

Proton Beam Radiation Therapy (for Kansas Only)

Policy Number: CS105KS.02
Effective Date: August 1, 2025

[Instructions for Use](#)

Table of Contents	Page
Application	1
Coverage Rationale	1
Applicable Codes	1
Description of Services	3
Clinical Evidence	4
U.S. Food and Drug Administration	17
References	17
Policy History/Revision Information	22
Instructions for Use	22

Related Policies

- [Intensity-Modulated Radiation Therapy \(for Kansas Only\)](#)
- [Radiation Therapy: Fractionation, Image-Guidance, and Special Services \(for Kansas Only\)](#)
- [Stereotactic Body Radiation Therapy and Stereotactic Radiosurgery \(for Kansas Only\)](#)

Application

This Medical Policy only applies to the state of Kansas.

Coverage Rationale

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

If medical necessity for prostate cancer cannot be determined using these criteria, note that 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 all other indications including glioma and retroperitoneal sarcoma. However, PBT may be covered for other diagnoses, 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 for the specific individual

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 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

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

Diagnosis Code	Description
C11.0	Malignant neoplasm of superior wall of nasopharynx
C11.1	Malignant neoplasm of posterior wall of nasopharynx
C11.2	Malignant neoplasm of lateral wall of nasopharynx
C11.3	Malignant neoplasm of anterior wall of nasopharynx
C11.8	Malignant neoplasm of overlapping sites of nasopharynx
C11.9	Malignant neoplasm of nasopharynx, unspecified
C22.0	Liver cell carcinoma
C30.0	Malignant neoplasm of nasal cavity
C31.0	Malignant neoplasm of maxillary sinus
C31.1	Malignant neoplasm of ethmoidal sinus
C31.2	Malignant neoplasm of frontal sinus
C31.3	Malignant neoplasm of sphenoid sinus
C31.8	Malignant neoplasm of overlapping sites of accessory sinuses
C31.9	Malignant neoplasm of accessory sinus, unspecified
C41.0	Malignant neoplasm of bones of skull and face
C61	Malignant neoplasm of prostate
C69.0	Malignant neoplasm of conjunctiva
C69.00	Malignant neoplasm of unspecified conjunctiva
C69.01	Malignant neoplasm of right conjunctiva
C69.02	Malignant neoplasm of left conjunctiva
C69.1	Malignant neoplasm of cornea
C69.10	Malignant neoplasm of unspecified cornea

Diagnosis Code	Description
C69.11	Malignant neoplasm of right cornea
C69.12	Malignant neoplasm of left cornea
C69.20	Malignant neoplasm of unspecified retina
C69.21	Malignant neoplasm of right retina
C69.22	Malignant neoplasm of left retina
C69.30	Malignant neoplasm of unspecified choroid
C69.31	Malignant neoplasm of right choroid
C69.32	Malignant neoplasm of left choroid
C69.40	Malignant neoplasm of unspecified ciliary body
C69.41	Malignant neoplasm of right ciliary body
C69.42	Malignant neoplasm of left ciliary body
C69.50	Malignant neoplasm of unspecified lacrimal gland and duct
C69.51	Malignant neoplasm of right lacrimal gland and duct
C69.52	Malignant neoplasm of left lacrimal gland and duct
C69.6	Malignant neoplasm of orbit
C69.60	Malignant neoplasm of unspecified orbit
C69.61	Malignant neoplasm of right orbit
C69.62	Malignant neoplasm of left orbit
C69.8	Malignant neoplasm of overlapping sites of eye and adnexa
C69.80	Malignant neoplasm of overlapping sites of unspecified eye and adnexa
C69.81	Malignant neoplasm of overlapping sites of right eye and adnexa
C69.82	Malignant neoplasm of overlapping sites of left eye and adnexa
C69.9	Malignant neoplasm of unspecified site of eye
C69.90	Malignant neoplasm of unspecified site of unspecified eye
C69.91	Malignant neoplasm of unspecified site of right eye
C69.92	Malignant neoplasm of unspecified site of left eye
D09.20	Carcinoma in situ of unspecified eye
D09.21	Carcinoma in situ of right eye
D09.22	Carcinoma in situ of left eye
D14.0	Benign neoplasm of middle ear, nasal cavity and accessory sinuses
D16.4	Benign neoplasm of bones of skull and face
D31.30	Benign neoplasm of unspecified choroid
D31.31	Benign neoplasm of right choroid
D31.32	Benign neoplasm of left choroid
D31.40	Benign neoplasm of unspecified ciliary body
D31.41	Benign neoplasm of right ciliary body
D31.42	Benign neoplasm of left ciliary body
Q28.2	Arteriovenous malformation of cerebral vessels
Q28.3	Other malformations of cerebral vessels

Description of Services

Unlike other types of radiation therapy (RT) that use X-rays or photons to destroy cancer cells, proton beam therapy (PBT) uses a beam of special particles (protons) that carry a positive charge. There is no significant difference in the

biological effects of protons versus photons; however, protons can deliver a dose of radiation in a more confined way to the tumor tissue than photons. After they enter the body, protons release most of their energy within the tumor region and, unlike photons, deliver only a minimal dose beyond the tumor boundaries [American College of Radiology (ACR) website, updated 2024].

