Charged-Particle (Proton or Helium) Radiation Therapy

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Definitions of Decision Determinations

**Medically Necessary:** A treatment, procedure or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

**Investigational/Experimental:** A treatment, procedure or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

**Split Evaluation:** Blue Shield of California / Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a Split Evaluation, where a treatment, procedure or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Description

Charged-particle beams consisting of proton or helium ions are a type of particulate radiation therapy. They contrast with conventional electromagnetic (i.e. 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 (Bragg peak). Thus, radiation exposure of surrounding normal tissues is minimized.

Proton beam radiation therapy may be administered with or without stereotactic guidance. Stereotactic approaches are frequently utilized for uveal tract and skull-based tumors. For stereotactic techniques, three to five fixed beams of protons or helium ions are used.

**Policy**

Charged-particle irradiation with proton or helium ion beams may be considered **medically necessary** and a covered benefit in **any** of the following clinical situations:

- Primary therapy for melanoma of the uveal tract (iris, choroid, or ciliary body) and **both** of the following:
  - No evidence of metastasis or extrascleral extension
  - Tumor size up to 24 millimeters in largest diameter and 14 millimeters in height
- Postoperative therapy (with or without conventional high-energy x-rays) for residual localized tumor without metastasis in patients who have undergone biopsy or partial resection of **one** of the following:
  - Chordoma
  - Low-grade (I or II) chondrosarcoma of the basisphenoid region (e.g., skull-base chordoma or chondrosarcoma) or cervical spine
- Treatment of pediatric central nervous system tumors

Charged-particle irradiation with proton or helium beams is generally **not a covered service** for prostate cancer (clinically localized prostate cancer) because it is not cost-effective.

For requests for charged-particle irradiation with proton beams for the treatment of prostate cancer (clinically localized prostate cancer), Blue Shield will review the request in accordance with medical necessity criteria. If treatment is determined to be medically necessary, Blue Shield will apply cost-effectiveness criteria, which states that, if there are two or more medically necessary services that may be provided for an illness, injury or medical condition, Blue Shield will provide benefits based on the most cost-effective service. Since 3D-conformal radiation therapy (3D-CRT) or intensity modulated radiation therapy (IMRT) is more cost-effective than charged particle irradiation with proton beams, Blue Shield will provide benefits for 3D-CRT or IMRT for the treatment of clinically localized prostate cancer.

Other applications of charged-particle irradiation with proton beams are considered **investigational**, including, but not limited to:

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

Pediatric Central Nervous System Tumors

There are no data to define age parameters for the use of proton beam therapy in pediatric patients. Some studies using proton beam therapy in pediatric CNS tumors included mostly patients less than 3 years of age. However, experts cite the benefit of proton beam therapy in pediatric patients of all ages (<21 years of age).

Coding

The use of proton beam or helium beam radiation therapy typically consists of a series of CPT codes describing the individual steps required:

- Medical radiation physics: unlisted CPT code - 77399
- Clinical treatment planning: unlisted CPT code - 77299

The codes used for treatment delivery will depend on the energy source used, typically either photons or protons. For photons (i.e., with a Gamma Knife or LINAC device) nonspecific radiation therapy treatment delivery HCPCS codes may be used based on the voltage of the energy source (i.e., codes G6003-G6014).

When proton beam therapy is used, the following specific CPT codes are available:

- Treatment delivery (there are no specific CPT codes for helium ion radiation)
  - CPT code 77520: Proton treatment delivery; simple, without compensation
  - CPT code 77522: Proton treatment delivery; simple with compensation
  - CPT code 77523: Proton treatment delivery; intermediate
  - CPT code 77525: Proton treatment delivery; complex

Note: Codes for treatment delivery primarily reflect the costs related to the energy source used, and not physician work.

- Clinical treatment management: unlisted CPT code - 77499

Stereotactic charged particle radiosurgery would be reported with the stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator) codes for cranial lesions or spinal lesions (as applicable).

Internal Information

There is an MD Determination Form for this Medical Policy. It can be found on the following Web page:
http://myworkpath.com/healthcareservices/MedicalOperations/PSR_Determination_Pages.htm

Documentation Required for Clinical Review

- History and physical and/or radiation oncology consultation notes including:
Clinical justification for proton beam radiation treatment
- Past medical/surgical treatment(s) and responses
- Treatment plan
- Tumor location, size, number of lesions, grade (if applicable)
- Tumor node marker (TNM) classification (if applicable)
  - Pathology report(s)
  - Radiological reports within the past two months, including CTs and MRIs

Post Service
- Daily treatment records and progress notes

The materials provided to you are guidelines used by this plan to authorize, modify, or deny care for persons with similar illness or conditions. Specific care and treatment may vary depending on individual need and the benefits covered under your contract. These Policies are subject to change as new information becomes available.

**APPENDIX to Charged-Particle (Proton or Helium) Radiation Therapy Policy**

**Prior Authorization Requirements**

This service (or procedure) is considered **medically necessary** in certain instances and **investigational** in others (refer to policy for details).

For instances when the indication is **medically necessary**, clinical evidence is required to determine **medical necessity**.

For instances when the indication is **investigational**, you may submit additional information to the Prior Authorization Department.

Within five days before the actual date of service, the Provider MUST confirm with Blue Shield of California / Blue Shield of California Life & Health Insurance Company (Blue Shield) that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.
Questions regarding the applicability of this policy should also be directed to the Prior Authorization Department. Please call 1-800-541-6652 or visit the Provider Portal www.blueshieldca.com/provider.

**Evidence Basis for the Policy**

**Rationale**

Proton beam therapy (PBT) is a form of external beam radiation therapy (EBRT), also known as charged particle therapy. The theoretical advantages of protons and other charged-particle beams are that they may improve outcomes when the following conditions apply:

- Conventional treatment modalities do not provide adequate local tumor control
- Evidence shows local tumor response depends on the dose of radiation delivered
- 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 (RT) has been investigated in two general categories of tumors/abnormalities:

- 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 RT are impossible. These tumors/lesions include uveal melanomas, chordomas, and chondrosarcomas at the base of the skull and along the axial skeleton.
- 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 (i.e., stages C or D1 [without distant metastases], also classified as T3 or T4).

