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Medical Policy Manual

Topic: Charged-Particle (Proton or Helium Ion) Radiation Therapy

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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 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:

- 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.

- 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.

MEDICAL POLICY CRITERIA

I. Charged-particle irradiation with proton or helium ion beams may be considered **medically necessary** 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 the 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.

C. In the treatment of pediatric (less than 21 years of age) central nervous system tumors and retinoblastoma.

II. Charged-particle irradiation with proton beams is considered **not medically necessary** in patients with clinically localized prostate cancer. Clinical outcomes with this treatment have not been shown to be superior to other approaches such as intensity modulated radiation therapy (IMRT) or 3D-conformal radiation therapy, yet charged-particle irradiation with proton beams is more costly than these alternatives.

Clinically localized prostate cancer is defined as stage T1 to T2 with no regional lymph node (N0) or distant metastases (M0)[1] using the American Joint Committee on Cancer's TNM (Tumor-Node-Metastasis) system:[2]

- T1: Clinically unapparent tumor not palpable nor visible by imaging
  - T1a: Tumor incidental histologic finding in ≤5% of tissue resected
  - T1b: Tumor incidental histologic finding in >5% of tissue resected
  - T1c: Tumor identified by needle biopsy (e.g., because of elevated PSA)
- T2: Tumor confined within prostate*
  - T2a: Tumor involves 50% of one lobe or less
  - T2b: Tumor involves >50% of one lobe but not both lobes
  - T2c: Tumor involves both lobes

* Notes:
- Tumor that is found in one or both lobes by needle biopsy but is not palpable or reliably

visible by imaging is classified as T1c.
- Invasion into the prostatic apex or into (but not beyond) the prostatic capsule is classified as T2.

III. Other applications of charged-particle irradiation are considered **investigational**, including but not limited to the following:

A. Acoustic neuroma (vestibular schwannoma)

B. Axial skeleton tumors

C. Bladder cancer

D. Brain tumors other than pediatric central nervous system tumors

E. Breast tumors

F. Choroidal neovascularization (CNV)

G. Head and neck tumors other than skull-base tumors

H. Metastases from choroid tumors

I. Olfactory neuroblastomas or esthesioneuroblastomas

J. Pediatric tumors other than central nervous system tumors and retinoblastoma

K. Prostate cancer not meeting the clinically localized description in II. above.

L. Recurrent melanoma of the uveal tract

M. Sinonasal carcinoma

N. Solid organs, primary or metastatic (e.g., liver, lung, kidney, pancreas)

O. Spinal cord tumors

P. Uterine cancer

SCIENTIFIC EVIDENCE

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 radiation therapy for treatment of on these outcomes, well-designed randomized controlled trials (RCTs) that compare this therapy to standard radiation therapies, such as external-beam radiation therapy (delivered with photons) are needed.

Uveal Melanomas and Skull-base Tumors

Systematic Reviews

- A 1996 technology assessment from the BlueCross and BlueShield Association (BCBSA) Technology Evaluation Center (TEC) reached the following conclusions:[3]

  Charged-particle beam radiation therapy (CPB-RT) is as effective as an available alternative for improving net health outcomes in patients with uveal melanoma.
  - The research focus for CPB-RT has been on providing adequate local control while still preserving vision.
  - Compared with enucleation, CPB-RT yields comparable results for overall and metastasis-free survival at 5 years, a slightly greater risk for failure of local control, but a substantially greater preservation of vision in the treated eye for at least 5 years.
  - Compared with radioisotope-containing plaques or applicators, CPB-RT may result in a smaller probability of enucleation and, for proton beam radiotherapy, a slightly greater retention of vision.

  Charged-particle beam irradiation is at least as effective as, and may be superior to, alternative therapies including conventional radiation or resection as treatment for chordomas or chondrosarcomas of the skull base or cervical spine.
  - Compared with conventional x-ray treatment following partial resection or biopsy, CPB-RT yields greater rates of local control, overall survival, and disease-free survival at 5 years after therapy.
  - These results were obtained with no treatment-related fatalities and with a tolerable level of treatment-related morbidity.