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

Clinical Evidence

Proven Indications

Prostate Cancer

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

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

Vapiwala et al. (2021) conducted a multi-institutional analysis that compared late toxicity profiles of individuals with early-stage prostate cancer treated with moderately hypofractionated PBT and IMRT. The study included subjects (n = 1850) with low- or intermediate-risk biopsy-proven prostate adenocarcinoma treated from 1998 to 2018. The subjects 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 GI toxicity were the primary outcomes. Adjusted toxicity rates were calculated using inverse probability of treatment weighting, accounting for race, NCCN risk group, age, pretreatment International Prostate Symptom Score (GU only), and anticoagulant use (GI only). Of the 1850 subjects included, 1282 had IMRT and 568 had PBT. The majority of subjects 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 individuals 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 individuals 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 individuals remain free from cancer progression for five years or longer after treatment. These results are promising but none of the reviewed studies assessed the efficacy of PBT as the sole or primary therapy for prostate cancer relative to the efficacy of other common methods of RT. Ten of the reviewed studies found that the safety of PBT as sole or primary therapy was usually similar to the safety of other common RT; however, these studies are of low quality since they were retrospective. Moreover, these ten studies do not provide sufficient evidence of comparative safety since they were divided between evaluations of PBT relative to brachytherapy, conformal X-ray therapy, and IMRT. The other available studies do not provide clear evidence concerning the relative safety and efficacy of PBT for prostate cancer since these other studies evaluated it as an adjunct to X-ray therapy or did not compare it with another common RT. Additional well-designed studies are needed to establish the clinical role of PBT relative to other widely used therapies for localized prostate

cancer. The 2023 updated annual review included seven newly published studies, however, there was no change in the current rating (2020, updated 2023).

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

Several single-institution studies report favorable clinical outcomes of PBT in prostate cancer. Henderson et al. (2017) reported five-year outcomes of a prospective trial of image-guided accelerated hypofractionated proton therapy (AHPT) for prostate cancer from a single institution. Late radiation adverse events/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 five-year rates of significant ($\geq$ grade 3) late radiation-related GI adverse events/toxicities were 0.5%, and 1.7% for GU adverse events.

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 five-year FFBP rates were 99% for low-risk, 94% for intermediate-risk, and 76% for high-risk individuals. 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 participants with localized prostate cancer who received treatment with IMRT and PBT techniques and similar dose-fractionation schedules. A total of 394 participants were treated with either PBT (n = 181) or IMRT (n = 213). Participants 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 five-year clinical outcomes from three prospective trials of image-guided PBT for prostate cancer conducted at a single institution. From August 2006-September 2007, 211 participants (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. Five-year OS of 93%, 88%, and 86% were reported for low, intermediate, and high-risk participants, respectively. Freedom from biochemical and/or clinical progression rates for the same time period were 99% for both low and intermediate risk and 76% for high-risk participants. There was a single instance of acute grade 3 GU toxicity. One acute grade 3 and two late grade 3 GI events throughout the entire group resulted in a five-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 limited interpretation of the studies and did not allow assessment of PBT outcomes compared to other forms of RT.

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 individuals with specific conditions. The investigators identified individuals who were age 66 and older with prostate cancer and treated with IMRT or PBT. To evaluate toxicity, each individual who received PBT was matched with two individuals who received IMRT based on similar sociodemographic and clinical characteristics. Toxicity was reported at six months post-treatment and included 421 individuals who received PBT matched to 842 individuals who received IMRT, and at twelve months post-treatment and included 314 individuals who received PBT matched to 628 individuals who received IMRT. At six months, GU toxicity was significantly lower in individuals 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, individual 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 individuals were also less likely to receive additional cancer therapy. In a comparison between IMRT and PBT (n = 1,368), IMRT individuals 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 individuals treated with RT are more likely to have procedural interventions for GI toxicities than individuals with conservative management, and individuals treated with PBT therapy experienced greater GI morbidity relative to IMRT individuals. The elevated risk persisted beyond five years.

To further elucidate the clinical advantages and disadvantages between various types of RT used in prostate cancer, additional clinical trials are underway (NCT01617161, NCT00969111 and NCT03561220). For more information, refer to www.clinicaltrials.gov. (Accessed March 20, 2025)

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). Individuals 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 recommended proton therapy as a treatment option for prostate cancer, but states it had 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 for individuals with prostate cancer. 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, 2024).

Unproven Indications

Quality evidence in peer-reviewed medical literature evaluating PBRT 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 RT on neovascular AMD. A search was conducted using CENTRAL, MEDLINE, Embase, LILACS and three trials registers for RCTs in which RT 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 (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 RT with dosages ranging from 7.5 to 24 Gy. Three of these studies investigated brachytherapy (plaque and epimacular), the rest were studies of EBRT including one trial of stereotactic RT. The authors concluded that the evidence is uncertain regarding the use of RT for neovascular AMD. They stated that: 1) most studies took place before the routine use of anti-vascular endothelial growth factor (anti-VEGF), and before the development of modern RT techniques such as stereotactic RT; 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 RT combined with anti-VEGF is currently uncertain; and 4) further research on RT 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 individuals 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 individual 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 individuals with angiographic evidence of classic CNV resulting from AMD and best-corrected visual acuity of 20/320 or better. Participants were assigned randomly (1:1) to receive 16 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 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 participants receiving 16-CGE and 14.8% of participants receiving 24-CGE. The authors concluded that no significant differences in rates of visual loss were found between the two dose groups.

