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

Professional
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**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 indications, often for tumors that would benefit from the delivery of a high dose of radiation with limited scatter.

**OBJECTIVE**

The objective of this policy is to evaluate whether charged-particle irradiation with proton or helium ion beams improves the net health outcome in patients with neoplastic conditions.

**BACKGROUND**

Charged-particle beams consisting of protons or helium ions are a type of particulate radiation therapy. They contrast with conventional electromagnetic (ie, photon) radiation therapy due to several unique properties, 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 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.

The use of proton or helium ion radiation therapy has been investigated in two general categories of tumors/abnormalities:

1. Tumors located near vital structures, such as intracranial lesions or lesions along the axial skeleton, such that complete surgical excision or adequate doses of conventional radiation therapy are impossible. These tumors/lesions include uveal melanomas, chordomas, and chondrosarcomas at the base of the skull and along the axial skeleton.

2. Tumors associated with a high rate of local recurrence despite maximal doses of conventional RT. One tumor in this group is locally advanced prostate cancer (ie, Stages C or D1 [without distant metastases], also classified as T3 or T4).

Advances in photon-based RT such as 3-dimensional conformal radiotherapy, intensity-modulated radiotherapy, and stereotactic body radiotherapy allow improved targeting of conventional therapy.

Proton beam therapy can be given with or without stereotactic techniques. Stereotactic approaches are frequently utilized for uveal tract and skull-based tumors. For stereotactic techniques, 3 to 5 fixed beams of protons or helium ions are used.

**REGULATORY STATUS**

Radiotherapy is a procedure and, therefore, is 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. Senior staff at the FDA’s Center for Devices and Radiological Health have 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 1 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 patients 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. Patients eligible for this treatment have residual localized tumor without evidence of metastasis.

3. In the treatment of pediatric central nervous system tumors.

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

1. Non-small cell lung cancer (NSCLC) at any stage or for recurrence;
2. Pediatric non-central nervous system tumors;
3. Tumors of the head and neck (other than skull-based chordoma or chondrosarcoma).

C. Charged-particle irradiation with proton or helium ion beams for clinically localized prostate cancer is considered not medically necessary (see Policy Guidelines).

Policy Guidelines
1. Evidence is unavailable to define age parameters for the use of proton beam therapy in pediatric patients. Some studies using proton beam therapy in pediatric CNS tumors mostly included patients 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).

2. 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.
RATIONALE
The policy is updated regularly with reviews of the MEDLINE database. Most recently, the literature was reviewed through June 6, 2017.

Uveal Melanomas
The section was informed by a 1996 TEC Assessment that concluded proton therapy was at least as effective as alternative therapies for treating uveal melanoma.1 In 2013, Wang et al published a systematic review of the literature on charged-particle (proton, helium, carbon ion) radiotherapy (RT) for uveal melanoma.2 Reviewers included 27 controlled and uncontrolled studies that reported health outcomes (eg, mortality, local recurrence). Three studies were randomized controlled trials (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 primary treatment of uveal melanoma and is better at preserving vision.

Another RCT, published in 2015 by Mishra et al, compared charged-particle therapy using helium ions and iodine 125 (I-125) plaque therapy in 184 patients with uveal melanoma.3 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=0.006). Overall survival (OS) 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=0.02).

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 on 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 compared with brachytherapy and fewer adverse effects to vision.

Skull-Based Tumors
This section was based on a 1996 TEC Assessment that concluded, compared with treatment with conventional x-rays after partial resection or biopsy, charged-particle irradiation yields
greater rates of local control, overall survival (OS), and disease-free survival at 5 years after therapy.\textsuperscript{1} Subsequently, a 2007 systematic review of charged-particle therapy found that local tumor control and 5-year OS rates for skull-based chordomas treated with proton beam therapy (PBT) were 63\% and 81\%, respectively. Reviewers compared that finding with postsurgical treatment (that used conventional PBT) with reported local tumor control and 5-year OS rates of 25\% and 44\%, respectively, and compared that finding with surgery followed by fractionated stereotactic radiotherapy, which resulted in a 5-year local tumor control rate of 50\%.\textsuperscript{4} A summary of tumor control in published proton therapy studies of chondrosarcoma of the skull base was 95\% five-year local tumor control, similar to the results of conventional therapy.

