



Kansas City

An Independent Licensee of the Blue Cross and Blue Shield Association

Charged-Particle (Proton or Helium Ion) Radiation Therapy

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Next Review: 11/2014

Policy

Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for charged-particle radiation therapy when it is determined to be medically necessary because the criteria shown below are met.

When Policy Topic is covered

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

- primary therapy for melanoma of the uveal tract (iris, choroid, or ciliary body), with no evidence of metastasis or extrascleral 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.

When Policy Topic is not covered

Charged-particle irradiation with proton beams is considered **not medically necessary** in patients with clinically localized prostate cancer, because the clinical outcomes with this treatment have not been shown to be superior to other approaches including intensity modulated radiation therapy (IMRT) or conformal radiation therapy, yet proton beam therapy is generally more costly than these alternatives.

Other applications of charged-particle irradiation with proton beams are considered **investigational**.

This includes, but is 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).

Considerations

For treatment of localized prostate cancer, proton beam therapy has not been shown to be superior to conventional radiation therapy.

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 radiation therapy (RT) such as 3-D conformal RT, 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 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).

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

Rationale

Uveal Melanomas and Skull-based Tumors

A systematic review of charged particle therapy found that local tumor control rate and 5-year overall survival (OS) for skull base chordomas treated with proton therapy were 63% and 81%, respectively, compared to post-surgical treatment with conventional photon therapy with reported local tumor control rates and 5-year OS of 25% and 44%, respectively, and surgery followed by fractionated stereotactic radiotherapy, which resulted in 5-year local tumor control of 50%. (1) 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. (1)

Charged-particle beam radiation therapy has been most extensively studied in uveal melanomas, in which the focus has been to provide adequate local control while still preserving vision. Pooling data from 3 centers, Suit and Urie reported local control in 96% and a 5-year survival of 80%, results considered equivalent to enucleation. (2) A 2005 summary of results from the United Kingdom reports 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. (3) The available evidence also 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. (2) A TEC Assessment completed in 1996 (4) reached the same conclusions.

Pediatric Central Nervous System Tumors

Radiation therapy is an integral component of the 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. (5) 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 35-45 Gy in the absence of chemotherapy, and the risk of ototoxicity is increased in children who receive ototoxic platinum-based chemotherapy regimens. (6) 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 gastrointestinal tract. (6) 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. (6)

The development of more conformal radiation techniques has decreased inadvertent radiation to normal tissues; however, while intensity-modulated radiation therapy (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 ~50% of radiation to normal tissue.

A 2012 5-year update of a systematic review (1) drew similar conclusions to the original review, that except for rare indications such as childhood cancer, the gain from proton radiation therapy (RT) in clinical practice remains controversial. (7)

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. (6)

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. 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. (8) 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 7 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. (9)

Massachusetts General Hospital reported on the use of protons in 17 children with ependymoma. (10) 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, 2 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. (6) Massachusetts General Hospital reported on 5 children treated with combined photon/proton radiation or proton radiation alone with a median follow-up of 15.5 years. (11) All 5 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. (12) Local control was achieved in 14 of the 15 patients with follow-up data. Follow-up was 5 years; 3 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). (13) Radiation doses ranged from 30.6 to 57.6 cobalt Gray 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 central nervous system (CNS) recurrences and no deaths. Following radiation therapy, 2 patients developed growth hormone deficiency, and 2 patients developed central hypothyroidism. The authors stated that longer follow-up was necessary to assess the neurocognitive effects of therapy. In the same study, a dosimetric comparison of photons and protons for representative treatments with whole ventricular and involved field boost was done. Proton radiotherapy provided substantial sparing to the whole brain and temporal lobes, and reduced doses to the optic nerves.

Moeller and colleagues reported on 23 children who were enrolled in a prospective observational study and treated with proton beam therapy for medulloblastoma between the years 2006-2009. (14) 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 ⁶⁰Co-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; the rate of high-grade (grade 3 or 4) ototoxicity at 1 year was 5%. The authors compared this to a rate of grade 3-4 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 (15) 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 vs. 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 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 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 proton beam therapy in pediatric non-CNS tumors and includes dosimetric planning studies in a small number of pediatric patients with parameningeal rhabdomyosarcoma (16) and late toxicity outcomes in other solid tumors of childhood. (17, 18)

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. (19) The following is a summary of the main findings.