However, advances in photon-based RT such as 3-dimensional conformal RT (3D-CRT), intensity-modulated RT (IMRT), and stereotactic body radiotherapy (SBRT) also allow improved targeting of conventional therapy.

While PBT has been utilized in patients throughout the United States since the 1950’s, and although it has been shown to be effective in many malignancies, there is no published data clearly demonstrating superiority over conventional forms of RT (e.g., external photon beam therapy, electron beam therapy, or brachytherapy) (Brada et al., 2009).

A systematic review (Terasawa et al., 2009) of charged-particle radiation therapy for cancer concluded “evidence on the comparative effectiveness and safety of charged-particle radiation therapy in cancer is needed to assess the benefits, risks, and costs of treatment alternatives.”

The Emerging Technology Committee of the American Society for Radiation Oncology (ASTRO) published 2012 evidence-based recommendations (Allen et al., 2012) declaring a lack of evidence for PBT for malignancies outside of large ocular melanomas and chordomas. The recommendations stated:
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 [central nervous system] 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 patient's 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.

The following is a review of the literature of the major benign and malignant tumor sites where the role of PBT has been investigated.

**Ocular Tumors**

**Uveal Melanomas**

Charged-particle beam RT has been most extensively studied in uveal melanomas, in which the focus has been to provide adequate local control while preserving vision. Pooling data from three centers, Suit and Urie (1992) reported local control in 96% and 5-year survival of 80%, results considered equivalent to enucleation. A summary of results from the United Kingdom reported 5-year actuarial rates of 3.5% for local tumor recurrence, 9.4% for enucleation, 61.1% for conservation of vision of 20/200 or better, and 10.0% death from metastasis (Damato et al., 2005).

The National Cancer Institute (NCI, 2012) PDQ® advised that brachytherapy and PBT are forms of RT to treat ocular melanomas. Proton beam RT may be preferred to brachytherapy when used for larger tumors and tumors close to the fovea or optic disc, due to its dose distribution. An ASTRO report (Allen et al., 2012) also stated the evidence was sufficient to use PBT for the treatment of large melanomas that are unapproachable with brachytherapy or other RT methods.

**Age Related Macular Degeneration**

A randomized clinical trial was conducted by Zambarakji and colleagues (2006) to determine the safety and visual outcomes of 16-cobalt gray equivalent (CGE) or 24-CGE proton RT in 166 patients with choroidal neovascularization (CNV) secondary to age related macular degeneration (AMD). There were no significant differences in visual acuity or complications between the two RT methods.

In a systematic review of four RCTs and one case series (Bekkering et al., 2008), PBT was investigated for eye conditions, including CNV associated with AMD. In the trial that compared PBT to sham radiation, no significant differences in visual acuity were reported at 1 and 2 year follow-up. While one nonrandomized trial reported better vision outcomes, there were more complications with higher dosages of PBT. The case series reported stable to improved vision for 86% of patients at 3 months, and 61% at 18 months following PBT. The authors advised that the quality of the studies was poor and had only short-term follow-up. Further research was required.
The American Academy of Ophthalmology (AAO) summary benchmarks for preferred practice guidelines (2012) recommended various treatment options for AMD including observation, antioxidants and mineral supplements, intravitreal injections, photodynamic therapy and thermal laser photocoagulation surgery. However, the AAO did not discuss PBT as a treatment option for AMD.

**Choroidal Hemangioma**

While some studies investigating the use of PBT for choroidal hemangioma (Chan et al., 2010; Frau et al., 2004; Hocht et al., 2006; Levy-Gabriel et al., 2009; Zografos et al., 1998) report improvement of tumor regression and visual acuity following PBT; the studies are small and retrospective in nature.

In a report by Hayes Inc. (2004) regarding ocular tumors, including choroidal hemangiomas, the authors concluded there was a lack of evidence regarding PBT for choroidal hemangioma. Therefore, no conclusions could be established regarding the safety, efficacy, or appropriate clinical role of PBT for this indication (Hayes Inc., 2004).

Hocht et al. (2006) conducted a single-center, retrospective study of 44 consecutive patients with choroid hemangiomas treated with photon therapy (n=19) or PBT (n=25). While the authors reported that 91% of patients were treated successfully, there was no significant difference in outcomes between the two groups. The authors concluded that radiotherapy is effective in treating choroidal hemangiomas in reference to visual acuity and tumor thickness; however, the benefit of PBT could not be detected.

**Central Nervous System Tumors**

*Note: For Pediatric Central Nervous System Tumors see Pediatric Section later in the document.*

According to the National Institute of Neurological Disorders and Stroke (NINDS, 2012), central nervous system tumors include tumors that are located in the skull (i.e., intracranial), the base of the skull (i.e., skull-base tumors) or within or adjacent to the spinal cord. These tumors may be classified benign or malignant. Benign tumors include: acoustic neuromas, chondromyxoid fibroma, craniopharyngiomas, gangliomas, meningiomas, neurolemmomas, pituitary adenomas, and vestibular schwannomas. Malignant tumors include: chondrosarcomas, chordomas, medulloblastomas, metastatic tumors, primitive neuroectodermal tumors (PNETS), and sinonasal tumors. Gliomas are a category of CNS tumors and include: astrocytomas, brain stem gliomas, optic gliomas and mixed gliomas, ependymomas, oligodendrogliomas, PNETS, and subependymomas. Meningiomas, schwannomas, neurofibromas, pituitary tumors, and mesenchymal tumors are tumors located outside of the brain (extraxial) and spinal cord. Spinal cord tumors include (NINDS, 2012):

- Extradural tumors (originating in the vertebral body or the epidural space) and normally due to metastatic disease
- Intradural-extramedullary tumors (within the dura but outside the spinal cord) and include meningiomas, schwannomas, neurofibromas, and ependymomas
- Intradural-intramedullary tumors (originating from the spinal cord) and most commonly include astrocytomas and ependymomas, and rarely, lipomas
An evidence based review of PBT from ASTRO's emerging technology committee (Allen et al., 2012) stated the following:

Clinical data from PBT or mixed photon/PBT for base of skull tumors appear superior to previously published series of conformal photon radiotherapy; however, stereotactic photon radiosurgery may provide significant dosimetric and clinical advantage to standard conformal (3D or IMRT) radiotherapy techniques. Overall, more clinical data (published clinical trials) are needed to fully establish the role of PBT in CNS tumors.

