PROTON BEAM RADIATION THERAPY

Guideline Number: MMG113.M **Effective Date**: January 1, 2019

Instructions for Use

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Related Medical Management Guideline

- Intensity-Modulated Radiation Therapy

COVERAGE RATIONALE

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

The following are proven and medically necessary:

- PBT for Definitive Therapy of 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, chondrosarcomas, or paranasal sinus tumors)
  - Localized, unresectable hepatocellular carcinoma (HCC) in the curative setting when documentation is provided that sparing of the surrounding normal tissue cannot be achieved with standard radiation therapy techniques, including intensity-modulated radiation therapy (IMRT), and stereotactic body radiation therapy (SBRT), and selective internal radiation spheres, and transarterial therapy (for example, chemoembolization) is contraindicated or not technically feasible.
- PBT may be covered for a diagnosis that is not listed above as proven, including recurrences or metastases in selected cases. Requests for exceptions will be evaluated on a case-by-case basis when both of the following criteria are met:
  - Documentation is provided that sparing of the surrounding normal tissue cannot be achieved with standard radiation therapy techniques; **and**
  - Evaluation includes a comparison of treatment plans for PBT, IMRT and SBRT.

PBT and IMRT are proven and considered clinically equivalent for treating prostate cancer. Medical necessity will be determined based on the terms of the member's benefit plan.

PBT is unproven and not medically necessary due to insufficient evidence of efficacy for treating ALL other indications not listed above as proven, including but not limited to:

- Age-related macular degeneration (AMD)
- Bladder cancer
- Brain and spinal cord tumors
- Breast cancer
- Choroidal hemangioma
- Esophageal cancer
- Gynecologic cancers
- Head and neck cancers
- Lung cancer
- Lymphomas
- Pancreatic cancer

- Vestibular tumors (e.g., acoustic neuroma or vestibular schwannoma)
- PBT used in conjunction with IMRT

DOCUMENTATION REQUIREMENTS

Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The documentation requirements outlined below are used to assess whether the member meets the clinical criteria for coverage but do not guarantee coverage of the service requested.

Required Clinical Information
Proton Beam Radiation Therapy (PBT)
Medical notes documenting **all** of the following: • History of medical condition requiring treatment • Documentation that sparing of the surrounding normal tissue cannot be achieved with standard radiation therapy techniques • Evaluation includes a comparison of treatment plans for PBT, IMRT, and stereotactic body radiation therapy (SBRT) • For hypofractionated radiation, provide the prescribed total dose and dose per fraction • For delivery of radiation therapy course with standard fractionation, provide the dose prescription along with documentation in the form of a clearly labeled, color comparative proton, and IMRT dose volume histogram and dose table, in absolute doses noting that sparing of the surrounding normal tissue cannot be achieved with IMRT techniques **Note**: If citing an RTOG dose constraint, provide the RTOG protocol number • Physician's treatment plan **Note**: The color comparative proton and IMRT dose volume histogram and dose table images can be submitted via the external portal at http://www.uhcprovider.com/paan or via email at CCR@uhc.com; faxes of images will not be accepted.

DEFINITIONS

Definitive Therapy: Definitive therapy is treatment with curative intent. Treatment of a local recurrence of the primary tumor may be considered definitive if there has been a long disease free interval (generally ≥2 years) and treatment is with curative intent.

APPLICABLE CODES

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this guideline does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan 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 claim payment. Other Policies and Guidelines may apply.

CPT Code	Description
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
77385	Intensity modulated radiation treatment delivery (IMRT), includes guidance and tracking, when performed; simple
77386	Intensity modulated radiation treatment delivery (IMRT), includes guidance and tracking, when performed; complex
77387	Guidance for localization of target volume for delivery of radiation treatment, includes intrafraction tracking, when performed
77520	Proton treatment delivery; simple, without compensation
77522	Proton treatment delivery; simple, with compensation
77523	Proton treatment delivery; intermediate
77525	Proton treatment delivery; complex

HCPCS Code	Description
G6015	Intensity modulated treatment delivery, single or multiple fields/arcs, via narrow spatially and temporally modulated beams, binary, dynamic MLC, per treatment session
G6016	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
G6017	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

ICD-10 Diagnosis Code	Description
C22.0	Liver cell carcinoma
C31.0	Malignant neoplasm of maxillary sinus
C31.1	Malignant neoplasm of ethmoidal sinus
C31.2	Malignant neoplasm of frontal sinus
C31.3	Malignant neoplasm of sphenoid sinus
C31.8	Malignant neoplasm of overlapping sites of accessory sinuses
C31.9	Malignant neoplasm of accessory sinus, unspecified
C41.0	Malignant neoplasm of bones of skull and face
C61.0	Malignant neoplasm of prostate
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
D09.20	Carcinoma in situ of unspecified eye
D09.21	Carcinoma in situ of right eye
D09.22	Carcinoma in situ of left eye
D14.0	Benign neoplasm of middle ear, nasal cavity and accessory sinuses
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, 2017).

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

ECRI (2017) states that while PBRT has been used for several solid cancer tumor types (breast, lung, prostate, head and neck, CNS) in adults and in certain pediatric cancers, evidence is lacking regarding its benefits for many cancers over photon-based EBRT.