Clinical Practice Guidelines

American Academy of Ophthalmology (AAO)

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

Bladder Cancer

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

Takaoka and colleagues (2017) conducted a retrospective review to assess outcomes, prognostic factors, and toxicities of PBT as a component of trimodal bladder-preserving therapy for muscle-invasive bladder cancer. Trimodal bladder-preserving therapy consisted of maximal transurethral resection of the bladder tumor, small pelvis (conventional) photon radiation, intra-arterial chemotherapy and PBT. Seventy individuals 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 individuals' median age was 65 (range 36-85) years. The median follow-up period was 3.4 years (range 0.6-19.5 years). The five-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% CI 1.1-12; hazard ratio 5.0, 95% CI 1.3-17; $p < 0.05$ for all). As for toxicity, 26 (18%) individuals had grade 3-4 acute hematologic toxicities, and two (3%) individuals had grade 3 late GU toxicity. No individual 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 individuals. 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 participants who received PBT to the small pelvic space following intra-arterial chemotherapy. At five-year follow-up, the bladder was preserved in 76% of participants

and 65% were free of disease. The disease-specific survival rate was 91%. Participants with large and multiple tumors were more at risk of cancer recurrence than participants 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, 2024).

Brain and Spinal Cord Tumors

The systematic review by Goliot et al. (2024) focused on evaluating outcomes and toxicities related to PBT for treating adult-type diffuse gliomas. The review analyzed various studies to compare PBT with conventional RT in terms of survival outcomes, toxicity, and dosimetry. Preclinical studies, study protocols, reviews, case reports, letters, editorials, and meta-analyses were excluded from the review. Twelve studies from 2013 to 2023 were selected, consisting of three prospective and nine retrospective studies. The analysis covered 570 individuals with WHO grade 2-3 gliomas and 240 individuals with glioblastoma or WHO grade 4 gliomas. Proton therapy was found to be comparable to conventional RT in terms of survival outcomes. Its main advantage is the ability to minimize radiation exposure to healthy tissues. The authors concluded PBT provided survival outcomes similar to those of conventional RT for adult diffuse gliomas and may improve treatment tolerance, particularly in terms of neurocognitive function, with most individuals experiencing only grade 1 toxicity. The authors noted a significant limitation of this review is the heavy reliance on retrospective studies; future randomized trials with extended follow-up periods were recommended to validate the therapeutic potential of PBT.

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 individuals diagnosed with glioblastoma undergoing adjuvant conventional (n = 47) or proton (n = 19) RT with temozolomide after tumor resection underwent T1-weighted and arterial spin labeling magnetic resonance imaging. Changes in volume and perfusion before and three to six- months after were compared between therapies. A decrease in gray matter (GM) and white matter (WM) volume was observed in individuals 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 RT individuals, whereas the decrease in proton therapy individuals 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 on imaging and clinical outcomes.

Kabolizadeh et al. (2017) conducted a single-center, retrospective, case series to evaluate LC, OS, disease-specific survival, and distant failure in 40 individuals with unresected chordoma and treated with photon/proton RT. 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 individuals had sacrococcygeal chordoma, and the remaining individuals had mobile spine tumors, which included nine cervical, one thoracic, and three lumbar. Thirty-nine individuals underwent proton therapy only or predominantly proton therapy mixed with photons to limit the radiation dose to adjacent critical normal structures. Only four individuals received either concurrent or neoadjuvant systemic treatments. The median age was 67 years (range, 36-94 years) and median follow-up, after completion of RT, was 50.3 months (range, two–216.4 months). At five-years, LC, OS, disease-specific survival, and distant failure were 85.4%, 81.9%, 89.4%, and 20.2%, respectively. Nineteen individuals had complete sets of regular imaging scans (a total of 84 CT and MRI scans were reviewed) and of those, only four local failures had occurred at 34, 46, 78 and 82 months after treatment. The authors concluded that their results supported the use of high-dose definitive RT in select individuals with unresected spine and sacral chordomas, and that soft tissue target volume is the best indicator of tumor response. Limitations of this study included its design, the small number of individuals 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 individuals with chordomas and chondrosarcomas of the spine. Outcomes of interest included distant metastases, OS, cause-specific survival, LC and disease-free survival. A total of 51 individuals 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 individuals with chordomas, and seventeen individuals 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 RT was 70.2 Gy (range, 64.2-75.6 Gy). The four-year LC, freedom from distant metastases, disease-free survival, cause-specific survival, and OS rates were 58%, 86%, 57%, 72%, and 72%, respectively. A total of 25 individuals experienced disease recurrence: eighteen local recurrences, six local and distant recurrences, and one distant metastases. In individuals with a local relapse, the median time to progression was 1.7 years (range, 0.2- six years). The median survival after local progression was 1.7 years (range, 0.1-4.9 + years). Regression analysis results showed that younger individuals had a significantly higher risk for local reoccurrence and that individuals whose initial management was only surgery also had a higher rate of reoccurrence. However, these individuals 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 individuals at the time of initial diagnosis. Limitations of this study included 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 individuals (n = 20) with low-grade glioma who were treated with PBRT. Individuals with World Health Organization (WHO) grade 2 glioma who were eligible for RT were enrolled in the study. All individuals 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 individuals. 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 individuals 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 individuals, 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 individuals 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 recommended 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 included small sample size, lack of comparative group and randomization.

