Proton Beam Radiation Therapy

MEDICAL POLICY NUMBER: 167

Effective Date: 10/1/2023

Last Review Date: 7/2023

Next Annual Review: 7/2024

INSTRUCTIONS FOR USE: Company Medical Policies serve as guidance for the administration of plan benefits. Medical policies do not constitute medical advice nor a guarantee of coverage. Company Medical Policies are reviewed annually and are based upon published, peer-reviewed scientific evidence and evidence-based clinical practice guidelines that are available as of the last policy update. The Company reserves the right to determine the application of medical policies and make revisions to medical policies at any time. The scope and availability of all plan benefits are determined in accordance with the applicable coverage agreement. Any conflict or variance between the terms of the coverage agreement and Company Medical Policy will be resolved in favor of the coverage agreement. Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case. In cases where medical necessity is not established by policy for specific treatment modalities, evidence not previously considered regarding the efficacy of the modality that is presented shall be given consideration to determine if the policy represents current standards of care.

SCOPE: Providence Health Plan, Providence Health Assurance, and Providence Plan Partners as applicable (referred to individually as “Company” and collectively as “Companies”).

PLAN PRODUCT AND BENEFIT APPLICATION

☒ **Commercial** ☒ **Medicaid/OHP*** ☐ **Medicare****

*Medicaid/OHP Members

Oregon: Services requested for Oregon Health Plan (OHP) members follow the OHP Prioritized List and Oregon Administrative Rules (OARs) as the primary resource for coverage determinations. Medical policy criteria below may be applied when there are no criteria available in the OARs and the OHP Prioritized List.

**Medicare Members

This *Company* policy may be applied to Medicare Plan members only when directed by a separate *Medicare* policy. Note that investigational services are considered **"not medically necessary"** for Medicare members.

COVERAGE CRITERIA

- Proton beam radiation therapy may be used with or without stereotactic guidance for covered indications.
- This policy does not address proton beam radiation therapy in patients under 21 years of age.

I. Proton beam radiation therapy (PBRT) may be considered **medically necessary** for the treatment of prostate cancer.

II. Proton beam radiation therapy (PBRT) may be considered **medically necessary** for indications other than prostate cancer when **all** of the following (A.-B.) criteria are met:

A. When sparing the surrounding tissue cannot be achieved with photon-based radiotherapy; **and**
B. **At least one** of the following (1.-5.) indications are met:
1. Intracranial arteriovenous malformation (AVM) that is unresectable or adjacent to critical structures (e.g., brain stem); **or**
2. Central nervous system tumors when adjacent to critical structures in which other standard radiation therapies may pose a significant risk (see Policy Guidelines for more information); **or**
3. Intraocular (uveal) melanomas (see Policy Guidelines for more information); **or**
4. Primary head and neck cancers that are unresectable or incompletely resected and malignant; **or**
5. Chordomas or chondrosarcomas located at the skull base or spine.

III. Proton beam radiation therapy (PBRT) is considered **not medically necessary** when criterion I. or II. above is not met.

IV. Reirradiation with proton beam radiation therapy may be considered **medically necessary** when **all** of the following (A.-C.) criteria are met:

A. Documentation indicates the medical necessity of proton beam radiation therapy over standard 3D conformal radiation therapy or intensity-modulated radiation therapy (IMRT); **and**
B. The cumulative critical structure dose would exceed the tolerance dose; **and**
C. Criterion I. or II. above is met.

V. Reirradiation with proton beam radiation therapy is considered **not medically necessary** when criterion IV. above is not met.

VI. Proton beam radiation therapy is considered **not medically necessary** in **any** of the following (A.-D.) clinical scenarios:

A. Where PBT does not offer an advantage over photon-based therapies that otherwise deliver good clinical outcomes and low toxicity.
B. Spinal cord compression, superior vena cava syndrome, malignant airway obstruction, poorly controlled malignant bleeding and other scenarios of clinical urgency.
C. Inability to accommodate for organ motion.
D. Palliative treatment in a clinical situation where normal tissue tolerance would not be exceeded in previously irradiated areas.

VII. Proton beam radiation therapy is considered **not medically necessary** for all other indications. These include, but are not limited to, the following (A.-B.):

A. Oncologic indications (1.-11.):
    1. Breast cancer
    2. Esophageal cancers
    3. Gastric cancer
    4. Gynecological cancers (cervical, ovarian, vulvar and uterine)
    5. Hepatobiliary cancers
    6. Lung cancers (non-small cell and small cell)
    7. Lymphomas:
        a. Hodgkin lymphoma
        b. Non-Hodgkin's lymphomas:
            i. Chronic lymphocytic leukemia / small lymphocytic lymphoma
            ii. Hairy cell leukemia
            iii. Primary cutaneous B-cell lymphoma
            iv. B-Cell and T-Cell lymphomas
    8. Pancreatic adenocarcinoma
    9. Skin cancers, including but not limited to:
        a. Basal cell carcinoma
        b. Melanoma

c. Squamous cell carcinoma
10. Soft tissue sarcomas
11. Thymomas and thymic cancers

B. Non-oncologic indications, other than arteriovenous (AV) malformations, including but not limited to (1.-2.):
1. Age related macular degeneration
2. Cavernous hemangioma

Link to Evidence Summary

POLICY CROSS REFERENCES

None

The full Company portfolio of current Medical Policies is available online and can be accessed here.

POLICY GUIDELINES

DEFINITIONS

In patients with central nervous system tumors or uveal melanomas, the following guidelines should apply:

- If the patient is asymptomatic and receiving proton beam radiation therapy for curative purposes, no metastases should be present.
- If the patient is symptomatic and receiving proton beam radiation therapy for palliative purposes, metastases may be present.

BACKGROUND

Proton beam radiation therapy (PRBT), simply known as proton beam therapy (PBT) is a type of external radiation therapy in which positively charged protons are precisely targeted to a specific location using a sophisticated stereotaxic planning and delivery system. In comparison with conventional photo-based irradiation, it is purported that PBRT may deliver a higher dose to the target tissue, while minimizing exposure to surrounding healthy tissue.[1]

According to a 2019 Hayes review:[2]

> "In conventional radiation therapy with x-ray and gamma ray beams, the greatest energy release and biological damage occurs in the first few centimeters of tissue and the energy release decreases approximately linearly as the beam travels deeper into tissue. In contrast, most of the energy of a proton beam is released near the end of its path, a region called the Bragg peak. Since the energy release of the proton beam is concentrated in the narrow Bragg peak, alignment of the Bragg peak

with the tumor location limits collateral damage to the healthy tissues surrounding the tumor, which has the potential to reduce the undesirable side effects of radiation therapy.
Precise targeting of the Bragg peak is critical in PBT since most of the energy release and tissue damage occurs within the Bragg peak with little to no energy release outside of the peak. Penetration depth is controlled by the initial energy selected for the beam. Radiation dose from PBT is measured in cobalt Gy equivalents (CGE), which are calculated by multiplying the amount of energy delivered, measured in Gy, times a relative biological effectiveness (RBE) ratio. The RBE expresses the relative effect of the type of radiation compared with the same energy delivered as photon radiation. As with conventional RT, PBT usually involves fractionation of dose and multiport beam entry to limit the exposure to the skin and other non-target tissue." [2]

Proton beam facilities require a synchrotron, a beam transport system, a beam delivery system, isocentric gantries, and a patient alignment and imaging system.[2] As a result of the sophisticated set-up required, the construction and start-up of facilities and therefore proton beam treatment itself is typically more costly than other radiation therapy alternatives, such as stereotactic body radiation therapy (SBRT) or intensity-modulated radiation therapy (IMRT).

REGULATORY STATUS

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

Approval or clearance by the Food and Drug Administration (FDA) does not in itself establish medical necessity or serve as a basis for coverage. Therefore, this section is provided for informational purposes only.

CLINICAL EVIDENCE AND LITERATURE REVIEW

EVIDENCE REVIEW

A review of the ECRI, Hayes, Cochrane, and PubMed databases was conducted regarding the use of proton beam radiation therapy (PBRT) as a treatment for various conditions, with a focus on studies reporting patient-relevant health outcomes (e.g., survival outcomes and local control rates) as well as those reporting on treatment-related toxicities.

For indications determined to be medically necessary, per the medical policy criteria above, evidence was updated through May 2023. Due to the large and extensive body of evidence surrounding cancer treatments, the evidence supporting these medically necessary indications has been limited to systematic reviews.

For all other indications, a full evidence review was conducted, focusing primarily on comparative studies and systematic reviews for each indication. A summary of the available evidence identified through May 2023 is presented below.

Oncologic Indications

Systematic Reviews of the use of PBRT for Mixed Oncologic Indications

- In 2012, Allen et al. published an evidence-based review of proton beam radiation therapy (PBRT) on behalf of the American Society of Radiation Oncology's (ASTRO's) emerging technology committee.[3] Data was reviewed through 2009 for PBRT in central nervous system tumors, gastrointestinal malignancies, lung, head and neck, and prostate. The ASTRO review concluded that current data did not provide sufficient evidence to recommend PBRT in lung cancer, head and neck cancer, and gastrointestinal malignancies. In addition, for hepatocellular carcinoma and prostate cancer, there was evidence for the efficacy of PBRT but no suggestion that it is superior to photon based approaches. Lastly, the review found that, for large ocular melanomas and chordomas, there was evidence for a benefit of PBRT over photon approaches.

