BlueCross BlueShield Federal Employee Program.

FEP Medical Policy Manual

FEP 8.01.10 Charged-Particle (Proton or Helium Ion) Radiotherapy for Neoplastic Conditions

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Related Policies:

6.01.10 - Stereotactic Radiosurgery and Stereotactic Body Radiotherapy
8.01.46 - Intensity-Modulated Radiotherapy of the Breast and Lung
8.01.48 - Intensity-Modulated Radiotherapy: Cancer of the Head and Neck or Thyroid
8.01.49 - Intensity-Modulated Radiotherapy: Abdomen, Pelvis and Chest

Charged-Particle (Proton or Helium Ion) Radiotherapy for Neoplastic Conditions

Description

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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.

OBJECTIVE

The objective of this evidence review is to determine whether charged-particle irradiation with proton or helium ion beams improves the net health outcome in individuals with neoplastic conditions.

POLICY STATEMENT

Charged-particle irradiation with proton or helium ion beams may be considered **medically necessary** for treatment in the following clinical situations:

- primary therapy for melanoma of the uveal tract (iris, choroid, or ciliary body), with no evidence of metastasis or extrascleral extension, and with tumors up to 24 mm in largest diameter and 14 mm in height;
- postoperative therapy (with or without conventional high-energy x-rays) in patients who have undergone biopsy or partial resection of chordoma or low-grade (I or II) chondrosarcoma of the basisphenoid region (skull-base chordoma or chondrosarcoma) or cervical spine. Patients eligible for this treatment have residual localized tumor without evidence of metastasis;
- pediatric central nervous system tumors.

Charged-particle irradiation with proton or helium ion beams may be considered **medically necessary** where treatment with conventional or advanced photon-based radiotherapy cannot meet dose-volume constraints for normal tissue radiation tolerance (see Policy Guidelines section) in the following clinical situations:

- in the curative treatment of primary or benign solid pediatric non-central nervous system tumors, including Ewing sarcoma;
- in the curative treatment of nonmetastatic primary non-small cell lung cancer;
- head and neck cancers.

Other applications of charged-particle irradiation with proton or helium ion beams may be considered **investigational**. This includes, but may not be limited to:

- clinically localized prostate cancer;
- non-curative treatment of primary or benign solid pediatric non-central nervous system tumors, including Ewing sarcoma;
- non-curative treatment of non-small cell lung cancer.

POLICY GUIDELINES

Policy criteria are informed by clinical input and published guidelines. Further details from clinical input are included in the Appendix.

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 are defined as normal tissues whose radiation sensitivity may significantly influence treatment and/or prescribed radiation dose. These organs at risk may be particularly vulnerable to clinically important complications from radiation toxicity. Table PG1 outlines radiation doses that are generally considered tolerance thresholds for these normal structures in various organ regions. Clinical documentation based on dosimetry plans may be used to demonstrate that radiation by conventional or advanced photon-based radiotherapy, including intensity-modulated radiotherapy (IMRT), volume-modulated arc therapy (VMAT), stereotactic radiosurgery (SRS), or stereotactic body radiation therapy (SBRT), would exceed tolerance doses to structures at risk. 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.

Table PG1. Radiation Tolerance Doses for Normal Tissues

Site	TD 5/5 (Gray)[a]			TD 50/5 (Gray)[b]			Complication End Point
	Portion of Organ Involved			Portion of Organ Involved			
	1/3	2/3	3/3	1/3	2/3	3/3	
Heart	60	45	40	70	55	50	Pericarditis
Lung	45	30	17.5	65	40	24.5	Pneumonitis
Spinal cord	50	50	47	70	70	NP	Myelitis/necrosis
Salivary glands	32	32	32	46	46	46	Xerostemia
Kidney	50	30	23	NP	40	28	Clinical nephritis
Liver	50	35	30	55	45	40	Liver failure
Esophagus	60	58	55	72	70	68	Stricture, perforation
Stomach	60	55	50	70	67	65	Ulceration, perforation
Small intestine	50	NP	40	60	NP	55	Obstruction, perforation
Colon	55	NP	45	65	NP	55	Obstruction, perforation, ulceration, fistula
Rectum	NP	NP	60	NP	NP	80	Severe proctitis, necrosis, stenosis, fistula
Femoral head	NP	NP	52	NP	NP	65	Necrosis

Compiled from 2 sources: (1) Morgan MA (2011). Radiation Oncology. In DeVita, Lawrence, and Rosenberg, Cancer (p.308). Philadelphia: Lippincott Williams and Wilkins; and (2) Kehwar TS, Sharma SC. Use of normal tissue tolerance doses into linear quadratic equation to estimate normal tissue complication probability. Available online at: http://www.rooj.com/Radiation%20Tissue%20Tolerance.htm.
NP: not provided; TD: tolerance dose.