A 2016 systematic review by Matloob et al evaluated the literature on PBT for skull-based chordomas.\textsuperscript{5} Reviewers included controlled trials and case series with more than 5 patients. Twelve studies met eligibility criteria. Reviewers did not report study type, but it appears they only identified case series. Sample sizes ranged from 9 to 367 patients and 6 studies reported 5-year survival rates that ranged from 67\% to 94\%.

**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\%.

**Pediatric Central Nervous System Tumors**

In 2008, Merchant et al published a modeling study evaluating whether RT has clinical advantages over photon RT in childhood brain tumors.\textsuperscript{6} Three-dimensional imaging and treatment planning data, which included targeted tumor and normal tissues contours, were acquired for 40 patients. Histologic subtypes in the 40 patients were 10 each with optic pathway glioma, craniopharyngioma, infratentorial ependymoma, or medulloblastoma. Dose-volume data were collected for the entire brain, temporal lobes, cochlea, and hypothalamus; data were averaged and compared based on treatment modality (protons vs photons) using dose-cognitive effects models. Clinical outcomes were estimated over 5 years. With protons (vs photons), relatively small critical normal tissue volumes (eg, cochlea, hypothalamus) were spared from radiation exposure when not adjacent to the primary tumor volume. Larger normal tissue volumes (eg, supratentorial brain or temporal lobes) received less of the intermediate and low doses. When these results were applied to longitudinal models of radiation dose-cognitive effects, the differences resulted in clinically significant higher IQ scores for patients with medulloblastoma and craniopharyngioma and academic reading scores in patients with optic pathway glioma. There were extreme differences between proton and photon dose distributions for the patients with ependymoma, which precluded meaningful comparison of the effects of protons vs photons. The authors concluded that the differences in the overall dose distributions, as evidenced by modeling changes in cognitive function, showed that these reductions in the lower dose volumes or mean dose would result in long-term, improved clinical outcomes for children with medulloblastoma, craniopharyngioma, and glioma of the optic pathway.

In 2016, Leroy et al published a systematic review of the literature on PBT for the treatment of pediatric cancers.\textsuperscript{7} Their findings on pediatric central nervous system (CNS) tumors include the following:
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- **Cranioopharyngioma:** Three studies were identified, 2 retrospective case series and 1 retrospective comparative study of PBT and intensity-modulated radiotherapy (IMRT). They found very low level evidence that survival outcomes with PBT and IMRT are similar.
- **Ependymoma:** One prospective case series and another retrospective case series were identified. They concluded that the evidence did not support or refute the use of PBT for this condition.
- **Medulloblastoma:** One prospective case series and 2 retrospective case series were identified. They concluded that the evidence did not support or refute the use of PBT for this condition.
- **CNS germinoma:** One retrospective case series was identified. They concluded that the evidence did not support or refute the use of PBT for this condition.

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

In 2002, Hug et al reported on proton radiation in the treatment of low-grade gliomas in 27 pediatric patients.\(^8\) 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. A 1999 dosimetric comparison of protons to photons for 7 optic pathway gliomas treated showed a decrease in radiation dose to the contralateral optic nerve, temporal lobes, pituitary gland, and optic chiasm with the use of protons.\(^9\)

In 2014, Bishop et al reported on 52 children with craniopharyngioma treated at 2 centers; 21 received PBT and 31 received IMRT.\(^10\) Patients received a median dose of 50.4 gray (Gy). At 3 years, OS was 94.1% in the PBT group and 96.8% in the IMRT group (p=0.742). Three-year nodular and cystic failure-free survival rates were also similar between groups. 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.\(^11\) Radiation doses ranged from 30.6 to 57.6 cobalt Gray equivalents (CGE). All nongerminomatous germ cell tumor patients received chemotherapy before RT. Twenty-one patients were treated with cranial spinal irradiation, whole ventricular RT, or whole-brain radiotherapy followed by an involved field boost; 1 patient received involved field alone. Median follow-up was 28 months. There were no CNS recurrences or deaths. Following RT, 2 patients developed growth hormone deficiency and 2 patients developed central hypothyroidism. The authors stated that longer follow-up was necessary to assess the neurocognitive effects of therapy. In the same study, a dosimetric comparison of photons and protons for representative treatments with whole ventricular and involved field boost 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.\(^12\) Because hearing loss is common after chemoradiotherapy for children with medulloblastoma, the authors sought to compare 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, 19-43). Hearing sensitivity significantly declined following RT across all frequencies analyzed (p<0.05). There was partial sparing of mean postradiation hearing thresholds at low- to mid-range frequencies; the rate of high-grade (grade 3 or 4) ototoxicity at 1 year was 5%. The authors compared high-grade rates with the rate of grade 3 or 4 toxicity following IMRT (18%) in a separate case series. They concluded that preservation of hearing in the audible speech range, as observed in their study, might improve both quality of life and cognitive functioning for these patients.

