific clinical pathways for this topic and/or any relevant scientific citations (including the PMID) with evidence that demonstrates health outcomes you would like to highlight.

#	Additional Comments
1	NA
2	NR
3	Penn Medicine has worked with commercial insurers on innovative and successful proton therapy coverage initiatives for the past 10 years. These initiatives have been described in the academic and lay literature (see

#	Additional Comments
	below). Penn Medicine specifically has established coverage policies for proton therapy with Independence Blue Cross and Horizon that have been resoundingly successful in providing access to proton therapy while still ensuring that any necessary comparative effectiveness research is conducted. These initiatives have led to important research findings (both positive and negative) that have impacted patient care nationally and have led to large funded pragmatic trials from the NCI and PCORI. Investigators at have collaborated with BCBS Association in some of these efforts. Penn Medicine also participates in Aetna's recently announced coverage with trial participation policy for NCI and PCORI randomized trials. Penn Medicine is a national leader in innovative strategies to provide access to new medical technology while ensuring the technology is safe and effective. Clinical and managed care leaders at Penn Medicine would be delighted to meet with the BCBS Association as it conducts its review. See for example: • Bekelman JE and Hahn SM. J Clin Oncol. 2014 May 20;32(15):1540-2. doi: 10.1200/JCO.2014.55.6613. Epub 2014 Apr 21. • Reference pricing with evidence development: a way forward for proton therapy. PMID: 24752049 PMCID: PMC4026577 DOI: 10.1200/JCO.2014.55.6613 • Bekelman JE, Denicoff A, Buchsbaum J. J Clin Oncol. 2018 Aug 20;36(24):2461-2464. doi: 10.1200/JCO.2018.77.7078. Epub 2018 Jul 9. • Randomized Trials of Proton Therapy: Why They Are at Risk, Proposed Solutions, and Implications for Evaluating Advanced Technologies to Diagnose and Treat Cancer. PMID: 29985746 PMCID: PMC6366815 DOI: 10.1200/JCO.2018.77.7078

NR = not reported

3. Is there any evidence missing from the attached draft review of evidence that demonstrates clinically meaningful improvement in net health outcome?

#	YES / NO	Citations of Missing Evidence
1	No	NA
2	NR	NR
3	No	NR

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

Wellmark Blue Cross and Blue Shield
Medical Policy Analyst
PO Box 9232
Des Moines, IA 50306-9232

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