[a] TD 5/5 is the average dose that results in a 5% complication risk within 5 years.

[b] TD 50/5 is the average dose that results in a 50% complication risk within 5 years.

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 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.

IMRT of the lung is addressed in evidence review 8.01.46. IMRT of the prostate is addressed in evidence review 8.01.47. IMRT of the head or neck is addressed in evidence review 8.01.48.

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

Charged-particle radiotherapy is a specialized procedure that may need an out-of-network referral.

FDA 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

Summary of Evidence

For individuals who have uveal melanoma(s) who receive charged-particle (proton or helium ion) radiotherapy, evidence includes long-term studies, randomized controlled trials (RCTs), and systematic reviews. Relevant outcomes are overall survival, disease-free survival, change in disease status, and treatment-related morbidity. Systematic reviews, including a 1996 TEC Assessment and a 2013 review of randomized and nonrandomized studies, concluded that the technology is at least as effective as alternative therapies for treating uveal melanomas and is better at preserving vision. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have a skull-based tumor(s) (ie, cervical chordoma, chondrosarcoma) who receive charged-particle (proton or helium ion) radiotherapy, the evidence includes observational studies and systematic reviews. Relevant outcomes are overall survival, disease-free survival, change in disease status, and treatment-related morbidity. A 2007 systematic review found a 5-year overall survival rate of 81% with proton beam therapy (PBT) compared with 44% with surgery plus photon therapy. In 2018, a meta-analysis found 5-year and 10-year overall survival rates for PBT of 78% and 60% compared with 46% and 21% for conventional radiotherapy. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have pediatric central nervous system tumor(s) who receive charged-particle (proton or helium ion) radiotherapy, the evidence includes case series, nonrandomized comparative studies, and systematic reviews. Relevant outcomes are overall survival, disease-free survival, change in disease status, and treatment-related morbidity. There are few comparative studies, and they tend to have small sample sizes. The available observational studies do not provide sufficient evidence on the efficacy of charged-particle therapy compared with other treatments (eg, intensity-modulated radiotherapy [IMRT]). The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have pediatric non-central nervous system tumor(s) who receive charged-particle (proton or helium ion) radiotherapy, the evidence includes dosimetric studies in a small number of patients. Relevant outcomes are overall survival, disease-free survival, change in disease status, and treatment-related morbidity. For this population, there is a lack of randomized and observational studies evaluating the efficacy and safety of this technology. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have localized prostate cancer who receive charged-particle (proton or helium ion) radiotherapy, the evidence includes 2 RCTs, systematic reviews, a single-arm study, and a database analysis. Relevant outcomes are overall survival, disease-free survival, change in disease status, and treatment-related morbidity. A 2010 TEC Assessment addressed the use of PBT for prostate cancer and concluded that it had not been established whether PBT improves outcomes in any setting for clinically localized prostate cancer. The TEC Assessment included 2 RCTs, only one of which had a comparison group of patients that did not receive PBT. A 2021 analysis of the National Cancer Database reported inferior survival outcomes with external-beam radiotherapy (EBRT) compared to PBT, 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 Composite scores from 1 to 3 years follow-up between IMRT and PBT. A large, ongoing phase 3 RCT comparing proton therapy to IMRT in prostate cancer may alter the conclusions of the TEC Assessment. 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 charged-particle (proton or helium ion) radiotherapy, the evidence includes one RCT, case series and systematic reviews. Relevant outcomes are overall survival, disease-free survival, change in disease status, and treatment-related morbidity. A 2010 TEC Assessment, which included 8 case series, concluded that the evidence was insufficient to permit conclusions about PBT for any stage of non-small-cell lung cancer. 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 that PBT 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. An ongoing RCT comparing proton versus photon chemoradiation may alter the conclusions of the TEC Assessment. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have head and neck tumors other than skull-based who receive charged-particle (proton or helium ion) radiotherapy, the evidence includes case series, nonrandomized comparative studies, and a systematic review. Relevant outcomes are overall survival, disease-free survival, change in disease status, and treatment-related morbidity. The systematic review noted that the studies on charged-particle therapy were heterogenous in terms of the types of particles and delivery techniques used; further, there are no prospective head-to-head trials comparing charged-particle therapy with other treatments. Ongoing RCTs comparing intensity-modulated proton therapy (IMPT) to IMRT may elucidate effects on net health outcome. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

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.