- In 2013 Wang et al published a systematic review on charged-particle (proton, helium or carbon ion) radiation therapy for uveal melanoma. The review included 27 controlled and uncontrolled studies that reported health outcomes e.g., mortality, local recurrence. Three of the studies were randomized controlled trials (RCTs). One of the RCTs compared helium ion therapy brachytherapy. The other 2 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-naïve patients (all but one of the identified studies). In a pooled analysis of data from 9 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.

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.[4] 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.[5] 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

An initial systemic review[6] and a 2012 5-year updated systematic review[7] 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:[8]

- 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.[9] 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.[10]
- Massachusetts General Hospital reported on the use of protons in 17 children with ependymoma.[11] 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.[8] 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.[12] 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.[13] 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).[14] 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.
- 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.

One additional published study was not addressed in the Cotter et al 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.[16] 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.

Retinoblastoma

Retinoblastoma is a rare (approximately 300 new cases per year in the U.S.) childhood malignancy that usually occurs in children under 5 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.[17] 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. 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. 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.

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[18] and late toxicity outcomes in other solid tumors of childhood.[19,20]

Prostate Cancer

The published literature indicates that dose escalation is an accepted concept in treating organ-confined prostate cancer.[21] 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.[22]

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.[23] A total of 9 studies were included in the review; 4 were comparative and 5 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.

- A 2008 comparative effectiveness review of therapies for clinically localized prostate cancer from the AHRQ indicated that the quality of evidence was low, and based on nonrandomized comparisons, the absolute rates of outcomes after proton radiation appear similar to other treatments.[24] The report noted the following:

  "Based on nonrandomized reports, the rates of clinical outcomes and toxicity after proton therapy may be comparable with conformal radiation. There was no direct evidence that proton EBRT results in better overall or disease-free survival than other therapies."

  "Limitations in the existing evidence included the following:
  - Few randomized trials directly compared the relative effectiveness between (rather than within) major treatment categories.
  - Many randomized trials were inadequately powered to provide long-term survival outcomes, with the majority reporting biochemical progression or recurrence as the main outcomes.
  - Some randomized trials were old, conducted prior to prostate cancer detection with PSA testing, when tumors are diagnosed in an earlier stage, giving more lead time, and there is a higher percentage of benign tumors, resulting in length bias and over diagnosis. The older studies also used technical aspects of treatment that may not reflect current practice; therefore, their results may not be generalizable to modern practice settings.
  - Wide variation existed in reporting and definitions of outcomes.
  - There was little reporting of outcomes according to major patient and tumor characteristics.
  - Emerging technologies have not been evaluated in randomized trials.
  - Data from nonrandomized trials are inadequate to reliably assess comparative effectiveness and adverse effects."

- Brada and colleagues reported on a systematic review of evidence for proton beam therapy, discussing prostate cancer among other indications.[25] 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.[26] 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.[27] They also commented on uncertainties surrounding the physical properties of PBT, perceived clinical gain, and economic viability.

Subsequent to the above early randomized trials, new sophisticated treatment planning techniques, referred to as 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.[28,29] 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-CRTproton beam radiation therapy.[30] 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.[31] 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.[32] 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.[33] 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.[34] The following are findings from the TEC Assessment:

  Citing the lack of comparative randomized clinical trials, the TEC Assessment concluded that the evidence was 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 was uncertain. Limitations of the current evidence included the following:

  - Adverse events were generally poorly reported and were difficult to interpret due to lack of consistent reporting across studies, detail about observation periods and information about rating criteria and grades.
  - There was no mention of use of an independent assessor of patient-reported adverse events.
  - Details were 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 was 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 were 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.[35] 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 1 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, 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.