Noel et al. (2002) conducted a retrospective review of seventeen individuals with meningioma to evaluate the efficacy and the tolerance of an escalated dose of external conformal fractionated RT combining photons and protons. Five individuals presented a histologically atypical or malignant meningioma, twelve individuals 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 four-year LC and OS rates were 87.5 +/- 12% and 88.9 +/- 11%, respectively. Radiologically, there were eleven stable diseases and five partial responses. The authors concluded that in both benign and more aggressive meningiomas, the combination of conformal photons and protons with a dose escalated by 10-15% offers clinical improvements in most individuals as well as radiological long-term stabilization. Limitations of this study included small sample size and study design.

Several clinical trials studying PBT in individuals with various types of brain tumors are active or recruiting. For more information, refer to www.clinicaltrials.gov. (Accessed March 20, 2025).

Clinical Practice Guidelines

American Society for Radiation Oncology (ASTRO)

ASTRO's guideline regarding RT 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 individuals 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. For leptomeningeal metastases, the volume and dose are determined by the primary

tumor's histology and the care objectives. For craniospinal irradiation (CSI) in individuals with metastatic solid tumors, techniques that maximize bone marrow sparing, such as using protons when available or conformal photon-based techniques/IMRT may be considered (NCCN, 2024).

Breast Cancer

Holt et al. (2023) conducted a systematic review and meta-analysis aimed to evaluate the clinical outcomes of adjuvant PBT for early breast cancer, comparing it to standard photon RT. A total of 32 studies published between 2000 and 2022, involving 1452 individuals with early breast cancer were analyzed. Scattering PBT was delivered in seven studies (258 individuals) starting 2003-2015 and scanning PBT in 22 studies (1041 individuals). Two studies used both types. Adverse events were less severe after scanning than after scattering PBT. They also varied by clinical target. For partial breast PBT, 498 adverse events were reported (eight studies, 358 individuals). None were categorized as severe after scanning PBT. For whole breast or chest wall +/- regional lymph nodes PBT, 1344 adverse events were reported (19 studies, 933 individuals). After scanning PBT, 4% (44/1026) of events were severe. The most prevalent severe outcome after scanning PBT was dermatitis which occurred in 5.7% (95% CI 4.2-7.6) of individuals. Other severe adverse outcomes included infection, pain and pneumonitis (each $\leq 1\%$). Of the 141 reconstruction events reported (13 studies, 459 individuals), the most prevalent after scanning PBT was prosthetic implant removal (34/181, 19%). There were no RCTs that directly compared PBT with photon RT. The authors concluded that PBT shows promise in reduction of adverse events and providing better dose distributions for early breast cancer. However, the authors recommended future, high-quality RCTs with longer follow-ups to establish the efficacy and safety of PBT compared to standard photon RT. Limitations included lack of randomized trials, heterogeneity of studies, and short follow-up periods. (DeCesaris 2019, Verma 2017, and Bradley 2016, which were previously cited in this policy, are included in this review).

A Hayes Technology Assessment related to PBT for breast cancer treatment states the overall body of evidence is low in quality, but suggests PBT is relatively safe and potentially effective for the treatment of non-metastatic breast cancer. A small number of studies compared conventional radiation with PBT and found better QOL, disease control, and safety outcomes with PBT. The assessment suggests additional studies are required to evaluate the effectiveness and safety of PBT compared to other forms of conventional RT in individuals with breast cancer without distant metastasis. The updated 2023 assessment included two newly published studies that met the original inclusion criteria but resulted in no change to the current Hayes rating. (Hayes, 2022; updated 2023).

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 individuals 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, the rates of seroma/hematoma and fat necrosis were comparable to those reported in the existing data. Radiation pneumonitis and rib fractures remain rare. PBT offers the potential to minimize the risk of cardiac events, keeping the mean heart dose at $\leq$ one 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 individuals with breast cancer. Retrospectively collected data from consecutive individuals diagnosed with non-metastatic breast cancer, no prior history of chest wall radiation and treated with PBT postoperatively were studied. Individuals with unfavorable cardiopulmonary anatomy were usually referred to this institution. Post-lumpectomy individuals with large breast size were not offered treatment due to a higher propensity for day-to-day measurement differences in the target position. Individuals were evaluated weekly while on RT, four weeks after RT was completed, and at 12 to 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 volume was achieved, and it significantly spared the heart, lungs, and contralateral breast. Of those with greater than three 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 individuals, 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., IMRT.

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 RT used in breast cancer, additional clinical trials are underway, NCT02603341, NCT01245712, and NCT03391388, refer to <https://clinicaltrials.gov/>. (Accessed March 20, 2025).

Clinical Practice Guidelines

National Comprehensive Cancer Network (NCCN)

NCCN guidelines do not address the use of PBT for treating breast cancer (NCCN, 2024).

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 individuals with a diagnosis of choroidal hemangioma, 119 individuals (62.3%) were treated by PDT and 72 individuals 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 individuals (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 individuals 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 > 3 mm, 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 included 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 individuals 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 individuals, 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).

Esophageal Cancer

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

and future RCTs are recommended to verify benefits provided by PBT. (Lin 2020, Xi 2017, and Lin 2017 which were previously cited in this policy, are included in the Zhou systematic review and meta-analysis).

A Hayes Health Technology Assessment 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 three-dimensional conformal radiation therapy (3D-CRT) 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. The 2023 annual review included no newly published studies and there was no change in the rating (Hayes, 2022; updated 2023).

