Proton Beam Radiation Therapy (for Louisiana Only)

Policy Number: CS105LA.~~L~~M
Effective Date: ~~January 1, 2019~~TBD

➲ Instructions for Use

Certain content mandated by Louisiana Department of Health

Table of Contents **Page**

Application

This Medical Policy only applies to the state of Louisiana. Portions of this coverage rationale contained in this policy represents Louisiana Medicaid coverage policy and is set forth below in accordance with State requirements ~~This Medical Policy only applies to the state of Louisiana~~

Coverage Rationale

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

Individuals younger than 19 years of age

Proton beam radiation therapy (PBRT, PBT) is covered without further review for persons younger than 19 years of age.

Individuals age 19 and 20

The following are proven and medically necessary:

- PBT for **Definitive Therapy** ~~Definitive Therapy~~ of the following indications:
  - ~~Intracranial arteriovenous malformations (AVMs)~~
  - ~~Ocular tumors, including intraocular/uveal melanoma (includes the iris, ciliary body and choroid)~~

  - ~~Skull-based tumors (e.g., chordomas, chondrosarcomas~~**Hepatocellular** ~~or paranasal sinus tumors)~~
  - ~~Localized, unresectable 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)**
  - **Skull-based tumors (e.g., chordomas, chondrosarcomas, paranasal sinus or nasopharyngeal tumors)**
- 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~~ALL~~ other indications not listed above as proven, including but not limited to:

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

Individuals age 21 and older

The Louisiana Medicaid Program does not cover proton beam radiation therapy (PBRT) for beneficiaries 21 years of age and older.

(Louisiana Medicaid Provider Manual, Chapter 25: Hospital Services, Section 25.3: Outpatient Services)

Definitions

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

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy 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 federal, state, or contractual requirements and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

CPT Code	Description
77301	Intensity modulated radiotherapy plan, including dose-volume histograms for target and critical structure partial tolerance specifications
77338	Multi-leaf collimator (MLC) device(s) for intensity modulated radiation therapy (IMRT), design and construction per IMRT plan
77385	Intensity modulated radiation treatment delivery (IMRT), includes guidance and tracking, when performed; simple
77386	Intensity modulated radiation treatment delivery (IMRT), includes guidance and tracking, when performed; complex
77387	Guidance for localization of target volume for delivery of radiation treatment, includes intrafraction tracking, when performed
77520	Proton treatment delivery; simple, without compensation
77522	Proton treatment delivery; simple, with compensation
77523	Proton treatment delivery; intermediate
77525	**Proton treatment delivery; complex**

CPT© is a registered trademark of the American Medical Association

HCPCS Code	Description
*G6015	Intensity modulated treatment delivery, single or multiple fields/arcs, via narrow spatially and temporally modulated beams, binary, dynamic MLC, per treatment session
*G6016	Compensator-based beam modulation treatment delivery of inverse planned treatment using 3 or more high resolution (milled or cast) compensator, convergent beam modulated fields, per treatment session
*G6017	Intra-fraction localization and tracking of target or patient motion during delivery of radiation therapy (e.g., 3D positional tracking, gating, 3D surface tracking), each fraction of treatment

Codes labeled with an asterisk (*) are not on the Louisiana Medicaid Fee Schedule and therefore may not be covered by the state of Louisiana Medicaid Program.

Diagnosis~~ICD Procedure~~ 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~~.0~~	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
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

Diagnosis~~ICD Procedure~~ Code	Description
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** ~~2017~~).

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).
~~The greatest energy release with conventional radiation (photons) is at the surface of the tissue and decreases exponentially the farther it travels. In contrast, the energy of~~

~~a proton beam is released at the end of its path, a region called the Bragg peak. Since the energy release of the proton beam is confined to the narrow Bragg peak, collateral damage to the surrounding tissues should be reduced, while an increased dose of radiation can be delivered to the tumor.~~

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

Clinical Evidence

~~and neck, CNS) in adults and in certain pediatric cancers, evidence is lacking regarding its benefits for many cancers over photon based EBRT.~~

~~**Professional Societies**~~

~~*American Society for Radiation Oncology (ASTRO)*~~

Proven Indications

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

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 13, 2022)

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, 2022).

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.

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

Hattangadi-Gluth et al. (2014) evaluated the obliteration rate and potential ~~(~~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**~~15~~ Gy.~~–~~ At a median follow-up time of 35 months, 64.6% of AVMs were obliterated. The median time to total obliteration was 31 months, and the 5- and 10-year cumulative incidence of total obliteration was 70% and 91%, respectively. On univariable analysis, smaller target volume, smaller treatment volume, higher prescription dose and higher maximum dose were associated with total obliteration. Deep/critical location was also associated with decreased likelihood of obliteration. On

multivariable analysis, critical location and smaller target volume remained associated with total obliteration. Post-treatment hemorrhage occurred in **thirteen**~~13~~ cases (5-year cumulative incidence of 7%), all among patients with less than total obliteration.~~—~~ Three of these events were fatal. The most common complication was seizure. The authors reported that this is the largest modern series of PSRS for cerebral AVMs and concluded that PSRS can achieve a high obliteration rate with minimal morbidity. Post-treatment hemorrhage remains a potentially fatal risk among patients who have not yet responded to treatment.

Hattangadi et al. (2012) evaluated 59 patients with high-risk cerebral AVMs, based on brain location or large size, who underwent planned two-fraction PSRS. Median nidus volume was 23 cc. Seventy percent of cases had nidus volume ≥ 14 cc, and 34% were in critical locations (brainstem, basal ganglia). Many patients had prior surgery or embolization (40%) or prior PSRS (12%). The most common dose was **sixteen**~~16~~ Gy in **2**~~two~~ fractions. At a median follow-up of 56.1 months, **nine**~~9~~ patients (15%) had total and **twenty**~~20~~ patients (34%) had partial obliteration. Patients with total obliteration received higher total dose than those with partial or no obliteration. Median time to total obliteration was 62 months, and 5-year actuarial rate of partial or total obliteration was 33%. Five-year actuarial rate of hemorrhage was 22% and 14% (n=8) suffered fatal hemorrhage. Lesions with higher AVM scores were more likely to hemorrhage and less responsive to radiation. The most common complication was headache. One patient developed a generalized seizure disorder, and two had mild neurologic deficits. The authors concluded that high-risk AVMs can be safely treated with 2-fraction PSRS, although total obliteration rate is low**,** and patients remain at risk for future hemorrhage. Future studies should include higher doses or a multistaged PSRS approach for lesions more resistant to obliteration with radiation.

Ocular Tumors

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 13, 2022).

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

~~*In the*~~ *National Comprehensive Cancer Network (NCCN)*

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, 2022).**

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 (2022).

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 (2020, Updated 2022).

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 ≤ .01), treatment modality was not associated with differences in clinician-reported acute or late GU/GI toxicities (all P ≥ .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 ≥ .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~~PBT is not cited in the list of radiotherapies~~ 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~~for treatment (2018~~), 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 13, 2022)

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).

Skull-Based Tumors

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 (2019, Updated 2022).

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

~~Kabolizadeh et al.~~ The use of PBT~~(2017) performed a retrospective analysis at a single institution assessing outcome and tumor response to Definitive photon/proton radiotherapy when used in cases of unresected spine and sacral chordoma. Forty patients were identified between 1975 and 2012. Except for 1 patient, all underwent proton therapy only, or predominantly proton therapy combined with photons to limit the exit dose of~~

~~radiation to any adjacent normal structures at risk. Three-dimensional conformal radiotherapy (3DCRT) was the specific photon treatment used until January 2002 when it was replaced by IMRT (primarily for skin-sparing effects). Local control (LC), OS, disease-specific survival (DFS), and distant failure at 5 years were 85.4%, 81.9%, 89.4%, and 20.2%, respectively. The authors concluded that for selected patients with unresected spine and sacral chordomas, the use of high dose Definitive radiation Therapy can be supported with these results.~~

~~The use of proton therapy (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**~~radiotherapy~~ with photons are lacking. In a systematic review, Amichetti et al. (2010) reported that studies of PBT for skull-based chondrosarcoma resulted in LC ranging from 75% to 99% at **five**~~5~~ years. There were no prospective trials (randomized or **non-randomized**~~nonrandomized~~), but **four**~~4~~ uncontrolled single-arm studies with 254 patients were included.~~—~~ The authors concluded that PBT following surgical resection showed a very high probability of medium- and long-term cure with a relatively low risk of significant complications.

A systematic review of **seven**~~7~~ uncontrolled single-arm studies concluded that the use of protons has shown better results in comparison to the use of conventional photon irradiation, resulting in the best long-term (10 years) outcome for skull-based chordomas with relatively few significant complications (Amichetti et al., 2009).

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 (2017). (Accessed September 13, 2022)

National Comprehensive Cancer Network (~~Early studies evaluating PBT for the treatment of intracranial or skull base tumors include 4 case series, 4 retrospective studies, and 2 prospective, uncontrolled, clinical studies (Kjellberg, 1968; Suit, 1982; Hug, 1995; Al-Mefty and Borba, 1997; McAllister, 1997; Gudjonsson, 1999; Wenkel, 2000; Vernimmen, 2001). The studies included 10 to 47 patients with pituitary gland adenoma, para-CNS sarcomas, osteogenic and chondrogenic tumors, chordomas, and meningiomas. LC was achieved in 71% to 100% of patients. Complications were radiation dose/volume and site dependent, and were mild to severe.~~

NCCN)

NCCN guidelines for bone cancer states that specialized techniques, including particle beam **RT**~~radiation therapy~~ with protons, should be considered as indicated in order to allow high-dose therapy while maximizing normal tissue sparing in patients with chondrosarcoma **or chordoma. PBT may be considered for patients with good long-term prognosis to better spare uninvolved brain and preserve cognitive function (NCCN, 2023**~~(2019)~~).

