Proton Beam Radiation Therapy

Guideline Number: MMG113.R
Effective Date: February 1, 2024

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 (PBRT, 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:
  - Base of skull tumors (e.g., chordomas, chondrosarcomas, paranasal sinus, or nasopharyngeal tumors)
  - Hepatocellular carcinoma (HCC) (localized, unresectable) 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)
  - Intracranial arteriovenous malformations (AVMs)
  - Ocular tumors, including intraocular/uveal melanoma (includes the iris, ciliary body, and choroid)
- 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, 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 tumors not noted above as proven
- 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 the following, when applicable: • 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; faxes of images will not be accepted.

Definitions

Definitive Therapy: Definitive Therapy is treatment with curative intent. (American Society of Clinical Oncology (ASCO), Cancer.Net, 2022)

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

CPT Code	Description
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 three 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

Diagnosis Code	Description
C11.0	Malignant neoplasm of superior wall of nasopharynx
C11.1	Malignant neoplasm of posterior wall of nasopharynx
C11.2	Malignant neoplasm of lateral wall of nasopharynx
C11.3	Malignant neoplasm of anterior wall of nasopharynx
C11.8	Malignant neoplasm of overlapping sites of nasopharynx
C11.9	Malignant neoplasm of nasopharynx, unspecified
C22.0	Liver cell carcinoma
C30.0	Malignant neoplasm of nasal cavity
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	Malignant neoplasm of prostate
C69.0	Malignant neoplasm of conjunctiva
C69.00	Malignant neoplasm of unspecified conjunctiva
C69.01	Malignant neoplasm of right conjunctiva
C69.02	Malignant neoplasm of left conjunctiva
C69.1	Malignant neoplasm of cornea
C69.10	Malignant neoplasm of unspecified cornea

Diagnosis Code	Description
C69.11	Malignant neoplasm of right cornea
C69.12	Malignant neoplasm of left cornea
C69.20	Malignant neoplasm of unspecified retina
C69.21	Malignant neoplasm of right retina
C69.22	Malignant neoplasm of left retina
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
C69.50	Malignant neoplasm of unspecified lacrimal gland and duct
C69.51	Malignant neoplasm of right lacrimal gland and duct
C69.52	Malignant neoplasm of left lacrimal gland and duct
C69.6	Malignant neoplasm of orbit
C69.60	Malignant neoplasm of unspecified orbit
C69.61	Malignant neoplasm of right orbit
C69.62	Malignant neoplasm of left orbit
C69.8	Malignant neoplasm of overlapping sites of eye and adnexa
C69.80	Malignant neoplasm of overlapping sites of unspecified eye and adnexa
C69.81	Malignant neoplasm of overlapping sites of right eye and adnexa
C69.82	Malignant neoplasm of overlapping sites of left eye and adnexa
C69.9	Malignant neoplasm of unspecified site of eye
C69.90	Malignant neoplasm of unspecified site of unspecified eye
C69.91	Malignant neoplasm of unspecified site of right eye
C69.92	Malignant neoplasm of unspecified site of left eye
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 (RT) 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 (ACR) website, updated 2021)

Proton beam radiation therapy (PBRT) is intended to deliver higher, more targeted radiation with less damage to collateral healthy tissue than external beam radiation therapy (EBRT) using photons (x-rays) when used to treat solid tumors. While PBRT has been used for several solid cancer tumor types (e.g., breast, lung, prostate, head and neck, central nervous system (CNS)) in adults and in certain pediatric cancers, evidence is lacking regarding clear benefits over EBRT. (ECRI, 2017)

Clinical Evidence

Proven Indications

Base of Skull Tumors

Nie et al. (2022) conducted a systematic review to analyze clinical outcomes and potential toxicities of skull base chordomas and chondrosarcomas after treatment with PBT. The review included seven, moderate- to high-quality studies, with a total of 478 patients diagnosed with chordoma or chondrosarcoma. The follow-up time of the cohort ranged from 21 to 61.7 months. For PBT planning, the median target volume ranged from 15cc to 40 cc, and the administered median dose varied from 63 to 78.4 Gy at 1.8-2.0 Gy per fraction. The one-, two-, three-, five-, and seven-year local control (LC) and overall survival (OS) rates were 100%, 93%, 87%, 78%, and 68%, and 100%, 99%, 89%, 85%, and 68%, respectively. The late grade 3 or higher toxicities were reported in only two involved articles. The authors concluded PBT demonstrated favorable LC and survival rates with a low incidence of severe radiation-induced toxicities. Limitations include lack of follow-up time longer than seven years and limited studies consisting of mostly retrospective and observational cohort studies, The authors recommend multicenter randomized controlled trials (RCTs) in the future.

In a Cochrane review, El Sayed et al. (2021) compared the effects and toxicity of proton and photon adjuvant radiation therapy in people with chordoma confirmed by biopsy. The study included six observational studies that were all judged to be at a high risk of bias; four studies were included in the meta-analysis. Adults with pathologically confirmed primary chordoma, irradiated with curative intent, with protons or photons, in the form of fractionated RT, SRS, SBRT or IMRT were included. The primary outcomes were local control, mortality, recurrence, and treatment-related toxicity. The authors concluded there was very low-certainty evidence to show an advantage for proton therapy in comparison to photon therapy with respect to local control, mortality, recurrence, and treatment related toxicity. The authors note that as radiation techniques evolve, multi-institutional data should be collected prospectively and published, to help identify patients that would most benefit from the available radiation treatment techniques. Limitations include a non-randomized design and small sample sizes.

Lee et al. (2021) conducted a systematic review on proton therapy for patients with nasopharyngeal cancer (NPC), focusing on the toxicity endpoints. A total of 491 studies were found on the topic (no randomized data), and nine studies were found to have sufficient focus and relevance to be included. NPC patients were examined in all nine retrospective studies, except one, which included paranasal sinus cancer. One study was a reirradiation study. Four studies used 3D or double scatter technique, while all others used intensity-modulated proton therapy. Oncologic outcomes were similar to IMRT rates, with 2-year local and regional PFS ranging from 84% to 100%, 2-year PFS ranging from 75% to 88.9%, and 2-year OS ranging from 88% to 95% in the up-front setting. Four comparison studies with IMRT found significantly lower feeding tube rates (20% versus 65%,, $p = .015$; and 14% versus 85%, $p < .001$) with proton therapy as well as lower mucositis (G2 46% versus 70%, $p = .019$; and G3 11% versus 76%, $p = .0002$). All other acute and late effects were not statistically significant but largely improved with proton therapy. The authors concluded NPC patients maintained good outcomes with improved toxicity profile, likely due to sparing of dose to normal structures when receiving proton therapy. The authors recommend further prospective studies to better quantify the magnitude of benefit. Limitations include small number of studies, short follow-up periods and retrospective study design.

In a Hayes technology assessment for PBT for treatment of chordoma and chondrosarcoma of the skull base, PBT was reported to be relatively safe, with a moderate risk of acute toxicities and a lower risk of long-term complications. The

assessment notes that PBT has similar efficacy as photon-based EBRT technologies and may reduce the risk of certain complications in adult patients. Additional well-designed, long-term studies comparing PBT with other therapies is recommended. The 2023 update included eleven new studies, however there was no rating change. (Hayes, 2019; Updated 2023)

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 OS rates were higher for stereotactic RT (SRT), PBT, and CIT than for conventional RT. 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 conventional RT. After ten 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.

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 RT 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 five years. There were no prospective trials (randomized or non-randomized), but four 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 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)

Clinical Practice Guidelines

American Society for Radiation Oncology (ASTRO)

ASTRO's model policy states PBT is considered reasonable in instances where sparing the surrounding tissue cannot be adequately achieved with photon-based radiotherapy and is of added clinical benefit to the patient. Disease sites that frequently support the use of PBT include tumors that approach or are located at the base of skull, including chordoma and chondrosarcomas. (ASTRO, 2017)

National Comprehensive Cancer Network (NCCN)

NCCN guidelines for bone cancer states that specialized techniques, including particle beam RT with protons, should be considered as indicated in order to allow high-dose therapy while maximizing normal tissue sparing in patients with chondrosarcoma or chordoma. PBT may be considered for patients with good long-term prognosis to better spare uninvolved brain and preserve cognitive function. (NCCN, 2024)

NCCN guidelines on HNC state that use of proton therapy is an area of active investigation. In cancers of the oropharynx, nasopharynx, supraglottic larynx, salivary glands, mucosal melanoma, and other primary tumors of the head and neck, proton therapy can be considered when normal tissue constraints cannot be met by photon-based therapy. Additionally, either IMRT or proton therapy is recommended for maxillary sinus or paranasal/ethmoid sinus tumors to minimize dose to critical structures. (NCCN, 2023)

Hepatocellular Carcinoma (HCC)

In a randomized phase III trial (NCT01963429), Kim et al. (2021) compared the outcomes of PBT and radiofrequency ablation (RFA) in patients with recurrent/residual HCC (size < 3 cm, number ≤ 2). The primary endpoint was 2-year local progression-free survival (LPFS), with a non-inferiority margin of 15% in the per-protocol (PP) population. Complementary analysis was performed in the intention-to-treat (ITT) population. Patients were randomly assigned to receive PBT or RFA according to tumor stage and Child-Pugh score. Crossover was permitted after randomization if the assigned treatment was technically possible. The ITT population included 144 patients, PBT (n = 72) or RFA (n = 72). Nineteen patients switched from the RFA arm to the PBT arm and six patients switched from the PBT arm to RFA. In the PP population, the 2-year LPFS rate with PBT (n = 80) vs. RFA (n = 56) was 94.8% vs. 83.9%, a difference of 10.9 percentage points ($p < 0.001$); in the ITT population, the 2-year LPFS rate with PBT vs. RFA was 92.8% vs. 83.2%, a difference of 9.6 percentage points ($p < 0.001$), meeting the criteria for non-inferiority. The 3- and 4-year LPFS rates for PBT were also non-inferior to those for RFA. The most common adverse events were

radiation pneumonitis (32.5%) and decreased leukocyte counts (23.8%) for PBT and increased alanine aminotransferase levels (96.4%) and abdominal pain (30.4%) for RFA. No Grade 4 adverse events or mortality were noted. The authors concluded PBT is associated with LPFS rates that are comparable to those observed for RFA in patients with recurrent/residual HCC. PBT was also tolerable and safe. Limitations noted by the authors include the primary outcome measure of 2-year LPFS, rather than progression-free survival (PFS) or overall survival (OS), single-center design, and most patients had chronic hepatitis B. The authors recommend further studies across other institutions including patients with various etiologies.

