Charged Particle (Proton or Helium Ion) Radiotherapy

Effective: August 1, 2017

Next Review: June 2018
Last Review: July 2017

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Charged particle radiation therapy conforms to the target tumor, minimizing radiation exposure to surrounding healthy tissue.

MEDICAL POLICY CRITERIA

I. Charged-particle irradiation such as proton or helium ion may be considered medically necessary for any of the following:

   A. Ocular tumors including intraocular/uveal melanoma (e.g., iris, choroid, or ciliary body); or

   B. Cervical spinal cord or skull base central nervous system tumors (including but not limited to chordoma, chondrosarcoma, paranasal sinus with base of skull invasion) including definitive, adjuvant, or salvage treatment; or

   C. Pediatric (less than 21 years of age) central nervous system and malignant solid tumors.

II. Charged-particle irradiation with proton beam is considered not medically necessary in patients with clinically localized (T1 or T2, N0, M0) prostate cancer. Clinical outcomes with this treatment have not been shown to be superior to other approaches...
such as intensity modulated radiotherapy (IMRT) photon irradiation, yet it is more costly.

III. Other applications of charged-particle irradiation are considered investigational, including but not limited to the following:
A. All other tumors that do not meet Criteria I. above
B. Adult solid organ tumors, primary or metastatic (e.g., liver, lung, kidney, pancreas)
C. Choroidal neovascularization (CNV) in age-related macular degeneration (ARMD)
D. Regional (locally advanced) or metastatic prostate cancer.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

It is critical that the list of information below is submitted for review to determine whether the policy criteria are met. If these items are not submitted, it could impact our review and decision outcome.

- History and physical chart notes including information regarding specific diagnosis and any pertinent imaging results

CROSS REFERENCES

1. Intraocular Radiation Therapy for Age-Related Macular Degeneration, Medicine, Policy No. 134
2. Radioembolization for Primary and Metastatic Tumors of the Liver, Medicine, Policy No. 140
3. Stereotactic Radiosurgery and Stereotactic Body Radiation Therapy, Surgery, Policy No. 16

BACKGROUND

Charged-particle beams consisting of protons or helium ions are a type of particulate radiation therapy that contrast with conventional electromagnetic (i.e., photon) radiation therapy due to the unique properties of minimal scatter as the particulate beams pass through the tissue, and deposition of the ionizing energy at a precise depth (i.e., the Bragg Peak). Thus radiation exposure to surrounding normal tissues is minimized. Advances in photon-based radiation therapy such as 3-D conformal radiation therapy, intensity-modulated radiation therapy (IMRT), and stereotactic body radiotherapy (SBRT) have also allowed improved targeting of conventional therapy. 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 an adequate radiation dose 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:

1. Tumors located next to 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.

2. Tumors that are associated with a high rate of local recurrence despite maximal doses of conventional radiation therapy. The most common tumor in this group is locally advanced prostate cancer (i.e., Stages C or D1 [without distant metastases], also classified as T3 or T4 and tumors with Gleason scores of 8 to 10). These patients are generally not candidates for surgical resection.

REGULATORY STATUS

Radiotherapy is a procedure and, therefore, is not subject to U.S. Food and Drug Administration (FDA) regulations. However, the accelerators and other equipment used to generate and deliver charged particle radiation (including proton beam) are devices that require FDA oversight. Senior staff at the FDA’s Center for Devices and Radiological Health have indicated that the proton beam facilities constructed in the United States prior to enactment of the 1976 Medical Device Amendments were cleared for use in the treatment of human diseases on a “grandfathered” basis, while at least one that was constructed subsequently received a 510(k) marketing clearance. There are 510(k) clearances for devices used for delivery of proton beam therapy and devices considered to be accessory to treatment delivery systems such as the Proton Therapy Multileaf Collimator (which was cleared in December 2009). Since 2001, several devices classified as medical charged-particle radiation therapy systems have received 510(k) marketing clearance. FDA Product Code LHN.

