Proton Beam Radiation Therapy (for New Mexico Only)

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➲ Instructions for Use

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Related Policies

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

Application

This Medical Policy only applies to the state of New Mexico.

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 for the following:

- Definitive Therapy for the following indications:
  - Base of Skull Tumors (e.g., chordomas, chondrosarcomas, paranasal sinus or, nasopharyngeal tumors)
  - Primary Head and Neck Cancers (not included above) when all the following criteria are met:
    - The tumors are near critical anatomical structures, such as the orbit, skull base, or cavernous sinus or with intracranial extension or perineural invasion; and
    - When documentation is provided that sparing of the surrounding normal tissue cannot be achieved with standard photon radiation therapy techniques
  - Primary Central Nervous System Tumors (e.g., brain or spinal cord) when all the following criteria are met:
    - The tumors are near critical anatomical structures such as the optic nerve, brainstem, or spinal cord; and
    - When documentation is provided that sparing of the surrounding normal tissue cannot be achieved with standard photon radiation therapy techniques
  - Intracranial arteriovenous malformations
  - Ocular tumors, including intraocular/uveal melanoma (includes the iris, ciliary body, and choroid)
  - Primary liver malignancies, such as hepatocellular carcinoma and intrahepatic cancer (localized, unresectable) in the curative setting when documentation is provided that sparing of the surrounding normal tissue cannot be achieved with standard radiation therapy techniques, including intensity-modulated radiation therapy (IMRT), stereotactic body radiation therapy, and selective internal radiation spheres, and transarterial therapy (for example, chemoembolization) is contraindicated or not technically feasible
  - Primary mediastinal tumors (e.g., thymomas, mediastinal lymphomas, thoracic sarcomas)
  - Reirradiation when all the following criteria are met:

- Individuals have previously undergone radiation therapy to a specific anatomical site and now require an additional course of radiation to the same specific anatomical site; and
- Documentation is provided that sparing of the surrounding normal tissue cannot be achieved with standard photon radiation therapy techniques

PBT and IMRT are proven and considered clinically equivalent for treating prostate cancer. Medical necessity will be determined based on the terms of the member specific benefit plan.

PBT is unproven and not medically necessary due to insufficient evidence of efficacy for treating all other indications; however, PBT may be covered for a diagnosis that is not listed above as proven, including recurrences or metastases in selected cases. Requests for exceptions will be evaluated on a case-by-case basis when both of the following criteria are met:

- Documentation is provided that sparing of the surrounding normal tissue cannot be achieved with standard radiation therapy techniques; and
- Evaluation includes a comparison of treatment plans for PBT 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.

Definitions

Refer to the federal, state, or contractual definitions that supersede the definitions below.

Base of Skull Tumors: A diverse group of lesions that vary in aggressiveness and arise in the anatomically complex region at the base of the skull. This area includes critical structures such as the anterior cranial fossa, clivus, petrous bone, middle cranial fossa, cavernous sinus, and infratemporal fossa, which house essential endocrine, neurological, and vascular components. Common tumor types in this region include chordomas and chondrosarcomas (Combs et al., 2021).

Central Nervous System Tumors: A tumor that originates in the central nervous system, which includes types such as brainstem glioma, craniopharyngioma, medulloblastoma, and meningioma. These are collectively referred to as Central Nervous System Tumors [National Cancer Institute (NCI), 2025].

Definitive Therapy: Radiation treatments for cancer with a curative intent (National Comprehensive Cancer Network, 2025; Landsteiner et al., 2023). The NCI defines curative-intent therapy as a treatment designed to eliminate a disease or illness, aiming for a full recovery while maintaining a satisfactory quality of life. In cancer care, the suitability of a curative approach depends on the specific type and stage of cancer (NCI, 2025).

Head and Neck Cancer: Refers to a group of cancers that originate in various tissues of the head and neck region. These cancers typically form in areas such as the nasal cavity, sinuses, lips, mouth, salivary glands, throat, and larynx. Head and Neck Cancers typically originate in squamous cells. Key risk factors include tobacco use, excessive alcohol consumption, and infection with high-risk strains of human papillomavirus (NCI, 2025).

Applicable Codes

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

CPT Code	Description
77301	Intensity modulated radiotherapy plan, including dose-volume histograms for target and critical structure partial tolerance specifications
77338	Multi-leaf collimator (MLC) device(s) for intensity modulated radiation therapy (IMRT), design and construction per IMRT plan
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
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

Diagnosis Code	Description
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

Base of Skull Tumors

In their 2025 study, Dong et al. conducted a comprehensive meta-analysis to investigate the therapeutic efficacy and safety profile of proton beam radiation therapy (PBRT) in those diagnosed with chondrosarcoma. The study included research involving individuals with pathologically confirmed chondrosarcoma and provided data on survival outcomes,

such as overall survival (OS) and local control (LC) rate, as well as toxicity related to PBRT. Studies were excluded if they involved other radiation modalities, contained duplicate data, lacked sufficient detail, or were case reports, letters, abstracts, protocol reviews, or meta-analyses. Additional exclusions applied to reirradiation studies, studies with fewer than 10 individuals, non-English publications, and those unrelated to the research focus. Six studies were included in the meta-analysis, comprising one prospective and five retrospective designs. Together, they involved 282 individuals with chondrosarcoma who received proton beam therapy (PBT) between 1990 and 2020. Across the six included studies, the median number of individuals was 47 (ranging from 10 to 107), with a mean median age of 38.9 years (spanning 10.2 to 89 years). The median follow-up duration was at least 12 months, extending up to 91 months. LC rates remained consistently high, with 100% reported at years 1 through 4 and year 10 and 95% at year 5. OS rates were similarly strong, showing 100% at years 1 through 4 and year 10 and 99% at year 5. Reported toxicities related to PBT were generally mild, with most studies noting grade 2 or lower adverse effects. The authors concluded that PBT is an effective treatment for chondrosarcoma, particularly for tumors located at the skull base, demonstrating high rates of LC and OS. Additionally, treatment-related toxicity was generally mild and well tolerated. However, they emphasized the need for further prospective studies and extended follow-up to better understand potential late-onset toxicities. Limitations include the small sample size and retrospective nature of the majority of the included studies.

ECRI's evidence review on PBT for skull base chondrosarcomas found that PBT delivers more precise radiation, with less damage to surrounding healthy tissue, than conventional photon therapy, although supporting data remain limited. A separate analysis for skull base chordomas reported that combining PBT with surgical resection improves 5-year OS rates compared with surgery alone or surgery plus photon radiation therapy (RT). Overall, the Evidence Bar indicates a favorable rating (ECRI, 2025).

