Proton Beam Radiation Therapy (for Kentucky Only)

Policy Number: CS105KY.11
Effective Date: May 1, 2026

➲ Instructions for Use

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Related Policies

- Radiation Therapy: Fractionation, Image-Guidance, and Special Services (for Kentucky Only)
- Stereotactic Body Radiation Therapy and Stereotactic Radiosurgery (for Kentucky Only)

Application

This Medical Policy only applies to the state of Kentucky.

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 and photon-based radiation therapy (such as IMRT or stereotactic body radiation therapy) for the specific individual

Medical Records Documentation Used for Reviews

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. Medical records documentation may be required to assess whether the member meets the clinical criteria for coverage but does not guarantee coverage of the services requested.

The patient's medical record must contain documentation that fully supports the medical necessity for the requested services. This documentation includes, but is not limited to, relevant medical history, physical examination, and results of pertinent diagnostic tests or procedures. Documentation supporting the medical necessity should be legible, maintained in the patient's medical record, and must be made available upon request.

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
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

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
C69.11	Malignant neoplasm of right cornea

Diagnosis Code	Description
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 that use x-rays or photons to destroy cancer cells, proton beam therapy uses a beam of special particles (protons) that carry a positive charge. There is no significant difference in the biological effects of protons vs 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 in the tumor region and, unlike photons, deliver only a minimal dose beyond the tumor boundaries (American College of Radiology website, updated 2024).

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

Clinical Evidence

Proven Indications

Prostate Cancer

An ECRI Clinical Evidence Assessment for PBT and localized prostate cancer concluded that PBT is relatively safe for the treatment of prostate cancer; however, it is unclear whether PBT is more effective than photon EBRT or brachytherapy or if it 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 with that with 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 and 2015 were included. A total of 4,900 (1.8%) received PBT, while 158,111 (57.1%) received photon-based EBRT, and 113,869 (41.1%) received brachytherapy. Compared with those who received EBRT and brachytherapy, PBT individuals were younger and were less likely to be in the high-risk group. On multivariable analysis, compared with PBT, men had worse OS after EBRT or brachytherapy. After propensity score matching, the OS benefit with PBT remained significant compared with that with EBRT but not brachytherapy. The improvement in OS with PBT was most prominent in men ≤ 65 years old with low-risk disease compared with other subgroups (interaction $p < 0.001$). The median follow-up time was 80.9 months. The authors concluded that 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 encouraged 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 in individuals with early-stage prostate cancer treated with moderately hypofractionated PBT and IMRT. The study included individuals (n = 1,850) with low- or intermediate-risk biopsy-proven prostate adenocarcinoma treated from 1998 to 2018. The individuals were treated with moderately hypofractionated radiation, defined as 250 to 300 cGy per daily fraction given for 4 to 6 weeks, and stratified by use of IMRT or PBT. Late genitourinary (GU) and GI toxicity was the primary outcome. Adjusted toxicity rates were calculated using inverse probability of treatment weighting, accounting for race, National Comprehensive Cancer Network risk group, age, pretreatment International Prostate Symptom Score (GU only), and anticoagulant use (GI only). Of the 1,850 individuals included, 1,282 had IMRT, and 568 had PBT. The majority of individuals experienced no late GU or GI toxicity, with late grade ≥ 3 GU toxicity of 2.0% vs 3.9% and late grade ≥ 2 GI toxicity of 14.6% vs 4.7% in 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 12 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 concluded 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 5 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 the sole or primary therapy was usually similar to the safety of other common RTs; however, these studies are of low quality, since they were retrospective. Moreover, these 10 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, no change in the current rating occurred (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 vs PBT. Individuals with prostate cancer who received adjuvant or salvage IMRT or PBT (70.2 Gy 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). Overall, 70 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 in the IMRT and PBT groups, respectively. While PBT was superior at reducing low-range (volumes receiving 10%-40% of the dose, respectively) bladder and rectal doses (all $p \leq 0.01$), treatment modality was not associated with differences in clinician-reported acute or late GU/GI toxicities (all $p \geq 0.05$). The 5-year grade ≥ 2 GU and grade ≥ 1 GI TFS was 61.1% and 73.7% with IMRT, respectively, and 70.7% and 75.3% with PBT; the 5-year grade ≥ 3 GU and GI TFS was > 95% in both groups (all $p \geq 0.05$). 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 ongoing follow-up to determine whether dosimetric differences between IMRT and PBT lead to clinically meaningful differences in long-term outcomes. Limitations include the lack of randomization and a retrospective study design.

Several single-institution studies report favorable clinical outcomes with PBT in prostate cancer. Henderson et al. (2017) reported 5-year outcomes of a prospective trial of image-guided, accelerated, hypofractionated proton therapy 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. The 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. The actuarial 5-year rate for significant (grade ≥ 3) late radiation-related GI adverse events/toxicities was 0.5% and was 1.7% for GU adverse events.

Bryant et al. (2016) performed a single-center study in 1,327 men with localized prostate cancer who received image-guided PBT between 2006 and 2010. The 5-year FFBP rates were 99% for low-risk, 94% for intermediate-risk, and 76% for high-risk participants. 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 from individuals with localized prostate cancer who received treatment with IMRT and PBT techniques and similar dose-fractionation schedules. A total of 394 individuals were treated with either PBT (n = 181) or IMRT (n = 213). Individuals were case matched on risk group, age, and prior GI and GU disorders, resulting in 94 matched pairs. The risks of acute and late GI/GU toxicities did not differ significantly after adjustment for confounders and predictive factors.