EVIDENCE SUMMARY

The principal outcomes associated with treatment of malignancies are typically measured in units of survival past treatment: disease-free survival (DFS), a period of time following treatment where the disease is undetectable; progression-free survival (PFS), the duration of time after treatment before the advancement or progression of disease; and overall survival (OS), the period of time the patient remains alive following treatment. Patient quality of life may be another primary outcome, particularly among patients living with refractory disease, or when considering treatment of slow-progressing diseases (such as prostate cancer). In order to understand the impact of charged particle irradiation using photons or helium ion therapy on health outcomes, well-designed studies that compare the use of protons to other radiation therapies, such as external-beam radiation therapy (delivered with photons) are needed.

UVEAL MELANOMAS AND SKULL-BASE TUMORS

UVEAL MELANOMA

Systematic Reviews

Verma and Mehta published a systematic review of fourteen studies reporting clinical outcomes of proton beam radiotherapy (PBT) for uveal melanoma in 2016. Studies occurring between 2000 and 2015 were included; review was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Meta-
analyses were not conducted due to substantial methodological heterogeneity between studies. Included studies enrolled 59 to 3088 patients, median follow-up ranged from 38 to 148 months, and most tumors were choroidal and medium to medium-large-sized, and received 50-70 Cobalt Gray equivalent dose (studies conducted more recently reported lower doses). Five year local control, overall survival, and metastasis-free survival and disease-specific survival rates were > 90% (persisting at ten and fifteen years), 75 to 90%, and between 7 and 10%. The authors concluded that although PBT is associated with low toxicity and enucleation rates, recent developments to support radiation toxicity will aid in decreasing clinical adverse events, and overall, PBT is an excellent treatment for uveal melanomas.

In 2013 Wang et al published a systematic review on charged-particle (proton, helium or carbon ion) radiation therapy for uveal melanoma.[2] 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 brachytherapy. The other two RCTs compared different proton beam protocols so could not be used to draw conclusions about the efficacy of charged-ion particle therapy relative to other treatments. The overall quality of the studies was low; most of the observational studies did not adjust for potential confounding variables. The analysis focused on studies of treatment-naive patients (all but one of the identified studies). In a pooled analysis of data from nine studies, there was not a statistically significant difference in mortality with charged-particle therapy compared with brachytherapy (odds ratio [OR], 0.13; 95% confidence interval [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 vs 0.42 and 0.23 vs 0.68, respectively). According to this review, there is low-quality evidence that charged-particle therapy was at least as effective as alternative therapies as primary treatment of uveal melanoma and was superior in preserving vision. The review included controlled trials and case series with more than 5 patients. Twelve studies met eligibility criteria. The authors did not report study type, but they did not appear to identify only controlled trials, only case series. Sample sizes ranged from 9 to 367 patients. Six studies reported a 5-year survival rates that ranged from 67% to 94%.

Randomized Controlled Trials

No randomized controlled trials not already addressed in the above systematic reviews were identified.

SKULL BASED TUMORS

A 2016 systematic review by Matloob evaluated the literature on proton beam therapy for skull-based chordomas.[3] The review included controlled trials and case series with more than 5 patients. Twelve studies met eligibility criteria. The authors did not report study type, but they did not appear to identify only controlled trials, only case series. Sample sizes ranged from 9 to 367 patients. Six studies reported a 5-year survival rates that ranged from 67% to 94%.

PEDIATRIC TUMORS

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. 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. 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. 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.

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.

**Systematic Reviews**

In 2016, Leroy published a systematic review of the literature on PBT for treatment of pediatric cancers. Their findings on pediatric CNS tumors include the following:

- **Craniopharyngioma**: Three studies were identified, 2 retrospective case series and 1 retrospective comparative study of PBT versus IMRT. They concluded that there is very low level evidence that survival outcomes are similar with PBT and IMRT.
- **Ependymoma**: One prospective case series and 1 retrospective case series were identified. They concluded that the evidence is insufficient to support or refute the use of PBT for this condition.
- **Medulloblastoma**: One prospective case series and 2 retrospective case series were identified. They concluded that the evidence is insufficient to support or refute the use of PBT for this condition.
- **CNS germinoma**: One retrospective case series was identified. They concluded that the evidence is insufficient to support or refute the use of PBT for this condition.