A total of 9 studies were included in the review; 4 were comparative and 5 were noncomparative. 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 2 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 2 studies on proton beam alone gave data on biochemical failure. Prostate cancer symptoms were addressed in 2 studies and quality of life in one. Eight of 9 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 4 comparisons, there was one good quality randomized trial each for 2 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 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. (20)

A 2005 randomized-controlled trial treating 393 patients with prostate cancer using either a conventional-dose or high-dose proton beam therapy demonstrated results comparable to those obtained with conventional techniques. (21)

In 2004, investigators at Loma Linda, CA reported their experience with 1,255 patients with prostate cancer who underwent 3D-conformal radiotherapy (3D-CRT) proton beam radiation therapy. (22) 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 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 that dose escalation is an accepted concept in treating organ-confined prostate cancer. (23) 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 external-beam radiation therapy 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 proton beam therapy. (24) Ongoing randomized studies are examining the outcomes of dose escalation for conventional external-beam radiation therapy (EBRT). (25)

One of 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 proton beam therapy (PBT). (26) 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 5- 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 3-dimensional conformal radiotherapy (3D-CRT) or image-modulated radiation therapy (IMRT), have permitted dose escalation of conventional radiation therapy to 80 Gy, a dose higher than that achieved with proton therapy in the above study. (27, 28) Furthermore, these gains were achieved without increasing radiation damage to adjacent structures.

In a 2007 editorial, Zeitman comments that while proton beam therapy 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. (29) The editorial notes that proton beam therapy could show benefit by either allowing greater dose escalation (if improved outcomes were demonstrated) or by allowing certain doses of radiation therapy to be delivered with fewer adverse effects compared to 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 5-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 proton beam therapy 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 proton beam therapy to the doses currently used in IMRT therapy (around 79 to 81 Gy); 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. (30) 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 intensity-modulated radiation therapy (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 and colleagues 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. (31) 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 and colleagues 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. (32) 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). (33) This TEC Assessment addressed the key question of how health outcomes (overall survival, disease-specific survival, local control, disease-free survival, and adverse events) with proton beam therapy (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 7 studies reporting 2-year overall survival, probabilities ranged between 39% and 98%. At 5 years, the range across 5 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.

Pijls-Johannesma and colleagues conducted a 2010 systematic literature review through November 2009 examining the evidence on the use of particle therapy in lung cancer. (34) Study inclusion criteria included that the series had at least 20 patients and a follow-up period ≥ 24 months. Eleven studies, all dealing with NSCLC, mainly stage I, were included in the review, 5 investigating protons (n=214) and 6, C-ions (n=210). The proton studies included one Phase 2 study, 2 prospective studies, and 2 retrospective studies. The C-ion studies were all prospective and conducted at the same institution in Japan. No Phase 3 studies were identified. Most patients had stage 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 (OS) and 2- and 5-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 5-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.” (35)

A 2010 indirect meta-analysis reviewed in the 2010 TEC Assessment found a nonsignificant difference of 9 percentage points between pooled 2-year overall survival estimates favoring SBRT over PBT. (36) The nonsignificant difference of 2.4 percentage points at 5 years also favored SBRT over PBT. Based on separate groups of single-arm studies on SBRT and PBT, it is unclear if this indirect meta-analysis adequately addressed the possible influence of confounding on the comparison of SBRT and PBT.

The combination of proton beam radiotherapy with transpupillary thermotherapy in the treatment of ocular melanoma was being studied in a 2006 randomized-controlled trial. (37)

Head and Neck tumors, other than skull-based

The literature on the use of proton beam therapy for head and neck tumors (other than skull-based) is scant and consists of dosimetric planning studies for nasopharyngeal carcinoma, (38) and a case series of 91 patients who received combined proton and photon radiotherapy for advanced paranasal sinus tumors. (39)

National Cancer Institute Clinical Trials

Two Phase III trials are comparing photon versus carbon ion radiation therapy in patients with low and intermediate grade chondrosarcoma of the skull base (NCT01182753) and chordoma of the skull base (CT01182779).

A Phase III trial is comparing hypofractionated proton radiation versus standard dose for prostate cancer (NCT01230866).

Clinical input Received through Physician Specialty Society and Academic Medical Center

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, input was received from 2 physician specialty societies (4 responses) and 4 academic medical centers while this policy was under review for March 2013. There was uniform support for the use of proton beam therapy in pediatric CNS tumors. Two reviewers expressed support for the use of proton beam therapy 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 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 (V3.2012) state that “proton beams can be added as an alternative radiation source. 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.” (40)

Non-Small Cell Lung Cancer: NCCN guidelines for Non-Small Cell Lung Cancer (V3.2012) state that “use of more advanced technologies is appropriate when needed to deliver adequate tumor doses while respecting normal tissue dose constraints.” These technologies include proton beam therapy 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.” (41)

Bone Cancer: NCCN guidelines for Bone Cancer (V2.2012) state that “proton and/or photon beam RT may be useful for patients with chondrosarcomas of the skull base and axial skeleton with tumors in unfavorable location not amenable to resection.” (42)

