Medical Policy

BlueCross BlueShield Kansas
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Title: Charged-Particle (Proton or Helium Ion) Radiotherapy for Neoplastic Conditions

Related Policies:	▪ *Stereotactic Radiosurgery and Stereotactic Body Radiotherapy* ▪ *Intensity Modulated Radiotherapy (IMRT)*

Professional / Institutional
Original Effective Date: May 1, 2007 / October 6, 2011
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Populations	Interventions	Comparators	Outcomes
Individuals: ▪ With uveal melanoma(s)	Interventions of interest are: ▪ Charged-particle (proton or helium ion) radiotherapy	Comparators of interest are: ▪ Plaque radiotherapy ▪ Surgical resection ▪ Transpupillary thermotherapy	Relevant outcomes include: ▪ Overall survival ▪ Disease-free survival ▪ Change in disease status ▪ Treatment-related morbidity
Individuals: ▪ With skull-based tumor(s) (i.e., cervical	Interventions of interest are:	Comparators of interest are: ▪ Other types of radiotherapy	Relevant outcomes include: ▪ Overall survival ▪ Disease-free survival

Populations	Interventions	Comparators	Outcomes
chordoma, chondrosarcoma)	▪ Charged-particle (proton or helium ion) radiotherapy	▪ Surgical resection ▪ Other types of therapy for localized tumor	▪ Change in disease status ▪ Treatment-related morbidity
Individuals: ▪ With pediatric central nervous system tumor(s)	Interventions of interest are: ▪ Charged-particle (proton or helium ion) radiotherapy	Comparators of interest are: ▪ Other types of radiotherapy ▪ Surgical resection ▪ Other types of therapy for localized tumor	Relevant outcomes include: ▪ Overall survival ▪ Disease-free survival ▪ Change in disease status ▪ Treatment-related morbidity
Individuals: ▪ With pediatric non–central nervous system tumor(s)	Interventions of interest are: ▪ Charged-particle (proton or helium ion) radiotherapy	Comparators of interest are: ▪ Other types of radiotherapy ▪ Surgical resection ▪ Other types of therapy for localized tumor	Relevant outcomes include: ▪ Overall survival ▪ Disease-free survival ▪ Change in disease status ▪ Treatment-related morbidity
Individuals: ▪ With localized prostate cancer	Interventions of interest are: ▪ Charged-particle (proton or helium ion) radiotherapy	Comparators of interest are: ▪ Other types of radiotherapy ▪ Surgical resection ▪ Other types of therapy for localized tumor	Relevant outcomes include: ▪ Overall survival ▪ Disease-free survival ▪ Change in disease status ▪ Treatment-related morbidity
Individuals: ▪ With non-small cell lung cancer	Interventions of interest are: ▪ Charged-particle (proton or helium ion) radiotherapy	Comparators of interest are: ▪ Other types of radiotherapy ▪ Surgical resection ▪ Other types of therapy for localized tumor	Relevant outcomes include: ▪ Overall survival ▪ Disease-free survival ▪ Change in disease status ▪ Treatment-related morbidity
Individuals: ▪ With head and neck tumors other than skull-based	Interventions of interest are: ▪ Charged-particle (proton or helium ion) radiotherapy	Comparators of interest are: ▪ Other types of radiotherapy ▪ Surgical resection ▪ Other types of therapy for localized tumor	Relevant outcomes include: ▪ Overall survival ▪ Disease-free survival ▪ Change in disease status ▪ Treatment-related morbidity

DESCRIPTION

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.

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 (ie, photon) radiotherapy, including minimal scatter as particulate beams pass through tissue, and deposition of ionizing energy at precise depths (ie, 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.

POLICY

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

1. Primary therapy for melanoma of the uveal tract (iris, choroid, or ciliary body)

    a. with no evidence of metastasis or extrascleral extension, **AND**
    b. with tumors up to 24 mm in largest diameter and 14 mm in height.

2. Postoperative therapy (with or without conventional high-energy x-rays) in individuals who have undergone biopsy or partial resection of chordoma, or low-grade (I or II) chondrosarcoma of the basisphenoid region (skull-based chordoma or chondrosarcoma) or cervical spine. Individuals eligible for this treatment have residual localized tumor without evidence of metastasis.

3. Pediatric central nervous system tumors.

B. 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:

1. in the curative treatment of primary or benign solid pediatric non-central nervous system tumors, including Ewing sarcoma;

2. in the curative treatment of nonmetastatic primary non-small cell lung cancer; **OR**

3. head and neck cancers.

C. Other applications of charged-particle irradiation with proton or helium ion beams are considered **experimental / investigational**. This includes, but is not limited to:

1. clinically localized prostate cancer;

2. non-curative treatment of primary or benign solid pediatric non-central nervous system tumors, including Ewing sarcoma;

3. non-curative treatment of non-small cell lung cancer.

POLICY GUIDELINES

A. 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).

B. For a service to be considered medically necessary, it should not be more costly than an alternative service or supply or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results for the illness, injury, or disease.

C. 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**			
	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.

D. 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.

Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

RATIONALE

The evidence review has been updated regularly with searches of the PubMed database. The most recent literature update was performed through March 23, 202 4.

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 function¾including 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.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA

(Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

CHARGED-PARTICLE (PROTON OR HELIUM ION) RADIOTHERAPY FOR UVEAL MELANOMAS

Clinical Context and Therapy Purpose

The purpose of charged-particle (proton or helium ion) radiotherapy (RT) in individuals who have uveal melanoma(s) 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 uveal melanoma(s). Uveal melanoma, although rare, is the most common primary intraocular malignancy in adults. Mean age-adjusted incidence of uveal melanoma in the United States is 6.3 per million people among Whites, 0.9 among Hispanics, and 0.24 among Blacks. Uveal melanoma has a progressively rising, age-specific, incidence rate that peaks near age 70 years.[1,]

Interventions

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

Comparators

The following practices are currently being used to make decisions about the treatment of uveal melanoma(s): plaque RT, surgical resection, and transpupillary thermotherapy. Primary, localized uveal melanoma can be treated by surgery or RT. In general, larger tumors require enucleation surgery and smaller tumors can be treated with RT, but specific treatment parameters are lacking. The most common treatment of localized uveal melanoma is RT, which is preferred because it can spare vision in most cases. For smaller lesions, RCTs have shown that patients receiving RT or enucleation progress to metastatic disease at similar rates after treatment.[2,] RT can be delivered by various mechanisms, most commonly brachytherapy and PBT. Treatment of primary uveal melanoma improves local control and spares vision; however, the 5-year survival rate (81.6%) has not changed over the last 3 decades, suggesting that life expectancy is independent of successful local eye treatment.[3,]

Outcomes

The general outcomes of interest are overall survival (OS), disease-free survival, change in disease status (local recurrence), and treatment-related morbidity. RT is used as part of first-line treatment for uveal melanoma. One- and 5-year outcomes are indicators of successful treatment.