An initial systemic review and a 2012 5-year updated systematic review drew similar conclusions, that except for rare indications such as childhood cancer, the gain from proton radiation therapy (RT) in clinical practice remains controversial.

In 2012 Cotter et al published a 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. 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.[10] 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.[11]

Massachusetts General Hospital reported on the use of protons in 17 children with ependymoma.[12] 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.

MD Anderson Cancer Center and Methodist Hospital in Houston reported on 52 children treated at two centers in Texas; 21 received PBT and 31 received IMRT.[13] Patients received a median dose of 50.4 Gy. At three years, OS was 94.1% in the PBT group and 96.8% in the IMRT group (p=0.742). Three-year nodular and cystic failure-free survival rates were also similar between groups. Seventeen patients (33%) were found on imaging to have cyst growth within three months of RT and 14 patients had late cyst growth (more than three months after therapy); rates did not differ significantly between groups. In 14 of the 17 patients with early cyst growth, enlargement was transient.

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.[14] 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.[15] 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
debunking 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 nine with non-germinomatous germ cell tumors (NGGCTs). 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, two patients developed growth hormone deficiency, and two patients developed central hypothyroidism. The authors stated that longer follow-up was necessary to assess the neurocognitive effects of therapy. In the same study, a dosimetric comparison of photons and protons for representative treatments with whole ventricular and involved field boost was done. Proton radiotherapy provided substantial sparing to the whole brain and temporal lobes, and reduced doses to the optic nerves.

Merchant and colleagues 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 five 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.

One additional published study was not addressed in the Cotter systematic review. 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. 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-
tissue 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 one 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.

RETINOBLASTOMA

Retinoblastoma is a rare (approximately 300 new cases per year in the U.S.) childhood malignancy that usually occurs in children under five years of age. External beam radiation therapy (EBRT) is an effective treatment for retinoblastoma, but had fallen out of favor due to the adverse effects on adjacent normal tissue. With the increasing availability of more conformal EBRT techniques, there has been renewed interest in EBRT for retinoblastoma. As noted previously, proton therapy eliminates the exit dose of radiation to normal tissues and may eliminate ~50% of radiation to normal tissue.

Current evidence from small studies has consistently reported decreased radiation exposure with proton therapy compared to other EBRT. Because this tumor is rare, it seems unlikely that large comparative trials will ever become available. The following is a summary of currently available published evidence:

Lee et al. reported on a small retrospective study of eight children with malignancies, including three cases of retinoblastoma, comparing proton therapy with 3D-CRT, IMRT, single 3D lateral beam, and 3D anterolateral beam with and without lens block.[19] Proton therapy resulted in better target coverage and less orbital bone radiation exposure (10%, 25%, 69%, 41%, 51%, and 65%, respectively). The authors concluded that proton therapy should be considered as the preferred technique for radiation therapy.

Krengli et al. compared various intraocular retinoblastoma locations and proton beam arrangements.[20] Only 15% of orbital bone received doses higher than 20 Gy, with no appreciable dose to the contralateral eye, brain, or pituitary gland.

Chang et al. reported on proton beam therapy in three children with retinoblastomas that were resistant to chemotherapy and focal treatment.[21] All three showed tumor regression with proton therapy, though two eventually had recurrence resulting in enucleation.

Munier et al. reported successful outcomes in six patients who received proton therapy as second-line or salvage therapy.[22]

Since retinoblastoma is sensitive to radiation therapy, EBRT may eliminate or delay the need for enucleation and improve survival, particularly in patients who have not responded adequately to chemotherapy. Due to the close proximity of these tumors to vital eye structures, the orbital bone, and the brain, inadvertent radiation to normal tissues must be minimized. Proton therapy 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 normal tissue.

OTHER PEDIATRIC TUMORS

There is scant data on the use of proton beam therapy in other pediatric tumors and includes
dosimetric planning studies in a small number of pediatric patients with parameningeal
rhabdomyosarcoma[23] and late toxicity outcomes in other solid tumors of childhood.[24,25]

HEAD AND NECK TUMORS OTHER THAN SKULL-BASE TUMORS

In treating head and neck cancer other than skull-based tumors, the data from comparative
studies are lacking and noncomparative data are insufficient.

