

PROTON BEAM RADIATION THERAPY

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INSTRUCTIONS FOR USE

This Medical Policy provides assistance in interpreting UnitedHealthcare benefit plans. When deciding coverage, the enrollee specific document must be referenced. The terms of an enrollee's document (e.g., Certificate of Coverage (COC) or Summary Plan Description (SPD) and Medicaid State Contracts) may differ greatly from the standard benefit plans upon which this Medical Policy is based. In the event of a conflict, the enrollee's specific benefit document supersedes this Medical Policy. All reviewers must first identify enrollee eligibility, any federal or state regulatory requirements and the enrollee specific plan benefit coverage prior to use of this Medical Policy. Other Policies and Coverage Determination Guidelines may apply. UnitedHealthcare reserves the right, in its sole discretion, to modify its Policies and Guidelines as necessary. This Medical Policy is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. The MCG™ Care Guidelines are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

BENEFIT CONSIDERATIONS

Essential Health Benefits for Individual and Small Group:

For plan years beginning on or after January 1, 2014, the Affordable Care Act of 2010 (ACA) requires fully insured non-grandfathered individual and small group plans (inside and outside of Exchanges) to provide coverage for ten categories of Essential Health Benefits ("EHBs"). Large group plans (both self-funded and fully insured), and small group ASO plans, are not subject to the requirement to offer coverage for EHBs. However, if such plans choose to provide coverage for benefits which are deemed EHBs (such as maternity benefits), the ACA requires all dollar limits on those benefits to be removed on all Grandfathered and Non-Grandfathered plans. The determination of which benefits constitute EHBs is made on a state by state basis. As such, when using this guideline, it is important to refer to the enrollee's specific plan document to determine benefit coverage.

This policy applies to persons 19 years of age and older. Proton beam radiation therapy is covered without further review for persons younger than 19 years of age.

Where proton beam therapy is deemed proven, in-network benefits may be available for what is otherwise an out-of-area or out-of-network service. The enrollee-specific benefit document must be consulted to determine what form of coverage exists.

- If an enrollee has benefits for out-of-network services ("Plus"), proton beam therapy would be covered at the out-of-network benefit level. Additional coverage for travel costs would not be allowed in this situation.
- If an enrollee does not have benefits for out-of-network services ("Standard"), no out-of-network benefit would be available for proton beam therapy as long as external beam radiation therapy is available within the network.

Some Certificates of Coverage allow coverage of experimental/investigational/unproven treatments for life-threatening illnesses when certain conditions are met. The enrollee-specific benefit document must be consulted to make coverage decisions for this service. Benefit coverage for an otherwise unproven service for the treatment of serious rare diseases may occur when certain conditions are met.

COVERAGE RATIONALE

Proton beam radiation therapy is proven and medically necessary for the following indications:

- Intracranial arteriovenous malformations (AVMs)
- Ocular tumors, including intraocular/uveal melanoma (includes the iris, ciliary body and choroid)
- Skull-based tumors (e.g., chordomas or chondrosarcomas)

Proton beam radiation therapy is unproven and not medically necessary for treating ALL other indications, including but not limited to:

- Age-related macular degeneration (AMD)
- Bladder cancer
- Brain and spinal cord tumors
- Choroidal hemangioma
- Gastrointestinal cancers, including esophageal and pancreatic
- Gynecologic cancers
- Head and neck cancers
- Hepatocellular carcinoma
- Lung cancer
- Lymphomas
- Prostate cancer
- Vestibular tumors (e.g. acoustic neuroma or vestibular schwannoma)

There is limited clinical evidence that directly compares proton beam therapy (PBT) with other types of radiation therapy. Current published evidence does not allow for any definitive conclusions about the safety and efficacy of proton beam therapy to treat conditions other than those noted above as proven and medically necessary.

Proton beam radiation therapy used in conjunction with intensity-modulated radiation therapy (IMRT) is unproven and not medically necessary.

Clinical evidence is insufficient to support the combined use of these technologies in a single treatment plan. Comparative effectiveness studies including randomized controlled trials are needed to demonstrate the safety and long-term efficacy of combined therapy.

APPLICABLE CODES

The Current Procedural Terminology (CPT[®]) codes and Healthcare Common Procedure Coding System (HCPCS) codes listed in this policy are for reference purposes only. Listing of a service code in this policy does not imply that the service described by this code is a covered or non-covered health service. Coverage is determined by the enrollee specific benefit document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claims payment. Other policies and coverage determination guidelines may apply. This list of codes may not be all inclusive.

CPT [®] Code	Description
0073T	Compensator-based beam modulation treatment delivery of inverse planned treatment using 3 or more high resolution (milled or cast) compensator convergent beam modulated fields, per treatment session
0197T	Intra-fraction localization and tracking of target or patient motion during delivery of radiation therapy (e.g., 3D positional tracking, gating, 3D surface tracking), each fraction of treatment
77301	Intensity modulated radiotherapy plan, including dose-volume histograms for target and critical structure partial tolerance specifications
77338	Multi-leaf collimator (MLC) device(s) for intensity modulated radiation therapy (IMRT), design and construction per IMRT plan
77418	Intensity modulated treatment delivery, single or multiple fields/arcs, via narrow spatially and temporally modulated beams, binary, dynamic MLC, per treatment session
77520	Proton treatment delivery; simple, without compensation
77522	Proton treatment delivery; simple, with compensation
77523	Proton treatment delivery; intermediate
77525	Proton treatment delivery; complex

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Proven ICD-9 Diagnosis Code	Description
170.0	Malignant neoplasm of bones of skull and face, except mandible
190.0	Malignant neoplasm of eyeball, except conjunctiva, cornea, retina, and choroid
190.6	Malignant neoplasm of choroid
191.9	Malignant neoplasm of brain, unspecified site
213.0	Benign neoplasm of bones of skull and face
224.0	Benign neoplasm of eyeball, except conjunctiva, cornea, retina, and choroid
224.6	Benign neoplasm of choroid
234.0	Carcinoma in situ of eye
747.81	Congenital anomaly of cerebrovascular system

ICD-10 Codes (Preview Draft)

In preparation for the transition from ICD-9 to ICD-10 medical coding on **October 1, 2015**^{*}, a sample listing of the ICD-10 CM and/or ICD-10 PCS codes associated with this policy has been provided below for your reference. This list of codes may not be all inclusive and will be updated to reflect any applicable revisions to the ICD-10 code set and/or clinical guidelines outlined in this policy. ^{*}*The effective date for ICD-10 code set implementation is subject to change.*

ICD-10 Diagnosis Code (Effective 10/01/15)	Description
C41.0	Malignant neoplasm of bones of skull and face
C69.30	Malignant neoplasm of unspecified choroid
C69.31	Malignant neoplasm of right choroid
C69.32	Malignant neoplasm of left choroid
C69.40	Malignant neoplasm of unspecified ciliary body
C69.41	Malignant neoplasm of right ciliary body
C69.42	Malignant neoplasm of left ciliary body
C71.9	Malignant neoplasm of brain, unspecified
D09.20	Carcinoma in situ of unspecified eye
D09.21	Carcinoma in situ of right eye
D09.22	Carcinoma in situ of left eye
D16.4	Benign neoplasm of bones of skull and face
D31.30	Benign neoplasm of unspecified choroid
D31.31	Benign neoplasm of right choroid
D31.32	Benign neoplasm of left choroid
D31.40	Benign neoplasm of unspecified ciliary body
D31.41	Benign neoplasm of right ciliary body
D31.42	Benign neoplasm of left ciliary body
Q28.2	Arteriovenous malformation of cerebral vessels
Q28.3	Other malformations of cerebral vessels

DESCRIPTION OF SERVICES

Unlike other types of radiation therapy that use x-rays or photons to destroy cancer cells, proton beam therapy (PBT) uses a beam of special particles (protons) that carry a positive charge. There is no significant difference in the biological effects of protons versus photons; however, protons can deliver a dose of radiation in a more confined way to the tumor tissue than photons. After they enter the body, protons release most of their energy within the tumor region and, unlike photons, deliver only a minimal dose beyond the tumor boundaries (American College of Radiology website, 2012).