Systematic Reviews

This section was informed by a TEC Assessment (1996) that concluded that proton therapy was at least as effective as alternative therapies for treating uveal melanoma.[4,]

Subsequently, Wang et al (2013) published a systematic review of the literature on charged-particle (proton, helium, carbon ion) RT for uveal melanoma.[5,] Reviewers included 27 controlled and uncontrolled studies that reported health outcomes (e.g., mortality, local recurrence). Three studies were RCTs. One RCT compared helium ion therapy with an alternative treatment (brachytherapy). The other 2 RCTs compared different proton beam protocols and so cannot be used to draw conclusions about the efficacy of charged-ion particle therapy relative to other treatments. The overall quality of the studies was low; most of the observational studies did not adjust for potential confounding variables. The analysis focused on studies of treatment-naive patients (all but one of the identified studies). In a pooled analysis of data from 9 studies, there was no statistically significant difference in mortality rates with charged-particle therapy compared with brachytherapy (odds ratio [OR], 0.13; 95% confidence interval [CI], 0.01 to 1.63). However, there was a significantly lower rate of local recurrence with charged-particle therapy compared with brachytherapy in a pooled analysis of 14 studies (OR , 0.22; 95% CI, 0.21 to 0.23). There were also significantly lower rates of radiation retinopathy and cataract formation in patients treated with charged-particle therapy than brachytherapy (pooled rates of 0.28 vs. 0.42 and 0.23 vs. 0.68, respectively). Reviewers concluded there was low-quality evidence that charged-particle therapy is at least as effective as alternative therapies for the primary treatment of uveal melanoma and is better at preserving vision.

Randomized Controlled Trials

An RCT by Mishra et al (2015) compared charged-particle therapy using helium ions and iodine 125 (I-125) plaque therapy in 184 patients with uveal melanoma.[6,] The primary end point was local tumor control. Median follow-up was 14.6 years in the charged-particle therapy group and 12.3 years in the I-125 plaque therapy group. The rate of local control at 12 years was significantly higher in the helium ion group (98%; 95% CI, 88% to 100%) than in the I-125 plaque therapy group (79%; 95% CI, 68% to 87%; p=.006). The OS rate at 12 years was 67% (95% CI, 55% to 76%) in the helium ion group and 54% (95% CI, 43% to 63%) in the I-125 plaque therapy group (p=.02).

Comparative Observational Studies

Lin et al (2017) published a retrospective review of 1224 patients in the National Cancer Database who had choroid melanoma and were treated with brachytherapy (n=996) or proton therapy (n=228) between 2004 and 2013.[7,] For the brachytherapy group, median follow-up was 37 months; for proton-treated patients, median follow-up was 29 months. Proton-treated patients were propensity-matched with a smaller cohort of brachytherapy-treated patients (n=228 each). The OS rate at 2 years was 97% for brachytherapy-treated patients and 93% for proton-treated patients. The 5-year OS rates were 77% and 51% for brachytherapy- and proton-treated groups, respectively (p=.008). Factors likely to predict poorer survival rates included the following: older age (hazard ratio [HR], 1.06; 95% CI, 1.03 to 1.09; p<.02); tumor diameter of 12 to 18 mm (HR, 2.48; 95% CI, 1.40 to 4.42; p<.02); tumor diameter greater than 18 mm (HR, 6.41; 95% CI, 1.45 to 28.35; p<.02); and proton treatment (HR, 1.89; 95% CI, 1.06 to 3.37; p<.02).

Long-Term Studies
Toutee et al (2019) reported 5-year visual outcomes for patients with stage T1 uveal melanoma (N=424) treated by proton therapy, as a function of their distance to the fovea-optic disc in a long-term retrospective study.[8,]With a mean follow-up duration of 122 months, no tumor recurrences were observed. Mean baseline and final best corrected visual acuities were measured for patients with posterior edge of tumor located at ≥3 mm (n=75) or <3 mm (n=317) as 20/25 & 20/32 and 20/40 & 20/80. The frequency of a 20/200 or greater conservation was 93.2% and 60.1%, respectively (p<.001). Thus, PBT for stage T1 uveal melanoma was shown to yield excellent tumor control and good long-term visual outcomes, particularly for tumors located ≥3 mm from the fovea-optic disc.

Section Summary: Uveal Melanoma
Systematic reviews, including a 1996 TEC Assessment, have concluded that charged-particle RT is at least as effective as alternative therapies for treating uveal melanomas and is better at preserving vision. A 2013 systematic review of charged-particle therapy for uveal melanoma identified 3 RCTs and a number of observational studies. This systematic review found that charged-particle therapy was associated with a significantly lower rate of local recurrence than brachytherapy and fewer adverse events to vision. A 2017 database review found comparable 2-year OS rates but lower 5-year OS rates for PBT than for brachytherapy.

CHARGED-PARTICLE (PROTON OR HELIUM ION) RADIOTHERAPY FOR INDIVIDUALS WITH SKULL-BASED TUMORS

Clinical Context and Therapy Purpose
The purpose of charged-particle (proton or helium ion) RT in individuals who have skull-based tumors 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 skull-based tumors. The skull base is the anatomic area that supports the brain and includes the entry and exit passages for nerve and vascular bundles. Tumors located near these vital structures such as chordoma and chondrosarcoma that arise in the skull base may not be amenable to complete surgical excision or adequate doses of conventional RT are impossible.

Interventions
The therapy being considered is charged-particle (proton or helium ion) RT. Charged-particle irradiation theoretically affords protection from radiation damage to surrounding structures. Charged-particle therapy is administered in specially equipped treatment centers. PBT can be administered with or without stereotactic techniques.

Comparators
The following practices are currently being used to make decisions about skull-based tumors: other types of RT including conventional and high-dose photon therapies, surgical resection, and other therapeutic modalities 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 survival outcomes for charged-particle therapy for skull-base tumors have been reported at 1 year and 5 years.

Systematic Reviews

This section was informed by a TEC Assessment (1996) that concluded, compared with treatment using conventional RT after partial resection or biopsy, charged-particle irradiation yields greater rates of local control, OS, and disease-free survival at 5 years after therapy.[4,] Subsequently, Lodge et al (2007) published a systematic review of charged-particle therapy and found local tumor control and 5-year OS rates of 63% and 81%, respectively, for skull-based chordomas treated with surgery and PBT.[9,] Comparable local tumor control and 5-year OS rates were 25% and 44% for postsurgical photon therapy. For chondrosarcomas of the skull-base, proton therapy achieved a 5-year tumor control rate of 95% and photon therapy a rate of 100%.