SYSTEMATIC REVIEWS

A 2014 systematic review evaluated the literature on charged particle therapy versus photon
therapy for the treatment of paranasal sinus and nasal cavity malignant disease.[26] The
authors identified 41 observational studies that included 13 cohorts treated with charged
particle therapy (total N=286 patients) and 30 cohorts treated with photon therapy (total
N=1186 patients). There were no head-to-head trials. In a meta-analysis, the pooled event rate
of OS was significantly higher with charged particle therapy than photon therapy at the longest
duration of follow-up (RR=1.27; 95% CI, 1.01 to 1.59). Findings were similar for the outcome
survival at five years (RR=1.51; 95% CI, 1.14 to 1.99). Findings were mixed for the outcomes
locoregional control and disease-free survival; photon therapy was significantly better for only
one of the two timeframes (longest follow-up or 5-year follow-up). In terms of adverse effects,
there were significantly more neurologic toxic effects with charged particle therapy compared
with photon therapy (p<0.001) but other toxic adverse event rates e.g., eye, nasal and
hematologic did not differ significantly between groups. The authors noted that the charged
particle studies were heterogeneous, e.g., type of charged particles (carbon ion, proton),
delivery techniques. It should also be noted that comparisons were indirect, and none of the
studies included in the review actually compared the two types of treatment in the same patient
sample.

NONRANDOMIZED STUDIES

In 2014, Zenda et al. reported on late toxicity in 90 patients after PBT for nasal cavity,
paranasal sinuses, or skull base malignancies.[27] Eighty seven of the 90 patients had
paranasal sinus or nasal cavity cancer. The median observation period was 57.5 months.
Grade 3 late toxicities occurred in 17 patients (19%) and grade 4 occurred in six patients (7%).
Five patients developed cataracts, and five had optic nerve disorders. Late toxicities (other
than cataracts) developed a median of 39.2 months after PBT.

PROSTATE CANCER

The published literature indicates that dose escalation is an accepted concept in treating
organ-confined prostate cancer.[28] 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 intensity modulated radiation therapy (IMRT) or three-
dimensional conformal radiotherapy (3D-CRT) permits improved delineation of the target
volume, if the dose is not accurately delivered, the complications of dose escalation can be
serious, as the bladder and rectal tissues would be exposed to even higher radiation doses. The accuracy of dose delivery applies to both conventional and proton beam therapy.\textsuperscript{[29]}

**SYSTEMATIC REVIEWS**

A 2010 BCSBA 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 health outcomes in any setting for prostate cancer.\textsuperscript{[30]} A total of nine studies were included in the review; 4 were comparative and five were noncomparative. The following is a summary of the key findings and conclusions:

There was inadequate evidence from comparative studies to permit conclusions concerning the impact of proton beam therapy compared with other treatments for prostate cancer.

Regarding the two randomized, controlled trials (both of good quality) that have been published, one trial showed significantly improved incidence of biochemical failure, an intermediate outcome, for patients receiving high-dose proton beam boost compared with conventional-dose proton boost. No difference between groups was observed in overall survival. Although grade 2 acute gastrointestinal toxicity was significantly more frequent in the group receiving high-dose proton beam boost, acute genitourinary toxicity and late toxicities did not significantly differ. Nevertheless, a single study with intermediate outcome data of uncertain relation to survival is insufficient to permit conclusions about the comparative effects of x-ray external-beam radiotherapy plus either a conventional-dose proton beam boost or a high-dose proton beam boost. The other randomized 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. This trial used x-ray external-beam radiotherapy methods that are no longer relevant to clinical practice, precluding conclusions about the comparative effects of x-ray external-beam radiotherapy plus either an x-ray boost or a proton beam boost.

The only other comparative study was not randomized, used inadequate statistical methods, and compared quality of life and symptom scale outcomes for x-ray external-beam radiotherapy plus a proton beam boost, watchful waiting, radical prostatectomy, proton beam therapy alone, and x-ray external-beam radiotherapy alone. This study was too small and did not appear to use adequate confounder adjustment procedures, so the observed differences may be distorted by imbalances on important outcome predictors.