Mendenhall et al. (2014) reported 5-year clinical outcomes from three prospective trials of image-guided PBT for prostate cancer conducted at a single institution. From August 2006 to September 2007, 211 participants (low risk, n = 89; intermediate risk, n = 82; high risk, n = 40) were enrolled in one of the three trials. The doses delivered were 78 cobalt Gy equivalents (CGEs) for low risk and 78 to 82 CGEs for intermediate risk. Participants with high-risk disease received 78 CGEs with weekly concomitant chemotherapy, followed by 6 months of androgen deprivation therapy. The 5-year OS rates of 93%, 88%, and 86% were reported in low-, intermediate-, and high-risk participants, respectively. FFBP and/or clinical progression rates for the same time period were 99% in both low- and intermediate-risk participants and 76% in high-risk participants. A single instance of acute grade 3 GU toxicity occurred. One acute grade 3 and two late grade 3 GI events throughout the entire group resulted in a 5-year incidence of 1%. Limitations to this study include the 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 a control group limited interpretation of the studies and did not allow assessment of PBT outcomes compared with 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, in patients with specific conditions. The investigators identified patients who were aged 66 years or older with prostate cancer and treated with IMRT or PBT. To evaluate toxicity, each patient who received PBT was matched with two patients who received IMRT, based on similar sociodemographic and clinical characteristics. Toxicity was reported at 6 months post treatment and included 421 patients who received PBT matched to 842 patients who received IMRT; at 12 months post treatment, 314 patients who received PBT, matched to 628 patients who received IMRT, were included. At 6 months, GU toxicity was significantly lower in patients who received PBT vs IMRT (5.9% vs 9.5%; odds ratio, 0.60; 95% CI, 0.38-0.96; $p = 0.03$). However, no difference was observed at 12 months post treatment (18.8% vs 17.5%; odds ratio, 1.08; 95% CI, 0.76-1.54; $p = 0.66$). At 6 months and 12 months post treatment, no difference in GI or other toxicities was observed. The authors concluded that in a national sample of Medicare beneficiaries, patients who were treated with IMRT or PBT for prostate cancer had no difference in toxicity rates

at 12 months post treatment and that additional longitudinal studies evaluating the effectiveness of PBT compared with that of IMRT are needed prior to widespread use of PBT for prostate cancer.

Sheets et al. (2012) evaluated the comparative morbidity and disease control with IMRT, PBT, and conformal RT for primary prostate cancer treatment. The 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 of IMRT and PBT (n = 1,368), IMRT individuals had a lower rate of GI morbidity. No significant differences in the rates of other morbidities or additional therapies between IMRT and PBT were observed.

Several large, population-based cohort studies using Surveillance, Epidemiology, and End Results 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 5 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, go to www.ClinicalTrials.gov (accessed November 6, 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. 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 that 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 guidelines note that both photon RT and PBRT are considered appropriate forms of EBRT, and current evidence suggests that they yield comparable outcomes in terms of toxicity, QOL, and tumor control (NCCN, 2026).

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

Evans et al. (2020) updated a previously conducted systematic review (Evans et al., 2010) that examined the effects of RT on neovascular age-related macular degeneration (AMD). A search was conducted using the Cochrane Central Register of Controlled Trials, MEDLINE, Embase, LILACS (Latin American and Caribbean Literature on Health Sciences), and three trial registers for RCTs in which RT was compared with another treatment, sham treatment, low-dose irradiation, or no treatment in individuals with choroidal neovascularization 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 18 studies (n = 2,430 individuals, 2,432 eyes) were included as well as the RT, with doses ranging from 7.5 to 24 Gy. Three of these studies investigated brachytherapy (plaque and epimacular), and 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 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–vascular endothelial growth factor 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 of and side effects with PBT for indications of the eye. All studies that included at least 10 individuals and 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, or AMD. The methodological quality of these studies was poor. Studies were

characterized by large differences in radiation techniques applied in the studies and by variation in individual characteristics in 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. Evidence of the effectiveness and safety of PBT is limited due to the lack of well-designed and well-reported studies.

An RCT by Zambarakji et al. (2006) studied 166 participants with angiographic evidence of classic choroidal neovascularization resulting from AMD and a 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 ophthalmologic examinations, color fundus photography, and fluorescein angiography were performed before and 3, 6, 12, 18, and 24 months after treatment. At 12 months after treatment, 36 eyes (42%) and 27 eyes (35%) lost three or more lines of vision in the 16-CGE and 24-CGE groups, respectively. Rates increased to 62% in the 16-CGE group and 53% in the 24-CGE group by 24 months after treatment. Radiation complications developed in 15.7% of participants receiving 16 CGEs and 14.8% of participants receiving 24 CGEs. 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)

The updated AAO Preferred Practice Pattern for AMD lists RT as a current treatment option for choroidal neovascularization lesions; however, due to insufficient clinical evidence of its effectiveness, it is not considered a proven beneficial therapy. Additionally, the guidelines note that further research is needed to evaluate the long-term safety and efficacy of stereotactic RT for treating neovascular AMD (Vemulakonda et al., 2024).