A meta-analysis by Zhou et al (2018) compared the effectiveness of photon- and particle-based RT for the treatment of chordoma after surgery.[10,] A fixed-effects model was used to perform an analysis of 3-, 5-, and 10-year OS rates. A total of 25 studies were included, 11 on the use of conventional RT (CRT) or stereotactic RT (SRT), 9 on the use of PBT, and 5 on the use of carbon-ion RT (CIRT). A total of 21 studies reported 3-yr OS data, 15 studies reported 5-yr OS data, and 9 studies reported 10-yr OS data. Characteristics and results are summarized in Tables 1 and 2. PBT was found to have a statistically significant benefit on 10-yr OS rates compared to both CRT ($p<.001$) and SRT ($p=.004$).

Table 1. Systematic Review & Meta-analysis Characteristics

Study	Dates	Trials	Participants[1]	N (Range)	Design	Duration (Range)
Zhou et al (2018)[10,]	1983-2016 (All) 1995-2016 (Proton) 2003-2014 (Carbon)	25 (All) 9 (Proton) 5 (Carbon)	Studies containing OS rates for patients with chordoma. Patients with chordoma that received at least one surgery prior to RT. Exact RT type used is described.	N=996 (All) N=351 (13-100) (Proton) N=361 (32-155) (Carbon)	Single-arm trials	15-72 months

OS: overall survival; RT: radiotherapy

[1] Key eligibility criteria.

Table 2. Systematic Review & Meta-analysis Results

Study	3-yr Outcomes		5-yr Outcomes		10-yr Outcomes	
Zhou et al (2018)[10,]	OS, % (95% CI)	p-value[1]	OS, % (95% CI)	p-value[1]	OS, % (95% CI)	p-value[1]
CRT	70 (60-81)	---	46 (36-56)	---	21 (10-33)	---
SRT	92 (88-96)	<.001	81 (75-86)	<.001	40 (30-55)	.004
PBT	89 (85-93)	<.001	78 (23-84)	<.001	60 (43-77)	<.001
CIRT	93 (90-95)	<.001	87 (84-91)	<.001	45 (36-55)	<.001

CI: confidence interval; CIRT: carbon-ion radiotherapy; CRT: conventional radiotherapy; OS: overall survival; PBT: proton beam therapy; SRT: stereotactic radiotherapy.
[1]p-value indicates significance for difference compared to CRT.

Section Summary: Skull-Based Tumors
Several systematic reviews, including a TEC Assessment, have been published. A 2007 systematic review found 5-year OS rates of 81% with PBT compared with 44% with surgery and photon therapy. A 2016 systematic review of observational studies found 5-year survival rates after PBT ranging from 67% to 94%. In 2018, a meta-analysis found 5-year and 10-year OS rates for PBT of 78% and 60% compared with 46% and 21% for conventional radiotherapy. The published evidence supports a meaningful improvement in the net health outcome.

CHARGED-PARTICLE (PROTON OR HELIUM ION) RADIOTHERAPY FOR PEDIATRIC CENTRAL NERVOUS SYSTEM TUMORS

Clinical Context and Therapy Purpose
The purpose of charged-particle (proton or helium ion) RT in children who have central nervous system (CNS) tumors 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 pediatric CNS tumors. Primary malignant tumors of the CNS are the second most common childhood malignancies after hematologic malignancies. Specific types include craniopharyngioma, astrocytoma, ependymoma, glioblastoma, and medulloblastoma. There are multiple genetic syndromes that confer additional risk for the development of CNS tumors: neurofibromatosis, tuberous sclerosis, as well as von Hippel-Lindau, basal cell nevus and Li Fraumeni and Turcot syndromes.

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

Comparators
The following practices are currently being used to make decisions about pediatric CNS tumors: other types of RT, surgical resection, and other therapeutic modalities 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 tumor control and OS would be assessed at 1 and 3 years.

Systematic Reviews
Upadhyay et al (2022) conducted a systematic review and meta-analysis of secondary malignant neoplasm risk in children treated with PBT versus photon RT for primary CNS tumors.[11,] Twenty-four studies were included for analysis representing 418 secondary malignancies among 38,163 patients. Most common secondary malignancies included gliomas (40.6%), meningioma (38.7%), sarcoma (4.8%), thyroid cancer (4.2%), and basal cell carcinoma (1.3%). The incidence of secondary malignancies with photons was 1.8% (95% CI, 1.1 to 2.6; I^2=94%) compared to 1.5% (95% CI, 0 to 4.5; I^2=81%) with protons, and this difference was not significantly different (p=.91). The overall cumulative incidence of secondary malignancies at 10 years ranged from 1.4% to 8.9% for photons versus 0% to 5.4% with protons. A shorter latency to secondary cancers was also observed in PBT patients (5.9 years vs 11.9 years, respectively). The median follow-up was slightly shorter in the PBT group, at 6.9 years compared to 8.8 years in patients treated with photons. The authors suggest this may bias observed outcomes, in addition to general study heterogeneity and potentially confounding effects of concurrent treatment with chemotherapy.

Young et al (2023) conducted a systematic review of clinical outcomes of PBT for medulloblastoma. Thirty-five studies were included, representing an estimated 630 to 654 unique patients treated with PBT.[12,] None of the studies were randomized, 12 were comparative, 9 were prospective, and 22 were retrospective. The average mean/median follow-up was 5.0 years (range, 4 weeks to 12.6 years). OS at 10 years ranged from 85.3% to 86.9% for standard-risk medulloblastoma patients treated with PBT. A cumulative risk of secondary malignancy of 2.1% to 8% was reported in 2 studies. Patients treated with PBT had superior neurocognitive outcomes on the NOS from 3.7 to 5.3 years follow-up over photon RT. Patients in the PBT group had reduced acute toxicities compared to photon RT (grade 3 esophagitis, diarrhea, and weight loss). The authors conclude there is moderate-grade evidence supporting PBT as a preferred treatment for craniospinal RT of medulloblastoma based on equivalent disease control and comparable-to-improved toxicity versus photon RT.