Section Summary: Pediatric Central Nervous System Tumors
A 2016 systematic review identified several case series evaluating PBT for several types of pediatric CNS tumors including craniopharyngioma, ependymoma, medulloblastoma, and CNS germinoma. One small comparative observational study was identified. It compared PBT with IMRT for children with craniopharyngioma and found similar outcomes with both types of treatment.

Pediatric Non-CNS Tumors
There are scant data on the use of PBT in pediatric non-CNS tumors. Data include dosimetric planning studies in a small number of pediatric patients with parameningeal rhabdomyosarcoma and late toxicity outcomes in other solid tumors of childhood.

Section Summary: Pediatric Non-CNS Tumors
There are few data on charged-particle therapy for treating pediatric non-CNS tumors.

Localized Prostate Cancer
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. A total of 9 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 1995 trial, by Shipley et al, compared treatment with external-beam radiotherapy (EBRT) using photons and either a photon or proton beam boost. 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 vs photon boost, but survival outcomes did not differ. Actuarial 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 (2D) methods of RT, that are now outmoded. The other RCT, known as Proton Radiation Oncology Group (PROG/ACR 95-09), 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.

Taking into account data from all 9 studies included in the review, TEC Assessment authors concluded that there was inadequate evidence from comparative studies to permit conclusions about the impact of PBT on health outcomes. Ideally, RCTs would have to report long-term health outcomes or intermediate outcomes that consistently predict health outcomes.

No RCTs, published since the TEC Assessment, have compared health outcomes in patients treated with PBT to patients treated by other RT modalities.

An RCT did compare different protocols for administering hypofractionated PBT, but because there was no comparison with an alternative intervention, conclusions cannot be drawn about the efficacy and safety of PBT. This Korean study, published by Kim et al (2013), included men with androgen-deprivation therapy-naive stage T1-T3 prostate cancer. 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.

In 2014, the Agency for Healthcare Research and Quality reviewed therapies for localized prostate cancer. Reviewers compared the risk and benefits of a number of treatments for localized prostate cancer, including: radical prostatectomy, EBRT (standard therapy as well as PBT, 3-dimensional conformal radiotherapy [3D-CRT], 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; eg, current RT protocols allow 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 in the time 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 that dose escalation is an accepted concept in treating organ-confined prostate cancer. PBT, using CRT planning or IMRT, is used to provide dose escalation to a more well-defined target volume. However, dose escalation is more commonly offered with conventional EBRT using 3D-CRT 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 3D-CRT 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.\textsuperscript{22}

Section Summary: Localized Prostate Cancer
The evidence on PBT for treating localized prostate cancer includes 2 RCTs and systematic reviews. 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.

Non-Small-Cell Lung Cancer
A 2010 TEC Assessment assessed the use of PBT for non-small-cell lung cancer (NSCLC).\textsuperscript{23} This TEC 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 (total 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, 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 and 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 within stage IA, sex ratio, and percent medically inoperable. There was a high degree of treatment heterogeneity among the PBT studies, particularly with respect to planning 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, 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.