The greatest energy release with conventional radiation (photons) is at the surface of the tissue and decreases exponentially the farther it travels. In contrast, the energy of a proton beam is released at the end of its path, a region called the Bragg peak. Since the energy release of the proton beam is confined to the narrow Bragg peak, collateral damage to the surrounding tissues should be reduced, while an increased dose of radiation can be delivered to the tumor.

Because of these physical properties, PBT may be useful when the target volume is in close proximity to one or more critical structures and sparing the surrounding normal tissue cannot be adequately achieved with photon-based radiation therapy.

CLINICAL EVIDENCE

AHRQ published a report on particle beam therapy for treating a variety of cancers. More than half of the publications the AHRQ identified described treatment of ocular cancers (uveal melanoma in particular), and cancers of the head and neck (brain tumors, and tumors arising from skull base, cervical spine and nearby structures). In order of decreasing number of studies, the following types of malignancies were also described: gastrointestinal (esophageal cancer, hepatocellular carcinomas of the liver, pancreatic cancer), prostate, lung, spine and sacrum, bone and soft tissue, uterine (cervix and corpus), bladder, and miscellaneous (skin cancer or a compilation of a center's experience with a variety of cancers treated there).

According to the AHRQ report, there are many publications on particle (mainly proton) beam therapy for the treatment of cancer. However, they typically do not use a concurrent control, focus on heterogeneous populations and they employ different definitions for outcomes and harms. These studies do not document the circumstances in contemporary treatment strategies in which radiotherapy with charged particles is superior to other modalities. Comparative effectiveness studies including randomized controlled trials are needed to document the theoretical advantages of charged particle radiotherapy to specific clinical situations. At present, there is very limited evidence comparing the safety and effectiveness of PBRT with other types of radiation therapies for cancer. Therefore, it is not possible to draw conclusions about the comparative safety and effectiveness of PBRT at this time (AHRQ, 2009).

In an emerging technology report, ECRI detailed major clinical and operational issues related to proton beam radiation therapy. However, no analysis of the evidence was possible due to the lack of appropriately designed studies comparing the efficacy of proton therapy to other modes of radiation therapy (ECRI, 2010; updated 2013).

Several systematic reviews (Terasawa, 2009; Brada, 2009; Lodge, 2007; Olsen, 2007) previously reported the lack of evidence supporting proton beam therapy and the need for well-designed prospective studies comparing proton beam therapy to other forms of radiation therapy.

Professional Societies

American Society for Radiation Oncology (ASTRO)

ASTRO's Emerging Technology Committee concluded that current data do not provide sufficient evidence to recommend proton beam therapy (PBT) outside of clinical trials in lung cancer, head and neck cancer, GI malignancies (with the exception of hepatocellular carcinoma) and pediatric non-central nervous system (CNS) malignancies. In hepatocellular carcinoma and prostate cancer, there is evidence of the efficacy of PBT but no suggestion that it is superior to photon based approaches. In pediatric CNS malignancies, PBT appears superior to photon approaches, but more data is needed. In large ocular melanomas and chordomas, ASTRO states that there is evidence for a benefit of PBT over photon approaches. More robust prospective clinical trials are needed to determine the appropriate clinical setting for PBT (Allen et al., 2012).

Intracranial Arteriovenous Malformations

In a Cochrane review, Ross et al. (2010) assessed the clinical effects of various interventions to treat brain arteriovenous malformations (AVMs) in adults. Interventions include neurosurgical excision, stereotactic radiotherapy/radiosurgery (using gamma knife, linear accelerator, proton beam or CyberKnife), endovascular embolization (using glues, particles, fibres, coils or balloons) and staged combinations of these interventions. The authors concluded that there is no evidence from randomized trials with clear clinical outcomes comparing different interventional treatments for brain AVMs against each other or against usual medical therapy to guide the interventional treatment of brain AVMs in adults.

Hattangadi-Gluth et al. (2014) evaluated the obliteration rate and potential adverse effects of single-fraction proton beam stereotactic radiosurgery (PSRS) in patients with cerebral arteriovenous malformations (AVMs). From 1991 to 2010, 248 consecutive patients with 254 cerebral AVMs received single-fraction PSRS at a single institution. The median AVM nidus volume was 3.5 cc, 23% of AVMs were in critical/deep locations (basal ganglia, thalamus or brainstem) and the most common dose was 15 Gy. At a median follow-up time of 35 months, 64.6% of AVMs were obliterated. The median time to total obliteration was 31 months, and the 5- and 10-year cumulative incidence of total obliteration was 70% and 91%, respectively. On univariable analysis, smaller target volume, smaller treatment volume, higher prescription dose and higher maximum dose were associated with total obliteration. Deep/critical location was also associated with decreased likelihood of obliteration. On multivariable analysis, critical location and smaller target volume remained associated with total obliteration. Post-treatment hemorrhage occurred in 13 cases (5-year cumulative incidence of 7%), all among patients with less than total obliteration. Three of these events were fatal. The most common complication was seizure. The

authors reported that this is the largest modern series of PSRS for cerebral AVMs and concluded that PSRS can achieve a high obliteration rate with minimal morbidity. Post-treatment hemorrhage remains a potentially fatal risk among patients who have not yet responded to treatment.

Hattangadi et al. (2012) evaluated 59 patients with high-risk cerebral arteriovenous malformations (AVMs), based on brain location or large size, who underwent planned two-fraction proton stereotactic radiosurgery (PSRS). Median nidus volume was 23 cc. Seventy percent of cases had nidus volume ≥ 14 cc, and 34% were in critical locations (brainstem, basal ganglia). Many patients had prior surgery or embolization (40%) or prior PSRS (12%). The most common dose was 16 Gy in two fractions. At a median follow-up of 56.1 months, 9 patients (15%) had total and 20 patients (34%) had partial obliteration. Patients with total obliteration received higher total dose than those with partial or no obliteration. Median time to total obliteration was 62 months, and 5-year actuarial rate of partial or total obliteration was 33%. Five-year actuarial rate of hemorrhage was 22% and 14% (n = 8) suffered fatal hemorrhage. Lesions with higher AVM scores were more likely to hemorrhage and less responsive to radiation. The most common complication was headache. One patient developed a generalized seizure disorder, and two had mild neurologic deficits. The authors concluded that high-risk AVMs can be safely treated with two-fraction PSRS, although total obliteration rate is low and patients remain at risk for future hemorrhage. Future studies should include higher doses or a multistaged PSRS approach for lesions more resistant to obliteration with radiation.