Parzen et al. (2021) conducted a nine institution multicenter study to evaluate the safety and efficacy of hypofractionated PBT for HCC and intrahepatic cholangiocarcinoma (ICC). The study evaluated the prospective registry of the Proton Collaborative Group for patients undergoing definitive PBT for liver tumors. Information compiled included demographic, clinicopathic, toxicity and dosimetry data. Between 2013 and 2019, 63 patients were treated, 30 patients had HCC and 25 had ICC. The median dose and biological equivalent dose (BED) delivered was 58.05 GyE and 80.5 GyE, respectively. The median mean liver BED was 13.9 GyE. At least one grade ≥ 3 toxicity was experienced by three patients. With median follow-up of 5.1 months the local control (LC) rate at 1 year was 91.2% for HCC and 90.9% for ICC. The 1-year LC was significantly higher (95.7%) for patients receiving BED greater than 75.2 GyE than for patients receiving BED of 75.2 GyE or lower (84.6%, p = 0.029). The OS rate at 1 year was 65.6% for HCC and 81.8% for ICC. The authors concluded hypofractionated PBT resulted in low toxicity, sparing of the uninvolved liver, and excellent LC, even in the setting of dose-escalation. The study found higher dose correlated with improved LC. Limitations include lack of comparison group and limited follow-up time.

Fukuda et al. (2017) performed an observational study to assess the long-term efficacy of PBT in patients with previously untreated HCC. Between January 2002 and December 2009, 129 patients at a single institution received PBT via one of three protocols based on tumor location with dose volumes of 77.0 GyE in 35 fractions, 72.6 GyE in 22 fractions and 66.0 GyE in 10 fractions for the gastrointestinal (GI), hilar and standard protocols, respectively. Primary outcome measures were local tumor control (LTC), OS, and PFS. All 129 patients completed PBT without experiencing severe complications, and no treatment-related deaths were observed. The median patient observation period was 55 months. The 5-year LTC, PFS, and OS rates were 94%, 28%, and 69% for patients with 0/A stage disease (n = 9/21), 87%, 23%, and 66% for patients with B stage disease (n = 34), and 75%, 9%, and 25% for patients with C stage disease (n = 65), respectively. The 5-year LTC and OS rates of fifteen patients with tumor thrombi in major vessels were 90% and 34%, respectively. The major study limitation cited was the heterogeneous patient population, with most subjects selecting receiving PBT because they refused surgery or conventional interventional RT. The authors concluded that PBT achieved long term tumor control with less toxicity and is a viable treatment option for localized HCC. The authors are now planning a multicenter controlled study comparing PBT and hepatectomy.

Bush et al. (2016) conducted a single-center, prospective random controlled trial (RCT), comparing outcomes of 69 patients with newly diagnosed HCC who received either trans arterial chemoembolization (TACE) or PBT as definitive or bridge therapy while awaiting transplantation. Thirty-three subjects were randomized to PBT, and 36 subjects were randomized to TACE, Patients randomized to TACE received at least one TACE with additional TACE for persistent disease. The PBT group had proton therapy delivered to all areas of gross disease to a total dose of 70.2 Gy in 15 daily fractions over three weeks. The median follow-up for all subjects was 28 months. The primary endpoint was PFS, with secondary endpoints including OS, local disease control, transplant outcomes, and toxicity including days of hospitalization after treatment. The 2-year OS for the entire group was 59%, with no significant difference between treatment assignments. Regarding local control and PFS between treatment groups, there was a trend toward improved 2-year LTC (88% vs 45%, p = .06) and PFS (48% vs 31%, p = .06) favoring the PBT group. For the entire group of study subjects, 22 went on to have liver transplantation. The 2-year OS after transplantation was 82% for the entire group, with no difference seen between proton and TACE groups. The authors concluded that this study indicates similar OS rates for PBT and TACE. While there is a trend toward improved local tumor control and PFS favoring proton therapy, it is too early to determine whether this trend will be maintained.

Hong et al. (2016) conducted a single-arm, phase II, multi-institutional study to evaluate the safety and efficacy of high-dose, hypofractionated PBT for HCC and ICC. Eighty-three participants ≥ 18 years with unresectable or locally recurrent HCC or ICC were included. With 42 HCC patients (95.5%) and 36 ICC patients (92.3%) having completed their prescribed dose, the median dose delivered was 58.0 GyE (in 15 fractions; range, 15.1 to 67.5 GyE). Of the 83 patients, 71 (85.5%) experienced at least one radiation-related toxicity event while in the study, most commonly fatigue (54/83, 65.1%), rash (51/83, 61.4%), nausea (25/83, 30.1%), or anorexia (21/83, 25.3%). Median follow-up among the 50 survivors was 19.5 months (range, 0.6 to 55.9 months). For patients with HCC, the 1-year and 2-year PFS rates were 56.1% and 39.9%, respectively. The 1- and 2-year OS was 76.5% and 63.2%, respectively. Three patients with HCC underwent successful liver transplantation, two of whom remain alive. For patients with ICC, 1-year and 2-year PFS rates were 41.4% and 25.7%, respectively; with 1-year and 2-year OS rates of 69.7% and 46.5%,

respectively. 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 RCTs of proton versus photon RT for HCC, and for chemotherapy with or without RT for ICC.

A phase III randomized trial comparing PBT to radiofrequency ablation (NCT02640924) was in progress, but the study has passed its completion date and status has not been verified in more than two years. Another clinical trial that compares protons to photons (NCT03186898) is in the recruiting stage. For more information on this and other clinical trials studying PBT and HCC, go to www.clinicaltrials.gov. (Accessed September 14, 2023)

Clinical Practice Guidelines

American Society for Radiation Oncology (ASTRO)

An ASTRO clinical practice guideline states that for patients with HCC receiving dose-escalated ultra- or moderately hypofractionated EBRT, IMRT or proton therapy is strongly recommended, with choice of regimen based on tumor location, underlying liver function, and available technology. For patients with unresectable intrahepatic cholangiocarcinoma (IHC) receiving dose-escalated ultra- or moderately hypofractionated EBRT, IMRT or proton therapy is conditionally recommended with choice of regimen based on tumor location, underlying liver function, and available technology. (Apisarnthanarax et al., 2022)

National Comprehensive Cancer Network (NCCN)

NCCN guidelines state that hypofractionation with photons or protons at an experienced center is an acceptable option for unresectable intrahepatic tumors. (NCCN, 2023)

Intracranial Arteriovenous Malformations (AVM)

Zuurbier et al. (2019) updated a previously conducted systematic review (Ross, 2010) that aimed to determine the effectiveness and safety of the different interventions, alone or in combination, for treating brain AVMs in adults compared against either each other, or conservative management, in RCTs. A search was conducted using the Cochrane Stroke Group Trials Register, the Cochrane Central Register of Controlled Trials, the Cochrane Library, MEDLINE, OVID and Embase OVID. The search identified fourteen eligible RCTs and of those, thirteen were excluded (ten did not meet the inclusion criteria and three were still ongoing), and one RCT with 226 participants was included (Mohr, 2013). The study titled, A Randomized trial of Unruptured Brain Arteriovenous malformations (ARUBA) was an international, multi-center, randomized, controlled, open, prospective clinical trial comparing interventional treatment (endovascular, surgical, and/or radiation therapy) to conservative management for unruptured brain AVMs in adults. The primary outcome was death or dependence from any cause (modified Rankin Scale score ≥ 2), and secondary outcomes included symptomatic intracranial hemorrhage, epileptic seizure, symptomatic radiation necrosis detected by MRI, and quality of life (QOL). Data on functional outcome and death at twelve months of follow-up were provided for 218 (96%) of the participants. Intervention compared to conservative management increased death or dependency with a risk ratio (RR) of 2.53, 95% CI 1.28 to 4.98, and higher proportion of participants with symptomatic intracranial hemorrhage (RR 6.75, 95% CI 2.07 to 21.96). There was no difference in the frequency of epileptic seizures (RR 1.14, 95% CI 0.63 to 2.06). The authors reported that moderate-quality evidence from one RCT (of adults with unruptured brain AVMs) showed that conservative management was superior to intervention with respect to functional outcome and symptomatic intracranial hemorrhage during the 1-year period after randomization however, more RCTs are needed to confirm or refute these findings.

