HEALTH PLANS
UNIVERSITY OF UTAH

Medical Policy

Proton Beam Therapy

Policy MP-009

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Disclaimer:

1. Policies are subject to change in accordance with State and Federal notice requirements.
2. Policies outline coverage determinations for U of U Health Plans Commercial, and Healthy U (Medicaid) plans. Refer to the "Policy" section for more information.

Description:

Proton beam radiation therapy (PBRT) is a type of external beam radiation therapy (EBRT) that utilizes protons (positively charged subatomic particles) that are precisely targeted to a specific tissue mass. Proton beams have the ability to penetrate deep into tissues to reach tumors, while delivering less radiation to superficial tissues such as the skin. This may make PBRT more effective for inoperable tumors or for those individuals in which damage to healthy tissue would pose an unacceptable risk.

Proton beams have less scatter than other sources of energy such as gamma rays, x-rays, or electrons. Because of this feature, called the Bragg Peak, proton beam radiotherapy (PBRT) has been used to escalate radiation dose to diseased tissues while minimizing damage to adjacent normal tissues. Proton beam radiotherapy has been shown to be particularly useful in treating radiosensitive tumors that are located next to vital structures, where complete surgical excision or administration of adequate doses of conventional radiation is difficult or impossible.

Policy Statement and Criteria

1. Commercial Plans

U of U Health Plans covers proton beam therapy (PBT) in the following limited circumstances:

A. Chordomas or chondrosarcomas arising at the base of the skull or along the axial skeleton without distant metastases;

B. Other central nervous system tumors located near vital structures; such as optic chiasm, optic nerves, brainstem

C. Localized, unresectable hepatocellular Carcinoma;

D. Ocular tumors including intraocular/uveal melanoma (not distant metastases);

E. Intracranial arteriovenous malformation (AVM) not amenable to surgical excision or other conventional forms of treatment;

F. Pediatric (under 18 years of age) central nervous system or solid tumors.

G. Reirradiation cases (where cumulative critical structure doses would exceed tolerance doses)

U of U Health Plans does NOT cover proton beam radiotherapy for treatment of prostate cancer. It is not medically necessary for individuals with localized prostate cancer because it has not been proven to be more effective than other radiotherapy modalities for this indication. Proton beam therapy for metastatic prostate cancer is considered experimental and investigational.

U of U Health Plans does NOT cover proton beam therapy for any other indication as use in any other circumstance is unproven and considered investigational.

2. **Medicaid Plans**
   Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the U of U Health Plans Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website at: http://health.utah.gov/medicaid/manuals/directory.php or the Utah Medicaid code Look-Up tool

3. **Medicare Plans**
   Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS and InterQual criteria are not available, the U of U Health Plans Commercial criteria will apply. For the most up-to-date Medicare policies and coverage, please visit their search website at: http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp& or the manual website

Clinical Rationale

The issues related to coverage of proton beam therapy (PBT) as a treatment of various medical conditions is not isolated to the safety and efficacy of the therapy. Given the greatly increased costs of this therapy compared to standard electron beam therapy and other therapies used to treat the various conditions is employed on, it is equally important to assess the cost effectiveness of proton beam therapy compared to other therapies used to treat similar conditions.

Published systematic reviews have been fairly uniform in their position as it relates to PBT. In 2010 the Agency for Healthcare Research and Quality (AHRQ) published guidelines on PBT for treating a variety of cancers in the adult and pediatric populations. The tumor sites considered for treatment referral include a specific list on CNS (Central Nervous System) and non-CNS tumors, with a disclaimer that individual

patients should be discussed on a case-by-case basis. PBT is generally not recommended in cases of prostate cancer, non-small cell lung cancer, or most lymphomas based on insufficient evidence.