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, 2022).

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)

~~In a Cochrane review,~~ 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** ~~All RCTs~~ 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** ~~. Thirteen trials (n=1154) investigated EBRT~~ with dosages ranging from 7.5 to 24 Gy**. Three of these studies investigated** ~~; one additional trial (n=88) used plaque~~ brachytherapy (**plaque and epimacular), the rest were studies of external beam radiotherapy (EBM) including one trial of stereotactic radiotherapy.** ~~15Gy at 1.75mm for 54 minutes/12.6 Gy at 4mm for 11 minutes). Most studies found effects (not always significant) that favored treatment. Overall there was a small statistically significant reduction in risk of visual acuity loss in the treatment group. There was considerable inconsistency between trials and the trials were considered to be at risk of bias, in particular because of the lack of masking of treatment group. Subgroup analyses did not reveal any significant interactions; however, there were small numbers of trials in each subgroup (range three to five). There was some indication that trials with no sham irradiation in the control group reported a greater effect of treatment. The incidence of AEs was low in all trials; there were no reported cases of radiation retinopathy, optic neuropathy or malignancy. Three trials found non-significant higher rates of cataract progression in the treatment group.~~ The authors concluded that **the** ~~this review does not provide convincing~~ evidence ~~that radiotherapy~~ is **uncertain regarding the use of radiotherapy** ~~an effective treatment~~ 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)** ~~If~~ further **research on radiotherapy for neovascular AMD may not** ~~trials are to~~ be **justified until current ongoing studies have reported their results** ~~considered to evaluate radiotherapy in AMD then adequate masking of the control group must be considered~~.

In a systematic review, Bekkering et al. (2009) evaluated the effects and side effects of **PBT** ~~proton therapy~~ for indications of the eye. All studies that included at least **ten**~~10~~ patients and that assessed the efficacy or safety of **PBT**~~proton therapy~~ for any indication of the eye were included. Five controlled trials, **two**~~2~~ comparative studies and 30 case series were found, most often reporting on uveal melanoma, choroidal melanoma and AMD. Methodological quality of these studies was poor. Studies were characterized by large differences in radiation techniques applied within the studies, and by variation in patient characteristics within and between studies. Results for uveal melanoma and

choroidal melanoma suggest favorable survival, although side effects are significant. Results for choroidal hemangioma and AMD did not reveal beneficial effects from proton radiation. There is limited evidence on the effectiveness and safety of ~~proton radiation~~ due to the lack of well-designed and well-reported studies.

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

Clinical Practice Guidelines

~~Professional Societies~~

American Academy of Ophthalmology (AAO)

AAO preferred practice patterns state that **RT has insufficient data to demonstrate clinical efficacy and** ~~radiation therapy~~ is not recommended in the treatment of AMD (**Flaxel et al., 2019** ~~2015~~).

Bladder Cancer

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, 2022** ~~2017~~).

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

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 1 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** ~~17~~ patients with meningioma to evaluate the efficacy and the tolerance of an escalated dose of external conformal fractionated **RT**~~radiation therapy~~ combining photons and protons. Five patients presented a histologically atypical or malignant meningioma, **twelve** ~~12~~ patients had a benign tumor that was recurrent or rapidly progressive. In **two**~~2~~ cases, **RT** ~~radiotherapy~~ was administered in the initial course of the disease and in **fifteen** ~~15~~ cases at the time of relapse. A highly conformal approach was used combining high-energy photons and protons for approximately 2/3 and 1/3 of the total dose. The median total dose delivered within gross tumor volume was 61 ~~Cobalt Gray Equivalent~~ CGE (25-69). Median follow-up was 37 months (17-60). The 4-year **LC**~~local control~~ and OS rates were 87.5 +/- 12% and 88.9 +/- 11%, respectively. Radiologically, there were **eleven**~~11~~ stable diseases and 5 partial responses. The authors concluded that in both benign and more aggressive meningiomas, the combination of conformal photons and protons with a dose escalated by 10-15% offers clinical improvements in most patients as well as radiological long-term stabilization. **Limitations of this study include small sample size and study design.**

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

Several clinical trials studying PBT in patients with various types of brain tumors are active or recruiting.
For more information, go to www.clinicaltrials.gov. (Accessed **September 13, 2022** ~~October 31, 2018~~)

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, 2022).

Breast Cancer

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 6 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. ~~Verma et al. (2016) performed a systematic review of clinical outcomes and toxicity of PBT for treating breast cancer.~~ Nine original studies were analyzed, however the types of studies and the volume of patients in those studies were not specifically cited by the authors. Conventionally fractionated breast/chest wall PBT **produced** ~~**produces**~~ grade 1 dermatitis rates of approximately 25% and grade 2 dermatitis in 71%-75%. This is comparable or improved over the published rates for photons. The incidence of esophagitis was decreased if the target coverage was compromised in the medial supraclavicular volume, a finding that echoes previous results with photon **RT. From the limited available data, the rate** ~~radiotherapy. The rates~~ of grade **2** esophagitis **ranged from 12%** ~~were also comparable~~ to **29%.** ~~the previous data for photons.~~ Using PBT-based accelerated partial breast irradiation (PBI), the rates of seroma/hematoma and fat necrosis were comparable to those reported in the existing data. Radiation pneumonitis **(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.

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

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

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 13, 2022).

Clinical Practice Guidelines

National Comprehensive Cancer Network (NCCN)

NCCN guidelines do not address the use of PBT for treating breast cancer (NCCN, **2022** ~~2018~~).

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

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**~~. There~~ was no significant difference in the outcomes between the **two** ~~2~~ groups. The authors concluded that **RT**~~radiotherapy~~ is effective in treating choroidal hemangiomas with respect to visual acuity and tumor thickness**,** but a benefit of proton versus photon therapy could not be detected.

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

Gastrointestinal (GI) Cancers

Fok et al. (2021) conducted a ~~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** ~~by Verma, et al. (2016)~~ 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** ~~and~~ 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 ~~outcomes~~ where **IMRT was used and nausea/emesis were numerically lower than what had been reported among patients who received IMRT**~~individuals with multiple types of GI cancers were treated with PBT. Thirty-eight studies published between 2010-2015 were included in the review,~~ however**, direct head-to-head comparisons**

were not made. For hepatocellular carcinoma, ten studies were analyzed, and these had ~~the types of studies and the volume of patients in those studies were not specifically cited by~~ the **strongest evidence to support use of PBT. Those studies reported very low** ~~authors. Reduced~~ toxicities**, and a** ~~with PBT versus photon therapy were identified in malignancies of the esophagus, pancreas, and in HCC. Fewer toxicities and improved PFS were also found using PBT versus transarterial chemoembolization (TACE) in a~~ phase III trial **comparing PBT to TACE showed a trend toward better LC and PFS with PBT. For** ~~. Survival and toxicity data for~~ cholangiocarcinoma, liver metastases, and retroperitoneal sarcoma**, survival and toxicity data is comparable to historical** ~~were nearly equivalent to~~ photon controls**, and stomach and biliary system/gallbladder cancer studies consisted of case** ~~. There were 2 small~~ reports ~~for gastric cancer~~ and **small cohort experiences.** ~~3 for anorectal cancer identified, but these were not addressed.~~ The authors concluded that ~~although studies in this review were of limited quality and quantity,~~ PBT ~~potentially~~ offers **the potential of lower** ~~significant reduction in treatment-related~~ 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** ~~in GI cancers. Several phase II/III clinical trials are now in progress conducting further research~~.

Clinical Practice Guidelines

National Comprehensive Cancer Network (NCCN)

NCCN guidelines do not address PBT in the treatment of gastric cancers (NCCN, 2022).

Esophageal Cancer

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.

Lin et al. (2020) conducted a phase IIB RCT that compared total toxicity burden (TTB) and PFS between IMRT and PBT. Patients were randomly assigned to PBT or IMRT (50.4 Gy) ranked for histology, resectability, induction chemotherapy, and stage. TTB, included a composite score of eleven AEs, including common toxicities as well as POCs in operated patients. The trial began in April 2012 and was approved for closure and analysis upon activation of NRG-GI006 in March 2019, which occurred immediately prior to the planned 67% interim analysis. One-hundred and seven patients (61 IMRT, 46 PBT) of the 145 randomly assigned patients (72 IMRT, 73 PBT), were evaluable. Median follow-up was 44.1 months. Fifty-one patients (30 IMRT, 21 PBT) underwent esophagectomy; 80% of PBT was passive scattering. The posterior mean TTB was 2.3 times higher for IMRT (39.9; 95% highest posterior density interval, 26.2-54.9) than PBT (17.4; 10.5-25.0). The mean POC score was 7.6 times higher for IMRT (19.1; 7.3-32.3) versus PBT (2.5; 0.3-5.2). The posterior probability that mean TTB was lower for PBT compared with IMRT was 0.9989, which exceeded the trial's stopping boundary of 0.9942 at the 67% interim analysis. The 3-year PFS rate (50.8% v 51.2%) and 3-year overall survival rates (44.5% v 44.5%) were similar. The authors concluded for locally advanced esophageal cancer, PBT reduced the risk and severity of AEs compared with IMRT while maintaining similar PFS. Limitations include small sample sizes, open-label, non-blinding, and single institution design.

