Proton Beam Radiation Therapy (for Kentucky Only)

Policy Number: CS105KY.07
Effective Date: May 1, 2023

Instructions for Use

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Related Policy

- Intensity-Modulated Radiation Therapy (for Kentucky Only)

Application

This Medical Policy only applies to the state of Kentucky.

Coverage Rationale

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

Proton beam radiation therapy is proven and medically necessary under certain circumstances. For medical necessity clinical coverage criteria, refer to the InterQual® CP: Procedures, Proton Beam Radiotherapy (PBRT).

Click here to view the InterQual® criteria.

PBT and IMRT are proven and considered clinically equivalent for treating prostate cancer. As a result, the principles of medical necessity will be applied.

PBT is unproven and not medically necessary due to insufficient evidence of efficacy for treating some indications, including but not limited to:

- Age related macular degeneration (AMD)
- Bladder cancer
- Brain and spinal cord tumors
- Breast cancer
- Choroidal hemangioma
- Esophageal cancer
- Gynecologic cancers
- Head and neck tumors not addressed in the InterQual® criteria
- Lung cancer
- Lymphomas

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

Definitions

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

Applicable Codes

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

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

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

Diagnosis Code	Description
C11.0	Malignant neoplasm of superior wall of nasopharynx
C11.1	Malignant neoplasm of posterior wall of nasopharynx
C11.2	Malignant neoplasm of lateral wall of nasopharynx
C11.3	Malignant neoplasm of anterior wall of nasopharynx
C11.8	Malignant neoplasm of overlapping sites of nasopharynx

Diagnosis Code	Description
C11.9	Malignant neoplasm of nasopharynx, unspecified
C22.0	Liver cell carcinoma
C30.0	Malignant neoplasm of nasal cavity
C31.0	Malignant neoplasm of maxillary sinus
C31.1	Malignant neoplasm of ethmoidal sinus
C31.2	Malignant neoplasm of frontal sinus
C31.3	Malignant neoplasm of sphenoid sinus
C31.8	Malignant neoplasm of overlapping sites of accessory sinuses
C31.9	Malignant neoplasm of accessory sinus, unspecified
C41.0	Malignant neoplasm of bones of skull and face
C61	Malignant neoplasm of prostate
C69.0	Malignant neoplasm of conjunctiva
C69.00	Malignant neoplasm of unspecified conjunctiva
C69.01	Malignant neoplasm of right conjunctiva
C69.02	Malignant neoplasm of left conjunctiva
C69.1	Malignant neoplasm of cornea
C69.10	Malignant neoplasm of unspecified cornea
C69.11	Malignant neoplasm of right cornea
C69.12	Malignant neoplasm of left cornea
C69.20	Malignant neoplasm of unspecified retina
C69.21	Malignant neoplasm of right retina
C69.22	Malignant neoplasm of left retina
C69.30	Malignant neoplasm of unspecified choroid
C69.31	Malignant neoplasm of right choroid
C69.32	Malignant neoplasm of left choroid
C69.40	Malignant neoplasm of unspecified ciliary body
C69.41	Malignant neoplasm of right ciliary body
C69.42	Malignant neoplasm of left ciliary body
C69.50	Malignant neoplasm of unspecified lacrimal gland and duct
C69.51	Malignant neoplasm of right lacrimal gland and duct
C69.52	Malignant neoplasm of left lacrimal gland and duct
C69.6	Malignant neoplasm of orbit
C69.60	Malignant neoplasm of unspecified orbit
C69.61	Malignant neoplasm of right orbit
C69.62	Malignant neoplasm of left orbit
C69.8	Malignant neoplasm of overlapping sites of eye and adnexa
C69.80	Malignant neoplasm of overlapping sites of unspecified eye and adnexa
C69.81	Malignant neoplasm of overlapping sites of right eye and adnexa
C69.82	Malignant neoplasm of overlapping sites of left eye and adnexa
C69.9	Malignant neoplasm of unspecified site of eye
C69.90	Malignant neoplasm of unspecified site of unspecified eye
C69.91	Malignant neoplasm of unspecified site of right eye