Regarding use of proton beam therapy without x-ray external-beam radiotherapy, evidence is insufficient. The flawed nonrandomized comparative study noted above included a group treated with proton beam therapy alone. Additional noncomparative evidence comes from a case series mixing patients receiving proton beam therapy alone or combined protons and x-rays; reports from 2 other centers provide insufficient evidence.

In 2014, the Agency for Healthcare Research and Quality (AHRQ) published an updated review of the risk and benefits of a number of therapies for localized prostate cancer.\textsuperscript{[31]} The authors compared risk and benefits of a number of treatments for localized prostate cancer including radical prostatectomy, EBRT (standard therapy as well as PBT, 3D conformal RT,
IMRT and stereotactic body radiotherapy (SBRT]), interstitial brachytherapy, cryotherapy, watchful waiting, active surveillance, hormonal therapy, and high-intensity focused ultrasound. The review concluded that the evidence for most treatment comparisons is inadequate to draw conclusions about comparative risks and benefits. Limited evidence appeared to favor surgery over watchful waiting or EBRT, and RT plus hormonal therapy over RT alone. The authors noted that there are advances in technology for many of the treatment options for clinically localized prostate cancer; for example, current RT protocols allow higher doses than those administered in many of the trials included in the report. Moreover, the patient population has changed since most of the studies were conducted. In recent years, most patients with localized prostate cancer are identified via prostate-specific antigen (PSA) testing and may be younger and healthier than prostate cancer patients identified in the pre-PSA era. Thus, the authors recommend additional studies to validate the comparative effectiveness of emerging therapies such as PBT, robotic-assisted surgery and SBRT.

Brada and colleagues reported on a systematic review of evidence for proton beam therapy, discussing prostate cancer among other indications. The researchers concluded that the current published literature on proton beam therapy does not support any definitive benefit for survival, tumor control, or toxicity over other forms of high-dose conformal radiation in the treatment of localized prostate cancer.

Grimm and colleagues from the Prostate Cancer Results Study Group (PCRSG) published results from a systematic review of the literature on prostate-specific antigen free survival (an intermediate outcome) in localized prostate cancer by treatment type and risk group. Proton beam radiation therapy was included as a type of radiation therapy (along with external beam, conformal, and intensity modulated radiotherapy). The authors concluded that brachytherapy with and without EBRT provided the strongest evidence for treatment benefit in patients with low and intermediate risk of disease. Proton beam radiation therapy was not specifically recommended. However, interpretation of results from this analysis is limited by the lack of study of primary health outcomes. Although intermediate health outcomes (such as prostate-specific antigen free survival) are important to understand, such outcomes do not correlate exactly with overall survival, patient quality of life, or other primary health outcomes.

Efstathiou and colleagues concluded that the current evidence did not support any definitive benefit to PBT over other forms of high-dose conformal radiation in the treatment of localized prostate cancer. They also commented on uncertainties surrounding the physical properties of PBT, perceived clinical gain, and economic viability.

Subsequent to the above early randomized trials, newer sophisticated treatment planning techniques (i.e., 3-dimensional conformal radiotherapy (3D-CRT) or intensity-modulated radiation therapy [IMRT]) permitted dose escalation of conventional radiation therapy to 80 Gy, a dose higher than that achieved with proton therapy in the above studies. Furthermore, these gains were achieved without increasing radiation damage to adjacent structures. For example, in 2004, investigators at Loma Linda reported their experience with 1,255 patients with prostate cancer who underwent 3D-CRT proton beam radiation therapy. Outcomes were measured in terms of toxicity and biochemical control, as evidenced by 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.
Additional data have been published concerning use of proton beam therapy in localized prostate cancer.\[38\] Reports from treating large numbers of patients with prostate cancer using this modality have not demonstrated results superior to those obtained with alternative techniques for delivering radiation therapy. For example:

In 2012, Sheets and colleagues published results from a population-based cohort study on the impact of several radiation therapies on morbidity in treatment of localized prostate cancer.\[39\] Specifically, rates of gastrointestinal and urinary morbidities (nonincontinence and incontinence), along with rates of sexual dysfunction, and hip fractures were compared between treatment groups (proton therapy versus IMRT) among a cohort of 10,122 men treated from 2000 to 2008. Using statistical analysis, and following these men until December 31, 2009, the researchers found that, controlling for age, region, stage of disease and other demographic and disease-related variables, almost no differences were identified in rates of radiation-related comorbidities, with the exception of increased risk of gastrointestinal events among patients receiving proton therapy. Citing organ movement during radiation therapy as a possible reason for this difference, the researchers concluded, “Overall, our results do not clearly demonstrate a clinical benefit to support the recent increase in proton therapy use for prostate cancer.” Although this is a large, population-based study, results from this analysis are limited by the use of claims data (which may not be intended for use in clinical research studies), along with the non-randomized nature of the study itself. Outcomes from this trial should be included in large randomized controlled trials before conclusions regarding the relative effectiveness of these different radiation therapies can be made.

Yu et al. retrospectively reviewed all Medicare beneficiaries 66 years of age or older who received proton therapy (n=553) or IMRT (n=27,094) during 2008 and 2009.\[40\] There was heterogeneity in patient demographics; specifically, the patients receiving proton therapy were younger, healthier and from more affluent areas than patients receiving IMRT. At 6 months follow-up, PRT was associated with a statistically significant reduction in genitourinary (GU) toxicity compared with IMRT (p=0.03). However, by 12 months post-treatment, there was no significant difference in GU toxicity between the two groups. There was no statistically significant difference in gastrointestinal or other toxicity at 6 or 12 months post-treatment. The authors concluded that, although proton therapy was significantly more costly than IMRT, there was no difference in toxicity in this patient population at 12 months post-treatment.

NON-SMALL CELL LUNG CANCER (NSCLC)

SYSTEMATIC REVIEWS

A 2010 BCSBA TEC Assessment addressed the key question of how health outcomes (overall survival, disease-specific survival, local control, disease-free survival, and adverse events) for NSCLC treated with PBT compared with outcomes observed for stereotactic body radiotherapy (SBRT), which is an accepted radiation therapy approach to treat NSCLC.\[41\] The following are findings from the TEC Assessment:

Citing the lack of comparative randomized clinical trials, the TEC Assessment concluded that the evidence is insufficient to permit conclusions about the results of PBT for any stage of NSCLC. In the absence of randomized controlled trials, the comparative effectiveness of PBT and SBRT is uncertain. The evidence is limited by
poor adverse events reporting. Reports are difficult to interpret due to lack of consistency across studies, detail about observation periods, and information about rating criteria and grades. There is no mention of use of an independent assessor of patient-reported adverse events.

Details are lacking on several aspects of PBT treatment regimens. Subjects in the PBT studies were similar in age, but there was great variability in proportion of patients within each stage of cancer, sex ratio, and proportion of medically inoperable cancers. 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, ranging from 39% - 98% for reported probability of 2-year overall survival in 7 studies and 25% - 78% for 5-year overall survival in 5 studies. It is unclear whether the heterogeneity of results can be explained by differences in patient and treatment characteristics. Indirect comparisons between PBT and SBRT, comparing separate sets of single-arm studies on PBT and SBRT, may be distorted by confounding.

Pijls-Johannesma and colleagues conducted a 2010 systematic literature review examining the evidence on the use of charged particle therapy in lung cancer.\[^{42}\] Study inclusion criteria included series with at least 20 patients and a minimum follow-up period of 24 months. Eleven studies all dealing with NSCLC, mainly stage I, were included in the review, five investigating protons (n=214) and six investigating C-ions (n=210). The proton studies included one phase 2 study, two prospective studies, and two retrospective studies. The C-ion studies were all prospective and conducted at the same institution in Japan. No phase 3 studies were identified. Most patients had stage 1 disease; however, a wide variety of radiation schedules, along with varied definitions of control rates were used, making comparisons of results difficult. 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) rates were 31%–74% and 23%, respectively, and 2- and 5-year cause-specific survival (CSS) rates were 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.