In a retrospective study by Vernimmen et al. (2005), 64 patients with arteriovenous malformation were reviewed to investigate hypofractionated stereotactic proton therapy of predominantly large intracranial arteriovenous malformations (AVMs) by analyzing retrospectively the results from a cohort of patients. The AVMs were grouped by volume: <14 cc (26 patients) and ≥ 14 cc (38 patients). Treatment was delivered with a fixed horizontal 200 MeV proton beam under stereotactic conditions, using a stereophotogrammetric positioning system. The majority of patients were hypofractionated (2 or 3 fractions), and the proton doses are presented as single-fraction equivalent cobalt Gray equivalent doses (SFECyE). The overall mean minimum target volume dose was 17.37 SFECyE, ranging from 10.38-22.05 SFECyE. Analysis by volume group showed obliteration in 67% for volumes <14 cc and 43% for volumes ≥ 14 cc. Grade IV acute complications were observed in 3% of patients. Transient delayed effects were seen in 15 patients (23%), becoming permanent in 3 patients. One patient also developed a cyst 8 years after therapy. Vernimmen concluded that stereotactic proton beam therapy applied in a hypofractionated schedule allows for the safe treatment of large AVMs, with acceptable results and is an alternative to other treatment strategies for large AVMs.

Ocular Tumors

A report on proton beam therapy from the Institute for Clinical and Economic Review (ICER) rated the net health benefit of PBT relative to alternative treatments to be superior in ocular tumors.

In a systematic review, Wang et al. (2013) evaluated the efficacy and adverse effects of charged particle therapy (CPT), delivered with protons, helium ions or carbon ions, for treating uveal melanoma. Twenty-seven studies enrolling 8809 uveal melanoma patients met inclusion criteria. The rate of local recurrence was significantly less with CPT than with brachytherapy. There were no significant differences in mortality or enucleation rates. CPT was also associated with lower retinopathy and cataract formation rates. The authors reported that the overall quality of the evidence is low, and higher quality comparative effectiveness studies are needed to provide better evidence.

A systematic review concluded that there is evidence for a benefit of proton beam therapy over photon approaches in treating large ocular melanomas (Allen et al., 2012).

Ocular cancers are included in the AHRQ report (2009) referenced above, which states that the evidence is insufficient to draw any definitive conclusions as to whether PBT has any advantages over traditional therapies

The National Comprehensive Cancer Network (NCCN) does not address ocular cancers in a guideline.

Skull-Based Tumors

NCCN states that specialized techniques, including particle beam radiation therapy with protons, should be considered in order to allow high-dose therapy while maximizing normal tissue sparing in patients with primary bone cancer (NCCN, 2014).

A systematic review concluded that there is evidence for a benefit of proton beam therapy over photon approaches in treating chordomas (Allen et al., 2012).

A systematic review of seven uncontrolled single-arm studies concluded that the use of protons has shown better results in comparison to the use of conventional photon irradiation, resulting in the best long-term (10 years) outcome for skull-based chordomas with relatively few significant complications (Amichetti et al., 2009).

The use of proton therapy (PT) to treat chondrosarcoma (CSA) of the skull base (SB) after surgery is widely accepted, but studies demonstrating the need for PT and its superiority in comparison to radiotherapy with photons are lacking. In a systematic review, Amichetti et al. (2010) reported that studies of proton beam therapy for skull-based chondrosarcoma resulted in local control ranging from 75% to 99% at 5 years. There were no prospective trials (randomized or nonrandomized), but four uncontrolled single-arm studies with 254 patients were included. The authors concluded that PT following surgical resection showed a very high probability of medium- and long-term cure with a relatively low risk of significant complications.

Early studies evaluating PBT for the treatment of intracranial or skull base tumors include four case series, four retrospective studies, and two prospective, uncontrolled, clinical studies (Kjellberg, 1968; Suit, 1982; Hug, 1995; Al-Mefty and Borba, 1997; McAllister, 1997; Gudjonsson, 1999; Wenkel, 2000; Vernimmen, 2001). The studies included 10 to 47 patients with pituitary gland adenoma, para-CNS sarcomas, osteogenic and chondrogenic tumors, chordomas, and meningiomas. Local control was achieved in 71% to 100% of patients. Complications were radiation dose/volume and site dependent, and were mild to severe.

In a retrospective review by Weber et al. (2005), 29 patients with skull base chordomas (n=18) and low-grade chondrosarcomas (CS) (n=11) were reviewed to assess the clinical results of spot scanning proton beam radiation therapy (PT). Tumor conformal application of proton beams was realized by spot scanning technology. The median chordoma and CS dose was 74 and 68 cobalt Gy equivalent, respectively (cobalt Gy equivalent = proton Gy x 1.1). Median gross tumor volumes (GTV) were 16.4 mL (range, 1.8-48.1 mL) and 15.2 mL (range, 2.3-57.3 mL) for chordoma and CS, respectively. Median follow-up time was 29 months (range, 6-68 months). Three year local control rates were 87.5% and 100% for chordoma and CS, respectively. Actuarial 3-year complication-free survival was 82.2%. Radiation-induced pituitary dysfunction was observed in 4 (14%) patients (CTCAE Grade 2). No patient presented with post-PT brainstem or optic pathways necrosis or dysfunction. The authors concluded that spot-scanning PT offers high tumor control rates of skull base chordoma and chondrosarcomas. These preliminary results are encouraging but should be confirmed during a longer follow-up.

Age-Related Macular Degeneration (AMD)

In a Cochrane review, Evans et al. (2010) examined the effects of radiotherapy on neovascular age-related macular degeneration (AMD). All randomized controlled trials in which radiotherapy was compared to another treatment, sham treatment, low dosage irradiation or no treatment were included. Thirteen trials (n=1154) investigated external beam radiotherapy with dosages ranging

from 7.5 to 24 Gy; one additional trial (n=88) used plaque brachytherapy (15Gy at 1.75mm for 54 minutes/12.6 Gy at 4mm for 11 minutes). Most studies found effects (not always significant) that favored treatment. Overall there was a small statistically significant reduction in risk of visual acuity loss in the treatment group. There was considerable inconsistency between trials and the trials were considered to be at risk of bias, in particular because of the lack of masking of treatment group. Subgroup analyses did not reveal any significant interactions, however, there were small numbers of trials in each subgroup (range three to five). There was some indication that trials with no sham irradiation in the control group reported a greater effect of treatment. The incidence of adverse events was low in all trials; there were no reported cases of radiation retinopathy, optic neuropathy or malignancy. Three trials found non-significant higher rates of cataract progression in the treatment group. The authors concluded that this review does not provide convincing evidence that radiotherapy is an effective treatment for neovascular AMD. If further trials are to be considered to evaluate radiotherapy in AMD then adequate masking of the control group must be considered.

In a systematic review, Bekkering et al. (2009) evaluated the effects and side effects of proton therapy for indications of the eye. All studies that included at least ten patients and that assessed the efficacy or safety of proton therapy for any indication of the eye were included. Five controlled trials, two comparative studies and 30 case series were found, most often reporting on uveal melanoma, choroidal melanoma and age-related macular degeneration (AMD). Methodological quality of these studies was poor. Studies were characterized by large differences in radiation techniques applied within the studies, and by variation in patient characteristics within and between studies. Results for uveal melanoma and choroidal melanoma suggest favorable survival, although side effects are significant. Results for choroidal hemangioma and AMD did not reveal beneficial effects from proton radiation. There is limited evidence on the effectiveness and safety of proton radiation due to the lack of well-designed and well-reported studies.