Diagnosis Code	Description
C69.92	Malignant neoplasm of unspecified site of left eye
D09.20	Carcinoma in situ of unspecified eye
D09.21	Carcinoma in situ of right eye
D09.22	Carcinoma in situ of left eye
D14.0	Benign neoplasm of middle ear, nasal cavity and accessory sinuses
D16.4	Benign neoplasm of bones of skull and face
D31.30	Benign neoplasm of unspecified choroid
D31.31	Benign neoplasm of right choroid
D31.32	Benign neoplasm of left choroid
D31.40	Benign neoplasm of unspecified ciliary body
D31.41	Benign neoplasm of right ciliary body
D31.42	Benign neoplasm of left ciliary body
Q28.2	Arteriovenous malformation of cerebral vessels
Q28.3	Other malformations of cerebral vessels

Description of Services

Unlike other types of radiation therapy (RT) that use x-rays or photons to destroy cancer cells, proton beam therapy (PBT) uses a beam of special particles (protons) that carry a positive charge. There is no significant difference in the biological effects of protons versus photons; however, protons can deliver a dose of radiation in a more confined way to the tumor tissue than photons. After they enter the body, protons release most of their energy within the tumor region and, unlike photons, deliver only a minimal dose beyond the tumor boundaries (American College of Radiology (ACR) website, updated 2021).

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

Clinical Evidence

Unproven Indications

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

Age-Related Macular Degeneration (AMD)

Evans et al. (2020) updated a previously conducted systematic review (Evans, 2010) that examined the effects of radiotherapy on neovascular AMD. A search was conducted using CENTRAL, MEDLINE, Embase, LILACS and three trials registers for randomized controlled trials in which radiotherapy was compared to another treatment, sham treatment, low dosage irradiation or no treatment in people with choroidal neovascularization (CNV) secondary to AMD. Outcomes included best-corrected visual acuity (BCVA) (loss of three or more lines, change in visual acuity), contrast sensitivity, new vessel growth, quality of life (QOL) and adverse effects at any time point. A total of eighteen studies (n = 2,430 people, 2,432 eyes) were included, and the radiation therapy with dosages ranging from 7.5 to 24 Gy. Three of these studies investigated brachytherapy (plaque and epimacular), the rest were studies of external beam radiotherapy (EBM) including one trial of stereotactic radiotherapy. The authors concluded that the evidence is uncertain regarding the use of radiotherapy for neovascular AMD. They stated that: 1) most studies took place before the routine use of anti-VEGF, and before the development of modern radiotherapy techniques such as stereotactic radiotherapy; 2) visual outcomes with epimacular brachytherapy are likely to be worse, with an increased risk of adverse events, probably related to vitrectomy; 3) the role of stereotactic radiotherapy combined with anti-VEGF is

currently uncertain; and 4) further research on radiotherapy for neovascular AMD may not be justified until current ongoing studies have reported their results.

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

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

Clinical Practice Guidelines

American Academy of Ophthalmology (AAO)

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

Bladder Cancer

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).

Brain and Spinal Cord Tumors

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

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

Indelicato et al. (2016) conducted descriptive analysis using data from a single-institution. In this prospective case series study, researchers sought to evaluate the effectiveness of definitive or adjuvant external beam proton therapy in patients with chordomas and chondrosarcomas of the spine. Outcomes of interest included distant metastases (DM), OS, cause-specific survival, local control (LC) and disease-free survival (DFS). A total of 51 patients participated with a median age of 58 years (range, 22-83 years) and median follow-up of 3.7 years (range, 0.3-7.7 years). There were 34 patients with chordomas, and seventeen patients with chondrosarcomas, which were all grade 2 or higher. The anatomic distribution was as follows: sacrum (n = 21), cervical spine (n = 20), and thoracolumbar spine (n = 10). The median dose of radiation therapy was 70.2 Gy (range, 64.2-75.6 Gy). The 4-year LC, freedom from distant metastases, DFS, cause-specific survival, and OS rates were 58%, 86%, 57%, 72%, and 72%, respectively. A total of 25 patients experienced disease recurrence: eighteen local recurrences, six local and distant recurrences, and 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 patients with meningioma to evaluate the efficacy and the tolerance of an escalated dose of external conformal fractionated RT combining photons and protons. Five patients presented a histologically atypical or malignant meningioma, twelve patients had a benign tumor that was recurrent or rapidly progressive. In two cases, RT was administered in the initial course of the disease and in fifteen cases at the time of relapse. A highly conformal approach was used combining high-energy photons and protons for approximately 2/3 and 1/3 of the total dose. The median total dose delivered within gross tumor volume was 61 CGE (25-69). Median follow-up was 37 months (17-60). The 4-year LC and OS rates were 87.5 +/- 12% and 88.9 +/- 11%, respectively. Radiologically, there were eleven stable diseases and 5 partial responses. The authors concluded that in both benign and more aggressive meningiomas, the combination of conformal photons and protons with a dose escalated by 10-15% offers clinical improvements in most patients as well as radiological long-term stabilization. Limitations of this study include small sample size and study design.