Bladder Cancer

Araya et al. (2023) performed a registry data analysis designed to assess the safety and efficacy of PBT in 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. OS, PFS, and LC rates were 90.8%, 71.4%, and 84.6%, respectively, after 3 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 3-year outcomes of photon RT were 57% to 84.8% in OS, 39% to 78% in PFS, and 51% to 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 that PBT is expected to have the same toxicity as photon-based combined-modality therapy for stages II to III muscle-invasive bladder cancer. The authors noted that data from long-term follow-up are needed to validate efficacy. Limitations include the 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 the outcomes with and 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. Overall, 70 patients with cT2-3N0M0 muscle-invasive bladder cancer were included, who received treatment from 1990 to 2015 at a single institution. The OS and PFS rate, time to progression, predictive factors for progression, and toxicities were analyzed. Progression was defined as when muscle-invasive recurrence, distant metastasis, or upper urinary tract recurrence was observed. The patients' median age was 65 years (range, 36-85 years). The median follow-up period was 3.4 years (range, 0.6-19.5 years). The 5-year cumulative OS rate, PFS rate, and time to progression rate were 82%, 77%, and 82%, respectively. In univariate and multivariate analyses, tumor multiplicity and tumor size (≥ 5 cm) were significant and independent factors associated with progression (hazard ratio, 3.5, 95% CI, 1.1-12; hazard ratio, 5.0, 95% CI, 1.3-17; $p < 0.05$ for all). As for toxicity, 26 patients (18%) had grade 3/4 acute hematologic toxicities, and two patients (3%) had grade 3 late GU toxicity. No patient had to discontinue the treatment due to acute toxicity. The authors concluded that trimodal therapy, including both conventional and proton radiation, was well tolerated and may be an effective treatment option for selected individuals with muscle-invasive bladder cancer. Further studies are needed to determine whether PBT is integral to this multimodality 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 the 5-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

American Urological Association (AUA)/American Society of Clinical Oncology (ASCO)/American Society for Radiation Oncology (ASTRO)/Society of Urologic Oncology (SUO)

Holzbeierlein et al. (2024) developed a multidisciplinary evidence-based guideline for managing nonmetastatic muscle-invasive bladder cancer. The guideline strongly advises against using RT alone as a curative approach. For those pursuing bladder preservation through trimodality therapy, the recommended strategy includes maximal transurethral resection of the bladder tumor, followed by chemotherapy and EBRT. However, PBT is not specifically addressed in the guideline.

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines do not address the use of PBT for treating bladder cancer (NCCN, 2025).

Breast Cancer

Holt et al. (2023) conducted a systematic review and meta-analysis aimed to evaluate the clinical outcomes with adjuvant PBT for early breast cancer compared with those with standard photon RT. A total of 32 studies published between 2000 and 2022, involving 1,452 individuals with early breast cancer, were analyzed. Scattering PBT was delivered in seven studies (258 individuals), starting from 2003 to 2015, and scanning PBT was delivered in 22 studies (1,041 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, 1,344 adverse events were reported (19 studies, 933 individuals). After scanning PBT, 4% (44/1,026) 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 ≤ 1%). Of the 141 reconstruction events reported (13 studies, 459 individuals), the most prevalent after scanning PBT was prosthetic implant removal [34/181 (19%)]. No RCTs directly compared PBT with photon RT. The authors concluded that PBT shows promise in reducing 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 with those of standard photon RT. Limitations include the lack of randomized trials, heterogeneity of studies, and short follow-up periods. (DeCesaris et al., 2019, Verma et al., 2017, and Bradley et al., 2016, previously cited in this policy, are included in this review.)

A Hayes Technology Assessment related to PBT for breast cancer treatment stated that the overall body of evidence is low quality but suggested that PBT is relatively safe and potentially effective for the treatment of nonmetastatic 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 suggested that additional studies are required to evaluate the effectiveness and safety of PBT compared with those of other forms of conventional RT in individuals with breast cancer without distant metastasis. The updated 2024 assessment included four newly published studies that met the original inclusion criteria but resulted in no change to the current Hayes rating (Hayes, 2022; updated 2024).

Verma et al. (2016a) performed a systematic review of clinical outcomes with and toxicity of PBT for treating breast cancer. Nine original studies were analyzed; however, the types of studies and 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% to 75%. This is comparable to 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%. With 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 ≤ 1 Gy. However, definitive clinical experiences remain sparse. Results from clinical trials in progress, comparing protons to photons, will further aid in providing conclusions. Limitations to this review include a general lack of data and low number of individuals in the available studies.