Professional Societies

American Society for Radiation Oncology (ASTRO)

ASTRO's Emerging Technology Committee concluded that current data do not provide sufficient evidence to recommend PBT outside of clinical trials in lung cancer, head and neck cancer, GI malignancies (with the exception of hepatocellular carcinoma) and pediatric non CNS malignancies. In HCC 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 (AVM)

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 'Cyber Knife'), 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 (AEs)of single-fraction proton beam stereotactic radiosurgery (PSRS) in patients with cerebral 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 AVMs, based on brain location or large size, who underwent planned two-fraction 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 2 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 2-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.

Ocular Tumors

In a systematic review, Wang et al. (2013) evaluated the efficacy and AEs of charged particle therapy (CPT), delivered with protons, helium ions or carbon ions, for treating uveal melanoma. Twenty-seven studies enrolling 8809 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.

In the National Comprehensive Cancer Network (NCCN) guidelines on uveal melanoma, PBT is not cited in the list of radiotherapies recommended for treatment. (2018)

Skull Base Tumors

Zhou et al. (2018) performed a meta-analysis to compare the effectiveness of photon therapy, PBT, and carbon ion therapy (CIT) for chordoma. Twenty-five studies were included, with results showing that the 3-, 5-, and 10-year overall survival (OS) rates were higher for stereotactic radiotherapy (SRT), PBT, and CIT than for conventional radiotherapy (CRT). The 10-year OS was higher for PBT than for SRT. The analysis revealed that particle therapy was more effective following surgery for chordoma than CRT. After 10 years, PBT was more beneficial than SRT. However, future studies should include more studies to enable accurate meta-analysis and a better exploration of prognosis.

Kabolizadeh et al. (2017) performed a retrospective analysis at a single institution assessing outcome and tumor response to Definitive photon/proton radiotherapy when used in cases of unresected spine and sacral chordoma. Forty patients were identified between 1975 and 2012. Except for 1 patient, all underwent proton therapy only, or predominantly proton therapy combined with photons to limit the exit dose of radiation to any adjacent normal structures at risk. Three-dimensional conformal radiotherapy (3DCRT) was the specific photon treatment used until January 2002 when it was replaced by IMRT (primarily for skin-sparing effects). Local control (LC), OS, disease-specific survival (DFS), and distant failure at 5 years were 85.4%, 81.9%, 89.4%, and 20.2%, respectively. The authors concluded that for selected patients with unresected spine and sacral chordomas, the use of high-dose Definitive radiation Therapy can be supported with these results.

The use of PBT to treat chondrosarcoma of the skull base after surgery is widely accepted, but studies demonstrating the need for PBT and its superiority in comparison to radiotherapy with photons are lacking. In a systematic review, Amichetti et al. (2010) reported that studies of PBT for skull-based chondrosarcoma resulted in LC ranging from 75% to 99% at 5 years. There were no prospective trials (randomized or nonrandomized), but 4 uncontrolled single-arm studies with 254 patients were included. The authors concluded that PBT following surgical resection showed a very high probability of medium- and long-term cure with a relatively low risk of significant complications.

A systematic review of 7 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).

Early studies evaluating PBT for the treatment of intracranial or skull base tumors include 4 case series, 4 retrospective studies, and 2 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. LC was achieved in 71% to 100% of patients. Complications were radiation dose/volume and site dependent, and were mild to severe.

NCCN states that specialized techniques, including particle beam radiation therapy with protons, should be considered as indicated in order to allow high-dose therapy while maximizing normal tissue sparing in patients with chondrosarcoma (2019).

Age-Related Macular Degeneration (AMD)

In a Cochrane review, Evans et al. (2010) examined the effects of radiotherapy on neovascular AMD. All RCTs in which radiotherapy was compared to another treatment, sham treatment, low dosage irradiation or no treatment were included. Thirteen trials (n=1154) investigated EBRT 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 AEs 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 10 patients and that assessed the efficacy or safety of proton therapy for any indication of the eye were included. Five controlled trials, 2 comparative studies and 30 case series were found, most often reporting on uveal melanoma, choroidal melanoma and 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 RCT 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 2 dose groups.

Professional Societies

American Academy of Ophthalmology (AAO)

AAO preferred practice patterns state that radiation therapy is not recommended in the treatment of AMD. (2015).

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.

NCCN guidelines do not address the use of PBT for treating bladder cancer (2018).

Brain and Spinal Cord Tumors

Petr et al. assessed structural and hemodynamic changes of healthy brain tissue in the cerebral hemisphere contralateral to the tumor following photon and proton radiochemotherapy. Sixty seven adult patients diagnosed with glioblastoma undergoing adjuvant photon (n = 47) or proton (n = 19) radiochemotherapy with temozolomide after tumor resection underwent T1-weighted and arterial spin labeling magnetic resonance imaging. Changes in volume and perfusion before and 3-6 months after were compared between therapies. A decrease in gray matter (GM) and white matter (WM) volume was observed in photon therapy patients compared to the pre-radiotherapy baseline. In contrast, for the proton therapy group, no significant differences in GM or WM volume were observed. GM volume decreased with 0.9% per 10 Gy dose increase and differed between the radiation modalities. Perfusion decreased in photon therapy patients, whereas the decrease in proton therapy patients was not statistically significant. There was no correlation between perfusion decrease and either dose or radiation modality. The authors concluded that proton therapy may reduce brain volume loss compared to photon therapy, with decrease in perfusion being comparable for both modalities (2018).