The AHRQ findings were further supported by a report by the Canadian Agency for Drugs and Technologies in Health (CADTH, 2016) which found: "Two systematic reviews of clinical evidence, two systematic reviews of economic evidence, and one primary economic evaluation were identified regarding the clinical and cost-effectiveness of proton beam therapy compared to photon radiotherapy for the treatment of cancer patients. There was limited comparative evidence, with insufficient evidence available for many indications, comparators, and outcomes. Comparable benefits and harms were demonstrated by most studies for the majority of outcomes in prostate, esophageal, lung, and breast cancer, as well as medulloblastoma, and pediatric brain tumors. An increased risk of patient harms was observed for some outcomes in breast, esophageal, prostate and lung cancer. As well, reduced survival was reported for spinal cord gliomas. Reduced harms were reported for some outcomes in patients with medulloblastoma, as well as lung, esophageal, and prostate cancer, and pediatric retinoblastoma. There was insufficient evidence to draw conclusions for recurrent liver and brain cancers, meningioma, head and neck cancers, uveal hemangioma, and for the outcome of secondary malignancies. The identified economic evidence is likely not generalizable to the Canadian context, and may not reflect accurate and up-to-date cost and benefit estimates. Most evaluations reported that PBT was not cost-effective; however, the technology was more likely to be cost-effective in pediatric populations, and under specific circumstances in younger adults, and patients with more advanced disease (e.g., high risk head and neck, lung cancer, and breast cancer patients). Overall, current comparative evidence does not suggest that PBT is superior to photon therapy from a clinical or cost perspective for the majority of indications. There are concerns regarding the quantity, quality and generalizability of the available evidence. Current ongoing studies and future investigation into differences in hard clinical endpoints and long-term outcomes may resolve some of this uncertainty."

In 2017 ECRI (Emergency Care Research Institute) and CADTH again published reports related to PBT. The former stated that while PPBT has been used for several solid cancer tumor types in adults and certain pediatric cancers, including breast, lung, prostate, head and neck, evidence is still lacking in regards to its benefits over Photon based external beam radiation therapy.

Whereas CADTH found: "A review of the clinical evidence from nine systematic reviews found that PBT, alone or in combination with photon radiotherapy, is comparable to other types of radiotherapy for most types of cancer. Exceptions include meningioma and subgroups of malignant meningioma, and poorly differentiated tumors of prostate cancer in adults, for which greater benefits were found with PBT; some intramedullary spinal cord glioma in both children and adults, for which lower benefits were found with PBT; and eye cancer in adults, for which both greater benefits and lower benefits, depending on the specific type of eye cancer, were found with PBT. The clinical evidence also found that the safety of PBT, alone or in combination with photon radiotherapy, varies by the type of cancer it is used to treat, compared with other types of radiotherapy. It was found to be associated with greater harms in breast cancer and prostate cancer in adults; lower harms in retinoblastoma in children and medulloblastoma in adults; and both greater harms and lower harms in adults depending on the specific type of the following cancers: esophageal cancer, optic nerve sheath meningioma, and lung cancer."

An Emerging Technology Committee from ASTRO (American Society for Radiation Oncology) concluded that current data does not provide sufficient evidence to recommend PBT outside of clinical trials in lung cancer, head and neck cancer, GI malignancies (with the exception of hepatocellular carcinoma) and pediatric non-central nervous system (CNS) malignancies (Allen et al., 2012). In hepatocellular carcinoma and prostate cancer, there is evidence of the efficacy of PBT but no suggestion that it is superior to photon based approaches. In pediatric CNS malignancies, PBT appears superior to photon approaches,

but more data is needed. In large ocular melanomas and chordomas, ASTRO states that there is evidence for a benefit of PBT over photon approaches. More robust prospective clinical trials are needed to determine the appropriate clinical setting for PBT.

ASTRO's model policy for PBRT (2017) addresses indications and limitations of coverage and/or medical necessity for PBRT in the treatment of prostate cancer. Although more individuals with prostate cancer have been treated with PBRT compared to any other cancer site, ASTRO does not support the routine use of PBRT for prostate cancer, stating: 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.

Prostate Cancer NCCN's clinical practice guideline (CPG) on "Prostate cancer" (Version 2.2021) states that "The NNCN panel believes no clear evidence supports a benefit or decrement to proton therapy over IMRT for either treatment efficacy or long-term toxicity." Also, both photon and proton beam radiation have similar and acceptable biochemical control and long-term side effects, as well as being effective at achieving highly conformal radiotherapy. However, the discussion section states "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" The guidelines also included "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."