A randomized controlled trial by Zambarakji et al. (2006) studied 166 patients with angiographic evidence of classic choroidal neovascularization resulting from AMD and best-corrected visual acuity of 20/320 or better. Patients were assigned randomly (1:1) to receive 16-cobalt gray equivalent (CGE) or 24-CGE proton radiation in 2 equal fractions. Complete ophthalmological examinations, color fundus photography, and fluorescein angiography were performed before and 3, 6, 12, 18, and 24 months after treatment. At 12 months after treatment, 36 eyes (42%) and 27 eyes (35%) lost three or more lines of vision in the 16-CGE and 24-CGE groups, respectively. Rates increased to 62% in the 16-CGE group and 53% in the 24-CGE group by 24 months after treatment. Radiation complications developed in 15.7% of patients receiving 16-CGE and 14.8% of patients receiving 24-CGE. The authors concluded that no significant differences in rates of visual loss were found between the two dose groups.

A randomized, sham-controlled, double-blind study by Ciulla et al. (2002) studied 37 patients to examine the effect of proton beam irradiation on subfoveal choroidal neovascular membranes (CNVM) associated with age-related macular degeneration. Patients were randomly assigned to 16-Gy proton irradiation delivered in two fractions 24 hours apart or to sham control treatment. Recruitment was halted at 37 subjects for ethical reasons regarding randomization to sham treatment when U.S. Food and Drug Administration approval of Visudyne® (verteporfin) was anticipated. Proton irradiation was associated with a trend toward stabilization of visual acuity, but this association did not reach statistical significance. The authors concluded that with the acceptance of photodynamic therapy, future studies will require more complex design and larger sample size to determine whether radiation can play either a primary or adjunctive role in treating these lesions. In addition, newer more effective therapies for AMD, e.g., Lucentis® (ranibizumab) and Avastin® (bevacizumab) have made previously available therapies obsolete.

Professional Societies

American Academy of Ophthalmology (AAO)

AAO preferred practice patterns do not address PBT as a treatment option for age-related macular degeneration (AMD) (AAO, 2008).

Bladder Cancer

Miyanaga et al. (2000) conducted a prospective uncontrolled clinical study to assess the efficacy and safety of PBT and/or photon therapy for bladder cancer. The study involved 42 patients who received PBT to the small pelvic space following intra-arterial chemotherapy. At 5-year follow-up, the bladder was preserved in 76% of patients and 65% were free of disease. The disease-specific survival rate was 91%. Patients with large and multiple tumors were more at risk of cancer recurrence than patients with single, small tumors. Nausea and vomiting, irritable bladder and ischialgia were the main side effects.

Bladder cancer is included in the AHRQ report (2009) referenced above, which states that the evidence is insufficient to draw any definitive conclusions as to whether PBT has any advantages over traditional therapies.

Brain and Spinal Cord Tumors

NCCN suggests considering protons over photons for craniospinal irradiation in adults with medulloblastoma (NCCN, 2014).

Noel et al. (2002) conducted a retrospective review of 17 patients with meningioma to evaluate the efficacy and the tolerance of an escalated dose of external conformal fractionated radiation therapy combining photons and protons. Five patients presented a histologically atypical or malignant meningioma, twelve patients a benign one that was recurrent or rapidly progressive. In two cases radiotherapy was administered in the initial course of the disease and in 15 cases at the time of relapse. A highly conformal approach was used combining high-energy photons and protons for approximately 2/3 and 1/3 of the total dose. The median total dose delivered within gross tumor volume was 61 Cobalt Gray Equivalent CGE (25-69). Median follow-up was 37 months (17-60). The 4-year local control and overall survival rates were 87.5 +/- 12% and 88.9 +/- 11%, respectively. One patient failed locally within the clinical tumor volume. One patient died of intercurrent disease. Radiologically, there were eleven stable diseases and five partial responses. The authors concluded that in both benign and more aggressive meningiomas, the combination of conformal photons and protons with a dose escalated by 10-15% offers clinical improvements in most patients as well as radiological long-term stabilization.

Choroidal Hemangiomas

Hocht et al. (2006) conducted a single-center, retrospective study of 44 consecutive patients with choroid hemangiomas treated with photon therapy (n=19) or proton therapy (n=25). Outcomes were measured by visual acuity, tumor thickness, resolution of retinal detachment, and post-treatment complications. Mean follow-up was 38.9 months and 26.3 months, and median follow-up was 29 months and 23.7 months for photon and proton patients, respectively. Tumor thickness was greater in the photon group than in the proton group. Ninety-one percent of all patients were treated successfully. There was no significant difference in the outcomes between the two groups. The authors concluded that radiotherapy is effective in treating choroidal hemangiomas with respect to visual acuity and tumor thickness but a benefit of proton therapy could not be detected.

Three additional studies showed some improvement in tumor regression and visual acuity following PBT; however, these studies were small and retrospective in nature (Chan et al., 2010); Levy-Gabriel et al., 2009; Frau et al., 2004).

Gastrointestinal Cancers

A systematic review concluded that there is insufficient evidence to recommend proton beam therapy outside of clinical trials for gastrointestinal malignancies (Allen et al., 2012).

Mizumoto et al. (2010) evaluated the efficacy and safety of proton-beam therapy for locoregionally advanced esophageal cancer. Fifty-one patients were treated using proton beams with or without X-rays. All but one had squamous cell carcinoma. Of the 51 patients, 33 received

combinations of X-rays and protons as a boost. The other 18 patients received proton-beam therapy alone. The overall 5-year actuarial survival rate for the 51 patients was 21.1% and the median survival time was 20.5 months. Of the 51 patients, 40 (78%) showed a complete response within 4 months after completing treatment and seven (14%) showed a partial response, giving a response rate of 92% (47/51). The 5-year local control rate for all 51 patients was 38.0% and the median local control time was 25.5 months. The authors concluded that these results suggest that proton-beam therapy is an effective treatment for patients with locally advanced esophageal cancer. Further studies are required to determine the optimal total dose, fractionation schedules and best combination of proton therapy with chemotherapy.

Koyama and Tsujii (2003) evaluated the efficacy of PBT combined with photon radiation for the treatment of esophageal cancer in a prospective uncontrolled study. The study included 30 patients with superficial and advanced esophageal cancer. PBT increased 5- and 10-year survival rates from a range of 6 % to 10% (reported in the medical literature) to 67.1% and 61.0%, respectively, and were significantly improved for patients with superficial esophageal cancer (100%; 87.5%) compared with patients with advanced-stage tumors (49.0%; 38.1%). The main long-term side effect was esophageal ulceration in 2 patients.

Gastrointestinal cancers are included in the AHRQ report (2009) referenced above, which states that the evidence is insufficient to draw any definitive conclusions as to whether PBT has any advantages over traditional therapies.

NCCN guidelines do not address the use of proton beam radiation therapy for treating esophageal or pancreatic cancer (NCCN, 2014).

Gynecologic Cancers

The efficacy of PBT combined with photon radiation for the treatment of cervical cancer was investigated in a prospective uncontrolled study involving 25 patients (Kagei et al., 2003). In this study, 5-year and 10-year survival rates were similar to conventional therapies as reported in the literature. The 10-year survival rate was higher for patients with low stage (89%) compared with advanced stages (40%) of cervical cancer. The treatment caused severe late complications in 4% of patients.

Uterine cancers are included in the AHRQ report (2009) referenced above, which states that the evidence is insufficient to draw any definitive conclusions as to whether PBT has any advantages over traditional therapies.