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, 12 patients had a benign tumor that was recurrent or rapidly progressive. In 2 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 LC and OSI rates were 87.5 +/- 12% and 88.9 +/- 11%, respectively. Radiologically, there were 11 stable diseases and 5 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.

NCCN guidelines state that when toxicity from craniospinal irradiation is a concern during management of spinal ependymoma or medulloblastoma , proton beam radiotherapy should be considered if available. (2018).

Several clinical trials studying PBT in patients with various types of brain tumors are active or recruiting. For more information, please go to www.clinicaltrials.gov. (Accessed October 31, 2018)

Breast Cancer

Verma et al. (2016) performed a systematic review of clinical outcomes and toxicity of PBT for treating breast cancer. Nine original studies were analyzed, however the types of studies and the volume of patients in those studies were not specifically cited by the authors. Conventionally fractionated breast/chest wall PBT produces grade 1 dermatitis rates of approximately 25% and grade 2 dermatitis in 71% - 75%. This is comparable or improved over the published rates for photons. The incidence of esophagitis was decreased if the target coverage was compromised in the medial supraclavicular volume, a finding that echoes previous results with photon radiotherapy. The rates of esophagitis were also comparable to the previous data for photons. Using PBT-based accelerated partial breast irradiation (PBI), the rates of seroma/hematoma and fat necrosis were comparable to those reported in the existing data. Radiation pneumonitis and rib fractures remain rare. PBT offers potential to minimize the risk of cardiac events, keeping the mean heart dose at ≤ 1 Gy. However, definitive clinical experiences remain sparse. Results from clinical trials in progress, comparing protons to photons, will further aid in providing conclusions.

Verma et al. (2017) conducted a retrospective single institution cohort study to evaluate acute toxicity in patients with locally advanced breast cancer (n=91) receiving comprehensive regional nodal irradiation (CRNI) with adjuvant PBT between 2011 – 2016. PBT consisted of a 3-dimensional uniform scanning (US) technique, and transitioned to a pencil beam scanning (PBS) technique in 2016. Change in technique was driven by anticipated dosimetric advantages including decreased dose to the skin surface and to cardiopulmonary organs, and shorter planning and treatment delivery time. Toxicities were assessed weekly during treatment, one month following treatment completion, and then every 6 months with a median follow up period of 15.5 months. The most common toxicities were dermatitis and/or skin infections, but also seen were esophagitis and fatigue. The authors concluded that PBT for breast cancer as part of CRNI appears to have appropriate toxicity. While using PBT in the setting of CRNI is presumed to be advantageous relative to cardiac dose reduction, further studies with longer follow-up are needed.

Bush et al. (2014) performed a single center study of 100 subjects who received postoperative PBI using PBT after undergoing partial mastectomy with negative margins and axillary lymph nodes. After following these individuals for an average of 5 years, the researchers concluded that ipsilateral recurrence-free survival with minimal toxicity was excellent. While the authors acknowledged that cosmetic results may be improved with PBT over those reported with photon-based techniques, there was nothing in the study demonstrating that PBT outcomes were superior to the current standard of care.

NCCN guidelines do not address the use of PBT for treating breast cancer (2018).

A phase III RCT (NCT02603341) is in progress, comparing PBRT to photon therapy in patients with non-metastatic breast cancer. . For more information on this and other clinical trials studying PBT and breast cancer, please go to www.clinicaltrials.gov. (Accessed October 30, 2018)

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. In the collective groups, 91% were treated successfully. There was no significant difference in the outcomes between the 2 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 versus photon 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 (GI) Cancers

A systematic review by Verma, et al. (2016) reported survival and toxicity outcomes where individuals with multiple types of GI cancers were treated with PBT. Thirty-eight studies published between 2010-2015 were included in the review, however the types of studies and the volume of patients in those studies were not specifically cited by the

authors. Reduced toxicities with PBT versus photon therapy were identified in malignancies of the esophagus, pancreas, and in HCC. Fewer toxicities and improved PFS were also found using PBT versus transarterial chemoembolization (TACE) in a phase III trial. Survival and toxicity data for cholangiocarcinoma, liver metastases, and retroperitoneal sarcoma were nearly equivalent to photon controls. There were 2 small reports for gastric cancer and 3 for anorectal cancer identified, but these were not addressed. The authors concluded that although studies in this review were of limited quality and quantity, PBT potentially offers significant reduction in treatment-related toxicities without compromising survival in GI cancers. Several phase II/III clinical trials are now in progress conducting further research.

Esophageal Cancer

In a retrospective analysis, Wang et al. (2013) reported that advanced radiation technologies, such as IMRT or PBT significantly reduced postoperative pulmonary and GI complication rates compared to 3D-CRT in esophageal cancer patients. These results need to be confirmed in prospective studies.

