



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 planning 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 planning 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	Portion of Organ Involved	Portion of Organ Involved	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	Xerostomia
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 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.

IMRT of the lung is addressed in evidence review 8.01.46. 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 proton beam therapy 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). 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 planning 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 two 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 EBRT compared to PBT, but no significant survival difference when compared to brachytherapy. A large, ongoing phase 3 RCT comparing proton therapy to intensity-modulated radiotherapy (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. 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 heterogeneous 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..."⁴⁴,

In 2021, PTCOG published consensus guidelines on particle therapy for the management of head and neck cancer.⁴⁵ 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."⁴⁶

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.⁴⁷ 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.

National Comprehensive Cancer Network

Uveal Melanoma

National Comprehensive Cancer Network (NCCN) guidelines for uveal melanoma (v.2.2022) 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.⁴⁸ Treatment recommendations for intraocular tumors include:

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

Prostate Cancer

NCCN guidelines for prostate cancer (v.1.2023) 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."⁴⁹ 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 planning 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.2.2023)offer the following recommendations:⁵⁰ "[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, [image-guided radiation therapy], 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."NCCN recommends that highly conformal radiation therapies such as proton therapy be used in the setting of prior radiation therapy, potentially with hyperfractionation, to reduce risk of toxicity.

Head and Neck Cancer

NCCN guidelines for head and neck cancers (v.1.2023) indicate that proton therapy may be used per the discretion of the treating physician but is an active area of investigation.⁵¹ 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.2.2023) indicate that proton therapy offers maximal sparing of normal tissue and may be considered for patients with better prognoses (e.g., *IDH1*-mutated tumors, 1p/19q-codeletions, or younger age) as most data are derived from studies involving pediatric cases of low-grade glioma.⁵²

American Society for Radiation Oncology

The American Society for Radiation Oncology (ASTRO) (2017) updated its model policy on the medical necessity requirements for the use of proton therapy.⁵³ ASTRO deemed the following disease sites those for which the evidence frequently supports the use of proton beam therapy:

- 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
- 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 and retinoblastoma patients
- Malignant and benign primary central nervous system tumors
- Advanced (eg, T4) and/or unresectable head and neck cancers
- Cancers of the paranasal sinuses and other accessory sinuses
- Nonmetastatic retroperitoneal sarcomas
- Re-irradiation cases (where cumulative critical structure dose would exceed tolerance dose).

The model policy also made a specific statement on proton beam therapy for treating prostate cancer: "..., ASTRO believes the comparative efficacy evidence of proton beam therapy with other prostate cancer treatments is still being developed, and thus the role of proton beam therapy for localized prostate cancer within the current availability of treatment options remains unclear.”

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.