Chondrosarcomas and Chordomas of the Skull Base

Chondrosarcomas and chordomas of the skull base are rare primary malignant tumors that are primarily treated by surgery and postoperative RT. Earlier evidence suggested that charged-particle beam irradiation is at least as effective as, and may be superior to, alternative therapies, including conventional radiation or resection to treat chordomas or chondrosarcoma of the skull base or cervical spine (Suit & Urie, 1992). A Blue Cross Blue Shield Association (BCBSA) Technology Evaluation Center (TEC) Assessment completed in 1996 reached the same conclusions.

A systematic review of charged particle therapy found that local tumor control rate and 5-year overall survival for skull-based chordomas treated with proton therapy were 63% and 81%, respectively, compared to postsurgical treatment with conventional photon therapy with reported local tumor control rates and 5-year overall survival of 25% and 44%, respectively, and surgery followed by fractionated stereotactic radiotherapy, which resulted in 5-year local tumor control of 50% (Lodge et al., 2007). A summary of tumor control in published proton therapy studies of chondrosarcoma of the skull base was 95% 5-year local tumor control, similar to the results of conventional therapy (Lodge et al., 2007).

More recently, many small case series and retrospective reviews have supported PBT for the treatment of these tumors (Amichetti et al., 2010; Habrand et al., 2008; Noel et al., 2005; Rutz et al., 2008). However, there are limitations to PBT studies and no randomized trials (Di Maio et al., 2011), as well as, no evidence of superiority of PBT over conventional therapy in these tumors (Brada et al., 2009). Comparison to older historical data of conformal photon RT might imply some benefit to PBT, however, stereotactic radiosurgery (SRS) outcomes compare more favorably with PBT results. Despite the mixed evidence, due to the rarity of these tumors and their adjacency to critical CNS structures therefore impairing the ability to completely surgically remove them, PBT has become an established treatment option.

The National Comprehensive Cancer Network (NCCN) Guidelines™ for Bone Cancer (Version 2.2013) advised that specialized techniques including IMRT, particle beam RT with protons, carbon ions or other heavy ions, SRS, or fractionated- SRS should be considered in order to allow high-dose therapy while maximizing normal tissue sparing. In their discussion of RT, the NCCN advised that PBT alone or in combination with photon beam RT has been associated with excellent tumor control and long-term survival in the treatment of patients with low-grade skull base and cervical spine chondrosarcomas. Additionally, for sarcoma, PBT has been shown to be effective for local control in some patients with unresectable or incompletely resected osteosarcoma.
Gliomas

The published literature is limited and mixed in regard to treatment of gliomas with PBT over conventional treatment. One study (Fitzek et al., 2001) reported no significant benefit to PBT over conventional treatment. Another small study showed that PBT had a slightly longer median survival of 20 months, when compared to standard photon therapy (Fitzek et al., 1999). Overall, there is no data supporting significant clinical benefit of PBT for the treatment of gliomas.

Acoustic Neuroma

Proton beam RT has been proposed for the treatment of acoustic neuromas, also known as vestibular schwannomas or neurolemmomas, which are benign CNS tumors. These conditions can be treated with EBRT including 3D-CRT, IMRT, and SRS. A systematic review of 58 studies (prospective or retrospective) by Bassim and colleagues (2010) evaluated the outcomes of RT of vestibular schwannomas. Radiation therapies included gamma-knife radiation (42.9%), linear accelerator (LINAC) (35.6%), PBT (6.8%), mixed therapy (6.8%) and other treatments (1.7%). Due to the poor methodology of the studies including various outcome measures, lack of reporting standardization, and short-term follow-ups, conclusions could not be drawn and meta-analysis could not be performed. Additionally, the patient population had considerable overlap in patient populations from study to study. The authors concluded that RT as a primary treatment modality should be used cautiously.

In a retrospective review by Vernimmen et al. (2009) hypofractionated stereotactic PBT was evaluated for the treatment of acoustic neuroma in 51 patients. The indications for PBT included postoperative recurrence, inoperability, unresectability or patient's choice. Patients were followed between 24 to 129 months with a mean of 72 months. Local control was reported in 96% of patients with two patients having progression. Freedom from progression was 98% at 2 and 5 years, and 87% at 10 years. Facial nerve functional preservation was 93.5% and 90.5% at 2 years and 5 years, respectively, and stable for up to 10 years. Trigeminal nerve preservation was 96% and 93% at 2 years and 5 years, respectively, and stable for up to 10 years. In the patients with useful hearing prior to PBT, the 2-year preservation rate was 74% and the 5-year rate was 42% and remained stable at 10 years.

More recently, in a critical review by Murphy and Suh (2011), the radiotherapeutic options for treating vestibular schwannomas, which included single-session SRS, fractionated conventional RT, fractionated stereotactic radiotherapy, and PBT, were summarized. The authors advised that comparisons of these RT modalities were based on single-institution experiences and reported excellent tumor control rates of 91% to 100%. While earlier studies showed that using PBT for the treatment of vestibular schwannomas had local control rates of 84% to 100%, hearing preservation rates were unfavorable at 33% to 42%. The authors concluded that due to mixed data regarding ideal hearing preservation therapy, inherent bias in the patient selection, and outcome analysis differences, the comparison of these RT techniques was difficult.

Pituitary Adenoma

Pituitary adenomas have also been treated with PBT however; conventional techniques and relatively safe doses of radiation also yield excellent results (Ronson et al., 2006).
Meningiomas

While meningiomas have been treated with PBT with good outcomes (Boskos et al., 2009), there is no evidence that PBT treatment is superior to conventional therapy.