- In 2016, the Oregon Health Authority (Health Evidence Review Commission, HERC) published an evidence-based report on PBRT, including six RCTs and 37 nonrandomized comparative studies across all 19 condition types.[4] The number of comparative studies was extremely limited for certain conditions and entirely absent for others, and most had major quality concerns, including lack of randomization, retrospective study design. Five of the six RCTs involved different treatment protocols for PBRT and had no other comparison groups. Other limitations noted by the review included: most of the comparative studies involved comparisons of a PBRT cohort to a non-contemporaneous group receiving alternative therapy, and major differences in patient demographics, baseline clinical characteristics and duration of follow-up were often noted. One of the six RCTs identified was deemed of good quality and four were fair quality. Approximately half of the non-randomized comparative studies were of fair quality (n=20) and the other half of poor quality (n=16). The HERC review reported that PBRT had superior net health benefit for ocular tumors (moderate quality of evidence) and incremental net health benefit for brain/spinal tumors. The review also reported that PBRT was comparable to alternative treatment options for patients with liver, lung, and prostate cancer. However, the strength of evidence was low for all of these conditions. The evidence base for all other condition types was insufficient to determine net health benefit. The review concluded by stating: "While further study may reduce uncertainty and clarify differences between treatments, it is currently the case that PBRT is far more expensive than its major alternatives, and evidence of its short or long-term relative cost-effectiveness is lacking for many of these conditions."

- In 2019, the Washington State Health Care Authority published a health technology assessment (HTA) of PBRT for variety of cancers and noncancerous conditions.[5] Independent investigators systematically searched the literature through 2018, identified eligible studies, assessed study quality and extracted data. No meta-analysis was performed due to heterogeneity across studies with regard to designs, patient populations, treatments and clinical methods. In total, 215 studies were included for review (56 addressing pediatric tumors, including 13 retrospective comparative cohorts, 41 case series and 2 cost-effectiveness studies.) An additional, 155 publications addressed adult tumors, including two RCTs, one quasi-RCT, 33 retrospective comparative cohorts and 115 case series. The majority of evidence in adults was for esophageal, head and neck, brain, lung, ocular and prostate cancers. Evidence of PBRT's comparative clinical effectiveness and comparative value was lacking for nearly all conditions evaluated. Overall

quality of evidence was assessed as "poor," as most comparative evidence derived from retrospective and non-randomized studies considered to be at "moderately high risk of bias." Most studies formed treatment groups on the basis of historical consecutive controls with differential length of follow-up by treatment group (i.e. patients received more conventional photon radiation therapy, including 3DCRT, before PBT became more available.) Additional limitations included differences in patients characteristics, presentation, tumor stage, comorbidities, prior or concurrent treatments and surgical factors.

In its subsequent "findings and decisions" document,[6] the Washington State Health Care Authority designated proton beam therapy as a covered benefit for children/adolescents younger than 21 years old, and as a covered benefit for individuals 21 years old and older with any the following cancers: esophageal, head/neck, skull-based, primary hepatocellular carcinoma, brain/spinal, ocular, and other cancers where all other treatment options are contraindicated after review by a multidisciplinary tumor board.

- Additional reviews of outcomes following PBRT for mixed indications have been published, reporting patient reported outcomes such as quality of life (QOL) measures and other measures.[7] These reviews have included small numbers of studies for each indication evaluated, with the majority being noncomparative in nature. The reviews have concluded that based on limited data, PBT provides favorable outcomes for select brain, head/neck, and lung; while outcomes for prostate and breast cancers were not as favorable. Future data could substantially change the conclusions of this review.

Nonrandomized Studies of the use of PBRT for Mixed Oncologic Indications

In 2019, Baumann and colleagues reported findings from a single-institution retrospective analysis of proton- vs photon-based radiotherapy for patients receiving concurrent chemotherapy for 11 types of locally advanced cancers.[8] In total, 1,483 patients with non-metastatic, locally advanced cancer were assessed, 391 of whom received proton therapy and 1,092 of whom received photon therapy. The primary outcome of interest was 90-day adverse events associated with unplanned hospitalizations. In propensity score weighted–analyses, proton chemoradiotherapy was associated with a significantly lower relative risk of 90-day adverse events of at least grade 3 (0.31; 95%CI, 0.15-0.66, P = .002), 90-day adverse events of at least grade 2 (0.78; 95%CI, 0.65-0.93, P = .006), and decline in performance status during treatment (0.51; 95%CI, 0.37-0.71; P < .001). No difference in disease-free or overall survival was reported. Limitations include the study's retrospective design, lack of randomization and heterogeneous patient characteristics. Authors concluded that while proton chemoradiotherapy was associated with significantly reduced acute adverse events and overall survival, prospective trails are needed to validate these findings.

Systematic Reviews for Medically Necessary Indications

Head and Neck Cancers

- In 2014, Patel et al. published a systematic review that evaluated charged particle therapy versus photon therapy for the treatment of paranasal sinus and nasal cavity malignant disease, including 41 observational studies on charged particle therapy (13 cohorts, N=286 patients) and photon therapy (30 cohorts, N=1186 patients).[9] No comparative studies were identified. The

reviewers reported that pooled OS was significantly higher with charged particle therapy than photon therapy at five years (RR=1.51; 95% CI: 1.14 to 1.99; p=0.0038) and at longest follow-up (RR=1.27, 95% CI: 1.01-1.59; p=0.037). However, other outcomes, such as locoregional control and disease-free survival, had conflicting findings between 5-year and longest follow-up. Lastly, there were significantly more neurologic toxic effects with charged particle therapy compared with photon therapy (p<0.001) but other toxic adverse event rates did not differ significantly between groups. The reviewers concluded that charged particle therapy could be associated with better outcomes for patients with malignant diseases of the nasal cavity and paranasal sinuses, compared with photon therapy.

- In 2019 (reviewed in 2022), Hayes conducted a systematic review evaluating the safety and efficacy of PBRT for the treatment of head and neck cancer (HNC).[10] Searching the literature through July 2019, investigators included 13 studies for review (3 retrospective cohort studies, 2 prospective cohort studies with case-matched historical controls, and 8 retrospective noncomparative cohort studies. Sample sizes ranged from 24 to 150 patients; follow-up varied from 8 months to 81 months. Outcomes of interest included disease-free survival, local control, overall survival, regional control, distant control, progression-free survival, acute and late toxicities, weight loss and mortality.

  Five retrospective comparative cohort studies evaluated PBT versus another EBRT modality (most commonly IMRT) and reported no significant differences in efficacy. These results suggest that PBT might provide similar benefits compared with EBRT in adults with HNC. Eight noncomparative retrospective cohort studies supported the feasibility of using PBT to treat patients with HNC. Primary PBT appeared to show similar efficacy as photon-based EBRT technologies. Cumulative evidence on the use of PBT in this patient population indicated an impact on local and regional control, intermediate measures of survival, and overall survival. Evidence was insufficient, however, to evaluate PBT in adult patients with HNC previously treated with radiation therapy.

  The overall quality of evidence was assessed as “low.” Major limitations included studies’ retrospective design, lack of power analysis and predefined primary endpoint, lack of randomization, use of historical comparison group, small group size, differences in length of follow-up, insufficient follow-up times to evaluate long-term outcomes, and limited reporting of efficacy and/or safety outcomes. Hayes ultimately assigned a “C” rating (potential but unproven benefit) for the use of PBT as primary radiotherapy in adults with HNC not previously treated by radiation therapy. Additional studies were judged necessary to establish the validity of findings reported to date and to establish definitive patient selection criteria.

<u>Non-randomized Studies</u>

- In 2017, Dagan and colleagues reported outcomes among sinonasal cancer patients treated with proton therapy.[11] Investigators assessed 84 patients at 2.4 years follow-up, reporting rates of 83% for achieving local control, 94% for neck control, 73% freedom from distant metastasis, 63% disease-free survival, 70% cause-specific survival, and 68% overall survival rates. Gross total resection and PBRT resulted in a 90% 3-year local control rate. Gross disease was the only significant factor for local control on multivariate analysis, whereas grade and continuous LC were prognostic for overall survival. Late toxicity occurred in 24% of patients. Limitations

included the heterogeneity of cancers treated, lack of long-term follow-up, lack of a comparator groups and lack of randomization. Investigators concluded that local control was the most predictive factor of cure rate, with PBRT patients experiencing far higher rates of local control than rates experienced by patients receiving conventional radiotherapy and IMRT.

Ocular Cancers

- The 2012 ASTRO evidence review described above, included a review of PBRT for uveal melanoma.[3] The reviewers stated the use of PBRT had been reported in thousands of cases of uveal melanoma, with combined results of leading centers in the United States and Europe showing 95% control rate and 90% eye retention rate. The technique was noted as especially useful in large and posteriorly located melanomas that are unapproachable by other techniques such as brachytherapy.