Wilson et al (2024) conducted a systematic review of the effects of PBT in children and young adults with CNS tumors. Thirty-one studies were included (N=1731 patients) from 10 proton therapy centers.[13,] Eleven studies involved children with medulloblastoma or primitive neuroectodermal tumors (n=712), with OS ranging from 68% to 89% for newly diagnosed patients. Five studies investigated ependymoma (n=398), reporting 3-year OS rates from 90% to 97% for patients receiving first-line therapy. Four studies examined atypical teratoid/rhabdoid tumor (n=72), with OS ranging from 53% at 2 years to 90% at 2.3 years. Six studies looked at craniopharyngioma (n=272), with 3-year OS of 94% for PBT and 97% for photon RT in one comparative study, and 5-year OS of 97.7% in another proton therapy study. Three studies investigated low-grade gliomas (n=233), reporting OS rates of 85%, 92%, and 100% at 3.3, 5.0, and 8.0 years follow-up, respectively. One study examined germ cell tumors (n=22), finding 100% OS at 2.3 years. Lastly, one study looked at pineoblastoma (n=22), reporting 90% OS at 3.2 years. Serious adverse events included endocrinopathies (range, 3% to 96%), ototoxicity

(range, 0% to 70%), radio-necrosis (range, 0% to 21%), stroke (range, 1.7% to 10%), and brainstem toxicity (range, 0.5% to 15%). The authors conclude that while PBT has been widely implemented for pediatric CNS tumors, improved outcome data, particularly with respect to late effects, is still needed to inform the continued evolution of standard indications for this treatment modality.

Lassaletta et al (2023) conducted a systematic review and meta-analysis comparing neurocognitive outcomes in pediatric brain tumor patients treated with PBT versus photon RT.[14,] Ten studies were included (N=630 patients), with an average age ranging from 1 to 20 years. Patients who received PBT achieved significantly higher scores than those treated with photon RT on measures of full-scale intelligence quotient (IQ) (Z-score difference, 0.75; 95% CI, 0.52 to 0.99; p<.001), verbal comprehension (Z-score difference, 0.46; 95% CI, 0.20 to 0.73; p=.001), perceptual reasoning (Z-score difference, 0.69; 95% CI, 0.44 to 0.94; p<.001), working memory (Z-score difference, 0.35; 95% CI, 0.07 to 0.63; p=.016), processing speed (Z-score difference, 0.29; 95% CI, 0.01 to 0.56; p=.046), visual motor integration (Z-score difference, 0.52; 95% CI, 0.15 to 0.88; p=.006), verbal memory (Z-score difference, 0.64; 95% CI, 0.31 to 0.96; p<.001), and focused attention (Z-score difference, 0.29; 95% CI, 0.01 to 0.57; p=.044). Sensitivity analyses confirmed significant differences for IQ, verbal comprehension and perceptual reasoning indices, visual motor integration, and verbal memory. No robust differences were found for nonverbal memory (Z-score difference, 0.43; 95% CI, -0.53 to 1.40; p=.377). The authors conclude that pediatric brain tumor patients who receive PBT achieve significantly higher scores on most neurocognitive outcomes compared to those treated with photon RT, but larger studies with long-term follow-up are needed to confirm these results.

Case Series

Representative case series of PBT used to treat multiple pediatric CNS tumor types are described next.

Bischoff et al (2024) published a retrospective analysis of PBT for pediatric craniopharyngioma in 74 patients from the prospective KiProReg registry study. The median follow-up since diagnosis was 4.3 years (range, 0.8 to 14.7).[15,] The majority of patients (75.7%) received PBT at the time of disease progression or recurrence, while 24.3% received it as part of their primary therapy. The median total dose was 54 gray (Gy). The estimated 3-year OS, progression-free survival, and cystic failure-free survival rates after PBT were 98.2%, 94.7%, and 76.8%, respectively. All local failures (n=3) occurred in patients receiving PBT at progression or recurrence. Early cystic enlargements after PBT were typically asymptomatic and self-limiting. The most common late toxicities were fatigue, headaches, vision disorders, obesity, and endocrinopathies.

Baliga et al (2022) reported on 178 pediatric medulloblastoma patients treated with PBT between 2002 and 2016.[16,] Median longitudinal follow-up was 9.3 years with 156 patients (89.3%) undergoing a gross total resection. Ten-year OS for the whole cohort, standard-risk cohort, and intermediate/high-risk cohort was 79.3% (95% CI, 73.1 to 85.9), 86.9% (95% CI, 79.9 to 94.4), and 68.9% (95% CI, 58.7 to 80.8) respectively. Corresponding rates of 10-year event-free survival (EFS) were 73.8% (95% CI, 67.1 to 81.1), 79.5% (95% CI, 71.1 to 88.9), and 66.2% (95% CI, 56.3 to 78.0), respectively. Intermediate/high-risk status was associated with inferior EFS and OS in univariate analysis. The 10-year cumulative incidence of any secondary tumors, secondary malignancies, or secondary benign tumors was 5.6% (95% CI, 2.2 to 11.3), 2.1% (95% CI, 0.6 to 5.8), and 3.4% (95% CI, 0.9 to 8.9), respectively. Two patients who developed

in-field secondary glioblastoma died. The cumulative incidence rates of brainstem injury at 5 and 10 years were 1.1% (95% CI, 0.2 to 3.7) and 1.9% (95% CI, 0.5 to 5.1). The authors noted that the 5-year EFS of 83% for standard-risk and 70% for high-risk patients in the St. Jude Medulloblastoma-86 Study which used 3-dimensional conformal RT was comparable to the 5-year EFS rates of 87.3% and 68.9% in this study. Additionally, the rate of secondary malignancies in the proton-treated cohort was nearly half the rate historically observed in patients treated with photons (2.1% vs. 3.7%).

Indelicato et al (2018) reported on 179 children with nonmetastatic grade II/III intracranial ependymoma who were treated with proton therapy at a single institution.[17,] Three-year local control, progression-free survival, and OS rates were 85%, 76%, and 90%, respectively. The authors noted that these disease control rates were comparable to photon series. The 3-year grade 2+ brainstem toxicity rate was 5.5% (95% CI, 2.9 to 10.2). Subtotal resection and male sex were associated with inferior disease control rates.

Bishop et al (2014) reported on 52 children with craniopharyngioma treated at 2 centers; 21 received PBT and 31 received IMRT.[18,] Patients received a median dose of 50.4 Gy. At 3 years, the OS rate was 94.1% in the PBT group and 96.8% in the IMRT group (p=.742). Three-year nodular and cystic failure-free survival rates were also similar between groups. Based on imaging, 17 (33%) patients had cyst growth within 3 months of RT, and 14 patients had late cyst growth (>3 months after therapy); rates did not differ significantly between groups. In 14 of the 17 patients with early cyst growth, enlargement was transient.

