Medical Policy

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

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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

Populations	Interventions	Comparators	Outcomes
• With skull-based tumor(s) (ie, cervical chordoma, chondrosarcoma)	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 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 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 determine 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.

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 May 24, 2018.

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

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 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. 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.

Charged-Particle (Proton or Helium Ion) Radiotherapy for Uveal Melanomas
Clinical Context and Test Purpose
The purpose of charged-particle (proton or helium ion) radiotherapy (RT) in patients who have uveal melanoma(s) is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does charged-particle RT improve the net health outcome in patients who have uveal melanoma(s)?

The following PICOTS were used to select literature to inform this review.

Patients
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.[1]

Interventions
The therapy being considered is charged-particle (proton or helium ion) RT.

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 proton beam therapy (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.

Timing
RT is used as part of first-line treatment for uveal melanoma. One- and 5-year outcomes are indicators of successful treatment.

Setting
Charged-particle therapy is administered in specially equipped treatment centers. PBT can be administered with or without stereotactic techniques.

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

More recently, 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 (eg, 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, 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 (odds ratio, 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=0.006). 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=0.02).

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=0.008). 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<0.02); tumor diameter of 12 to 18 mm (HR=2.48; 95% CI, 1.40 to 4.42; p<0.02); tumor diameter greater than 18 mm

(HR=6.41; 95% CI, 1.45 to 28.35; p<0.02); and proton treatment (HR=1.89; 95% CI, 1.06 to 3.37; 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 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) RT for Individuals with Skull-Based Tumors
Clinical Context and Test Purpose
The purpose of charged-particle (proton or helium ion) RT in patients who have skull-based tumors is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does charged-particle RT improve the net health outcome in individuals with skull-based tumors?

The following PICOTS were used to select literature to inform this review.

Patients
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.

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.

Timing
Local control and survival outcomes for charged-particle therapy for skull-base tumors have been reported at 1 year and 5 years.

Setting
Charged-particle therapy is administered in specially equipped treatment centers. PBT can be administered with or without stereotactic techniques.

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] More recently, 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.[8] 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 systematic review by Matloob et al (2016) evaluated the literature on PBT for skull-based chordomas.[9] Reviewers selected controlled trials and case series with more than 5 patients, with 12 studies meeting 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%.

Charged-Particle (Proton or Helium Ion) RT for Pediatric Central Nervous System Tumors
Clinical Context and Test Purpose
The purpose of charged-particle (proton or helium ion) RT in children who have CNS tumors is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does charged-particle RT improve the net health outcome in children with CNS tumors?

The following PICOTS were used to select literature to inform this review.

Patients
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.

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.

Timing
Local tumor control and OS would be assessed at 1 and 3 years.

Setting
Charged-particle therapy is administered in specially equipped treatment centers. PBT can be administered with or without stereotactic techniques.

Systematic Reviews
Leroy et al (2016) published a systematic review of the literature on PBT for the treatment of pediatric cancers.[10] Their findings included the following:

- For craniopharyngioma, three studies were identified two retrospective case series and one 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.
- For ependymoma, 1 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.
- For medulloblastoma, 1 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.
- For CNS germinoma, 1 retrospective case series was identified. They concluded that the evidence did not support or refute the use of PBT for this condition.

Case Series
Representative case series of PBT used to treat multiple pediatric CNS tumor types are described next. For example,

Bishop et al (2014) reported on 52 children with craniopharyngioma treated at 2 centers; 21 received PBT and 31 received IMRT.[11] Patients received a median dose of 50.4 gray (Gy). At 3 years, the OS rate 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. 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.[12] 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.[13] 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, 19-43 CGE). 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%, 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.[14] 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.[15]

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. The current evidence base is not sufficiently robust to draw conclusions about the efficacy of PBT for pediatric CNS tumors.

Charged-Particle (Proton or Helium Ion) RT for Pediatric Non-CNS Tumors
Clinical Context and Test 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 question addressed in this evidence review is: Does charged-particle RT improve net health outcomes in children with non-CNS tumors?

The following PICOTS were used to select literature to inform this review.

Patients
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.

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.

Timing
Local control and OS would be assessed at 1 and 3 years.

Setting
Charged-particle therapy is administered in specially equipped treatment centers. PBT can be administered with or without stereotactic techniques.

Case Series
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[16] and late toxicity outcomes in other solid tumors of childhood.[17,18]

Vogel et al (2018) published a retrospective case series of proton-based radiotherapy to treat nonhematologic head and neck malignancies in 69 pediatric patients.[19] Thirty-five of the patients had rhabdomyosarcoma and were treated with a median dose of 50.4 Gy (range 36.0-59.4 Gy) in 1.8 Gy fractions. A number of patients had Ewing sarcoma (n=10; median dose, 55.8 Gy; range, 55.8-65.6 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 mucosities (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 Ewin sarcoma, in addition to other histologies. The current evidence base is not sufficiently robust to draw conclusions about the efficacy of PBT for pediatric non-CNS tumors.