- In 2013 Wang et al published a systematic review on charged-particle therapy (CPT) (proton, helium and carbon ion) for uveal melanoma, including 11 controlled and 16 uncontrolled studies.[12] Of the three RCTs included, only two evaluated PBRT, but both compared different proton beam protocols. The rate of local recurrence was significantly less with CPT than with brachytherapy (odds ratio [OR] = 0.22, 95% confidence interval [CI], 0.21-0.23). There were no significant differences in mortality or enucleation rates between treatments. However, there were significantly lower rates of radiation retinopathy and cataract formation in patients treated with CPT compared with brachytherapy (pooled rates of 0.28 vs 0.42 and 0.23 vs 0.68, respectively). This review concluded that there was evidence that CPT was at least as effective as alternative therapies as primary treatment of uveal melanoma and was superior in preserving vision.

- In 2016, Verma and Mehta published a systematic review of PBRT for uveal melanoma, including 14 studies ranging from 78 to 3088 patients with median follow-up periods ranging from 34 to 148 months.[13]No randomized controlled trials met inclusion criteria. Meta-analyses were not conducted due to substantial methodological and technical treatment heterogeneity between studies. Five year local control rates exceeded 90%, which persisted at 10 and 15 years. Five-year overall survival rates ranged from 70- 85%, and 5-year metastasis-free survival and disease-specific survival rates were from 75 to 90%, with more recent series reporting higher values. Five year enucleation rates were consistently between 7-10%. Many patients (60-70%) showed a post-PBRT visual acuity decrease, but still retained purposeful vision with more recent, higher-volume series reporting superior numbers. Complication rates showed improvements compared with historical plaque brachytherapy data. The reviewers concluded that PBRT treatment for uveal melanomas had excellent survival and ophthalmological outcomes.

Skull-base Cancers

- In 2009, Amichetti published the results of a systematic review that assessed tumor control and toxicity of PBRT as a treatment for skull-base chordoma, including seven studies (N=416 patients from five institutions).[14] The reviewers reported that the average five-year local tumor control rate was 69% (range 46-73%) and the average overall survival rate was 80% (range 67-81%). One study included in the review reported 10-year overall survival and local control rates of 54%. The reviewers concluded that use of protons has shown better results in comparison to the use of

conventional photon irradiation, resulting in the best long-term (10-year) outcome with relatively few major complications considering the high doses delivered with this therapeutic modality.

- In 2016, Matloob et al. published a systematic review that evaluated PBRT for skull-base chordomas, including 12 controlled trials and case series ranging from nine to 367 patients.[15] Of the included studies that reported long-term outcomes (six studies), 5-year survival rates ranged from 67% to 94%. The reviewers concluded that the evidence suggested that PBRT given post-operatively for skull base chordomas resulted in better survival with less damage to surrounding tissue. In comparison to other treatment modalities long-term local control and survival may be improved with PBRT.

- In 2019 (reviewed in 2023), Hayes conducted a systematic review evaluating the safety and efficacy of PBT for the treatment of chordoma and chondrosarcoma of the skull base.[16] Searching the literature through October 2018, investigators included 10 studies for review (3 retrospective cohort studies, 1 retrospective pooled comparative database analysis, and 6 retrospective noncomparative cohort studies). Sample size ranged from 24 to 251 patients; median follow-up ranged from 38 to 91 months. Outcomes of interest included cause-specific survival, disease specific survival, local control (LC), local failure, distant metastasis-free survival (DMFS), and overall survival.

  Two comparative studies with data assessing local control found no significant differences between PBT and CIBT patients. Conversely, 3 noncomparative studies reported variable rates of LC in patients with skull base chordoma, including 87% at 3 years, 68% at 5 years, and 71% at 7 years. Five noncomparative studies reported variable rates of LC in patients with skull base chondrosarcoma, including 100% at 2 years, 94% at 3 years, 94% at 7 years, and 89.7% at 8 years. Non-comparative cohort studies reported 92% DMFS at 5 and 7 years in patients with skull base chordoma and 100% DMFS at 5 years in patients with skull base chondrosarcoma. Comparative studies reported no significant difference between PBRT and comparators regarding cause-specific survival, disease-specific survival, failure-free survival, progression-free survival, toxicity-free survival and overall survival. In general, PBRT patients experience similar efficacy to photon-based EBRT technologies while also potentially reducing the risk of certain complications in adult patients with these tumors.

  Overall evidence quality was assessed as “low” due to individual study limitations and imprecision owing to the small number of studies comparing PBT with other treatment modalities. Hayes ultimately assigned a “C” rating (potential but unproven benefit) for PBRT as primary or adjuvant radiotherapy in adult patients with chordoma or chondrosarcoma of the skull base. Despite calling for additional, well-designed, long-term comparative studies are needed to compare it with other therapies, Hayes concluded that PBT appears to be an established treatment modality for patients with certain types of chordoma and chondrosarcoma of the skull base.

Systematic Reviews Evaluating Reirradiation for Mixed Indications

While research is limited supporting reirradiation overall, there is a growing body of evidence that consistently supports the ability of PBT to reduce toxicity from head and neck and CNS reirradiation.

- In 2017, Verma et al. published the results of a systematic review, including 14 studies reporting clinical outcomes of PBT for reirradiation RT.[17] None of the included studies were comparative in design, and the reviewers were unable to conduct meta-analyses due to substantial heterogeneity between studies. However, the following is a summary of the key findings and conclusions regarding the most promising indications:

- Ocular: One case series reported local recurrence (LR) rates of 31%, with a 5-year eye retention rate of 55% in patients with recurrent uveal melanoma. The median time to reirradiation was 36 months. The reviewers concluded that re-irradiation was well-tolerated with no major complications, but patients experienced a greater incidence of cataracts. This likely has implications for QOL over eye enucleation.

- CNS (adult): Three case series addressed CNS tumors (mostly gliomas), chordomas, and gliomas. Follow-up after reirradiation was reported between 8-24 months. Median overall survival rates reported for glioma patients ranged from 8-19.4 months. Two-year survival rates for patients with chordomas was 80%. All three included studies concluded that results were comparable to existing data using photons. The review concluded that "among CNS malignancies, PBT displays appropriate safety profiles in the reRT setting. Although outcomes of reRT with PBT versus photons are likely not changed, especially in poor-prognostic cohorts such as high-grade gliomas, PBT may allow for fewer toxicities and more safely maintain functional/performance status and quality of life (QOL). Next, because some CNS malignancies often have short intervals from initial treatment to recurrence, reRT dose-escalation is likely most easily achieved with PBT owing to the higher risks of toxicities with such short intervals."

- Head and Neck: Four were included that addressed reirradiation of various head and neck cancers – including three large case series (n= 61 to 92 patients). Median reirradiation times ranged from 18-47 months. Two-year overall survival, when reported, ranged from 33-69% with 2-year local control rates ranging from 62-73% (two studies). The review concluded that head and neck "neoplasms are among the most challenging to re-irradiate, especially to full dose levels. Collectively, PBT reRT appears safe and effective, especially with increasing intervals between irradiation and for lower-volumes of gross disease. In fact, toxicity rates with PBT reRT appear to be more favorable than for reRT with IMRT, and potentially even IMRT for primary RT."

<u>Systematic Reviews for Not Medically Necessary Indications</u>

Prostate Cancer

- In 2009, Brada et al. reported on a systematic review of PBRT as treatment for a number of indications, including prostate cancer.[18] The review included three studies that evaluated the use of PBRT for prostate cancer (N=1642 patients), but none of the included studies directly compared the efficacy of proton to photons. The researchers concluded that the current published literature on PBRT did not support a definitive benefit in terms of survival, tumor control, or toxicity over other forms of high-dose conformal radiation in the treatment of localized prostate cancer.

- In 2009, Efstathiou et al. published results from a systematic review and concluded that the current evidence did not support any definitive benefit to PBRT over other forms of high-dose conformal radiation in the treatment of localized prostate cancer.[19] The reviewers did not identify any studies that published patient-reported outcomes for prostate cancer patients treated with IMRT versus PBRT, nor did they identify any prospective studies comparing these modalities. The reviewers also noted the uncertainties surrounding the physical properties of PBRT, perceived clinical gain, and economic viability with regards to PBRT treatment for prostate cancer.

- In 2012, Grimm et al. published results from a systematic review comparing a variety of different treatments for patients with low, intermediate and high risk prostate cancer, including two studies on PBRT (N=388 patients).[20] The outcomes assessed were prostate-specific antigen free survival outcomes. PBRT was assessed as a type of radiation therapy (along with external beam, conformal, and IMRT). The reviewers reported that brachytherapy with or without EBRT provided greatest treatment benefit in patients with low and intermediate risk of disease. PBRT was not recommended for any risk group.

- The 2012 ASTRO review by Allen et al., described in detail above, stated that although there was evidence for the efficacy and sparing of normal tissue when conformal PBRT in the "low to moderate range (< 60-70Gy)" when used as treatment for localized prostate cancer; that PBRT was not superior to photon-based approaches.[3] The review stated that:

  > "The outcome is similar to IMRT therapy, however, with no clear advantage from clinical data for either technique in disease control or prevention of late toxicity. This is a site where further head-to-head clinical trials may be needed to determine the role of PBT. In addition, careful attention must be paid to the role of dosimetric issues including correction for organ motion in this disease. Based on current data, PBT is an option for prostate cancer, but no clear benefit over the existing therapy of IMRT photons has been demonstrated."