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 [gastrointestinal] malignancies (with the exception of hepatocellular) and pediatric non-CNS malignancies. In hepatocellular carcinoma and prostate cancer, there is evidence for the efficacy of PBT but no suggestion that it is superior to photon-based approaches. In pediatric CNS malignancies, there is a suggestion from the literature that PBT is superior to photon approaches, but there is currently insufficient data to support a firm recommendation for PBT. In the setting of craniospinal irradiation for pediatric patients, protons appear to offer a dosimetric benefit over photons, but more clinical data are needed. In large ocular melanomas and chordomas, we believe that there is evidence for a benefit of PBT over photon approaches. In all fields, however, further clinical trials are needed and should be encouraged.” (43)

Medicare National Coverage

There is no national coverage determination.

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Billing Coding/Physician Documentation Information

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|--------------|--|
| 77299 | Unlisted procedure, therapeutic radiology clinical treatment planning |
| 77399 | Unlisted procedure, medical radiation physics, dosimetry and treatment devices, and special services |
| 77402 | Radiation treatment delivery, single treatment area, single port or parallel opposed ports, simple blocks or no blocks; up to 5 MeV |
| 77403 | Radiation treatment delivery, single treatment area, single port or parallel opposed ports, simple blocks or no blocks; 6-10 MeV |
| 77404 | Radiation treatment delivery, single treatment area, single port or parallel opposed ports, simple blocks or no blocks; 11-19 MeV |
| 77406 | Radiation treatment delivery, single treatment area, single port or parallel opposed ports, simple blocks or no blocks; 20 MeV or greater |
| 77407 | Radiation treatment delivery, two separate treatment areas, three or more ports on a single treatment area, use of multiple blocks; up to 5 MeV |
| 77408 | Radiation treatment delivery, two separate treatment areas, three or more ports on a single treatment area, use of multiple blocks; 6-10 MeV |
| 77409 | Radiation treatment delivery, two separate treatment areas, three or more ports on a single treatment area, use of multiple blocks; 11-19 MeV |
| 77411 | Radiation treatment delivery, two separate treatment areas, three or more ports on a single treatment area, use of multiple blocks; 20 MeV or greater |
| 77412 | Radiation treatment delivery, three or more separate treatment areas, custom blocking, tangential ports, wedges, rotational beam, compensators, electron beam; up to 5 MeV |

- 77413** Radiation treatment delivery, three or more separate treatment areas, custom blocking, tangential ports, wedges, rotational beam, compensators, electron beam; 6-10 MeV
- 77414** Radiation treatment delivery, three or more separate treatment areas, custom blocking, tangential ports, wedges, rotational beam, compensators, electron beam; 11-19 MeV
- 77416** Radiation treatment delivery, three or more separate treatment areas, custom blocking, tangential ports, wedges, rotational beam, compensators, electron beam; 20 MeV or greater
- 77499** Unlisted procedure, therapeutic radiology treatment management
- 77520** Proton treatment delivery; simple, without compensation
- 77522** Proton treatment delivery; simple, with compensation
- 77523** Proton treatment delivery; intermediate
- 77525** Proton treatment delivery; complex

The use of proton beam or helium ion radiation therapy typically consists of a series of CPT codes describing the individual steps required: medical radiation physics, clinical treatment planning, treatment delivery and clinical treatment management. It should be noted that the code for treatment delivery primarily reflects the costs related to the energy source used, and not physician work.

Treatment delivery

The codes used for treatment delivery will depend on the energy source used, typically either photons or protons. For photons (i.e., with a Gamma Knife or Linac device) nonspecific radiation therapy treatment delivery CPT codes may be used based on the voltage of the energy source (i.e., codes 77402-77416).

When proton beam therapy is used the specific CPT codes (77520-77525) are available:

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

Clinical treatment management

77499: Unlisted procedure, therapeutic radiology clinical treatment management

Note: If stereotactic guidance is used, please refer to the separate policy.

Additional Policy Key Words

N/A

Policy Implementation/Update Information

- 11/1/06 New policy.
 - 11/1/07 No policy statement changes.
 - 11/1/08 No policy statement changes.
 - 11/1/09 Policy statement changed to indicate that proton beam therapy is not medically necessary in the treatment of localized prostate cancer.
 - 11/1/10 No policy statement changes.
 - 11/1/11 No policy statement changes.
 - 11/1/12 No policy statement changes.
 - 11/1/13 Change to policy statement that proton radiotherapy may be considered medically necessary for the treatment of pediatric CNS tumors. Investigational policy statement expanded to include examples.
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