Charged-Particle (Proton or Helium Ion) RT for Localized Prostate Cancer
Clinical Context and Test 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 question addressed in this evidence review is: Does charged-particle RT improve the net health outcome in individuals with localized prostate cancer?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is patients who have locally advanced prostate cancer (ie, stages C or D1 [without distant metastases], also classified as T3 or T4). These tumors may be associated with a high rate of local recurrence despite maximal doses of conventional RT.

Interventions
The test being considered is charged-particle (proton or helium ion) RT.

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.

Timing
Local control and OS would be assessed at 1 and 5 years.

Setting
Charged-particle therapy is administered in specially equipped treatment centers. PBT can be administered with or without stereotactic techniques.

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. 20 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.[21] 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 methods of RT, which are now outmoded. The other RCT, known as Proton Radiation Oncology Group, was reported by Zietman et al (2005).[22] 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.[23] 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. 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.[24] 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 (eg, 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.[25] PBT, using CRT planning or IMRT, is used to provide dose escalation to a more well-defined target volume. However, dose escalation is more commonly offered with conventional EBRT using 3-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.[26]

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.

Charged-Particle (Proton or Helium Ion) RT for Non-Small-Cell Lung Cancer

Clinical Context and Test Purpose

The purpose of charged-particle (proton or helium ion) RT in patients 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 question addressed in this evidence review is: Does charged-particle RT improve the net health outcome for patients with NSCLC?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest is individuals with NSCLC. NSCLC is the most common cause 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.

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.

Timing

Local control and OS would be assessed at 1 and 5 years.

Setting

Charged-particle therapy is administered in specially equipped treatment centers. PBT can be administered with or without stereotactic techniques.

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 (total N=340 patients). No comparative studies, randomized or nonrandomized, were found. For these studies, stage I comprised 88. 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 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 (eg, 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.[28] 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.[29] 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 patients) and 6, C-ions (n=210 patients). The proton studies included 1 phase 2 study, 2 prospective studies, and 2 retrospective studies. The C-ion studies were all prospective and conducted at the same institution in Japan. No phase 3 studies were identified. Most patients had stage I disease, but because a wide variety of radiation schedules were used, comparisons of results were difficult, and local control rates were defined differently across studies. For proton therapy, 2-year local control rates were 74% and 85%, respectively, in the 2 studies reporting this outcome; 5-year local control rates ranged from 57% to 96% (4 studies). The 2-year OS rates ranged from 31% to 74%, and the 5-year OS rates ranged from 31% to 50% (2- and 5-year OS each reported in 4 studies). These local control and survival rates are equivalent or inferior to those achieved with SBRT. Radiation-induced pneumonitis was observed in about 10% of patients. For C-ion therapy, the overall local tumor control rate was 77%, and it was 95% when using a hypofractionated dosing schedule. The 5-year OS and cause-specific survival rates with C-ion therapy were 42% and 60%, respectively. Slightly better results were reported when using hypofractionation (50% and 76%, respectively). Reviewers concluded that, although the results with protons and heavier charged particles were promising, additional well-designed trials would be needed.

Nonrandomized Studies
To date, no RCTs comparing health outcomes in patients treated with PBT or with an alternative treatment have been identified.

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).[30] 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 322%). 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 grate 3 or 4 adverse events were rare. Poor OS was predicted by Karnofsky Performance Status score of 70 to 80, compared with 90 to 100 (HR=2.48; 95% CI, 1.33 to 4.65; p=0.004). 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=0.04), and a pretreatment tumor size greater than 7 cm (p=0.03). 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.[31] In 14 (70%) patients, tumors were clinically inoperable; overall median tumor diameter was 39.5 mm (range, 24-81 mm). PBT was administered 3.2 Gy per fraction. Median follow-up as 27.5 months (range, 12-72 months), and the 1-year OS rate was 95.0% (95% CI, 87.7 to 100%). At 2 years, the OS rate was 73.8% (95% CI, 53.9% to 93.7%); no statistically significant difference was found between operable (n=6) and inoperable patients (n=14) for 2-year OS (p=0.109), 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. No subsequent randomized or nonrandomized comparative studies have been published. Final results from a 2017 open-label phase 2 study included 5-year survival rates for patients who had PBT with concurrent chemotherapy.

Charged-Particle (Proton or Helium Ion) RT for Head and Neck Tumors, Other Than Skull-Based
Clinical Context and Test Purpose
The purpose of charged-particle (proton or helium ion) RT in patients 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 question addressed in this evidence review is: Does charged-particle RT improve the net health outcome in patients with head and neck tumors, other than skull-based?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is patients 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.

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.

Timing
Local control and OS would be assessed at 1 and 5 years.

Setting
Charged-particle therapy is administered in specially equipped treatment centers. PBT can be administered with or without stereotactic techniques.

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.[32] 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<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.

Zenda et al (2015) reported on late toxicity in 90 patients after PBT for nasal cavity, paranasal sinuses, or skull-based malignancies.[33] 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.