- In 2014, the Agency for Healthcare Research and Quality (AHRQ) published an updated review of therapies for clinically localized prostate cancer, comparing the risks and benefits of a number of treatments for localized cancer, including PBRT.[21] This conclusion was similar to that of the 2008 review, which found that no single therapy could be considered the preferred treatment for localized prostate cancer because of limitations of evidence. For all treatment modalities there were tradeoffs between estimated treatment effectiveness, necessity, and adverse effects. Limited evidence appeared to favor surgery over watchful waiting or EBRT, and RT plus hormonal therapy over RT alone. The reviewers concluded that additional studies validating the comparative effectiveness of emerging therapies such as PBRT were needed.

- In 2020 (reviewed in 2023), Hayes published a review that evaluated PBRT for prostate cancer.[1] Searching the literature through January 2020, investigators included 20 studies for review (4 RCTs, 2 prospective cohort studies, 2 retrospective comparative registry analysis studies, 12 retrospective comparative studies). Sample size ranged from 82-41,737 patients; follow-up varied from 1- to 9 years. Outcomes of interest included overall survival, local recurrence-free survival, disease-specific survival, total tumor-free survival, biochemical failure, treatment-related morbidity, and quality of life. Three of the RCTs compared different PBRT protocols.

When PBRT was used as an adjunct to brachytherapy, both included studies reported similar recurrence rates five and eight years post-treatment, whether PBRT was used as an adjunct or not. When used as an adjunct to X-ray therapy, the two included studies reported conflicting results at 5-year follow-up. The relative incidence of treatment-related complications was similar when PBRT was compared to other treatments.
The review stated that "the body of evidence concerning PBRT for prostate cancer was large in size and overall low in quality." The majority of studies were deemed to be of low to very-low quality and suffered from a number of limitations, including: retrospective and/or nonrandomized study design, limited or unequal follow-up, variations in treatment protocols, unclear or no reporting of radiation dosage, and either absence of control groups or comparison with an uninformative intervention (e.g., different PBRT protocol). Due to these limitations, definitive conclusions cannot be drawn about the efficacy and safety of PRBT. Therefore, for PBRT for the treatment of localized prostate cancer, the review graded the treatment as a "C" (potential but unproven benefit), with investigators calling for additional studies to establish the clinical role of PBT relative to other widely used therapies.

Observational studies for not medically necessary indications

- In 2021, Barsky and colleagues published a case-matched analysis comparing 5-year clinical outcomes and patterns of failure of PBRT versus IMRT for prostate cancer in postoperative settings.[22] The study included 260 men (n=65 PBRT; 195 IMRT). At a median follow up of 59 months, biochemical failure (45% v 41%), local failure (2% v 3%), regional failure (9% 7%), distant failure (9% v 9%), and mortality (2% v 5%) rates were not significantly different between the two groups. Type of radiation therapy was not significantly associated with biochemical, local, regional, or distant failure or all-cause mortality. The authors concluded that PBRT yielded similar long-term outcomes and patterns of failure compared to IMRT in post-proctectomy settings. This study's limitations include a retrospective design, single-institution sample, and small sample size.

- In 2021, Vapiwala and colleagues published a retrospective study on the pooled toxicity of moderately hypofractionated PBRT and IMRT in early-stage prostate cancer.[23] A total of 1850 patients were included, 1282 IMRT and 568 PBRT. Overall toxicity rates were low, with the majority of patients experiencing no late gernitourinary (56.6%, n = 1048) or late gastrointestinal (74.4%, n = 1377) toxicity. No difference was seen in the rates of late toxicity between the groups, with late grade 3+ GU toxicity of 2.0% versus 3.9% (odds ratio [OR] 0.47; 95% confidence interval 0.17-1.28) and late grade 2+ GI toxicity of 14.6% versus 4.7% (OR 2.69; confidence interval 0.80-9.05) for the PBT and IMRT cohorts, respectively. The authors concluded that that IMRT and PBRT have similar low rates of toxicity after long-term follow up.

Systematic Reviews for Investigational Indications

Breast Cancer

- In 2016, Verma et al. published a systematic review that evaluated the clinical outcomes and toxicity of PBRT for breast cancer, including six peer-reviewed studies (n=18 to 100 patients).[24] Of the six studies included, only one was comparative in design. Overall, the reviewers reported that PBRT to the breast/chest produced skin toxicity rates similar or to published rate for photon

therapy, with grade 1 dermatitis rates of 25% and grade 2 dermatitis rates of 71% to 75%. The incidence of esophagitis due to protons was also comparable to photons. Using PBRT-based accelerated partial breast irradiation, the rates of seroma/hematoma and fat necrosis were comparable to those reported in the existing data. In addition, the reviewers noted that although PBRT offers potential to minimize the risk of cardiac events, definitive clinical experiences remain sparse.

The sole comparative study included in the review reported on long-term cosmetic outcomes and toxicities of PBRT compared with photon-based 3-D conformal accelerated partial-breast irradiation.[25] Nineteen patients were treated with PBRT and 79 with photons or mixed photons/electrons. Median follow-up was 82.5 months (range: 2-104 months). At seven years, skin toxicities were more common for the PBRT group: telangiectasia, 69% and 16% (p=0.0013); pigmentation changes, 54% and 22% (p=0.02); and other late skin toxicities, 62% and 18% (p=0.029) for PBRT and photons, respectively. There were no significant differences between the groups in the incidences of breast pain, edema, fibrosis, fat necrosis, skin desquamation, rib pain or fracture, and local failure rates.

- In 2018, Chan et al. published a systematic review of several RT techniques for early stage node-negative breast cancer treatment, including four studies (two comparative studies).[26] Two small (n=10 and 20 patients) comparative studies included in the review reported significant does reductions to the lung, heart, and left anterior descending artery (LAD) using PBRT compared to 3-D conformal RT.[27,28] The reviewers concluded that although PBRT shows dosimetric promise, the data is sparse regarding late cardiac and pulmonary events exist due to lack of long-term follow-up.

- Similarly, a recent review of PBRT for locally advanced breast cancer included 13 studies, three of which were small (n=11, 20, and 20 patients) but comparative in nature.[29] This review indicated that PBR allows better sparing of the heart than photon therapy with similar level of cutaneous toxicity, but larger studies were needed to confirm the clinical benefit for PBRT. Overall, systematic reviews of PBRT for breast cancer have considerable limitations, including on or more of the following:

    - the majority of included studies are noncomparative in nature
    - the majority of included studies are small in sample size (less than 100 patients)
    - included studies are heterogeneous in terms of
        - cancer stage (e.g., early-stage noninvasive, locally advanced)
        - clinical indication (e.g., accelerated partial breast irradiation, whole breast irradiation with or without regional node RT, postmastectomy RT)
        - type of PBRT used (e.g., passive proton therapy [double scattering], pencil beam scanning)
    - comparative studies differ in terms of comparator treatment used (IMRT or 3D-conformal RT)
    - comparative studies did not include more than 20 patients treated with PBRT

Esophageal Cancer

- In the 2012 systematic review by ASTRO's emerging technology committee, described in detail above, PBRT was evaluated as a treatment for GI malignancies, including esophageal cancer.[3] The reviewers stated that there may be a rationale for PBRT in esophageal cancer since it is often associated with "localized unresectable disease near critical organs at risk, but almost no clinical data exists."

- Similarly, in 2016 Verma et al. published a systematic review of clinical outcomes and toxicities of PBRT for GI neoplasms, including three comparative studies and 9 case series (n= 5 to 100 patients) on esophageal cancer.[30] Of note, one large included comparative study by Wang et al. reported significantly higher pulmonary complications in patients treated with 3-D CRT and IMRT compared to those treated with PBRT and higher GI complications in patients treated with PBRT (but not IMRT) compared to PBRT.[31] Limitations of this primary study include retrospective study design, significant difference in treatment groups concerning induction chemotherapy, and confidence intervals (CIs) for the odds ratios were very broad with Cis for both treatment groups indicating no statistical difference between treatments.

Gastric Cancer

In the 2012 systematic review by ASTRO's emerging technology committee, described in detail above, PBRT was evaluated as a treatment for GI malignancies including gastric cancer.[3] The reviewers stated that:

"PBT is mostly untested in GI malignancies, and the number of patients with GI malignancies who are eligible for PBT will be very small until indications for its use become clearer. In gastric cancer there appears to be little role for PBT".

Gynecological Cancers

In 2016, Verma et al. published the results of a systematic review of PBRT for treatment of gynecologic neoplasms, including 16 small dosimetric studies (n= 1-25 patients/study) that compared PBRT to various other treatment modalities.[32] Studies included recruited women with a number of different gynecological cancers: uterine, cervical, peritoneal papillary serous carcinoma, vaginal, post-operative gynecological cancers, and endometrial. The reviewers noted that the available evidence for PBRT in treating gynecologic cancers was of low quantity and quality, preventing robust conclusions regarding safety and efficacy. However, the reviewers reported that the existing evidence indicated that when compared to other treatment modalities, PBRT significantly decreased dose to organs-at-risk (OARs), such as the rectum, bladder, bowel, kidneys, BM, and femoral heads. This dose reduction to OARs with PBRT was more pronounced within the low-dose volumes than the higher dose volumes. In addition, stage-specific tumor control and outcomes were improved with PBRT treatment, along with low toxicity rates compared to other treatments. However, these results have not been confirmed in RCTs. The reviewers concluded that larger scale and higher quality studies addressing whether PBRT could provide clinically meaningful differences in toxicities and outcomes in women with gynecologic neoplasms are warranted.