NCCN guidelines do not address the use of proton beam radiation therapy for treating gynecologic cancers.

Head and Neck Cancers

A systematic review concluded that there is insufficient evidence to recommend proton beam therapy outside of clinical trials for head and neck cancer (Allen et al., 2012).

NCCN states that the role of proton therapy in treating sinus tumors is being investigated (NCCN, 2014).

Patel et al. (2014) conducted a systematic review and meta-analysis comparing the clinical outcomes of patients with malignant tumors of the nasal cavity and paranasal sinuses treated with charged particle therapy with those of individuals receiving photon therapy. Primary outcomes of interest were overall survival, disease-free survival and locoregional control, at 5 years and at longest follow-up. A total of 43 cohorts from 41 non-comparative observational studies were included. Median follow-up for the charged particle therapy group was 38 months and for the photon therapy group was 40 months. Pooled overall survival was significantly higher at 5 years for charged particle therapy than for photon therapy and at longest follow-up. At 5 years, disease-free survival was significantly higher for charged particle therapy than for photon

therapy but, at longest follow-up, this event rate did not differ between groups. Locoregional control did not differ between treatment groups at 5 years, but it was higher for charged particle therapy than for photon therapy at longest follow-up. A subgroup analysis comparing proton beam therapy with intensity-modulated radiation therapy showed significantly higher disease-free survival at 5 years and locoregional control at longest follow-up. The authors concluded that, compared with photon therapy, charged particle therapy could be associated with better outcomes for patients with malignant diseases of the nasal cavity and paranasal sinuses. Prospective studies emphasizing collection of patient-reported and functional outcomes are strongly encouraged.

Head and neck cancers are included in the AHRQ report (2009) referenced above, which states that the evidence is insufficient to draw any definitive conclusions as to whether PBT has any advantages over traditional therapies.

An Agency for Healthcare Research and Quality (AHRQ) comparative effectiveness review on radiation therapy for head and neck cancer concluded that the strength of evidence comparing proton beam therapy to other techniques is insufficient to draw conclusions (Samson et al., 2010).

Ramaekers et al. (2011) compared evidence evaluating the effectiveness of carbon-ion, proton and photon radiotherapy for head and neck cancer. A systematic review and meta-analyses were performed to retrieve evidence on tumor control, survival and late treatment toxicity. Eighty-six observational studies (74 photon, 5 carbon-ion and 7 proton) and eight comparative in-silico studies were included. Five-year local control after proton therapy was significantly higher for paranasal and sinonasal cancer compared to intensity modulated photon therapy (88% versus 66%). Although poorly reported, toxicity tended to be less frequent in carbon-ion and proton studies compared to photons. In-silico studies showed a lower dose to the organs at risk, independently of the tumor site. Except for paranasal and sinonasal cancer, survival and tumor control for proton therapy were generally similar to the best available photon radiotherapy. In agreement with included in-silico studies, limited available clinical data indicates that toxicity tends to be lower for proton compared to photon radiotherapy. Since the overall quantity and quality of data regarding proton therapy is poor, the authors recommend the construction of an international particle therapy register to facilitate definitive comparisons.

van de Water et al. (2011) reviewed the literature regarding the potential benefits of protons compared with the currently used photons in terms of lower doses to normal tissue and the potential for fewer subsequent radiation-induced side effects. Fourteen relevant studies were identified and included in this review. Four studies included paranasal sinus cancer cases, three included nasopharyngeal cancer cases and seven included oropharyngeal, hypopharyngeal, and/or laryngeal cancer cases. Seven studies compared the most sophisticated photon and proton techniques: intensity-modulated photon therapy versus intensity-modulated proton therapy (IMPT). Four studies compared different proton techniques. All studies showed that protons had a lower normal tissue dose, while keeping similar or better target coverage. Two studies found that these lower doses theoretically translated into a significantly lower incidence of salivary dysfunction. The results indicate that protons have the potential for a significantly lower normal tissue dose, while keeping similar or better target coverage. The authors concluded that scanned IMPT offers the most advantage and allows for a substantially lower probability of radiation-induced side effects. The results of these studies should be confirmed in properly designed clinical trials.

Hepatocellular Carcinoma

A systematic review concluded that there is evidence for the efficacy of proton beam therapy for treating hepatocellular carcinoma but no suggestion that it is superior to photon based approaches (Allen et al., 2012).

In a phase 2 trial, seventy-six patients were treated and followed prospectively to evaluate the safety and efficacy of proton beam therapy (PBT) for hepatocellular carcinoma (HCC). Median

progression-free survival for the group was 36 months. Eighteen patients subsequently underwent liver transplantation; 6 (33%) explants showed pathological complete response and 7 (39%) showed only microscopic residual. PBT was found to be a safe and effective local-regional therapy for inoperable HCC. A randomized controlled trial to compare its efficacy to a standard therapy has been initiated (Bush et al., 2011).

NCCN guidelines do not address the use of proton beam radiation therapy for treating hepatocellular carcinoma (NCCN, 2014).

Mizumoto et al. (2011) evaluated three protocols to determine late complications following proton beam therapy for hepatocellular carcinoma (HCC). A total of 266 patients received proton therapy, with the fractionation schedule depending on tumor location: 77 GyE in 35 fractions for HCC <2 cm from the gastrointestinal tract, 72.6 GyE in 22 fractions for HCC <2 cm from the porta hepatis and 66 GyE in 10 fractions for others. No significant survival differences were seen among the 3 doses. Survival at 1, 3 and 5 years for the whole cohort was 87%, 61% and 48%, respectively. The authors concluded that the results showed good local control for HCC using each of three treatment protocols and suggest that selection of treatment schedules based on tumor location may be used to reduce the risk of late toxicity. This study is limited by lack of randomization and control.

Komatsu et al. (2011) evaluated the clinical outcome of proton and carbon ion therapy for hepatocellular carcinoma (HCC). A total of , 343 consecutive patients with 386 tumors, including 242 patients (with 278 tumors) who received proton therapy and 101 patients (with 108 tumors) who received carbon ion therapy, were treated on 8 different protocols of proton therapy (52.8-84.0 gray equivalents [GyE] in 4-38 fractions) and on 4 different protocols of carbon ion therapy (52.8-76.0 GyE in 4-20 fractions). The 5-year local control and overall survival rates for all patients were 90.8% and 38.2%, respectively. Regarding proton and carbon ion therapy, the 5-year local control rates were 90.2% and 93%, respectively, and the 5-year overall survival rates were 38% and 36.3%, respectively. These rates did not differ significantly between the 2 therapies. Univariate analysis identified tumor size as an independent risk factor for local recurrence in proton therapy, carbon ion therapy and in all patients. Multivariate analysis identified tumor size as the only independent risk factor for local recurrence in proton therapy and in all patients. Child-Pugh status was the only independent risk factor for overall survival in proton therapy, in carbon ion therapy, and in all patients. No patients died of treatment-related toxicities. The authors concluded that proton and carbon ion therapies for HCC were comparable in terms of local control and overall survival rates. Randomized trials and/or comparative effectiveness research are needed to determine which patients are more likely to benefit from charged particles over photon radiation therapy.

Lung Cancer

A Blue Cross Blue Shield technology assessment evaluated health outcomes following proton beam therapy (PBT) compared to stereotactic body radiotherapy (SBRT) for the management of non-small-cell lung cancer. The report concluded that, overall, evidence is insufficient to permit conclusions about the results of PBT for any stage of non-small-cell lung cancer. All PBT studies are case series, and there are no studies directly comparing proton beam therapy (PBT) and stereotactic body radiotherapy (SBRT). In the absence of randomized, controlled trials, the comparative effectiveness of PBT and SBRT is uncertain (BCBS, 2011b).