A 2010 indirect meta-analysis\textsuperscript{24} 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. 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 use of particle therapy in lung cancer.\textsuperscript{25} Study selection criteria included that the series have 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 patients) and 6, C-ions (n=210 patients). The proton studies included 1 phase 2 study, 2 prospective studies, and 2 retrospective studies. All 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). Two-year OS ranged from 31% to 74%, and 5-year OS ranged from 31% to 50% (2- and 5-year OS each reported in 4 studies). These local control and survival rates are equivalent or inferior to those achieved with SBRT. Radiation-induced pneumonitis was observed in about 10% of patients. For C-ion therapy, the overall local tumor control rate was 77%, and it was 95% when using a hypofractionated dosing schedule. The 5-year OS and cause-specific survival rates with C-ion therapy were 42% and 60%, respectively. Slightly better results were reported when using hypofractionation (50% and 76%, respectively). Reviewers concluded that, although the results with protons and heavier charged particles were promising, additional well-designed trials would be needed.

To date, no RCTs or nonrandomized trials comparing health outcomes in patients treated with PBT to an alternative treatment have been published.

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 non-small-cell lung cancer. Another systematic review, also published in 2010, only identified case series. No subsequent randomized or nonrandomized comparative studies have been published.

Head and Neck Tumors, Other Than Skull-Based
A 2014 systematic review evaluated the literature comparing charged-particle therapy with PBT in the treatment of paranasal sinus and nasal cavity malignant disease.\textsuperscript{26} 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 [RR], 1.27; 95% CI, 1.01 to 1.59). Findings were similar for 5-year survival outcomes (RR=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 only one of the 2 timeframes (longest follow-up or 5-year follow-up). In terms of adverse effects, there were significantly more neurologic toxic effects with charged-particle therapy than with photon therapy (p<0.001), but other toxic adverse event rates (eg, eye, nasal, hematologic) did not differ significantly between groups. Reviewers noted that the charged-particle studies were heterogeneous (eg, 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.
Also in 2015, Zenda et al reported on late toxicity in 90 patients after PBT for nasal cavity, paranasal sinuses, or skull-based malignancies. 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 on charged-particle therapy were heterogenous in terms of the type of particle and delivery techniques. No studies were identified that compared charged-particle therapy with other treatments.

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

For individuals who have skull-based tumor(s) (ie, cervical chordoma, chondrosarcoma) who receive charged-particle (proton or helium ion) radiotherapy, the evidence includes observational studies and systematic reviews. Relevant outcomes are overall survival, disease-free survival, change in disease status, and treatment-related morbidity. A 1996 TEC Assessment concluded that the technology is at least as effective as alternative therapies for treating skull-based tumors. A 2016 systematic review of observational studies found 5-year survival rates after proton beam therapy (PBT) ranging from 67% to 94%. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

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

For individuals who have pediatric non-central nervous system tumor(s) who receive charged-particle (proton or helium ion) radiotherapy, the evidence includes dosimetric planning studies in a small number of patients. Relevant outcomes are overall survival, disease-free survival, change in disease status, and treatment-related morbidity. There is a lack of randomized and observational studies evaluating the efficacy and safety of the technology. The evidence is insufficient to determine the effects of the technology on health outcomes.
For individuals who have localized prostate cancer who receive charged-particle (proton or helium ion) radiotherapy, the evidence includes 2 RCTs and systematic reviews. Relevant outcomes are overall survival, disease-free survival, change in disease status, and treatment-related morbidity. A 2010 TEC Assessment addressed the use of PBT for prostate cancer and concluded that it had not yet been established whether PBT improves outcomes in any setting for clinically localized prostate cancer. The TEC Assessment included 2 RCTs, only 1 of which included a comparison group of patients who did not receive proton PBT. No data on the use of PBT for prostate cancer published since 2010 would alter the conclusions of the TEC Assessment.

For individuals who have non-small cell lung cancer who receive charged-particle (proton or helium ion) radiotherapy, the evidence includes case series and systematic reviews. Relevant outcomes are overall survival, disease-free survival, change in disease status, and treatment-related morbidity. A 2010 TEC Assessment included 8 case series and concluded that the evidence is insufficient to permit conclusions about PBT for any stage of non-small cell lung cancer. No subsequent randomized or nonrandomized comparative studies have been published. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have head and neck tumors other than skull-based who receive charged-particle (proton or helium ion) radiotherapy, the evidence includes case series and a systematic review. Relevant outcomes are overall survival, disease-free survival, change in disease status, and treatment-related morbidity. The evidence is insufficient to determine the effects of the technology on health outcomes. The systematic review noted that the studies on charged-particle therapy were heterogenous in terms of type of particle and delivery techniques, and that there are no head-to-head trials comparing charged-particle therapy to other treatments. The evidence is insufficient to determine the effects of the technology on health outcomes.