Hepatobiliary Cancers

- In the 2012 systematic review for ASTRO, described above, the reviewers stated that fractionated PBRT has been extensively studied in hepatocellular carcinoma (HCC) with good success, providing local control rates between 70% and 85%.[3]
- In 2015, Qi et al. performed a systematic review and meta-analysis comparing the clinical outcomes and toxicity in individuals with HCC who were treated with either charged particle therapy (CPT) or conventional radiotherapy (CRT), including 70 non-comparative observational studies.[33] There were no randomized controlled trials or controlled studies that compared charged particle therapy with photon therapy directly. The methodological quality of the included studies reported as fair. Pooled OS was significantly higher at 1, 3, 5 years for CPT than for CRT (relative risk [RR]=1.68, 95% CI: 1.22–2.31, p < 0.001; RR=3.46, 95% CI: 1.72–3.51, p < 0.001; and RR=25.9, 95% CI: 1.64–408.5, p = 0.02; respectively). Progression free survival (PFS) and local control (LC) at longest follow-up were also significantly higher for CPT than for CRT (p = 0.013 and p < 0.001, respectively), while comparable efficacy was found between CPT and SBRT in terms of OS, PFS and LC at longest follow-up. Additionally, high-grade acute and late toxicity associated with CPT was lower than that of CRT (p = 0.003 and p = 0.011, respectively). In addition, there was significantly less late toxicity in the CPT group than in the SBRT group (p = 0.011). However, the reviewers noted that there might be potential risk of bias in comparisons between observation studies, since the CPT studies are overall older than the SBRT and CRT studies.

- In 2016 Verma et al. published a systematic review of clinical outcomes and toxicities of PBRT for GI neoplasms, including one small comparative study (n=22) and two small case series that included 14-37 patients with cholangiocarcinoma.[30] Of note, the small included comparative study reported similar median survival in the photon and proton (helium ions) RT groups. One-year survival ranged from 44-70% and one-year progression-free survival ranged from 30-40%. All studies reported grade three toxicities. All three studies reported mixed patient populations in terms of stage and/or presence of extrahepatic disease.

- In 2017, Igaki et al. published the results of a systematic review of publications on charged particle therapy (proton beam therapy and carbon ion therapy) as a treatment of HCC, including 13 cohorts from 11 studies.[34] The studies included one RCT comparing PBRT with transarterial chemoembolization (TACE), nine phase I or II trials and two retrospective studies. Most cohorts had inclusion criteria of unresectable HCCs. The review reported local control rates ranged from 71.4-95% at three years, and the overall survival rates ranged from 25-42.3% at five years. In addition, although not reported in all included studies, late severe radiation morbidities were uncommon, with a total of 18 patients (2.3%) with grade ≥3 late adverse events reported. The reviewers cautioned that comparative evidence and patient selection were at a high risk of bias for most of the included studies, and that although future RCTs may not be feasible, additional comparative studies are needed.

Non-Small Cell Lung Cancer

- In 2010, Grutters et al. published the results of a meta-analysis of uncontrolled studies that compared PBRT with a number of other therapies for stage I NSCLC.[35] Treatment with PBRT was not associated with any statistically significant differences in 2-year overall survival (9%

difference between treatments) or disease-specific survival. Five-year overall survival for PBRT (40%) was significantly higher than CRT (20%), but similar to SBRT (42%) and carbon-ion therapy (42%). However, the reviewers advised that caution be taken in interpreting these results due to limited numbers of patients and limited follow-up. Specifically, only five studies on PBRT were included in the review (N=180 patients) and median follow-up in these studies was either not reported or was short in duration (14 - 30 months).

In the 2012 systematic review for ASTRO, described above, the reviewers stated that Grutters meta-analysis (described above) showed no difference between photon based SBRT to PBRT in terms of local tumor control rates and that very little published data existed for locally advanced lung cancer.[3] In addition, "PBT has been used in the treatment of stage I NSCLC although no clear clinical benefit over photon therapy has currently been shown. Data regarding the use of PBT did not provide sufficient evidence to recommend PBT for lung cancer outside of clinical trials. Lastly, unlike in some other disease sites, the issue of organ motion and changes in lung density during respiration is critical and adds an additional challenge to the use of PBT for this indication."

- In 2010, Pijls-Johannesma and et al. conducted systematic review that examined the use of charged particle therapy in lung cancer, including 11 studies primarily focused on stage I NSCLC, five evaluating protons (N=214 patients) and six evaluating carbon ions (N=210 patients).[36] Eleven studies all dealing with NSCLC, mainly stage I, were included in the review, five investigating protons (n=214) and six investigating C-ions (n=210). The proton studies included one phase 2 study, two prospective studies, and two retrospective studies. No phase 3 studies were identified. Significant heterogeneity existed between included studies in terms of radiation schedules and definitions of control rates, making comparisons of results difficult. For PBRT, reported 2- to 5-year local control (LC) rates ranged from 57% to 87%. The 2- and 5-year OS rates were 31%–74% and 23%, respectively, and 2- and 5-year cause-specific survival (CSS) rates were 58%–86% and 46%, respectively. The authors noted that the LC rates, although better than those reported for photon RT, were inferior to LC rates reported for SBRT for stage I NSCLC. The reviewers concluded that the results with protons are promising, but that because of the lack of evidence on clinical efficacy, further well-designed trials are needed to predict the magnitude of benefit.

- In 2017 (archived in 2022), Hayes published a review of PBRT for NSCLC, including 12 studies (10 of which were nonrandomized comparative studies).[2] Three studies evaluated specific safety outcomes only and the majority of the studies were retrospective. Six studies evaluated PBRT versus IMRT, CRT, or CBT for NSCLC and five of these studies found very few differences in survival outcomes between techniques. However, one large database study found improved overall survival for PBRT compared with non-PBRT radiotherapies for all stages combined. In terms of safety, the majority of the studies that compared PBRT to other therapies found no difference in the incidence of complications. The review reported that all but one of the included studies was of poor quality and that the results reported between studies were conflicting. Limitations of the of the body of evidence included retrospective and/or nonrandomized study design, small study size, use of a historical control groups, incomplete reporting of outcomes, lack of blinded assessment of outcomes, and potential bias due to statistically significant differences between treatment groups at baseline or lack of analysis to determine whether differences at baseline were significant. The review concluded that there

was insufficient evidence that PBRT was safer or consistently more effective than conventional methods of radiation therapy, and rated PBRT for NSCLC with a grade of "C".

The Hayes review was updated in 2019. Although there was one new case series identified reporting on the safety and efficacy of PBRT for NSCLC cancer, the results of this study did not change the conclusions and/or ratings in the existing Hayes report.

- In 2017, Chi et al. published a systematic review that compared PBRT to SBRT for early stage NSCLC, including 9 studies on hypo-fractionated PBRT and 72 studies on SBRT.[37] PBRT was associated with improved overall survival (OS; p=0.005) and progression-free survival (PFS; p=0.01) in the univariate meta-analysis. However, in the in the multivariate meta-analysis, although the 3-year local control (LC) still favored PBT (p=0.03), the OS benefit was no longer significant (p=0.11). The reviewers concluded that although hypo-fractionated PBRT may lead to additional clinical benefit when compared with photon SBRT, no statistically significant survival benefit from PBRT over SBRT was observed in the treatment of early stage NSCLC after adjusting for potential confounding variables.

Pancreatic Cancer

- In the 2012 systematic review by ASTRO's emerging technology committee, described in detail above, PBRT was evaluated as a treatment for GI malignancies including pancreatic cancer.[3] The reviewers stated that there might be a rationale for PBRT in pancreatic cancer since it is often associated with "localized unresectable disease near critical organs at risk, but almost no clinical data exists."

- In 2016 Verma et al. published a systematic review of clinical outcomes and toxicities of PBRT for GI neoplasms, including three small case series that included 15-50 patients with pancreatic cancer.[30] Of note, all three studies reviewed recruited different patient populations in terms of tumor characteristics/resectability and all three studies treated patients with different doses and fractionation techniques. All studies suffer from lack of a comparator group, small sample size and lack of long term follow-up (follow-up was reported between 11-13 months).One recent study published after the review that compared PBRT to hyper-fractionated accelerated chemoradiotherapy for locally advanced pancreatic cancer also suffered from small sample size (n=25) and short-term (15.4 months) follow-up.[38]

Soft Tissue Sarcomas

In 2016 Verma et al. published a systematic review of clinical outcomes and toxicities of PBRT for GI neoplasms, including one small study including patients treated with PBRT and/or IMRT, n=28) and one small case series (n=31).[30] The study reporting outcomes of patients treated with PBRT and/or IMRT (median follow-up of 33 months) did not report results separately by treatment type and therefore was not comparative in nature.[39] Of note, both studies reviewed recruited heterogeneous patient populations in terms of sarcoma type within and between studies. In addition, each study used different doses and fractionation techniques.