Blomquist et al. (2016) performed a retrospective review of 65 patients with AVMs treated with PBT. Information collected from patient medical records, treatment protocols and radiological results included gender, age, presenting symptoms, clinical course, and AVM nidus size and rate of occlusion. Outcome parameters were the occlusion of the AVM, clinical outcome and side effects. The overall rate of occlusion was 68%. For target volume 0-2 cm^3 it was 77%, for 3-10 cm^3 80%, for 11-15 cm^3 50% and for 16-51 cm^3 20%. Those with total regress of the AVM had significantly smaller target volumes ($p < 0.009$) higher fraction dose ($p < 0.001$) as well as total dose ($p < 0.004$) compared to the rest. The target volume was an independent predictor of total occlusion ($p = 0.03$). There was no difference between those with and without total occlusion regarding mean age, gender distribution or symptoms at diagnosis. Mild radiation-induced brain edema developed in 41 patients and was more common in those that had total occlusion of the AVM. Brain hemorrhage after treatment was experienced by two patients. Two thirds of those presenting with seizures reported an improved seizure situation after treatment. The authors concluded that PBT is a

treatment alternative for brain AVMs due to the high occlusion rate even in large AVMs. Limitations include the retrospective study design, lack of comparative group and small study size.

Hattangadi-Gluth et al. (2014) evaluated the obliteration rate and potential 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 fifteen 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 thirteen 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 sixteen Gy in 2 fractions. At a median follow-up of 56.1 months, nine patients (15%) had total and twenty 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 multistage PSRS approach for lesions more resistant to obliteration with radiation.

Ocular Tumors

Hartsell et al. (2016) conducted a case series study to determine feasibility of treating patients with ocular melanoma using volumetric imaging and planning for PBT. Twenty-six patients met eligibility criteria, and all were able to complete and tolerate treatment. Visual outcomes were assessed on routine ophthalmologic follow-up over a median time frame of 31 months. Four patients had poor vision in the treated eye prior to PBT; three of those four patients had serous retinal detachment prior to treatment. None of those patients had significant improvement in visual acuity after treatment. Of the remaining 22 patients, nine had visual acuity equal to pre-treatment acuity at the most recent follow-up visit, four had stable vision with a loss of two to five lines on the Snellen chart, and eight patients had lost more than five lines of visual acuity. The visual acuity status for one patient was unknown prior to his death from metastatic melanoma. The treatment was well tolerated by patients with minimal acute toxicity. Relatively low mean doses to the anterior structures (ciliary body and lens) were maintained, even in patients with large tumors. The authors concluded that while they continue evaluating outcomes of these patients in a prospective manner, this treatment technique appears to be feasible with excellent early outcomes.

Verma and Mehta (2016c) conducted systematic review to identify studies on PBT and uveal melanoma. The search was conducted using PubMed, EMBASE, abstracts from meetings of the American Societies for Radiation Oncology and Clinical Oncology, and the Particle Therapy Co-Operative Group. Articles included addressed clinical outcomes of proton radiotherapy for ocular melanoma with the following headings: proton, proton radiation therapy, proton beam therapy, ocular melanoma, uveal melanoma, choroidal melanoma, eye melanoma, and were published from 2000 to 2015. Articles excluded were those without specific assessments on clinically relevant outcomes of proton radiotherapy for previously untreated melanoma of the eye, letters to the editor, direct commentary to other articles, and small reports (< 25 patients). A total of fourteen original investigations from 10 institutions were analyzed. Results revealed that the majority of tumors were choroidal and medium to large-sized, and received 50–70 Gy equivalent doses however, more recent data reported use of lower doses. The five-year local control rates exceeded 90% and remained high at fifteen years. The 5-year OS rates ranged from 70–85%, and 5-year metastasis-free survival and disease-specific survival rates ranged from 75-90%, with more recent series reporting higher values. With the removal of smaller studies, 5-year enucleation rates were consistently between seven and ten percent. Many patients

(60–70%) showed a post-PBT visual acuity decrease but still retained purposeful vision (> 20/200). Complication rates were variable but showed improvements compared with historical plaque brachytherapy data. The authors concluded that PBT has shown excellent oncological and ophthalmological outcomes, and these have been sustained in the long-term.

Clinical Practice Guidelines

American Society for Radiation Oncology (ASTRO)

ASTRO's model policy states PBT is considered reasonable in instances where sparing the surrounding tissue cannot be adequately achieved with photon-based radiotherapy and is of added clinical benefit to the patient. Disease sites that frequently support the use of PBT include treatment of ocular tumors, including intraocular melanomas. (2017) (Accessed September 14, 2023)

National Comprehensive Cancer Network (NCCN)

In the NCCN guidelines on uveal melanoma, particle beam therapy is noted as a common form of definitive RT for the primary tumor. It is considered appropriate as an upfront therapy after initial diagnosis, after margin-positive enucleation, or for intraocular or orbital recurrence. It should be performed by an experienced multidisciplinary team including an ophthalmic oncologist, radiation oncologist, and particle beam physicist. (NCCN, 2023)

Prostate Cancer

An ECRI Clinical Evidence Assessment for PBT and localized prostate cancer concluded PBT is relatively safe for treatment of prostate cancer; however, it is unclear whether PBT is more effective than photon EBRT or brachytherapy, or has fewer adverse effects or complications. (ECRI, 2022)

Liu et al. (2021) performed a national database study comparing the effect of PBT on OS compared to photon-based EBRT and brachytherapy (BT) in patients with localized prostate cancer. Men (n = 276,880) with clinical stage T1–3, N0, M0 prostate cancer treated with radiation, without surgery, or chemotherapy, between the years of 2004-2015 were included. A total of 4900 (1.8%) received PBT, while 158,111 (57.1%) received photon-based EBRT and 113,869 (41.1%) BT. Compared to EBRT and BT, PBT patients were younger and were less likely to be in the high-risk group. On multivariable analysis, compared to PBT, men had worse OS after EBRT or BT. After propensity score matching, the OS benefit of PBT remained significant compared to EBRT but not BT. The improvement in OS with PBT was most prominent in men ≤ 65 years old with low-risk disease compared to other subgroups (interaction $p < .001$). The median follow-up time was 80.9 months. The authors concluded PBR had similar outcomes to BT, but was associated with more favorable OS than EBRT. Limitations include the retrospective nature of the study. The authors encourage future prospective comparative clinical trials to further define the role of PBT in the treatment of localized prostate cancer.

Vapiwala et al. (2021) conducted a multi-institutional analysis that compared late toxicity profiles of patients with early-stage prostate cancer treated with moderately hypofractionated PBT and IMRT. The study included patients (n = 1850) with low- or intermediate-risk biopsy-proven prostate adenocarcinoma treated from 1998 to 2018. The patients were treated with moderately hypofractionated radiation, defined as 250 to 300 cGy per daily fraction given for four to six weeks, and stratified by use of IMRT or PBT. Late genitourinary (GU) and gastrointestinal (GI) toxicity were the primary outcomes. Adjusted toxicity rates were calculated using inverse probability of treatment weighting, accounting for race, National Comprehensive Cancer Network risk group, age, pretreatment International Prostate Symptom Score (GU only), and anticoagulant use (GI only). Of the 1850 patients included, 1282 had IMRT and 568 had PBT. The majority of patients experienced no late GU or GI toxicity, with late grade 3+ GU toxicity of 2.0% versus 3.9% and late grade 2+ GI toxicity of 14.6% versus 4.7% for the PBT and IMRT cohorts, respectively. Only anticoagulant use was significantly predictive of GI toxicity and no factors were significantly predictive of GU toxicity. The authors concluded that treatment with moderately hypofractionated IMRT and PBT resulted in low rates of toxicity in patients with early-stage prostate cancer. No difference was seen in late GI and GU toxicity between the modalities during long-term follow-up and both treatments were well tolerated and safe.

A Hayes report assessed 20 studies, including four RCTs, two prospective cohort studies, two retrospective registry analysis studies, and twelve retrospective comparative or case-matched cohort studies that evaluated the efficacy and safety of PBT in patients with localized or locally advanced prostate cancer. The report concludes that the best available studies of PBT for localized prostate cancer have consistently found that most or nearly all patients remain free from cancer progression for five years or longer after treatment. These results are promising but none of the reviewed studies assessed the efficacy of PBT as

the sole or primary therapy for prostate cancer relative to the efficacy of other common methods of RT. Ten of the reviewed studies found that the safety of PBT as sole or primary therapy was usually similar to the safety of other common RT; however, these studies are of low quality since they were retrospective. Moreover, these ten studies do not provide sufficient evidence of comparative safety since they were divided between evaluations of PBT relative to brachytherapy, conformal X-ray therapy, and IMRT. The other available studies do not provide clear evidence concerning the relative safety and efficacy of PBT for prostate cancer since these other studies evaluated it as an adjunct to X-ray therapy or did not compare it with another common RT. Additional well-designed studies are needed to establish the clinical role of PBT relative to other widely used therapies for localized prostate cancer. The 2023 updated annual review included seven newly published studies, however, there was no change in the current rating. (2020, Updated 2023)