**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.

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 PBT in pediatric CNS tumors. Two reviewers expressed support for the use of PBT in pediatric non-CNS tumors; data for this use are scant. Input on head and neck tumors (non-skull-based) was mixed.

**PRACTICE GUIDELINES AND POSITION STATEMENTS**

International Particle Therapy Co-operative Group

A 2016 consensus statement by the International Particle Therapy Co-operative Group made 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..."
American College of Radiology Appropriateness Criteria

A 2014 guideline on external beam irradiation in stage T1 and T2 prostate cancer states:

- “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.”

National Comprehensive Cancer Network

Prostate Cancer

National Comprehensive Cancer Network (NCCN) guidelines for prostate cancer (v.2.2017) 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.”

Non-Small Cell Lung Cancer

NCCN guidelines for NSCLC (v.2.2017) state that “more advanced technologies are appropriate when needed to deliver curative RT [radiotherapy] safely. These technologies include (but are not limited to) 4D-CT [4-dimensional computed tomography] and/or PET/CT [positron emission tomography/ computed tomography] simulation, IMRT/VMAT [intensity-modulated radiotherapy/volumetric modulated arc therapy], IGRT [image-guided radiotherapy], motion management and proton therapy.”

Bone Cancer

NCCN guidelines for bone cancer (v.2.2017) state that “specialized techniques such intensity-modulated radiotherapy (IMRT), particle beam RT with protons, carbon ions or other heavy ions, stereotactic radiosurgery or fractionated stereotactic RT should be considered as indicated in order to allow high-dose therapy while maximizing normal tissue sparing.”

American Society for Radiation Oncology

ASTRO’s Emerging Technology Committee published 2012 evidence-based recommendations declaring a lack of evidence for PBT for malignancies outside of large ocular melanomas and chordomas:

“Current data do not provide sufficient evidence to recommend PBT outside of clinical trials in lung cancer, head and neck cancer, GI [gastrointestinal] malignancies (with the exception of hepatocellular) and pediatric non-CNS malignancies. In hepatocellular carcinoma and prostate cancer, there is evidence for the efficacy of PBT but no suggestion that it is superior to photon-based approaches. In pediatric CNS malignancies, there is a suggestion from the literature that PBT is superior to photon approaches, but there is currently insufficient data to support a firm recommendation for PBT. In the setting of craniospinal irradiation for pediatric patients, protons appear to offer a dosimetric benefit over photons, but more clinical data are
needed. In large ocular melanomas and chordomas, we believe that there is evidence for a benefit of PBT over photon approaches. In all fields, however, further clinical trials are needed and should be encouraged.\textsuperscript{33}

In September 2013, as part of its national “Choosing Wisely” initiative, ASTRO listed PBT for prostate cancer as one of 5 radiation oncology practices that should not be routinely used because they are not supported by evidence.\textsuperscript{34}

In June 2014, ASTRO published a model policy on use of PBT.\textsuperscript{35} The document stated that ASTRO supports PBT for the treatment of the following conditions:

"Ocular tumors, including intraocular melanomas
Tumors that approach or are located at the base of the skull, including but not limited to:
  Chordoma
  Chondrosarcoma
Primary or metastatic tumors of the spine... (selected patients)
Primary hepatocellular cancer treated in a hypofractionated regimen
Primary or benign solid tumors in children... (selected patients)
Patients with genetic syndromes making total volume of radiation minimization crucial such as but not limited to NF-1 patients and retinoblastoma patients."

The model policy stated the following regarding PBT for treating prostate cancer:

“...It is essential to collect further data, especially to understand how the effectiveness of proton therapy compares to other radiation therapy modalities such as IMRT and brachytherapy. There is a need for more well-designed registries and studies with sizable comparator cohorts to help accelerate data collection. Proton beam therapy for primary treatment of prostate cancer should only be performed within the context of a prospective clinical trial or registry.”