Prostate Cancer

One of the earliest published trials on PBT to treat prostate cancer was a randomized clinical trial published in 1995 comparing outcomes of conventional RT with or without an additional radiation “boost” of PBT (Shipley et al., 1995). Patients treated in the control arm received a total of 67.2 gray (Gy), while those in the “high-dose” arm received a total of 75.6 Gy (these doses are below those often currently given). This study, initiated in 1982, was designed to determine if this dose escalation of 12.5% would increase the 5-year and 8-year rates of local control, disease-specific survival, overall survival, or total tumor-free survival with acceptable adverse effects. There was no statistically significant difference in any of the outcomes measured. On subgroup analysis, patients with poorly differentiated cancer achieved a statistically significant improvement in the rate of local control but not in other outcomes, such as overall survival or disease-specific survival. Patients in the high-dose arm experienced a significantly increased rate of complications, most notably rectal bleeding. Subsequently, new sophisticated treatment planning techniques, referred to as 3D-CRT or IMRT, have permitted dose escalation of conventional RT to 80 Gy, a dose higher than that achieved with PBT in the above study (Hanks, 1995; Cox, 1995). Furthermore, these gains were achieved without increasing radiation damage to adjacent structures.

Many of the reports published document the experience of the Loma Linda University Medical Center (Loma Linda, CA). In 2004, investigators at Loma Linda reported their experience with 1,255 patients with prostate cancer who underwent 3D-CRT-proton beam RT (Slater et al., 2004). Outcomes were measured in terms of toxicity and biochemical control, as evidenced by prostate specific antigen (PSA) levels. The overall biochemical disease-free survival rate was 73% and 90% in patients with an initial PSA less than or equal to 4.0. The long-term survival outcomes were comparable with those reported for other modalities intended for cure.

From the published literature, it appears dose escalation is an accepted concept in treating organ-confined prostate cancer (Nilsson et al., 2004). Proton beam therapy, using 3D-CRT planning or IMRT is one technique 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. The 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, as the bladder and rectal tissues are now exposed to even higher doses. The accuracy of dose delivery applies to both conventional and PBT (Kuban et al., 2003). Ongoing randomized studies are examining the outcomes of dose escalation for conventional EBRT (Michalski et al., 2004).

Zietman and colleagues (2005) reported that while there had been no randomized studies, and only comparative planning studies, reports from treating large numbers of patients with localized prostate cancer using PBT demonstrated results comparable to those obtained with alternative techniques and clinical efficacy was growing (Zietman et al., 2005; Zietman, 2007). Whether
there would be gains by treating with PBT to the doses currently used in IMRT therapy (around 79 to 81 Gy) was not known. Zietman also hypothesized that delivery of 91.8 Gy could yield a 10% improvement in 5-year freedom from biochemical failure for men with intermediate risk (15% to 20% of those with prostate cancer) of disease.

In 2010, Zietman and colleagues tested the hypothesis (described above) that increasing radiation dose delivered to men with early-stage prostate cancer improves clinical outcomes. Men (n=393) with T1b to T2b prostate cancer and PSA ≤ 15 ng/mL were randomly assigned to a total dose of either 70.2 Gy equivalents (GyE; conventional) or 79.2 GyE (high). Local failure, biochemical failure, and OS were outcomes. Patients were followed up a median of 8.9 years. The men receiving high-dose RT were significantly less likely to have local failure. In comparison, the 10-year ASTRO biochemical failure rates were 32.4% for conventional-dose RT and 16.7% for high-dose RT. This difference held when only those with low-risk disease (n=227; 58% of total) were examined: 28.2% for conventional and 7.1% for high dose. There was a strong trend in the same direction for the intermediate-risk patients (n=144; 37% of total; 42.1% versus 30.4%). Eleven percent of patients subsequently required androgen deprivation for recurrence after conventional dose compared with 6% after high dose. There was no difference in overall survival rates between the treatment arms (78.4% versus 83.4%). Two percent of patients in both arms of the study experienced late grade ≥ 3 genitourinary toxicity, and 1% of patients in the high-dose arm experienced late grade ≥ 3 gastrointestinal toxicity.

A 2008 Agency for Healthcare Research and Quality (AHRQ) comparative effectiveness review of therapies for clinically localized prostate cancer indicated, based on non-randomized comparisons, the absolute rates of outcomes after proton radiation appeared similar to other treatments (Wilt et al., 2008).

Brada and colleagues (2009) reported on an updated systematic review of published peer-reviewed literature for proton beam and concluded it was devoid of any clinical data demonstrating benefit in terms of survival, tumor control, or toxicity in comparison with best conventional treatment for any of the tumors so far treated, including prostate cancer. They noted the current lack of evidence for benefit of protons should provide a stimulus for continued research with well-designed clinical trials.

In another review article, Efstathiou and colleagues (2009) concluded the current evidence did not support any definitive benefit to PBT over other forms of high-dose CRT in the treatment of localized prostate cancer. They also commented on uncertainties surrounding the physical properties of PBT, perceived clinical gain, and economic viability.

A Hayes Inc., Medical Technology Directory report (2006; updated 2010) concluded that while there was some evidence that PBT is safe and can effectively provide tumor control in prostate cancer patients, there was limited research and methodological limitations to the studies available. Further, definitive selection criteria for PBT use in prostate cancer had not been established and RCTs comparing clinical outcomes of patients treated with PBT versus those treated by conventional methods were needed.

The 2010 Blue Cross Blue Shield Association (BCBSA) Technology Evaluation Center (TEC) Assessment compared the effects of PBT, with or without photon EBRT, against alternative RT modalities and other treatments of prostate cancer. The assessment concluded PBT as a boost to
photon EBRT or PBT without photon EBT in the treatment of prostate cancer did not meet TEC criteria. Further, it has not been established whether PBT improves outcomes in any setting in prostate cancer. The following is a summary of the main findings:

- A total of nine studies were included in the review; four were comparative and five were noncomparative. Five studies included patients who received x-ray EBRT plus proton beam boost, one study included a mix of patients with separate results for those given only protons and those given x-rays plus protons, one mixed study lacked separate results and two studies only included patients receiving PBT without x-ray EBRT. Among studies using proton beam boost, only one study provided survival outcome data for currently applicable methods of x-ray EBRT. Thus, data on survival outcomes were insufficient to permit conclusions about effects. Three studies on proton beam boost and two studies on proton beam alone gave data on biochemical failure. Prostate cancer symptoms were addressed in two studies and quality of life in one. Eight of nine studies reported on genitourinary and gastrointestinal toxicity.