Santos et al. (2019) compared acute and late GU and GI toxicity outcomes in patients with prostate cancer who received treatment with postprostatectomy IMRT versus PBT. Patients with prostate cancer who received adjuvant or salvage IMRT or PBT (70.2 gray with an endorectal balloon) after prostatectomy from 2009 through 2017 were reviewed. A case-matched cohort analysis was performed using nearest-neighbor 3-to-1 matching by age, and GU/GI disorder history. The Kaplan-Meier method was used to assess toxicity-free survival (TFS). Seventy matched pairs were generated from the 307 men identified (IMRT, n = 237, PBT, n = 70). The median follow-up was 48.6 and 46.1 months for the IMRT and PBT groups, respectively. While PBT was superior at reducing low-range (volumes receiving 10% to 40% of the dose, respectively) bladder and rectal doses (all $p \leq .01$), treatment modality was not associated with differences in clinician-reported acute or late GU/GI toxicities (all $p \geq .05$). Five-year grade ≥ 2 GU and grade ≥ 1 GI TFS was 61.1% and 73.7% for IMRT, respectively, and 70.7% and 75.3% for PBT, respectively; and 5-year grade ≥ 3 GU and GI TFS was > 95% for both groups (all $p \geq .05$). The authors concluded that postprostatectomy PBT minimized low-range bladder and rectal dose relative to IMRT; however, treatment modality was not associated with clinician-reported GU/GI toxicities. The authors recommended future prospective studies and on-going follow-up to determine whether dosimetric differences between IMRT and PBT lead to clinically meaningful differences in long-term outcomes. Limitations include lack of randomization and retrospective study design.

Several single-institution studies report favorable clinical outcomes of PBT in prostate cancer. 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 freedom from biochemical and/or clinical progression (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) late radiation-related GI AEs/toxicities were 0.5%, and 1.7% for GU AEs.

Bryant et al. (2016) performed a single-center study on 1,327 men with localized prostate cancer who received image guided PBT between 2006-2010. The 5-year 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 PBT and other types of RT.

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.

Mendenhall et al. (2014) reported 5-year clinical outcomes from 3 prospective trials of image-guided PBT for prostate cancer conducted at a single institution. From August 2006-September 2007, 211 patients (low risk n = 89, intermediate risk n = 82, and high-risk n = 40) were enrolled in one of the three trials. Dosages delivered were 78 cobalt gray equivalents (CGE) for low risk and 78 to 82 CGE for intermediate-risk. Participants with high-risk disease received 78 CGE with weekly concomitant chemotherapy, followed by six months of androgen deprivation therapy (ADT). Five-year OS of 93%, 88%, and 86% were reported for low, intermediate, and high-risk patients, respectively. FFBP rates for the same time period were 99% for both low and intermediate risk and 76% for high-risk patients. There was a single instance of acute grade 3 GU toxicity. One acute grade 3 and 2 late grade 3 GI events throughout the entire group resulted in a 5-year incidence of 1%. Limitations to this study include overall study design and lack of a control group. The authors concluded that image-guided PBT was highly effective with minimal toxicities. While outcomes were favorable, the lack of control group limits interpretation of the studies and does not allow assessment of PBT outcomes compared to other forms of radiation therapy.

Yu et al. (2013) conducted a retrospective cohort analysis using data from the Chronic Condition Warehouse, a national database for Medicare fee-for-service claims from patients with specific conditions. The investigators identified patients who were age 66 and older with prostate cancer and treated with IMRT or PBT. To evaluate toxicity, each patient who received PBT was matched with two patients who received IMRT based on similar sociodemographic and clinical characteristics. Toxicity was reported at six months post-treatment and included 421 patients who received PBT matched to 842 patients who received IMRT, and at twelve months post-treatment and included 314 patients who received PBT matched to 628 patients who received IMRT. At six months, GU toxicity was significantly lower in patients who received PBT vs. IMRT (5.9% vs. 9.5%; OR = 0.60, 95% CI = 0.38 – 0.96, p = 0.03). However, there was no difference at twelve months post-treatment (18.8% vs. 17.5%; OR = 1.08, 95% CI = 0.76 – 1.54, p = 0.66). At six months and twelve months post-treatment, there was no difference in GI or other toxicities. The authors concluded that in a national sample of Medicare beneficiaries, patient who were treated with IMRT or PBT for prostate cancer had no difference in toxicity rates at twelve months post-treatment, and that additional longitudinal studies evaluating the effectiveness of PBT in comparison to IMRT are needed prior to widespread use of PBT for prostate cancer.

Sheets et al. (2012) evaluated the comparative morbidity and disease control of IMRT, PBT and conformal RT for primary prostate cancer treatment. Main outcomes were rates of GI and GU morbidity, erectile dysfunction, hip fractures and additional cancer therapy. In a comparison between IMRT and conformal RT (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 = 1,368), 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.

Several large population-based cohort studies using Surveillance Epidemiology and End Results (SEER) data, have found greater GI toxicity with PBT than IMRT. Kim et al. (2011) reported that patients treated with RT are more likely to have procedural interventions for GI toxicities than patients with conservative management, and patients treated with PBT therapy experienced greater GI morbidity relative to IMRT patients. The elevated risk persisted beyond 5 years.

To further elucidate the clinical advantages and disadvantages between various types of radiation therapy used in prostate cancer, additional clinical trials are underway (NCT01617161, NCT00969111 and NCT03561220). For more information, go to www.clinicaltrials.gov. (Accessed September 14, 2023)

Clinical Practice Guidelines

American Urological Association (AUA)/American Society for Radiation Oncology (ASTRO)

In a 2022 systematic review, the AUA and ASTRO developed a clinical guideline regarding localized prostate cancer. This guideline was endorsed by the Society of Urologic Oncology (SUO). Patients with clinically localized prostate cancer, defined as up to clinical stage T3 prostate cancer without nodal or distant metastasis (N0M0) on conventional imaging, were the target population. The guideline conditionally recommends proton therapy as a treatment option for prostate cancer, but states it has not been found to be superior to other radiation modalities in terms of cancer outcomes or toxicity profile. (Eastham et al., 2022)

National Comprehensive Cancer Network (NCCN)

The NCCN Panel believes that photon and PBRT are both effective at achieving highly conformal RT with acceptable and similar biochemical control and long-term side effect profiles. No clear evidence supports a benefit or decrement of one treatment over another. Conventionally fractionated PBT can be considered a reasonable alternative to x-ray-based regimens at clinics with appropriate technology, physics, and clinical expertise. (NCCN, 2023)

Unproven Indications

Quality evidence in peer-reviewed medical literature evaluating proton beam radiation therapy for the following indications is limited. Future robust RCTs are warranted along with long-term outcomes to establish the safety and efficacy of this treatment.

Age-Related Macular Degeneration (AMD)

Evans et al. (2020) updated a previously conducted systematic review (Evans, 2010) that examined the effects of radiotherapy on neovascular AMD. A search was conducted using CENTRAL, MEDLINE, Embase, LILACS and three trials registers for randomized controlled trials in which radiotherapy was compared to another treatment, sham treatment, low dosage irradiation

or no treatment in people with choroidal neovascularization (CNV) secondary to AMD. Outcomes included best-corrected visual acuity (BCVA) (loss of three or more lines, change in visual acuity), contrast sensitivity, new vessel growth, QOL and adverse effects at any time point. A total of eighteen studies (n = 2,430 people, 2,432 eyes) were included, and the radiation therapy with dosages ranging from 7.5 to 24 Gy. Three of these studies investigated brachytherapy (plaque and epimacular), the rest were studies of external beam radiotherapy (EBM) including one trial of stereotactic radiotherapy. The authors concluded that the evidence is uncertain regarding the use of radiotherapy for neovascular AMD. They stated that: 1) most studies took place before the routine use of anti-VEGF, and before the development of modern radiotherapy techniques such as stereotactic radiotherapy; 2) visual outcomes with epimacular brachytherapy are likely to be worse, with an increased risk of adverse events, probably related to vitrectomy; 3) the role of stereotactic radiotherapy combined with anti-VEGF is currently uncertain; and 4) further research on radiotherapy for neovascular AMD may not be justified until current ongoing studies have reported their results.

In a systematic review, Bekkering et al. (2009) evaluated the effects and side effects of PBT for indications of the eye. All studies that included at least ten patients and that assessed the efficacy or safety of PBT 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 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 PBT 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 PBT in two equal fractions. Complete ophthalmological examinations, color fundus photography, and fluorescein angiography were performed before and three, six, twelve, eighteen, and 24 months after treatment. At twelve 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.

Clinical Practice Guidelines

American Academy of Ophthalmology (AAO)

AAO preferred practice patterns state that RT has insufficient data to demonstrate clinical efficacy and is not recommended in the treatment of AMD. (Flaxel et al., 2019)

Bladder Cancer

Araya et al. (2023) performed a registry data analysis designed to assess the safety and efficacy of PBT for patients (n = 36) with muscle-invasive bladder cancer (cT2-4aN0M0) who received PBT with concurrent chemotherapy. Additionally, a systematic review was performed that compared PBT with photon radiotherapy. Patients underwent radiation to the entire bladder or pelvic cavity using photon or proton beams followed by a boost to all tumor sites in the bladder along with either Cisplatin alone, or in combination with Methotrexate, or Gemcitabine. Overall survival, PFS and LC rates were 90.8, 71.4 and 84.6%, respectively, after three years. Only one case (2.8%) experienced a treatment-related late adverse event of Grade 3 urinary tract obstruction, and no severe gastrointestinal adverse events occurred. According to the findings of the systematic review, the 3-year outcomes of photon radiotherapy were 57-84.8% in OS, 39-78% in PFS and 51-68% in LC. The weighted mean frequency of adverse events of Grade 3 or higher in the gastrointestinal and genitourinary systems was 6.2 and 2.2%, respectively. The authors concluded PBT is expected to have the same toxicity as photon based combined modality therapy for stages II-III muscle-invasive bladder cancer. The authors note that data from long-term follow-up is needed to validate efficacy. Limitations include short-term follow-up and small sample size. The Takaoka et al. (2017) retrospective review is included in this systematic review.

