Charged-Particle (Proton or Helium Ion) Radiation Therapy

Policy Number: MM.05.005
Line(s) of Business: HMO; PPO
Section: Radiology
Place(s) of Service: Outpatient

I. Description

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 for uveal tract and skull-based tumors. For stereotactic techniques, 3 to 5 fixed beams of protons or helium ions are used.

II. Criteria/Guidelines

Charged-particle irradiation with proton or helium ion beams is covered (subject to Limitations/Exclusions and Administrative Guidelines) in the following clinical situations:

A. 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;

B. 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.

III. Limitations/Exclusions

A. Charged-particle irradiation with proton beams using standard treatment doses is not covered 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. In addition, proton beam therapy is generally more costly than these alternatives.

B. Other applications of charged-particle irradiation are not covered, including but not limited to use of proton beam therapy for non-small-cell lung cancer (NSCLC) at any stage or for recurrence, because it has not been shown to be more effective in improving health outcomes and is more costly when compared to other approaches.

IV. Administrative Guidelines

A. Precertification is required. To precertify, fill out HMSA’s Precertification Request and mail or fax the form as indicated. Include the following documentation:

1. History and physical
2. Imaging studies
3. Pathology reports
4. Prior therapies, if applicable.
5. Radiation oncology consultation notes.

B. 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. See the following table for applicable CPT codes:
<table>
<thead>
<tr>
<th>CPT</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>77299</td>
<td>Unlisted procedure, therapeutic radiology clinical treatment planning</td>
</tr>
<tr>
<td>77399</td>
<td>Unlisted procedure, medical radiation physics, dosimetry and treatment devices, and special services</td>
</tr>
<tr>
<td>77499</td>
<td>Unlisted procedure, therapeutic radiology treatment management</td>
</tr>
<tr>
<td>77520*</td>
<td>Proton treatment delivery; simple, without compensation</td>
</tr>
<tr>
<td>77522*</td>
<td>Proton treatment delivery; simple with compensation</td>
</tr>
<tr>
<td>77523*</td>
<td>Proton treatment delivery; intermediate</td>
</tr>
<tr>
<td>77525*</td>
<td>Proton treatment delivery; complex</td>
</tr>
</tbody>
</table>

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

V. Rationale

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. Pooling data from three centers, Suit and Urie reported local control in 96% and 5-year survival of 80%, results considered equivalent to enucleation. (1) A recent 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. (2) 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. (1) A previous BCBSA TEC Assessment (3) reached the same conclusions.

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 proton beam therapy (PBT). (4) 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. (5, 6) 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 radiation therapy. (7) 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. (8) Proton beam therapy, using 3-D 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 3-D 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 3-D 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. (9) Ongoing randomized studies are examining the outcomes of dose escalation for conventional external beam radiation therapy (EBRT). (10)

Additional data have been published concerning use of proton beam therapy in localized prostate cancer. (11) While there have not been randomized studies, reports from treating large numbers of patients with prostate cancer using this modality have demonstrated results comparable to those obtained with alternative techniques.

A number of case series describe initial results using proton beam therapy in hepatocellular cancer, non-small cell lung cancer, metastatic tumors of the choroid, and recurrent uveal melanoma. However, these results are not sufficient to determine if proton beam therapy offers any advantage over conventional treatments for these conditions.

Publications describe initial, preliminary results of using proton beam radiotherapy in other malignancies such as breast cancer. In addition, the combination of proton beam radiotherapy with transpupillary thermotherapy in the treatment of ocular melanoma is being studied. (12) A recent Agency of Healthcare Research and Quality (AHRQ) comparative effectiveness review of therapies
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for clinically localized prostate cancer from the indicated that, based on nonrandomized comparisons, the absolute rates of outcomes after proton radiation appear similar to other treatments. (13)

In an 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 3-D CRT or IMRT. (14) 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 comments 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 where 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 where studies are needed.

Since the last update, no randomized trials of charged particle radiation therapy for cancer were identified. Case series are reporting early results for use of proton beam therapy in cancer involving the lung and the liver. A recent systematic review 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.” (15)

The policy was updated following a TEC assessment on the use of proton beam therapy for NSCLC (16). The TEC assessment addressed the key question of how health outcomes (overall survival, 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 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.

A recent indirect meta-analysis reviewed in the Assessment found a nonsignificant difference of 9 percentage points between pooled 2-year overall survival estimates favoring SBRT over PBT. (17) 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 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.

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.

Prostate Cancer

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. (18) They note that while projected dose distribution for PBT suggests reduced rated 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. (19) 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, Efstatthiou 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. (20) They also comment on uncertainties surrounding the physical properties of PBT, perceived clinical gain, and economic viability. Thus, the policy statement remains unchanged.

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. (22) 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 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.

Lung Cancer

Pijls-Johannesma and colleagues conducted a systematic literature review through November 2009 examining the evidence on the use of particle therapy in lung cancer. (21) Study inclusion criteria included that the series had at least 20 patients and a follow-up period ≥24 months. Eleven studies were included in the review, five investigating protons (n=214) and six 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.

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).

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.

- 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 covered 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 not covered.

Practice Guidelines and Position Statements

2011 National Comprehensive Cancer Network (NCCN) guidelines

NCCN guidelines for prostate cancer (v 4.2011) state that 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 the treatment of prostate cancer.

NCCN guidelines for non-small cell lung cancer (v 3.2011) state that under strictly defined protocols, proton therapy may be allowed.
NCCN guidelines for bone cancer (v 2.2011) state that proton beam radiation therapy has been associated with excellent local tumor control and long-term survival in patients with low-grade base of skull chondrosarcomas.

Medicare National Coverage

There is no national coverage determination.

VI. Important Reminder

The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.

Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

This Medical Policy has been developed through consideration of the medical necessity criteria under Hawaii's Patients' Bill of Rights and Responsibilities Act (Hawaii Revised Statutes § 432E-1.4), generally accepted standards of medical practice, and review of medical literature and government approval status. HMSA has determined that services not covered under this Medical Policy will not be medically necessary under Hawaii law in most cases. If a treating physician disagrees with HMSA's determination as to medical necessity in a given case, the physician may request that HMSA reconsider the application of the medical necessity criteria to the case at issue in light of any supporting documentation.

VII. References

3. 1996 BCBSA TEC Assessments; Tab 1
16. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Proton beam therapy for non-small-cell lung cancer. TEC Assessments 2010; Volume 25, Tab 7