Name of Policy: Charged-Particle (Proton or Helium Ion) Radiation Therapy

Policy #: 348
Category: Radiology

Latest Review Date: March 2014
Policy Grade: B

Background/Definitions:
As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. The technology must have final approval from the appropriate government regulatory bodies;
2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;
3. The technology must improve the net health outcome;
4. The technology must be as beneficial as any established alternatives;
5. The improvement must be attainable outside the investigational setting.

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. In accordance with generally accepted standards of medical practice; and
2. Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient's illness, injury or disease; and
3. Not primarily for the convenience of the patient, physician or other health care provider; and
4. Not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient’s illness, injury or disease.
Description of Procedure or Service:
Charged-particle beams consisting of protons 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 (i.e., the Bragg peak). Thus, radiation exposure of surrounding normal tissues is minimized. The theoretical advantages of protons and other charged-particle beams may improve outcomes when the following conditions apply:

- Conventional treatment modalities do not provide adequate local tumor control;
- Evidence shows that local tumor response depends on the dose of radiation delivered; and
- Delivery of adequate radiation doses to the tumor is limited by the proximity of vital radiosensitive tissues or structures.

The use of proton or helium ion radiation therapy has been investigated in two general categories of tumors/abnormalities. However, advances in photon-based RT such as 3-D conformal RT (3D-CRT), intensity modulated RT (IMRT), and stereotactic body radiotherapy (SBRT) allow improved targeting of conventional therapy:

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

2. Tumors associated with a high rate of local recurrence despite maximal doses of conventional radiation therapy. 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).

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

Policy:
Effective for dates of service on or after March 14, 2013:
Charged-particle irradiation with proton or helium ion beams meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage in the following clinical situations:

- Primary therapy for melanoma of the uveal tract (iris, choroid, or ciliary body), with no evidence of metastasis or extracocular extension, and with tumors up to 24 mm in largest diameter and 14 mm in height;

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

• In the treatment of pediatric central nervous system tumors.

**Charged-particle irradiation with proton beams does not meet** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage 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.

Other applications of charged-particle irradiation, including but not limited to use of proton beam therapy for non-small-cell lung cancer (NSCLC) at any stage or for recurrence, pediatric non-central nervous system tumors, and tumors of the head and neck (other than skull-based chordoma or chondrosarcoma) are considered **investigational**.

*Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the member’s contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.*

**Key Points:**
**Uveal Melanomas and Skull-based Tumors**
The available 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. A TEC Assessment completed in 1996 reached the same conclusions. A systematic review of charged-particle therapy found that local tumor control rate and five-year overall survival (OS) for skull base chordomas treated with proton therapy were 63% and 81%, respectively, compared with postsurgical treatment with conventional photon therapy with reported local tumor control rates and five-year OS of 25% and 44%, respectively, and compared with surgery followed by fractionated stereotactic radiotherapy, which resulted in a five-year local tumor control rate of 50%. A summary of tumor control in published proton therapy studies of chondrosarcoma of the skull base was 95% five-year local tumor control, similar to the results of conventional therapy.

Charged-particle beam radiation therapy has been most extensively studied in uveal melanomas, where the focus has been to provide adequate local control while still preserving vision. For example, in 1992, Suit and Urie combined data from three centers and reported local control in 96% and five-year survival of 80%, results considered equivalent to enucleation. A 2005 summary of results from the United Kingdom reports five-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.

In 2013, Wang et al published a systematic review on charged-particle (proton, helium or carbon ion) radiation therapy for uveal melanoma. The review included 27 controlled and uncontrolled studies that reported health outcomes e.g., mortality, local recurrence. Three of the studies were randomized controlled trials (RCTs). One of the RCTs compared helium ion therapy with an alternative treatment (in this case, brachytherapy). The other two RCTs compared different proton beam protocols 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-naïve patients (all but one of the identified studies). In a pooled analysis of data from nine studies, there was not a statistically significant difference in mortality with charged-particle therapy compared with brachytherapy (odds ratio [OR]=0.13, 95% CI, 0.01 to 1.63). However, there was a significantly lower rate of local control with charged-particle therapy compared with brachytherapy in a pooled analysis of 14 studies (OR=0.22, 95% CI, 0.21 to 0.23). There were significantly lower rates of radiation retinopathy and cataract formation in patients treated with charged-particle therapy compared with brachytherapy (pooled rates of 0.28 versus 0.42 and 0.23 versus 0.68, respectively). According to this review, there is low-quality evidence that charged-particle therapy is at least as effective as alternative therapies as primary treatment of uveal melanoma and is better at preserving vision.