Lin et al. (2012) reported preliminary results using concurrent chemotherapy and PBT (CChT/PBT) in 62 patients with esophageal cancer. The median follow-up time was 20.1 months for survivors. Acute treatment-related toxicities and perioperative morbidities were relatively low and the tumor response and disease related outcomes were encouraging. The authors concluded that CChT/PBT holds promise in the management of esophageal cancers. This study is limited by retrospective design, lack of randomization and short-term follow-up.

Mizumoto et al. (2011) evaluated the efficacy and safety of hyperfractionated concomitant boost PBT in 19 patients with esophageal cancer. The overall 1- and 5-year actuarial survival rates for all 19 patients were 79.0% and 42.8%, respectively. The median survival time was 31.5 months. Of the 19 patients, 17 (89%) showed a complete response within 4 months after completing treatment and 2 (11%) showed a partial response, giving a response rate of 100% (19/19). The 1- and 5-year LC rates for all 19 patients were 93.8% and 84.4 %, respectively. The results suggest that hyperfractionated PBT is safe and effective for patients with esophageal cancer. Further studies are needed to establish the appropriate role and treatment schedule for use of PBT for esophageal cancer.

Mizumoto et al. (2010) evaluated the efficacy and safety of PBT for locoregionally advanced esophageal cancer. Fifty-one patients were treated using PBT 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 PBT 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 LC rate for all 51 patients was 38.0% and the median LC time was 25.5 months. The authors concluded that these results suggest that PBT 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.

NCCN guidelines state that PBT is appropriate when treating esophageal and esophagogastric junction cancers in settings where dose reduction to organs at risk is necessary and cannot be achieved by 3DCRT. Because data is early and evolving, patients should receive PBT within a clinical trial. (2018)

Gastric Cancer

NCCN guidelines do not address PBT in the treatment of gastric cancers (2018).

Pancreatic Cancer

Studies evaluating PBT for the treatment of pancreatic cancer are in the very early stages (Hong et al., 2014; Terashima et al., 2012; Hong et al., 2011). Further research from prospective studies is needed to determine the long-term safety and efficacy of this treatment modality.

NCCN guidelines do not address PBT in the treatment of pancreatic adenocarcinoma (2018).

Numerous clinical trials are currently in progress studying the use of PBT in multiple types of GI cancer (e.g., esophageal, pancreatic, and retroperitoneal sarcoma). For more information, please go to www.clinicaltrials.gov. (Accessed October 30, 2018)

Hepatocellular Carcinoma (HCC)

Fukuda et al. (2017) performed an observational study of 129 patients, concluding that PBT achieved long term (5 year) tumor control with minimal toxicity. It is a viable treatment option for localized HCC, it showed favorable long-term efficacies with mild AEs in Barcelona Clinic Liver Cancer stage 0-C, and it can be an alternative treatment for localized HCC especially when accompanied with tumor thrombi. The authors are now planning a multicenter controlled study comparing PBT and hepatectomy.

Hong et al. conducted a single-arm, phase II, multi-institutional study to evaluate the safety and efficacy of high-dose, hypofractionated PBT for HCC and intrahepatic cholangiocarcinoma (ICC). Eighty-three participants ages 18 years and over were included, and follow up continued for 5 years. The authors concluded that high-dose, hypofractionated PBT is safe and associated with high rates of LC and OS for both HCC and ICC. These data provide the strong rationale for RCT of proton versus photon radiotherapy for HCC, and for chemotherapy with or without radiation therapy for ICC (2016).

A RCT by Bush et al. (2016) compared treatment outcomes in 69 patients with newly diagnosed HCC who received either TACE or PBRT over 3 weeks. The primary endpoint was progression-free survival, with secondary endpoints of OS, LC, and treatment-related toxicities as represented by post-treatment days of hospitalization. The interim analysis indicates similar OS rates for PBRT and TACE. There is a trend toward improved LC and PFS with proton beam. There are significantly fewer hospitalization days after proton treatment, which may indicate reduced toxicity with PBT.

Qi et al. (2015) performed a systematic review and meta-analysis to compare the clinical outcomes and toxicity of HCC patients treated with CPT with those of individuals receiving CRT. A total of 73 cohorts from 70 non-comparative observational studies were included. The clinical evidence for HCC indicates that survival rates for CPT are significantly higher than those for CRT, but are similar to SBRT. Toxicity tends to be lower for CPT when compared to photon radiotherapy. The authors reported that the overall quantity and quality of data regarding carbon-ion and proton therapy is poor, and there is a potential risk of bias in comparisons between observation studies. Therefore, the reported results do not allow for definite conclusions. Prospective randomized studies, comparing survival and toxicity between particle and photon radiotherapy, are strongly encouraged.

In another systematic review, Dionisi et al. (2014) assessed the use of proton therapy in the treatment of HCC. Of 16 studies from 7 institutions worldwide, 7 were clinical in nature, 3 reported on treatment-related toxicity and 1 reported on both. More than 900 patients with heterogeneous stages of disease were treated with various fractionation schedules. Only 1 prospective full paper was found. LC was approximately 80% at 3-5 years, and average OS at 5 years was 32%, with data comparable to surgery in the most favorable groups. Toxicity was low (mainly GI). The authors reported that the good clinical results are counterbalanced by a low level of evidence. The rationale to enroll patients in prospective studies appears to be strong.