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...."[50,]

In 2021, PTCOG published consensus guidelines on particle therapy for the management of head and neck cancer.[51,] 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."

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 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."[52,]

American Urological Association et al

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.[53,] 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 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 to fewer side effects or improvements in quality of life.

National Comprehensive Cancer Network

Uveal Melanoma

National Comprehensive Cancer Network (NCCN) guidelines for uveal melanoma (v.1.2023) support the use of particle beam therapy for definitive radiotherapy of the primary tumor and that its use is appropriate as upfront therapy after diagnosis, after margin-positive enucleation, or for intraocular or orbital recurrence.[54,] Treatment recommendations for intraocular tumors include:

- "Using protons, 50-70 cobalt Gray equivalent (CGyE) in 4-5 fractions should be prescribed to encompass the target volume surrounding the tumor.
- Using carbon ions, 60-85 CGyE in 5 fractions should be prescribed to encompass the target volume surrounding the tumor."

Prostate Cancer

NCCN guidelines for prostate cancer (v.3.2024) offer the following conclusion on proton therapy: "The NCCN panel believes no clear evidence supports a benefit or decrement to proton therapy over IMRT [intensity-modulated radiotherapy] for either treatment efficacy or long-term toxicity. Conventionally fractionated prostate proton therapy can be considered a reasonable alternative to x-ray-based regimens at clinics with appropriate technology, physics, and clinical expertise."[55,] The NCCN adds that a prospective randomized trial comparing prostate PBT with x-ray-based IMRT is ongoing and may help to elucidate outcomes, as the evidence to date has not demonstrated a significant difference in benefit, particularly in regard to short and long-term toxicities. The NCCN acknowledges that PBT may deliver less radiation to surrounding tissues (eg, muscle, bone, vessels, fat), but that these tissues do not routinely contribute to the morbidity of prostate radiation. Of greater clinical relevance, is the volume of rectum and bladder that is exposed to radiation. Higher volume, lower dose exposures may minimize risk of long-term treatment morbidity. While in silico dosimetric studies have suggested that the right treatment can make an IMRT plan more favorable compared to a proton therapy plan or vice versa, these studies often do not accurately predict clinically meaningful endpoints.

Non-Small-Cell Lung Cancer

NCCN guidelines for non-small cell lung cancer (NSCLC)(v.4.2024)offer the following recommendations:[56,] "[Radiation therapy] has a potential role in all stages of NSCLC as either definitive or palliative therapy... More advanced techniques are appropriate when needed to deliver curative [radiation therapy] safely. These techniques include (but are not limited to) 4D-CT and/or PET/CT stimulation, IMRT/VMAT, motion management, and proton therapy... Image-guided radiation therapy is recommended when using proton with steep dose gradients around the target, when [organs at risk] are in close proximity to high-dose regions, and when using complex motion management techniques." Highly conformal radiation therapies, such as proton therapy, can be used in the setting of prior radiation therapy, potentially with hyperfractionation, to reduce the risk of toxicity. In patients with high-risk N2 disease (eg, extracapsular extension, multi-station involvement, inadequate lymph node dissection/sampling, and/or refusal or intolerance of adjuvant systemic therapy), or those with advanced/metastatic NSCLC or receiving palliative radiotherapy at higher doses (>30 Gy), technologies to reduce normal tissue irradiation such as IMRT or proton therapy are preferred.

Head and Neck Cancer

NCCN guidelines for head and neck cancers (v.3.2024) indicate that proton therapy may be used per the discretion of the treating physician but is an active area of investigation.[57,] Proton therapy may be considered when normal tissue constraints cannot be met by photon-based therapy. Otherwise, IMRT or 3D conformal RT is recommended. The safety and efficacy of PBT when highly conformal dose distributions are important has been established, and is particularly important for patient with primary periocular tumors, tumors invading the orbit, skull base, cavernous sinus, and for

patients with intracranial extension or perineural invasion. These treatment approaches are recommended for those being treated with curative intent and/or those with long life expectancies following treatment. However, NCCN adds that without "high-quality prospective comparative data, it is premature to conclude that proton therapy has been established as superior to other established radiation techniques such as IMRT, particularly with regard to tumor control."