**Pediatric Central Nervous System Tumors**

Radiation therapy is an integral component of treatment of many pediatric central nervous system (CNS) tumors including high-grade gliomas, primitive neuroectodermal tumors (PNETs), medulloblastomas, ependymomas, germ cell tumors, some craniopharyngiomas and subtotally resected low-grade astrocytomas. Children who are cured of their tumors live to experience the long-term sequelae of radiation treatment including developmental, neurocognitive, neuroendocrine and hearing late effects. Radiation to the cochlea can lead to hearing loss at doses greater than 35-45 Gy in the absence of chemotherapy. The risk of ototoxicity is markedly increased in children who receive ototoxic platinum based chemotherapy regimens. Craniospinal irradiation, most commonly given as part of medulloblastoma treatment, can lead to primary thyroid dysfunction, and damage to the lungs, heart and intestinal tract. Additionally, patients irradiated at a young age are at an increased risk of developing a radiation induced second tumor compared to their adult counterparts.

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. On the other hand, proton RT eliminates exit dose to normal tissue, thereby eliminating ~50% of radiation to normal tissue.

A 2012 five-year update of a systematic review 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 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 proton beam therapy 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. the optic nerves or chiasm, brainstem, diencephalon, cervical-medullary junction), are often treated with chemotherapy in young patients to delay radiotherapy, 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. Six patients experienced local failure; acute side effects were minimal. After a median follow-up of three 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.

- Massachusetts General Hospital reported on the use of protons in 17 children with ependymoma. 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. 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. 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 50.4-59.4 cobalt Gy equivalent. 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.

- The Massachusetts General Hospital reported on the use of protons in the treatment of germ cell tumors. Among the 22 patients treated, 13 had germinoma and nine had non-germinomatous germ cell tumors (NGGCTs). Twenty-one patients were treated with cranial spinal irradiation, whole ventricular radiation therapy (WVRT), or whole brain radiation followed by an involved field boost, while one patient received involved field alone. Radiation doses ranged from 30.6 to 57.6 CGE and all NGGCT patients received chemotherapy prior to radiation therapy. At a median follow-up of 28 months, there were no CNS recurrences and no deaths. Following radiation two patients developed growth hormone deficiency and two developed central hypothyroidism. Longer follow-up was felt to be necessary to define neurocognitive effects. In the same study, the authors compared dosimetric outcomes of photons and protons for a representative WVRT and involved field boost treatment. Proton radiotherapy provided substantial sparing to the whole brain and temporal lobes. Dose savings were also noted for the optic nerves.

Moeller et al reported on 23 children who were enrolled on a prospective observational study and treated with proton beam therapy for medulloblastoma between the years 2006-2009. 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 one-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 19-43). 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 and, consequently, the rate of high-grade (Grade 3 or 4) ototoxicity at one year was favorable (5%). The authors compared this to a rate of Grade 3-4 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 et al sought to determine whether proton radiotherapy has clinical advantages over photon radiotherapy in childhood brain tumors. Three-dimensional imaging and treatment planning data, including targeted tumor and normal tissues contours, were acquired for 40 patients, ten each with optic pathway glioma, craniopharyngioma, infratentorial ependymoma, or medulloblastoma. Dose-volume data were collected for the entire brain, temporal lobes, cochlea, and hypothalamus from each patient. The data were averaged and compared based on treatment modality (protons vs. photons) using dose-cognitive effects models. Outcomes were estimated over five years. With protons, when compared to photons, relatively small critical normal tissue volumes such as the cochlea and hypothalamus were spared from radiation exposure when not adjacent to the primary tumor volume. Larger normal tissue volumes such as the supratentorial brain or temporal lobes received less of the low and intermediate doses. When applied to longitudinal models of radiation dose-cognitive effects, these differences
resulted in clinically significant higher IQ scores for patients with medulloblastoma and craniopharyngioma and academic reading scores in patients with optic pathway glioma. Extreme differences between proton and photon dose distributions precluded meaningful comparison of protons and photons for patients with ependymoma. The authors concluded that the differences in the overall dose distributions, as indicated by modeling changes in cognitive function, showed that a reduction in the lower-dose volumes or mean dose would have long-term, clinical advantages for children with medulloblastoma, craniopharyngioma, and optic pathway glioma.