Nie et al. (2022) conducted a systematic review to analyze clinical outcomes with and potential toxicities of skull base chordomas and chondrosarcomas after treatment with PBT. The review included seven moderate- to high-quality studies, with a total of 478 individuals diagnosed with chordoma or chondrosarcoma. The follow-up time in the cohort ranged from 21 to 61.7 months. For PBT planning, the median target volume ranged from 15 cc to 40 cc, and the administered median dose varied from 63 to 78.4 Gy at 1.8 to 2.0 Gy per fraction. The 1-, 2-, 3-, 5-, and 7-year LC and OS rates were 100%, 93%, 87%, 78%, and 68% and 100%, 99%, 89%, 85%, and 68%, respectively. The late grade 3 or higher toxicities were reported in only two involved articles. The authors concluded that PBT demonstrated favorable LC and survival rates, with a low incidence of severe radiation-induced toxicities. Limitations include a lack of follow-up time longer than 7 years and limited studies, which mostly consisted of retrospective and observational cohort studies. The authors recommended multicenter randomized controlled trials (RCTs) in the future.

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

Lee et al. (2021) conducted a systematic review on proton therapy in individuals with nasopharyngeal cancer (NPC), focusing on the toxicity end points. A total of 491 studies were found on the topic (no randomized data), and nine studies were found to have sufficient focus and relevance to be included. Individuals with NPC were examined in all nine retrospective studies, except one, which included paranasal sinus cancer. One study was a reirradiation study. Four studies used a three-dimensional or double-scatter technique, while all others used intensity-modulated proton therapy. Oncological outcomes were similar to IMRT rates, with 2-year local and regional progression-free survival (PFS) ranging from 84% to 100%, 2-year PFS ranging from 75% to 88.9%, and 2-year OS ranging from 88% to 95% in the up-front setting. Four comparison studies with IMRT found significantly lower feeding tube rates (20% vs 65%, $p = 0.015$ and 14% vs 85%, $p < 0.001$) with proton therapy as well as lower mucositis (grade 2: 46% vs 70%, $p = 0.019$; grade 3: 11% vs 76%, $p = 0.0002$). All other acute and late effects were not statistically significant but largely improved with proton therapy. The authors concluded that individuals with NPC maintained good outcomes, with an improved toxicity profile, likely due to sparing of the dose to normal structures when receiving proton therapy. The authors recommended further prospective studies to better quantify the magnitude of benefit. Limitations include a small number of studies, short follow-up periods, and a retrospective study design.

In a Hayes Technology Assessment for PBT for the treatment of chordoma and chondrosarcoma of the skull base, PBT was reported to be relatively safe, with a moderate risk of acute toxicities and lower risk of long-term complications. The assessment noted that PBT has similar efficacy as photon-based external beam radiation therapy (EBRT) technologies and may reduce the risk of certain complications in adult individuals. Additional well-designed, long-term studies comparing PBT with other therapies are recommended. The 2023 update included 11 new studies; however, no rating change occurred (Hayes, 2019; updated 2023).

Zhou et al. (2018) performed a meta-analysis to compare the effectiveness of photon therapy, PBT, and carbon ion therapy for chordoma. Overall, 25 studies were included, with results showing that the 3-, 5-, and 10-year OS rates were higher with stereotactic RT, PBT, and carbon ion therapy than with conventional RT. The 10-year OS was higher with PBT than stereotactic RT. The analysis revealed that particle therapy was more effective following surgery for chordoma than conventional RT. After 10 years, PBT was more beneficial than stereotactic RT. However, future studies should include more studies to enable accurate meta-analysis and a better exploration of prognosis.

The use of PBT to treat chondrosarcoma of the skull base after surgery is widely accepted, but studies demonstrating the need for PBT and its superiority compared with RT with photons are lacking. In a systematic review, Amichetti et al. (2010) reported that studies of PBT for skull-based chondrosarcoma resulted in LC ranging from 75% to 99% at 5 years. No prospective trials (randomized or nonrandomized) were included, but four uncontrolled, single-arm studies with 254 individuals were included. The authors concluded that PBT following surgical resection showed a very high probability of medium- and long-term cure, with a relatively low risk of significant complications.

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

Clinical Practice Guidelines

American Society for Radiation Oncology (ASTRO)

ASTRO's model policy states that PBT is considered reasonable in instances in which sparing the surrounding tissue cannot be adequately achieved with photon-based RT and is of added clinical benefit to the individual. Disease sites that frequently support the use of PBT include tumors that approach or are located at the base of skull, including chordoma and chondrosarcomas (ASTRO, 2022).

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines for bone cancer state that specialized techniques, including particle beam RT with protons, should be considered as indicated in order to allow high-dose therapy while maximizing normal tissue sparing in individuals with chondrosarcoma or chordoma. (NCCN, 2026).

The NCCN guidelines on head and neck cancers state that the use of proton therapy is an area of active investigation. In cancers of the oropharynx, nasopharynx, supraglottic larynx, paranasal sinus, or salivary glands or mucosal melanoma and other primary tumors of the head and neck, proton therapy can be considered when normal tissue constraints cannot be met by photon-based therapy or when photon-based therapy causes compromise of standard radiation dosing to the tumor or postoperative volumes. Additionally, either IMRT or proton therapy is recommended for maxillary sinus or paranasal/ethmoid sinus tumors to minimize the dose to critical structures (NCCN, 2025).

Head and Neck Cancers

Razavian et al. (2025) conducted a systematic review and meta-analysis to evaluate the safety and efficacy of PBT in individuals with oropharyngeal cancer (OPC). The study aimed to evaluate toxicity rates and oncological outcomes, including PFS and OS. Patient-reported outcomes, patterns of failure, and comparisons between PBT and IMRT were also examined. Researchers searched four electronic databases for studies published between January 1, 1980, and May 1, 2024. To be included, studies had to report on at least 10 individuals treated with PBT as initial therapy and provide data on oncological outcomes, clinician-rated toxicity, or patient-reported outcomes. Studies involving IMRT alone, IMRT combined with PBT, or PBT used for reirradiation were excluded from the analysis. Pooled outcomes in the study were calculated using random-effects models, with comparisons between PBT and IMRT based on log odds ratios. The analysis incorporated 18 studies, 16 retrospective and two prospective, covering a total of 956 individuals. Reported rates of acute grade 3 or higher toxicities were 19% for dermatitis, 32% for mucositis, 1.3% for xerostomia, 13% for dysphagia, and 1.4% for weight loss. Additionally, 10% of individuals experienced acute hospitalizations. Among studies that reported late toxicities, grade ≥ 3 xerostomia and dysphagia occurred at rates of 1.1% and 1.6%, respectively. Compared with IMRT, PBT was linked to significantly lower rates of acute feeding tube use (21% vs 31%; p = 0.0012), although long-term feeding tube use did not differ significantly (1.4% vs 2.7%; p = 0.24). Survival outcomes following PBT were high, with 2-

and 3-year OS rates at 98% and 96% and PFS rates at 93% and 86%, respectively. The authors concluded that PBT for OPC was linked to favorable toxicity profiles and strong oncological outcomes. Although RCTs are still underway, the current evidence supports the effectiveness of PBT as an initial treatment option for OPC. The study has notable limitations, including restricted direct comparisons between PBT and IMRT as well as the absence of RCTs, which limits the strength of the evidence and ability to draw definitive conclusions.