National Association for Proton Therapy
In March 2015, National Association for Proton Therapy published a model coverage policy.\textsuperscript{36} Prostate carcinoma was an indication considered medically necessary in this document. The model policy did not include a discussion of the published evidence.

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS
Not applicable.

ONGOING AND UNPUBLISHED CLINICAL TRIALS
Some currently unpublished trials that might influence this policy are listed in Table 1.

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
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<tbody>
<tr>
<td>NCT01617161</td>
<td>Proton Therapy vs. IMRT for Low or Intermediate Risk Prostate Cancer (PARTIQoL)</td>
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<td>Dec 2026</td>
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<td>NCT01230866</td>
<td>Study of Hypo-fractionated Proton Radiation for Low Risk Prostate Cancer</td>
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<td>Dec 2018</td>
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<tr>
<td>NCT01993810</td>
<td>Comparing Photon Therapy To Proton Therapy To Treat Patients With Lung Cancer</td>
<td>560</td>
<td>Dec 2020</td>
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### CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. 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.

<table>
<thead>
<tr>
<th>CPT/HCPCS</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>61796</td>
<td>Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); 1 simple cranial lesion</td>
</tr>
<tr>
<td>61797</td>
<td>Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); each additional cranial lesion, simple (List separately in addition to code for primary procedure)</td>
</tr>
<tr>
<td>61798</td>
<td>Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); 1 complex cranial lesion</td>
</tr>
<tr>
<td>61799</td>
<td>Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); each additional cranial lesion, complex (List separately in addition to code for primary procedure)</td>
</tr>
<tr>
<td>63620</td>
<td>Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); 1 spinal lesion</td>
</tr>
<tr>
<td>63621</td>
<td>Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); each additional spinal lesion (List separately in addition to code for primary procedure)</td>
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<tr>
<td>77299</td>
<td>Unlisted procedure, therapeutic radiology clinical treatment planning</td>
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<tr>
<td>77399</td>
<td>Unlisted procedure, medical radiation physics, dosimetry and treatment devices, and special services</td>
</tr>
<tr>
<td>77499</td>
<td>Unlisted procedure, therapeutic radiology treatment management</td>
</tr>
<tr>
<td>77520</td>
<td>Proton treatment delivery; simple, without compensation</td>
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<tr>
<td>77522</td>
<td>Proton treatment delivery; simple, with compensation</td>
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<tr>
<td>77523</td>
<td>Proton treatment delivery; intermediate</td>
</tr>
<tr>
<td>77525</td>
<td>Proton treatment delivery; complex</td>
</tr>
</tbody>
</table>

- 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 (ie, 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 (ie, 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

ICD-9 Diagnoses
170.0  Malignant neoplasm of bone and articular cartilage; Bones of skull and face, except mandible
170.2  Malignant neoplasm of bone and articular cartilage; Vertebral column, excluding sacrum and coccyx
170.9  Malignant neoplasm of bone and articular cartilage; site unspecified
190.0  Malignant neoplasm of Eyeball, except conjunctiva, cornea, retina, and choroid
190.1  Malignant neoplasm of Orbit
190.2  Malignant neoplasm of Lacrimal gland
190.3  Malignant neoplasm of Conjunctiva
190.4  Malignant neoplasm of Cornea
190.5  Malignant neoplasm of Retina
190.6  Malignant neoplasm of Choroid
190.7  Malignant neoplasm of Lacrimal duct
190.8  Malignant neoplasm of Other specified sites of eye
190.9  Malignant neoplasm of Eye, part unspecified
191.0  Malignant neoplasm of brain; Cerebrum, except lobes and ventricles
191.1  Malignant neoplasm of brain; frontal lobe
191.2  Malignant neoplasm of brain; temporal lobe
191.3  Malignant neoplasm of brain; parietal lobe
191.4  Malignant neoplasm of brain; occipital lobe
191.5  Malignant neoplasm of brain; ventricles
191.6  Malignant neoplasm of brain; cerebellum NOS
191.7  Malignant neoplasm of brain; brain stem
191.8  Malignant neoplasm of brain; other parts of brain
191.9  Malignant neoplasm of brain; brain, unspecified
192.0  Malignant neoplasm of other and unspecified part of nervous system; cranial nerves
192.1  Malignant neoplasm of other and unspecified part of nervous system; cerebral meninges
192.2  Malignant neoplasm of other and unspecified part of nervous system; spinal cord
192.3  Malignant neoplasm of other and unspecified part of nervous system; spinal meninges
192.8  Malignant neoplasm of other and unspecified part of nervous system
192.9  Malignant neoplasm of other and unspecified part of nervous system; nervous system, part unspecified
198.5 Secondary malignant neoplasm of other specified sites; Bone and bone marrow