NCCN states that the use of advanced technologies, such as proton therapy, for treating non-small-cell lung cancers have been shown to reduce toxicity and increase survival in nonrandomized trials (NCCN, 2014).

A systematic review concluded that there is insufficient evidence to recommend proton beam therapy outside of clinical trials for lung cancer (Allen et al., 2012).

Sejpal et al. (2011) compared the toxicity of proton therapy plus concurrent chemotherapy in patients with NSCLC (n=62) with toxicity for patients with similar disease given 3-dimensional conformal radiation therapy (3D-CRT) plus chemotherapy (n = 74) or intensity-modulated radiation therapy (IMRT) plus chemotherapy (n = 66). Median follow-up times were 15.2 months (proton), 17.9 months (3D-CRT) and 17.4 months (IMRT). Median total radiation dose was 74 Gy(RBE) for the proton group versus 63 Gy for the other groups. Rates of severe (grade ≥ 3) pneumonitis and esophagitis in the proton group (2% and 5%) were lower despite the higher radiation dose (3D-CRT, 30% and 18%; IMRT, 9% and 44%). The authors found that higher doses of proton radiation could be delivered to lung tumors with a lower risk of esophagitis and pneumonitis. Tumor control and survival were not evaluated due to the short follow-up time. A randomized comparison of IMRT versus proton therapy has been initiated.

Chang et al. (2011) reported early results of a phase 2 study of high-dose proton therapy and concurrent chemotherapy in terms of toxicity, failure patterns and survival. Forty-four patients with stage III NSCLC were treated with proton therapy with weekly carboplatin and paclitaxel. Median follow-up time was 19.7 months, and median overall survival time was 29.4 months. The most common nonhematologic grade 3 toxicities were dermatitis (n = 5), esophagitis (n = 5) and pneumonitis (n = 1). Nine (20.5%) patients experienced local disease recurrence, but only 4 (9.1%) had isolated local failure. Four (9.1%) patients had regional lymph node recurrence, but only 1 (2.3%) had isolated regional recurrence. Nineteen (43.2%) patients developed distant metastasis. The overall survival and progression-free survival rates were 86% and 63% at 1 year. The authors concluded that concurrent high-dose proton therapy and chemotherapy are well tolerated, and the median survival time of 29.4 months is encouraging for unresectable stage III NSCLC.

Widesott et al. (2008) reviewed the literature to determine if proton therapy (PT) has a role in the treatment of non-small-cell lung cancer (NSCLC). The authors assessed safety and efficacy and evaluated the main technical issues related to this treatment. Seventeen studies were included in the analysis. There were no prospective trials (randomized or non-randomized). Nine uncontrolled single-arm studies were available from three PT centers, providing clinical outcomes for 214 patients in total. These reports were mainly related to stage I-II tumors. The authors concluded that from a physical point of view PT is a good option for the treatment of NSCLC; however, limited data are available on its application in the clinical practice. Furthermore, the application of PT to lung cancer does present technical challenges. Because of the small number of institutions involved in the treatment of this disease, number of patients and methodological weaknesses of the trials, it is not possible to draw definitive conclusions about the superiority of PT with respect to the photon techniques currently available for the treatment of NSCLC.

Grutters et al. (2010) conducted a metaanalysis of observational studies comparing radiotherapy with photons, protons and carbon-ions in the treatment of non-small-cell lung cancer (NSCLC). Eligible studies included conventional radiotherapy (CRT), stereotactic radiotherapy (SBRT), concurrent chemoradiation (CCR), proton therapy and carbon-ion therapy. Corrected pooled estimates for 2-year overall survival in stage I inoperable NSCLC ranged from 53% for CRT to 74% for carbon-ion therapy. Five-year overall survival for CRT (20%) was statistically significantly lower than that for SBRT (42%), proton therapy (40%) and carbon-ion therapy (42%). However, caution is warranted due to the limited number of patients and limited length of follow-up of the particle studies.

Pijls-Johannesma et al. (2010) conducted a systematic review to test the theory that radiotherapy with beams of protons and heavier charged particles (e.g., carbon ions) leads to superior results, compared with photon beams. The authors searched for clinical evidence to justify implementation of particle therapy as standard treatment in lung cancer. Eleven studies, all dealing with non-small cell lung cancer (NSCLC), mainly stage I, were identified. No phase III trials were found. For proton therapy, 2- to 5-year local tumor control rates varied in the range of 57%-87%. The 2- and 5-year overall survival (OS) and 2- and 5-year cause-specific survival (CSS) rates were 31%-74% and 23% and 58%-86% and 46%, respectively. Radiation-induced

pneumonitis was observed in about 10% of patients. For carbon 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 results with protons and heavier charged particles are promising. However, the current lack of evidence on the clinical effectiveness of particle therapy emphasizes the need to further investigate the efficiency of particle therapy. The authors concluded that until these results are available for lung cancer, charged particle therapy should be considered experimental.

The efficacy and safety of PBT for the treatment of non-small-cell lung cancer was assessed in a prospective, uncontrolled, nonrandomized study, with results described in two reports (Bush, 1998; Bonnet, 2001). The study involved 37 patients who received either PBT alone or PBT combined with photon therapy. Efficacy and safety was assessed in all patients; the effect of dose escalation on pulmonary function was tested in a subset of 25 patients (Bonnet, 2001). In these studies, the 2-year disease-free survival for stage I and stage IIIa patients was 86% and 19%, respectively. PBT dose escalation did not impede lung function and two patients experienced side effects. Both patients developed pneumonitis.

Lung cancers are included in the AHRQ report (2009) referenced above, which states that the evidence is insufficient to draw any definitive conclusions as to whether PBT has any advantages over traditional therapies.

Professional Societies

American College of Radiology (ACR)

ACR appropriateness criteria state that the physical characteristics of the proton beam would seem to allow for greater sparing of normal tissues, although there are unique concerns about its use for lung tumors due to respiratory motion and low lung parenchymal density. There are 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. ACR is hopeful that larger prospective controlled trials that are underway will clarify the role of proton beam for lung cancer in the near future (ACR, 2014).

Lymphoma

NCCN states that preliminary results from single-institution studies have shown that significant dose reduction to organs at risk (e.g., lung, heart, breasts) can be achieved with proton beam radiation therapy, which can reduce the risk of late effects. Long-term follow-up is needed to confirm the efficacy of proton beam therapy for treating lymphomas (NCCN, 2014).

Prostate Cancer

An American Society for Radiation Oncology (ASTRO) position statement concludes that the comparative efficacy evidence of proton beam therapy with other prostate cancer treatments is still being developed. Thus the role of proton beam therapy for localized prostate cancer within the current availability of treatment options remains unclear (ASTRO, 2013).

NCCN states that based on current data, proton therapy is an option for prostate cancer, but no clear benefit over the existing therapy of intensity-modulated radiation therapy has been demonstrated (NCCN, 2014).

A systematic review concluded that there is evidence for the efficacy of proton beam therapy for treating prostate cancer but no suggestion that it is superior to photon based approaches (Allen et al., 2012).

A retrospective study comparing 553 patients treated with proton beam therapy and 27,094 treated with IMRT for early stage prostate cancer detected no difference in genitourinary toxicity at 12 months post-treatment (Yu et al., 2013).