Cuaron et al. (2015) conducted a single-institution case series study to report dosimetry and early toxicity data in patients with breast cancer. Retrospectively collected data from consecutive patients diagnosed with nonmetastatic breast cancer, who had no prior history of chest wall radiation and were treated with PBT post operation, were studied. Patients with

unfavorable cardiopulmonary anatomy were usually referred to this institution. Post lumpectomy, patients with large breast size were not offered treatment due to a higher propensity for day-to-day measurement differences in the target position. Patients were evaluated weekly while on RT, 4 weeks after RT was completed, and in 12- to 24-week intervals thereafter. Toxicity was recorded using the Common Terminology Criteria for Adverse Events 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, 20 had stage III, and two had chest wall recurrence. The median follow-up was 9.3 months (range, 2.3-18.6 months). With PBT, full coverage of the planned target value was achieved, and it significantly spared the heart, lungs, and contralateral breast. Of those with greater than 3 months of follow-up (n = 28), 71.4% developed grade 2 dermatitis, and of them, 28.6% experienced moist desquamation. Eight (28.6%) developed grade 2 esophagitis, and one developed grade 3 reconstructive complications. The authors concluded that (1) in this series of 30 patients, PBT achieved excellent coverage of the target volume while sparing the heart, lungs, and contralateral breast; (2) the treatment was well tolerated; and (3) additional studies assessing long-term outcomes and toxicity are needed. Limitations of this study include its design, the exclusion of women with large breast size, and the higher toxicity rates compared with those seen with other forms of RT (e.g., IMRT).

Clinical Practice Guidelines

American Society for Radiation Oncology (ASTRO)/American Society of Clinical Oncology (ASCO)/ Society of Surgical Oncology (SSO)

Jimenez et al. (2025) assembled a multidisciplinary team to develop evidence-based guidelines for the use of postmastectomy RT in breast cancer treatment. According to the guideline, PBT is still being actively studied, with early data from single-institution and registry studies showing better target coverage and cardiac preservation than 3D-CRT and IMRT, especially during regional nodal irradiation, including internal mammary node treatment. Ongoing trials are expected to clarify its role in reducing major cardiac events and guide future use in postmastectomy RT.

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines do not address the use of PBT for treating breast cancer (NCCN, 2025).

Choroidal Hemangiomas

Mathis et al. (2021) conducted a retrospective multicenter study that compared the functional and anatomical effectiveness of PBT vs that of photodynamic therapy (PDT) in a real-life setting for the treatment of circumscribed choroidal hemangioma. The study included a total of 191 patients with a diagnosis of choroidal hemangioma; 119 (62.3%) were treated with PDT and 72 with PBT. The final best-corrected visual acuity did not differ significantly between the two groups ($p = 0.932$), and the final thickness was lower in the PBT group than the PDT group ($p = 0.001$). Overall, 53 patients (44.5%) initially treated with PDT required at least one other therapy and were associated with worse final best-corrected visual acuity ($p = 0.037$). None of the patients treated with PBT needed second-line therapy. In a multivariate analysis, only an initial thickness of greater than 3 mm remained significant ($p = 0.01$) to predict PDT failure. The authors concluded that PDT and PBT have similar functional and anatomical outcomes in circumscribed choroidal hemangiomas of ≤ 3 mm, although PDT sometimes requires multiple sessions. Additionally, for tumors of > 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 that which PDT is less efficient. Limitations include the retrospective nature of the study, lack of randomization, and small study size.

Hocht et al. (2006) conducted a single-center retrospective study in 44 consecutive patients with choroidal 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 posttreatment complications. In photon and proton patients, the mean follow-up was 38.9 months and 26.3 months, respectively, and the median follow-up was 29 months and 23.7 months. Tumor thickness was greater in the photon group than in the proton group. In the collective groups, 91% were treated successfully, and no significant difference in the outcomes was observed 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 with proton vs 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 was conducted by Zhou et al. (2023) to explore whether PBT provided better efficacy and safety outcomes than photon therapy in individuals with esophageal cancer. Overall, 45 studies were included in the meta-analysis, with the primary outcomes being OAR dosimetric outcomes, OS, PFS, objective response rate, and radiation-

related toxic effects. In the dosimetric analysis, proton therapy was associated with a significantly reduced OAR dose. A meta-analysis showed that photon therapy was associated with poor OS, but no difference in PFS was observed. A 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. A single-rate analysis of proton therapy found 89% OS and 65% PFS at 1 year; 71% OS and 56% PFS at 2 years; 63% OS and 48% PFS at 3 years; and 56% OS and 42% PFS at 5 years. The incidence of grade 2 or higher radiation esophagitis was 50%; the incidence was 2% for grade 2 or higher radiation pneumonitis, 4% for grade 2 or higher pleural effusion, 3% for grade 2 or higher pericardial effusion, 8% for grade 3 or higher radiation esophagitis, and 17% for grade 4 or higher lymphocytopenia. The authors concluded that significantly reduced OAR doses and toxic effects and improved prognosis were associated with PBT for esophageal cancer compared with photon therapy. Limitations include the significant heterogeneity in the OAR dosimetric analysis, small study sizes, and lack of RCTs. The authors stated that caution was warranted with PBT for esophageal cancer, and future RCTs are recommended to verify the benefits provided by PBT. (Lin et al., 2020, Xi et al., 2017, and Lin et al., 2017, 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 stated that PBT may have effectiveness that is comparable to that of both IMRT and 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 was 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 3 years. The 2025 annual review included no newly published studies, and no change in the rating was observed (Hayes, 2022; updated 2025).