MacDonald et al (2011) reported on the use of protons to treat germ cell tumors in 22 patients, 13 with germinoma and 9 with nongerminomatous germ cell tumors.[19,] Radiation doses ranged from 30.6 to 57.6 cobalt Gray equivalents (CGE). All nongerminomatous germ cell tumor patients also received chemotherapy before RT. Median follow-up was 28 months. There were no CNS recurrences or deaths. Following RT, 2 patients developed growth hormone deficiency and 2 other patients developed central hypothyroidism. The authors indicated that longer follow-up was necessary to assess the neurocognitive effects of therapy. In the same study, a dosimetric comparison of photons and protons was performed. PBT provided substantial sparing to the whole brain and temporal lobes, and reduced doses to the optic nerves.

Moeller et al (2011) reported on 23 children enrolled in a prospective series and treated with PBT for medulloblastoma between 2006 and 2009.[20,] Because hearing loss is common after chemoradiotherapy for children with medulloblastoma, the authors evaluated whether PBT led to a clinical benefit in audiometric outcomes (because, compared with photons, protons reduce radiation dose to the cochlea for these patients). The children underwent pre- and 1-year post-RT pure-tone audiometric testing. Ears with moderate-to-severe hearing loss before therapy were censored, leaving 35 ears in 19 patients available for analysis. The predicted mean cochlear radiation dose was 30 CGE (range, 19 to 43 CGE). Hearing sensitivity significantly declined following RT across all frequencies analyzed (p<.05). There was partial sparing of mean post radiation hearing thresholds at low- to mid-range frequencies; the rate of high-grade (grade 3 or 4) ototoxicity at 1 year was 5%, which compared favorably to the rate of grade 3 or 4 toxicity following IMRT (18%) reported in a separate case series.

Hug et al (2002) reported on proton radiation in the treatment of low-grade gliomas in 27 pediatric patients.[21,] Six patients experienced local failure; acute adverse events were minimal.

After a median follow-up of 3 years, all children with local control maintained performance status. In a dosimetric comparison of protons to photons for 7 optic pathway gliomas treated, Fuss et al (1999) showed a decrease in radiation dose to the contralateral optic nerve, temporal lobes, pituitary gland, and optic chiasm with the use of protons.[22,]

Section Summary: Pediatric Central Nervous System Tumors
Several systematic reviews and meta-analyses have evaluated the use of PBT for various pediatric CNS tumors. The evidence suggests that PBT may offer similar survival outcomes compared to photon radiotherapy for craniopharyngioma, medulloblastoma, ependymoma, and CNS germinoma. However, the strength of evidence is limited by the lack of RCTs and the heterogeneity of the included studies. PBT appears to be associated with superior neurocognitive outcomes and reduced acute toxicities compared to photon radiotherapy in medulloblastoma patients. A meta-analysis found no significant difference in the incidence of secondary malignancies between PBT and photon radiotherapy, although PBT was associated with a shorter latency period. Retrospective case series have reported favorable outcomes with PBT for various pediatric CNS tumors, with OS rates ranging from 53% to 100% depending on the tumor type and follow-up duration. Common adverse events included endocrinopathies, ototoxicity, radio-necrosis, stroke, and brainstem toxicity. While some studies suggest sparing of normal tissues and reduced toxicities, limitations of the published evidence preclude determining the effects of the technology on the net health outcome.

CHARGED-PARTICLE (PROTON OR HELIUM ION) RADIOTHERAPY FOR PEDIATRIC NON-CNS TUMORS

Clinical Context and Therapy Purpose
The purpose of charged-particle (proton or helium ion) RT in children who have non-CNS tumors 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 pediatric non-CNS tumors. Tumors of the axial skeleton require conformal radiotherapy with the intent of avoiding damage to vital structures.

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

Comparators
The following practices are currently being used to make decisions about pediatric non-CNS tumors: other types of RT, 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 3 years.

Case Series
There are scant data on the use of PBT in pediatric non-CNS tumors. Data include dosimetric studies in a small number of pediatric patients with parameningeal rhabdomyosarcoma[23,] and late toxicity outcomes in other solid tumors of childhood.[24,25,]

Vogel et al (2018) published a retrospective case series of proton-based radiotherapy to treat nonhematologic head and neck malignancies in 69 pediatric patients.[26,] Thirty-five of the patients had rhabdomyosarcoma and were treated with a median dose of 50.4 Gy (range, 36.0 to 59.4 Gy) in 1.8 Gy fractions. A number of patients had Ewing sarcoma (n=10; median dose, 55.8 Gy; range, 55.8 to 65.6 Gy), and there were other histologies (n=24; median dose, 63.0 Gy). For the overall cohort, 92% (95% CI, 80% to 97%) were free from local recurrence at 1 year; at 3 years, 85% (95% CI, 68% to 93%). The OS rate at 1 year was 93% (95% CI, 79% to 98%); at 3 years, it was 90% (95% CI, 74% to 96%). Incidences of grade 3 toxicities were as follows: oral mucositis (4%), anorexia (22%), dysphagia (7%), dehydration (1%), and radiation dermatitis (1%). Despite the small and heterogenous sample, and the varying dosages and modalities administered, reviewers concluded that PBT was safe for the population in question, given the low rates of toxicity.

Section Summary: Pediatric Non-CNS Tumors
There are few data on charged-particle therapy for treating pediatric non-CNS tumors. A 2018 case series evaluated pediatric patients treated with PBT for rhabdomyosarcoma and Ewing sarcoma. The current evidence base is not sufficiently robust to draw conclusions about the efficacy of PBT for pediatric non-CNS tumors. While this modality of treatment has the potential to reduce toxicity to organs at risk and may minimize the development of radiation-induced secondary malignancies, limitations of the published evidence preclude determining the effects of the technology on the net health outcome.

CHARGED-PARTICLE (PROTON OR HELIUM ION) RADIOTHERAPY FOR LOCALIZED PROSTATE CANCER

Clinical Context and Therapy Purpose
The purpose of charged-particle (proton or helium ion) RT in patients 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 (ie, 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 charged-particle RT. Charged-particle therapy is administered in specially equipped treatment centers. PBT 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.