Lin et al. (2017) conducted a multi-center retrospective cohort study of patients diagnosed with EC and treated with neoadjuvant chemoradiation. The purpose of this study was to assess the association between RT modality and postoperative outcomes. The outcomes included pulmonary, cardiac and wound complications, and length of stay (LOS), readmission and mortality. A total of 580 EC patients were included and of these, 214 (37%) received 3D-CRT, 255 (44%) received IMRT and 111 (19%) receive PBT. IMRT and PBT were associated with a reduced risk of pulmonary complications compared with 3D-CRT (p=.001), and PBT was trending toward being better than IMRT (OR 0.584, p=.077). Both IMRT and PBT were associated with a reduced risk of cardiac complications as were older age and history of coronary artery bypass grafting or atrial fibrillation. PBT was associated with a reduced risk of wound complications (OR 0.255, p=0.006, PBT vs. 3D-CRT; OR 0.276, p=0.009, PBT vs. IMRT) yet there was no difference between IMRT and 3D-CRT. Mean LOS was significantly associated with RT modality (13.2 days for 3D-CRT, 11.6 days for IMRT and 9.3 days for PBT (p<0.0001). There was no difference in 60-day readmission rates or deaths during the same hospitalization, or 30, 60 or 90-day postoperative mortality. The authors concluded that IMRT and PBT were associated with significantly reduced rates of POCs compared to 3D-CRT, that these results may show an advantage of PBT over IMRT however, prospective randomized clinical trials will better establish the role of PBT in EC.

Xi et al. (2017) conducted a single-center retrospective cohort study to evaluate outcomes of patients diagnosed with esophageal cancer (EC) and treated with PBT or IMRT. Outcomes included treatment-related toxicity, OS, PFS, locoregional failure-free survival (LRFFS) and distant metastasis-free survival (DMFS). Patients were followed every three months for the first year after radiation therapy, every six months for the following 2 years and then yearly until five years. A total of 343 patients were included and of those ,211 received IMRT and 132 received PBT. The median follow-up period for the IMRT group was 65.1 months (range, 19.4-115.3) and for the PBT group was 44.8 months (range, 11.9 – 110.3 months). The median radiation dose was 50.4 Gy in both the IMRT and PBT groups (ranges, 41.4-66.0 Gy and 45.0-63.0 Gy, respectively). There was no difference in treatment-related toxicities between the groups. The PBT group had better OS (p=.011), PFS (p=.001), and DMFS (p=.031) compared with the IMRT group. In subset analyses, patients with stage I/II disease had no differences in survival. In patients with stage III disease, those who received PBT had higher rates of OS (34.6% vs. 25.0%, p=.038) and PFS (33.5% vs. 13.2%, p=.005). The authors concluded that PBT was associated with improved OS, PFS and LRFFS, particularly in EC patients with advanced disease and that their results may suggest a benefit of PBT over IMRT. Limitations of this study include its design, that the type of radiation therapy each patient received was based on the multidisciplinary team and the patients' intent rather than randomization, there were differences in patient demographics and baseline characteristics between the groups, and that for some patients, accurate long-term documentation was lacking. Prospective, randomized controlled studies are needed to clarify the role of PBT in EC.

In a retrospective analysis, Wang et al. (**2013a** ~~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**~~esophageal cancer~~ patients. These results need to be confirmed in prospective studies.

~~Lin et al.~~ ~~(2012) reported preliminary results using concurrent chemotherapy and PBT (CChT/PBT) in 62 patients with esophageal cancer. The median follow-up time was 20.1 months for survivors. Acute treatment-related toxicities and perioperative morbidities were relatively low and the tumor response and disease related outcomes were encouraging.~~

~~The authors concluded that CChT/PBT holds promise in the management of esophageal cancers. This study is limited by retrospective design, lack of randomization and short-term follow-up.~~

Mizumoto et al. (2011) evaluated the efficacy and safety of hyperfractionated concomitant boost PBT in **nineteen** ~~19~~ patients with esophageal cancer. The overall 1- and 5-year actuarial survival rates for all **nineteen** ~~19~~ patients were 79~~.0~~% and 42.8%, respectively. The median survival time was 31.5 months. Of the **nineteen** ~~19~~ patients, **seventeen** ~~17~~ (89%) showed a complete response within **four** ~~4~~ months after completing treatment and **two** ~~2~~ (11%) showed a partial response, giving a response rate of 100% (19/19). The 1- and 5-year LC rates for all **nineteen** ~~19~~ patients were 93.8% and 84.4~~-~~%, respectively. The results suggest that hyperfractionated PBT is safe and effective for patients with esophageal cancer. Further studies are needed to establish the appropriate role and treatment schedule for use of PBT for esophageal cancer.

Mizumoto et al. (2010) evaluated the efficacy and safety of PBT for **locoregionally** ~~loco regionally~~ 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** ~~18~~ patients received PBT alone.~~—~~ The overall 5-year actuarial survival rate for the 51 patients was 21.1% and the median survival time was 20.5 months. Of the 51 patients, 40 (78%) showed a complete response within four~~4~~ months after completing treatment and seven (14%) showed a partial response, giving a response rate of 92% (47/51). The 5-year LC rate for all 51 patients was 38~~.0~~% and the median LC time was 25.5 months. The authors concluded that these results suggest that PBT is an effective treatment for patients with locally advanced esophageal cancer. Further studies are required to determine the optimal total dose, fractionation schedules and best combination of proton therapy with chemotherapy.

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 13, 2022).

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**~~organs at risk~~ is necessary and cannot be achieved by **3D-CRT** ~~3DCRT~~. Because data is early and evolving, patients should receive PBT within a clinical trial (**NCCN, 2022** ~~2018~~).

~~Gastric Cancer~~

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

~~Pancreatic Cancer~~

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

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

~~Numerous clinical trials are currently in progress studying the use of PBT in multiple types of GI cancer (e.g., esophageal, pancreatic, and retroperitoneal sarcoma). For more~~

~~information, go to www.clinicaltrials.gov. (Accessed October 30, 2018)~~

~~Hepatocellular Carcinoma (HCC)~~

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

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

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

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

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

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

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

~~***Professional Societies***~~

~~*American Society for Radiation Oncology (ASTRO)*~~

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

~~**American College of Radiology (ACR)**~~

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

~~***Gynecologic Cancers***~~

~~The efficacy of PBT combined with photon radiation for the treatment of cervical cancer was investigated in a prospective uncontrolled study involving 25 patients (Kagei, 2003).~~

Gynecologic Cancers

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

~~NCCN guidelines do not address the use of PBT when treating any type of gynecologic cancer (2017).~~

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 **September13, 2022**~~October 30, 2018~~)

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, 2022), Ovarian Cancer (NCCN, 2022), Uterine Neoplasms (NCCN, 2022) or Vulvar Cancer (NCCN, 2022).

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

A **2019** 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.**~~neck cancers.~~ 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. (Updated 2021** ~~this technology (2016~~).

~~Patel et al. (2014) conducted a systematic review and meta-analysis comparing the clinical outcomes of patients with malignant tumors of the nasal cavity and paranasal sinuses treated with CPT with those of individuals receiving photon therapy. Primary outcomes of interest were OS, DFS and LC, both at 5 years and at longest follow-up. A total of 43 cohorts from 41 non-comparative observational studies were included. Median follow-up for the CPT group was 38 months and for the photon therapy group was 40 months. Pooled OS was significantly higher at 5 years CPT than for photon therapy and at longest follow-up. At 5 years, DFS was significantly higher for CPT than for photon therapy but, at longest follow-up, this event rate did not differ between groups. LC did not differ between treatment groups at 5 years, but it was higher for CPT than for photon therapy at longest follow-up. A subgroup analysis comparing PBT with IMRT showed significantly higher DFS at 5 years and LC at longest follow-up. The authors concluded that,~~

~~compared with photon therapy, CPT could be associated with better outcomes for patients with malignant diseases of the nasal cavity and paranasal sinuses. Prospective studies emphasizing collection of patient-reported and functional outcomes are strongly encouraged.~~

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

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

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

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

Seeking to improve LC rate and reduce late AEs, Takayama et al. **(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** ~~2~~ systemic chemotherapy courses and whole-neck irradiation (36 Gy in 20 fractions), participants were administered concurrent chemoradiotherapy comprising PBT for the primary tumor and ~~for~~ the metastatic neck lymph node with weekly retrograde IACT of cisplatin with sodium thiosulfate by continuous infusion. The median follow-up duration was 43 months. The 3-year OS, PFS, LC rate, and regional control rate for the neck were 87%, 74.1%, 86.6%, and 83.9%, respectively. Major acute toxicities > grade 3 included mucositis in 26 cases (79–%), neutropenia in **seventeen** ~~17~~ cases (51–%), and dermatitis in 11 cases (33–%). Late grade 2 osteoradionecrosis was observed in 1 case (3–%). The authors concluded that PBT-IACT for stage III-IVB tongue cancer has an acceptable toxicity profile and showed good treatment results, and that this protocol should be considered as a treatment option for locally advanced tongue cancer**. This study is limited by the lack of data comparing toxicity to conventional radiation therapy.** ~~(2016).~~

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 ~~guidelines on HNC indicate that PBT~~ is **an active area of investigation, and that proton therapy may** ~~safe and effective and can~~ be considered ~~for treatment of multiple types of head and neck tumors~~ when normal tissue constraints cannot be met by photon-based therapy **in cancers of the oropharynx, nasopharynx, supraglottic larynx, and salivary glands, as well as mucosal melanoma and other**~~. It is valuable in patients whose~~ primary tumors **of the head and neck Either IMRT** ~~are periocular in location and/or invade the orbit, skull base, and/~~or **proton therapy is recommended for maxillary** ~~cavernous~~ sinus~~; that extend intracranially,~~ or **paranasal/ethmoid sinus tumors to minimize the dose to critical structures (NCCN, 2022**~~exhibit extensive perineural invasion. They no longer recommend neutron therapy as a general solution for salivary gland cancers due to the diminishing demand, concerns regarding the methodologic robustness of available randomized trial data, and closure of all but one center in the U.S. (2018~~).