Takaoka and colleagues (2017) conducted a retrospective review to assess outcomes, prognostic factors and toxicities of PBT as a component of trimodal bladder-preserving therapy for muscle-invasive bladder cancer. Trimodal bladder-preserving therapy consisted of maximal transurethral resection of the bladder tumor, small pelvis (conventional) photon radiation, intra-arterial chemotherapy and PBT. Seventy patients with cT2-3N0M0 muscle-invasive bladder cancer were included who received

treatment from 1990 to 2015 at a single institution. The OS and PFS rate, time to progression, predictive factors for progression and toxicities were analyzed. Progression was defined as when muscle-invasive recurrence, distant metastasis or upper urinary tract recurrence was observed. The patients' median age was 65 (range 36-85) years. The median follow-up period was 3.4 years (range 0.6-19.5 years). The 5-year cumulative OS rate, PFS rate and time to progression rate were 82%, 77%, and 82%, respectively. In univariate and multivariate analyses, tumor multiplicity and tumor size (≥ 5 cm) were significant and independent factors associated with progression (hazard ratio 3.5, 95% confidence interval 1.1-12; hazard ratio 5.0, 95% confidence interval 1.3-17; $p < 0.05$ for all). As for toxicity, 26 (18%) patients had grade 3-4 acute hematologic toxicities and two (3%) patients had grade 3 late GU toxicity. No patient had to discontinue the treatment due to acute toxicity. The authors concluded that trimodal therapy including both conventional and proton radiation was well tolerated and may be an effective treatment option for selected muscle-invasive bladder cancer patients. Further studies are needed to determine whether PBT is integral to this multi-modality therapy.

Miyanaga et al. (2000) conducted a small prospective uncontrolled clinical study to assess the efficacy and safety of PBT and/or conventional 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.

Clinical Practice Guidelines

National Comprehensive Cancer Network (NCCN)

NCCN guidelines do not address the use of PBT for treating bladder cancer. (NCCN, 2023)

Brain and Spinal Cord Tumors

Petr et al. (2018) assessed structural and hemodynamic changes of healthy brain tissue in the cerebral hemisphere contralateral to the tumor following conventional (photon) and proton radiation with concurrent chemotherapy. Sixty seven adult patients diagnosed with glioblastoma undergoing adjuvant conventional (n = 47) or proton (n = 19) radiotherapy 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 patients receiving conventional radiation compared to the pre-RT 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 conventional radiation 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 . As this was an uncontrolled retrospective study with a surrogate end-point (brain volume loss on imaging), prospective randomized trials are needed to compare the effect of proton and conventional radiotherapy (CRT) on imaging and clinical outcomes.

Kabolizadeh et al. (2017) conducted a single-center, retrospective, case series to evaluate local control (LC), OS, disease-specific survival, and distant failure in 40 patients with unresected chordoma and treated with photon/proton radiation therapy. Tumor response was assessed using the modified Response Evaluation Criteria in Solid Tumors (mRECIST). To characterize tumor response the soft tissue and bone compartments of the tumor were defined separately as the soft tissue target volume, bone target volume and combined total target volume. Twenty-seven patients had sacrococcygeal chordoma, and the remaining patients had mobile spine tumors, which included nine cervical, one thoracic, and three lumbar. Thirty-nine patients underwent proton therapy only or predominantly proton therapy mixed with photons to limit the radiation dose to adjacent critical normal structures. Only 4 patients received either concurrent or neoadjuvant systemic treatments. The median age was 67 years (range, 36-94 years) and median follow-up, after completion of radiation therapy, was 50.3 months (range, 2–216.4 months). At 5-years, LC, OS, disease-specific survival, and distant failure were 85.4%, 81.9%, 89.4%, and 20.2%, respectively. Nineteen patients had complete sets of regular imaging scans (a total of 84 CT and MRI scans were reviewed) and of those, only 4 local failures had occurred at 34, 46, 78 and 82 months after treatment. The authors concluded that their results support the use of high-dose definitive radiation therapy in select patients with unresected spine and sacral chordomas, and that soft tissue target volume is the best indicator of tumor response. Limitations of this study include its design, the small number of patients with local failure and limited follow-up periods.

Indelicato et al. (2016) conducted descriptive analysis using data from a single-institution. In this prospective case series study, researchers sought to evaluate the effectiveness of definitive or adjuvant external beam proton therapy in patients with chordomas and chondrosarcomas of the spine. Outcomes of interest included distant metastases (DM), OS, cause-specific survival, local control (LC) and disease-free survival (DFS). A total of 51 patients participated with a median age of 58 years (range, 22-83 years) and median follow-up of 3.7 years (range, 0.3-7.7 years). There were 34 patients with chordomas, and seventeen patients with chondrosarcomas, which were all grade 2 or higher. The anatomic distribution was as follows: sacrum (n = 21), cervical spine (n = 20), and thoracolumbar spine (n = 10). The median dose of radiation therapy was 70.2 Gy (range, 64.2-75.6 Gy). The 4-year LC, freedom from distant metastases, DFS, cause-specific survival, and OS rates were 58%, 86%, 57%, 72%, and 72%, respectively. A total of 25 patients experienced disease recurrence: eighteen local recurrences, six local and distant recurrences, and one DM. In patients with a local relapse, the median time to progression was 1.7 years (range, 0.2-6 years). The median survival after local progression was 1.7 years (range, 0.1-4.9+ years). Regression analysis results showed that younger patients had a significantly higher risk for local reoccurrence and that patients whose initial management was only surgery also had a higher rate of reoccurrence however, these patients may represent a high-risk subset. The authors concluded that high-dose proton therapy controls more than half of spinal chordomas and chondrosarcomas and compares favorably with historic photon data. Local progression is the dominant mode of treatment failure and it may be reduced by treating patients at the time of initial diagnosis. Limitations of this study include its design, small sample size and small number of select events, which may have impacted the statistical validity of the regression analysis results.

Shih et al. (2015) conducted a prospective single arm trial to evaluate potential treatment toxicity and PFS in patients (n = 20) with low-grade glioma who were treated with PBRT. Patients with World Health Organization (WHO) grade 2 glioma who were eligible for radiation therapy were enrolled in the study. All patients received proton therapy at a dose of 54Gy in 30 fractions. Baseline and regular post-treatment evaluations of neuroendocrine function, QOL, and neurocognitive function were performed. PBRT was tolerated without difficulty by all twenty patients. The median follow-up after proton therapy was 5.1 years. Intellectual functioning was within the normal range for the group at baseline, and remained stable over time. Executive functioning, attention/working memory, and visuospatial ability also were within normal limits; however, eight patients had baseline neurocognitive impairments observed in language, memory, and processing speed. There was no overall decline in cognitive functioning over time. New endocrine dysfunction was detected in six patients, and all but one had received direct irradiation of the hypothalamic-pituitary axis. No changes were noted in QOL over time. The PFS rate at three years was 85% but fell to 40% at five years. The authors concluded patients with low-grade glioma tolerate proton therapy well, and a subset develops neuroendocrine deficiencies. Additionally, there was no evidence for overall decline in QOL or cognitive function. The authors recommend larger studies that include the integration of standardized, contemporary chemotherapy regimens with randomization of proton versus photon therapy to characterize potential differences in radiation late effects. Limitations of this study include small sample size, lack of comparative group and randomization.

Noel et al. (2002) conducted a retrospective review of seventeen patients with meningioma to evaluate the efficacy and the tolerance of an escalated dose of external conformal fractionated RT combining photons and protons. Five patients presented a histologically atypical or malignant meningioma, twelve patients had a benign tumor that was recurrent or rapidly progressive. In two cases RT was administered in the initial course of the disease and in fifteen 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 CGE (25-69). Median follow-up was 37 months (17-60). The 4-year LC and OS rates were 87.5 +/- 12% and 88.9 +/- 11%, respectively. Radiologically, there were eleven 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. Limitations of this study include small sample size and study design.