Seeking to improve the LC rate and reduce late adverse events, Takayama et al. (2016) evaluated therapeutic results and toxicities with PBT combined with selective intra-arterial infusion chemotherapy (IACT) in participants with stage III to IVB squamous cell carcinoma of the tongue. Between February 2009 and September 2012, 33 participants were enrolled. After two systemic chemotherapy courses and whole-neck irradiation (36 Gy in 20 fractions), participants were administered concurrent chemoradiotherapy comprising PBT for the primary tumor and the metastatic neck lymph node, with weekly retrograde IACT of cisplatin with sodium thiosulfate by continuous infusion. The median follow-up duration was 43 months. The 3-year OS rate, PFS rate, LC rate, and regional control rate for the neck were 87%, 74.1%, 86.6%, and 83.9%, respectively. Major acute toxicities of grade > 3 included mucositis in 26 cases (79%), neutropenia in 17 cases (51%), and dermatitis in 11 cases (33%). Late grade 2 osteoradionecrosis was observed in one case (3%). The authors concluded that PBT-IACT shows promising results for advanced tongue cancer and offers effective treatment with manageable side effects. However, the study had a small sample size and lacked direct comparisons to conventional RT.

Clinical Practice Guidelines

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

The ACR/ARS practice parameter indicates that PBT minimizes the radiation dose to vital structures in the head and neck area, which may enhance quality of life (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 (Frank et al., 2024).

American Society for Radiation Oncology (ASTRO)

Margalit et al. (2024) developed an evidence-based guideline for ASTRO addressing treatment recommendations for individuals with human papillomavirus–associated oropharyngeal squamous cell carcinoma. The guideline strongly recommends using IMRT over three-dimensional conformal radiation therapy (3D-CRT) in both the definitive and postoperative settings due to better organ-at-risk (OAR) sparing and improved dose uniformity. The guideline also notes that delivery of RT in the definitive or postoperative setting can be accomplished by using a variety of techniques, including 3D-CRT, IMRT, or proton therapy.

National Comprehensive Cancer Network (NCCN)

According to NCCN guidelines, IMRT is the preferred technique for treating head and neck cancers. However, other advanced modalities like volumetric modulated arc therapy (VMAT) and PBT may be appropriate, depending on factors such as tumor stage and location, physician expertise, and available physics support. These technologies can offer meaningful benefits in select cases by sparing OARs and reducing the likelihood of long-term tissue damage while maintaining effective tumor control. PBT is particularly valuable for tumors near sensitive areas such as the orbit, skull base, or cavernous sinus and for cases with intracranial extension or extensive perineural invasion. It is especially considered for individuals being treated with curative intent or those expected to have long survival post treatment. PBT may be appropriate when photon-based therapies cannot meet normal tissue dose constraints (NCCN, 2025).

Central Nervous System Tumors (Primary)

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 World Health Organization (WHO) grade 2 to 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 that 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 that 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.

Kabolizadeh et al. (2017) conducted a single-center, retrospective case series to evaluate LC, OS, disease-specific survival, and distant failure in 40 patients with unresected chordoma treated with photon/proton RT. Tumor response was assessed using the modified Response Evaluation Criteria in Solid Tumors. 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. Overall, 27 patients had sacrococcygeal chordoma, and the remaining patients had mobile spine tumors, which included nine cervical, one thoracic, and three lumbar. In total, 39 patients underwent proton therapy only or predominantly proton therapy mixed with photons to limit the radiation dose to adjacent critical normal structures. Only four patients received either concurrent or neoadjuvant systemic treatments. The median age was 67 years (range, 36-94 years), and the median follow-up, after completion of RT, was 50.3 months (range, 2-216.4 months). At 5 years, rates for LC, OS, disease-specific survival, and distant failure were 85.4%, 81.9%, 89.4%, and 20.2%, respectively. Nineteen patients had complete sets of regular imaging scans (a total of 84 computed tomography and magnetic resonance imaging scans were reviewed); of those, only four local failures had occurred at 34, 46, 78, and 82 months after treatment. The authors concluded that their results support the use of high-dose definitive 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 include its design, small number of patients with local failure, and limited follow-up periods.

Indelicato et al. (2016) conducted a 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 the median follow-up was 3.7 years (range, 0.3-7.7 years). Overall, 34 individuals with chordomas and 17 individuals with chondrosarcomas, which were all grade 2 or higher, were included. The anatomical 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 4-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: 18 local recurrences, six local and distant recurrences, and one distant metastasis. In individuals with a local relapse, the median time to progression was 1.7 years (range, 0.2-6 years). The median survival after local progression was 1.7 years (range, 0.1-4.9+ years). Regression analysis results showed that younger 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 historical 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 include its design, small sample size, and small number of select events, which may have impacted the statistical validity of the regression analysis results.

Shih et al. (2015) conducted a prospective single-arm trial to evaluate potential treatment toxicity and PFS in participants (n = 20) with low-grade glioma who were treated with PBRT. Participants with WHO grade 2 glioma who were eligible for RT were enrolled in the study. All participants received proton therapy at a dose of 54 Gy 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 20 participants. 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 participants had baseline neurocognitive impairments observed in language, memory, and processing speed. No overall decline in cognitive functioning occurred over time. New endocrine dysfunction was detected in six participants, 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 3 years was 85% but fell to 40% at 5 years. The authors concluded that individuals with low-grade glioma tolerate proton therapy well, and a subset develops neuroendocrine deficiencies. Additionally, no evidence for overall decline in QOL or cognitive function was observed. The authors recommended larger studies that include the integration of standardized, contemporary chemotherapy regimens, with randomization of proton vs photon therapy to characterize potential differences in radiation late effects. Limitations of this study include a small sample size and lack of a comparative group and randomization.

Clinical Practice Guidelines

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

According to the ACR-ARS practice parameter, PBT is especially useful for treating brain tumors because it minimizes radiation exposure to healthy brain structures like the brainstem, eyes, pituitary gland, hippocampus, and cochleae. This precision reduces the risk of long-term cognitive and QOL issues. Additionally, the stable setup and accurate targeting of the cranium allow for safer dose escalation and limit unintended radiation to surrounding tissue. Additionally, spinal and

paraspinal tumors are well suited for PBT due to their location and the precision of proton beams. Unlike x-rays, protons stop abruptly, which helps limit radiation exposure to nearby organs such as the thyroid, heart, lungs, kidneys, and spinal cord. This targeted approach reduces the risk of damage to healthy tissues and allows for safer treatment (Frank et al., 2024).