A Hayes Health Technology Assessment regarding the use of PBT for the treatment of esophageal squamous cell carcinoma as an adjunct to chemotherapy with or without surgery, suggests PBT may be as effective as conventional (X-ray) photon radiotherapy (XRT). PBT may result in fewer or similar complications and delivers lower doses of radiation to nearby OARs than XRT. Additionally, PBT can reduce the rate of recurrence, improve survival, and induce a complete response. However, the body of evidence is noted as very low-quality, consisting of small- to moderate-sized retrospective studies with limited follow-up, with most studies lacking a comparator group. The assessment found the evidence base was insufficient to evaluate efficacy and safety of PBT, and recommended future studies. The 2023 update included one newly published study that met the inclusion criteria, but no change was made in the Hayes rating (Hayes, 2022; updated 2023).

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

Mizumoto et al. (2011) evaluated the efficacy and safety of hyperfractionated concomitant boost PBT in nineteen individuals with esophageal cancer. The overall one- and five-year actuarial survival rates for all nineteen individuals were 79% and 42.8%, respectively. The median survival time was 31.5 months. Of the nineteen individuals, seventeen (89%) showed a complete response within four months after completing treatment and two (11%) showed a partial response, giving a response rate of 100% (19/19). The one- and five-year LC rates for all nineteen individuals were 93.8% and 84.4%, respectively. The results suggest that hyperfractionated PBT is safe and effective for individuals with esophageal cancer. The authors noted 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 individuals were treated using PBT with or without X-rays. All but one had squamous cell carcinoma. Of the 51 fives, 33 received combinations of X-rays and protons as a boost. The other eighteen individuals received PBT alone. The overall five-year actuarial survival rate for the 51 individuals was 21.1% and the median survival time was 20.5 months. Of the 51 individuals, 40 (78%) showed a complete response within four months after completing treatment and seven (14%) showed a partial response, giving a response rate of 92% (47/51). The five-year LC rate for all 51 individuals was 38% and the median LC time was 25.5 months. The authors concluded that these results suggested that PBT is an effective treatment for individuals with locally advanced esophageal cancer. The authors noted 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 individuals to compare the use of PBT to photon therapy in those with esophageal cancer (Clinical Trial ID: NCT03801876). For more information, refer to <http://www.clinicaltrials.gov/>. (Accessed March 20, 2025).

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, individuals should receive PBT within a clinical trial (NCCN, 2024).

Gastrointestinal (GI) Cancers

Le et al. (2024) conducted a systematic review aimed to investigate the adverse effects, compare dosimetric data, and evaluate the oncological outcomes of PBT versus conventional RT in individuals with non-metastatic rectal cancer (non-stage IV). Inclusion criteria included full-text, peer-reviewed RCTs, prospective or retrospective cohort studies, in English,

which evaluated adults with non-metastatic rectal cancer treated with either PBT or conventional RT. Exclusion criteria included those under 18 years of age, those with metastatic rectal cancer or other cancers, and studies that used other RT modalities. Eight studies were included in the review. There was insufficient evidence to determine the adverse treatment outcomes of PBT versus conventional RT. No current studies assessed radiotoxicities nor oncological outcomes. Pooled dosimetric comparisons between PBT and various conventional RTs were associated with reduced radiation exposure to the pelvis, bowel and bladder. The authors concluded there was insufficient evidence to establish the superiority of PBT over conventional RT in reducing adverse treatment outcomes and improving oncological outcomes for individuals with non-metastatic rectal cancer, due to the limited data available. The authors noted pooled dosimetric analyses indicated that PBT reduces radiation exposure to surrounding tissues; however, these findings were based on a small number of studies with high clinical heterogeneity and a moderate risk of bias. The authors call for more rigorous, prospective, RCTs with larger sample sizes to better evaluate the efficacy and safety of PBT in non-metastatic rectal cancer.

Fok et al. (2021) conducted a systematic review and meta-analysis that compares dosimetric irradiation of OARs and oncological outcomes for PBT versus conventional photon-based RT in locally advanced rectal cancer. Eight articles with a total of 127 individuals met the inclusion criteria. There was significantly less irradiated small bowel with PBT compared to 3D-CRT 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 OS 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 RT. The authors noted 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 included small sample sizes and lack of RCTs.

Verma et al. (2016b) conducted a systematic review to identify studies on PBT and GI malignancies. The search included PubMed, EMBASE, and abstracts from meetings ASTRO, Particle Therapy Co-Operative Group (PTCOG), and American Society of Clinical Oncology (ASCO). 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 while achieving comparable LC and OS. However, for some of the studies, contemporaneous comparison groups were lacking, or comparisons were made between PBT and XRT, which consisted of either 3D-CRT or IMRT rather than IMRT only. For pancreatic cancer, five 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 individuals 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 offered the potential of lower toxicities without compromising survival or LC. The authors acknowledged there was limited high quality evidence for select GI malignancies and further multi-institution RCTs are needed.

Clinical Practice Guidelines

National Comprehensive Cancer Network (NCCN)

NCCN guidelines do not address PBT in the treatment of gastric cancers (NCCN, 2024).