- There was inadequate evidence from comparative studies to permit conclusions for any of the comparisons considered. Ideally, randomized, controlled trials (RCTs) would report long-term health outcomes or intermediate outcomes that consistently predict health outcomes. Of the four comparisons, there was one good quality randomized trial each for two of them. One showed significantly improved incidence of biochemical failure, an intermediate outcome of uncertain relation to survival, for patients receiving high-dose proton beam boost compared with conventional dose proton boost. No difference between groups has been observed in overall survival. Grade 2 acute gastrointestinal toxicity was significantly more frequent in the group receiving high-dose proton beam boost but acute genitourinary toxicity and late toxicities did not significantly differ. The other trial found no significant differences between patients receiving x-ray versus proton beam boost on overall survival or disease-specific survival, but rectal bleeding was significantly more frequent among patients who had a proton beam boost. Good quality comparative studies were lacking for other comparisons addressed in the TEC Assessment.

In a 2010 review, Kagan and Schulz commented about the lack of data related to improved outcomes with use of PBT for prostate cancer and made a number of additional important observations. They noted while projected dose distribution for PBT suggested reduced rates of bladder and rectal toxicity, toxicity reports for PBT in prostate cancer are similar to those for IMRT. The authors also commented that the role of dose escalation and the optimum doses and dose rates are yet to be established. Finally, they reported the potential for treatment errors with PBT is much greater than with photons.

Sheets et al. (2012) evaluated the comparative morbidity and disease control of prostate cancer of IMRT, PBT and 3D-CRT for primary prostate cancer treatment. Main outcomes were rates of gastrointestinal and urinary morbidity, erectile dysfunction, hip fractures and additional cancer therapy. In comparison between IMRT and PBT (n=1368), IMRT patients had a lower rate of gastrointestinal morbidity. There were no significant differences in rates of other morbidities or additional therapies between IMRT and PBT. Additionally, the authors suggested that IMRT may be associated with improved disease control without compromising morbidity compared
with conformal radiation therapy, although proton therapy does not appear to provide additional benefit."

In October of 2012, the California Technology Assessment Forum (CTAF) concluded that while PBT has been widely used for the treatment of localized prostate cancer, there was "limited evidence of comparative efficacy with other prostate cancer treatments" (Walsh, 2012). Additionally, "the role of PBT for localized prostate cancer within the current list of treatment options remains unclear." The CTAF recommendation stated that PBT therapy for localized prostate cancer did not meet CTAF criteria 4 or 5 for safety, efficacy and improvement in health outcomes.

Yu and colleagues (2013) performed a retrospective study of all Medicare beneficiaries aged greater than or equal to 66 years of age who received PBT or IMRT for prostate cancer during 2008 and/or 2009. The main outcome measures were receipt of PBT or IMRT, Medicare reimbursement for each treatment, and early genitourinary, gastrointestinal, and other toxicity. The study identified 27,647 men; 553 (2%) received PBT and 27,094 (98%) received IMRT. It was noted that patients receiving PBT were younger, healthier, and from higher socioeconomic areas than patients receiving IMRT. The authors found that PBT was associated with a statistically significant reduction in genitourinary toxicity at 6 months compared with IMRT, however at 12 months post-treatment there was no significant difference in genitourinary toxicity. Further, no significant differences were found in gastrointestinal or other toxicities at 6 and 12 months post-treatment. The authors concluded that while PBT is "substantially more costly than IMRT", there was "no difference in toxicity" in these Medicare beneficiaries with prostate cancer at 12 months post-treatment.

Recently, the emerging technology committee of ASTRO published an evidence-based review of PBT (as referenced earlier), which concluded that, although PBT holds promise, there is insufficient evidence that it is superior or even comparable to photon radiotherapy in most cancer sites, including prostate cancer (Allen et al., 2012).

The National Cancer Institute (2013) in a discussion of prostate cancer treatment options advised that while PBT may theoretically improve the therapeutic ratio of prostate radiation, no RCTs have been conducted to compare efficacy and toxicity with other forms of RT.

The 2013 NCCN Guidelines for prostate cancer (Version 1.2013) noted that "3D conformal RT or IMRT techniques should be used to treat prostate cancer. IGRT is required if dose is >/= 78 Gy. IMRT, if available, is preferred." Further in the discussion section of the Guidelines, the following was stated:

Proton beams can be used as an alternative radiation source. Theoretically, protons may reach deeply-located tumors with less damage to surrounding tissues. However, proton therapy is not recommended for routine use at this time, since clinical trials have not yet yielded data that demonstrates superiority to, or equivalence of, proton beam and conventional external beam for treatment of prostate cancer.

In summary, results of proton beam studies for clinically localized prostate cancer have shown similar results and outcomes when compared to other radiation treatment modalities. Given these
conclusions, along with information that PBT is generally more costly than alternative radiation treatments, PBT is considered not medically necessary for treating prostate cancer.

**Non-Small Cell Lung Cancer**

A systematic review (Terasawa et al., 2009) of charged-particle radiation therapy for cancer concluded “evidence on the comparative effectiveness and safety of charged-particle radiation therapy in NSCLC cancer is needed to assess the benefits, risks, and costs of treatment alternatives.”

The 2010 TEC Assessment also focused on non-small cell lung cancer (NSCLC) and addressed the key question of how health outcomes (overall survival, disease-specific survival, local control, disease-free survival, and adverse events) with PBT compared with outcomes observed for SBRT, which is an accepted approach for using RT to treat NSCLC.

- Eight PBT case series were identified in the Assessment which included a total of 340 patients. No comparative studies, randomized or non-randomized, were found. For these studies, stage I comprised 88.5% of all patients, and only 39 patients were in other stages or had recurrent disease. Among seven studies reporting 2-year overall survival, probabilities ranged between 39% and 98%. At 5 years, the range across five studies was 25% to 78%. It is unclear if the heterogeneity of results can be explained by differences in patient and treatment characteristics.

- The report concluded that the evidence is insufficient to permit conclusions about the results of PBT for any stage of NSCLC. All PBT studies are case series; there are no studies directly comparing 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 treatment regimens. The PBT studies were similar in patient age, but there was great variability in percent within stage IA, sex ratio, and percent medically inoperable. There is a high degree of treatment heterogeneity among the PBT studies, particularly with respect to planning volume, total dose, number of fractions, and number of beams. Survival results are highly variable. It is unclear whether the heterogeneity of results can 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 may be distorted by confounding. In the absence of RCTs, the comparative effectiveness of PBT and SBRT is uncertain.