American Society for Radiation Oncology (ASTRO)

According to ASTRO guidelines, proton therapy is conditionally recommended for treating IDH-mutant WHO grade 2 and 3 diffuse gliomas, particularly when tumors are located near critical OARs, as it may help reduce both acute and long-term toxicity (Halasz et al., 2022).

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines for central nervous system (CNS) cancers state 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, such as proton therapy, are recommended for treating meningiomas to minimize exposure to critical structures and preserve surrounding healthy tissue. Proton therapy may be considered for those with a favorable long-term prognosis, such as those with grade 2 gliomas, grade 3 IDH-mutant tumors, or 1p/19q codeleted tumors, to better spare uninvolved brain tissue and help preserve cognitive function. Preliminary data indicate that proton therapy may lower radiation exposure to developing brain tissue and reduce treatment-related toxicities while maintaining effective disease control. Proton therapy can be beneficial for treating primary spinal cord tumors because it helps protect nearby healthy tissues, including unaffected parts of the spinal cord and surrounding nerve roots. For glioma reirradiation, highly precise modalities such as IMRT, PBT, or SRS are often necessary to optimize dose distribution to critical structures and minimize overlap with a previously treated region. For leptomeningeal metastases, the volume and dose are determined by the primary tumor's histology and the care objectives. For craniospinal irradiation in individuals with metastatic solid tumors, techniques that maximize bone marrow sparing, such as using protons when available or IMRT, may be considered (NCCN, 2025).

Intracranial Arteriovenous Malformations

Zuurbier et al. (2019) updated a previously conducted systematic review (Ross and Al-Shahi Salman, 2010) that aimed to determine the effectiveness and safety of the different interventions, alone or in combination, for treating brain arteriovenous malformations (AVMs) in adults compared against either each other or conservative management in RCTs. A search was conducted using the Cochrane Stroke Group Trials Register, the Cochrane Central Register of Controlled Trials, the Cochrane Library, MEDLINE, Ovid, and Embase Ovid. The search identified 14 eligible RCTs; of those, 13 were excluded (10 did not meet the inclusion criteria, and three were still ongoing), and one RCT, with 226 individuals, was included (Mohr et al., 2013). The study titled A Randomized Trial of Unruptured Brain Arteriovenous Malformations (ARUBA) was an international, multicenter, randomized controlled, open, prospective clinical trial comparing interventional treatment (endovascular, surgical, and/or RT) with conservative management for unruptured brain AVMs in adults. The primary outcome was death or dependence from any cause (modified Rankin Scale score ≥ 2), and secondary outcomes included symptomatic intracranial hemorrhage, epileptic seizure, symptomatic radiation necrosis detected by magnetic resonance imaging, and QOL. Data on functional outcome and death at 12 months of follow-up were provided for 218 of the individuals (96%). Intervention compared with conservative management increased death or dependency, with a risk ratio (RR) of 2.53, 95% CI of 1.28 to 4.98, and a higher proportion of individuals with symptomatic intracranial hemorrhage (RR, 6.75; 95% CI, 2.07-21.96). No difference in the frequency of epileptic seizures (RR, 1.14; 95% CI, 0.63-2.06) was observed. The authors reported that moderate-quality evidence from one RCT (of adults with unruptured brain AVMs) showed that conservative management was superior to intervention, with respect to functional outcome and symptomatic intracranial hemorrhage during the 1-year period after randomization; however, more RCTs are needed to confirm or refute these findings.

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

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

Hattangadi-Gluth et al. (2014) evaluated the obliteration rate and potential adverse events with single-fraction proton beam stereotactic radiosurgery (PSRS) in individuals with cerebral AVMs. From 1991 to 2010, 248 consecutive individuals with 254 cerebral AVMs received single-fraction PSRS at a single institution. The median AVM nidus volume was 3.5 cc, 23% of AVMs were in critical/deep locations (basal ganglia, thalamus, or brainstem), and the most common dose was 15 Gy. At a median follow-up time of 35 months, 64.6% of AVMs were obliterated. The median time to total obliteration was 31 months, and the 5- and 10-year cumulative incidence of total obliteration was 70% and 91%, respectively. On univariable analysis, a smaller target volume, smaller treatment volume, higher prescription dose, and higher maximum dose were associated with total obliteration. A deep/critical location was also associated with decreased likelihood of obliteration. On multivariable analysis, a critical location and smaller target volume remained associated with total obliteration. Posttreatment hemorrhage occurred in 13 cases (5-year cumulative incidence of 7%), all among individuals with less than total obliteration. Three of these events were fatal. The most common complication was seizure. The authors reported that this is the largest modern series of PSRS for cerebral AVMs and concluded that PSRS can achieve a high obliteration rate, with minimal morbidity. Posttreatment hemorrhage remains a potentially fatal risk among individuals who have not yet responded to treatment.

Hattangadi et al. (2012) evaluated 59 participants with high-risk cerebral AVMs, based on brain location or large size, who underwent planned two-fraction PSRS. The median nidus volume was 23 cc. Overall, 70% of cases had a nidus volume of ≥ 14 cc, and 34% were in critical locations (brainstem or basal ganglia). Many participants had prior surgery or embolization (40%) or prior PSRS (12%). The most common dose was 16 Gy in two fractions. At a median follow-up of 56.1 months, nine participants (15%) had total obliteration, and 20 participants (34%) had partial. Participants with total obliteration received a higher total dose than those with partial or no obliteration. The median time to total obliteration was 62 months, and the 5-year actuarial rate of partial or total obliteration was 33%. The 5-year actuarial rate of hemorrhage was 22%, and 14% (n = 8) experienced fatal hemorrhage. Lesions with higher AVM scores were more likely to hemorrhage and were less responsive to radiation. The most common complication was headache. One participant developed a generalized seizure disorder, and two had mild neurological deficits. The authors concluded that high-risk AVMs can be safely treated with two-fraction PSRS, although the total obliteration rate is low, and participants remain at risk for future hemorrhage. Future studies should include higher doses or a multistage PSRS approach for lesions that are more resistant to obliteration with radiation.

Ocular Tumors

According to a 2025 ECRI analysis, PBT appeared to offer good outcomes in treating uveal melanoma, including OS, metastasis-free survival, and local tumor control, and offers potential benefits. However, the supporting evidence is limited and mostly based on retrospective case series.