**Pediatric Non-Central Nervous System Tumors**

There is scant data on the use of proton beam therapy in pediatric non-CNS tumors and includes dosimetric planning studies in a small number of pediatric patients with parameningeal rhabdomyosarcoma and late toxicity outcomes in other solid tumors of childhood.

**Localized Prostate Cancer**

A 2010 TEC Assessment addressed the use of proton beam therapy for prostate cancer and concluded that it has not yet been established whether proton beam therapy 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 non-comparative. Five studies included patients who received x-ray external beam radiotherapy 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 proton beam therapy without x-ray external beam radiotherapy. Among studies using proton beam boost, only one study provided survival outcome data for currently applicable methods of x-ray external beam radiotherapy. 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 report 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 OS. 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 OS 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 Assessment.
A 2008 Agency for Healthcare Research and Quality (AHRQ) comparative effectiveness review of therapies for clinically localized prostate cancer indicated that, based on nonrandomized comparisons, the absolute rates of outcomes after proton radiation appear similar to other treatments.

One if the earliest published trials on proton beam therapy to treat prostate cancer was a randomized clinical trial published in 1995 comparing outcomes of conventional radiation therapy with versus without an additional radiation “boost” of PBT. Patients treated in the control arm received a total of 67.2 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 five- and eight-year rates of local control, disease-specific survival, OS, 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 OS 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 three-dimensional conformal radiotherapy (3D-CRT) or IMRT, have permitted dose escalation of conventional radiation therapy to 80 Gy, a dose higher than that achieved with proton therapy in the previous study. Furthermore, these gains were achieved without increasing radiation damage to adjacent structures.

Subsequently, a 2005 RCT treated 393 patients with prostate cancer using either a conventional-dose or high-dose proton beam therapy and found results comparable with those obtained with conventional techniques.

A 2013 RCT by Kim et al in Korea compared five protocols for administering hypofractionated proton therapy in men with androgen-deprivation therapy-naïve stage T1-T3 prostate cancer. The protocols were as follows: arm 1, 60 CGE (cobalt gray equivalent/20 fractions for five weeks; arm 2, 54 CGE/15 fractions for five weeks; arm 3, 47 CGE/10 fractions for five weeks; arm 4, 35 CGE/5 fractions for 2.5 weeks; or arm 5, 35 CGE/5 fractions for five weeks. Eighty-two patients were randomized, and there was a median follow-up of 42 months. Patients assigned to arm three had the lowest rate of acute genitourinary toxicity and those assigned to arm two had the lowest rate of late gastrointestinal toxicity. In this study, proton therapy was not compared with an alternative prostate cancer treatment.

In 2004, investigators at Loma Linda, CA reported their experience with 1255 patients with prostate cancer who underwent 3D-conformal radiotherapy (3D-CRT) PBT. 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 was 90% in patients with initial prostate specific antigen 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 that dose escalation is an accepted concept in treating organ-confined prostate cancer. PBT, 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 external-beam radiation therapy (EBRT) using 3D-CRT or IMRT. The morbidity related to radiation therapy 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. Ongoing randomized studies are examining the outcomes of dose escalation for conventional EBRT.

In a 2007 editorial, Zeitman comments that while PBT has been used in prostate cancer for some time, and there is a growing body of evidence confirming clinical efficacy, apart from some comparative planning studies, there is no proof that it is superior to alternatives such as 3D-CRT or IMRT. The editorial notes that PBT could show benefit by either allowing greater dose escalation (if improved outcomes were demonstrated) or by allowing certain doses of RT to be delivered with fewer adverse effects compared with other modalities. In terms of dose escalation, the editorial reports on a model (proposed by Konski) that speculates delivering 91.8 Gy could yield a 10% improvement in five-year freedom from biochemical failure for men with intermediate risk (15% to 20% of those with prostate cancer) of disease. The editorial also comments that the ability to deliver this dose of radiation has yet to be studied. In terms of PBT leading to reduced side effects, the editorial notes that work is just beginning. The author comments that we do not know whether there would be gains by treating with PBT to the doses currently used in IMRT therapy (around 79 to 81Gy); this is a topic for which studies are needed.