**NONRANDOMIZED STUDIES**

No studies have been published that directly compare health outcomes in patients with NSCLC treated with PBT versus an alternative treatment. For example, 2013, Bush et al published data on a relatively large series of patients (n=111) treated at one U.S. facility over 12 years.\[^{43}\] 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 1 disease. The 4-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 4 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. The lack of comparison group does not permit conclusion about the effectiveness and toxicity of PBT compared with alternative therapies.

OTHER INDICATIONS

Current research on the use of charged particle radiation therapy for other indications is limited. A number of case series describe initial results using proton beam therapy for a variety of indications including but not limited to gastrointestinal neoplasms (including hepatocellular carcinoma), breast, uterine, age-related macular degeneration, and axial skeletal tumors.\(^{[44-59]}\) The combination of proton beam radiotherapy with transpupillary thermotherapy in the treatment of ocular melanoma is being studied.\(^{[60]}\)

PRACTICE GUIDELINE SUMMARY

NATIONAL COMPREHENSIVE CANCER NETWORK

The National Comprehensive Cancer Network (NCCN) Guidelines for Bone Cancer (2.2017) state “specialized techniques such intensity-modulated radiotherapy (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.”\(^{[61]}\)

The NCCN Guidelines for Prostate Cancer (2.2017) refer to ASTRO's current policy, i.e., proton beam therapy for primary treatment of prostate cancer should only be performed within the context of a prospective clinical trial.\(^{[62]}\) The costs associated with proton beam facility construction and proton beam treatment are high compared with the expense of building and using the more common photon linear accelerator based practice. The NCCN panel concluded that there is no clear evidence supporting a benefit or decrement to proton therapy over IMRT for either treatment efficacy or long-term toxicity.

The NCCN Guidelines for Central Nervous System Cancers (1.2016) includes a footnote stating that “Considering protons over photons (if available) for craniospinal irradiation in adults is reasonable.”\(^{[63]}\)

The NCCN Guidelines for Non-Small Cell Lung Cancer (7.2017) states that, more advanced technologies, including proton therapy, “are appropriate when needed to deliver curative RT safely. . . Nonrandomized comparisons of using advanced technologies versus older techniques demonstrate reduced toxicity and improved survival.”\(^{[64]}\) No comparative studies are cited with this discussion point.

AMERICAN SOCIETY OF RADIATION ONCOLOGY

A literature review with clinical recommendations from the American Society of Radiation Oncology (ASTRO) considered the use of charged particle therapy in several indications, including uveal melanoma.\(^{[65]}\) The society concluded that “[Charged particle therapy] has been shown to be effective in the treatment of large ocular melanomas not approachable via brachytherapy.” Nevertheless, due to the absence of a clear appraisal of the literature, these recommendations are best considered consensus-based.

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.”[66] In September 2013, as part of its national “Choosing Wisely” initiative, ASTRO listed proton beam therapy for prostate cancer as one of 5 radiation oncology practices that should not be routinely used because they are not supported by evidence.[67] “There is no clear evidence that proton beam therapy for prostate cancer offers any clinical advantage over other forms of definitive radiation therapy. Clinical trials are necessary to establish a possible advantage of this expensive therapy.”

In its 2012 review, the ASTRO also considered the use of charged particle therapy in prostate cancer.[65] The society concluded that “The outcome [from charged particle therapy] is similar to IMRT therapy however, with no clear advantage from clinical data for either technique in disease control or prevention of late toxicity.” As stated above, conclusions from this review are limited by lack of evidence appraisal.

The 2012 ASTRO evidence-based review of proton beam therapy note there are “multiple theoretical advantages” for PBT over photon RT for CNS tumors.[65] However, the authors concluded that, “Overall, more clinical data are needed to fully establish the role of PBT in CNS tumors. The 2012 ASTRO evidence-based guideline for radiotherapeutic and surgical management for newly diagnosed brain metastases do not address PBT.

The ASTRO guidelines considered the use of charged particle therapy in non-small cell lung cancer in its 2012 evidence review.[65] For the treatment of stage 1 NSCLC, the review concluded, “no clear clinical benefit over photon therapy has currently been shown” and that evidence is not sufficient to recommend charged particle therapy in other stages of disease.