**ICD-10 Diagnoses (Effective October 1, 2015)**

- C41.0 Malignant neoplasm of bones of skull and face
- C41.2 Malignant neoplasm of vertebral column
- C41.9 Malignant neoplasm of bone and articular cartilage, unspecified
- C69.01 Malignant neoplasm of right conjunctiva
- C69.02 Malignant neoplasm of left conjunctiva
- C69.11 Malignant neoplasm of right cornea
- C69.12 Malignant neoplasm of left cornea
- C69.21 Malignant neoplasm of right retina
- C69.22 Malignant neoplasm of left retina
- C69.31 Malignant neoplasm of right choroid
- C69.32 Malignant neoplasm of left choroid
- C69.41 Malignant neoplasm of right ciliary body
- C69.42 Malignant neoplasm of left ciliary body
- C69.51 Malignant neoplasm of right lacrimal gland and duct
- C69.52 Malignant neoplasm of left lacrimal gland and duct
- C69.61 Malignant neoplasm of right orbit
- C69.62 Malignant neoplasm of left orbit
- C69.81 Malignant neoplasm of overlapping sites of right eye and adnexa
- C69.82 Malignant neoplasm of overlapping sites of left eye and adnexa
- C69.91 Malignant neoplasm of unspecified site of right eye
- C69.92 Malignant neoplasm of unspecified site of left eye
- C72.0 Malignant neoplasm of spinal cord
- C79.51 Secondary malignant neoplasm of bone
- C79.52 Secondary malignant neoplasm of bone marrow

**REVISIONS**

<table>
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<tr>
<td>10-06-2011</td>
<td>Policy added to the bcbsks.com web site.</td>
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| 08-06-2013 | In Policy section:  
  - In Item A, added #3, "In the treatment of pediatric central nervous system tumors.
  - 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:  
  - 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:  
  - Added ICD-10 Diagnosis (Effective October 1, 2014)
  
  Updated Reference section. |
| 11-12-2015 | Updated Description section.                                        |
|            | In Policy section:  
  - 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."

- 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 / 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)."

<table>
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<td>Title revised from &quot;Charged-Particle (Proton or Helium Ion) Radiation Therapy&quot;</td>
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<td></td>
<td>In Policy section:</td>
</tr>
<tr>
<td></td>
<td>- In Item B, added &quot;or helium ion&quot; to read, &quot;Other applications of charged-particle irradiation with proton or helium ion beams are considered experimental / investigational. This includes, but is not limited to:&quot;</td>
</tr>
<tr>
<td></td>
<td>Updated Rationale section.</td>
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<td>Updated References section.</td>
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<tr>
<td>04-12-2017</td>
<td>In Policy section:</td>
</tr>
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<td></td>
<td>- Removed Item B 1, &quot;Clinically localized prostate cancer;&quot;</td>
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<tr>
<td></td>
<td>- Added Item C, &quot;Charged-particle irradiation with proton or helium ion beams for clinically localized prostate cancer is considered not medically necessary (see Policy Guidelines).&quot;</td>
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<td>- Added Policy Guidelines Item 2.</td>
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<td>Updated References section.</td>
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**REFERENCES**

1. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Charged particle (proton or helium ion) irradiation for uveal melanoma and for chordoma or chondrosarcoma of the skull base or cervical spine. TEC Assessments 1996;Volume 11:Tab 1.


Other References
1. Blue Cross and Blue Shield of Kansas Urology Liaison Committee, August 2013.
2. BCBSKS Medical Consultant, Practicing Board Certified Radiation Oncologist, March 2017.