Three recent review articles comment that current data do not demonstrate improved outcomes with use of PBT for prostate cancer. In a 2010 review, Kagan and Schulz comment about the lack of data related to improved outcomes and make a number of additional, important comments. They note that while projected dose distribution for PBT suggests reduced rates of bladder and rectal toxicity, toxicity reports for PBT in prostate cancer are similar to those for IMRT. They also comment that the role of dose escalation and the optimum doses and dose rates are yet to be established. Finally, they note that the potential for treatment errors with PBT is much greater than with photons. Brada et al reported on an updated systematic review of published peer-reviewed literature for PBT 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 note that 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 et al concluded that the current evidence does not support any definitive benefit to PBT over other forms of high-dose conformal radiation in the treatment of localized prostate cancer. They also comment on uncertainties surrounding the physical properties of PBT, perceived clinical gain, and economic viability. Thus, the policy statement regarding use for prostate cancer is unchanged.
Non-Small Cell Lung Cancer
A 2010 TEC Assessment assessed the use of proton beam therapy for non-small cell lung cancer (NSCLC). This TEC Assessment addressed the key question of how health outcomes (OS, disease-specific survival, local control, disease-free survival, and adverse events) with PBT compare with outcomes observed for stereotactic body radiotherapy (SBRT), which is an accepted approach for using radiation therapy to treat NSCLC.

- Eight PBT case series were identified in the Assessment that included a total of 340 patients. No comparative studies, randomized or nonrandomized, were found. For these studies, Stage I comprised 88.5% of all patients, and only 39 patients were in other stages or had recurrent disease. Among seven studies reporting two-year overall survival, probabilities ranged between 39% and 98%. At five 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 randomized controlled trials, 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.

A 2010 indirect meta-analysis reviewed in the TEC Assessment found a nonsignificant difference of nine percentage points between pooled two-year OS estimates favoring SBRT over PBT for treatment of NSCLC. The nonsignificant difference of 2.4 percentage points at five 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.

Pijls-Johannesma et al conducted a 2010 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 of 24 months or more.
Eleven studies, all dealing with NSCLC, mainly Stage I, were included in the review, five investigating protons (n=214) and six, C-ions (n=210). The proton studies included one Phase II 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 III studies were identified. Most patients had Stage I 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, two- to five-year local tumor control rates varied in the range of 57%–87%. The two- and five-year OS and two- and five-year cause-specific survival (CSS) rates were 31%–74% and 23% and 58%–86% 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 five-year OS and CSS 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.

A 2010 systematic review 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.” As of February 2014, no RCTs or non-RCTs reporting health outcomes in patients treated with PBT versus an alternative treatment have been published. In 2013, Bush et al published data on a relatively large series of patients (n=111) treated at one U.S. facility over 12 years. Patients had NSCLC that was inoperable (or refused surgery) and were treated with high-dose hypofractionated PBT to the primary tumor. Most patients (64%) had Stage II disease and the remainder had Stage I disease. The four-year actuarial OS rate was 51% and the CSS rate was 74%. The subgroup of patients with peripheral Stage I tumors treated with either 60 or 70 Gy had an OS of 60% at four years. In terms of adverse events, four patients had rib fractures determined to be related to treatment; in all cases, this occurred in patients with tumors adjacent to the chest wall. The authors noted that a 70-Gy regimen is now used to treat Stage I patients at their institution. A limitation of the study was a lack of comparison group.

**Head and Neck Tumors, other than Skull-based**
The literature on the use of PBT for head and neck tumors (other than skull-based) is scant and consists of dosimetric planning studies for nasopharyngeal carcinoma, and a case series of 91 patients who received combined proton and photon radiotherapy for advanced paranasal sinus tumors.