~~***Professional Societies***~~

~~**American College of Radiology (ACR)**~~

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

Lung Cancer

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 ~~non-small cell lung cancer (~~NSCLC.~~).~~ 5-year OS, PFS, actuarial distant metastases and locoregional recurrence were 29%, 22%, 54%, and 28%, respectively. Acute and late toxic effects with PBT (compared to historical studies with **3D-CRT** ~~3DCRT~~ and/or IMRT) with chemotherapy were very promising.~~—~~ The authors concluded that the study demonstrated that concurrent PBT and chemotherapy was safe and effective in the long term, and that further prospective studies are warranted.~~ (2017).~~

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

~~Liao et al.~~ **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.** ~~(2016) conducted a phase II single institution randomized trial comparing IMRT to passive scattering 3D proton therapy (3DPT), both with concurrent chemotherapy, for locally advanced NSCLC. Of 255 enrolled patients, 149 were randomly allocated to IMRT (n=92) or 3DPT (n=57), and 106 received non-randomized (NR)IMRT (n=70) or NR3DPT (n=36). The primary end points assessed were grade ≥ 3 radiation pneumonitis (RP) and local failure (LF). Their article published in 2016 reported outcomes at 12 months. LF rates for all were 20.7%; the randomized IMRT group were 15.6% and the randomized 3DPT group was 24.6%. RP for all were 8.7%, randomized IMRT and 3DPT were~~

~~7.2% and 11%, respectively. 3DPT Continued monitoring resulted in a follow up article in 2018. The median follow-up time for the IMRT group for all patients was 24 months and 36.4 months for those still alive. For the 3DPT group, the follow up time was 25.7 months for all patients and 48.8 months for those surviving. The authors concluded that there was no statistically significant difference in the primary end points after IMRT or 3DPT for patients with locally advanced NSCLC. They did state that findings from 2 ongoing trials (NCT01993810 and NCT01629498) will provide additional evidence of the efficacy of proton and photon therapies.~~

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

Oshiro et al. (2014) initiated a **phase** ~~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** ~~1~~) and vinorelbine (on Days **one** ~~1~~ and **eight** ~~8~~). The treatment doses were 74 Gy RBE for the primary site and 66 Gy RBE for the lymph nodes without elective lymph nodes. The median follow-up period was 21.7 months. None of the patients experienced Grade 4 or 5 non-hematologic toxicities. Acute pneumonitis was observed in **three** ~~3~~ patients (Grade 1 in one, and Grade 3 in two), but Grade 3 pneumonitis was considered to be non-proton-related. Grade 3 acute esophagitis and dermatitis were observed in **one** ~~1~~ and **two** ~~2~~ patients, respectively. Severe **(≥**~~(≥~~ Grade 3) leukocytopenia, neutropenia and thrombocytopenia were observed in **ten, seven** ~~10, 7~~, and **one** ~~1~~ patients, respectively. Late **RP (grades** ~~radiation Grades~~ 2 and 3)~~ pneumonitis~~ was observed in one patient each. Six patients (40%) experienced local recurrence at the primary site and were treated with 74 Gy RBE. Disease progression was observed in **eleven** ~~11~~ 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** ~~to use~~ in the **multimodality therapy for**~~treatment of~~ unresectable~~ stage III~~ NSCLC.

Sejpal et al. (2011) **conducted a single-center, retrospective case series study to evaluate the use** ~~compared the toxicity~~ 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** ~~NSCLC (n=62)~~ with **concurrent chemotherapy) were made using historical controls from the same center. A total of 202** ~~toxicity for~~ patients **were included in the analysis: 74 received 3D-CRT, 66 IMRT and 62 PBT.** ~~with similar disease given 3DCRT) plus chemotherapy (n=74) or IMRT plus chemotherapy (n=66).~~ Median

follow-up **periods** ~~times~~ were ~~15.2 months (proton),~~ 17.9 months (3D-CRT**) ,**~~) and~~ 17.4 months (IMRT**) and 15.2 months (proton) .**~~).~~ Median total radiation dose was **higher in** ~~74 Gy(RBE) for~~ the **PBT** ~~proton~~ group **at 74 Gy** versus 63 Gy for the other groups. **Despite the higher radiation dose in the PBT group, rates**~~Rates~~ of severe (grade ≥ 3) pneumonitis and esophagitis ~~in the proton group (2% and 5%)~~ were lower **(2% and 5%, respectively) compared with the other groups** ~~despite the higher radiation dose~~ (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,**~~found that~~ higher doses of PBT could be delivered to lung tumors with a lower risk of esophagitis and pneumonitis**, and** ~~. Tumor control and survival were not evaluated due to the short follow-up time. A randomized comparison of IMRT versus PBT has been initiated.~~

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

Pijls-Johannesma et al. (2010) conducted a systematic review to test the theory that **RT**~~radiotherapy~~ with beams of protons and heavier charged particles (e.g., carbon ions) leads to superior results, compared with photon beams. The authors searched for clinical evidence to justify implementation of particle therapy as standard treatment in lung cancer. ~~-~~Eleven studies, all dealing with NSCLC, mainly stage I, were identified.~~-~~ No phase III trials were found. For PBT, 2- to 5-year LC rates varied in the range of 57%-87%. The 2- and 5-year OS and 2- and 5-year cause-specific survival rates were 31%-74% and 23% and 58%-86% and 46%, respectively. RP was observed in about 10% of patients. For CIT, the overall LC rate was 77%, but it was 95% when using a hypofractionated radiation schedule. The 5-year OS and cause-specific survival rates were 42% and 60%, respectively. Slightly better results **(at 50% and 76%, respectively)** were reported when using hypofractionation**.**~~, at 50% and 76%, respectively.~~ The results with protons and heavier charged particles are promising. However, the current lack of evidence on the clinical effectiveness of particle therapy emphasizes the need to further investigate the efficiency of particle therapy. ~~-~~The authors concluded that until these results are available for lung cancer, CPT should be considered experimental.

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

A phase III RCT comparing photon to proton chemoradiotherapy for patients with inoperable NSCLC (NCT01993810) is in progress. For more information, go to www.clinicaltrials.gov. (Accessed **September 13, 2022** ~~October 30, 2018~~)

Clinical Practice Guidelines

~~***Professional Societies***~~

American College of Radiology (ACR)

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

~~**Lymphoma**~~**National Comprehensive Cancer Network (NCCN)**

NCCN guidelines state that advanced technologies such as PBT are appropriate when needed to deliver curative RT safely when treating NSCLC (NCCN, 2022) and may be appropriate to limit normal tissue toxicity in the treatment of small cell lung cancer (NCCN, 2023).

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**~~radiation therapy~~ technologies, such as PBT, may offer significant and clinically relevant advantages in specific instances to spare important **OARs** ~~organs at risk~~ 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, 2022-2023**~~ (2018)~~.

Pancreatic Cancer

There
~~NCCN~~ is **a lack** ~~silent on the use~~ of ~~PBT in the treatment of primary cutaneous B-cell lymphoma (2018).~~

~~***Prostate Cancer***~~

robust~~A Hayes report assessed multiple~~ clinical **evidence** ~~studies published between 1983-2016~~ evaluating ~~the efficacy and safety of PBT in patients with localized prostate cancer. The report concludes that the reviewed studies found that PBT as an adjunct to X-ray therapy (XRT) usually had good or excellent safety and efficacy outcomes. Several controlled or comparative studies of PBT alone reported similar safety to IMRT, conformal XRT, and brachytherapy, but these did not assess the efficacy of PBT alone relative to other techniques for prostate cancer treatment. Additional well-designed studies are needed to establish the clinical role of PBT relative to other widely used therapies for localized prostate cancer for patients with prostate cancer and distant metastases, PBT has no proven benefit. Published evidence shows that the technology does not improve health outcomes or patient management in this patient population. Evidence addressing the safety & efficacy of PBT compared to other common radiation therapies for this indication are inadequate (2018).~~