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

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 organs at risk, toxicities observed with its use demonstrates the need for randomized controlled trials comparing PBT to other radiation modalities.

Bradley et al. (2016) conducted a prospective case series study to evaluate the clinical feasibility and potential benefits of PBT in breast cancer patients who were at risk for regional nodal disease. In this pilot study, the primary endpoint was cardiac V5, testing the hypothesis that PBT could reduce the volume of the heart receiving 5 Gy by ≥ 50% when compared to CRT. The secondary endpoints included acute toxicity and other dosimetric parameters of target coverage and exposure to at-risk organs. PBT and CRT plans, targeting the regional nodes, were created for each patient. Patients were evaluated weekly while on RT, 4 weeks after RT was completed and at 6-month intervals thereafter. Toxicity was recorded using the Common Terminology Criteria for Adverse Events (CTCAE, v4.0). A total of 18 women enrolled with a median age of 51.8 years (range, 42–73 years) and a median follow-up period of 20 months (range, 2–31 months). Ten of the women received only PBT and 8 received combination therapy of PBT and photon beam RT. All patients had improved heart and lung dose with PBT. The primary endpoint, which was to determine if PBT could reduce cardiac V5 by ≥ 50%, was achieved. Of the nine patients with left-sided breast cancer, the median cardiac dose decreased from 5.9 Gy with CRT to 0.6 Gy with PBT (p = 0.004). In patients with right-sided breast cancer, the median cardiac dose decreased from 2.9 Gy with CRT to 0.5 Gy with PBT (p = 0.004). No patients developed grade 4 + toxicities. Four (22%) patients developed grade 3 dermatitis and of these, 3 were treated with PBT and 1 was treated with combination PBT and CRT. All of the patients developed grade 2 dermatitis, which resolved within 1 month of the completion of therapy. However, 1 patient developed cellulitis and required a course of antibiotics. Additional acute grade 2 toxicities included: fatigue (n = 6), esophagitis (n = 5), nausea (n = 1) and dyspnea (n = 1). The authors acknowledged that their rate of patients with grade 3 acute skin toxicity was not unexpected given the higher skin dose with PBT and concluded that PBT for regional node irradiation after mastectomy or breast conserving surgery offers a lower cardiac dose particularly for patients with left-sided breast cancer and without grade 4 + toxicities. Limitations of this study include its design, small sample size and higher toxicity rates compared with other forms of RT, e.g., intensity modulated RT.

Verma et al. (2016a) performed a systematic review of clinical outcomes and toxicity of PBT for treating breast cancer. Nine original studies were analyzed, however the types of studies and the volume of patients in those studies were not specifically cited by the authors. Conventionally fractionated breast/chest wall PBT produced grade 1 dermatitis rates of approximately 25% and grade 2 dermatitis in 71%-75%. This is comparable or improved over the published rates for photons. The incidence of esophagitis was decreased if the target coverage was compromised in the medial supraclavicular volume, a finding that echoes previous results with photon RT. From the limited available data, the rate of grade 2 esophagitis ranged from 12% to 29%. Using PBT-based accelerated partial breast irradiation (PBI), the rates of seroma/hematoma and fat necrosis were comparable to those reported in the existing data. Radiation pneumonitis (RP) and rib fractures remain rare. PBT offers the potential to minimize the risk of cardiac events, keeping the mean heart dose at ≤ 1 Gy. However, definitive clinical experiences remain sparse. Results from clinical trials in progress, comparing protons to photons, will further aid in providing conclusions. Limitations to this review included a general lack of data and low number of participants in the available studies.

Cuaron et al. (2015) conducted a single-institution case series study to report dosimetry and early toxicity data in patients with breast cancer. Retrospectively collected data from consecutive patients diagnosed with non-metastatic breast cancer, no prior history of chest wall radiation and treated with PBT postoperatively were studied. Patients with unfavorable cardiopulmonary anatomy were usually referred to this institution. Post-lumpectomy patients with large breast size were not offered treatment due to a higher propensity for day-to-day measurement differences in the target position. Patients were evaluated weekly while