REFERENCES

1. Spagnolo F, Caltabiano G, Queirolo P. Uveal melanoma. *Cancer Treat Rev.* Aug 2012; 38(5): 549-53. PMID 22270078
2. Hawkins BS. Collaborative ocular melanoma study randomized trial of I-125 brachytherapy. *Clin Trials.* Oct 2011; 8(5): 661-73. PMID 22013172
3. Pereira PR, Odashiro AN, Lim LA, et al. Current and emerging treatment options for uveal melanoma. *Clin Ophthalmol.* 2013; 7: 1669-82. PMID 24003303
4. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Charged particle (proton or helium ion) irradiation for uveal melanoma and for chordoma or chondrosarcoma of the skull base or cervical spine. *TEC Assessments 1996;Volume 11:Tab 1.*
5. Wang Z, Nabhan M, Schild SE, et al. Charged particle radiation therapy for uveal melanoma: a systematic review and meta-analysis. *Int J Radiat Oncol Biol Phys.* May 01 2013; 86(1): 18-26. PMID 23040219
6. Mishra KK, Quivey JM, Daftari IK, et al. Long-term Results of the UCSF-LBNL Randomized Trial: Charged Particle With Helium Ion Versus Iodine-125 Plaque Therapy for Choroidal and Ciliary Body Melanoma. *Int J Radiat Oncol Biol Phys.* Jun 01 2015; 92(2): 376-83. PMID 25841624
7. Lin AJ, Rao YJ, Acharya S, et al. Patterns of care and outcomes of proton and eye plaque brachytherapy for uveal melanoma: Review of the National Cancer Database. *Brachytherapy.* 2017; 16(6): 1225-1231. PMID 28966081
8. Touth A, Angi M, Dureau S, et al. Long-Term Visual Outcomes for Small Uveal Melanoma Staged T1 Treated by Proton Beam Radiotherapy. *Cancers (Basel).* Jul 24 2019; 11(8). PMID 31344948
9. Lodge M, Pijls-Johannesma M, Stirk L, et al. A systematic literature review of the clinical and cost-effectiveness of hadron therapy in cancer. *Radiother Oncol.* May 2007; 83(2): 110-22. PMID 17502116
10. Zhou J, Yang B, Wang X, et al. Comparison of the Effectiveness of Radiotherapy with Photons and Particles for Chordoma After Surgery: A Meta-Analysis. *World Neurosurg.* Sep 2018; 117: 46-53. PMID 29879512
11. Leroy R, Benahmed N, Hulstaert F, et al. Proton Therapy in Children: A Systematic Review of Clinical Effectiveness in 15 Pediatric Cancers. *Int J Radiat Oncol Biol Phys.* May 01 2016; 95(1): 267-278. PMID 27084646
12. Upadhyay R, Yadav D, Venkatesulu BP, et al. Risk of secondary malignant neoplasms in children following proton therapy vs. photon therapy for primary CNS tumors: A systematic review and meta-analysis. *Front Oncol.* 2022; 12: 893855. PMID 36033525
13. Peterson RK, King TZ. A systemic review of pediatric neuropsychological outcomes with proton versus photon radiation therapy: A call for equity in access to treatment. *J Int Neuropsychol Soc.* Nov 03 2022: 1-14. PMID 36323679
14. Baliga S, Gallotto S, Bajaj B, et al. Decade-long disease, secondary malignancy, and brainstem injury outcomes in pediatric and young adult medulloblastoma patients treated with proton radiotherapy. *Neuro Oncol.* Jun 01 2022; 24(6): 1010-1019. PMID 34788463
15. Indelicato DJ, Bradley JA, Rotondo RL, et al. Outcomes following proton therapy for pediatric ependymoma. *Acta Oncol.* May 2018; 57(5): 644-648. PMID 29239262