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

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

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

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

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

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

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

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

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

~~Zietman et al. (2010) tested the hypothesis that increasing radiation dose delivered to men with early-stage prostate cancer improves clinical outcomes. Men (n=393) with T1b-T2b prostate cancer and prostate-specific antigen </= 15 ng/mL were randomly assigned to a total dose of either 70.2 Gray equivalents (GyE; conventional) or 79.2 GyE (high). LF, biochemical failure (BF) and OS were outcomes. Median follow-up was 8.9 years. Men receiving high-dose radiation therapy were significantly less likely to have LF. The 10-year ASTRO BF rates were 32.4% for conventional-dose and 16.7% for high-dose radiation therapy. This difference held when only those with low-risk disease (n=227; 58% of total) were examined: 28.2% for conventional and 7.1% for high dose. There was a strong trend in the same direction for the intermediate-risk patients (n=144; 37% of total; 42.1% v 30.4%). Eleven percent of patients subsequently required androgen deprivation for recurrence after conventional dose compared with 6% after high dose. There remains no difference in OS rates between the treatment arms (78.4% v 83.4%). Two percent of patients in both arms experienced late grade >/= 3 genitourinary toxicity, and 1% of patients in the high-dose arm experienced late grade >/= 3 GI toxicity.~~

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

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

~~Professional Societies~~

~~American Urological Association (AUA)~~PBT

~~In collaboration with the Society of Urologic Oncology (SUO) and ASTRO, the AUA guidelines~~ for treating ~~clinically localized prostate cancer discuss PBT as an option~~

~~within the category of EBRT. The guidelines also state that PBT offers no clinical advantage over other forms of Definitive treatment (Sanda et al., 2017).~~

~~*American Society for Radiation Oncology (ASTRO)*~~

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

~~American~~ pancreatic cancer although research continues (Kim et al., 2018, Hong et al.,~~ ~~College of Radiology (ACR)**~~

~~Appropriateness criteria from the ACR for the treatment of stage T1 and T2 prostate cancer states that there are only limited data comparing PBT to other methods of irradiation or to radical prostatectomy.~~ **2014; Terashima et al., 2012; Hong et al., 2011).** Further **larger scaled prospective** studies are **warranted** ~~needed~~ to **determine the long-term safety and efficacy of this** ~~clearly define its role for such~~ treatment **modality.** ~~(2013).~~

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 13, 2022)

Clinical Practice Guidelines

National Comprehensive Cancer Network (NCCN)

NCCN guidelines do not address PBT in the treatment of pancreatic adenocarcinoma (NCCN, 2022).

Vestibular Tumors

In a critical review, Murphy and Suh (2011) summarized the radiotherapeutic options for treating vestibular schwannomas, 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** ~~2~~ prospective uncontrolled studies involving 30 patients with acoustic neuromas (Bush et al., 2002) and 68 patients with vestibular schwannomas (Harsh et al., 2002). Fractionated PBT effectively controlled tumor growth in all patients with acoustic neuroma, and 37.5% of patients experienced tumor regression. Hearing was preserved in 31% of patients. The actuarial 5-year tumor control rate for patients with vestibular schwannomas was 84%; 54.7% of tumors regressed, 39.1% remained unchanged, and 3 tumors enlarged. The procedure caused some serious side effects in patients with vestibular schwannoma (severe facial weakness), but most side effects were either transient or could be successfully treated.

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). ~~In a critical review, Murphy and Suh (2011) summarized the radiotherapeutic options for treating vestibular schwannomas, including single-session stereotactic radiosurgery, fractionated conventional radiotherapy, fractionated stereotactic radiotherapy and PBT.~~**Combined Therapies**

~~The comparisons of the various modalities have been based on single institution experiences, which have shown excellent tumor control rates of 91-100%. Early experience using PBT for treating vestibular schwannomas demonstrated LC rates of 84-100% but disappointing hearing preservation rates of 33-42%. The authors report that mixed data regarding the ideal hearing preservation therapy, inherent biases in patient selection and differences in outcome analysis have made comparison across radiotherapeutic modalities difficult.~~

~~Combined Therapies~~

No evidence was identified in the clinical literature supporting the combined use of PBT and IMRT in a single treatment plan.

U.S. Food and Drug Administration (FDA)

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**~~proton beam radiation therapy~~ are regulated by the FDA.~~—~~ See the following website for more information (use product code LHN):
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm. (Accessed September 13, 2022~~http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm. (Accessed October 30, 2018~~)

~~CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)~~

~~Medicare does not have a National Coverage Determination (NCD) for Proton Beam Radiation Therapy. Local Coverage Determinations (LCDs) exist; see the LCDs for Proton Beam Radiotherapy and Proton Beam Therapy.~~
~~(Accessed August 29, 2018)~~

References

~~Allen AM, Pawlicki T, Dong L, et al. An evidence based review of proton beam therapy: the report of ASTRO's emerging technology committee. Radiother Oncol. 2012 Apr;103(1):8-11.~~

~~Al-Mefty O, Borba LAB. Skull base chordomas: a management challenge. J Neurosurg. 1997;86:182-189.~~

~~American Academy of Ophthalmology. Preferred Practice Pattern® Guidelines. Age-related macular degeneration. January 2015.~~

American College of Radiology (ACR) ~~website. Proton therapy. May 2013; updated January 25, 2017. Available at: http://www.radiologyinfo.org/en/info.cfm?PG=protonthera&bhcp=1. (Accessed October 30, 2018)~~

~~American College of Radiology (ACR). ACR Appropriateness Criteria. Nonsurgical treatment for locally advanced non-small-cell lung cancer. Last reviewed 2014.~~

~~American College of Radiology (ACR). ACR Appropriateness Criteria® definitive external-beam irradiation in stage T1~~ and ~~T2 prostate cancer. 2013.~~

American Society for Radiation Oncology (ASTRO). **Practice parameter for the performance of proton beam radiation therapy. https://www.acr.org/-/media/ACR/Files/Practice-Parameters/RadOnc.pdf. Revised 2018. (Accessed September 13, 2022)** ~~Model policy. Proton beam therapy. June 2017.~~

American College of Radiology (ACR). Proton therapy. May 2013; updated July 30, 2021. Available at: https://www.radiologyinfo.org/en/info/protonthera. (Accessed September 13, 2022)

American Society for Radiation Oncology (ASTRO). Proton beam therapy for prostate cancer position statement. June 2017. Available at: https://www.astro.org/Daily-Practice/Reimbursement/Model-Policies/Proton-Beam-Therapy-for-Prostate-Cancer-Position-S. (Accessed September 13, 2022)

~~American Society for Radiation Oncology (ASTRO). Proton Beam Therapy for Prostate Cancer Position Statement. Website. 2018.~~

Amichetti M, Amelio D, Cianchetti M, et al. A systematic review of proton therapy in the treatment of chondrosarcoma of the skull base. Neurosurg Rev. 2010 Apr;33(2):155-65.

Amichetti M, Cianchetti M, Amelio D, et al. Proton therapy in chordoma of the base of the skull: a systematic review. Neurosurg Rev. 2009 Oct;32(4):403-16.

Apisarnthanarax S, Barry A, Cao M, et al. External beam radiation therapy for primary liver cancers: An ASTRO Clinical Practice Guideline. Pract Radiat Oncol. 2022 Jan-Feb;12(1):28-51.

Bekkering GE, Rutjes AW, Vlassov VV, et al. The effectiveness and safety of proton radiation therapy for indications of the eye: a systematic review. Strahlenther Onkol. 2009 Apr;185(4):211-21.

Blomquist E, Engström ER, Borota L, et al. Positive correlation between occlusion rate and nidus size of proton beam treated brain arteriovenous malformations (AVMs). Acta Oncol. 2016;55(1):105-12.

Bradley JA, Dagan R, Ho MW, et al. Initial report of a prospective dosimetric and clinical feasibility trial demonstrates the potential of protons to increase the therapeutic ratio in breast cancer compared with photons. Int J Radiat Oncol Biol Phys. 2016 May 1;95(1):411-21.

Bryant C, Smith TL, Henderson RH, et al. Five-**year biochemical results, toxicity, and patient-reported quality of life after delivery of dose-escalated image guided proton therapy** ~~Year Biochemical Results, Toxicity, and Patient-Reported Quality of Life After Delivery of Dose-Escalated Image Guided Proton Therapy~~ for **prostate cancer** ~~Prostate Cancer~~. Int J Radiat Oncol Biol Phys. 2016 May 1;95(1):422-34.

Bush DA, Do S, Lum S, et al. Partial breast radiation therapy with proton beam: 5-year results with cosmetic outcomes. Int J Radiat Oncol Biol Phys. 2014 Nov 1;90(3):501-5.

Bush DA, McAllister CJ, Loredo LN, et al. Fractionated proton beam radiotherapy for acoustic neuroma. Neurosurgery. 2002;50(2):270-275.

Bush DA, Smith JC, Slater JD, et al. Randomized **clinical trial comparing proton beam radiation therapy**~~Clinical Trial Comparing Proton Beam Radiation Therapy~~ with **transarterial chemoembolization** ~~Transarterial Chemoembolization~~ for **hepatocellular carcinoma: results** ~~Hepatocellular Carcinoma: Results~~ of an **interim analysis** ~~Interim Analysis~~. Int J Radiat Oncol Biol Phys. 2016 May 1;95(1):477-82.

Chan RV, Yonekawa Y, Lane AM, et al. Proton beam irradiation using a light-field technique for the treatment of choroidal hemangiomas. Ophthalmologica. 2010;224(4):209-16.