Several clinical trials studying PBT in patients with various types of brain tumors are active or recruiting. For more information, go to www.clinicaltrials.gov. (Accessed September 14, 2023)

Clinical Practice Guidelines

American Society for Radiation Oncology (ASTRO)

ASTRO's guideline regarding radiation therapy for IDH-mutant WHO grade 2 and grade 3 diffuse glioma conditionally recommends proton therapy as an option to reduce acute and late toxicity, especially for tumors located near critical organs at risk (OARs). (Halasz et al., 2022)

National Comprehensive Cancer Network (NCCN)

NCCN guidelines for CNS cancers states that when toxicity is a concern during management of spinal ependymoma or medulloblastoma in adults, PBRT should be considered if available. Highly conformal fractionated RT techniques may be conditionally considered for meningiomas to spare critical structures and uninvolved tissue. Proton therapy for patients with good long-term prognosis to better spare uninvolved brain and preserve cognitive function may be conditionally considered for anaplastic gliomas/glioblastoma high-grade and astrocytoma IDH-Wild Type. Preliminary data suggest that proton therapy could reduce the radiation dose to developing brain tissue and potentially diminish toxicities without compromising disease control. (NCCN, 2023)

Breast Cancer

A Hayes Technology Assessment related to PBT for breast cancer treatment states the overall body of evidence is low in quality, but suggests PBT is relatively safe and potentially effective for the treatment of non-metastatic breast cancer. A small number of studies compared conventional radiation with PBT and found better QOL, disease control, and safety outcomes with PBT. The assessment suggests additional studies are required to evaluate the effectiveness and safety of PBT compared to other forms of conventional RT in patients with breast cancer without distant metastasis. (Hayes, 2022)

DeCesaris (2019) conducted single-institution, retrospective cohort analysis to evaluate acute skin toxicity, i.e., radiation dermatitis (RD) or skin hyperpigmentation (SH) in patients with primary invasive breast cancer who underwent radiation therapy with either photon or proton radiation therapy. Skin toxicity was recorded using Common Terminology Criteria for Adverse Events version 4.0 criteria and scored by treating physicians on a weekly basis. For each patient, the highest recorded grades of RD and SH were analyzed. A total of 86 patients received treatment with a median age of 53 years (range, 245 – 78 years) and median RT dose of 60 Gy (range, 45 – 70 Gy). Of those, 47 (55%) received photon beam therapy and 39 (45%) received PBT. Patients treated with proton beam radiation therapy had a statistically significant higher rate of grade ≥ 2 RD compared with patients who were treated with photon radiation therapy (69.2% vs. 29.8%, $p < 0.001$). There was no difference in the rates of grade 3 RD or SH between the modalities. The authors concluded that women who will be undergoing proton beam radiation therapy should receive counseling regarding its potential for grade ≥ 2 skin toxicities. Limitations of this study include its design, use of subjective assessments, and that during treatment optically stimulated luminescent dosimeters were not used to measure patients' radiation exposure.

Verma et al. (2017) conducted a single-institution retrospective cohort study to evaluate acute toxicity in patients with locally advanced breast cancer and receiving comprehensive regional nodal irradiation (CRNI) with adjuvant PBT from 2011–2016. PBT targeting the intact breast/chest wall and CRNI including the axilla, supraclavicular fossa, and internal mammary lymph nodes consisted of a 3-dimensional uniform scanning technique. In 2016, the institution transitioned to a pencil beam scanning (PBS) technique. The 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 six months. A total of 91 patients were treated with a median follow-up period of 15.5 months. The most common toxicities were dermatitis and/or skin infections, but esophagitis and fatigue were also observed. Acute dermatitis of grades 1, 2, and 3 occurred in 23%, 72%, and 5%, respectively. Eight percent (n = 7) required treatment breaks due to dermatitis and the median time to resolution of acute skin toxicity was 32 days. Grades 1, 2, and 3 esophagitis developed in 31%, 33%, and 0%, respectively. The authors concluded that PBT for breast cancer as part of CRNI appears to have toxicity rates comparable to prior published studies e.g., Cuaron et al. (2015) reported 71.4% of those who received PBT developed grade 2 dermatitis however, Bradley et al. (2016) reported 100% developed grade 2 dermatitis. While the use of PBT with CRNI may have dosimetric advantages, particularly to the heart and other OARs, toxicities observed with its use demonstrates the need for randomized controlled trials comparing PBT to other radiation modalities.

Bradley et al. (2016) conducted a prospective case series study to evaluate the clinical feasibility and potential benefits of PBT in breast cancer patients who were at risk for regional nodal disease. In this pilot study, the primary endpoint was cardiac V5, testing the hypothesis that PBT could reduce the volume of the heart receiving 5 Gy by ≥ 50% when compared to CRT. The secondary endpoints included acute toxicity and other dosimetric parameters of target coverage and exposure to at-risk organs. PBT and CRT plans, targeting the regional nodes, were created for each patient. Patients were evaluated weekly while on RT, 4 weeks after RT was completed and at 6-month intervals thereafter. Toxicity was recorded using the Common Terminology Criteria for Adverse Events (CTCAE, v4.0). A total of 18 women enrolled with a median age of 51.8 years (range, 42–73 years) and a median follow-up period of 20 months (range, 2–31 months). Ten of the women received only PBT and 8

received combination therapy of PBT and photon beam RT. All patients had improved heart and lung dose with PBT. The primary endpoint, which was to determine if PBT could reduce cardiac V5 by ≥ 50%, was achieved. Of the nine patients with left-sided breast cancer, the median cardiac dose decreased from 5.9 Gy with CRT to 0.6 Gy with PBT (p = 0.004). In patients with right-sided breast cancer, the median cardiac dose decreased from 2.9 Gy with CRT to 0.5 Gy with PBT (p = 0.004). No patients developed grade 4+ toxicities. Four (22%) patients developed grade 3 dermatitis and of these, 3 were treated with PBT and 1 was treated with combination PBT and CRT. All of the patients developed grade 2 dermatitis, which resolved within 1 month of the completion of therapy. However, 1 patient developed cellulitis and required a course of antibiotics. Additional acute grade 2 toxicities included: fatigue (n = 6), esophagitis (n = 5), nausea (n = 1) and dyspnea (n = 1). The authors acknowledged that their rate of patients with grade 3 acute skin toxicity was not unexpected given the higher skin dose with PBT and concluded that PBT for regional node irradiation after mastectomy or breast conserving surgery offers a lower cardiac dose particularly for patients with left-sided breast cancer and without grade 4+ toxicities. Limitations of this study include its design, small sample size and higher toxicity rates compared with other forms of RT, e.g., intensity modulated RT.

Verma et al. (2016a) 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 produced 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 RT. From the limited available data, the rate of grade 2 esophagitis ranged from 12% to 29%. 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 (RP) and rib fractures remain rare. PBT offers the 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. Limitations to this review included a general lack of data and low number of participants in the available studies.

Cuaron et al. (2015) conducted a single-institution case series study to report dosimetry and early toxicity data in patients with breast cancer. Retrospectively collected data from consecutive patients diagnosed with non-metastatic breast cancer, no prior history of chest wall radiation and treated with PBT postoperatively were studied. Patients with unfavorable cardiopulmonary anatomy were usually referred to this institution. Post-lumpectomy patients with large breast size were not offered treatment due to a higher propensity for day-to-day measurement differences in the target position. Patients were evaluated weekly while on RT, 4 weeks after RT was completed, and at 12–24 week intervals thereafter. Toxicity was recorded using the Common Terminology Criteria for Adverse Events (CTCAE, v4.0). A total of 30 women were included in the study with a median age of 49 years (range, 29–86 years), cancer staging was as follows: eight had stage II, twenty had stage III and two had chest wall recurrence. The median follow-up was 9.3 months (range, 2.3–18.6 months). With PBT, full coverage of the planned target value was achieved, and it significantly spared the heart, lungs and contralateral breast. Of those with greater than 3 months of follow-up (n = 28), 71.4% developed grade 2 dermatitis and of those, 28.6% experienced moist desquamation. Eight (28.6%) developed grade 2 esophagitis and one developed grade 3 reconstructive complications. The authors concluded that in this series of 30 patients, PBT achieved excellent coverage of the target volume while sparing the heart, lungs, and contralateral breast, that the treatment was well tolerated, and that additional studies assessing long-term outcomes and toxicity are needed. Limitations of this study include its design, exclusion of women with large breast size, and higher toxicity rates compared with other forms of RT, e.g., intensity modulated RT.

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 five 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.

To further elucidate the clinical advantages and disadvantages between PBT and other types of radiation therapy used in breast cancer, additional clinical trials are underway, NCT02603341, NCT01245712, and NCT03391388, go to https://clinicaltrials.gov/. (Accessed September 14, 2023)

Clinical Practice Guidelines

National Comprehensive Cancer Network (NCCN)

NCCN guidelines do not address the use of PBT for treating breast cancer. (NCCN, 2023)

Choroidal Hemangiomas

Mathis et al. (2021) conducted a retrospective multi-center study that compared the functional and anatomical effectiveness of PBT versus photodynamic therapy (PDT) in a real-life setting for the treatment of circumscribed choroidal hemangioma. The study included a total of 191 patients with a diagnosis of choroidal hemangioma, 119 patients (62.3%) were treated by PDT and 72 patients treated by PBT. The final best-corrected visual acuity did not differ significantly between the two groups ($p = 0.932$) and final thickness was lower in the PBT compared with the PDT group ($p = 0.001$). Fifty-three patients (44.5%) initially treated by PDT required at least one other therapy and were associated with worse final best-corrected visual acuity ($p = 0.037$). None of the patients treated by PBT needed second-line therapy. In multivariate analysis, only an initial thickness greater than 3 mm remained significant ($p = 0.01$) to predict PDT failure. The authors concluded PDT and PBT have similar functional and anatomical outcomes for circumscribed choroidal hemangioma ≤ 3 mm; although PDT sometimes requires multiple sessions. Additionally, for tumors > 3mm, PBT seems preferable as it can treat the tumor in one session with better anatomical and functional outcomes. The authors recommended further large-scale studies to better define a thickness threshold above which PDT is less efficient. Limitations include the retrospective nature of the study, lack of randomization and small study size.