Pediatric Central Nervous System Cancer

NCCN guidelines for pediatric central nervous system cancers (v.1.2024) indicate that proton therapy offers maximal sparing of normal tissue and may be considered for patients with better prognoses (eg, *IDH1*-mutated tumors, 1p/19q-codeletions, or younger age) as most data are derived from studies involving pediatric cases of low-grade glioma.[58,]

American Society for Radiation Oncology

ASTRO (2022) updated its model policy on the medical necessity requirements for the use of proton therapy.[59,] ASTRO deemed the following disease sites those for which the evidence frequently supports the use of proton beam therapy:

- Medically inoperable patients with a diagnosis of cancer typically treated with surgery where dose escalation is required due to the inability to receive surgery
- Ocular tumors, including intraocular melanomas
- Tumors that approach or are located at the base of the skull, including but not limited to chordoma and chondrosarcomas
- Primary or metastatic tumors of the spine where the spinal cord tolerance may be exceeded with conventional treatment or where the spinal cord has previously been irradiated
- Hepatocellular cancer and intra-hepatic biliary cancers
- Primary malignant or benign bone tumors
- Primary or benign solid tumors in children treated with curative intent and occasional palliative treatment of childhood tumors
- Patients with genetic syndromes making total volume of radiation minimization crucial such as but not limited to NF-1 patients, deleterious ataxia telangiectasia mutated *(*ATM) mutations, Li-Fraumeni, and retinoblastoma patients
- Malignant and benign primary central nervous system tumors (excluding isocitrate dehydrogenase [IDH] wild-type glioblastoma multiforme [GBM])
- Advanced (eg, T4) and/or unresectable head and neck cancers
- Cancers of the nasopharynx, nasal cavity, paranasal sinuses and other accessory sinuses
- Nonmetastatic retroperitoneal sarcomas
- Re-irradiation cases (where cumulative critical structure dose would exceed tolerance dose).
- Primary cancers of the esophagus
- Primary tumors of the mediastinum, including thymic tumors, mediastinal tumors, mediastinal lymphomas and thoracic sarcomas
- Malignant pleural mesothelioma
- Primary and metastatic tumors requiring craniospinal irradiation
- 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

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

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POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
June 2012	New policy	
June 2013	Replace policy	Policy updated with literature search. References added, reordered and some removed. Change to policy statement that proton radiotherapy maybe considered medically necessary for the treatment of pediatric CNS tumors. Not medically necessary policy statements added for pediatric non-CNS tumors and head and neck tumors (non-skull based).
June 2014	Replace policy	Policy updated with literature search through February 6, 2014. References 5, 26, 39, 46 and 47 added. No change in policy statements.
September 2015	Replace policy	Policy updated with literature review through March 17, 2015; references 12, 22-25, 33-35, and 41-43 added. Title changed from ,“radiation therapy, to ,“radiotherapy, to be consistent with other MPRM policies. Editorial changes made to policy statement for prostate cancer with no changes to intent.
September 2016	Replace policy	Policy updated with literature review; references 4-5, 9, and 31 added. ,“For Neoplastic Conditions, added to title. Policy statements unchanged.
December 2018	Replace policy	Policy updated with literature search through May 24, 2018; references 1-3, 7, 19, 30-31, and 38-39 added. Policy statements unchanged.
December 2019	Replace policy	Policy archived by BCBSA without update from 2018. Policy statements unchanged.
June 2024	New policy	Policy reactivated and updated with literature search through April 3, 2023; references added. Based on clinical input and published guidelines, medically necessary policy statements were added for the following indications: where treatment planning with conventional or advanced photon-based radiotherapy cannot meet dose-volume constraints for normal tissue radiation tolerance: curative treatment of primary or benign solid pediatric non-central nervous system tumors, including Ewing sarcoma; curative treatment of nonmetastatic primary non-small cell lung cancer; and head and neck cancers. The investigational policy statement for the localized prostate cancer indication was retained and additional editorial changes for clarity were added. Adopted policy for FEP to support benefit brochure.
June 2025	Replace policy	Policy updated with literature search through March 23, 2024; references added. Policy statements unchanged.