Miao et al. (2025) performed a systematic review and meta-analysis to evaluate the efficacy and adverse effects of PBT for the treatment of choroidal melanoma. The inclusion criteria consisted of studies involving individuals of any age diagnosed with choroidal melanoma at any stage, with independently reported data. Eligible studies had to report at least two of the following outcomes: OS, LC rate, metastasis-free survival, or incidence of ocular adverse reactions. Studies were excluded if they had fewer than 10 individuals, were duplicate publications, had research involving cells and animal models, focused on reirradiation, or lacked detailed outcome data. Six case series were included in the review, for a total of 1,059 individuals. A meta-analysis, using a random-effects model, found that individuals with choroidal melanoma treated with PBT had OS rates of 97% at 2 years, 92% at 3 years, 73% at 5 years, and 39% at 10 years. Metastasis-free survival rates were 92% at 2 years, 89% at 3 years, and 76% at 5 years. LC rates were 98% at 1 year, 92% at 3 years, 94% at 5 years, and 88% at 10 years. Adverse reactions were reported in four studies, with the most common being glaucoma, optic neuropathy, and cataracts, occurring at rates of 17.9% to 27%, 12.8% to 64%, and 29.6% to 39.8%, respectively. The authors concluded that PBT is an important local treatment option for choroidal melanoma, demonstrating strong results in both OS and local tumor control. However, they emphasized the need for more prospective clinical trials to better compare its effectiveness with that of standard therapies. Limitations include the retrospective nature of the studies; additionally, some studies reported incomplete data. This systematic review and meta-analysis is included in the ECRI analysis above.

Hartsell et al. (2016) conducted a case series study to determine the feasibility of treating individuals with ocular melanoma using volumetric imaging and planning for PBT. Overall, 26 individuals met the eligibility criteria, and all were able to complete and tolerate treatment. Visual outcomes were assessed on routine ophthalmologic follow-up over a median time of 31 months. Four individuals had poor vision in the treated eye prior to PBT; three of those four individuals had serous retinal detachment prior to treatment. None of those individuals had significant improvement in visual acuity after treatment. Of the remaining 22 individuals, nine had visual acuity equal to pretreatment acuity at the most recent

follow-up visit; four had stable vision, with a loss of two to five lines on the Snellen chart; and eight had lost more than five lines of visual acuity. The visual acuity status for one individual was unknown prior to their death due to metastatic melanoma. The treatment was well tolerated by individuals, with minimal acute toxicity. Relatively low mean doses to the anterior structures (ciliary body and lens) were maintained, even in individuals with large tumors. The authors concluded that while they continue evaluating outcomes in these individuals in a prospective manner, this treatment technique appeared to be feasible, with excellent early outcomes.

Verma and Mehta (2016c) conducted a systematic review to identify studies of PBT and uveal melanoma. The search was conducted using PubMed, Embase, abstracts from meetings of the American Society for Radiation Oncology and American Society of Clinical Oncology, and the Particle Therapy Co-Operative Group. The articles included addressed clinical outcomes with proton RT for ocular melanoma, with the following headings: “proton,” “proton RT,” “proton beam therapy,” “ocular melanoma,” “uveal melanoma,” “choroidal melanoma,” and “eye melanoma.” The articles were published from 2000 to 2015. The articles excluded were those without specific assessments on clinically relevant outcomes of proton RT for previously untreated melanoma of the eye, letters to the editor, direct commentary to other articles, and small reports (< 25 individuals). A total of 14 original investigations from 10 institutions were analyzed. Results revealed that the majority of tumors were choroidal, were medium to large sized, and received 50 to 70 Gy equivalent doses; however, more recent data reported use of lower doses. The 5-year LC rates exceeded 90% and remained high at 15 years. The 5-year OS rates ranged from 70% to 85%, and 5-year metastasis-free survival and disease-specific survival rates ranged from 75% to 90%, with more recent series reporting higher values. With the removal of smaller studies, 5-year enucleation rates were consistently between 7% and 10%. Many individuals (60%-70%) had a post-PBT visual acuity decrease but still retained purposeful vision (> 20/200). Complication rates were variable but showed improvements compared with historical plaque brachytherapy data. The authors concluded that PBT has shown excellent oncological and ophthalmologic outcomes, and these have been sustained in the long term.

Clinical Practice Guidelines

American Society for Radiation Oncology (ASTRO)

ASTRO’s model policy states that PBT is considered reasonable in instances in which sparing the surrounding tissue cannot be adequately achieved with photon-based RT and is of added clinical benefit to the individual. Disease sites that frequently support the use of PBT include treatment of ocular tumors, including intraocular melanomas (2022).

National Comprehensive Cancer Network (NCCN)

In the NCCN guidelines on uveal melanoma, particle beam therapy is noted as a common form of definitive RT for the primary tumor. It is considered appropriate as an up-front therapy after initial diagnosis, after margin-positive enucleation, or for intraocular or orbital recurrence. It should be performed by an experienced multidisciplinary team, including an ophthalmic oncologist, radiation oncologist, and particle beam physicist (NCCN, 2025).

Primary Liver Malignancies

In a systematic review and meta-analysis, Bae et al. (2024) performed a comprehensive search of multiple databases, including PubMed, Embase, and the Cochrane Library, up to February 2024, to identify studies that reported on OS, PFS, LC, and treatment-related toxicities with PBT in individuals with liver-confined hepatocellular carcinoma (HCC). The meta-analysis included data from 22 studies, for a total of 1,858 individuals. Inclusion criteria were prospective or retrospective studies that treated liver-confined HCC with PBT with curative intent; studies with 10 or more individuals; and studies reporting at least one end point of interest. Exclusion criteria were studies in which PBT was applied to pediatric individuals, individuals with distant metastases, and individuals with a history of prior RT to the liver. The median proportion of Child-Pugh class A was 86% (range, 41%-100%), and the median tumor size was 3.6 cm (range, 1.2-9.0 cm). The median total dose ranged from 55 GyE to 76 GyE (median, 69 GyE). The pooled rates of 3- and 5-year local PFS after PBT were 88% and 86%, respectively. The pooled 3- and 5-year overall rates were 60% and 46%, respectively. The pooled rates of grade 3 hepatic toxicity, classic radiation-induced liver disease, and nonclassic radiation-induced liver disease were 1%, 2%, and 1%, respectively. According to the authors, this study endorsed PBT for HCC, highlighting its favorable long-term survival rates and lower hepatic toxicities compared with other RT modalities. However, the authors noted that additional research is necessary to pinpoint the specific individual subgroups that would most benefit from PBT. Limitations include the heterogeneity of studies and lack of RCTs. (Kim et al., 2021, previously cited in this policy, is included in this review.)