AMERICAN COLLEGE OF RADIOLOGY

The American College of Radiology (ACR) Appropriateness Criteria (2015) for induction and adjuvant therapy for N2 NSCLC state that the utility of intensity-modulated radiation therapy (IMRT) or protons to potentially reduce normal tissue toxicity remains to be explored.[68] The 2014 ACR Appropriateness Criteria® concluded that “There are only limited data comparing proton beam therapy to other methods of irradiation or to radical prostatectomy for treating stage T1 and T2 prostate cancer.[69] Further studies are needed to clearly define its role for such treatment.”


INTERNATIONAL PARTICLE THERAPY CO-OPERATIVE GROUP

A 2016 consensus statement by the International Particle Therapy Co-operative Group made the following conclusion about proton therapy for non-small-cell lung cancer (NSCLC).[73] The statement is based on expert consensus opinion:
“...Promising preliminary clinical outcomes have been reported for patients with early-stage or locally advanced NSCLC who receive proton therapy. However, the expense and technical challenges of proton therapy demand further technique optimization and more clinical studies....”

SUMMARY

OCULAR, CERVICAL SPINE, AND SKULL BASE TUMORS

There is enough research to show reduced harms when using charged-particle irradiation such as proton or helium ion compared to other modalities for cervical spinal cord or skull base central nervous system tumors. Therefore, the use of charged-particle irradiation such as proton or helium ion may be considered medically necessary to treat ocular, cervical spine, and skull base tumors when policy criteria are met.

For all other tumors or indications when policy criteria is not met, there is not enough research to show improved health outcomes with charged-particle irradiation such as proton or helium ion compared to other radiotherapy techniques and therefore, are considered investigational.

PEDIATRIC TUMORS

For pediatric central nervous system and malignant solid tumors, there is limited research but some studies suggest reduced harms and a reduction in cancer recurrence when using charged-particle irradiation. Therefore, charged-particle irradiation such as proton or helium ion may be considered medically necessary in the treatment of pediatric central nervous system and malignant solid tumors.

There is not enough research to show an improvement in health outcomes for all other pediatric tumors. Therefore, charged-particle irradiation such as proton or helium ion is considered investigational for all other pediatric tumors when policy is not met.

PROSTATE CANCER

For clinically localized prostate cancer using charged-particle irradiation such as proton or helium ion, current research has not demonstrated better health outcomes compared to other techniques and is generally more costly. Therefore, the use of charged-particle irradiation such as proton or helium ion to treat clinically localized prostate cancer is considered not medically necessary.

There is not enough research to show an improvement in health outcomes using charged-particle irradiation such as proton or helium ion to treat regional (locally advanced) or metastatic prostate cancer. Therefore, the use of charged-particle irradiation such as proton or helium ion to treat regional (locally advanced) or metastatic prostate cancer is considered investigational.

REFERENCES


33. Grimm, P, Billiet, I, Bostwick, D, et al. Comparative analysis of prostate-specific antigen free survival outcomes for patients with low, intermediate and high risk prostate cancer
treatment by radical therapy. Results from the Prostate Cancer Results Study Group. *BJU international.* 2012 Feb;109 Suppl 1:22-9. PMID: 22239226


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. Unlisted procedure codes for medical radiation physics, clinical treatment planning and treatment management may be used.

Treatment delivery:

The codes 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. CPT codes 77402-77416). When proton therapy is used the following specific CPT codes are available:

<table>
<thead>
<tr>
<th>Codes</th>
<th>Number</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td>77520</td>
<td>Proton beam delivery, simple, without compensation</td>
</tr>
<tr>
<td></td>
<td>77522</td>
<td>Proton beam delivery; simple with compensation</td>
</tr>
<tr>
<td></td>
<td>77523</td>
<td>Proton beam delivery; intermediate</td>
</tr>
<tr>
<td></td>
<td>77525</td>
<td>Proton beam delivery; complex</td>
</tr>
</tbody>
</table>

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

HCPCS None

*Date of Origin: April 1998*