A meta-analysis of randomized dose escalation trials demonstrated that late toxicity rates increase with radiation therapy dose. Series where dose escalated radiation is delivered using IMRT or PBT have relatively short follow up but report lower late gastrointestinal toxicity rates than those employing 3-D radiation therapy (Ohri et al., 2012).

In a large cohort study using Surveillance Epidemiology and End Results (SEER) data, Kim et al. (2011) reported that patients treated with radiation therapy are more likely to have procedural interventions for gastrointestinal (GI) toxicities than patients with conservative management. The elevated risk persists beyond 5 years. Results showed higher GI morbidity rates in patients treated with PBT therapy relative to IMRT patients.

Sheets et al. (2012) evaluated the comparative morbidity and disease control of IMRT, proton therapy and conformal radiation therapy for primary prostate cancer treatment. The authors conducted a population-based study using Surveillance, Epidemiology, and End Results-Medicare-linked data. Main outcomes were rates of gastrointestinal and urinary morbidity, erectile dysfunction, hip fractures and additional cancer therapy. In a comparison between IMRT and conformal radiation therapy (n=12,976), men who received IMRT were less likely to experience gastrointestinal morbidity and fewer hip fractures but more likely to experience erectile dysfunction. IMRT patients were also less likely to receive additional cancer therapy. In a comparison between IMRT and proton therapy (n=1368), IMRT patients had a lower rate of gastrointestinal morbidity. There were no significant differences in rates of other morbidities or additional therapies between IMRT and proton therapy.

A Blue Cross Blue Shield technology assessment compared the effects of proton beam therapy, with or without x-ray external beam radiotherapy, against alternative radiotherapy modalities and other treatments of prostate cancer. The report concluded that there is inadequate evidence from comparative studies to permit conclusions. Whether proton beam therapy improves outcomes in any setting in prostate cancer has not yet been established (BCBS, 2011a).

An updated AHRQ review on radiation therapy for localized prostate cancer did not identify any comparative studies evaluating the role of particle radiation therapy (e.g., proton). Definitive benefits of radiation treatments compared to no treatment or no initial treatment for localized prostate cancer could not be determined because available data were insufficient. Data on comparative effectiveness between different forms of radiation treatments (brachytherapy (BT), external beam radiation therapy (EBRT), stereotactic body radiation therapy (SBRT)) are also inconclusive whether one form of radiation therapy is superior to another form in terms of overall or disease-specific survival. Studies suggest that higher EBRT dose results in increased rates of long-term biochemical control than lower EBRT dose. EBRT administered as a standard fractionation or moderate hypofractionation does not appear to differ with respect to biochemical control and late genitourinary and gastrointestinal toxicities. However, more and better quality studies are needed to either confirm or refute these suggested findings (AHRQ, 2010).

Zietman et al. (2010) tested the hypothesis that increasing radiation dose delivered to men with early-stage prostate cancer improves clinical outcomes. Men (n=393) with T1b-T2b prostate cancer and prostate-specific antigen \leq 15 ng/mL were randomly assigned to a total dose of either 70.2 Gray equivalents (GyE; conventional) or 79.2 GyE (high). Local failure (LF), biochemical failure (BF) and overall survival (OS) were outcomes. Median follow-up was 8.9 years. Men receiving high-dose radiation therapy were significantly less likely to have LF. The 10-year American Society for Therapeutic Radiology and Oncology BF rates were 32.4% for conventional-dose and 16.7% for high-dose radiation therapy. This difference held when only those with low-risk disease (n = 227; 58% of total) were examined: 28.2% for conventional and 7.1% for high dose. There was a strong trend in the same direction for the intermediate-risk patients (n = 144; 37% of total; 42.1% v 30.4%). Eleven percent of patients subsequently required androgen deprivation for recurrence after conventional dose compared with 6% after high dose. There remains no difference in OS rates between the treatment arms (78.4% v 83.4%). Two

percent of patients in both arms experienced late grade ≥ 3 genitourinary toxicity, and 1% of patients in the high-dose arm experienced late grade ≥ 3 GI toxicity.

Schulte et al. (2000) retrospectively compared outcomes for patients who received proton beam therapy or XRT with a proton boost with patients who underwent radical prostatectomy. The study included 911 patients with stage T1 to T3 prostate cancer. Patients in the proton therapy group received a total dose of 74 to 75 CGE. The estimated 5-year disease-free rate was 82.2%. Using an evidence-based theoretical model to estimate and compare disease-free rates, patients with localized prostate cancer treated with radical prostatectomy and those treated with external proton irradiation had equivalent disease-free rates. The 3-year actuarial incidence of grade 2 toxicities was 3.5% for gastrointestinal and 5.4% for genitourinary symptoms. No late grade 3 and 4 side effects were observed.

Gardner et al. (2002) retrospectively reviewed the side effects in 39 men of a pool of 167 men who were originally treated at the Harvard Cyclotron Laboratory (Duttenhaver, 1983; Shipley, 1995). This study was a long-term follow-up of prostate cancer patients who had received conventional XRT (50.4 Gy) followed with a proton boost (to a total dose of 77.4 Gy). The most common complications were rectal bleeding and hematuria. The incidence of gastrointestinal morbidity was stable for 5 years, but new genitourinary complications continued to appear. These findings suggest that high-dose conformal radiation will not result in a high incidence of late normal tissue sequelae, but that hematuria may be common.

Rossi et al. (2004) conducted a retrospective review to evaluate the impact of age on bNED survival in 1038 patients with organ-confined prostate cancer who underwent conformal PBT. The investigators reported that there were no statistically significant differences in bNED survival with regard to patient age. For patients younger than 60 years, 5- and 8-year bNED survival rates were 82% and 75%, respectively, compared with 75% and 74%, respectively, for patients 60 years and older. As expected, significant predictors of treatment outcome were pretreatment PSA level, clinical stage at diagnosis, and Gleason score. These results are consistent with the findings of other studies. The authors concluded that patient age alone should not be used to recommend one type of treatment over another.

Slater et al. (2004) conducted a retrospective review to evaluate the effect of conformal PBT on biochemical relapse and toxicity in 1255 patients with localized prostate cancer. Patients received either proton therapy alone or a combination of proton and photon therapy (both administered conformally). The investigators reported that conformal PBT yielded disease-free (bNED) survival rates that were comparable with other forms of local treatment (based on historical information), and treatment-related morbidity was minimal.

In a phase II clinical trial, comparative study by Vargas et al. (2008), 10 consecutive patients were studied to evaluate the contrast in dose distribution between proton radiotherapy (RT) and intensity-modulated RT (IMRT), particularly in regard to critical structures such as the rectum and bladder. The patients were treated to 78 Gray-equivalents (GE) in 2-GE fractions with a biologically equivalent dose of 1.1. All rectal and rectal wall volumes treated to 10-80 GE (percentage of volume receiving 10-80 GE [V(10)-V(80)]) were significantly lower with proton therapy ($p < 0.05$). The rectal V(50) was reduced from 31.3% \pm 4.1% with IMRT to 14.6% \pm 3.0% with proton therapy for a relative improvement of 53.4% and an absolute benefit of 16.7%. The mean rectal dose decreased 59% with proton therapy. For the bladder and bladder wall, proton therapy produced significantly smaller volumes treated to doses of 10-35 GE with a non-significant advantage demonstrated for the volume receiving $<$ or $=$ 60 GE. The bladder V(30) was reduced with proton therapy for a relative improvement of 35.3% and an absolute benefit of 15.1%. The mean bladder dose decreased 35% with proton therapy. The authors concluded that compared with IMRT, proton therapy reduced the dose to the dose-limiting normal structures while maintaining excellent planning target volume coverage.