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, and there was no significant difference in the outcomes between the two groups. The authors concluded that RT 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

Fok et al. (2021) conducted a systematic review and meta-analysis that compares dosimetric irradiation of OARs and oncological outcomes for PBT versus conventional photon-based radiotherapy in locally advanced rectal cancer. Eight articles with a total of 127 patients met the inclusion criteria. There was significantly less irradiated small bowel with PBT compared to 3DCRT and IMRT (MD -17.01, CI [-24.06, − 9.96], $p < 0.00001$ and MD -6.96, CI [-12.99,− 0.94], $p = 0.02$, respectively). Similar dosimetric results were observed for bladder and pelvic bone marrow. Three studies reported clinical and oncological results for PBT in recurrent rectal cancer with overall survival reported as 43 %, 68 % and 77.2 %, and one study in primary rectal cancer with 100 % disease free survival. The authors concluded PBT treatment plans resulted significantly less irradiation of OARs for rectal cancer when compared to conventional photon-based radiation therapy. The authors note there are currently no ongoing clinical trials for primary rectal cancer and PBT and more research is required to validated PBTs role in organ preservation without increasing toxicity, complete response rate, and dose escalation. Limitations include small sample size and lack of RCTs.

Verma et al. (2016b) conducted a systematic review to identify studies on PBT and gastrointestinal malignancies. The search included PubMed, EMBASE, and abstracts from meetings of the American Society for Radiation Oncology, Particle Therapy Co-Operative Group, and American Society of Clinical Oncology. A total of 39 original investigations were analyzed. For esophageal cancer, twelve studies were analyzed and several of those reported that PBT resulted in a significant dose reduction to intrathoracic OARs and is associated with reduced toxicity, postoperative complications (POCs) while achieving comparable local control and overall survival. However, for some of the studies, contemporaneous comparison groups were lacking or comparisons were made between PBT and x-ray radiotherapy (XRT), which consisted of either 3D-CRT or IMRT rather than IMRT only. For pancreatic cancer, 5 studies were analyzed. Survival for resected/unresected cases was similar to existing data where IMRT was used and nausea/emesis were numerically lower than what had been reported among patients who received IMRT however, direct head-to-head comparisons were not made. For hepatocellular carcinoma, ten studies were analyzed, and these had the strongest evidence to support use of PBT. Those studies reported very low toxicities, and a phase

III trial comparing PBT to TACE showed a trend toward better LC and PFS with PBT. For cholangiocarcinoma, liver metastases, and retroperitoneal sarcoma, survival and toxicity data is comparable to historical photon controls, and stomach and biliary system/gallbladder cancer studies consisted of case reports and small cohort experiences. The authors concluded that PBT offers the potential of lower toxicities without compromising survival or local control. However, there was limited high quality evidence for select gastrointestinal malignancies and that multi-institution, randomized controlled trials are needed.

Clinical Practice Guidelines

National Comprehensive Cancer Network (NCCN)

NCCN guidelines do not address PBT in the treatment of gastric cancers. (NCCN, 2023)

Esophageal Cancer

A meta-analysis by Zhou et al. (2023) to explore whether PBT provided better efficacy and safety outcomes compared to photon therapy in patients with esophageal cancer. Forty-five studies were included in the meta-analysis with the primary outcomes being OARs dosimetric outcomes, OS, PFS, objective response rate (ORR) and radiation-related toxic effects. For dosimetric analysis, proton therapy was associated with significantly reduced OARs dose. Meta-analysis showed that photon therapy was associated with poor OS, but no difference in PFS was observed. Subgroup analysis showed worse OS and PFS in the radical therapy group with photon therapy. The pathological complete response rate was similar between groups. Proton therapy was associated with significantly decreased grade 2 or higher radiation pneumonitis and pericardial effusion, and grade 4 or higher lymphocytopenia. Single-rate analysis of proton therapy found 89% OS and 65% PFS at one year, 71% OS and 56% PFS at two years, 63% OS and 48% PFS at three years, and 56% OS and 42% PFS at 5 years. The incidence of grade 2 or higher radiation esophagitis was 50%, grade 2 or higher radiation pneumonitis was 2%, grade 2 or higher pleural effusion was 4%, grade 2 or higher pericardial effusion was 3%, grade 3 or higher radiation esophagitis was 8%, and grade 4 or higher lymphocytopenia was 17%. The authors concluded significantly reduced OARs doses and toxic effects, and improved prognosis were associated with PBT for esophageal cancer when compared to photon therapy. Limitations include significant heterogeneity in the OARs dosimetric analysis, small study sizes, and lack of RCTs. The authors recommend caution is warranted with PBT for esophageal cancer and future RCTs are recommended to verify benefits provided by PBT. (Lin 2020, Xi 2017, and Lin 2017 which were previously cited in this policy, are included in the Zhou systematic review and meta-analysis)

A Hayes Health Technology Assessment (2022) for the use of PBT in adults with esophageal adenocarcinoma as an adjunct to chemotherapy and surgery states PBT may have effectiveness that is comparable to both IMRT and 3DCRT and results in significantly lower radiation exposure to nearby OARs, with possibly fewer complications in those undergoing esophagectomy. However, the statistical significance of those findings were mixed. PBT and IMRT were found to have similar rates of nonoperative complications. The overall quality of the body of evidence for PBT for the treatment of esophageal adenocarcinoma was rated as low due to limitations of the individual studies, diverse treatment protocols, and scarcity of evidence for efficacy beyond three years.

A Hayes Health Technology Assessment regarding the use of PBT for the treatment of esophageal squamous cell carcinoma as an adjunct to chemotherapy with or without surgery, suggests PBT may be as effective as conventional (x-ray) photon radiotherapy (XRT). PBT may result in fewer or similar complications and delivers lower doses of radiation to nearby OARs than XRT. Additionally, PBT can reduce the rate of recurrence, improve survival, and induce a complete response. However, the body of evidence is noted as very low-quality, consisting of small- to moderate-sized retrospective studies with limited follow-up, with most studies lacking a comparator group. The assessment found the evidence base was insufficient to evaluate efficacy and safety of PBT, and recommends future studies. (Hayes, 2022)

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 EC patients. These results need to be confirmed in prospective studies.

Mizumoto et al. (2011) evaluated the efficacy and safety of hyperfractionated concomitant boost PBT in nineteen patients with esophageal cancer. The overall 1- and 5-year actuarial survival rates for all nineteen patients were 79% and 42.8%, respectively. The median survival time was 31.5 months. Of the nineteen patients, seventeen (89%) showed a complete response within four months after completing treatment and two (11%) showed a partial response, giving a response rate of 100% (19/19). The 1- and 5-year LC rates for all nineteen 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 eighteen 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 four 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% 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.

An ongoing phase III study is recruiting patients to compare the use of PBT to photon therapy in EC patients (Clinical Trial ID: NCT03801876). For more information, go to http://www.clinicaltrials.gov/. (Accessed September 14, 2023)

Clinical Practice Guidelines

National Comprehensive Cancer Network (NCCN)

NCCN guidelines state that PBT is appropriate when treating esophageal and esophagogastric junction cancers in settings where dose reduction to OARs is necessary and cannot be achieved by 3D-CRT. Because data is early and evolving, patients should receive PBT within a clinical trial. (NCCN, 2023)

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.

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, go to www.clinicaltrials.gov. (Accessed September 14, 2023)

Clinical Practice Guidelines

National Comprehensive Cancer Network (NCCN)

NCCN guidelines do not address the use of PBT when treating any type of gynecologic cancer (i.e., Cervical Cancer (NCCN, 2023), Ovarian Cancer (NCCN, 2023), Uterine Neoplasms (NCCN, 2024) or Vulvar Cancer (NCCN, 2024)).

Head and Neck Cancers (HNC) Not Listed in the Coverage Rationale as Proven

A Hayes report, Proton Beam Therapy for Treatment of Head and Neck Cancer, assessed multiple clinical studies evaluating the efficacy and safety of PBT in patients with HNC. The majority of the evidence included retrospective studies, data analyses, and systematic reviews. They noted there was some overlap of investigators and, possibly, overlap of patient groups as well. The report concludes that the study abstracts present conflicting findings regarding the use of PBT for treatment of HNC. The updated 2022 Hayes report includes 25 new studies that met inclusion criteria; however, no change was made to the rating. (Hayes, 2019; Updated 2022)

Seeking to improve LC rate and reduce late AEs, Takayama et al. (2016) 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 two systemic chemotherapy courses and whole-neck irradiation (36 Gy in 20 fractions), participants were administered concurrent chemoradiotherapy comprising PBT for the primary tumor and 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 seventeen 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. This study is limited by the lack of data comparing toxicity to conventional radiation therapy.