Clinical 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 1 U.S. facility over 12 years.[36] 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, 4 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

Available scientific evidence 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 hepatocellular cancer, metastatic tumors of the choroid, breast cancer, bladder cancer, uterine cancer, sinonasal undifferentiated carcinoma, medulloblastoma, age-related macular degeneration, choroidal neovascularization, and axial skeletal tumors.[37-49]
- The combination of proton beam radiotherapy with transpupillary thermotherapy in the treatment of ocular melanoma is being studied.[50]
- The literature on the use of proton beam therapy for head and neck tumors other than skull-base is scant and consists of dosimetric planning studies for nasopharyngeal carcinoma[51] and a case series of 91 patients who received combined proton and photon radiotherapy for advanced paranasal sinus tumors.[52]

Results from case series are not sufficient to determine if proton beam therapy offers any advantage over conventional treatments for these conditions. In most studies proton beam therapy is used in combination with other therapies, without comparison to groups treated without proton beam therapy. This makes it difficult to isolate the independent contribution of proton beam therapy on health

outcomes. Results from long-term comparative studies are needed to evaluate impact of proton beam therapy on treatment of these indications relative to standard medical care.

Clinical Practice Guidelines

Uveal Melanomas and Skull-base Tumors

National Comprehensive Cancer Network (NCCN)[53]

The NCCN guidelines for bone cancer state that proton beam radiation therapy, "may be useful in patients with chondrosarcomas of the skull base and axial skeleton with tumors in unfavorable location not amenable to resection."

American Society of Radiation Oncology (ASTRO)[54]

A literature review with clinical recommendations from ASTRO considered the use of charged particle therapy in several indications, including uveal melanoma. 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.

Prostate Cancer

National Comprehensive Cancer Network (NCCN)[55]

- The NCCN guidelines for prostate cancer (V2.2014) stated that, "proton beams can be used as an alternative radiation source. The costs associated with proton beam facility construction and proton beam treatment are high. . . The NCCN panel echoed the following statement by ASTRO in its review of proton beam therapy: 'The outcome [with proton 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. This is a site where further head-to-head clinical trials may be needed to determine the role of proton beam therapy.'"

American College of Radiology (ACR)[56]

The 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. Further studies are needed to clearly define its role for such treatment."

American Society of Radiation Oncology (ASTRO)

- 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."[57]
- 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.[58] "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.[54] Contrasting with the popularity of this technology, 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.

Adult Brain Tumors

National Comprehensive Cancer Network (NCCN)[59]

A new footnote was added in the V1.2014 NCCN guidelines on central nervous system cancers stating that "Considering protons over photons (if available) for craniospinal irradiation in adults is reasonable." The only reference listed was the 2013 Brown et al. retrospective review of 40 adult patients treated for medulloblastoma.

American Society of Radiation Oncology (ASTRO)

The 2012 ASTRO evidence-based review of proton beam therapy noted "multiple theoretical advantages" for PBT over photon RT for CNS tumors. [54] 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 did not address PBT.

Non-small Cell Lung Cancer (NSCLC)

National Comprehensive Cancer Network (NCCN)[60]

NCCN guidelines for non-small cell lung cancer stated that more advanced, 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."

American College of Radiology (ACR)

- The 2013 ACR Appropriateness Criteria® for induction and adjuvant therapy for N2 NSCLC stated that "the utility of intensity-modulated radiation therapy (IMRT) or protons to potentially reduce normal tissue toxicity remains to be explored.[61]
- The 2014 ACR Appropriateness Criteria for nonsurgical treatment of NSCLC noted that, "due to physical characteristics, protons can spare more normal tissues and may allow further dose escalation/acceleration. However, there are more uncertainties about proton therapy in lung cancer, and much improvement and optimization is still needed. Protons may not be suitable for all lung cancer patients, and proper case selection and proper proton techniques based on motion and anatomy are crucial to improve the therapeutic ratio."[62]
- The 2012 ACR Appropriateness Criteria® (ACR) for nonsurgical treatment of poor-performance NSCLC or palliative intent do not include charged particle radiation therapy as an appropriate treatment for non-small cell lung cancer.[63-65]

American Society of Radiation Oncology (ASTRO)[54]

The ASTRO guidelines considered the use of charged particle therapy in non-small cell lung cancer in its 2012 evidence review. 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.