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 participants (Kagei et al., 2003). In this study, five-year and 10-year survival rates were similar to conventional therapies as reported in the literature. The 10-year survival rate was higher for participants with low stage (89%) compared with advanced stages (40%) of cervical cancer. The treatment caused severe late complications in 4% of participants.

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, refer to www.clinicaltrials.gov. (Accessed October 9, 2024)

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, 2024), Ovarian Cancer (NCCN, 2024), Uterine Neoplasms (NCCN, 2024) or Vulvar Cancer (NCCN, 2024).

Head and Neck Cancers (HNC)

A Hayes report, Proton Beam Therapy for Treatment of Head and Neck Cancer, assessed multiple clinical studies evaluating the efficacy and safety of PBT in individuals 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 individual groups as well. The report concludes that the study abstracts present conflicting findings regarding the use of PBT for treatment of HNC. The updated 2022 Hayes report includes 25 new studies that met inclusion criteria; however, no change was made to the rating. (Hayes, 2019; Updated 2022).

Seeking to improve LC rate and reduce late adverse events, Takayama et al. (2016) evaluated therapeutic results and toxicities of PBT combined with selective intra-arterial infusion chemotherapy (PBT-IACT) in individuals with stage III-IVB squamous cell carcinoma of the tongue. Between February 2009 and September 2012, 33 individuals 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 three-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 one 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 may be considered as a treatment option for locally advanced tongue cancer. This study was limited by the lack of data comparing toxicity to conventional RT.

Clinical Practice Guidelines

American College of Radiology (ACR)/American Radium Society (ARS)

The ACR/ARS Practice Parameter indicates that PBRT minimizes the radiation dose to vital structures in the head and neck area which may enhance QOL and decrease complications affecting the optic nerves, optic chiasm, pituitary gland, brain, brainstem, spinal cord, salivary glands, pharyngeal constrictor muscles, oral cavity, and emetogenic sites in the posterior fossa (2023).

National Comprehensive Cancer Network (NCCN)

NCCN's HNCs guideline makes no mention of PBRT for cancer of the lip (mucosa), oral cavity, hypopharynx or glottic larynx. (NCCN, 2024).

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 or local failure. Eligible participants 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 participant. Participants 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 five to ten Gy relative biologic effectiveness (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 radiation pneumonitis 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 local failure (10.9% and 10.5% for IMRT and PSPT, respectively). Exploratory analysis showed that the radiation pneumonitis and local failure rates at twelve months for participants 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 two ongoing trials (NCT01993810 and NCT01629498) may provide additional evidence of the efficacy of proton and photon therapies.

Chang et al. (2017) reported five-year results of a prospective phase II single-institution study evaluating chemotherapy with concurrent high dose PBT in 64 participants with unresectable phase III NSCLC. Five-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 were 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 nine hypo-fractionated PBT studies (mostly single-arm) were included. Proton beam therapy 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 three-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/m² (2), day one] and oral S-1 (80, 100 or 120 mg based on body surface area, days one-14), repeated as four cycles every four weeks. Dose-limiting toxicity (DLT) was defined as grade 3 (severe) toxicities related to PBT during days one-90. Each dose level was performed in three individuals and then escalated to the next level if no DLT occurred. When one individual developed a DLT, three additional individuals were enrolled. Overall, nine individuals were enrolled, including six in Arm one and three in Arm two. The median follow-up time was 43 months, and the median PFS was 15 months. In Arm one, grade 3 infection occurred in one of six individuals, but no other DLT was reported. Similarly, no DLT occurred in Arm two. However, one individual in Arm two developed grade 3 esophageal fistula at nine months after the initiation of PBT. From a clinical perspective, the authors concluded that 66 Gy RBE was 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. Participants (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 participants experienced Grade 4 or 5 non-hematologic toxicities. Acute pneumonitis was observed in three participants (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 participants, respectively. Severe ($\geq$ Grade 3) leukocytopenia, neutropenia and thrombocytopenia were observed in ten, seven, and one participants, respectively. Late RP (grades 2 and 3) was observed in one participant each. Six participants (40%) experienced local recurrence at the primary site and were treated with 74 Gy RBE. Disease progression was observed in eleven participants, with the mean survival time being 26.7 months. The authors cited short follow-up period as a limitation to this study and concluded that high-dose PBT with concurrent chemotherapy was 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 individuals with NSCLC. 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 individuals 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 $\geq$ 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 individuals diagnosed with NSCLC.

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, two- to five-year LC rates varied in the range of 57%-87%. The two- and five-year OS and two- and five-year cause-specific survival rates

were 31%-74% and 23% and 58%-86% and 46%, respectively. Radiation-induced pneumonitis was observed in about 10% of individuals. For C-ion therapy, the overall LC rate was 77%, but it was 95% when using a hypofractionated radiation schedule. The five-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 authors concluded the current findings with protons and heavier charged particles are encouraging. However, the absence of substantial evidence regarding the clinical effectiveness of particle therapy highlights the necessity for thorough investigation into its efficiency. Until such data is available for lung cancer, the authors noted charged particle therapy should be considered experimental.

A phase III RCT comparing photon to proton chemoradiotherapy for individuals with inoperable NSCLC (NCT01993810) is in progress. For more information, refer to www.clinicaltrials.gov. (Accessed March 20, 2025)

Clinical Practice Guidelines

American College of Radiology (ACR)

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

National Comprehensive Cancer Network (NCCN)

NCCN guidelines state that advanced technologies such as 4D-CT and/or positron emission tomography–computed tomography (PET/CT) simulation, IMRT/ volumetric modulated arc therapy (VMAT), image-guided radiation therapy (IGRT), motion management, and PBT are appropriate when needed to deliver curative RT safely when treating NSCLC (NCCN, 2024) and may be appropriate to limit normal tissue toxicity in the treatment of small cell lung cancer (NCCN, 2025).