Chang JY, ~~Verma V, Li M, et al. Proton Beam Radiotherapy and Concurrent Chemotherapy for Unresectable Stage III Non-Small Cell Lung Cancer: Final Results of a Phase 2 Study. JAMA Oncol. 2017 Aug 10; 3(8):e172032.~~

~~Chang JY,~~ Kestin LL, Barriger RB, et al.~~., Expert Panel on Radiation Oncology-Lung.~~ ACR Appropriateness Criteria® nonsurgical treatment for locally advanced non-small-cell lung cancer: good performance status/definitive intent [online publication]. Reston (VA): American College of Radiology (ACR); 2014.

Chang JY, Verma V, Li M, et al. Proton beam radiotherapy and concurrent chemotherapy for unresectable stage iii non-small cell lung cancer: final results of a phase 2 study. JAMA Oncol. 2017 Aug 10; 3(8): e172032.

Chi A, Chen H, Wen S, et al. Comparison of particle beam therapy and stereotactic body radiotherapy for early-~~-~~stage non-small cell lung cancer: A systematic review and hypothesis-generating meta-analysis. Radiother Oncol. 2017 Jun;123(3):346-354.

Cuaron JJ, Chon B, Tsai H ~~Dionisi F, Widesott L, Lorentini S~~, et al. **Early toxicity in patients treated with postoperative** ~~Is there a role for~~ proton therapy **for locally advanced breast cancer. Int J** Radiat ~~in the treatment of hepatocellular carcinoma? A systematic review. Radiother~~ Oncol **Biol Phys. 2015 Jun** ~~. 2014 Apr;111~~(1**;92(2):284-91**~~):1-10~~.

DeCesaris CM, Rice SR, Bentzen SM, et al. Quantification of acute skin toxicities in patients with breast cancer undergoing adjuvant proton versus photon radiation therapy: a single institutional experience. Int J Radiat Oncol Biol Phys. 2019 Aug 1;104(5):1084-1090.

Eastham JA, Auffenberg GB, Barocas DA et al: Clinically localized prostate cancer: AUA/ASTRO guideline. Part I,II, and III. https://www.auanet.org/guidelines-and-quality/guidelines/clinically-localized-prostate-cancer-aua/astro-guideline-2022 . Accessed September 22, 2022.

ECRI. Proton beam therapy for localized prostate cancer. Plymouth Meeting (PA): ECRI; 2022 Jun. (Clinical Evidence Assessment).

ECRI Institute. **Proton Beam Radiation Therapy Systems for Cancer. Plymouth Meeting (PA): ECRI Institute; 2017 May 01. (**~~Health~~ Technology Forecast**).**

El Sayed I, Trifiletti DM, Lehrer EJ, et al. Protons versus photons for the treatment of chordoma. Cochrane Database Syst Rev. 2021 Jul 1;7(7):CD013224.

Evans JR, Igwe C, Jackson TL, et al. Radiotherapy for neovascular age-related macular degeneration. Cochrane Database Syst Rev. 2020 Aug 26;8:CD004004 ~~. Proton beam radiation therapy systems for cancer. July 2014. Updated May 2017~~.

Evans JR, Sivagnanavel V, Chong V.~~—~~ Radiotherapy for neovascular age-related macular degeneration. Cochrane Database Syst Rev. 2010 May 12;5:CD004004.

Fang P, Mick R, Deville C, et al. A case-matched study of toxicity outcomes after proton therapy and intensity-modulated radiation therapy for prostate cancer. Cancer. 2015 Apr 1;121(7):1118-27.

Flaxel CJ, Adelman RA, Bailey ST, et al. Age-related macular degeneration Preferred Practice Pattern®. Ophthalmology. 2020 Jan;127(1):P1-P65.

Fok M, Toh S, Easow J, et al. Proton beam therapy in rectal cancer: A systematic review and meta-analysis. Surg Oncol. 2021 Sep; 38:101638.

Frau E, Rumen F, Noel G, et al. Low-dose proton beam therapy for circumscribed choroidal hemangiomas. Arch Ophthalmol. 2004 Oct;122(10):1471-5.

Fukuda K, Okumura T, Abei M, et al. Long-term outcomes of proton beam therapy in patients with previously untreated hepatocellular carcinoma. Cancer Sci. 2017 Mar;108(3):497-503.

Germano IM, Sheehan J, Parish J, et al. Congress of Neurological Surgeons systematic review and evidence-based guidelines on the role of radiosurgery and radiation therapy in the management of patients With vestibular schwannomas. Neurosurgery. 2018 Feb 1;82(2): E49-E51.

Halasz LM, Attia A, Bradfield L, et al. Radiation therapy for IDH-mutant grade 2 and grade 3 diffuse glioma: An ASTRO Clinical Practice Guideline. Pract Radiat Oncol. 2022 Sep-Oct;12(5):370-386.

~~Gudjonsson O, Blomquist E, Nyberg G, et al. Stereotactic irradiation of skull base meningiomas with high energy protons. Acta Neurochir (Wien). 1999;141(9):933-940.~~

Harada H, Fuji H, Ono A, et al. Dose escalation study of proton beam therapy with concurrent chemotherapy for stage III non-small cell lung cancer. Cancer Sci. 2016 Jul;107(7):1018-21.

Harsh GR, Thornton AF, Chapman PH, et al. Proton beam stereotactic radiosurgery of vestibular schwannomas. Int J Radiat Oncol Biol Phys. 2002;54(1):35-44.

Hartsell WF, Kapur R, Hartsell SO, et al. Feasibility of proton beam therapy for ocular melanoma using a novel 3d treatment planning technique. Int J Radiat Oncol Biol Phys. 2016 May 1;95(1):353-9.

Hattangadi JA, Chapman PH, Bussière MR, et al. Planned two-fraction proton beam stereotactic radiosurgery for high-risk inoperable cerebral arteriovenous malformations. Int J Radiat Oncol Biol Phys. 2012 Jun 1;83(2):533-41.

Hattangadi-Gluth JA, Chapman PH, Kim D, et al. Single-fraction proton beam stereotactic radiosurgery for cerebral arteriovenous malformations. Int J Radiat Oncol Biol Phys. 2014 Jun 1;89(2):338-46.

Hayes, Inc. Hayes **Evidence Analysis Research Brief.** ~~Directory.~~ Proton **beam therapy** ~~Beam Therapy~~ for **head and neck cancer.**~~Non-Small Cell Lung Cancer.~~ Lansdale, PA: Hayes, Inc. **October 30, 2019. Updated December 20, 2021**~~January 2018~~.

Hayes, Inc. Hayes **Health Technology Assessment.**~~Search and Summary.~~ Proton **beam therapy** ~~Beam Therapy~~ for **esophageal adenocarcinoma.**~~Treatment of Neck Cancers.~~ Lansdale, PA: Hayes, Inc.; **October 21, 2022.** ~~December 2016. Archived January 2018.~~

Hayes, Inc. Hayes **Health Technology Assessment.** ~~Directory.~~ Proton beam therapy for prostate cancer. Lansdale, PA: Hayes, Inc.; **March 4, 2020.**~~June 2016.~~ Updated **February 14, 2022.**

Hayes, Inc. Hayes Health Technology Assessment. Proton beam therapy for treatment of chordoma and chondrosarcoma of the skull base. Lansdale, PA: Hayes, Inc.; December 31, 2019. Updated January 19, 2022 ~~May 2018~~.

Henderson RH, Bryant C, Hoppe BS, et al. Five-year outcomes from a prospective trial of image-guided accelerated hypofractionated proton therapy for prostate cancer. Acta Oncol. 2017 Jul;56(7):963-970.

Hocht S, Wachtlin J, Bechrakis NE, et al. Proton or photon irradiation for hemangiomas of the choroid? A retrospective comparison. Int J Radiat Oncol Biol Phys. 2006 Oct 1;66(2):345-51.

~~Holliday EB, Frank SJ. Proton radiation therapy for head and neck cancer: a review of the clinical experience to date. Int J Radiat Oncol Biol Phys. 2014 Jun 1;89(2):292-302.~~

Hong TS, Ryan DP, Blaszkowsky LS, et al. Phase I study of preoperative short-course chemoradiation with proton beam therapy and capecitabine for resectable pancreatic ductal adenocarcinoma of the head. Int J Radiat Oncol Biol Phys. 2011 Jan 1;79(1):151-7.

Hong TS, Ryan DP, Borger DR, et al. A phase 1/2 and biomarker study of preoperative short course chemoradiation with proton beam therapy and capecitabine followed by early surgery for resectable pancreatic ductal adenocarcinoma. Int J Radiat Oncol Biol Phys. 2014 Jul 15;89(4):830-8.

Hong TS, Wo JY, Yeap BY, et al. **Multi-institutional phase ii study of high-dose hypofractionated proton beam therapy in patients with localized, unresectable hepatocellular carcinoma and intrahepatic cholangiocarcinoma.** ~~Multi-Institutional Phase II Study of High-Dose Hypofractionated Proton Beam Therapy in Patients With Localized, Unresectable Hepatocellular Carcinoma and Intrahepatic Cholangiocarcinoma.~~ J Clin Oncol. 2016 Feb 10;34(5):460-8.