In 2014, the Agency for Healthcare Research and Quality (AHRQ) published an update of the 2008 comparative effectiveness review for localized prostate cancer (Sun, 2014). The risk and benefits were compared in a number of treatments for localized prostate cancer including radical prostatectomy, EBRT (standard therapy as well as PBRT, 3D-CRT, IMRT and SBRT), interstitial brachytherapy, cryotherapy, watchful waiting (WW), active surveillance, hormonal therapy, and high-intensity focused ultrasound (HIFU). Eight randomized controlled trials and 44 nonrandomized comparative studies evaluating numerous treatment options met inclusion criteria. The authors concluded that the evidence for most treatment comparisons is largely inadequate to determine comparative risks and benefits of therapies for clinically localized prostate cancer. This conclusion is similar to that of the 2008 review, which found that no single therapy can be considered the preferred treatment for localized prostate cancer because of limitations in the body of evidence as well as the likely tradeoffs a patient must make between estimated treatment effectiveness, necessity, and adverse effects. Although limited evidence appears to favor surgery over WW or external beam radiotherapy, or favors 3D-CRT plus ADT over 3D-CRT alone, the patients most likely to benefit and the applicability of these study findings to contemporary patients and practice remain uncertain. More RCTs and better designed observational studies that can control for many of the known and unknown confounding factors that can affect long-term outcomes are needed to evaluate comparative risks and benefits of therapies for clinically localized prostate cancer.

Non-cell Lung Cancer (NSCLC) A Hayes 2017 technology report on PBT for NSCLC, concluded that the best available studies of PBT for NSCLC, including 1 fair-quality study and 11 poor-quality studies do not provide sufficient evidence that PBT is safer or consistently more effective than conventional methods of radiation therapy. Findings are somewhat conflicting, but in general, PBT, CRT, and IMRT appear to have approximately the same safety and efficacy for NSCLC. Three nonrandomized studies compared

PBT with CBT for lung cancer and found similar efficacy and safety outcomes with these 2 techniques. However, CBT is not a widely available or well-studied technology. One large retrospective comparative database study showed that PBT was significantly more efficacious with regard to overall survival than other non-PBT radiotherapies, except for IMRT. However, in a propensity score–matched analysis, the trend toward improvement was not significant. Two other nonrandomized studies evaluated lung cancer treatment with PBT versus CRT or IMRT and found inconsistent or no statistically significant differences in patient survival. A nonrandomized study found that PBT was associated with a statistically significant reduction in esophagitis compared with IMRT; however, 4 other nonrandomized studies of PBT versus CRT or IMRT found no significant differences or largely offsetting differences in the incidence of complications.

Uveal Melanoma The 2017 CADTH Technology Assessment included two unique primary studies, analyzed in two SRs, reporting on PBT for treatment of uveal melanoma. In one study, statistically significantly lower rates of local recurrence and higher mortality rate were reported for PBT in comparison to brachytherapy for choroidal melanoma. In the other study, there were late recurrences following brachytherapy but not after PBT or helium ion RT, but statistical results were not reported. The assessment authors concluded that there were both greater and lower benefits of PBT for eye cancers. The 2014 Washington Technology Assessment reviewed two studies on the use of PBT for ocular tumors that compared PBT alone to combination therapy including PBT. PBT was compared to PBT plus chemotherapy for uveal melanoma. Overall survival was reported and there was no statistically significant difference between groups. PBT was compared to PBT plus laser photocoagulation for choroidal melanoma. Visual acuity was reported and there was no statistically significant difference between groups.

Verma and Mehta published a systematic review of fourteen studies reporting clinical outcomes of proton beam radiotherapy (PBT) for uveal melanoma in 2016. Studies occurring between 2000 and 2015 were included; review was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Meta-analyses were not conducted due to substantial methodological heterogeneity between studies. Included studies enrolled 59 to 3088 patients, median follow-up ranged from 38 to 148 months, and most tumors were choroidal and medium to medium-large-sized, and received 50-70 Cobalt Gray equivalent dose (studies conducted more recently reported lower doses). Five-year local control, overall survival, and metastasis-free survival and disease-specific survival rates were > 90% (persisting at ten and fifteen years), 75 to 90%, and between 7 and 10%. The authors concluded that although PBT is associated with low toxicity and enucleation rates, recent developments to support radiation toxicity will aid in decreasing clinical adverse events, and overall, PBT is an excellent treatment for uveal melanomas.