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, 2024).

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, refer to www.clinicaltrials.gov. (Accessed March 20, 2025)

Clinical Practice Guidelines

National Comprehensive Cancer Network (NCCN)

NCCN guidelines do not address PBT in the treatment of pancreatic adenocarcinoma (NCCN, 2024).

Vestibular Tumors

The systematic review and meta-analysis by Santacroce et al. (2023) examined the effectiveness of PBRT for vestibular schwannomas (VS) treatment of tumor control and cranial nerve preservation, particularly in terms of facial and hearing preservation. The study included both retrospective and prospective studies written in English that reported on individuals with VS treated with PBRT, regardless of their history of previous surgery. Studies in languages other than English were excluded. Eight studies (587 individuals) met the inclusion criteria; two were single arm prospective studies and six were

retrospective studies. Overall rate of tumor control (both stability and decrease in volume) was 95.4% (range 93.5–97.2%, p heterogeneity = 0.77, $p < 0.001$). Overall rate of tumor progression was 4.6% (range 2.8–6.5%, p heterogeneity < 0.77, $p < 0.001$). Overall rate of trigeminal nerve preservation (absence of numbness) was 95.6% (range 93.5–97.7%, $I^2 = 11.44\%$, p heterogeneity = 0.34, $p < 0.001$). Overall rate of facial nerve preservation was 93.7% (range 89.6–97.7%, $I^2 = 76.27\%$, p heterogeneity < 0.001, $p < 0.001$). Overall rate of hearing preservation was 40.6% (range 29.4–5 International Stereotactic Radiosurgery 1.8%, $I^2 = 43.36\%$, p heterogeneity = 0.1, $p < 0.001$). The authors concluded that PBRT for VS achieved high tumor control rates, but the existing literature did not show an advantage in hearing preservation compared to standard SRS techniques. Additionally, the likelihood of facial nerve preservation is lower compared to most radiosurgery techniques. The authors noted that overall, PBRT for VS did not offer a significant benefit for facial and hearing preservation when compared to most currently reported SRS series. Limitations included a limited number of studies, most of which were retrospective in nature. (Authors Saraf 2022, Bush 2002, and Harsh 2002, which were previously cited in this policy, are included in this review).

In a critical review, Murphy, and Suh (2011) summarized the radiotherapeutic options for treating VS, including single-session SRS, 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 VS demonstrated LC rates of 84–100% but disappointing hearing preservation rates of 33–42%. The authors reported that mixed data regarding the ideal hearing preservation therapy, inherent biases in subject selection, and differences in outcome analysis have made comparison across radiotherapeutic modalities difficult.

Clinical Practice Guidelines

Congress of Neurological Surgeons (CNS)

CNS developed an evidence-based guideline on the role of radiosurgery and RT in the management of individuals 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 March 20, 2025)

References

American College of Radiology (ACR) and American Radium Society (ARS). Practice parameter for the performance of proton beam radiation therapy. <https://gravitas.acr.org/PPTS/GetDocumentView?docId=175+&releaseId=2>. Revised 2023. Accessed March 20, 2025.

American College of Radiology (ACR). Proton therapy. May 2013; updated March 11, 2024. Available at: <https://www.radiologyinfo.org/en/info/protonthera>. Accessed March 24, 2025.

American Society for Radiation Oncology (ASTRO) Model Policies: proton beam therapy (PBT). 2022. Available at: <https://www.astro.org/practice-support/reimbursement/model-policies>. Accessed March 24, 2025.

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 March 24, 2025.

Araya M, Ishikawa H, Nishioka K, et al. Proton beam therapy for muscle-invasive bladder cancer: A systematic review and analysis with Proton-Net, a multicenter prospective patient registry database. J Radiat Res. 2023 Jun 16;64(Supplement_1):i49-i58.

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.

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 for 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, Loreda LN, et al. Fractionated proton beam radiotherapy for acoustic neuroma. *Neurosurgery.* 2002;50(2):270-275.

Bush DA, Volk M, Smith JC. Proton beam radiotherapy versus transarterial chemoembolization for hepatocellular carcinoma: results of a randomized clinical trial. *Cancer.* 2023 Nov 15;129(22):3554-3563.

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, Kestin LL, Barriger RB, et al. 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, et al. Early toxicity in patients treated with postoperative proton therapy for locally advanced breast cancer. *Int J Radiat Oncol Biol Phys.* 2015 Jun 1;92(2):284-91.

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 March 24, 2025.

ECRI Institute. Proton beam radiation therapy systems for cancer. Plymouth Meeting (PA): ECRI Institute; 2017 May 01. (Technology Forecast).

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

Evans JR, Igwe C, Jackson TL, et al. Radiotherapy for neovascular age-related macular degeneration. *Cochrane Database Syst Rev.* 2020 Aug 26;8:CD004004.

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.

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.

Goliot N, Mohssine S, Stefan D, et al. Proton therapy for adult-type diffuse glioma: a systematic review. *Crit Rev Oncol Hematol*. 2024 Sep 7;204:104501.