Hoppe BS, Flampouri S, Lynch J ~~Hug EB, Fitzek MM, Liebsch NJ~~, et al. **Improving the therapeutic ratio in Hodgkin lymphoma through the use** ~~Locally challenging osteo- and chondrogenic tumors~~ of ~~the axial skeleton: results of combined~~ proton **therapy. Oncology (Williston Park). 2012 May;26(5):456-9, 462-5.**

Horn S, Fournier-Bidoz N, Pernin V, et al. Comparison of passive-beam proton therapy, helical tomotherapy and 3D conformal ~~and photon~~ radiation therapy **in Hodgkin's lymphoma female patients receiving involved-field or involved site radiation therapy. Cancer Radiother. 2016 Apr;20(2):98-103.**

Indelicato DJ, Rotondo RL, Begosh-Mayne D, et al. A prospective outcomes study of proton therapy for chordomas and chondrosarcomas of the spine. ~~using three-dimensional treatment planning.~~ Int J Radiat Oncol Biol Phys. **2016 May 1;95(1):297-303** ~~1995;31(3):467-476~~.

Kabolizadeh P, Chen YL, Liebsch N, et al. Updated **outcome** ~~Outcome~~ and **analysis** ~~Analysis~~ of **tumor response** ~~Tumor Response~~ in **mobile spine** ~~Mobile Spine~~ and **sacral chordoma treated with definitive high-dose photon/proton radiation therapy** ~~Sacral Chordoma Treated With Definitive High-Dose Photon/Proton Radiation Therapy~~. Int J Radiat Oncol Biol Phys. 2017 Feb 1;97(2):254-262.

Kagei K, Tokuuye K, Okumura T, et al. Long-term results of proton beam therapy for carcinoma of the uterine cervix. Int J Radiat Oncol Biol Phys. 2003;55(5):1265-1271.

Kim S, Shen S, Moore DF, et al. Late gastrointestinal toxicities following radiation therapy for prostate cancer. Eur Urol. 2011 Nov;60(5):908-16.

Kim TH, Koh YH, Kim BH, et al. Proton beam radiotherapy vs. radiofrequency ablation for recurrent hepatocellular carcinoma: A randomized phase III trial. J Hepatol. 2021 Mar;74(3):603-612.

Kim TH, Lee WJ, Woo SM, et al. Effectiveness and safety of simultaneous integrated boost-proton beam therapy for localized pancreatic cancer. Technol Cancer Res Treat. 2018 Jan 1;17:1533033818783879.

König L, Bougatf N, Hörner-Rieber J, et al. Consolidative mediastinal irradiation of malignant lymphoma using active scanning proton beams: clinical outcome and dosimetric comparison. Strahlenther Onkol. 2019 Jul;195(7):677-687.

Lee A, Kitpanit S, Chilov M, et al. A systematic review of proton therapy for the management of nasopharyngeal cancer. Int J Part Ther. 2021 Jun 25;8(1):119-130.

~~Kjellberg RN. Stereotactic Bragg peak proton beam radiosurgery for cerebral arteriovenous malformations. Ann Clin Res. 1986;18:17-19.~~

~~Kouri BE, Abrams RA, Al-Refaie WB, et al. ACR Appropriateness Criteria® radiologic management of hepatic malignancy. Reston (VA): American College of Radiology (ACR); 2015. 14 p.~~

Louisiana Department of Health Medicaid Provider Manual. Chapter Twenty-five of the Hospital Services Manual. Issued May 6, 2022. https://www.lamedicaid.com/provweb1/Providermanuals/manuals/Hosp/Hosp.pdf. Accessed January 18, 2023.

Levy-Gabriel C, Rouic LL, Plancher C, et al. Long-term results of low-dose proton beam therapy for circumscribed choroidal hemangiomas. Retina. 2009 Feb;29(2):170-5.

Liao **Z**~~ZX~~, Lee JJ, Komaki R, et al. Bayesian **adaptive randomization** ~~randomized~~ trial **of passive scattering proton therapy and** ~~comparing~~ intensity-~~-~~modulated **photon radiotherapy** ~~radiation therapy versus passively scattered proton therapy~~ for locally advanced non-small-~~-~~cell lung cancer. ~~J Clin Oncol 34, 2016 (suppl; abstr 8500).~~

~~Liao Z, Lee JJ, Komaki R, et al. Bayesian Adaptive Randomization Trial of Passive Scattering Proton Therapy and Intensity-Modulated Photon Radiotherapy for Locally Advanced Non-Small-Cell Lung Cancer.~~ J Clin Oncol. 2018 Jan 2:JCO2017740720.

Lin SH, **Hobbs BP, Verma V** ~~Komaki R, Liao Z~~, et al. **Randomized phase IIB trial of proton** ~~Proton~~ beam therapy **versus intensity-modulated radiation therapy for locally advanced esophageal cancer. J Clin Oncol. 2020 May 10;38(14):1569-1579.**

Lin SH, Merrell KW, Shen J, et al. Multi-institutional analysis of radiation modality use and **postoperative outcomes of neoadjuvant chemoradiation** ~~concurrent chemotherapy~~ for esophageal cancer. **Radiother** ~~Int J Radiat~~ Oncol**. 2017 Jun;123** ~~Biol Phys. 2012 Jul 1;83~~(3):**376-381** ~~e345-51~~.

Mathis T, Maschi C, Mosci C, et al . Comparative effectiveness of proton beam versus photodynamic therapy to spare the vision in circumscribed choroidal hemangioma. Retina. 2021 Feb 1;41(2):277-286.

~~McAllister B, Archambeau JO, Nguyen MC, et al. Proton therapy for pediatric cranial tumors: preliminary report on treatment and disease related morbidities. Int J Radiat Oncol Biol Phys. 1997;39:455-460.~~

Mendenhall NP, Hoppe BS, Nichols RC, et al. Five-year outcomes from 3 prospective trials of image-guided proton therapy for prostate cancer. Int J Radiat Oncol Biol Phys. 2014 Mar 1;88(3):596-602.

Miyanaga N, Akaza H, Okumura T, et al. A bladder preservation regimen using intra-arterial chemotherapy and radiotherapy for invasive bladder cancer: a prospective study. Int J Urol. 2000;7(2):41-48.

Mizumoto M, Sugahara S, Nakayama H, et al. Clinical results of proton-beam therapy for locoregionally advanced esophageal cancer. Strahlenther Onkol. 2010 Sep;186(9):482-8.

Mizumoto M, Sugahara S, Okumura T, et al. Hyperfractionated concomitant boost proton beam therapy for esophageal carcinoma. Int J Radiat Oncol Biol Phys. 2011 Nov 15;81(4):e601-6.

Mohr JP, Parides MK, Stapf C, et al. Medical management with or without interventional therapy for unruptured brain arteriovenous malformations (ARUBA): a multicentre, non-blinded, randomised trial. Lancet 2013;383(9917):614-21.

Murphy ES, Suh JH. Radiotherapy for vestibular schwannomas: a critical review. Int J Radiat Oncol Biol Phys. 2011 Mar 15;79(4):985-97.

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. B-cell **lymphoma. V5.2022** ~~Lymphoma. v4.2018~~.

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. ~~–~~Bladder **cancer. V2.2022.** ~~Cancer. v5.2018~~

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. ~~–~~Bone **cancer. V1.2023** ~~Cancer. v1.2019~~.

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Breast **cancer. V2.2022** ~~Cancer. V1.2018~~.

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. ~~–~~Central **nervous system cancers. V2.2022** ~~Nervous System Cancers. v1.2018~~.

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Cervical **cancer. V1.2022** ~~Cancer. v1.2019~~.

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Esophageal and **esophagogastric junction cancers. V4.2022** ~~Esophagogastric Junction Cancers. V24.2018~~.

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Gastric **cancer. V2.2022** ~~Cancer. v2.2018~~.

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Head and neck cancers. V2.2022.

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Hepatobiliary cancers. V2.2022.

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Hodgkin lymphoma. V2.2022.

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Melanoma: cutaneous. V3.2022.

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Melanoma: uveal. V2.2022.

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. **Non-small cell lung cancer. V4.2022** ~~Head and Neck Cancers. v2.2018~~.

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. **Ovarian cancer including fallopian tube cancer and primary peritoneal cancer. V4.2022** ~~Hepatobiliary Cancers. V42.2018~~.

~~National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Hodgkin Lymphoma. v3.2018.~~

~~National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Non-Small Cell Lung Cancer.v6.2018.~~

~~National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer. v2.2018.~~

~~National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Pancreatic Adenocarcinoma. v2.2018.~~

~~National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Primary Cutaneous B-cell Lymphoma. v2.2018.~~

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. **Pancreatic adenocarcinoma. V1.2022** ~~Prostate Cancer. v4.2018~~.

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. **Primary cutaneous lymphoma. V2.2022** ~~Small Cell Lung Cancer. v2.2018~~.

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. **Prostate cancer. V4.2022** ~~T-cell Lymphoma. v5.2018~~.

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. **Small cell lung cancer. V1.2023** ~~Uterine Neoplasms. v2.2018~~.

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. **T-cell lymphoma. V2.2022** ~~Uveal Melanoma. v1.2018~~.

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Uterine neoplasms. V1.2022.

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Vulvar cancer. V2.2022.

Noel G, Habrand JL, Mammar H, ~~—~~et al. Highly conformal therapy using proton component in the management of meningiomas. Preliminary experience of the Centre de Protontherapie d'Orsay. Strahlenther Onkol. 2002 Sep;178(9):480-5.