16. Bishop AJ, Greenfield B, Mahajan A, et al. Proton beam therapy versus conformal photon radiation therapy for childhood craniopharyngioma: multi-institutional analysis of outcomes, cyst dynamics, and toxicity. *Int J Radiat Oncol Biol Phys.* Oct 01 2014; 90(2): 354-61. PMID 25052561
17. MacDonald SM, Trofimov A, Safai S, et al. Proton radiotherapy for pediatric central nervous system germ cell tumors: early clinical outcomes. *Int J Radiat Oncol Biol Phys.* Jan 01 2011; 79(1): 121-9. PMID 20452141
18. Moeller BJ, Chintagumpala M, Philip JJ, et al. Low early ototoxicity rates for pediatric medulloblastoma patients treated with proton radiotherapy. *Radiat Oncol.* Jun 02 2011; 6: 58. PMID 21635776
19. Hug EB, Muentner MW, Archambeau JO, et al. Conformal proton radiation therapy for pediatric low-grade astrocytomas. *Strahlenther Onkol.* Jan 2002; 178(1): 10-7. PMID 11977386
20. Fuss M, Hug EB, Schaefer RA, et al. Proton radiation therapy (PRT) for pediatric optic pathway gliomas: comparison with 3D planned conventional photons and a standard photon technique. *Int J Radiat Oncol Biol Phys.* Dec 01 1999; 45(5): 1117-26. PMID 10613303
21. Kozak KR, Adams J, Krejcarek SJ, et al. A dosimetric comparison of proton and intensity-modulated photon radiotherapy for pediatric parameningeal rhabdomyosarcomas. *Int J Radiat Oncol Biol Phys.* May 01 2009; 74(1): 179-86. PMID 19019562
22. Merchant TE. Proton beam therapy in pediatric oncology. *Cancer J.* 2009; 15(4): 298-305. PMID 19672146
23. Timmermann B. Proton beam therapy for childhood malignancies: status report. *Klin Padiatr.* May 2010; 222(3): 127-33. PMID 20514614
24. Vogel J, Both S, Kirk M, et al. Proton therapy for pediatric head and neck malignancies. *Pediatr Blood Cancer.* Feb 2018; 65(2). PMID 29058370
25. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Proton beam therapy for prostate cancer. *TEC Assessments 2010;Volume 25:Tab 10.*
26. Shipley WU, Verhey LJ, Munzenrider JE, et al. Advanced prostate cancer: the results of a randomized comparative trial of high dose irradiation boosting with conformal protons compared with conventional dose irradiation using photons alone. *Int J Radiat Oncol Biol Phys.* Apr 30 1995; 32(1): 3-12. PMID 7721636
27. Zietman AL, DeSilvio ML, Slater JD, et al. Comparison of conventional-dose vs high-dose conformal radiation therapy in clinically localized adenocarcinoma of the prostate: a randomized controlled trial. *JAMA.* Sep 14 2005; 294(10): 1233-9. PMID 16160131
28. Kim YJ, Cho KH, Pyo HR, et al. A phase II study of hypofractionated proton therapy for prostate cancer. *Acta Oncol.* Apr 2013; 52(3): 477-85. PMID 23398594
29. Sun F, Oyesanmi O, Fontanarosa J, et al. Therapies for Clinically Localized Prostate Cancer: Update of a 2008 Systematic Review (Comparative Effectiveness Review No. 146). Rockville, MD: Agency for Healthcare Research and Quality; 2014.
30. Nilsson S, Norln BJ, Widmark A. A systematic overview of radiation therapy effects in prostate cancer. *Acta Oncol.* 2004; 43(4): 316-81. PMID 15303499