Summary

Uveal Melanoma and Skull-base Tumors

- Available evidence on the use of charged particle beam radiation therapy to treat uveal melanomas suggests treatment benefit (improved vision and rate of overall and metastasis-free survival and/or decreased risk of enucleation) compared with standard treatment. Therefore, use of charged particle therapy may be considered medically necessary in certain patients with this condition.

- Compared with x-ray therapy, evidence suggests treatment with charged particle therapy may be associated with greater local control and survival for patients with chordomas or chondrosarcomas of the skull base or cervical spine. Use of charged particle therapy in select patients with these conditions is therefore considered medically necessary.

Pediatric Tumors

- For pediatric central nervous system (CNS) tumors and retinoblastoma, there is a small body of literature on long-term outcomes with the use of proton beam therapy. This modality of treatment 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. Therefore, proton beam therapy may be considered medically necessary in the treatment of pediatric CNS tumors and retinoblastoma.
- Current evidence is insufficient to permit conclusions on the safety and efficacy of proton beam radiation therapy for pediatric tumors other than central nervous system tumors and retinoblastoma. The available evidence consists of dosimetric planning studies and a few case series in a small number of patients. Larger, longer-term studies are needed that compare proton therapy with other treatment for these tumors. Therefore, proton beam radiation therapy is considered investigational for pediatric tumors other than central nervous system tumors and retinoblastoma.

Prostate Cancer

While charged particle therapy is generally more costly than alternative treatments, available data has not demonstrated improved outcomes with proton or helium beam radiation therapy compared with alternative conventional techniques in the treatment of prostate cancer. Therefore, the use of charged particle therapy in prostate cancer is considered not medically necessary.

Non-Small Cell Lung Cancer (NSCLC)

Current evidence is insufficient to establish the effectiveness of charged particle (proton or helium beam) therapy compared with alternative treatments for non-small cell lung cancer (NSCLC). Comparative studies are needed to determine the treatment benefit associated with this therapy above

and beyond that conferred by alternative conventional techniques in the treatment of NSCLC. Therefore, the use of charged particle therapy is considered investigational in the treatment of NSCLC.

Other Indications

Proton beam therapy has been studied as a treatment for a number of other indications, including but not limited to hepatocellular cancer, breast cancer, uterine cancer, medulloblastoma in adults, head and neck cancer other than tumors of the skull base, choroidal neovascularization, and axial skeletal tumors. While these studies contribute to the body of literature on each indication, they are not sufficient to determine relative treatment benefit associated with proton or helium beam therapy. Therefore, the use of charged particle therapy in the treatment of one or more of these indications, or any other indication not specifically considered in the policy criteria, is considered investigational.