Bush et al. (2023) conducted an RCT to assess the comparative effectiveness and safety of PBT vs those of transarterial chemoembolization (TACE) in those with HCC who were not candidates for surgical resection or ablation. Eligible participants were adults with newly diagnosed, previously untreated HCC and tumors that met Milan or San Francisco criteria, although transplant eligibility was not required. Key exclusion criteria included vascular invasion, α-fetoprotein levels above 500, Child-Pugh class C cirrhosis, Model for End-Stage Liver Disease scores over 25, bilirubin levels greater

than 3 mg/dL, tumor proximity to the bowel, and large-volume, unstable ascites. The primary end point of the study was OS, while secondary end points included PFS, LC, and treatment-related toxicity. Of the 76 participants randomized, 74 were included in the final analysis. Two-year OS rates were similar between the PBT and TACE groups: 68% with PBT and 65% with TACE (p = 0.80). However, PFS was significantly longer in the PBT group, with the median not reached, compared with 12 months with TACE (p = 0.002). LC also favored PBT, with a hazard ratio of 5.64 (p = 0.003), indicating a substantially lower risk of local failure. Posttreatment hospitalization days were markedly fewer with PBT (24 days) than with TACE (166 days). The study concluded that while OS was comparable between PBT and TACE for HCC, PBT demonstrated clear advantages in disease control and treatment efficiency. Participants receiving PBT experienced improved PFS and local tumor control compared with those treated with TACE. Additionally, PBT required fewer treatment sessions and resulted in significantly fewer posttreatment hospitalizations. According to the authors, these findings support PBT as a strong alternative to TACE in those with HCC who meet transplant criteria but are not eligible for resection or ablation.

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

Fukuda et al. (2017) performed an observational study to assess the long-term efficacy of PBT in participants with previously untreated HCC. Between January 2002 and December 2009, 129 participants at a single institution received PBT via one of three protocols based on tumor location, with dose volumes of 77.0 GyE in 35 fractions, 72.6 GyE in 22 fractions, and 66.0 GyE in 10 fractions for the gastrointestinal (GI), hilar, and standard protocols, respectively. The primary outcome measures were local tumor control, OS, and PFS. All 129 participants completed PBT without experiencing severe complications, and no treatment-related deaths were observed. The median participant observation period was 55 months. The 5-year local tumor control, PFS, and OS rates were 94%, 28%, and 69% in participants with 0/A stage disease (n = 9/21); 87%, 23%, and 66% in participants with B stage disease (n = 34); and 75%, 9%, and 25% in participants with C stage disease (n = 65), respectively. The 5-year local tumor control and OS rates in 15 participants with tumor thrombi in major vessels were 90% and 34%, respectively. The major study limitation cited was the heterogeneous participant population, with most participants receiving PBT because they refused surgery or conventional interventional RT. The authors concluded that PBT achieved long-term tumor control, with less toxicity, and is a viable treatment option for localized HCC. The authors were planning a multicenter controlled study comparing PBT and hepatectomy.

Bush et al. (2016) conducted a single-center prospective RCT comparing outcomes in 69 participants with newly diagnosed HCC who received either TACE or PBT as definitive or bridge therapy while awaiting transplant. Overall, 33 participants were randomized to PBT, and 36 participants were randomized to TACE. Participants who were randomized to TACE received at least one TACE, with additional TACE for persistent disease. The PBT group had proton therapy delivered to all areas of gross disease to a total dose of 70.2 Gy in 15 daily fractions over 3 weeks. The median follow-up in all participants was 28 months. The primary end point was PFS, with secondary end points including OS, local disease control, transplant outcomes, and toxicity, including days of hospitalization after treatment. The 2-year OS in the entire group was 59%, with no significant difference between treatment assignments. Regarding LC and PFS between treatment groups, a trend toward improved 2-year local tumor control (88% vs 45%; p = 0.06) and PFS (48% vs 31%; p = 0.06) favoring the PBT group was observed. Among the entire group of study participants, 22 went on to have a liver transplant. The 2-year OS rate after transplant was 82% in the entire group, with no difference seen between the proton and TACE groups. The authors concluded that this study indicates similar OS rates with PBT and TACE. While a trend toward improved local tumor control and PFS favoring proton therapy was observed, it was too early to determine whether the trend would be maintained.

Hong et al. (2016) conducted a single-arm, phase 2, multi-institutional study to evaluate the safety and efficacy of high-dose, hypofractionated PBT for HCC and ICC. Over 83 participants aged ≥ 18 years with unresectable or locally recurrent HCC or ICC were included. With 42 participants with HCC (95.5%) and 36 participants with ICC (92.3%) having completed their prescribed dose, the median dose delivered was 58.0 GyE (in 15 fractions; range, 15.1-67.5 GyE). Of the

83 participants, 71 (85.5%) experienced at least one radiation-related toxicity event while in the study, most commonly fatigue [54/83 (65.1%)], rash [51/83 (61.4%)], nausea [25/83 (30.1%)], or anorexia [21/83 (25.3%)]. The median follow-up among the 50 survivors was 19.5 months (range, 0.6-55.9 months). In participants with HCC, the 1- and 2-year PFS rates were 56.1% and 39.9%, respectively. The 1- and 2-year OS rates were 76.5% and 63.2%, respectively. Three participants with HCC underwent successful liver transplant, two of whom remain alive. In participants with ICC, 1- and 2-year PFS rates were 41.4% and 25.7%, respectively, with 1- and 2-year OS rates of 69.7% and 46.5%. The authors concluded that high-dose, hypofractionated PBT is safe and associated with high rates of LC and OS in both HCC and ICC. These data provide a strong rationale for RCTs of proton vs photon RT for HCC and for chemotherapy with or without RT for ICC.

Clinical Practice Guidelines

American Society for Radiation Oncology (ASTRO)

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

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines regarding hepatocellular cancer state that hypofractionation with photons or protons at an experienced center is an acceptable option for unresectable intrahepatic tumors and may be appropriate in specific situations. Additionally, the NCCN guidelines note that treatment with photons or protons for unresectable tumors of biliary tract cancer is recommended at centers with experience (NCCN, 2025).