SUMMARY OF EVIDENCE

For individuals who have uveal melanoma(s) who receive charged-particle (proton or helium ion) radiotherapy, the evidence includes 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 a skull-based tumor(s) (ie, cervical chordoma, chondrosarcoma) who receive charged-particle (proton or helium ion) radiotherapy, the evidence includes observational studies and systematic reviews. Relevant outcomes are overall survival, disease-free survival, change in disease status, and treatment-related morbidity. A 2007 systematic review found a 5-year overall survival rate of 81% with PBT compared with 44% with surgery plus photon therapy. In 2016, a systematic review of observational studies found 5-year survival rates after 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 they tend to have small sample sizes. The available observational studies do not provide sufficient evidence on the efficacy of charged-particle therapy compared with other treatments (eg, intensity-modulated radiotherapy). The evidence is insufficient to determine the effects of the technology on health outcomes.

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

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, 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. No subsequent randomized or nonrandomized comparative studies were identified that would alter the conclusions of the TEC Assessment. 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 systematic review noted that the studies on charged-particle therapy were heterogenous in terms of the types of particles and delivery techniques used; further, there are no head-to-head trials comparing charged-particle therapy with 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)[34]:
  "...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."[35]

National Comprehensive Cancer Network
Prostate Cancer
National Comprehensive Cancer Network (NCCN) guidelines for prostate cancer (v.3.2018) 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.[36]

Non-Small Cell Lung Cancer
NCCN guidelines for NSCLC (v.4.2018) have been updated with the following for advanced-stage disease or palliation: "When higher doses (> 30 Gy) are warranted, technologies to reduce normal tissue irradiation (at least 3D-CRT [3-dimensioal conformal radiotherapy] and including IMRT and proton therapy as appropriate) may be used.[37]

Head and Neck Cancer
NCCN guidelines for head and neck cancers (v.2.2018) indicate 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.[38] The guidelines suggest that proton therapy can be considered for cancers of the paranasal sinuses and salivary glands if normal tissue constraints cannot be met by conventional photon radiotherapy.

American Society for Radiation Oncology
The American Society for Radiation Oncology (ASTRO) (2017) updated its model policy on the medical necessity requirements for the use of proton therapy.[39] ASTRO deemed the following disease sites those for which the evidence frequently supports the use of proton beam therapy:
- Ocular tumors, including intraocular melanomas
- Tumors that approach or are located at the base of the skull, including but not limited to chordoma and chondrosarcomas
- Primary or metastatic tumors of the spine where the spinal cord tolerance may be exceeded with conventional treatment or where the spinal cord has previously been irradiated
- Hepatocellular cancer
- Primary or benign solid tumors in children treated with curative intent and occasional palliative treatment of childhood tumors
- Patients with genetic syndromes making total volume of radiation minimization crucial such as but not limited to NF-1 patients and retinoblastoma patients
- Malignant and benign primary central nervous system tumors
- Advanced (eg, T4) and/or unresectable head and neck cancers
- Cancers of the paranasal sinuses and other accessory sinuses
- Nonmetastatic retroperitoneal sarcomas
- Re-irradiation cases (where cumulative critical structure dose would exceed tolerance dose).

The model policy also made a specific statement on proton beam therapy for treating prostate cancer: "..., ASTRO believes the comparative efficacy evidence of proton beam therapy with other

prostate cancer treatments is still being developed, and thus the role of proton beam therapy for localized prostate cancer within the current availability of treatment options remains unclear.

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

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

Table 1. Summary of Key Active Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT01617161	Proton Therapy vs. IMRT for Low or Intermediate Risk Prostate Cancer (PARTIQoL)	400	Dec 2026
NCT01230866	Study of Hypo-fractionated Proton Radiation for Low Risk Prostate Cancer	150	Dec 2020
NCT01993810	Comparing Photon Therapy To Proton Therapy To Treat Patients With Lung Cancer	560	Dec 2020
NCT02838602	Randomized Carbon Ions vs Standard Radiotherapy for Radioresistant Tumors (ETOILE)	250	May 2024
NCT02603341	Pragmatic Randomized Trial of Proton vs. Photon Therapy for Patients With Non-Metastatic Breast Cancer: A Radiotherapy Comparative Effectiveness (RADCOMP) Consortium Trial	1720	Nov 2030

NCT: national clinical trial.

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.**

CPT/HCPCS
61796	Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); 1 simple cranial lesion
61797	Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); each additional cranial lesion, simple (List separately in addition to code for primary procedure)
61798	Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); 1 complex cranial lesion
61799	Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); each additional cranial lesion, complex (List separately in addition to code for primary procedure)
63620	Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); 1 spinal lesion
63621	Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); each additional spinal lesion (List separately in addition to code for primary procedure)
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

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77520	Proton treatment delivery; simple, without compensation
77522	Proton treatment delivery; simple, with compensation
77523	Proton treatment delivery; intermediate
77525	Proton treatment delivery; complex

- 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-10 Diagnoses

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

10-06-2011	Policy added to the bcbsks.com web site.
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)."
	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: ▪ 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: ▪ Removed Item B 1, "Clinically localized prostate cancer;" ▪ 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)." ▪ 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: ▪ Removed ICD-9 codes.
	Updated References section.

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