REFERENCES

1. Thompson, I, Thrasher, JB, Aus, G, et al. Guideline for the management of clinically localized prostate cancer: 2007 update. *J Urol*. 2007 Jun;177(6):2106-31. PMID: 17509297
2. National Cancer Institute at the National Institutes of Health. Prostate Cancer Treatment (PDQ®) Staging Information for Prostate Cancer. [cited 06/20/2014]; Available from: http://www.cancer.gov/cancertopics/pdq/treatment/prostate/HealthProfessional/page2
3. TEC Assessment 1996. "Charged Particle (Proton or Helium Ion) Irradiation for Uveal Melanoma and for Chordoma or Chondrosarcoma of the Skull Base or Cervical Spine." BlueCross BlueShield Association Technology Evaluation Center, Vol. 11 Tab. 1.
4. Hoffman, KE, Yock, TI. Radiation therapy for pediatric central nervous system tumors. *J Child Neurol*. 2009 Nov;24(11):1387-96. PMID: 19841427
5. Borsting, E, Mitchell, GL, Kulp, MT, et al. Improvement in Academic Behaviors After Successful Treatment of Convergence Insufficiency. *Optom Vis Sci*. 2012 Jan;89(1):12-8. PMID: 22080400
6. Lodge, M, Pijls-Johannesma, M, Stirk, L, Munro, AJ, De Ruysscher, D, Jefferson, T. A systematic literature review of the clinical and cost-effectiveness of hadron therapy in cancer. *Radiother Oncol*. 2007 May;83(2):110-22. PMID: 17502116
7. De Ruysscher, D, Mark Lodge, M, Jones, B, et al. Charged particles in radiotherapy: a 5-year update of a systematic review. *Radiother Oncol*. 2012 Apr;103(1):5-7. PMID: 22326572
8. Cotter, SE, McBride, SM, Yock, TI. Proton radiotherapy for solid tumors of childhood. *Technology in cancer research & treatment*. 2012 Jun;11(3):267-78. PMID: 22417062
9. Hug, EB, Muenter, MW, Archambeau, JO, et al. Conformal proton radiation therapy for pediatric low-grade astrocytomas. *Strahlenther Onkol*. 2002 Jan;178(1):10-7. PMID: 11977386
10. Fuss, M, Hug, EB, Schaefer, RA, et al. Proton radiation therapy (PRT) for pediatric optic pathway gliomas: comparison with 3D planned conventional photons and a standard photon technique. *Int J Radiat Oncol Biol Phys*. 1999 Dec 1;45(5):1117-26. PMID: 10613303
11. MacDonald, SM, Safai, S, Trofimov, A, et al. Proton radiotherapy for childhood ependymoma: initial clinical outcomes and dose comparisons. *Int J Radiat Oncol Biol Phys*. 2008 Jul 15;71(4):979-86. PMID: 18325681
12. Fitzek, MM, Linggood, RM, Adams, J, Munzenrider, JE. Combined proton and photon irradiation for craniopharyngioma: long-term results of the early cohort of patients treated at Harvard Cyclotron Laboratory and Massachusetts General Hospital. *Int J Radiat Oncol Biol Phys*. 2006 Apr 1;64(5):1348-54. PMID: 16580494

13. Luu, QT, Loredo, LN, Archambeau, JO, Yonemoto, LT, Slater, JM, Slater, JD. Fractionated proton radiation treatment for pediatric craniopharyngioma: preliminary report. *Cancer J*. 2006 Mar-Apr;12(2):155-9. PMID: 16630407
14. MacDonald, SM, Trofimov, A, Safai, S, et al. Proton radiotherapy for pediatric central nervous system germ cell tumors: early clinical outcomes. *Int J Radiat Oncol Biol Phys*. 2011 Jan 1;79(1):121-9. PMID: 20452141
15. Merchant, TE, Hua, CH, Shukla, H, Ying, X, Nill, S, Oelfke, U. Proton versus photon radiotherapy for common pediatric brain tumors: comparison of models of dose characteristics and their relationship to cognitive function. *Pediatr Blood Cancer*. 2008 Jul;51(1):110-7. PMID: 18306274
16. Moeller, BJ, Chintagumpala, M, Philip, JJ, et al. Low early ototoxicity rates for pediatric medulloblastoma patients treated with proton radiotherapy. *Radiat Oncol*. 2011;6:58. PMID: 21635776
17. Lee, CT, Bilton, SD, Famiglietti, RM, et al. Treatment planning with protons for pediatric retinoblastoma, medulloblastoma, and pelvic sarcoma: how do protons compare with other conformal techniques? *Int J Radiat Oncol Biol Phys*. 2005 Oct 1;63(2):362-72. PMID: 16168831
18. Kozak, KR, Adams, J, Krejcarek, SJ, Tarbell, NJ, Yock, TI. A dosimetric comparison of proton and intensity-modulated photon radiotherapy for pediatric parameningeal rhabdomyosarcomas. *Int J Radiat Oncol Biol Phys*. 2009 May 1;74(1):179-86. PMID: 19019562
19. Merchant, TE. Proton beam therapy in pediatric oncology. *Cancer J*. 2009 Jul-Aug;15(4):298-305. PMID: 19672146
20. Timmermann, B. Proton beam therapy for childhood malignancies: status report. *Klinische Padiatrie*. 2010 May;222(3):127-33. PMID: 20514614
21. Nilsson, S, Norlen, BJ, Widmark, A. A systematic overview of radiation therapy effects in prostate cancer. *Acta Oncol*. 2004;43(4):316-81. PMID: 15303499
22. Kuban, D, Pollack, A, Huang, E, et al. Hazards of dose escalation in prostate cancer radiotherapy. *Int J Radiat Oncol Biol Phys*. 2003 Dec 1;57(5):1260-8. PMID: 14630260
23. TEC Assessment 2010. "Proton Beam Therapy for Prostate Cancer." BlueCross BlueShield Association Technology Evaluation Center, Vol. 25, Tab 10.
24. Comparative effectiveness of therapyies for clinically localized prostate cancer. *Comparative Effectiveness Review No. 13*. Agency for Healthcare Research and Quality. [cited 11/08/2012]; Available from: http://effectivehealthcare.ahrq.gov/healthInfo.cfm?infotype=rr&ProcessID=9&DocID=79
25. Brada, M, Pijls-Johannesma, M, De Ruysscher, D. Current clinical evidence for proton therapy. *Cancer J*. 2009 Jul-Aug;15(4):319-24. PMID: 19672149
26. 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 Int*. 2012 Feb;109 Suppl 1:22-9. PMID: 22239226
27. Efstathiou, JA, Trofimov, AV, Zietman, AL. Life, liberty, and the pursuit of protons: an evidence-based review of the role of particle therapy in the treatment of prostate cancer. *Cancer J*. 2009 Jul-Aug;15(4):312-8. PMID: 19672148
28. Hanks, GE. A question-filled future for dose escalation in prostate cancer. *Int J Radiat Oncol Biol Phys*. 1995 Apr 30;32(1):267-9. PMID: 7721628
29. Cox, JD. Dose escalation by proton irradiation for adenocarcinoma of the prostate. *Int J Radiat Oncol Biol Phys*. 1995 Apr 30;32(1):265-6. PMID: 7721627