NCCN guidelines state that radiotherapy with protons at an experienced center is an acceptable option for unresectable intrahepatic tumors (2018).

A phase III randomized trial comparing PBT to radiofrequency ablation (NCT02640924) and a RCT comparing PBT to TACE (NCT00857805) are both in progress. For more information on these and other clinical trials studying PBT and HCC, please go to www.clinicaltrials.gov. (Accessed October 30, 2018)

Professional Societies

American Society for Radiation Oncology (ASTRO)

ASTRO's model policy lists hepatocellular cancer as an indication for PBT (2017).

American College of Radiology (ACR)

PBT is not addressed in the ACR Appropriateness Criteria discussing radiologic management of HCC (Kouri et al., 2015).

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.

NCCN guidelines do not address the use of PBT when treating any type of gynecologic cancer (2018, 2019).

Several clinical trials are recruiting or in progress studying the use of PBT in multiple types of gynecologic cancer (e.g., cervical, ovarian, and uterine). For more information, please go to www.clinicaltrials.gov. (Accessed October 30, 2018)

Head and Neck Cancers (HNC)

A Hayes report assessed multiple clinical studies evaluating the efficacy and safety of PBT in patients with neck cancers. The majority of the evidence included retrospective studies, data analyses, and systematic reviews. The report concludes that the abstracts present conflicting findings regarding this technology (2016).

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 CPT with those of individuals receiving photon therapy. Primary outcomes of interest were OS, DFS and LC, both 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 CPT group was 38 months and for the photon therapy group was 40 months. Pooled OS was significantly higher at 5 years for CPT than for photon therapy and at longest follow-up. At 5 years, DFS was significantly higher for CPT than for photon therapy but, at longest follow-up, this event rate did not differ between groups. LC did not differ between treatment groups at 5 years, but it was higher for CPT than for photon therapy at longest follow-up. A subgroup analysis comparing PBT with IMRT showed significantly higher DFS at 5 years and LC at longest follow-up. The authors concluded that, CPT, 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.

Holliday and Frank performed a systematic review of the use of PBT for HNC. Literature search included articles published between January 1990 and September 2013. 18 articles (4 prospective non-randomized studies and 14 retrospective reviews, n=1074) met the review criteria for inclusion in the analysis. There were no RCTs which directly compared proton with photon-based therapy. They concluded that based on the reviewed literature, proton therapy is safe and may be superior to photon-based treatment by reducing toxicities and maintaining or improving LC in the treatment of on tumors of the skull base, nasal/paranasal area, and naso/oropharynx (2014).

Ramaekers et al. (2011) compared evidence evaluating the effectiveness of carbon-ion, proton and photon radiotherapy for HNC. 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 CITand 7 proton) and eight comparative in-silico studies were included. Five-year LC after PBT 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 CIT 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 PBT 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 PBT 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.

Zenda et al. (2016) conducted a prospective phase II study to examine the efficacy and safety of PBT for mucosal melanoma of the nasal cavity or para-nasal sinuses as an alternative treatment to surgery. Thirty-two patients were enrolled from June 2008 through October 2012, receiving PBT 3 times per week with a planned total dose of 60 GyE in 15 fractions. Primary outcome measurement was LC rate at 1 year post treatment, which was 75.8%. The OS rate at 3 years was 46.1%, with the primary cause of death being cancer due to distant metastases (93.3%). The authors concluded that PBT showed sufficient LC benefits for mucosal melanoma as an alternative treatment of surgery.

Seeking to improve LC rate and reduce late AEs, Takayama et al. evaluated therapeutic results and toxicities of PBT combined with selective intra-arterial infusion chemotherapy (PBT-IACT) in patients with stage III-IVB squamous cell carcinoma of the tongue. Between February 2009 and September 2012, 33 patients were enrolled. After 2 systemic chemotherapy courses and whole-neck irradiation (36 Gy in 20 fractions), participants were administered concurrent chemoradiotherapy comprising PBT for the primary tumor and for the metastatic neck lymph node with weekly retrograde IACT of cisplatin with sodium thiosulfate by continuous infusion. The median follow-up duration was 43 months. The 3-year OS, PFS, LC rate, and regional control rate for the neck were 87%, 74.1%, 86.6%, and 83.9%, respectively. Major acute toxicities > grade 3 included mucositis in 26 cases (79 %), neutropenia in 17 cases (51 %), and dermatitis in 11 cases (33 %). Late grade 2 osteoradionecrosis was observed in 1 case (3 %). The authors concluded that PBT-IACT for stage III-IVB tongue cancer has an acceptable toxicity profile and showed good

treatment results, and that this protocol should be considered as a treatment option for locally advanced tongue cancer (2016).

NCCN guidelines on HNC indicate that PBT is safe and effective and can be considered for treatment of multiple types of head and neck tumors when normal tissue constraints cannot be met by photon-based therapy.. It is valuable in patients whose primary tumors are periocular in location and/or invade the orbit, skull base, and/or cavernous sinus; that extend intracranially or exhibit extensive perineural invasion. They no longer recommend neutron therapy as a general solution for salivary gland cancers due to the diminishing demand, concerns regarding the methodologic robustness of available randomized trial data, and closure of all but one center in the U.S. (2018).