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, suggested that 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 that have limited follow-up, with most studies lacking a comparator group. The assessment found that the evidence base was insufficient to evaluate the efficacy and safety of PBT, and future studies were recommended. The 2025 update included no newly published studies that met the inclusion criteria, and no change was made in the Hayes rating (Hayes, 2022; updated 2025).

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 with 3D-CRT in patients 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 19 individuals with esophageal cancer. The overall 1- and 5-year actuarial survival rates in all 19 individuals were 79% and 42.8%, respectively. The median survival time was 31.5 months. Of the 19 individuals, 17 (89%) had a complete response within 4 months after completing treatment, and two (11%) had a partial response, resulting in a response rate of 100% (19/19). The 1- and 5-year LC rates in all 19 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 that further studies are needed to establish the appropriate role and treatment schedule for the use of PBT for esophageal cancer.

Mizumoto et al. (2010) evaluated the efficacy and safety of PBT for locoregionally advanced esophageal cancer. Overall, 51 individuals were treated using PBT, with or without x-rays. All but one had squamous cell carcinoma. Of the 51 individuals, 33 received combinations of x-rays and protons as a boost. The other 18 individuals received PBT alone. The overall 5-year actuarial survival rate in the 51 individuals was 21.1%, and the median survival time was 20.5 months. Of the 51 individuals, 40 (78%) had a complete response within 4 months after completing treatment, and seven (14%) had a partial response, resulting in a response rate of 92% (47/51). The 5-year LC rate in all 51 individuals was 38%, and the median LC time was 25.5 months. The authors concluded that these results suggest that PBT is an effective treatment for individuals with locally advanced esophageal cancer. The authors noted that further studies are required to determine the optimal total dose, fractionation schedules, and best combination of proton therapy with chemotherapy.

An ongoing phase 3 study is recruiting participants to compare the use of PBT with photon therapy in those with esophageal cancer (Clinical Trial ID: NCT03801876). For more information, go to http://www.ClinicalTrials.gov/. (Accessed November 6, 2025)

Clinical Practice Guidelines

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines state that PBT is appropriate when treating esophageal and esophagogastric junction cancers in settings in which dose reduction to OARs is necessary and cannot be achieved by 3D-CRT. Because data are early and evolving, individuals should receive PBT in a clinical trial (NCCN, 2025).

Society of Thoracic Surgeons (STS)/American Society for Radiation Oncology (ASTRO)

Worrell et al. (2024) developed guidelines for the STS and ASTRO regarding locally advanced cancer of the esophagus or gastroesophageal junction that do not specifically mention PBT. The guidelines note that IMRT is increasingly preferred over 3D-CRT for treating esophageal cancer due to its ability to better target tumors while sparing surrounding healthy tissues. In cases in which 3D-CRT cannot adequately protect OARs, IMRT is recommended to meet necessary dose constraints.

Gastrointestinal Cancers

Le et al. (2024) conducted a systematic review aimed to investigate the adverse effects with, compare dosimetric data for, and evaluate the oncological outcomes with PBT vs conventional RT in individuals with nonmetastatic rectal cancer (non–stage IV). Inclusion criteria included full-text, peer-reviewed RCTs and prospective or retrospective cohort studies, in English, that evaluated adults with nonmetastatic 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. Evidence to determine the adverse treatment outcomes with PBT vs conventional RT was insufficient. No current studies assess radiotoxicities or oncological outcomes. Pooled dosimetric comparisons between PBT and various conventional RTs were associated with reduced radiation exposure to the pelvis, bowel, and bladder. Due to the limited data available, the authors concluded that there is insufficient evidence to establish the superiority of PBT over conventional RT in reducing adverse treatment outcomes and improving oncological outcomes in individuals with nonmetastatic rectal cancer. The authors noted that pooled dosimetric analyses indicated that PBT reduces radiation exposure to surrounding tissues; however, these findings were based on a small number of studies that had high clinical heterogeneity and a moderate risk of bias. The authors called for more rigorous, prospective RCTs, with larger sample sizes, to better evaluate the efficacy and safety of PBT in nonmetastatic rectal cancer.

Fok et al. (2021) conducted a systematic review and meta-analysis that compared dosimetric irradiation of OARs and oncological outcomes with PBT vs conventional photon-based RT in locally advanced rectal cancer. Eight articles, with a total of 127 individuals, met the inclusion criteria. A significantly less irradiated small bowel was noted with PBT than with 3D-CRT and IMRT (mean difference, -17.01; CI, -24.06 to -9.96; $p < 0.00001$ and mean difference, -6.96; CI, -12.99 to -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 rates reported as 43%, 68%, and 77.2%; one study in primary rectal cancer showed 100% disease-free survival. The authors concluded that PBT treatment plans resulted in significantly less irradiation of OARs for rectal cancer than conventional photon-based RT. The authors noted that no clinical trials are currently ongoing for primary rectal cancer and PBT, and more research is required to validate PBT's role in organ preservation without increasing toxicity. Limitations include small sample sizes and a lack of RCTs.