30. Slater, JD, Rossi, CJ, Jr., Yonemoto, LT, et al. Proton therapy for prostate cancer: the initial Loma Linda University experience. *Int J Radiat Oncol Biol Phys*. 2004 Jun 1;59(2):348-52. PMID: 15145147
31. Zietman, AL, DeSilvio, ML, Slater, JD, et al. Comparison of conventional-dose vs high-dose conformal radiation therapy in clinically localized adenocarcinoma of the prostate: a randomized controlled trial. *JAMA*. 2005 Sep 14;294(10):1233-9. PMID: 16160131
32. Sheets, NC, Goldin, GH, Meyer, AM, et al. Intensity-modulated radiation therapy, proton therapy, or conformal radiation therapy and morbidity and disease control in localized prostate cancer. *JAMA*. 2012 Apr 18;307(15):1611-20. PMID: 22511689
33. Yu, JB, Soulos, PR, Herrin, J, et al. Proton versus intensity-modulated radiotherapy for prostate cancer: patterns of care and early toxicity. *J Natl Cancer Inst*. 2013 Jan 2;105(1):25-32. PMID: 23243199
34. TEC Assessment 2010. "Proton Beam Therapy for Non-Small-Cell Lung Cancer." BlueCross BlueShield Association Technology Evaluation Center, Vol. 25, Tab 7.
35. Pijls-Johannesma, M, Grutters, JP, Verhaegen, F, Lambin, P, De Ruysscher, D. Do we have enough evidence to implement particle therapy as standard treatment in lung cancer? A systematic literature review. *Oncologist*. 2010;15(1):93-103. PMID: 20067947
36. Bush, DA, Cheek, G, Zaheer, S, et al. High-dose hypofractionated proton beam radiation therapy is safe and effective for central and peripheral early-stage non-small cell lung cancer: results of a 12-year experience at Loma Linda University Medical Center. *Int J Radiat Oncol Biol Phys*. 2013 Aug 1;86(5):964-8. PMID: 23845845
37. Miyanaga, N, Akaza, H, Okumura, T, et al. A bladder preservation regimen using intra-arterial chemotherapy and radiotherapy for invasive bladder cancer: a prospective study. *Int J Urol*. 2000 Feb;7(2):41-8. PMID: 10710246
38. Bush, DA, Hillebrand, DJ, Slater, JM, Slater, JD. High-dose proton beam radiotherapy of hepatocellular carcinoma: preliminary results of a phase II trial. *Gastroenterology*. 2004 Nov;127(5 Suppl 1):S189-93. PMID: 15508084
39. Kagei, K, Tokuuye, K, Okumura, T, et al. Long-term results of proton beam therapy for carcinoma of the uterine cervix. *Int J Radiat Oncol Biol Phys*. 2003 Apr 1;55(5):1265-71. PMID: 12654436
40. Huang, D, Xia, P, Akazawa, P, et al. Comparison of treatment plans using intensity-modulated radiotherapy and three-dimensional conformal radiotherapy for paranasal sinus carcinoma. *Int J Radiat Oncol Biol Phys*. 2003 May 1;56(1):158-68. PMID: 12694834
41. Yuh, GE, Loredo, LN, Yonemoto, LT, et al. Reducing toxicity from craniospinal irradiation: using proton beams to treat medulloblastoma in young children. *Cancer J*. 2004 Nov-Dec;10(6):386-90. PMID: 15701271
42. St Clair, WH, Adams, JA, Bues, M, et al. Advantage of protons compared to conventional X-ray or IMRT in the treatment of a pediatric patient with medulloblastoma. *Int J Radiat Oncol Biol Phys*. 2004 Mar 1;58(3):727-34. PMID: 14967427
43. Hug, EB, Fitzek, MM, Liebsch, NJ, Munzenrider, JE. Locally challenging osteo- and chondrogenic tumors of the axial skeleton: results of combined proton and photon radiation therapy using three-dimensional treatment planning. *Int J Radiat Oncol Biol Phys*. 1995 Feb 1;31(3):467-76. PMID: 7852108
44. Ciulla, TA, Danis, RP, Klein, SB, et al. Proton therapy for exudative age-related macular degeneration: a randomized, sham-controlled clinical trial. *Am J Ophthalmol*. 2002 Dec;134(6):905-6. PMID: 12470761
45. Flaxel, CJ, Friedrichsen, EJ, Smith, JO, et al. Proton beam irradiation of subfoveal choroidal neovascularisation in age-related macular degeneration. *Eye (Lond)*. 2000 Apr;14 (Pt 2):155-64. PMID: 10845009