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.

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.

Hayes, Inc. Hayes Health Technology Assessment. Proton beam therapy for esophageal adenocarcinoma. Hayes, Inc.; October 21, 2022; updated November 29, 2023.

Hayes, Inc. Hayes Health Technology Assessment. Proton beam therapy for esophageal squamous cell carcinoma. Hayes, Inc.; November 2, 2022; updated December 1, 2023.

Hayes, Inc. Hayes Health Technology Assessment. Proton beam therapy for prostate cancer. Hayes, Inc.; March 4, 2020;. updated April 11, 2023.

Hayes, Inc. Hayes Health Technology Assessment. Proton beam therapy for treatment of breast cancer. Hayes, Inc.; October 14, 2022; updated December 11, 2023.

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.

Holt F, Probert J, Darby SC, et al. Proton beam therapy for early breast cancer: a systematic review and meta-analysis of clinical outcomes. *Int J Radiat Oncol Biol Phys*. 2023 Nov 15;117(4):869-882.

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.

Hoppe BS, Flampouri S, Lynch J, et al. Improving the therapeutic ratio in Hodgkin lymphoma through the use of 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 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. *Int J Radiat Oncol Biol Phys*. 2016 May 1;95(1):297-303.

Kabolizadeh P, Chen YL, Liebsch N, et al. Updated outcome and analysis of tumor response in mobile spine and 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, Tokuyue 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, 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.

Le K, Marchant JN, Le KDR. Evaluating the effectiveness of proton beam therapy compared to conventional radiotherapy in non-metastatic rectal cancer: a systematic review of clinical outcomes. *Medicina (Kaunas)*. 2024 Aug 31;60(9):1426.

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, 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, et al. Randomized phase iib trial of 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 for esophageal cancer. *Radiother Oncol*. 2017 Jun;123(3):376-381.

Liu Y, Patel SA, Jani AB, et al. Overall survival after treatment of localized prostate cancer with proton beam therapy, external-beam photon therapy, or brachytherapy. *Clin Genitourin Cancer*. 2021 Jun;19(3):255-266.e7.

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.

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.

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). Clinical Practice Guidelines in Oncology. B-cell lymphoma. V3.2024.

National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Biliary tract cancer. V4.2024.

National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Bladder cancer. V4.2024.

National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Breast cancer. V4.2024.

National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Central nervous system cancers. V3.2024.

National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Cervical cancer. V4.2024.

National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Esophageal and esophagogastric junction cancers. V4.2024.

National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Gastric cancer. V4.2024.

National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Hodgkin lymphoma. V3.2024.

National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Melanoma: cutaneous. V3.2024.

National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Non-small cell lung cancer. V10.2024.

National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Ovarian cancer including fallopian tube cancer and primary peritoneal cancer. V3.2024.

National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Pancreatic adenocarcinoma. V3.2024.

National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Primary cutaneous lymphoma. V3.2024.

National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Prostate cancer. V4.2024.

National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Small cell lung cancer. V2.2025.

National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. T-cell lymphoma. V4.2023.

National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Uterine neoplasms. V3.2024.

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Vulvar cancer. V4.2024.

National Comprehensive Cancer Network (NCCN) Radiation Therapy Compendium®.

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.

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.

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.

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

Santacroce A, Trandafirescu MF, Levivier M, et al. Proton beam radiation therapy for vestibular schwannomas-tumor control and hearing preservation rates: a systematic review and meta-analysis.

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.

Saraf A, Pike LRG, Franck KH, et al. Fractionated proton radiation therapy and hearing preservation for vestibular schwannoma: preliminary analysis of a prospective phase 2 clinical trial. *Neurosurgery*. 2022 May 1;90(5):506-514.

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.

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. *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 Aug;7(4):644-64.

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

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 Aug 1;86(5):885-91.

Xi M, Xu C, Liao Z, et al. Comparative outcomes after definitive chemoradiotherapy using proton beam therapy versus intensity modulated radiation therapy for esophageal cancer: a retrospective, single-institutional analysis. *Int J Radiat Oncol Biol Phys*. 2017 Nov 1;99(3):667-676.

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.

Zhou P, Du Y, Zhang Y, et al. Efficacy and safety in proton therapy and photon therapy for patients with esophageal cancer: a meta-analysis. *JAMA Netw Open*. 2023 Aug 1;6(8):e2328136.

Policy History/Revision Information

Date	Summary of Changes
08/01/2025	Coverage Rationale Unproven and Not Medically Necessary - Revised language to indicate proton beam radiation therapy (PBT) is unproven and not medically necessary due to insufficient evidence of efficacy for treating all other indications [not listed in the policy as proven and medically necessary] including glioma and retroperitoneal sarcoma - However, PBT may be covered for other diagnoses, 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 - Evaluation includes a comparison of treatment plans for PBT, IMRT, and SBRT for the specific individual Supporting Information - Updated <i>Clinical Evidence</i> and <i>References</i> sections to reflect the most current information - Archived previous policy version CS105KS.01

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 uses InterQual® for the primary medical/surgical criteria, and the American Society of Addiction Medicine (ASAM) criteria for substance use disorder (SUD) services, in administering health benefits. If InterQual® does not have applicable criteria, UnitedHealthcare may also use UnitedHealthcare Medical Policies that have been approved by the Kansas Department of Health and Environment. 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.