Systematic Reviews
A TEC Assessment (2010) 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.[27,]Nine studies were included in the review; 4 were comparative and 5 were noncomparative. There were 2 RCTs, and only one included a comparison group that did not receive PBT. This trial, by Shipley et al (1995), compared treatment with external-beam radiotherapy (EBRT) using photons and either a photon or proton beam boost.[28,] After a median follow-up of 61 months, the investigators found no statistically significant differences in OS, disease-specific survival, or recurrence-free survival. In a subgroup of patients with poorly differentiated tumors, there was superior local control with PBT versus photon boost, but survival outcomes did not differ. Actutimes incidence of urethral stricture and freedom from rectal bleeding were significantly better in the photon boost group. The TEC Assessment noted that higher doses were delivered to the proton beam boost group and, thus, better results on survival and tumor control outcomes would be expected. Moreover, the trial was published in the mid-1990s and used 2-dimensional methods of RT, which are now outmoded. The other RCT, known as Proton Radiation Oncology Group, was reported by Zietman et al (2005).[29,] They compared conventional- and high-dose conformal therapy using both conformal proton beams, proton boost, and EBRT. After a median follow-up of 8.9 years, there was no statistically significant difference between groups in survival. Biochemical failure (an intermediate outcome) was significantly lower in the high-dose proton beam group than in the conventional-dose proton beam group. The TEC Assessment noted that the outcome (biochemical failure) has an unclear relation to the more clinically important outcome, survival. The rate of acute gastrointestinal tract toxicity was worse with the high-dose proton beam boost.

Kim et al (2013), reported on an RCT of men with androgen-deprivation therapy-naive stage T1, T2, and T3 prostate cancer that compared different protocols for administering hypofractionated PBT.[30,] 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.[31,] 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.[32,] PBT, using CRT 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-dimentional 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-dimentional 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.[33,]

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.[34,] 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 of 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 Table 3).

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.[35,] 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, 00.81 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.[36,] 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.[37,] 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. OS 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 IPSS and 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.

Section Summary: Localized Prostate Cancer
The evidence on PBT for treating localized prostate cancer includes 2 RCTs, systematic reviews, 2 single-arm studies, a comparative retrospective cohort study, and a comparative effectiveness analysis of the NCDB. 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 included a comparison group that did not receive PBT. 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 BT groups, respectively. With propensity score matching, EBRT was associated with inferior survival compared to PBT, and differences between PBT and BT were not significantly different. One retrospective analysis found similar rates of IPSS and EPIC scores from 1 to 3 years follow-up between IMRT and PBT. Limitations of the published evidence preclude determining the effects of the technology on the net health outcome. Ongoing prospective studies comparing PBT to IMRT may alter the policy conclusions.

CHARGED-PARTICLE (PROTON OR HELIUM ION) RADIOTHERAPY FOR NON-SMALL-CELL LUNG CANCER

Clinical Context and Therapy Purpose
The purpose of 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 patients. The potential benefit of PBT is to reduce radiation toxicity to normal lung tissue and the heart.

Interventions
The therapy being considered is charged-particle (proton or helium ion) RT. Charged-particle therapy is administered in specially equipped treatment centers. PBT 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.

Systematic Reviews
A TEC Assessment (2010) assessed the use of PBT for NSCLC.[27,] This Assessment compared health outcomes (OS, disease-specific survival, local control, disease-free survival, adverse events) between PBT and SBRT, which is an accepted approach for using RT to treat NSCLC. Eight PBT case series were identified (N=340 patients). No comparative studies, randomized or nonrandomized, were found. For these studies, stage I comprised 88.5% of all patients, and only 39 patients had other stages or recurrent disease. Among 7 studies reporting 2-year OS rates, probabilities ranged between 39% and 98%. At 5 years, the range across 5 studies was 25% to 78%.

The review concluded that the evidence was insufficient to permit conclusions about PBT outcomes for any stage of NSCLC. All PBT studies were case series; no studies directly compared PBT with SBRT. Among study quality concerns, no study mentioned using an independent assessor of patient-reported adverse events; adverse events were generally poorly reported, and details were lacking on several aspects of PBT regimens. The PBT studies were similar in patient age, but there was great variability in percentages with stage IA cancer, the sex ratio, and the percentage of medically inoperable tumors. There was a high degree of treatment heterogeneity among the PBT studies, particularly with respect to volume, total dose, the number of fractions, and the number of beams. Survival results were highly variable. It is unclear whether the heterogeneity of results could be explained by differences in patient and treatment characteristics. In addition, indirect comparisons between PBT and SBRT (e.g., comparing separate sets of single-arm studies on PBT and SBRT) might have been distorted by confounding. Absent RCTs, the comparative effectiveness of PBT and SBRT was found to be uncertain. The Assessment noted that adverse events reported after PBT generally fell into several categories: rib fracture, cardiac, esophageal, pulmonary, skin, and soft tissue. Adverse events data in PBT studies are difficult to interpret due to lack of consistent reporting across studies, lack of detail about observation periods, and lack of information about rating criteria and grades.

An indirect meta-analysis by Grutters et al (2010) reviewed in the TEC Assessment found a nonsignificant difference of 9 percentage points between pooled 2-year OS estimates favoring SBRT over PBT for the treatment of NSCLC.[38,] The nonsignificant difference of 2.4 percentage 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.[39,] 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 investigating 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 were 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.

Randomized Controlled Studies

Liao et al (2018) conducted a RCT of passive scattering proton therapy (PSPT) versus IMRT in patients with inoperable NSCLC who were candidates for concurrent chemotherapy.[40,] 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 to 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 to 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 Table 3).

Nonrandomized Studies

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.[41,] 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.[42,] 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.[43,] 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).[44,] 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 nonstandardized 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.[45,] In 14 (70%) patients, tumors were clinically inoperable; overall median tumor diameter was 39.5 mm (range, 24 to 81 mm). PBT was administered 3.2 Gy per fraction. Median follow-up was 27.5 months (range, 12 to 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 2010 TEC Assessment, which included 8 case series, concluded that the evidence was insufficient to permit conclusions about PBT for any stage of NSCLC. Another systematic review, also published in 2010, only identified case series. Final results from a 2017 open-label phase 2 study included 5-year survival rates for patients who had PBT with concurrent chemotherapy. 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 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 in October 2023.

CHARGED-PARTICLE (PROTON OR HELIUM ION) RADIOTHERAPY FOR HEAD AND NECK TUMORS, OTHER THAN SKULL-BASED

Clinical Context and Therapy Purpose
The purpose of charged-particle (proton or helium ion) RT in individuals who have head and neck tumors, other than skull-based, 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 head and neck malignancies. The histology of the malignancies are predominantly of squamous cell type and may arise from, and involve multiple regions, including the oral cavity, pharynx, larynx, nasal cavity and paranasal sinuses, and the major salivary glands.

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

Comparators
The following practices are currently being used to make decisions about head and neck tumors, other than skull-based: 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.