Professional Societies

American Urological Association (AUA)

The AUA discusses proton beam therapy as an option within the category of external beam radiotherapy and states that dose escalation can be performed safely to 78 to 79 Gy. Such techniques include a computed tomography (CT) scan for treatment planning and either a multileaf collimator, intensity-modulated radiation therapy (IMRT) or proton radiotherapy using a high-energy (6 mV or higher) photon beam. However, study outcomes data do not provide clear-cut evidence for the superiority of any one treatment (Thompson et al., 2007; reaffirmed 2011).

Vestibular Tumors

The efficacy of PBT for the treatment of tumors of the vestibular system was assessed in two prospective uncontrolled studies involving 30 patients with acoustic neuromas (Bush et al., 2002) and 68 patients with vestibular schwannomas (Harsh et al., 2002). Fractionated PBT effectively controlled tumor growth in all patients with acoustic neuroma, and 37.5% of patients experienced tumor regression. Hearing was preserved in 31% of patients. The actuarial 5-year tumor control rate for patients with vestibular schwannomas was 84%; 54.7% of tumors regressed, 39.1% remained unchanged, and 3 tumors enlarged. The procedure caused some serious side effects in patients with vestibular schwannoma (severe facial weakness), but most side effects were either transient or could be successfully treated.

In a critical review, Murphy and Suh (2011) summarized the radiotherapeutic options for treating vestibular schwannomas, including single-session stereotactic radiosurgery, fractionated conventional radiotherapy, fractionated stereotactic radiotherapy and proton beam therapy. The comparisons of the various modalities have been based on single-institution experiences, which have shown excellent tumor control rates of 91-100%. Early experience using proton therapy for treating vestibular schwannomas demonstrated local control rates of 84-100% but disappointing hearing preservation rates of 33-42%. The authors report that mixed data regarding the ideal hearing preservation therapy, inherent biases in patient selection and differences in outcome analysis have made comparison across radiotherapeutic modalities difficult.

Combined Therapies

No evidence was identified in the clinical literature supporting the combined use of proton beam radiation therapy and intensity-modulated radiation therapy in a single treatment plan.

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

Radiation therapy is a procedure and, therefore, is not subject to FDA regulation. However, the accelerators and other equipment used to generate and deliver proton beam radiation therapy are regulated by the FDA. See the following website for more information (use product code LHN): <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmnm.cfm>. Accessed July 17, 2014.

CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

Medicare does not have a National Coverage Determination (NCD) for Proton Beam Therapy (PBT). Local Coverage Determinations (LCDs) do exist. Refer to the LCDs for [Category III Codes](#), [Category III CPT Codes](#), [Grenz Ray Treatment](#), [Intensity Modulated Radiation Therapy \(IMRT\)](#), [Proton Beam Radiotherapy](#), [Proton Beam Therapy](#), [Radiation Oncology Including Intensity Modulated Radiation Therapy \(IMRT\)](#), [Radiation Oncology: External Beam /Teletherapy](#), [Radiation Therapy for T1 Basal Cell and Squamous Cell Carcinomas of the Skin](#), [Radiation Therapy Services](#), [Radiology: Proton Beam Therapy](#), [Stereotactic Body Radiation Therapy](#), [Stereotactic Body Radiation Therapy \(SBRT\)](#) and [Radiation Therapy Services](#). (Accessed June 25, 2014)

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POLICY HISTORY/REVISION INFORMATION

Date	Action/Description
09/01/2014	<ul style="list-style-type: none"> • Reorganized policy content • Updated benefit considerations: <ul style="list-style-type: none"> ○ Added language for <i>Essential Health Benefits for Individual and Small Group</i> plans to indicate: <ul style="list-style-type: none"> ▪ For plan years beginning on or after January 1, 2014, the Affordable Care Act of 2010 (ACA) requires fully insured non-grandfathered individual and small group plans (inside and outside of Exchanges) to provide coverage for ten categories of Essential Health Benefits (“EHBs”) ▪ Large group plans (both self-funded and fully insured), and small group ASO plans, are not subject to the

	<p>requirement to offer coverage for EHBs; however, if such plans choose to provide coverage for benefits which are deemed EHBs (such as maternity benefits), the ACA requires all dollar limits on those benefits to be removed on all Grandfathered and Non-Grandfathered plans</p> <ul style="list-style-type: none"> ▪ The determination of which benefits constitute EHBs is made on a state by state basis; as such, when using this guideline, it is important to refer to the enrollee's specific plan document to determine benefit coverage ○ Added language to indicate some Certificates of Coverage allow coverage of experimental/ investigational/unproven treatments for life-threatening illnesses when certain conditions are met <ul style="list-style-type: none"> ▪ The enrollee-specific benefit document must be consulted to make coverage decisions for this service ▪ Benefit coverage for an otherwise unproven service for the treatment of serious rare diseases may occur when certain conditions are met • Revised coverage rationale: <ul style="list-style-type: none"> ○ Reformatted and relocated information pertaining to medical necessity review; added language to indicate if service is "medically necessary" or "not medically necessary" to applicable proven/unproven statement ○ Revised list of proven/medically necessary indications: <ul style="list-style-type: none"> ▪ Replaced "melanoma of the uveal tract" with "ocular tumors, including intraocular/uveal melanoma" ▪ Added "skull-based tumors (e.g., chordomas or chondrosarcomas)" ▪ Removed "primary intracranial and skull base tumors" and "spinal cord tumors" ○ Removed language indicating proton beam radiation therapy is proven non-preferentially as one form of external beam radiation therapy for the treatment of prostate cancer ○ Revised list of unproven/ not medically necessary indications to include <i>all indications not listed as proven/medically necessary</i>, including but not limited to: <ul style="list-style-type: none"> ▪ Age-related macular degeneration (AMD) ▪ Bladder cancer ▪ Brain and spinal cord tumors ▪ Choroidal hemangioma ▪ Gastrointestinal cancers, including esophageal and pancreatic ▪ Gynecologic cancers ▪ Head and neck cancers ▪ Hepatocellular carcinoma ▪ Lung cancer ▪ Lymphomas ▪ Prostate cancer ▪ Vestibular tumors (e.g., acoustic neuroma or vestibular schwannoma) • Updated list of applicable ICD-9 diagnosis codes: <ul style="list-style-type: none"> ○ Added 170.0, 213.0, 224.0 and 224.6 ○ Removed 185, 191.0 – 191.8, 192.2, 192.3, 225.0, 225.3, 225.4, 237.5, 237.6 and 239.6 • Updated list of applicable ICD-10 diagnosis codes (preview draft effective 10/01/15):
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	<ul style="list-style-type: none">○ Added C41.0, D16.4, D31.30 – D31.32 and D31.40 – D31.42○ Removed C61, C70.1, C71.0 – C71.8, C72.0, C72.1, D32.1, D33.0 – D33.2, D33.4, D42.0, D42.1, D42.9, D43.0 – D43.2, D43.4 and D49.6● Updated supporting information to reflect the most current description of services, clinical evidence, FDA and CMS information and references● Archived previous policy version 2014T0132P
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