Verma et al. (2016b) conducted a systematic review to identify studies of PBT and GI malignancies. The search included PubMed, Embase, and abstracts from the ASTRO, Particle Therapy Co-Operative Group, and American Society of Clinical Oncology meetings. A total of 39 original investigations were analyzed. For esophageal cancer, 12 studies were analyzed; several of those reported that PBT resulted in a significant dose reduction to intrathoracic OARs and was associated with reduced toxicity and 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 in resected/unresected cases was similar to existing data, in which 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 HCC, 10 studies were analyzed, and these had the strongest evidence to support the use of PBT. Those studies reported very low toxicities, and a phase 3 trial comparing PBT with TACE showed a trend toward better LC and PFS with PBT. For cholangiocarcinoma, liver metastases, and retroperitoneal sarcoma, survival and toxicity data are comparable to those for historical photon controls, and stomach and biliary system/gallbladder cancer studies consisted of case reports and small cohort experiences. The authors concluded that PBT offers the potential of lower toxicities, without compromising survival or LC. The authors acknowledged that high-quality evidence for select GI malignancies is limited, and further multi-institution RCTs are needed.

Clinical Practice Guidelines

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines do not address PBT in the treatment of gastric cancers (NCCN, 2025).

Gynecologic Cancers

Russo et al. (2025) conducted a prospective, phase 2 clinical trial to assess the safety and effectiveness of PBT using pencil-beam scanning in participants with node-positive uterine or cervical cancer. The study included 21 participants diagnosed with FIGO (International Federation of Gynecology and Obstetrics) stage IIIC uterine or N1 cervical cancer, all of whom had undergone hysterectomy and lymphadenectomy, followed by RT, between October 2013 and October 2018. The primary end point was a comparison of dose-volume histograms and toxicity profiles between PBT and IMRT. The secondary end points included PFS, OS, patterns of recurrence, and QOL. Eligibility criteria required histologically confirmed metastases to regional lymph nodes (parametrial, pelvic, or para-aortic), with no inclusion of participants with inguinal node involvement. Chemotherapy was allowed. Exclusion criteria included a life expectancy of less than 18 months, residual or measurable disease post surgery, poor performance status (Eastern Cooperative Oncology Group ≥ 3), and prior RT within the treatment field. With a median follow-up of 60.6 months (range, 11.2-68.8 months), 15 participants with uterine cancer and six participants with cervical cancer were included. Among them, four received pelvic RT, and 17 received extended-field radiation. Dose-volume histogram comparisons demonstrated that PBT reduced the volume of bowel, bone marrow, and kidney tissue exposed to radiation compared with 3D-CRT and IMRT, with statistically significant differences at all dose levels, except for V45 bladder and bowel. In terms of toxicity, acute grade 3 GI toxicity occurred in 14% of participants, while late grade 3 GI toxicity was observed in 4.7%. No grade 3 GU toxicities were reported. Hematologic toxicities of grade 3 were seen in 24% of participants acutely and 4.7% in the late phase. One participant experienced late grade 3 lymphedema. Survival outcomes were favorable, with PFS rates of 81% at 2 years and 76% at 5 years and OS rates of 86% at 2 years and 80% at 5 years. There were no in-field recurrences. QOL improved significantly over time, with an average increase of 10.7 points from baseline to 5 years ($p = 0.032$). According to the authors, compared with photon-based RT, PBT significantly reduces exposure to surrounding healthy tissues. It has shown effectiveness in preventing local and regional recurrence in those with node-positive uterine and cervical cancer, with minimal acute and late toxicities. Additionally, participant-reported QOL improved notably from baseline to 5 years post treatment. Limitations include the small sample size, single-arm design, and retrospective comparisons to photon therapies.

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, 5-year and 10-year survival rates were similar to those with conventional therapies, as reported in the literature. The 10-year survival rate was higher in participants with low-stage cervical cancer (89%) than in those with advanced stages (40%) of cervical cancer. The treatment caused severe late complications in 4% of participants.

Clinical Practice Guidelines

Society of Gynecologic Oncology (SGO)/American Society for Radiation Oncology (ASTRO)/ American Brachytherapy Society (ABS)

Neibart et al. (2025) developed a consensus statement endorsed by the SGO, ASTRO, and the ABS outlining minimum standards for RT in cervical cancer care. The statement recommends IMRT for adjuvant treatment and image-guided brachytherapy as essential quality benchmarks. PBT is not specifically addressed in the consensus.

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines do not address the use of PBT when treating ovarian cancer, uterine neoplasms, or vulvar cancer (NCCN, 2025).

Lung Cancer

Volpe et al. (2022) performed a systematic review and meta-analysis to evaluate hypofractionated PBT for the treatment of early-stage non-small cell lung cancer (NSCLC). Inclusion criteria consisted of studies that involved individuals with NSCLC treated with curative-intent PBT using hypofractionated radiation schedules, defined as doses of at least 3 Gy (RBE) per fraction. To be eligible, studies also needed to report clinical outcomes such as OS, LC, and both acute and late treatment-related toxicities. Furthermore, only studies with full-text availability were considered for inclusion. Eight studies, involving a total of 401 individuals, were included in the meta-analysis, with a median follow-up of 32.8 months. The median biologically effective dose delivered was 105.6 Gy (RBE). Those who received a biologically effective dose of 105.6 Gy (RBE) or higher consistently showed better clinical outcomes, including OS, cancer-specific survival, disease-

free survival, and LC. For example, the 4-year OS rate was 56% in those receiving less than 105.6 Gy (RBE) compared with 78% in those receiving the higher dose. The likelihood of experiencing acute grade ≥ 2 toxicity was similar between the two dose groups. However, late grade ≥ 2 toxicities were nearly three times more frequent in the higher-dose group, with rib fractures being notably more common. The authors concluded that hypofractionated PBT is a safe and effective treatment option for early-stage NSCLC. However, they noted that their analysis did not provide sufficient evidence to support PBT as a definitive alternative to SBRT for this population of individuals. The authors suggested that further studies are needed to clarify the role of PBT.