Primary Mediastinal Tumors

In a 2024 systematic review, Kowalska et al. aimed to evaluate the efficacy and safety of PBT for individuals with Hodgkin or non-Hodgkin lymphoma who were treated with mediastinal irradiation. Studies were included if they involved individuals with Hodgkin or non-Hodgkin lymphoma who received mediastinal irradiation using PBT. Eligible study designs included randomized and nonrandomized controlled trials, cohort studies, case-control studies, and case series with at least five individuals. Outcomes of interest were OS, PFS, local and distant disease control, QOL, and safety. Studies were excluded if they were reviews, conference abstracts, study protocols, or animal research or lacked relevant outcome data. Additionally, publications not in Polish or English and those focused solely on dosimetry were excluded. Eleven studies were included, encompassing a total of 529 individuals. All were case series published between 2011 and 2021. The median follow-up duration ranged from 15 to 63.6 months. In five studies, 2-year OS rates ranged from 91% to 98%, while three studies reported favorable 2-year PFS rates between 73% and 94%. The most commonly observed side effects were mild (grade 1-2) and included skin reactions, esophagitis, and fatigue. Importantly, no severe (grade 4 or higher) acute or late toxicities were reported. The authors concluded that PBT may be an effective treatment option for mediastinal Hodgkin and non-Hodgkin lymphoma. However, since all included studies were case series, the strength of the evidence is limited. As a result, the authors emphasized the need for well-designed RCTs to better determine the optimal use of PBT in these populations of individuals.

König et al. (2019) performed a retrospective clinical study that evaluated the effectiveness and safety of PBT in 20 patients with mediastinal malignant lymphoma treated between September 2014 and February 2017. The study aimed to assess whether PBT could reduce radiation exposure to OARs compared with IMRT. Clinical target volume coverage was similar between IMRT and PBT, with no significant differences. However, PBT demonstrated a more favorable homogeneity index (HI_{PBT} = 1.041 vs HI_{IMRT} = 1.075; $p < 0.001$). Across all OARs, PBT significantly reduced radiation exposure compared with IMRT. Notably, PBT lowered the mean heart dose by 3.3 Gy overall and by 4.2 Gy in those with pericardial involvement. In female patients, who are more susceptible to breast radiation exposure, PBT reduced the mean dose by 1.2 Gy on the right and 2.2 Gy on the left. After a median follow-up of 32 months (range, 21-48 months), both local and distant PFS rates were high: 95.5% and 95.0%, respectively. Treatment was well tolerated, with only mild (grade 1-2) acute and chronic side effects reported. The study concluded that PBT significantly reduced radiation exposure to surrounding OARs, including the breast, heart, lungs, esophagus, and spinal cord, compared with IMRT, without compromising the coverage of the target volume. The treatment was well tolerated, and based on these findings, the authors recommended considering PBT for select individuals with lymphoma who may benefit most from reduced exposure to critical structures. Limitations include the small sample size and retrospective nature of the study.

Vogel et al. (2016) conducted a prospective study to assess the effectiveness and safety of PBT in those with thymic tumors, including thymoma and thymic carcinoma. The study included 27 participants treated between 2011 and 2015, with a median age of 56 years. Most participants received adjuvant PBT following surgery, while others underwent definitive or salvage treatment. No participants experienced severe (grade 3 or higher) side effects during treatment.

Moderate (grade 2) acute toxicities were observed, with dermatitis being the most common (37%), followed by fatigue (11%), esophagitis (7%), and pneumonitis (4%). Only one participant developed a late grade 2 toxicity, which presented as chronic dyspnea. At a median follow-up of 2 years, local tumor control was achieved in all participants (100%). The 3-year outcomes showed high effectiveness, with regional control at 96% (95% CI, 76%-99%), distant control at 74% (95% CI, 41%-90%), and OS at 94% (95% CI, 63%-99%). The authors concluded that PBT appeared to be a safe and practical option for treating thymoma and thymic carcinoma. Participants treated with PBT experienced minimal acute side effects and received lower radiation doses to surrounding healthy tissues while maintaining excellent locoregional control. The authors suggested that further studies comparing radiation techniques and long-term follow-up are needed to fully assess the benefits of PBT. Limitations include the small sample size and short-term follow-up.

Clinical Practice Guidelines

American Radium Society (ARS)

In the development of the ARS Appropriate Use Criteria for RT in thymic carcinoma, Chun et al. (2023) recommended the use of advanced radiation techniques, specifically IMRT or PBT, over traditional 3D-CRT. This recommendation was based on the ability of IMRT and PBT to more precisely target tumors while minimizing radiation exposure to critical organs such as the heart and lungs. By reducing collateral damage to surrounding healthy tissue, these modalities aim to improve safety and reduce long-term treatment-related complications in those with thymic malignancies.

International Lymphoma Radiation Oncology Group

Dabaja et al. (2018) developed guidelines regarding PBT for the treatment of adult lymphomas involving the mediastinum. The guideline consensus recommendations address the individuals most likely to benefit from PBT, including:

- Those with mediastinal disease extending below the origin of the left main stem coronary artery and anterior to, posterior to, or on the left side of the heart
- Young female individuals, in whom proton therapy can significantly reduce breast radiation dose and lower the risk of secondary breast cancer
- Heavily pretreated individuals at an increased risk for radiation-related toxicity to the bone marrow, heart, and lungs

The guidelines note that PBT for mediastinal lymphomas offers significant potential to reduce radiation exposure to OARs, making it highly desirable in select cases. However, due to limited availability, careful selection of individuals is essential, focusing on scenarios in which the benefit over advanced photon techniques is clear.

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines for Hodgkin lymphoma (age ≥ 18 years) note that advanced RT techniques, such as IMRT and PBRT, can offer meaningful and clinically significant benefits in select cases. These modalities help spare critical normal OARs and reduce the likelihood of late-onset tissue damage while still maintaining the primary objective of local tumor control. In particular, proton therapy may provide dosimetric advantages in the treatment of mediastinal lymphoma, potentially lowering the risk of long-term toxicity. This approach is especially beneficial in cases involving mediastinal disease, in which it can significantly reduce radiation exposure to the heart and its substructures. Additionally, in younger individuals, proton therapy can help minimize the dose to breast tissue, further supporting long-term health outcomes (NCCN, 2025).

The NCCN guidelines for B-cell and T-cell lymphomas (2025) state that PBT may be appropriate, depending on clinical circumstances. They also state 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. Additionally, highly conformal dose delivery is crucial for those treated with curative intent or who are expected to have long-term survival. The NCCN is silent on the use of PBT in the treatment of primary cutaneous lymphoma (NCCN, 2025).

A minimum technological requirement for RT in treating thymomas and thymic carcinomas is 3D-CRT. However, more advanced techniques, such as IMRT and VMAT, are recommended to reduce the cardiac dose. Proton therapy offers further dosimetric advantages over IMRT, enabling better protection of surrounding healthy organs like the lungs and heart, while maintaining effective LC and minimizing toxicity (NCCN, 2026).