The evidence for the following investigational oncologic indications is limited to noncomparative studies:

- Lymphomas
  - Hodgkin lymphoma[40,41]
- Thymomas and thymic cancers[42-44]

These studies suffer from one or more of the following limitations:

- retrospective study design
- small sample size (less than 50 patients)
- heterogeneous patient populations in terms of purpose of treatment (definitive, salvage or adjuvant)
- lack of comparator group
- short-term follow-up, which precludes the ability to draw conclusions regarding any potential benefit of PBRT in reducing the risk of radiation-induced late effects

Oncologic Indications Evidence Summary

Despite the large number of studies published on PBRT for the treatment of cancer, there is a paucity of high-quality evidence such as comparative studies (particularly randomized controlled trials) and systematic reviews for the majority of oncologic indications, which report patient outcomes. Of note, the majority of literature on most of the investigational indications was dosimetry studies (not addressed here) reporting of comparisons of treatment plans and estimated risk to critical structures based on simulation, but not actual outcomes from treatment. These types of studies are typically retrospective in design and do not indicate actual equality or superiority of PBRT over other types of radiation therapy.

The overall low quality of the evidence base for PBRT may be due to several factors. There are a number of indications are so rare that controlled trials or large studies are not feasible and will not be forthcoming. However, for common cancers for which systematic reviews have been published, comparative studies (preferably randomized) are necessary to draw meaningful conclusions regarding safety and efficacy of PBRT compared to other treatment options in the context of current clinical practice. Without comparative studies for most common cancers, systematic reviews are unable to provide a definitive answer on the effectiveness and safety of PBRT.

Investigational Non-Oncologic Indications

Systematic Reviews

In 2009, Bekkering et al. published the results of a systematic review that evaluated the effectiveness and safety of PBRT for indications of the eye, including one comparative study and two case series for choroidal hemangioma and four controlled trials and one case series for age-related macular degeneration (AMD).[45] The reviewers noted that the methodological quality of all included studies was poor and limitations included differences in radiation techniques applied within the studies, and variation in patient characteristics within and between studies. Results for choroidal hemangioma and AMD did not reveal beneficial effects from proton radiation. The review concluded that the evidence on the safety and efficacy of PBRT was limited due to the lack of well-designed and well-reported studies

and that RCTs comparing PBRT versus standard alternatives and prospective case studies enrolling only patients treated with up-to-date techniques are needed.

Randomized Controlled Trials (RCTs)

In 2002, Ciulla et al. reported on a sham-controlled RCT that examined the effect of PBRT on subfoveal choroidal neovascular membranes (CNVM) associated with age-related macular degeneration (AMD).[46] This RCT was a prospective, sham-controlled, double-masked trial that included 37 patients that were randomly assigned to 16-Gy proton irradiation delivered in two fractions 24 hours apart or to sham control treatment. The investigators reported that PBRT was associated with a trend toward stabilization of visual acuity, but this association did not reach statistical significance.

More recently, a small RCT that compared two different PBRT dose regimens in patients with non-age-related macular degeneration (AMD) choroidal neovascularization (CNV).[47] This RCT reported short-term (2-year) visual acuity outcomes that were not significantly different between treatment protocols.

Nonrandomized Comparative Studies

- In 2006, Hocht et al. published the results of a poor-quality retrospective study evaluated PBRT's clinical effectiveness in 44 patients with diffuse or circumscribed ocular choroidal hemangiomas who were treated with either PBRT (20-23 GyE) or photon therapy (16-20 Gy) and followed for an average of 2.5 years.[48] In analyses adjusting for differential follow-up between treatment groups, neither modality was found to significantly stabilize visual acuity (p=0.43). Regression analysis adjusting for between-group differences indicated that there were no significant differences in any adverse events between the two treatment modalities, including retinopathy (p=0.12). In addition, no differences could be detected between patients with circumscribed choroidal hemangiomas treated with protons and photons.

- In 2012, Mosci et al. published a comparative study of clinical outcomes for patients with large choroidal melanoma after primary treatment with enucleation or PBRT.[49] This retrospective non-randomized study evaluated 132 consecutive patients and found that cumulative all-cause mortality, melanoma-related mortality and metastasis-free survival were not statistically different between the two groups. Although eye retention of the tumors treated with PBRT at 5 years was 74% (SD 6.2%), best-corrected visual acuity (BCVA) of 0.1 or better was observed in only 32% of the patients.

CLINICAL PRACTICE GUIDELINES

Non-Oncologic Indications

American Heart Association / American Stroke Association (AHA/ASA)

The 2017 joint AHA/ASA guidance on the management of brain arteriovenous malformations (bAVMs)[50] stated the following:

> "Stereotactic radiosurgery (SRS) is typically performed to achieve obliteration of bAVMs that are deemed too risky for resection because of anatomic factors such as location or general medical

problems…. A large number of published series demonstrate the clinical efficacy and general safety of SRS for the treatment of patients with bAVMs."

Oncologic Indications

National Comprehensive Cancer Network (NCCN)

The following NCCN guidelines address PBRT to varying extents, depending on the cancer.

B-cell Lymphomas

The NCCN B-cell Lymphomas Version 4.2023 guidelines recommend the following:[51]

- "Treatment with photons, electrons or protons is appropriate; selection depends upon clinical scenario."
- "Advance radiation technologies such as intensity-modulated radiation therapy (IMRT)/ volumetric modulated arc therapy (VMAT), proton therapy, breath-hold or respiratory gating, and/or image-guided therapy may offer significant and clinically relevant advantages in specific instances to spare important organs at risk (OARs)… and decrease the risk of late, normal tissue toxicity while still achieving the primary goal of local tumor control."
- "Achieving highly conformal dose distributions is especially important for patients who are being treated with curative intent or who have long life expectancies following therapy."
- "The treatment plan *can be* designed using conventional, 3-D conformal, or IMRT/VMAT or proton therapy techniques using clinical treatment planning considerations of target coverage and normal tissue avoidance."

Bone Cancer

The NCCN Bone Cancer Guidelines Version 3.2023 recommend the following:[52]

PBRT "should be considered as indicated in order to allow for high-dose therapy while maximizing normal tissue sparing." In this recommendation, PBRT is listed as one of several specialized techniques that should be considered for the following indications:

- Chondrosarcoma: (category 2B)
  - Low-grade and intra-compartmental: unresectable cancer only
  - High-grade (clear cell or extra-compartmental): postoperatively or unresectable
- Chordoma:
  - Extracranial (mobile spine/sacrum): postoperatively or unresectable
  - Cranial (base of skull): postoperatively or unresectable
  - PBRT may also be considered as one of several treatment options for recurrent cranial and extracranial chordomas that are either localize or metastatic in nature.

In addition, in the discussion section of the guidelines, the panel noted:

- Specialized techniques, such as proton therapy, should be considered in order to deliver high radiation doses while maximizing normal tissue sparing.

- Chondrosarcomas
  - "Proton beam radiation therapy (RT) alone or in combination with photon beam RT has been associated with excellent local tumor control and long-term survival in patients with low-grade skull base and cervical spine chondrosarcomas."
  - "Postoperative treatment with PBRT may be useful in patients with tumors in an unfavorable location not amenable to resection, especially in chondrosarcomas of the skull base or axial skeleton. RT *can be considered* in patients with unresectable lesions."
  - The recommendations for chondrosarcoma are category 2B due to lack of data.
- Chordomas
  - Proton beam RT (alone or in combination with photon beam RT) results in favorable local control rates in patients with skull-base or extracranial chordomas (involving the spine and sacrum). However, RT with carbon ions and "specialized techniques such as IMRT, SRS, and FSRT" have also been associated with good local control rates in cranial and extracranial chordomas."

Central Nervous System (CNS) Cancers

The NCCN CNS guidelines Version 1.2023 recommend the following:[53]

For Anaplastic Gliomas/Glioblastoma High Grade: "Consider proton therapy for patients with good long-term prognosis (grade III IDH-mutant tumors and grade III 1p19q co-deleted tumors) to better spare un-involved brain and preserve cognitive function."

For adult intracranial and spinal ependymoma and adult medulloblastoma: "To reduce toxicity from craniospinal irradiation in adults, consider the use of intensity-modulated radiotherapy or protons if available."

For Meningiomas: "Highly conformal fractionated RT techniques (e.g., 3D-CRT, IMRT, VMAT, proton therapy) are recommended to spare critical structures and uninvolved tissue."

Esophageal and Esophagogastric Junction Cancers

The NCCN Esophageal and Esophagogastric Junction Cancers Version 2.2023 guidelines recommend the following:[54]

- "Proton beam therapy is appropriate in clinical settings where reduction in dose to organs at risk (e.g., heart, lungs) is required that cannot be achieved by 3-dimensional [3-D] techniques, ideally within a clinical trial or registry study… Data regarding proton beam therapy are early and evolving. Ideally, patients should be treated with proton beam therapy within a clinical trial."

  In addition, in the discussion section of the guidelines, the panel stated the PBRT "is an *emerging RT technique* that may offer further sparing of normal tissues" and "may improve the therapeutic ratio by limiting cardiopulmonary toxicities."