~~Ohri N, Dicker AP, Showalter TN. Late toxicity rates following definitive radiotherapy for prostate cancer. Can J Urol. 2012 Aug;19(4):6373-80.~~

Oshiro Y, Okumura T, Kurishima K, et al. High-dose concurrent chemo-proton therapy for Stage III NSCLC: preliminary results of a Phase II study. J Radiat Res. 2014 Sep;55(5):959-65.

Parzen JS, Hartsell W, Chang J, et al. Hypofractionated proton beam radiotherapy in patients with unresectable liver tumors: multi-institutional prospective results from the Proton Collaborative Group. Radiat Oncol. 2020 Nov 4;15(1):255.

~~Patel SH, Wang Z, Wong WW, et al. Charged particle therapy versus photon therapy for paranasal sinus and nasal cavity malignant diseases: a systematic review and meta-analysis. Lancet Oncol. Aug;15(9):1027-38.~~

Petr J, Platzek I, Hofheinz F, et al.~~—~~ Photon vs. proton radiochemotherapy: Effects on brain tissue volume and perfusion. Radiother Oncol. 2018 Jul;128(1):121-127.

Pijls-Johannesma M, Grutters JP, Verhaegen F, et al. Do we have enough evidence to implement particle therapy as standard treatment in lung cancer? A systematic literature review. Oncologist. 2010;15(1):93-103.

~~Qi WX, Fu S, Zhang Q, et al. Charged particle therapy versus photon therapy for patients with hepatocellular carcinoma: a systematic review and meta-analysis. Radiother Oncol. 2015 Mar;114(3):289-95.~~

~~Ramaekers BL, Pijls-Johannesma M, Joore MA, et al. Systematic review and meta-analysis of radiotherapy in various head and neck cancers: comparing photons, carbon-ions and protons. Cancer Treat Rev. 2011 May;37(3):185-201.~~

Ross J, Al-Shahi Salman R. Interventions for treating brain arteriovenous malformations in adults. Cochrane Database Syst Rev. 2010 Jul 7;7:CD003436.

Sachsman S, Flampouri S, Li Z, et al. Proton therapy in the management of non-Hodgkin lymphoma. Leuk ~~Saba NF, Salama JK, Beitler JJ, et al. ACR Appropriateness Criteria® nasopharyngeal carcinoma. Reston (VA): American College of Radiology (ACR); 2015.~~

~~Sanda MG, Chen RC, Crispino T, et al. Clinically Localized Prostate Cancer: AUA/ASTRO/SUO Guideline. Presentations from the 2017 AUA Annual Meeting. http://www.auanet.org/guidelines/clinically-localized-prostate-cancer-new-(aua/astro/suo-guideline-2017). Accessed October 30, 2018.~~

Lymphoma. 2015;56(9):2608-12.

Santos PMG, Barsky AR, Hwang WT, et al. Comparative toxicity outcomes of proton-beam therapy versus intensity-modulated radiotherapy for prostate cancer in the postoperative setting. Cancer. 2019 Dec 1;125(23):4278-4293.

Sejpal S, Komaki R, Tsao A, et al. Early findings on toxicity of proton beam therapy with concurrent chemotherapy for non-small cell lung cancer. Cancer. 2011 Jul 1;117(13):3004-13.

Sheets NC, Goldin GH, Meyer AM, et al. Intensity-modulated radiation therapy, proton therapy, or conformal radiation therapy and morbidity and disease control in localized prostate cancer. JAMA. 2012 Apr 18;307(15):1611-20.

Shih HA, Sherman JC, Nachtigall LB, et al. Proton therapy for low-grade gliomas: Results from a prospective trial. Cancer. 2015 May 15;121(10):1712-9.

~~Suit HD, Goitein M, Munzenrider JE, et al. Definitive radiation therapy for chordoma and chondrosarcoma of base of skull and cervical spine. J Neurosurg. 1982;56:377-385.~~

Takagi M, Demizu Y, Terashima K, et al. Long-term outcomes in patients treated with proton therapy for localized prostate cancer. Cancer Med. 2017 Oct;6(10):2234-2243.

Takaoka EI, Miyazaki J, Ishikawa H, et al. Long-term single-institute experience with trimodal bladder-preserving therapy with proton beam therapy for muscle-invasive bladder cancer. Jpn J Clin Oncol. 2017 Jan;47(1):67-73.

Takayama K, Nakamura T, Takada A, et al. Treatment results of alternating chemoradiotherapy followed by proton beam therapy boost combined with intra-arterial infusion chemotherapy for stage III-IVB tongue cancer. J Cancer Res Clin Oncol. 2016 Mar;142(3):659-67.

Terashima K, Demizu Y, Hashimoto N, et al. A phase I/II study of gemcitabine-concurrent proton radiotherapy for locally advanced pancreatic cancer without distant metastasis. Radiother Oncol. 2012 Apr;103(1):25-31.

Vapiwala N, Wong JK, Handorf E, et al. A pooled toxicity analysis of moderately hypofractionated proton beam therapy and intensity modulated radiation therapy in early-stage prostate cancer patients ~~van de Water TA, Bijl HP, Schilstra C, et al. The potential benefit of radiotherapy with protons in head and neck cancer with respect to normal tissue sparing: a systematic review of literature. Oncologist. 2011;16(3):366-77.~~

. Int J Radiat Oncol Biol Phys. 2021 Jul 15;110(4):1082-1089.

Verma V, Iftekaruddin Z, Badar N, et al. Proton beam radiotherapy as part of comprehensive regional nodal irradiation for locally advanced breast cancer. Radiother Oncol. 2017 May;123(2):294-298.

Verma V, Lin SH, Simone CB 2nd, et al. Clinical outcomes and toxicities of proton radiotherapy for gastrointestinal neoplasms: a systematic review. J Gastrointest Oncol. **2016b** ~~2016~~ Aug;7(4):644-64.

Verma V, Mehta MP. Clinical outcomes of proton radiotherapy for uveal melanoma. Clin Oncol (R Coll Radiol). 2016c Aug;28(8):e17-27.

Verma V, Shah C, Mehta MP. Clinical outcomes and toxicity of proton radiotherapy for breast cancer. Clin Breast Cancer. **2016a** ~~2016~~ Jun;16(3):145-54.

~~Vernimmen FJ, Harris JK, Wilson JA, et al. Stereotactic proton beam therapy of skull base meningiomas. Int J Radiat Oncol Biol Phys. 2001;49(1):99-105.~~

Wang J, Wei C, Tucker SL, et al. Predictors of postoperative complications after trimodality therapy for esophageal cancer. Int J Radiat Oncol Biol Phys. **2013a** ~~2013~~ Aug 1;86(5):885-91.

Xi ~~Wang Z, Nabhan~~ M, **Xu C, Liao Z** ~~Schild SE~~, et al. **Comparative outcomes after definitive chemoradiotherapy using proton beam therapy versus intensity modulated** ~~Charged particle~~ radiation therapy for **esophageal cancer** ~~uveal melanoma~~: a **retrospective, single-institutional** ~~systematic review and meta-~~analysis. Int J Radiat Oncol Biol Phys. **2017 Nov** ~~2013 May~~ 1;~~86(1):18-26.~~

~~Wenkel E, Thornton AF, Finkelstein D, et al. Benign meningioma: partially resected, biopsied, and recurrent intracranial tumors treated with combined proton and photon radiotherapy. Int J Radiat Oncol Biol Phys.~~ **99(3):667-676** ~~2000;48(5):1363~~.

Yu JB, Soulos PR, Herrin J, et al. Proton versus intensity-modulated radiotherapy for prostate cancer: patterns of care and early toxicity. J Natl Cancer Inst. 2013 Jan 2;105(1):25-32.

Zambarakji HJ~~,.,~~ Lane~~,~~ AM, Ezra E, et al. Proton beam irradiation for neovascular age-related macular degeneration. Ophthalmology. 2006;113(11):2012-9.

~~Zenda S, Akimoto T, Mizumoto M, et al. Phase II study of proton beam therapy as a nonsurgical approach for mucosal melanoma of the nasal cavity or para-nasal sinuses. Radiother Oncol. 2016 Feb;118(2):267-71.~~

~~Zietman AL, Bae K, Slater JD, et al. Randomized trial comparing conventional-dose with high-dose conformal radiation therapy in early-stage adenocarcinoma of the prostate: long-term results from Proton Radiation Oncology Group/American College of Radiology 95-09. J Clin Oncol. 2010 Mar 1;28(7):1106-11.~~

Zhou J, Yang B, Wang X, et al. Comparison of the **effectiveness** ~~Effectiveness~~ of **radiotherapy** ~~Radiotherapy~~ with **photons** ~~Photons~~ and **particles for chordoma after surgery: a meta-analysis.** ~~Particles for Chordoma After Surgery: A Meta-Analysis.~~ World Neurosurg. 2018 Sep;117:46-53.

Zuurbier SM, Al-Shahi Salman R. Interventions for treating brain arteriovenous malformations in adults. Cochrane Database Syst Rev. 2019 Sep 10;9(9):CD003436.

Policy History/Revision Information

Instructions for Use

This Medical Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the federal, state or contractual requirements for benefit plan coverage must be referenced as the terms of the federal, state or contractual requirements for benefit plan coverage may differ from the standard benefit plan. In the event of a conflict, the federal, state or contractual requirements for benefit plan coverage govern. Before using this policy, please check the federal, state or contractual requirements for benefit plan coverage. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Policy is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the InterQual® criteria, to assist us in administering health benefits. The UnitedHealthcare Medical Policies 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.