46. Adams, JA, Paiva, KL, Munzenrider, JE, Miller, JW, Gragoudas, ES. Proton beam therapy for age-related macular degeneration: development of a standard plan. *Med Dosim*. 1999 Winter;24(4):233-8. PMID: 10643731
47. Taghian, AG, Kozak, KR, Katz, A, et al. Accelerated partial breast irradiation using proton beams: Initial dosimetric experience. *Int J Radiat Oncol Biol Phys*. 2006 Aug 1;65(5):1404-10. PMID: 16730137
48. Kozak, KR, Smith, BL, Adams, J, et al. Accelerated partial-breast irradiation using proton beams: initial clinical experience. *Int J Radiat Oncol Biol Phys*. 2006 Nov 1;66(3):691-8. PMID: 17011445
49. Brown, AP, Barney, CL, Grosshans, DR, et al. Proton beam craniospinal irradiation reduces acute toxicity for adults with medulloblastoma. *Int J Radiat Oncol Biol Phys*. 2013 Jun 1;86(2):277-84. PMID: 23433794
50. Desjardins, L, Lumbroso-Le Rouic, L, Levy-Gabriel, C, et al. Combined proton beam radiotherapy and transpupillary thermotherapy for large uveal melanomas: a randomized study of 151 patients. *Ophthalmic Res*. 2006;38(5):255-60. PMID: 16888407
51. Taheri-Kadkhoda, Z, Bjork-Eriksson, T, Nill, S, et al. Intensity-modulated radiotherapy of nasopharyngeal carcinoma: a comparative treatment planning study of photons and protons. *Radiat Oncol*. 2008;3:4. PMID: 18218078
52. Weber, DC, Chan, AW, Lessell, S, et al. Visual outcome of accelerated fractionated radiation for advanced sinonasal malignancies employing photons/protons. *Radiother Oncol*. 2006 Dec;81(3):243-9. PMID: 17050017
53. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in OncologyTM. Bone Cancer. v2.2013. [cited 07/30/2013]; Available from: http://www.nccn.org/professionals/physician_gls/pdf/bone.pdf
54. Allen, AM, Pawlicki, T, Dong, L, et al. An evidence based review of proton beam therapy: the report of ASTRO's emerging technology committee. *Radiother Oncol*. 2012 Apr;103(1):8-11. PMID: 22405807
55. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™. Prostate Cancer. v.2.2014. [cited 06/20/2014]; Available from: http://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf
56. Nguyen PL, Aizer A, Davis BJ, et al. American College of Radiology ACR Appropriateness Criteria®. Definitive external-beam irradiation in stage T1 and T2 prostate cancer. [cited 02/20/2014]; Available from: https://acsearch.acr.org/list
57. American Society for Radiation Oncology (ASTRO). ASTRO Position Statement: Use of Proton Beam Therapy for Prostate Cancer. 2013. [cited 06/20/2014]; Available from: https://www.astro.org/uploadedFiles/Main_Site/Practice_Management/Reimbursement/ProtonProstateStatement.pdf
58. American Society for Radiation Oncology (ASTRO). ASTRO Choosing Wisely® Initiatvie. Five Things Physicians and Patients Should Question. . [cited 06/20/2014]; Available from: http://www.choosingwisely.org/doctor-patient-lists/american-society-for-radiation-oncology
59. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™. Central Nervous System Cancers. v.1.2014. [cited 06/20/2014]; Available from: http://www.nccn.org/professionals/physician_gls/pdf/cns.pdf
60. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™. Non-Small Cell Lung Cancer. v.4.2014. [cited 06/20/2014]; Available from: http://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf
61. Willers H, Stinchcombe TE, Chang JY, et al. American College of Radiology ACR Appropriateness Criteria®. Induction and adjuvant therapy for N2 non-small-cell lung cancer. 2013. [cited 06/20/2014]; Available from: https://acsearch.acr.org/list