Professional Societies

American College of Radiology (ACR)

Appropriateness criteria from the ACR for the treatment of nasopharyngeal cancer states that intensity modulated proton therapy remains experimental (Saba, et al., 2015).

Lung Cancer

Chang et al. reported 5-year results of a prospective phase II single-institution study evaluating chemotherapy with concurrent high dose PBT in 64 patients with unresectable phase III non-small cell lung cancer (NSCLC). 5-year OS, PFS, actuarial distant metastases and locoregional recurrence were 29%, 22%, 54%, and 28%, respectively. Acute and late toxic effects with PBT (compared to historical studies with 3DCRT and/or IMRT) with chemotherapy were very promising. The authors concluded that the study demonstrated that concurrent PBT and chemotherapy was safe and effective in the long term, and that further prospective studies are warranted (2017).

A Hayes report (2018) concluded that the best available studies of PBT for NSCLC do not provide sufficient evidence that PBT is safer or consistently more effective than CRT and IMRT in the treatment of NSCLC.

Liao et al. (2016) conducted a phase II single institution randomized trial comparing IMRT to passive scattering 3D proton therapy (3DPT), both with concurrent chemotherapy, for locally advanced NSCLC.
Of 255 enrolled patients, 149 were randomly allocated to IMRT (n=92) or 3DPT (n=57), and 106 received non-randomized (NR)IMRT (n=70) or NR3DPT (n=36). . The primary end points assessed were grade $\geq$ 3 radiation pneumonitis (RP) and local failure (LF). Their article published in 2016 reported outcomes at 12 months. LF rates for all were 20.7%; the randomized IMRT group were 15.6% and the randomized 3DPT group was 24.6%. RP for all were 8.7%, randomized IMRT and 3DPT were 7.2% and 11%, respectively. Continued monitoring resulted in a follow up article in 2018. The median follow-up time for the IMRT group for all patients was 24 months and 36.4 months for those still alive. For the 3DPT group, the follow up time was 25.7 months for all patients and 48.8 months for those surviving. The authors concluded that there was no statistically significant difference in the primary end points after IMRT or 3DPT for patients with locally advanced NSCLC. They did state that findings from 2 ongoing trials (NCT01993810 and NCT01629498) will provide additional evidence of the efficacy of proton and photon therapies.

Harada et al. (2016) conducted a single-institutional, open label, dose escalation phase I trial to determine the recommended dose of PBT for inoperable stage III NSCLC. Two prescribed doses of PBT were tested: 66 Gy RBE in 33 fractions and 74 Gy RBE in 37 fractions in arms 1 and 2, respectively. The planning target volume included the primary tumor and metastatic lymph nodes with adequate margins. Concurrent chemotherapy included intravenous cisplatin (60 mg/m(2) , day 1) and oral S-1 (80, 100 or 120 mg based on body surface area, days 1-14), repeated as 4 cycles every 4 weeks. Dose-limiting toxicity (DLT) was defined as grade 3 (severe) toxicities related to PBT during days 1-90. Each dose level was performed in 3 patients, and then escalated to the next level if no DLT occurred. When 1 patient developed a DLT, 3 additional patients were enrolled. Overall, 9 patients were enrolled, including 6 in Arm 1 and 3 in Arm 2. The median follow-up time was 43 months, and the median PFS was 15 months. In Arm 1, grade 3 infection occurred in 1 of 6 patients, but no other DLT was reported. Similarly, no DLT occurred in Arm 2. However, one patient in Arm 2 developed grade 3 esophageal fistula at 9 months after the initiation of PBT. From a clinical perspective, the authors concluded that 66 Gy RBE is the recommended dose.

Oshiro et al. (2014) initiated a Phase II study to evaluate the safety and efficacy of high-dose PBT with concurrent chemotherapy for unresectable or medically inoperable advanced NSCLC. Patients (n=15) were treated with PBT and chemotherapy with monthly cisplatin (on Day 1) and vinorelbine (on Days 1 and 8). The treatment doses were 74 Gy RBE for the primary site and 66 Gy RBE for the lymph nodes without elective lymph nodes. The median follow-up period was 21.7 months. None of the patients experienced Grade 4 or 5 non-hematologic toxicities. Acute pneumonitis was observed in 3 patients (Grade 1 in one, and Grade 3 in two), but Grade 3 pneumonitis was considered to be non-proton-related. Grade 3 acute esophagitis and dermatitis were observed in 1 and 2 patients, respectively. Severe ($\geq$ Grade 3) leukocytopenia, neutropenia and thrombocytopenia were observed in 10, 7, and 1 patients, respectively. Late radiation Grades 2 and 3 pneumonitis was observed in one patient each. Six patients (40%) experienced local recurrence at the primary site and were treated with 74 Gy RBE. Disease progression was observed in 11 patients,

with the mean survival time being 26.7 months. The authors concluded that high-dose PBT with concurrent chemotherapy is safe to use in the treatment of unresectable stage III NSCLC.

Sejpal et al. (2011) compared the toxicity of PBT plus concurrent chemotherapy in patients with NSCLC (n=62) with toxicity for patients with similar disease given 3D-CRT plus chemotherapy (n = 74) or 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 PBT 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 PBT has been initiated.