Liao et al. (2018) conducted a single-center randomized trial that compared outcomes with passive scattering proton therapy (PSPT) vs those with 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 5 to 10 Gy RBE, which is the absorbed Gy dose multiplied by the RBE factor for protons, and exposed more lung tissue to ≥ 20 Gy RBE but exposed less heart tissue at all dose levels between 5 and 80 Gy RBE. Grade ≥ 3 radiation pneumonitis was greater with PSPT than IMRT (6.5% with IMRT and 10.5% with PSPT), although the difference did not reach statistical significance; no difference was observed in local failure (10.9% and 10.5% with IMRT and PSPT, respectively). An exploratory analysis showed that the radiation pneumonitis and local failure rates at 12 months in participants enrolled before vs after the trial midpoint were 21.1% (before) vs 18.2% (after) for the IMRT group and 31.0% (before) vs 13.1% (after) for the PSPT group, suggesting that outcomes with 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 the 5-year results of a prospective, phase 2, single-institution study evaluating chemotherapy with concurrent high-dose PBT in 64 participants with unresectable stage III NSCLC. The 5-year rates of OS, PFS, actuarial distant metastases, and locoregional recurrence were 29%, 22%, 54%, and 28%, respectively. Acute and late toxic effects with PBT (compared with 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 is 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 hypofractionated PBT's efficacy relative to that of photon SBRT for early-stage NSCLC. Overall, 72 SBRT studies and nine hypofractionated PBT studies (mostly single arm) were included. PBT was associated with improved OS and PFS in the univariate meta-analysis. The OS benefit did not reach its statistical significance after inclusion of operability into the final multivariate meta-analysis, while the 3-year LC still favored PBT. Researchers concluded that although hypofractionated PBT may lead to additional clinical benefit compared with photon SBRT, no statistically significant survival benefit with 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 1 trial to determine the recommended dose of PBT for inoperable stage III NSCLC. Two prescribed doses of PBT were tested: 66 Gy RBE in 33 fractions and 74 Gy RBE in 37 fractions in arms 1 and 2, respectively. The planning target volume included the primary tumor and metastatic lymph nodes with adequate margins. Concurrent chemotherapy included intravenous cisplatin [60 mg/m (2), day 1] and oral S-1 (80, 100, or 120 mg based on body surface area; days 1 to 14), repeated as four cycles every 4 weeks. Dose-limiting toxicity (DLT) was defined as grade 3 (severe) toxicities related to PBT during days 1 to 90. Each dose level was performed in three participants and then escalated to the next level if no DLT occurred. When one participant developed a DLT, three additional participants were enrolled. Overall, nine participants were enrolled, including six in arm 1 and three in arm 2. The median follow-up time was 43 months, and the median PFS was 15 months. In arm 1, grade 3 infection occurred in one of six participants, but no other DLT was reported. Similarly, no DLT occurred in arm 2. However, one participant in arm 2 developed grade 3 esophageal fistula at 9 months after the initiation of PBT. From a clinical perspective, the authors concluded that 66 Gy RBE was the recommended dose.

Oshiro et al. (2014) initiated a phase 2 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 1) and vinorelbine (on days 1 and 8). The treatment doses were 74 Gy RBE for the primary site and 66 Gy RBE for the lymph nodes without elective lymph nodes. The median follow-up period was 21.7 months. None of the participants experienced grade 4 or 5 nonhematologic 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

(grade ≥ 3) leukocytopenia, neutropenia, and thrombocytopenia were observed in 10, seven, and one participant(s), respectively. Late radiation (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 11 participants, with the mean survival time being 26.7 months. The authors cited a short follow-up period as a limitation to this study and concluded that high-dose PBT with concurrent chemotherapy is safe and useful in the multimodality therapy for unresectable NSCLC.

Sejpal et al. (2011) conducted a single-center, retrospective case series study to evaluate the use of PBT plus concurrent chemotherapy in patients with NSCLC. Outcomes included acute and subacute toxicity and were evaluated using Common Terminology Criteria (version 3.0) at least weekly during treatment; at 4 to 6 weeks after treatment; every 3 months for 2 years; and then every 6 months. Survival, time to progression, and failure patterns were also collected. Comparisons between other radiation treatment modalities (IMRT and 3D-CRT, each with concurrent chemotherapy) were made using historical controls from the same center. A total of 202 patients were included in the analysis: 74 received 3D-CRT, 66 received IMRT, and 62 received PBT. The median follow-up periods were 17.9 months (3D-CRT), 17.4 months (IMRT), and 15.2 months (proton). The median total radiation dose was higher in the PBT group at 74 Gy vs 63 Gy in the other groups. Despite the higher radiation dose in the PBT group, rates of severe (grade ≥ 3) pneumonitis and esophagitis were lower (2% and 5%, respectively) than those in 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 with 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 3 trials were found. For PBT, 2- to 5-year LC rates varied in the range of 57% to 87%. The 2- and 5-year OS and 2- and 5-year cause-specific survival rates were 31% to 74% and 23% and 58% to 86% and 46%, respectively. Radiation-induced pneumonitis was observed in approximately 10% of individuals. With C-ion therapy, the overall LC rate was 77%, but it was 95% when using a hypofractionated radiation schedule. The 5-year OS and cause-specific survival rates were 42% and 60%, respectively. Slightly better results (at 50% and 76%, respectively) were reported when using hypofractionation. The authors concluded that 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 need for thorough investigation into its efficiency. The authors noted that until such data are available for lung cancer, charged particle therapy should be considered experimental.