Head and Neck Cancers

The NCCN Head and Neck Cancers Version 2.2023 guidelines recommend the following:[55]

- For cancer of the oropharynx, cancer of the supraglottic larynx, and occult primary: "Either IMRT (preferred) or 3D conformal RT is recommended … in order to minimize dose to critical structures. Use of proton therapy is an area of active investigation. Proton therapy may be considered when normal tissue constraints cannot be met by photon-based therapy."
- For cancers of the nasopharynx, "IMRT (preferred) is recommended for cancers of the nasopharynx to minimize dose to critical structures. Proton therapy can be considered when normal tissue constraints cannot be met by photon-based therapy."
- For ethmoid and maxillary sinus tumors, "Either IMRT or proton therapy is recommended for maxillary sinus or paranasal/ethmoid sinus tumors to minimize dose to critical structures."
  For Salivary Gland Tumors and mucosal melanoma: "Either IMRT or 3D conformal RT is recommended. Proton therapy can be considered when normal tissue constraints cannot be met by photon-based therapy."

However, the panel states that "without high-quality prospective comparative data, it is premature to conclude that proton therapy has been established as superior to other modern radiation techniques such as IMRT, particularly in regard to tumor control… The panel supports ongoing efforts to develop models to predict which patients would benefit the most from proton therapy and the development of higher-level and/or randomized data demonstrating greater efficacy of QOL gains potentially achieved with PBT."[55]

Hepatobiliary Cancers

The NCCN Hepatobiliary Carcinoma Version 1.2023 guidelines recommend the following:[56]

- "Hypofractionation with photons or protons is an acceptable option for intrahepatic tumors."
- "Proton beam therapy *may be appropriate* in specific situations."

The NCCN Biliary Tract Cancers Version 2.2023 guidelines recommend the following:[57]

- Hypofractionation with photons or protons *is an acceptable option* for unresectable gallbladder cancer. Treatment centers with experience are recommended.

In addition, in the discussion section of the guidelines, the panel stated:

- For hepatocellular carcinoma (HCC), recent large meta-analyses comparing charged particle therapy to SBRT and conventional radiotherapy reported that overall survival, progression free survival and locoregional control through five years were greater for charged particle therapy than for conventional therapy and equal to SBRT.
- "The panel advises that PBRT *may be considered and appropriate* in select settings for treating HCC."
- Based on the results of one nonrandomized trial of 39 patients, NCCN stated, "hypofractionated proton therapy *may also be considered* for patients with unresectable intrahepatic cholangiocarcinoma, but this treatment should only be administered at experienced centers."

Hodgkin Lymphoma

The NCCN Hodgkin Lymphoma Version 2.2023 guidelines recommend the following:[58]

- For adults (≥ 18 years of age) "treatment with photon, electron, or protons *may all be appropriate*, depending upon clinical circumstances."
- "Advance RT technologies such as IMRT, breath hold or respiratory gating, IGRT, or proton therapy may offer significant and clinically relevant advantages in specific instances to spare important OARs… and decrease the risk of late, normal tissue damage."

Malignant Pleural Mesothelioma

The NCCN Pleural Mesothelioma Version 1.2023 guidelines recommend the following:[59]

- "Advanced technologies may be used, such as IGRT for treating involving IMRT/SRS/SBRT, and intensity-modulated proton therapy."

Non-Small Cell Lung Cancer (NSCLC)

The NCCN NSCLC Version 3.2023 guidelines recommend the following:[60]

- "More advanced technologies are appropriate when needed to deliver curative treatment safely. These technologies include (but are not limited to) 4D-CT and/or PET/CT simulation, IMRT/VMAT, IGRT, motion management, and proton therapy." This recommendation references the ASTRO Model Policy for PBRT.[61]
- "IGRT is recommended when using SABR, 3D-CRT/IMRT and proton therapy with steep dose gradients around the target, when OARs are in close proximity to high-dose regions, and when using complex motion management techniques".
- For palliative RT for advanced/metastatic NSCLC, "when higher doses are warranted, technologies used to reduce normal tissue irradiation including IMRT or proton therapy as appropriate) *may be* used."

Prostate Cancer

The NCCN Prostate Cancer Version 4.2022 guidelines state the following: [62]

- "Highly conformal RT (CRT) techniques should be used to treat localized prostate cancer. Photon or proton beam radiation are both effective at achieving highly CRT with acceptable and similar biochemical control and long-term side effect profiles."

However, in the discussion section of the guideline, the panel stated:

- "the weight of the current evidence about prostate cancer treatment morbidity supports the notion that the volume of the rectum and bladder that receives radiobiologically high doses of radiation near the prescription radiation dose accounts for the likelihood of long-term treatment morbidity."

- The comparative effectiveness studies published in an attempt to compare toxicity and oncologic outcomes between proton and photon therapies have all been retrospective and/or observational in design, and therefore "firm conclusions regarding differences in toxicity of effectiveness cannot be drawn because of the limitations inherent in the retrospective/observational studies".
- The discussion section on PBRT references the 2017 ASTRO Model Policy[61], which recommends coverage proton therapy for the treatment of non-metastatic prostate cancer only in the context of an IRB-approved study or a registry study. Based on this, NCCN stated, "in order for an informed consensus on proton beam therapy for prostate cancer to be reached, it is essential to collect further data."
- With one RCT currently underway, the panel believes that at the current time, "no clear evidence supports a benefit or decrement to proton therapy over intensity modulated radiotherapy (IMRT) for either treatment efficacy or long-term toxicity." However, "conventionally fractionated prostate proton therapy can be considered a reasonable alternative to x-ray based regimens at clinics with appropriate technology, physics, and clinical expertise."

Soft Tissue Sarcoma

The NCCN Soft Tissue Sarcoma Version 2.2023 guidelines recommend the following:[63]

- "When external beam RT (EBRT) is used, sophisticated treatment planning with IMRT, tomotherapy, and/or proton therapy *can be used* to improve the therapeutic effect. However, the safety and efficacy of adjuvant RT techniques have yet to be evaluated in multicenter randomized controlled studies."

T-cell Lymphomas

The NCCN T-cell Lymphoma Version 1.0223 guidelines recommend the following:[64]

- "Advance RT technologies such as IMRT, breath hold or respiratory gating, IGRT, or proton therapy *may offer* significant and clinically relevant advantages in specific instances to spare important OARs… and decrease the risk of late, normal tissue damage."
- "Achieving highly conformal dose distributions is especially important for patients who are being treated with curative intent or who have long life expectancies following therapy."
- "Treatment with photons, electrons, or protons *may all be appropriate*, depending on the clinical circumstances."

Thymomas and Thymic Cancers

The NCCN Thymomas and Thymic Cancers Version 1.2023 guidelines recommend the following:[65]

- "A minimum technological standard for RT is CR-planned 3D conformal radiation therapy (3D-CRT). More advanced technologies are appropriate when needed to deliver curative RT safely. These technologies include (but are not limited to) 4D-CT and/or PET/CT simulation, IMRT/VMAT. IGRT, motion management, and proton therapy. In particular, IMRT is preferred over 3D-CRT. Compared to IMRT, proton therapy has been shown to improve the dosimetry

allowing better sparing of the normal organs (lung, heart, and esophagus) with favorable local control and toxicity, and is appropriate for certain patients."

- This recommendation was based on two small case series (n=4 and 27 patients).

Uveal Melanoma

The NCCN Uveal Melanoma Version 1.2023 guidelines recommend the following:[66]

- "Tumor localization for proton beam therapy may be performed by indirect ophthalmoscopy, transillumination, and/or ultrasound (intraoperative or postoperative but before proton beam), MRI, and/or CT."

Carelon

In 2022, Carelon published clinical appropriateness guidelines addressing appropriate use criteria for proton beam therapy.[67] Based on a non-systematic review of evidence, the review concluded that proton beam therapy was appropriate for the following indications:

- *Chordoma, Chondrosarcoma* – as postoperative therapy for individuals who have undergone biopsy or partial resection of a chordoma or low-grade (I or II) chondrosarcoma of the basisphenoid region (e.g. skull-base chordoma or chondrosarcoma), cervical spine, or sacral/lower spine and have residual, localized tumor without evidence of metastasis.

- *Sinonasal cancer* – when tumor involves the base of skull and proton therapy is needed to spare the orbit, optic nerve, optic chiasm, or brainstem.

- *Arteriovenous Malformation (AVM)* – when intracranial AVM is not amendable to surgical excision or other conventional forms of treatment, or when AVM is adjacent to critical structures such as the optic nerve, brain stem or spinal cord

- *Central Nervous System (CNS) Tumors* – when primary or metastatic CNS malignancies, such as gliomas are both adjacent to critical structures such as the optic nerve, brain stem, or spinal cord, and other standard radiation techniques such as IMRT or standard stereotactic modalities would not sufficiently reduce the risk of radiation damage to the critical structure.

- *Hepatocellular carcinoma and intraphepatic cholangiocarncinom*- To treat unresectable, non-metastatic hepatocellular cancer or intrahepatic cholangiocarcinoma with curative intent

- *Ocular Melanoma* – when used to treat melanoma of the uveal tract (including the iris, choroid, or ciliary body) and no evidence of metastasis or extrascleral extension.

- *Pediatric tumors* – when radiation therapy is required.