Chi et al. conducted a systematic review and meta-analysis to assess hypo-fractionated PBT's efficacy relative to that of photon SBRT for early stage NSCLC. Seventy two SBRT studies and 9 hypo-fractionated PBT studies (mostly single-arm) were included. PBT was associated with improved OS and PFS in the univariate meta-analysis. The OS benefit did not reach its statistical significance after inclusion of operability into the final multivariate meta-analysis; while the 3-year LC still favored PBT. Researchers concluded that although hypo-fractionated PBT may lead to additional clinical benefit when compared with photon SBRT, no statistically significant survival benefit from PBT over SBRT was observed in the treatment of early stage NSCLC (2017).

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 NSCLC, mainly stage I, were identified. No phase III trials were found. For PBT, 2- to 5-year LC rates varied in the range of 57%-87%. The 2- and 5-year OS and 2- and 5-year cause-specific survival rates were 31%-74% and 23% and 58%-86% and 46%, respectively. RP was observed in about 10% of patients. For CIT, the overall LC rate was 77%, but it was 95% when using a hypofractionated radiation schedule. The 5-year OS and cause-specific survival rates were 42% and 60%, respectively. Slightly better results were reported when using hypofractionation, at 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, CPT should be considered experimental.

NCCN guidelines state that advanced technologies such as PBT have been shown to reduce toxicity and increase survival in nonrandomized trials. PBT is appropriate when needed for safe delivery of curative or palliative radiotherapy for NSCLC. NCCN is silent on the use of PBT in the treatment of small cell lung cancer (2018).

A phase III RCT comparing photon to proton chemoradiotherapy for patients with inoperable NSCLC (NCT01993810) is in progress. For more information, please go to www.clinicaltrials.gov. (Accessed October 30, 2018)

Professional Societies

American College of Radiology (ACR)

ACR appropriateness criteria addressing nonsurgical treatment for locally advanced NSCLC states that while PBT may have the potential to spare critical normal tissues, more prospective studies are needed (Chang, et al., 2014).

Lymphoma

NCCN guidelines for Hodgkin, B-cell, and T-cell lymphomas state that PBT may be appropriate, depending on clinical circumstances. It also states that advanced radiation therapy technologies, such as PBT, may offer significant and clinically relevant advantages in specific instances to spare important organs at risk and decrease the risk for late, normal tissue damage while still achieving the primary goal of LC. (2017, 2018)

NCCN is silent on the use of proton therapy in the treatment of primary cutaneous B-cell lymphoma (2018).

Prostate Cancer

A Hayes report assessed multiple clinical studies published between 1983-2016 evaluating the efficacy and safety of PBT in patients with localized prostate cancer. The report concludes that the reviewed studies found that PBT as an adjunct to X-ray therapy (XRT) usually had good or excellent safety and efficacy outcomes. Several controlled or comparative studies of PBT alone reported similar safety to IMRT, conformal XRT, and brachytherapy, but these did not assess the efficacy of PBT alone relative to other techniques for prostate cancer treatment. Additional well-designed studies are needed to establish the clinical role of PBT relative to other widely used therapies for localized prostate cancer. For patients with prostate cancer and distant metastases, PBT has no proven benefit. Published evidence shows that the technology does not improve health outcomes or patient management in this patient

population. Evidence addressing the safety & efficacy of PBT compared to other common radiation therapies for this indication is inadequate (2018).

Bryant et al. (2016) performed a single-center study on 1327 men with localized prostate cancer who received image guided proton therapy (PT) between 2006-2010. The 5-year freedom from biochemical progression (FFBP) rates were 99% for low-risk, 94% for intermediate-risk, and 76% for high-risk patients. The authors concluded that PBT provided excellent control of disease with low rates of GU/GI toxicity. Large prospective comparative studies with longer follow-up times are necessary for a true comparison between PT and other types of radiotherapy.

Mendenhall et al. (2016) reported 5-year clinical outcomes from trials of image-guided PBT for prostate cancer conducted at a single institution. From August 2006-September 2007, low, intermediate, and high risk patients (n=211) were enrolled in one of 3 prospective trials. GI/GU toxicities as well as biochemical and clinical freedom from disease progression were outcomes measured, citing 99%, 99%, and 76% FFBP at 5 years for low, intermediate, and high risk patients, respectively. The authors concluded that image-guided PBT was highly effective and safe, reporting minimal toxicities and positive patient-reported outcomes. While outcomes were very favorable, further follow-up and larger study groups were deemed necessary.

A retrospective study by Tagaki et al. (2017) reported long-term outcomes on patients receiving Definitive PBT for localized prostate cancer between April 2001-May 2014 at a single institution. A total of 1375 individuals were included, with primary outcome measurements including freedom from biochemical relapse (FFBR) and incidence of late GI/GU toxicities. Follow-up evaluations were performed at intervals of every 3 months for 5 years and every 6 months thereafter, with the median length of follow up being 70 months. Comparing PT to other EBRTs, FFBR at 5 years for low-, intermediate-, high-, and very high-risk patients were 99%, 91%, 86%, and 66%, respectively, similar to other published research (Bryant, 2016; Mendenhall, 2014). The authors concluded that PT is a favorable radiotherapy technique with lower late GU toxicity. Patient age was cited as a prognostic factor for both late GI and GU toxicities, indicating the need to consider patient age when determining the most advantageous treatment protocol. Although the results of PT in this and other studies are favorable, RCTs directly comparing the efficacy and toxicities of PT and other EBRTs are currently underway.