- The 2010 TEC Assessment noted that adverse events reported after PBT generally fell into the following 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.

Pijls-Johannesma and colleagues (2010) conducted a systematic literature review through November 2009 examining the evidence on the use of particle therapy in lung cancer. Study inclusion criteria included that the series had at least 20 patients and a follow-up period \( \geq 24 \) months. Eleven studies, all dealing with NSCLC, mainly stage I, were included in the review, five studies investigating protons (n=214) and six studies C-ions (n=210). The proton studies...
included one phase 2 study, two prospective studies and two 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 1 disease, however, a wide variety of radiation schedules were used making comparisons of results difficult and local control rates were defined differently across studies. For proton therapy, 2- to 5-year local tumor control rates varied in the range of 57%-87%. The 2- and 5-year overall survival and 2- and 5-year cause-specific survival rates were 71% to 74% and 45% and 46%, respectively. These local control and survival rates are equivalent to or inferior to those achieved with stereotactic radiation therapy. Radiation-induced pneumonitis was observed in about 10% of patients. For C-ion therapy, the overall local tumor control rate was 77%, but it was 95% when using a hypofractionated radiation schedule. The 5-year overall survival and cause-specific survival rates were 42% and 60%, respectively. Slightly better results were reported when using hypofractionation, 50% and 76%, respectively. The authors concluded that the results with protons and heavier charged particles are promising, but that because of the lack of evidence, there is a need for further investigation in an adequate manner with well-designed trials.

An indirect meta-analysis reviewed in the TEC Assessment found a nonsignificant difference of 9 percentage points between pooled 2-year overall survival estimates favoring SBRT over PBT (Grutters et al., 2010). The non-significant 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 if this indirect meta-analysis adequately addressed the possible influence of confounding on the comparison of SBRT and PBT.

The NCCN Guidelines for Non-Small Cell Lung Cancer (Version 3.2012) states that “use of more advanced technologies is appropriate when needed to deliver adequate tumor doses while respecting normal tissue dose constraints.” These technologies include PBT in addition to others. “A non-randomized retrospective comparison study in patients with locally advanced NSCLC showed that PBT reduced esophagitis and pneumonitis despite higher doses compared to 3D-CRT or IMRT and a prospective study reported favorable outcomes compared to historical results.”

**Head and Neck Tumors, Other Than Skull-Based Chordoma or Chondrosarcoma**

Earlier studies on the use of PBT for head and neck tumors (other than skull-based chordoma or chondrosarcoma) is scant and consisted of dosimetric planning studies for nasopharyngeal carcinoma (Taheri-Kadkhoda et al., 2008), and a case series of 91 patients who received combined proton and photon radiotherapy for advanced paranasal sinus tumors (Weber et al., 2006).

A published report from AHRQ (Samson et al., 2010) compared the effectiveness and safety of radiotherapy treatments for head and neck cancer. Four radiotherapy modalities (IMRT, 3D-CRT, two-dimensional RT, and PBT) were compared for effectiveness. Four key questions were evaluated including: adverse events and quality of life, tumor control and patient survival, specific patient and tumor characteristics, as well as, user experience, target volume delineation, or dosimetric parameters. When comparing PBT to other radiation techniques, the authors reported:
The strength of evidence is insufficient as there were no studies comparing proton beam therapy to any other radiotherapy modality. Therefore, no conclusions can be reached regarding the comparative effectiveness of proton beam therapy for any of the four key questions.

Ramaekers and colleagues (2011) conducted a systematic review and meta-analysis comparing evidence evaluating the effectiveness of carbon-ion, proton and photon RT for head and neck cancer. Evidence was gathered from 86 observational studies (seven were proton) and eight comparative in-silico studies evaluating tumor control, survival and late treatment toxicity. Tumor control and survival were similar between PBT and the best available photon RT, except in paranasal and sinonasal cancer. While the available clinical data for PBT was limited in the in-silico studies, toxicity tended to be lower for proton compared to photon RT. The authors concluded that the data quality for PBT was poor, and recommended the construction of an international particle therapy register to facilitate definitive comparisons.

van de Water et al. (2011) performed an evaluation of studies comparing photon RT to PBT in the treatment of paranasal sinus cancer, nasopharyngeal cancer, oropharyngeal, hypopharyngeal, and/or laryngeal cancer cases. Some studies used sophisticated photon and proton techniques including intensity-modulated photon therapy versus intensity-modulated proton therapy (IMPT). The results indicated there is the potential for significantly lower normal tissue doses with protons, and similar or better target coverage; IMPT offering the greatest advantage. The authors concluded that the study results require confirmation in properly designed clinical trials.

An evaluation of PBT was conducted by the Subcommittee of ASTRO’s Emerging Technologies (Allen et al., 2012). The authors advised "Currently, there is insufficient data to recommend PBT for routine head and neck radiation therapy outside of clinical trials."

Abdominal Tumors

Radiotherapy plays a role in two different settings for gastrointestinal malignancies. In diseases that require surgery as a primary role in their treatment (rectum, gastric, and esophagus), RT is used either as a neoadjuvant or an adjuvant role delivering moderate dose treatment (45 Gy) to a large volume to provide downstaging and microscopic coverage (Bush et al., 2004).

For hepatocellular, esophageal, and pancreatic cancers are treated definitively with RT, and higher doses to the targeted tissue, sparing normal tissue, is important and more relevant. While theoretically PBT may be useful in these cancers, for esophageal and pancreatic tumors there is minimal evidence on the clinical use of PBT (Hayes Inc., 2010; Mizumoto et al., 2010; Welsh et al., 2011).

The only area where PBT has been extensively investigated is hepatocellular carcinoma (HCC). There are a number of case series, predominantly from Asia, describing initial results using PBT in HCC (Bush et al., 2011; Hata et al., 2007; Fukumitsu et al., 2009; Nakayama et al., 2009; Sugahara et al., 2010). Proton beam therapy has been primarily studied when HCC is unresectable, and in tumors not amenable to radiofrequency ablation.