Systematic Reviews
A systematic review by Patel et al (2014) evaluated the literature comparing charged-particle therapy with PBT in the treatment of paranasal sinus and nasal cavity malignant disease.[46,] Reviewers identified 41 observational studies that included 13 cohorts treated with charged-particle therapy (n=286 patients) and 30 cohorts treated with PBT (n=1186 patients). There were no head-to-head trials. In a meta-analysis, the pooled OS event rate was significantly higher with charged-particle therapy than with photon therapy at the longest duration of follow-up (relative risk, 1.27; 95% CI, 1.01 to 1.59). Findings were similar for 5-year survival outcomes (relative risk, 1.51; 95% CI, 1.14 to 1.99). Findings were mixed for the outcomes of locoregional control and disease-free survival; photon therapy was significantly better for one of the 2 timeframes (longest follow-up or 5-year follow-up). In terms of adverse events, there were significantly more neurologic toxic effects with charged-particle therapy than with photon therapy (p<.001), but other toxic adverse event rates (e.g., eye, nasal, hematologic) did not differ significantly between groups. Reviewers noted that the charged-particle studies were heterogeneous (e.g., type of charged particles [carbon ion, proton], delivery techniques). In addition, comparisons were indirect, and none of the studies selected actually compared the 2 types of treatment in the same patient sample.

Nonrandomized Comparative Studies
Youssef et al (2022) conducted a retrospective cohort study comparing outcomes in 292 patients with newly diagnosed nonmetastatic oropharyngeal carcinoma treated with curative-intent intensity-modulated proton therapy (IMPT; n=58) or IMRT (n=234).[47,] Median follow-up was 26 months and 93% of tumors were HPV-p16-positive. There were no significant differences in 3-year rates of OS (97% IMPT vs. 91% IMRT; p=.18), progression-free survival (82% IMPT vs. 85% IMRT; p=.62) or locoregional recurrence (5% IMPT vs. 4% IMRT; p=.59). Incidence of acute toxicities was significantly higher for IMRT compared with IMPT for grade ≥2 oral pain (72% IMPT vs. 93% IMRT; p<.001), grade ≥2 xerostomia (21% IMPT vs. 29% IMRT; p<.001), grade ≥2 dysgeusia (28% IMPT vs. 57% IMRT; p<.001), grade 3 dysphagia (7% IMPT vs. 12% IMRT; p<.001), grade ≥3 mucositis (53% IMPT vs. 57% IMRT; p<.003), grade ≥2 nausea (0% IMPT vs. 8% IMRT; p=.04), and grade ≥2 weight loss (37% IMPT vs. 59% IMRT; p<.001). There were no significant differences in chronic grade ≥3 toxic effects. Four patients treated with IMRT required a G-tube for longer than 6 months compared to none treated with IMPT.

Blanchard et al (2016) case-matched 50 patients treated with IMPT with 100 patients treated with IMRT who were receiving treatment for oropharyngeal carcinoma.[48,] Patients were followed-up for a median of 32 months. No statistically significant differences in OS (HR, 0.55; 95% CI 0.12 to 2.50; p=0.44) or progression-free survival (HR, 1.02; 95% CI, 0.41 to 2.54; p=.96) were

observed. A pre-planned composite endpoint demonstrated reduced risks of grade 3 weight loss or G-tube presence at 3 months (OR, 0.44; 95% CI, 0.19 to 1.0; p=.05) and 1-year after treatment (OR, 0.23; 95% CI, 0.07 to 0.73; p=.01).

Adverse Events
Zenda et al (2015) reported on late toxicity in 90 patients after PBT for nasal cavity, paranasal sinuses, or skull-based malignancies.[49,] Eighty-seven of the 90 patients had paranasal sinus or nasal cavity cancer. The median observation period was 57.5 months. Grade 3 late toxicities occurred in 17 (19%) patients, and grade 4 occurred in 6 (7%) patients. Five patients developed cataracts, and 5 developed optic nerve disorders. Late toxicities (other than cataracts) developed a median of 39.2 months after PBT.

Section Summary: Head and Neck Tumors, Other Than Skull-Based
A 2014 systematic review identified only case series and noted that the studies of charged-particle therapy were heterogenous in terms of the types of particle and delivery techniques used. No studies identified compared charged-particle therapy with other treatments. A case-matched cohort study compared outcomes for oropharyngeal cancer patients receiving IMPT or IMRT. No statistically significant differences in OS or progression-free survival were observed ; however, a lower risk for treatment-related adverse events was noted with IMPT. A 2022 retrospective cohort study reported similar findings in patients with nonmetastatic oropharyngeal cancer treated with curative-intent IMPT versus IMRT. Limitations of the published evidence preclude determining the effects of the technology on net health outcome. Ongoing RCTs comparing IMPT to IMRT may elucidate effects on net health outcome.

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:

- Pediatric central nervous system tumors.

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 with conventional or advanced photon-based radiotherapy cannot meet dose-volume constraints for normal tissue radiation tolerance (see Policy Guidelines):

- 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;
- Head and neck cancers.

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.

2013 Input

In response to requests, input was received from 2 physician specialty societies (4 responses) and 4 academic medical centers while this policy was under review in 2013. There was uniform support for the use of proton beam therapy (PBT) in pediatric central nervous system tumors. Two reviewers supported the use of proton beam therapy in pediatric non-central nervous system tumors; data for this use are scant. Input on head and neck tumors (non-skull-based) was mixed.

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 (e.g., 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 (e.g., 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 (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.[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 (e.g., 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.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 3.

Table 3. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT03164460	Phase II Randomized Trial of Stereotactic Onco-Ablative Reirradiation Versus Conventionally Fractionated Conformal Radiotherapy for Patients With Small Inoperable Head and Neck Tumors (SOAR-HN)	100	May 2025
NCT03217188	A Phase II Study of Proton Re-Irradiation for Recurrent Head and Neck Cancer	87	Jul 2025
NCT01629498	Phase I/II Trial of Image-Guided, Intensity-Modulated Photon (IMRT) or Scanning Beam Proton Therapy (IMPT) Both With Simultaneous Integrated Boost (SIB) Dose Escalation to the Gross Tumor Volume (GTV) With Concurrent Chemotherapy for Stage II/III Non-Small Cell Lung Cancer (NSCLC)	100	Sep 2025
NCT01230866	Study of Hypo-fractionated Proton Radiation for Low Risk Prostate Cancer	150	Dec 2025
NCT02923570	A Phase II Randomized Study of Proton Versus Photon Beam Radiotherapy in the Treatment of Unilateral Head and Neck Cancer	108	Dec 2025
NCT01893307	Phase II/III Randomized Trial of Intensity-Modulated Proton Beam Therapy (IMPT) Versus Intensity-Modulated Photon Therapy (IMRT) for the Treatment of Oropharyngeal Cancer of the Head and Neck	442	Aug 2025
NCT01993810	Comparing Photon Therapy To Proton Therapy To Treat Patients With Lung Cancer	330	Oct 2025
NCT03561220	A Prospective Comparative Study of Outcomes With Proton and Photon Radiation in Prostate Cancer (COMPPARE)	3000	Apr 2026
NCT02838602	Randomized Carbon Ions vs Standard Radiotherapy for Radioresistant Tumors (ETOILE)	250	Dec 2026
NCT01617161	Proton Therapy vs. IMRT for Low or Intermediate Risk Prostate Cancer (PARTIQoL)	454	Dec 2026
ISRCTN16424014	A Trial of Proton Beam Radiotherapy for Oropharyngeal Cancer (TORPEdO)	183	Sep 2028