Clinical Practice Guidelines

American College of Radiology (ACR)/American Society for Radiation Oncology (ASTRO)

Regarding head and neck tumors, the ACR/ASTRO practice parameter states that PBRT reduces the dose delivered to critical normal structures in the head and neck region that may impact QOL, including optic nerves, optic chiasm, pituitary gland, brain, brainstem, spinal cord, salivary glands, pharyngeal constrictor muscles, oral cavity, and the emetogenic sites in the posterior fossa. (2018)

National Comprehensive Cancer Network (NCCN)

NCCN's HNCs guideline makes no mention of proton beam radiation therapy for cancer of the lip (mucosa), oral cavity, hypopharynx or glottic larynx. The guideline states that use of proton therapy is an active area of investigation, and that proton therapy may be considered when normal tissue constraints cannot be met by photon-based therapy in cancers of the oropharynx, nasopharynx, supraglottic larynx, and salivary glands, as well as mucosal melanoma and other primary tumors of the head and neck. Either IMRT or proton therapy is recommended for maxillary sinus or paranasal/ethmoid sinus tumors to minimize the dose to critical structures. (NCCN, 2023)

Lung Cancer

Liao et al. (2018) conducted a single-center randomized trial that compared outcomes of passive scattering proton therapy (PSPT) versus IMRT, both with concurrent chemotherapy, for inoperable NSCLC. The primary end point was the first occurrence of severe (grade ≥ 3) radiation pneumonitis (RP) or local failure (LF). Eligible patients had stage IIB to IIIB NSCLC (or stage IV NSCLC with a single brain metastasis or recurrent lung or mediastinal disease after surgery) and were candidates for concurrent chemoradiation therapy. Pairs of treatment plans for IMRT and PSPT were created for each patient. Patients were eligible for random assignment only if both plans satisfied the same prespecified dose-volume constraints for at-risk organs at the same tumor dose. Compared with IMRT (n = 92), PSPT (n = 57) exposed less lung tissue to doses of 5 to 10 Gy(RBE), which is the absorbed Gy dose multiplied by the relative biologic effectiveness (RBE) factor for protons; exposed more lung tissue to ≥ 20 Gy(RBE) but exposed less heart tissue at all dose levels between 5 and 80 Gy (RBE). The grade ≥ 3 RP was greater for PSPT than IMRT (6.5% for IMRT and 10.5% for PSPT) though the difference did not reach statistical significance; there was no difference observed in LF (10.9% and 10.5% for IMRT and PSPT, respectively). Exploratory analysis showed that the RP and LF rates at twelve months for patients enrolled before versus after the trial midpoint were 21.1% (before) versus 18.2% (after) for the IMRT group and 31.0% (before) versus 13.1% (after) for the PSPT group suggesting that that outcomes for proton therapy improved over the course of the trial as the investigators gained experience. The authors stated that findings from 2 ongoing trials (NCT01993810 and NCT01629498) will provide additional evidence of the efficacy of proton and photon therapies.

Chang et al. (2017) 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 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 3D-CRT 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.

Chi et al. (2017) 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 photon SBRT was observed in the treatment of early-stage NSCLC.

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 one and two, 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 four cycles every four 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 three patients, and then escalated to the next level if no DLT occurred. When one patient developed a DLT, three additional patients were enrolled. Overall, nine 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 nine 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 one) and vinorelbine (on Days one and eight). 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 three 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 one and two patients, respectively. Severe (≥ Grade 3) leukocytopenia, neutropenia and thrombocytopenia were observed in ten, seven, and one patients, respectively. Late RP (grades 2 and 3) 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 eleven patients, with the mean survival time being 26.7 months. The authors cited short follow up period as a limitation to this study. They concluded that high-dose PBT with concurrent chemotherapy is safe and useful in the multimodality therapy for unresectable NSCLC.

Sejpal et al. (2011) conducted a single-center, retrospective case series study to evaluate the use of PBT plus concurrent chemotherapy in patients with SNCLC. Outcomes included acute and subacute toxicity and were evaluated using Common Terminology Criteria (version 3.0) at least weekly during treatment, at four to six weeks after treatment, every three months for two years and then, every six months. Survival, time to progression and failure patterns were also collected. Comparisons between other radiation treatment modalities (IMRT and 3D-CRT, each with concurrent chemotherapy) were made using historical controls from the same center. A total of 202 patients were included in the analysis: 74 received 3D-CRT, 66 IMRT and 62 PBT. Median follow-up periods were 17.9 months (3D-CRT), 17.4 months (IMRT) and 15.2 months (proton). Median total radiation dose was higher in the PBT group at 74 Gy versus 63 Gy for the other groups. Despite the higher radiation dose in the PBT group, rates of severe (grade ≥ 3) pneumonitis and esophagitis were lower (2% and 5%, respectively) compared with the other groups (3D-CRT, 30% and 18%; IMRT, 9% and 44%, respectively). Due to the short follow-up periods, tumor control and survival were not reported. The authors concluded that in this early and promising study, higher doses of PBT could be delivered to lung tumors with a lower risk of esophagitis and pneumonitis, and that additional clinical trials may further clarify the benefits and risks of PBT in patients diagnosed with SNCLC.

Pijls-Johannesma et al. (2010) conducted a systematic review to test the theory that RT 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 (at 50% and 76%, respectively) were reported when using hypofractionation. 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.

A phase III RCT comparing photon to proton chemoradiotherapy for patients with inoperable NSCLC (NCT01993810) is in progress. For more information, go to www.clinicaltrials.gov. (Accessed September 14, 2023)

Clinical Practice Guidelines

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)

National Comprehensive Cancer Network (NCCN)

NCCN guidelines state that advanced technologies such as 4D-CT and/or PET/CT simulation, IMRT/VMAT, IGRT, motion management, and PBT are appropriate when needed to deliver curative RT safely when treating NSCLC (NCCN, 2023) and may be appropriate to limit normal tissue toxicity in the treatment of small cell lung cancer. (NCCN, 2024)

Lymphomas

Multiple small, lower quality studies have been published on the management of lymphomas with PBT, particularly focused on long term radiation toxicity (König et al., 2019; Horn et al., 2016; Sachsman et al., 2015; Hoppe et al., 2012). Early outcomes are encouraging, but larger prospective studies are needed to confirm long term efficacy.

Clinical Practice Guidelines

National Comprehensive Cancer Network (NCCN)

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 RT technologies, such as PBT, may offer significant and clinically relevant advantages in specific instances to spare important OARs and decrease the risk for late, normal tissue damage while still achieving the primary goal of LC. NCCN is silent on the use of PBT in the treatment of primary cutaneous lymphoma. (NCCN, 2023)

Pancreatic Cancer

There is a lack of robust clinical evidence evaluating PBT for treating pancreatic cancer although research continues (Kim et al., 2018, Hong et al., 2014; Terashima et al., 2012; Hong et al., 2011). Further larger scaled prospective studies are warranted to determine the long-term safety and efficacy of this treatment modality.

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, go to www.clinicaltrials.gov. (Accessed September 14, 2023)

Clinical Practice Guidelines

National Comprehensive Cancer Network (NCCN)

NCCN guidelines do not address PBT in the treatment of pancreatic adenocarcinoma. (NCCN, 2023)

Vestibular Tumors

Saraf et al. (2022) released a preliminary analysis of a prospective, single-arm, phase II clinical trial that was conducted to evaluate hearing preservation rates of fractionated PBT in adults (n = 20) with vestibular schwannomas (VS). Secondary outcomes evaluated were LC and treatment-related toxicity. All patients had serviceable hearing at baseline, received fractionated PBT 50.4 to 54 Gy over 28 to 30 fractions, and had a median follow-up of four years. Local control at four years was 100%. Serviceable hearing preservation at 1 year was 53%, and primary endpoint was not yet reached. Median pure tone average and median word recognition score both worsened one year after fractionated PBT ($p < .0001$). Word recognition score plateaued after six months, whereas pure tone average continued to worsen up to one year after fractionated PBT. Median cochlea D90 was lower in patients with serviceable hearing at one year, trending toward Wilcox on rank-sum test statistical significance ($p = .0863$). Treatment was well-tolerated, with one grade 1 cranial nerve V dysfunction and no grade 2+ cranial nerve dysfunction. The authors concluded the goal of serviceable hearing preservation was not met with fractionated PBT for patients with VS. Additionally, higher cochlea doses trended to worsening hearing preservation. Limitations include small sample size, and short-term follow-up.

In a critical review, Murphy and Suh (2011) summarized the radiotherapeutic options for treating VS, including single-session stereotactic radiosurgery, fractionated conventional RT, fractionated stereotactic RT 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.

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 VS (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 VS 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 VS (severe facial weakness), but most side effects were either transient or could be successfully treated.

Clinical Practice Guidelines

Congress of Neurological Surgeons (CNS)

CNS developed an evidence-based guideline on the role of radiosurgery and radiation therapy in the management of patients with vestibular schwannomas. CNS notes that no studies that compare two or all three modalities (Gamma Knife versus LINAC-based radiosurgery versus proton beam) were identified, therefore, no recommendations on outcome could be made. (Germano et al., 2018)

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)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Radiation therapy is a procedure and, therefore, is not subject to FDA regulation. However, the accelerators and other equipment used to generate and deliver PBRT are regulated by the FDA. Refer to the following website for more information (use product code LHN): http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm. (Accessed September 14, 2023)

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Guideline History/Revision Information

Date	Summary of Changes
02/01/2024	**Coverage Rationale** • Revised list of proven and medically necessary indications for proton beam radiation therapy (PBT) for Definitive Therapy; replaced "*skull-based* tumors (e.g., chordomas, chondrosarcomas, paranasal sinus, or nasopharyngeal tumors)" with "*base of skull* tumors (e.g., chordomas, chondrosarcomas, paranasal sinus, or nasopharyngeal tumors)" **Definitions** • Updated definition of "Definitive Therapy" **Supporting Information** • Updated *Clinical Evidence* and *References* sections to reflect the most current information • Archived previous policy version MMG113.Q

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 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 InterQual® criteria, 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.