**Summary**
- Studies on the use of charged-particle beam radiation therapy 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 central nervous system (CNS) tumors, there is a small body of literature on long-term outcomes with the use of proton beam therapy. 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 proton beam therapy. Therefore, proton beam therapy 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 proton beam therapy is generally more costly than alternative treatments, proton beam therapy is considered not medically necessary for treating prostate cancer.

- In treating lung cancer, definite evidence showing superior outcomes with proton beam radiation therapy versus 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), the data are scant and support from clinical input was mixed. Therefore, this indication is considered investigational.

**Practice Guidelines and Position Statements**

**National Comprehensive Cancer Network (NCCN) guidelines:**

**Prostate Cancer**

NCCN guidelines for Prostate Cancer (V1.2014) state that “proton beams can be added as an alternative radiation source. The costs associated with proton beam facility construction and proton beam treatment are high. However, theoretically, protons may reach deeply located tumors with less damage to surrounding tissues...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.”

**Non-Small Cell Lung Cancer**

NCCN guidelines for Non-Small Cell Lung Cancer (V3.2014) states that “use of more advanced technologies is appropriate when needed to deliver curative RT safely. These technologies include....proton therapy. Nonrandomized comparisons of using advanced technologies versus older techniques demonstrate reduced toxicity and improved survival.”

**Bone Cancer**

NCCN guidelines for Bone Cancer (V1.2014) state “specialized techniques such intensity-modulated radiation therapy (IMRT), particle beam RT with protons, carbon ions or other heavy
ions, stereotactic radiosurgery or fractionated stereotactic RT should be considered as indicated in order to allow high-dose therapy while maximizing normal tissue sparing.“

**American Society for Radiation Oncology (ASTRO):**
The Emerging Technology Committee of ASTRO published 2012 evidence-based recommendations declaring a lack of evidence for proton beam therapy (PBT) for malignancies outside of large ocular melanomas and chordomas:

“Current data do not provide sufficient evidence to recommend PBT outside of clinical trials in lung cancer, head and neck cancer, GI malignancies (with the exception of hepatocellular) and pediatric non-CNS malignancies. In hepatocellular carcinoma and prostate cancer there is evidence for the efficacy of PBT but no suggestion that it is superior to photon based approaches. In pediatric CNS malignancies there is a suggestion from the literature that PBT is superior to photon approaches but there is currently insufficient data to support a firm recommendation for PBT. In the setting of craniospinal irradiation for pediatric 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.”

ASTRO published a position statement in February 2013 which states the following: “At the present time, 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.”

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

**Key Words:**
Charged particle (Proton or Helium Ion) irradiation, irradiation, helium ion radiotherapy, proton beam radiotherapy

**Approved by Governing Bodies:**
Not applicable

**Benefit Application:**
Coverage is subject to member’s specific benefits. Group specific policy will supersede this policy when applicable.

ITS: Home Policy provisions apply
FEP contracts: Special benefit consideration may apply. Refer to member’s benefit plan. FEP does not consider investigational if FDA approved and will be reviewed for medical necessity.

**Current Coding:**

CPT Codes:

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

**References:**

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


Policy History:
Medical Policy Group, February 2009 (3)
Medical Policy Administration Committee, March 2009
Available for comment March 18-May 1, 2009
Medical Policy Group; October 2010 (1)
Medical Policy Group, October 2011 (3): Updated Description, Key Points and References with new literature & TEC Evaluation
Medical Policy Administration Committee November 2011
Medical Policy Panel, March 2013
Medical Policy Group, March 2013 (3): 2013 Updates to Policy (added treatment of pediatric central nervous system tumors), Key Points, and References
Medical Policy Administration Committee, April 2013
Available for comment April 18 through June 5, 2013
Medical Policy Panel, March 2014
Medical Policy Group, March 2014 (3): 2014 Updates to Description, Key Points & References; no change to policy statement
Medical Policy Group, June 2014 (3): Updated policy with link to CareCore National© medical policies effective August 1, 2014
Medical Policy Administration Committee, June 2014
Available for comment June 16 through July 31, 2014
Medical Policy Group, July 2014: Removed CareCore link. Transfer to CareCore is on hold until further notice. The policy has been returned to FINAL.

This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member’s plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield’s administration of plan contracts.