ISRCTN: International Standard Registered Clinical/Social Study Number; NCT: national clinical trial.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. This may not be a comprehensive list of procedure codes applicable to this policy.

Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

The code(s) listed below are medically necessary ONLY if the procedure is performed according to the "Policy" section of this document.

CPT/HCPCS	
77299	Unlisted procedure, therapeutic radiology clinical treatment planning
77399	Unlisted procedure, medical radiation physics, dosimetry and treatment devices, and special services
77499	Unlisted procedure, therapeutic radiology treatment management
77520	Proton treatment delivery; simple, without compensation
77522	Proton treatment delivery; simple, with compensation
77523	Proton treatment delivery; intermediate
77525	Proton treatment delivery; complex

REVISIONS	
10-06-2011	Policy added to the bcbsks.com web site.
08-06-2013	In Policy section: 1. In Item A, added #3, "In the treatment of pediatric central nervous system tumors. 2. In Item C, added "pediatric non-central nervous system tumors, and tumors of the head and neck (other than skull-based chordoma or chondrosarcoma)".
	Updated Rationale section.
	In Coding section: 1. Added ICD-9 codes: 191.0-191.9; 192.0, 192.1, 192.3, 192.8, 192.9
	Updated Reference section.
12-11-2013	In Coding section: 2. Added ICD-10 Diagnosis *(Effective October 1, 2014)*
	Updated Reference section.
11-12-2015	Updated Description section.
	In Policy section: 3. Removed Item B, "Charged-particle irradiation with proton beams using standard treatment doses is considered not medically necessary in patients with clinically localized prostate cancer because the clinical outcomes with this treatment have not been shown to be superior to other approaches including intensity modulated radiation therapy (IMRT) or conformal radiation therapy, yet proton beam therapy is generally more costly than these alternatives." 4. In Item B (formerly Item C), added "clinically localized prostate cancer," and revised to list criteria separately to read, "Other applications of charged-particle irradiation with use of proton beams therapy are considered experimental /

REVISIONS	
	investigational. This includes, but is not limited to: 1. Clinically localized prostate cancer, 2. Non-small-cell lung cancer (NSCLC) at any stage or for recurrence, 3. Pediatric non-central nervous system tumors, 4. Tumors of the head and neck (other than skull-based chordoma or chondrosarcoma)."
	Updated Rationale section.
	Updated References section.
09-01-2016	Title revised from "Charged-Particle (Proton or Helium Ion) Radiation Therapy"
	Updated Description section.
	In Policy section: A. In Item B, added "or helium ion" to read, "Other applications of charged-particle irradiation with proton or helium ion beams are considered experimental / investigational. This includes, but is not limited to:"
	Updated Rationale section.
	Updated References section.
04-12-2017	In Policy section: B. Removed Item B 1, "Clinically localized prostate cancer;" C. Added Item C, "Charged-particle irradiation with proton or helium ion beams for clinically localized prostate cancer is considered not medically necessary (see Policy Guidelines)." D. Added Policy Guidelines Item 2.
08-15-2017	Updated Description section.
	Updated Rationale section.
	Updated References section.
08-29-2018	Updated Description section.
	Updated Rationale section.
	In Coding section: 1. Removed ICD-9 codes.
	Updated References section.
03-09-2021	Archived
Posted 6-13-2023 Effective 7-13-2023	Unarchived
	Updated Description Section
	Updated Policy Section ▪ Added: Section B B. 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: 1. in the curative treatment of primary or benign solid pediatric non-central nervous system tumors, including Ewing sarcoma; 2. in the curative treatment of nonmetastatic primary non-small cell lung cancer; OR 3. head and neck cancers. ▪ Added: 1. clinically localized prostate cancer; 2. non-curative treatment of primary or benign solid pediatric non-central nervous system tumors, including Ewing sarcoma; 3. non-curative treatment of non-small cell lung cancer. To previous section B now Section C: "Other applications of charged-particle irradiation with proton or helium ion beams are considered experimental / investigational. This includes, but is not limited to:" And Removed: 1. Non-small cell lung cancer (NSCLC) at any stage or for recurrence;

REVISIONS	
	2. Pediatric non-central nervous system tumors; 3. Tumors of the head and neck (other than skull-based chordoma or chondrosarcoma). ▪ Removed: Previous section C "Charged-particle irradiation with proton or helium ion beams for clinically localized prostate cancer is considered not medically necessary (see Policy Guidelines)."
	Updated Rationale Section
	Updated Coding Section ▪ Removed: 61796, 61797, 61798, 61799, 63620, 63621 ▪ Removed Coding Bullets • The use of proton beam or helium ion radiation therapy typically consists of a series of CPT codes describing the individual steps required: medical radiation physics, clinical treatment planning, treatment delivery, and clinical treatment management. It should be noted that the code for treatment delivery primarily reflects the costs related to the energy source used and not physician work. The following CPT codes have been used: Medical radiation physics: 77399 Clinical treatment planning: 77299 • The codes used for treatment delivery will depend on the energy source used, typically either photons or protons. For photons (i.e., with a Gamma Knife or LINAC device) nonspecific radiation therapy treatment delivery, CPT codes may be used based on the voltage of the energy source (i.e., codes 77402–77416). When proton beam therapy is used, the following specific CPT codes are available: 77520, 77522, 77523, 77525 Note: Codes for treatment delivery primarily reflect the costs related to the energy source used, and not physician work. • Clinical treatment management: 77499 • Stereotactic charged particle radiosurgery would be reported with the following CPT codes: 61796, 61797, 61798, 61799, 63620, 63621 ▪ Removed ICD-10 Codes
	Updated References Section
06-27-2024	Updated Description Section
	Updated Rationale Section
	Updated References Section

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