Reirradiation

In a 2021 systematic review, Gamez et al. examined the use of charged particle therapy for reirradiation in individuals with recurrent or second primary skull base and head and neck tumors. The review included 26 retrospective studies involving 1,118 individuals who were treated with curative intent; 15 studies focused on proton therapy, 10 on carbon ion therapy, and one on helium/neon particles. The median reirradiation dose was 64.5 Gy [relative biological effectiveness (RBE), 1.1]

for proton therapy and 53.8 Gy (RBE, 2.5-3.0) for carbon ion therapy. Chemotherapy was used in 53% of proton cases and 18% of carbon ion cases. Two-year LC rates ranged from 50% to 86% for protons and 41% to 92% for carbon ions, with OS rates between 33% and 80% and 50% and 86%, respectively. Late grade 3 toxicities occurred in up to 37% of individuals, most commonly brain necrosis, hearing loss, vision impairment, and bleeding. Grade 5 toxicities were reported in 1.4% of cases, primarily due to fatal bleeding. The authors concluded that curative-intent reirradiation of skull base and head and neck tumors using charged particle therapy is considered feasible and safe in carefully selected individuals. According to the authors, current data suggest that it may offer comparable or even improved LC and toxicity outcomes compared with historical photon-based approaches. However, they endorsed further validation through prospective multi-institutional studies to better understand its clinical benefits. Limitations of the existing evidence include the retrospective design and predominance of single-institution studies.

A prospective study conducted by Guttmann et al. (2017) evaluated the safety and efficacy of charged particle-based (protons and carbon ions) reirradiation in those with recurrent or new primary soft tissue sarcoma. Eligible participants had a Karnofsky Performance Status above 60, a life expectancy of at least 3 months, and tumors overlapping the 50% isodose line from prior radiotherapy. Radiation was administered either before or after surgery in operable cases, while nonoperable participants received definitive RT. Exclusion criteria included a time interval of less than 3 months since the initial course of radiotherapy as well as the presence of metastatic disease prior to reirradiation. The primary outcome measured was acute toxicity, as reported by providers. Late-onset toxicities, rates of local tumor control, and OS were the secondary end points. Overall, 23 participants received proton reirradiation, with a median interval of 40.7 months between radiation courses (range, 10-272 months). No grade 4 or 5 toxicities were reported. One participant (4%) experienced acute grade 3 dysphagia, while common grade 2 acute toxicities included fatigue (26%), anorexia (17%), and urinary incontinence (13%). Late grade 3 complications included two wound infections (10%) and one wound-related issue (5%). Grade 2 late complications included lymphedema (10%), fracture (5%), and fibrosis (5%). At a median follow-up of 36 months, the 3-year cumulative incidence of local failure was 41% (95% CI, 20%-63%). Median OS was 44 months, and PFS was 29 months. Among participants with extremity tumors, limb preservation was achieved in 70% (seven of 10 cases). The authors reported that proton reirradiation for recurrent or secondary soft tissue sarcomas was generally well tolerated. Although extended follow-up is necessary to fully assess long-term outcomes, early survival data in this high-risk group appear promising. However, the study's findings are limited by a small sample size and heterogeneity of the participants represented. The authors suggested that PBT may offer the safest option for reirradiating those with locoregional cancer recurrences, potentially providing select individuals with a renewed opportunity for cure. While current data are encouraging, the evidence base remains limited. The authors emphasized the need for proton centers worldwide to systematically report their experiences, with the goal of strengthening clinical understanding and guiding treatment planning. Limitations include the small samples sizes; additionally, the vast majority of studies were retrospective in nature.

Clinical Practice Guidelines

American Society for Radiation Oncology (ASTRO)

ASTRO's guideline strongly supports IMRT for anal cancer, citing insufficient evidence to recommend for or against PBT. However, PBT may be considered in cases requiring reirradiation or when photon IMRT cannot meet dose constraints for OARs, such as in individuals with pelvic kidneys or younger individuals in whom minimizing radiation to reproductive organs is critical (Feng et al., 2025).

National Comprehensive Cancer Network (NCCN)

Proton therapy is recognized in the NCCN guidelines as a potentially appropriate option for reirradiation for several different types of cancers, including cervical cancer, head and neck cancers, and CNS tumors such as gliomas. According to the guidelines, these treatments must be highly individualized, taking into account factors such as the location of the target, proximity to critical organs, prior radiation dose, extent of overlap, and time since previous treatment. As a result, the radiation dose must be tailored to each individual's specific clinical scenario (NCCN, 2025).

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 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 New Mexico Only)*
	Coverage Rationale
	• Revised list of proven and medically necessary indications for proton beam radiation therapy (PBT) for Definitive Therapy:
	  ○ Added:
	  ▪ Primary Head and Neck Cancers [not listed in the policy] when all the following criteria are met:
	  – The tumors are near critical anatomical structures, such as the orbit, skull base, or cavernous sinus or with intracranial extension or perineural invasion
	  – When documentation is provided that sparing of the surrounding normal tissue cannot be achieved with standard photon radiation therapy techniques
	  ▪ Primary Central Nervous System Tumors (e.g., brain or spinal cord) when all the following criteria are met:
	  – The tumors are near critical anatomical structures such as the optic nerve, brainstem, or spinal cord
	  – When documentation is provided that sparing of the surrounding normal tissue cannot be achieved with standard photon radiation therapy techniques
	  ▪ Primary mediastinal tumors (e.g., thymomas, mediastinal lymphomas, thoracic sarcomas)
	  ▪ Reirradiation when all the following criteria are met:
	  – Individuals have previously undergone radiation therapy to a specific anatomical site and now require an additional course of radiation to the same specific anatomical site
	  – Documentation is provided that sparing of the surrounding normal tissue cannot be achieved with standard photon radiation therapy techniques
	  ○ Replaced “hepatocellular carcinoma (HCC) (localized, unresectable) in the curative setting when documentation is provided that sparing of the surrounding normal tissue cannot be achieved with standard radiation therapy techniques, including intensity-modulated radiation therapy (IMRT), stereotactic body radiation therapy (SBRT), and selective internal radiation spheres, and transarterial therapy (for example, chemoembolization) is contraindicated or not technically feasible” with “*primary liver malignancies, such as* hepatocellular carcinoma *and intrahepatic cancer* (localized, unresectable) in the curative setting when documentation is provided that sparing of the surrounding normal tissue cannot be achieved with standard radiation therapy techniques, including intensity-modulated radiation therapy (IMRT), stereotactic body radiation therapy, and selective internal radiation spheres, and transarterial therapy (for example, chemoembolization) is contraindicated or not technically feasible
	• Revised coverage criteria for evaluation of exception requests for a covered diagnosis of PBT that is not listed [in the policy] as proven; replaced criterion requiring the “evaluation includes a comparison of treatment plans for PBT, 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, IMRT, or stereotactic body radiation therapy) for a 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

Date	Summary of Changes
	○ 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 ○ 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 **Definitions** • Added definition of: ○ Base of Skull Tumors ○ Central Nervous System Tumors ○ Head and Neck Cancer • Updated definition of "Definitive Therapy" **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 CS105NM.C

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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