31. Kuban D, Pollack A, Huang E, et al. Hazards of dose escalation in prostate cancer radiotherapy. *Int J Radiat Oncol Biol Phys*. Dec 01 2003; 57(5): 1260-8. PMID 14630260
32. Liu Y, Patel SA, Jani AB, et al. Overall Survival After Treatment of Localized Prostate Cancer With Proton Beam Therapy, External-Beam Photon Therapy, or Brachytherapy. *Clin Genitourin Cancer*. Jun 2021; 19(3): 255-266.e7. PMID 32972877
33. Grewal AS, Schonewolf C, Min EJ, et al. Four-Year Outcomes From a Prospective Phase II Clinical Trial of Moderately Hypofractionated Proton Therapy for Localized Prostate Cancer. *Int J Radiat Oncol Biol Phys*. Nov 15 2019; 105(4): 713-722. PMID 31199994
34. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Proton beam therapy for non- small-cell lung cancer. *TEC Assessments*. 2010;Volume 25:Tab 7.
35. Grutters JP, Kessels AG, Pijls-Johannesma M, et al. Comparison of the effectiveness of radiotherapy with photons, protons and carbon-ions for non-small cell lung cancer: a meta-analysis. *Radiother Oncol*. Apr 2010; 95(1): 32-40. PMID 19733410
36. Pijls-Johannesma M, Grutters JP, Verhaegen F, et al. Do we have enough evidence to implement particle therapy as standard treatment in lung cancer? A systematic literature review. *Oncologist*. 2010; 15(1): 93-103. PMID 20067947
37. Liao Z, Lee JJ, Komaki R, et al. Bayesian Adaptive Randomization Trial of Passive Scattering Proton Therapy and Intensity-Modulated Photon Radiotherapy for Locally Advanced Non-Small-Cell Lung Cancer. *J Clin Oncol*. Jun 20 2018; 36(18): 1813-1822. PMID 29293386
38. Chang JY, Verma V, Li M, et al. Proton Beam Radiotherapy and Concurrent Chemotherapy for Unresectable Stage III Non-Small Cell Lung Cancer: Final Results of a Phase 2 Study. *JAMA Oncol*. Aug 10 2017; 3(8): e172032. PMID 28727865
39. Ono T, Yabuuchi T, Nakamura T, et al. High Dose Hypofractionated Proton Beam Therapy is a Safe and Feasible Treatment for Central Lung Cancer. *Radiol Oncol*. Sep 2017; 51(3): 324-330. PMID 28959169
40. Patel SH, Wang Z, Wong WW, et al. Charged particle therapy versus photon therapy for paranasal sinus and nasal cavity malignant diseases: a systematic review and meta-analysis. *Lancet Oncol*. Aug 2014; 15(9): 1027-38. PMID 24980873
41. Youssef I, Yoon J, Mohamed N, et al. Toxicity Profiles and Survival Outcomes Among Patients With Nonmetastatic Oropharyngeal Carcinoma Treated With Intensity-Modulated Proton Therapy vs Intensity-Modulated Radiation Therapy. *JAMA Netw Open*. Nov 01 2022; 5(11): e2241538. PMID 36367724
42. Blanchard P, Garden AS, Gunn GB, et al. Intensity-modulated proton beam therapy (IMPT) versus intensity-modulated photon therapy (IMRT) for patients with oropharynx cancer - A case matched analysis. *Radiother Oncol*. Jul 2016; 120(1): 48-55. PMID 27342249
43. Zenda S, Kawashima M, Arahira S, et al. Late toxicity of proton beam therapy for patients with the nasal cavity, para-nasal sinuses, or involving the skull base malignancy: importance of long-term follow-up. *Int J Clin Oncol*. Jun 2015; 20(3): 447-54. PMID 25135461
44. 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. *Int J Radiat Oncol Biol Phys*. May 01 2016; 95(1): 505-516. PMID 27084663
45. Lin A, Chang JHC, Grover RS, et al. PTCOG Head and Neck Subcommittee Consensus Guidelines on Particle Therapy for the Management of Head and Neck Tumors. *Int J Part Ther*. 2021; 8(1): 84-94. PMID 34285938
46. Nguyen PL, Aizer A, Assimos DG, et al. ACR Appropriateness Criteria Definitive External-Beam Irradiation in stage T1 and T2 prostate cancer. *Am J Clin Oncol*. Jun 2014; 37(3): 278-88. PMID 25180754
47. Eastham JA, Aufferberg GB, Barocas DA, et al. Clinically Localized Prostate Cancer: AUA/ASTRO Guideline. Part III: Principles of Radiation and Future Directions. *J Urol*. Jul 2022; 208(1): 26-33. PMID 35536141
48. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Uveal Melanoma. Version 2.2022. https://www.nccn.org/professionals/physician_gls/pdf/uveal.pdf. Accessed April 3, 2023.
49. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Prostate Cancer. Version 1.2023. https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf. Accessed April 4, 2023.
50. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer. Version 2.2023. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed April 5, 2023.
51. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Head and Neck Cancers. Version 1.2023. https://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf. Accessed April 6, 2023.
52. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Pediatric Central Nervous System Cancers. Version 2.2023. https://www.nccn.org/professionals/physician_gls/pdf/ped_cns.pdf. Accessed April 7, 2023.
53. American Society for Radiation Oncology (ASTRO). ASTRO Model Policies: Proton Beam Therapy (PBT). 2017; https://www.astro.org/uploadedFiles/_MAIN_SITE/Daily_Practice/Reimbursement/Model_Policies/Content_Pieces/ASTROPBTModelPolicy.pdf. Accessed April 3, 2023.

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.

The policies contained in the FEP Medical Policy Manual are developed to assist in administering contractual benefits and do not constitute medical advice. They are not intended to replace or substitute for the independent medical judgment of a practitioner or other health care professional in the treatment of an individual member. The Blue Cross and Blue Shield Association does not intend by the FEP Medical Policy Manual, or by any particular medical policy, to recommend, advocate, encourage or discourage any particular medical technologies. Medical decisions relative to medical technologies are to be made strictly by members/patients in consultation with their health care providers. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that the Blue Cross and Blue Shield Service Benefit Plan covers (or pays for) this service or supply for a particular member.