on RT, 4 weeks after RT was completed, and at 12–24 week intervals thereafter. Toxicity was recorded using the Common Terminology Criteria for Adverse Events (CTCAE, v4.0). A total of 30 women were included in the study with a median age of 49 years (range, 29–86 years), cancer staging was as follows: eight had stage II, twenty had stage III and two had chest wall recurrence. The median follow-up was 9.3 months (range, 2.3–18.6 months). With PBT, full coverage of the planned target value was achieved, and it significantly spared the heart, lungs and contralateral breast. Of those with greater than 3 months of follow-up (n = 28), 71.4% developed grade 2 dermatitis and of those, 28.6% experienced moist desquamation. Eight (28.6%) developed grade 2 esophagitis and one developed grade 3 reconstructive complications. The authors concluded that in this series of 30 patients, PBT achieved excellent coverage of the target volume while sparing the heart, lungs, and contralateral breast, that the treatment was well tolerated, and that additional studies assessing long-term outcomes and toxicity are needed. Limitations of this study include its design, exclusion of women with large breast size, and higher toxicity rates compared with other forms of RT, e.g., intensity modulated RT.

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

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

Choroidal Hemangiomas

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

Hocht et al. (2006) conducted a single-center, retrospective study of 44 consecutive patients with choroid hemangiomas treated with photon therapy (n = 19) or proton therapy (n = 25). Outcomes were measured by visual acuity, tumor thickness, resolution of retinal detachment, and post-treatment complications. Mean follow-up was 38.9 months and 26.3 months, and median follow-up was 29 months and 23.7 months for photon and proton patients, respectively. Tumor thickness was greater in the photon group than in the proton group. In the collective groups, 91% were treated successfully, and there was no significant difference in the outcomes between the two groups. The authors concluded that RT is effective in treating choroidal hemangiomas with respect to visual acuity and tumor thickness, but a benefit of proton versus photon therapy could not be detected.

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

Gastrointestinal (GI) Cancers

Fok et al. (2021) conducted a systematic review and meta-analysis that compares dosimetric irradiation of OAR and oncological outcomes for PBT versus conventional photon-based radiotherapy in locally advanced rectal cancer. Eight articles with a total of 127 patients met the inclusion criteria. There was significantly less irradiated small bowel with PBT compared to 3DCRT and IMRT (MD -17.01, CI [-24.06, − 9.96], p < 0.00001 and MD -6.96, CI [-12.99, − 0.94], p = 0.02, respectively). Similar dosimetric results were observed for bladder and pelvic bone marrow.

Three studies reported clinical and oncological results for PBT in recurrent rectal cancer with overall survival reported as 43 %, 68 % and 77.2 %, and one study in primary rectal cancer with 100 % disease free survival. The authors concluded PBT treatment plans resulted significantly less irradiation of OAR for rectal cancer when compared to conventional photon-based radiation therapy. The authors note there are currently no ongoing clinical trials for primary rectal cancer and PBT and more research is required to validated PBTs role in organ preservation without increasing toxicity, complete response rate, and dose escalation. Limitations include small sample size and lack of RCTs.

Verma et al. (2016b) conducted a systematic review to identify studies on PBT and gastrointestinal malignancies. The search included PubMed, EMBASE, and abstracts from meetings of the American Society for Radiation Oncology, Particle Therapy Co-Operative Group, and American Society of Clinical Oncology. A total of 39 original investigations were analyzed. For esophageal cancer, twelve studies were analyzed and several of those reported that PBT resulted in a significant dose reduction to intrathoracic OARs and is associated with reduced toxicity, postoperative complications (POCs) while achieving comparable local control and overall survival. However, for some of the studies, contemporaneous comparison groups were lacking or comparisons were made between PBT and x-ray radiotherapy (XRT), which consisted of either 3D-CRT or IMRT rather than IMRT only. For pancreatic cancer, 5 studies were analyzed. Survival for resected/unresected cases was similar to existing data where IMRT was used and nausea/emesis were numerically lower than what had been reported among patients who received IMRT however, direct head-to-head comparisons were not made. For hepatocellular carcinoma, ten studies were analyzed and these had the strongest evidence to support use of PBT. Those studies reported very low toxicities, and a phase III trial comparing PBT to (TACE) showed a trend toward better LC and PFS with PBT. For cholangiocarcinoma, liver metastases, and retroperitoneal sarcoma, survival and toxicity data is comparable to historical photon controls, and stomach and biliary system/gallbladder cancer studies consisted of case reports and small cohort experiences. The authors concluded that PBT offers the potential of lower toxicities without compromising survival or local control. However, there was limited high quality evidence for select gastrointestinal malignancies and that multi-institution, randomized controlled trials are needed.