62. Chang JY, Kestin LL, Barriger RB, et al. American College of Radiology ACR Appropriateness Criteria®. Nonsurgical treatment for locally advanced non-small-cell lung cancer: good performance status/definitive intent. 2014. [cited 6/20/2014]; Available from: https://acsearch.acr.org/list
63. Decker, RH, Langer, CJ, Rosenzweig, KE, et al. ACR Appropriateness Criteria(R) Postoperative Adjuvant Therapy in Non-Small Cell Lung Cancer. *Am J Clin Oncol*. 2011 Oct;34(5):537-44. PMID: 21946673
64. American College of Radiology. ACR appropriateness criteria on nonsurgical treatment for non-small-cell lung cancer: poor performance status or palliative intent. 2012. [cited 06/21/2013]; Available from: http://www.acr.org/~/media/ACR/Documents/AppCriteria/Oncology/NonsurgicalTreatmentForNSCLCPoorPerformanceStatusOrPalliativeIntent.pdf
65. Rosenzweig KE, Chang JY, Chetty IJ, et al. American College of Radiology ACR Appropriateness Criteria®. Nonsurgical treatment for non-small-cell lung cancer: poor performance status or palliative intent. 2012. [cited 06/20/2014]; Available from: https://acsearch.acr.org/list

CROSS REFERENCES

Intraocular Radiation Therapy for Age-Related Macular Degeneration. Medicine, Policy No. 134

Radioembolization for Primary and Metastatic Tumors of the Liver, Medicine, Policy No. 140

Stereotactic Radiosurgery and Stereotactic Body Radiation Therapy, Surgery, Policy No. 16

CODES	NUMBER	DESCRIPTION
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:		
CPT	77520	Proton beam delivery, simple, without compensation
	77522	Proton beam delivery; simple with compensation
	77523	Proton beam delivery; intermediate

CODES	NUMBER	DESCRIPTION
	77525	Proton beam delivery; complex
Note: Codes for treatment delivery primarily reflects the costs related to the energy source used, and not physician work.		
HCPCS	None	