According to the ASTRO report (Allen et al., 2012), while there is promise that PBT is an alternative option to photon based approaches, more rigorous study and prospective clinical trials are necessary to define the differences in toxicity and efficacy between protons and photons.
Other Malignant Tumors

The AHRQ report (2009) advised for bladder cancer and uterine cancers, there is insufficient evidence to draw definitive conclusions as to whether PBT has any advantages over conventional therapies.

In a Hayes Inc. report (2006; updated 2010) regarding PBT for thoracic and abdominal organs there were was limited evidence and few studies regarding use of PBT for NSCLC, bladder, breast, esophageal and cervical cancer. While limited studies suggested that PBT had a positive treatment effect, the magnitude of the effect of PBT on local tumor control or survival could not be determined. The authors noted that the studies did not reflect the outcomes of PBT when used alone. Other methodological limitations included small sample populations/sizes, changes in protocol and treatment sites over time, and heterogeneous study groups.

Due to minimal data on the clinical use of PBT in other malignancies, PBT is considered investigational.

Pediatric Central Nervous System Tumors

Radiation therapy is an integral component of the treatment of many pediatric CNS tumors including high-grade gliomas, primitive neuroectodermal tumors (PNETs), medulloblastomas, ependymomas, germ cell tumors, some craniopharyngiomas and subtotally resected low-grade astrocytomas (Hoffman & Yock, 2009). Children who are cured of their tumor experience long-term sequelae of radiation treatment, which may include developmental, neurocognitive, neuroendocrine, and hearing late effects. Radiation to the cochlea may lead to loss of hearing at doses greater than 35 to 45 Gy in the absence of chemotherapy, and the risk of ototoxicity is increased in children who receive ototoxic platinum-based chemotherapy regimens (Cotter et al., 2012). Craniospinal irradiation, most commonly used in the treatment of medulloblastoma, has been reported to lead to thyroid dysfunction, and damage to the lungs, heart and intestinal tract (Cotter et al., 2012). In addition, patients who receive radiation at a young age are at an increased risk of developing radiation-induced second tumors compared to their adult counterparts (Cotter et al., 2012).

The development of more conformal radiation techniques has decreased inadvertent radiation to normal tissues; however, while IMRT decreases high doses to nearby normal tissues, it delivers a larger volume of low- and intermediate-dose radiation. Proton beam radiotherapy eliminates the exit dose to normal tissues, and may eliminate approximately 50% of radiation to normal tissue.

A 2012 five-year update (De Ruysscher et al., 2012) of a systematic review (Lodge et al., 2007) drew similar conclusions to the original review, that except for rare indications such as childhood cancer, the gain from proton RT in clinical practice remains controversial.

A 2012 review of the literature by Cotter and colleagues on the use of proton radiotherapy for solid tumors of childhood, the most common of which are CNS tumors, offered the following summaries of studies and conclusions.

- Experience with the use of PBT for medulloblastoma, the most common malignant CNS tumor in the pediatric population, is relatively large. Although data on the late effects
comparing proton to photon therapy are still maturing, dosimetric studies suggest that proton therapy in medulloblastoma should lead to decreased long-term toxicity.

- Gliomas in locations where surgical resection can lead to unacceptable morbidity (e.g. optic nerves or chiasm, brainstem, diencephalon, cervical-medullary junction), are often treated with chemotherapy in young patients in order to delay radiation, with radiation to a dose of 54 Gy being reserved for unresectable lesions.

- Loma Linda University Medical Center reported on proton radiation in the treatment of low-grade gliomas in 27 pediatric patients (Hug et al., 2002). Six patients experienced local failure; acute side effects were minimal. After a median follow-up of 3 years, all of the children with local control maintained performance status.

- A dosimetric comparison of protons to photons for seven optic pathway gliomas treated at Loma Linda showed a decrease in radiation dose to the contralateral optic nerve, temporal lobes, pituitary gland and optic chiasm with the use of protons (Fuss et al., 1999).

- Massachusetts General Hospital reported on the use of protons in 17 children with ependymoma (MacDonald et al., 2008). Radiation doses ranged from 52.2 to 59.4 cobalt Gy equivalent. Median follow-up was 26 months, and local control, progression-free survival, and overall survival rates were 86%, 80%, and 89%, respectively. Local recurrences were seen in patients who had undergone subtotal resections. No deleterious acute effects were noted; the authors stated that longer follow-up was necessary to assess late effects. In the same study, two IMRT plans were generated to measure for dosimetric advantages with the use of protons for the treatment of infratentorial and supratentorial ependymomas. In both locations, the use of proton radiation provided significant decrease in dose to the whole brain, and specifically the temporal lobes. In addition, as compared to IMRT, proton radiation better spared the pituitary gland, hypothalamus, cochlea, and optic chiasm while providing equivalent target coverage of the resection cavity.

- Craniopharyngiomas are benign lesions, which occur most commonly in children in the late first and second decades of life (Cotter et al., 2012). Massachusetts General Hospital reported on five children treated with combined photon/proton radiation or proton radiation alone with a median follow-up of 15.5 years (Fitzek et al., 2006). All five patients achieved local control without evidence of long-term deficits from radiation in endocrine or cognitive function. Loma Linda reported on the use of proton radiation in 16 patients with craniopharyngioma who were treated to doses of 50.4 to 59.4 cobalt Gy equivalents (Luu et al., 2006). Local control was achieved in 14 of the 15 patients with follow-up data. Follow-up was five years; three patients died, one of recurrent disease, one of sepsis, and one of a stroke. Among the survivors, one patient developed panhypopituitarism 36 months after debulking surgeries and radiation, a second patient had a cerebrovascular accident 34 months after combined primary treatment, and a third patient developed a meningioma 59 months after initial photon radiation, followed by salvage resection and proton radiation.

Massachusetts General Hospital reported on the use of protons in the treatment of germ cell tumors in 22 patients, 13 with germinoma and 9 with non-germinomatous germ cell tumors (NGGCTs) (MacDonald et al., 2011). Radiation doses ranged from 30.6 to 57.6 cobalt Gy
equivalents. All of the NGGCT patients received chemotherapy prior to radiation therapy. Twenty-one patients were treated with cranial spinal irradiation, whole ventricular radiation therapy, or whole brain radiation followed by an involved field boost; one patient received involved field alone. Median follow-up was 28 months. There were no CNS recurrences and no deaths. Following radiation therapy, two patients developed growth hormone deficiency and two 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 done. Proton radiotherapy provided substantial sparing to the whole brain and temporal lobes, and reduced doses to the optic nerves.