Clinical Practice Guidelines

National Comprehensive Cancer Network (NCCN)

NCCN guidelines do not address PBT in the treatment of gastric cancers (NCCN, 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) reported that advanced radiation technologies such as IMRT or PBT significantly reduced postoperative pulmonary and GI complication rates compared to 3D-CRT in EC patients. These results need to be confirmed in prospective studies.

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

Mizumoto et al. (2010) evaluated the efficacy and safety of PBT for locoregionally advanced esophageal cancer. Fifty-one patients were treated using PBT with or without X-rays. All but one had squamous cell carcinoma. Of the 51 patients, 33 received combinations of X-rays and protons as a boost. The other eighteen patients received PBT alone. The overall 5-year actuarial survival rate for the 51 patients was 21.1% and the median survival time was 20.5 months. Of the 51 patients, 40 (78%) showed a complete response within 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% 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 is necessary and cannot be achieved by 3D-CRT. Because data is early and evolving, patients should receive PBT within a clinical trial (NCCN, 2022).

Gynecologic Cancers

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

Several clinical trials are recruiting or in progress studying the use of PBT in multiple types of gynecologic cancer (e.g., cervical, ovarian, and uterine). For more information, go to www.clinicaltrials.gov. (Accessed September 13, 2022)

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)

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. 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).

Seeking to improve LC rate and reduce late AEs, Takayama et al. (2016) evaluated therapeutic results and toxicities of PBT combined with selective intra-arterial infusion chemotherapy (PBT-IACT) in patients with stage III-IVB squamous cell carcinoma of the tongue. Between February 2009 and September 2012, 33 patients were enrolled. After two systemic chemotherapy courses and whole-neck irradiation (36 Gy in 20 fractions), participants were administered concurrent chemoradiotherapy comprising PBT for the primary tumor and the metastatic neck lymph node with weekly retrograde IACT of cisplatin with sodium thiosulfate by continuous infusion. The median follow-up duration was 43 months. The 3-year OS, PFS, LC rate, and regional control rate for the neck were 87%, 74.1%, 86.6%, and 83.9%, respectively. Major acute toxicities > grade 3 included mucositis in 26 cases (79%), neutropenia in seventeen cases (51%), and dermatitis in 11 cases (33%). Late grade 2 osteoradionecrosis was observed in 1 case (3%). The authors concluded that PBT-IACT for stage III-IVB tongue cancer has an acceptable toxicity profile and showed good treatment results, and that this protocol should be considered as a treatment option for locally advanced tongue cancer. This study is limited by the lack of data comparing toxicity to conventional radiation therapy.

Clinical Practice Guidelines

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

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

National Comprehensive Cancer Network (NCCN)

NCCN's HNCs guideline makes no mention of proton beam radiation therapy for cancer of the lip (mucosa), oral cavity, hypopharynx or glottic larynx. The guideline states that use of proton therapy is an active area of investigation, and that proton therapy may be considered when normal tissue constraints cannot be met by photon-based therapy in cancers of the oropharynx, nasopharynx, supraglottic larynx, and salivary glands, as well as mucosal melanoma and other primary tumors of the head and neck (2022). Either IMRT or proton therapy is recommended for maxillary sinus or paranasal/ethmoid sinus tumors to minimize the dose to critical structures (NCCN, 2022).

Lung Cancer

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

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

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

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

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

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

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

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

Clinical Practice Guidelines

American College of Radiology (ACR)

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

National Comprehensive Cancer Network (NCCN)

NCCN guidelines state that advanced technologies such as 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 technologies, such as PBT, may offer significant and clinically relevant advantages in specific instances to spare important OARs and decrease the risk for late, normal tissue damage while still achieving the primary goal of LC. NCCN is silent on the use of PBT in the treatment of primary cutaneous lymphoma (NCCN, 2022-2023).

Pancreatic Cancer

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

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

Combined Therapies

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

U.S. Food and Drug Administration (FDA)

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

Radiation therapy is a procedure and, therefore, is not subject to FDA regulation. However, the accelerators and other equipment used to generate and deliver PBRT are regulated by the FDA. Refer to the following website for more information (use product code LHN): http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm. (Accessed September 13, 2022)

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Policy History/Revision Information

Date	Summary of Changes
05/01/2023	Supporting Information • Updated *Clinical Evidence* and *References* sections to reflect the most current information • Archived previous policy version CS105KY.06

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,

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