A phase 3 RCT comparing photon with proton chemoradiotherapy in participants with inoperable NSCLC (NCT01993810) is in progress. For more information, go to www.ClinicalTrials.gov. (Accessed November 6, 2025)

Clinical Practice Guidelines

American College of Radiology (ACR)

The ACR appropriateness criteria addressing nonsurgical treatment for locally advanced NSCLC state 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)

The NCCN guidelines state that advanced technologies, such as four-dimensional computed tomography and/or positron emission tomography/computed tomography simulation, IMRT/VMAT, image-guided RT, motion management, and PBT, are appropriate when needed to deliver curative RT safely when treating NSCLC and may be appropriate to limit normal tissue toxicity in the treatment of small cell lung cancer (NCCN, 2025).

Pancreatic Cancer

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

Clinical Practice Guidelines

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines do not address PBT in the treatment of pancreatic adenocarcinoma (NCCN, 2025).

Vestibular Tumors

The systematic review and meta-analysis by Santacroce et al. (2023) examined the effectiveness of PBRT for the treatment of vestibular schwannomas (VSs), with regard to 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. The overall rate of tumor control (both stability and decrease in volume) was 95.4% (range, 93.5%-97.2%; p heterogeneity = 0.77; $p < 0.001$). The overall rate of tumor progression was 4.6% (range, 2.8%-6.5%; p heterogeneity, < 0.77; $p < 0.001$). The 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; $p < 0.001$). The overall rate of facial nerve preservation was 93.7% (range, 89.6%-97.7%; I^2, 76.27%; p heterogeneity < 0.001; $p < 0.001$). The overall rate of hearing preservation was 40.6% (range, 29.4%-51.8%; 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 with standard SRS techniques. Additionally, the likelihood of facial nerve preservation is lower compared with most radiosurgery techniques. The authors noted that overall, PBRT for VS did not offer a significant benefit for facial and hearing preservation compared with most currently reported SRS series. Limitations include a limited number of studies, most of which were retrospective in nature. (Authors Saraf et al., 2022, Bush et al., 2002, and Harsh et al., 2002, 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% to 100%. Early experience using PBT for treating VS demonstrated LC rates of 84% to 100% but disappointing hearing preservation rates of 33% to 42%. The authors reported that mixed data regarding the ideal hearing preservation therapy, inherent biases in the selection of individuals, and differences in outcome analysis have made comparison across radiotherapeutic modalities difficult.

Clinical Practice Guidelines

Congress of Neurological Surgeons (CNS)

The CNS published an updated systematic review and evidence-based guideline on the role of radiosurgery and RT in the management of individuals with VSs. The CNS notes that no studies that compare two or all three modalities (Gamma Knife vs LINAC-based radiosurgery vs proton beam) were identified; therefore, no recommendations on outcome could be made (Germano et al., 2025).

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 October 1, 2025)

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Policy History/Revision Information

Date	Summary of Changes

05/01/2026	**Related Policies**
	• Removed reference link to the Medical Policy titled *Intensity-Modulated Radiation Therapy (for Kentucky Only)*
	Coverage Rationale
	• Revised coverage criteria for evaluation of exception requests for a covered diagnosis of proton beam radiation therapy (PBT) that is not listed [in the policy] as proven; replaced criterion requiring the "evaluation includes a comparison of treatment plans for PBT, intensity modulated radiation therapy (IMRT), and stereotactic body radiation therapy for the specific individual" with "evaluation includes a comparison of treatment plans for PBT *and photon-based radiation therapy (such as* PBT, intensity modulated radiation therapy (IMRT), or stereotactic body radiation therapy) for the specific individual"
	Medical Records Documentation Used for Reviews
	• Added language to indicate:
	  ○ 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
	  ○ Medical records documentation may be required to assess whether the member meets the clinical criteria for coverage but does not guarantee coverage of the service requested
	  ○ The patient's medical record must contain documentation that fully supports the medical necessity for the requested services

Date	Summary of Changes
	○ This documentation includes but is not limited to relevant medical history, physical examination, and results of pertinent diagnostic tests or procedures ○ Documentation supporting the medical necessity should be legible, maintained in the patient's medical record, and must be made available upon request **Applicable Codes** • Removed CPT/HCPCS codes 77385, 77386, G6015, G6016, and G6017 **Supporting Information** • Updated *Clinical Evidence* and *References* sections to reflect the most current information • Archived previous policy version CS105KY.10

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, 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.

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