Moeller and colleagues (2011) reported on 23 children who were enrolled in a prospective observational study and treated with PBT for medulloblastoma between the years 2006 to 2009. As hearing loss is common following chemoradiotherapy for children with medulloblastoma, the authors sought to compare whether proton radiotherapy led to a clinical benefit in audiometric outcomes (since, compared to photons, protons reduce radiation dose to the cochlea for these patients). The children underwent pre- and 1-year post-radiotherapy pure-tone audiometric testing. Ears with moderate-to-severe hearing loss prior to therapy were censored, leaving 35 ears in 19 patients available for analysis. The predicted mean cochlear radiation dose was $30^{60}$ Co-Gy Equivalents (range 19 to 43). Hearing sensitivity significantly declined following radiotherapy across all frequencies analyzed (p<0.05). There was partial sparing of mean post-radiation hearing thresholds at low-to-midrange frequencies; the rate of high-grade (grade 3 or 4) ototoxicity at 1 year was 5%. The authors compared this to a rate of grade 3 to 4 toxicity following IMRT of 18% in a separate case series. The authors concluded that preservation of hearing in the audible speech range, as observed in their study, may improve both quality of life and cognitive functioning for these patients.

Merchant and colleagues (2008) sought to determine whether proton radiotherapy has clinical advantages over photon radiotherapy in childhood brain tumors. 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, and the data were averaged and compared based on treatment modality (protons versus photons) using dose-cognitive effects models. Clinical outcomes were estimated over 5 years. With protons (compared to photons), relatively small critical normal tissue volumes (e.g. cochlea and hypothalamus) were spared from radiation exposure when not adjacent to the primary tumor volume. Larger normal tissue volumes (e.g. 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 intelligence quotient (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 versus 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
A dose would result in long-term, improved clinical outcomes for children with medulloblastoma, craniopharyngioma, and glioma of the optic pathway.

**Pediatric Non-Central Nervous System Tumors**

There is scant data on the use of PBT in pediatric non-CNS tumors, which includes dosimetric planning studies in a small number of pediatric patients with parameningeal rhabdomyosarcoma (Kozak et al., 2009) and late toxicity outcomes in other solid tumors of childhood (Merchant, 2009; Timmermann, 2010).

**Clinical Input**

Clinical input was obtained by BCBSA from two physician specialty societies (four responses) and four academic medical centers in March of 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.

**Summary**

- Studies on the use of charged-particle beam RT to treat uveal melanomas have shown local control and survival rates considered equivalent to enucleation. Therefore, it is considered medically necessary for this indication.
- Available evidence suggests that charged-particle beam irradiation is at least as effective as, and may be superior to, alternative therapies, including conventional radiation or resection to treat chordomas or chondrosarcoma of the skull base or cervical spine. Therefore, it is considered medically necessary for this indication.
- For pediatric CNS tumors, there is a small body of literature on long-term outcomes with the use of PBT. This modality of treatment of pediatric CNS tumors has the potential to reduce long-term side effects, as dosimetric studies of proton therapy compared with best available photon-based treatment have shown significant dose-sparing to developing normal tissues. Clinical input uniformly supported this use of PBT. Therefore, PBT may be considered medically necessary in the treatment of pediatric CNS tumors.
- For pediatric non-CNS tumors, scant data exists and consists of dosimetric planning studies and a few case series in a small number of patients. Therefore, this indication is considered investigational.
- Results of proton beam studies for clinically localized prostate cancer have shown similar results and outcomes when compared to other radiation treatment modalities. Given these conclusions, along with information that PBT is generally more costly than alternative treatments, PBT is considered not medically necessary for treating prostate cancer.
- In treating lung cancer, definite evidence showing superior outcomes with PBT versus SBRT [stereotactic body radiation therapy] (an accepted approach for treating lung cancer with radiation), is lacking. Therefore, this indication is considered investigational.
- In treating head and neck cancer (other than skull-based tumors chordoma or chondrosarcoma), the data are scant and support from clinical input was mixed. Therefore, this indication is considered investigational.
Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. 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.

Some state or federal mandates (e.g., Federal Employee Program (FEP)) prohibit Plans from denying Food and Drug Administration (FDA) - approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

*This Policy relates only to the services or supplies described herein. Benefits may vary according to benefit design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement.*

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Tables

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Definitions

**Uveal tract** - The pigmented middle of the eye. The uveal tract is divided into three areas, the iris, ciliary body, and the choroid.

**Chordoma** - A rare tumor that usually occurs in the spine and base of the skull. Most chordomas occur at the base of the spine (sacrum), in the tailbone (coccyx), or at the base of the skull (40%), but they can occur other places in the spine. Most patients with chordomas are between 40 and 70 years of age with the average around 55 years. They are life-threatening. Chordomas spread to other organs.

**Chondrosarcoma** - A type of primary bone cancer which occurs most commonly in patients between 40 and 70 years of age. Most occur around the hip and pelvis or the shoulder.

Index / Cross Reference of Related BSC Medical Policies

The following Medical Policies share diagnoses and/or are equivalent BSC Medical Policies: N/A

Key / Related Searchable Words

- Charged particle
- Helium ion
- PBT
- Proton beam
- Radiation therapy

References

• Blue Cross Blue Shield Association. Technology Evaluation Center (TEC) Assessment: Charged particle (proton or helium ion) irradiation for uveal melanoma and for chordoma or chondrosarcoma of the skull base or cervical spine. 1996; Vol. 11, Tab 1.
• Blue Cross Blue Shield Association. Technology Evaluation Center (TEC) Assessment: Proton Beam Therapy for Prostate Cancer. 2010; Vol. 28, Tab 5.


Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

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The materials provided to you are guidelines used by this plan to authorize, modify, or deny care for persons with similar illness or conditions. Specific care and treatment may vary depending on individual need and the benefits covered under your contract. These Policies are subject to change as new information becomes available.