Henderson et al. (2017) reported 5-year outcomes of a prospective trial of image-guided accelerated hypofractionated proton therapy (AHPT) for prostate cancer from a single institution. Late radiation AEs/toxicities and FFBP were the outcome measurements for the 215 participants categorized as low and intermediate risk. Median follow-up was 5.2 years, with FFBP rates overall noted at 95.9%. For the subsets of low and intermediate risk, FFBP was 98.3% and 92.7%, respectively. Actuarial 5-year rates of significant (grade 3 or higher) late radiation-related GI AEs/toxicities were 0.5%, and 1.7% for GU AEs. The authors concluded that image-guided AHPT is highly effective with minimal toxicities in low and intermediate-risk patients, citing comparable results to the evidence published by Mendenhall (2014). Additional studies are suggested to further support these findings.

In a case-matched analysis, Fang et al. (2015) assessed prospectively collected toxicity data on patients with localized prostate cancer who received treatment with IMRT and PBT techniques and similar dose-fractionation schedules. A total of 394 patients were treated with either PBT (n=181) or IMRT (n=213). Patients were case-matched on risk group, age and prior GI and GU disorders, resulting in 94 matched pairs. The risks of acute and late GI/GU toxicities did not differ significantly after adjustment for confounders and predictive factors.

A retrospective study comparing 553 patients treated with PBT and 27,094 treated with IMRT for early stage prostate cancer detected no difference in GU 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 GI 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 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, PBT and conformal radiation therapy for primary prostate cancer treatment. The authors conducted a population-based study using SEER data. Main outcomes were rates of GI and GU 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 GI 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 PBT (n=1368), IMRT patients

had a lower rate of GI morbidity. There were no significant differences in rates of other morbidities or additional therapies between IMRT and PBT.

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 </= 15 ng/mL were randomly assigned to a total dose of either 70.2 Gray equivalents (GyE; conventional) or 79.2 GyE (high). LF, biochemical failure (BF) and 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 ASTRO 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.

The NCCN Panel believes that PBT and IMRT are equivalent with regard to efficacy and long-term toxicity in the treatment of prostate cancer. Conventionally fractionated proton therapy can be considered a reasonable alternative to x-ray based regimens at clinics with appropriate technology, physics, and clinical expertise (2018).

A randomized phase III trial (01617161) is in progress, with the objective to determine if IMRT or PBRT is more effective in the treatment of prostate cancer. For more information, please go to www.clinicaltrials.gov**.** (Accessed October 30, 2018)

Professional Societies

American Urological Association (AUA)

In collaboration with the Society of Urologic Oncology (SUO) and ASTRO, the AUA guidelines for treating clinically localized prostate cancer discuss PBT as an option within the category of EBRT. The guidelines also state that PBT offers no clinical advantage over other forms of Definitive treatment (Sanda et al., 2017).

American Society for Radiation Oncology (ASTRO)

An ASTRO position statement concludes that the evidence relating to the comparative efficacy of PBT with other prostate cancer treatments is still being developed. Thus the role of PBT for localized prostate cancer within the current availability of treatment options remains unclear (2018).

American College of Radiology (ACR)

Appropriateness criteria from the ACR for the treatment of stage T1 and T2 prostate cancer states that there are only limited data comparing PBT to other methods of irradiation or to radical prostatectomy. Further studies are needed to clearly define its role for such treatment (2013).

Vestibular Tumors

The efficacy of PBT for the treatment of tumors of the vestibular system was assessed in 2 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 PBT. 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 PBT for treating vestibular schwannomas demonstrated LC 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 PBT and IMRT 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/pmn.cfm (Accessed October 30, 2018)

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GUIDELINE HISTORY/REVISION INFORMATION

Date	Action/Description
07/01/2019	**Template Update** • Added *Documentation Requirements* section

01/01/2019	• Reorganized policy template:
	  ○ Simplified and relocated *Instructions for Use*
	  ○ Removed *Benefit Considerations* section
	• Updated and reformatted coverage rationale:
	  ○ Simplified content
	  ○ Replaced criterion requiring "willingness to comply with *an extensive period of* rehabilitation following surgery" with "willingness to comply with rehabilitation following surgery"
	• Archived previous policy version MMG113.L

INSTRUCTIONS FOR USE

This Medical Management Guideline provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard benefit plan. In the event of a conflict, the member specific benefit plan document governs. Before using this guideline, please check the member specific benefit plan document and any applicable federal or state mandates. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Management Guideline 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. UnitedHealthcare West Medical Management 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.

Member benefit coverage and limitations may vary based on the member's benefit plan Health Plan coverage provided by or through UnitedHealthcare of California, UnitedHealthcare Benefits Plan of California, UnitedHealthcare of

Oklahoma, Inc., UnitedHealthcare of Oregon, Inc., UnitedHealthcare Benefits of Texas, Inc., or UnitedHealthcare of Washington, Inc.