- *Re-irradiation* – when the dose tolerance of surrounding normal structures would be exceeded with 3D conformal radiation or IMRT.

The investigators judged proton beam therapy to be not medically necessary for the treatment of all other conditions, including: breast cancer, esophageal cancer, gastric cancer, gynecologic cancer, head and neck cancer, hepatobiliary cancer, lung cancer, lymphoma (Hodgkin and non-Hodgkin), pancreatic cancer, and prostate cancer.

American Society of Radiation Oncology (ASTRO)

In 2017, ASTRO published a Reimbursement Model Policy on proton beam therapy (PBT) with the following recommendations:[68]

Medically Necessary Criteria and Indications

"PBT is considered reasonable in instances where sparing the surrounding normal tissue cannot be adequately achieved with photon-based radiotherapy and is of added clinical benefit to the patient. Examples of such an advantage might be:

1. The target volume is in close proximity to one or more critical structures and a steep dose gradient outside the target must be achieved to avoid exceeding the tolerance dose to the critical structure(s).
2. A decrease in the amount of dose inhomogeneity in a large treatment volume is required to avoid an excessive dose "hotspot" within the treated volume to lessen the risk of excessive early or late normal tissue toxicity.
3. A photon-based technique would increase the probability of clinically meaningful normal tissue toxicity by exceeding an integral dose-based metric associated with toxicity.
4. The same or an immediately adjacent area has been previously irradiated, and the dose distribution within the patient must be sculpted to avoid exceeding the cumulative tolerance dose of nearby normal tissue.

Disease sites that frequently support the use of PBRT include the following:

- Ocular tumors, including intraocular melanomas
- Tumors that approach or are located at the base of skull, including but not limited to:
    - Chordoma
    - Chondrosarcomas
- Primary or metastatic tumors of the spine where the spinal cord tolerance may be exceeded with conventional treatment or where the spinal cord has previously been irradiated
- Hepatocellular cancer
- Primary or benign solid tumors in children treated with curative intent and occasional palliative treatment of childhood tumors when at least one of the four criteria noted above apply
- Patients with genetic syndromes making total volume of radiation minimization crucial such as but not limited to NF-1 patients and retinoblastoma patients
- Malignant and benign primary CNS tumors
- Advanced (eg, T4) and/or unresectable head and neck cancers
- Cancers of the paranasal sinuses and other accessory sinuses
- Non-metastatic retroperitoneal sarcomas
- Re-irradiation cases (where cumulative critical structure dose would exceed tolerance dose)"

Indications Suitable for Coverage with Evidence Development (CED)

"There is a need for continued clinical evidence development and comparative effectiveness analyses for the appropriate use of PBT for various disease sites. All other indications not listed in Group 1 are suitable for Coverage with Evidence Development (CED). Radiation therapy for patients treated under the CED paradigm should be covered by the insurance carrier as long as the patient is enrolled in either an IRB-approved clinical trial or in a multi-institutional patient registry adhering to Medicare requirements for CED. At this time, no indications are deemed inappropriate for CED and therefore includes various systems such as, but not limited to, the following:

- Non-T4 and resectable head and neck cancers
- Thoracic malignancies, including non-metastatic primary lung and esophageal cancers, and mediastinal lymphomas
- Abdominal malignancies, including non-metastatic primary pancreatic, biliary and adrenal cancers
- Pelvic malignancies, including non-metastatic rectal, anal, bladder and cervical cancers
- Non-metastatic prostate cancer
- Breast cancer

Use of PBT is not typically supported by the following clinical scenarios:

1. Where PBT does not offer an advantage over photon-based therapies that otherwise deliver good clinical outcomes and low toxicity.
2. Spinal cord compression, superior vena cava syndrome, malignant airway obstruction, poorly controlled malignant bleeding and other scenarios of clinical urgency.
3. Inability to accommodate for organ motion.
4. Palliative treatment in a clinical situation where normal tissue tolerance would not be exceeded in previously irradiated areas."

Prostate Cancer

In the 2017 update of the ASTRO model policy, the panel added additional language regarding their stance on PBRT for prostate cancer. This new language also reflects the language used in ASTRO's current position statement (updated 2018), and states the following:[68]

> "In the treatment of prostate cancer, the use of PBT is evolving as the comparative efficacy evidence is still being developed. In order for an informed consensus on the role of PBT for prostate cancer to be reached, it is essential to collect further data, especially to understand how the effectiveness of proton therapy compares to other radiation therapy modalities such as IMRT and brachytherapy. There is a need for more well-designed registries and studies with sizable comparator cohorts to help accelerate data collection. Proton beam therapy for primary treatment of prostate cancer should only be performed within the context of a prospective clinical trial or registry."

EVIDENCE SUMMARY

Oncologic Indications

Despite the large number of studies published on PBRT for the treatment of cancer, there is a paucity of high-quality evidence such as comparative studies (particularly randomized controlled trials) and systematic reviews for the majority of oncologic indications, which report patient outcomes. Of note, the majority of literature on most of the non covered indications was dosimetry studies (not addressed here) reporting comparisons of treatment plans and estimated risk to critical structures based on simulation, but not actual outcomes from treatment. These types of studies are typically retrospective in design and do not indicate equality or superiority of PBRT over other types of radiation therapy.

Despite limitations, the evidence suggests that PBRT has comparable or superior net health benefits when compared to other treatment modalities including conventional radiation therapy and newer, more sophisticated modalities such as stereotactic body radiation therapy (SBRT) and intensity-modulated radiation therapy (IMRT) for select cancers including ocular tumors, rare bone cancers of the head, neck or spine, prostate cancer, and central nervous system cancers. In addition, there are certain clinical situations for which the overall evidence-base for PBT is limited, but the use of proton PBT may be medically necessary, such as tumors in close proximity the critical structures, thereby making tradition techniques inappropriate.

For all other indications, the use of PBRT is considered not medically necessary due to lack of well-designed comparative studies with adequate follow-up periods.

Non-Oncologic Indications

For non-oncologic indications other than intracranial arteriovenous malformations, the overall body of evidence is poor and suffers from a number of limitations, including heterogeneity in dosing and fractionation protocols, variation in patient and tumor characteristics, and a general lack of well-designed and well-reported studies comparing PBRT to standard treatments.

There is insufficient evidence that PBRT improves health outcomes in patients with ocular conditions such as choroidal hemangiomas, choroidal neovascularization, or age-related macular degeneration. In addition, no clinical practice guidelines were identified that addressed the use of PBRT for these types of non-oncologic indications. Therefore, PBRT is considered not medically necessary for non-oncologic indications.

BILLING GUIDELINES AND CODING

- Codes 77520, 77522, 77523, and 77525 may be medically necessary when billed with diagnosis code C61 (malignant neoplasm of prostate).

- If proton beam radiation therapy (PBT) is deemed to be not covered per medical necessity criteria above, then services and codes associated with PBT will also be denied. The following are examples of codes that may be billed in addition to the specific PBT codes:

77014	77295	77321	77336	77427
77280	77300	77333	77370	77470

77290	77307	77334	77387	G6002

- HCPCS code S8030 is not recognized as a valid code for claim submission as indicated in the relevant Company Coding Policy (HCPCS S-Codes and H-Codes, 22.0). Providers need to use alternate available CPT or HCPCS codes to report for this service. If no specific CPT or HCPCS code is available, then an unlisted code may be used. Note that unlisted codes are reviewed for medical necessity, correct coding, and pricing at the claim level. Thus, if an unlisted code is billed related to a non-covered service addressed in this policy, it will be denied as not covered.

CODES*		
CPT	77520	Proton treatment delivery; simple, without compensation
	77522	Proton treatment delivery; simple, with compensation
	77523	Proton treatment delivery; intermediate
	77525	Proton treatment delivery; complex

***Coding Notes:**

- The above code list is provided as a courtesy and may not be all-inclusive. Inclusion or omission of a code from this policy neither implies nor guarantees reimbursement or coverage. Some codes may not require routine review for medical necessity, but they are subject to provider contracts, as well as member benefits, eligibility and potential utilization audit.
- All unlisted codes are reviewed for medical necessity, correct coding, and pricing at the claim level. If an unlisted code is submitted for non-covered services addressed in this policy then it will be **denied as not covered**. If an unlisted code is submitted for potentially covered services addressed in this policy, to avoid post-service denial, **prior authorization is recommended**.
- **See the non-covered and prior authorization lists on the Company Medical Policy, Reimbursement Policy, Pharmacy Policy and Provider Information website for additional information.**
- HCPCS/CPT code(s) may be subject to National Correct Coding Initiative (NCCI) procedure-to-procedure (PTP) bundling edits and daily maximum edits known as "medically unlikely edits" (MUEs) published by the Centers for Medicare and Medicaid Services (CMS). This policy does not take precedence over NCCI edits or MUEs. Please refer to the CMS website for coding guidelines and applicable code combinations.

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POLICY REVISION HISTORY

DATE	REVISION SUMMARY
2/2023	Converted to new policy template.
3/2023	AIM Specialty Health name change to Carelon
5/2023	Interim update. Code configuration fix, S code language included in Billing Guidelines, no changes to policy
10/2023	Annual update. Change denial language from “investigational” to “not medically necessary.”