Chondrosarcoma is the second most frequent primary malignant tumor of bone, representing approximately 25% of all primary osseous neoplasms. Chondrosarcoma may occur at any age, but is more common in older adults. Chondrosarcomas are a group of tumors with highly diverse features and behavior patterns, ranging from slow-growing non-metastasizing lesions to highly aggressive metastasizing sarcomas. Although the long bones (legs, arms, fingers, and toes), pelvis and shoulder blades are most commonly involved, occasionally chondrosarcoma has been found in the spine or skull bones. Symptoms of chondrosarcoma are usually mild and depend upon size and location. Individuals with pelvic or axial lesions typically present later in the disease course, as the associated pain has a more insidious onset and often occurs when the tumor has reached a significant size. Histologic grade and tumor locations are the most important variable that determines the choice of the primary treatment. The mainstay of treatment is surgical resection for both low-grade and high-grade lesions, as chondrosarcomas respond poorly to chemotherapy. Because residual, localized low-grade base of skull

chondrosarcomas may impinge upon the brain stem or spinal cord and can invade central nervous system tissue, PBRT, either alone or in combination with photon beam radiotherapy, has been associated with excellent local control and long-term survival in the treatment of individuals with chondrosarcomas of the skull base and axial skeleton (NCCN, V1.2020).

Pediatrics Indications Amsbaugh (2012) reported acute toxicities and preliminary outcomes for pediatric patients with ependymomas of the spine treated with proton beam therapy at the MD Anderson Cancer Center. A total of 8 pediatric patients received proton beam irradiation between October 2006 and September 2010 for spinal ependymomas. Toxicity data were collected weekly during radiation therapy and all follow-up visits. Toxicities were graded according to the Common Terminology Criteria for Adverse Events version 3.0. All patients had surgical resection of the tumor before irradiation (7 subtotal resection and 1 gross total resection). Six patients had World Health Organization Grade I ependymomas, and 2 had World Health Organization Grade II ependymomas. Patients had up to 3 surgical interventions before radiation therapy (range of 1 to 3; median, 1). Three patients received proton therapy after recurrence and 5 as part of their primary management. The entire vertebral body was treated in all but 2 patients. The mean radiation dose was 51.1 cobalt gray equivalents (range of 45 to 54 cobalt gray equivalents). With a mean follow-up of 26 months from the radiation therapy start date (range of 7 to 51 months), local control, event-free survival, and overall survival rates were all 100%. The most common toxicities during treatment were Grade 1 or 2 erythema (75 %) and Grade 1 fatigue (38 %). No patients had a Grade 3 or higher adverse event. Proton therapy dramatically reduced dose to all normal tissues anterior to the vertebral bodies in comparison to photon therapy. The authors concluded that preliminary outcomes showed the expected control rates with favorable acute toxicity profiles. They noted that proton beam therapy offers a powerful treatment option in the pediatric population, where adverse events related to radiation exposure are of concern. Moreover, they stated that extended follow-up will be required to assess for late recurrences and long-term adverse effects.

Greenberger et al (2014) reported their experience with pediatric patients treated with PBT. A total of 32 pediatric patients with low-grade gliomas of the brain or spinal cord were treated with PBT from 1995 to 2007; 16 patients received at least 1 regimen of chemotherapy before definitive radiotherapy (RT). The median radiation dose was 52.2 GyRBE (48.6 to 54 GyRBE). The median age at treatment was 11.0 years (range of 2.7 to 21.5 years), with a median follow-up time of 7.6 years (range of 3.2 to 18.2 years). The 6-year and 8-year rates of progression-free survival were 89.7 % and 82.8 %, respectively, with an 8-year overall survival of 100 %. For the subset of patients who received serial neurocognitive testing, there were no significant declines in Full-Scale Intelligence Quotient ($p = 0.80$), with a median neurocognitive testing interval of 4.5 years (range of 1.2 to 8.1 years) from baseline to follow-up, but subgroup analysis indicated some significant decline in neurocognitive outcomes for young children (less than 7 years) and those with significant dose to the left temporal lobe/hippocampus. The incidence of endocrinopathy correlated with a mean dose of greater than or equal to 40 GyRBE to the hypothalamus, pituitary, or optic chiasm. Stabilization or improvement of visual acuity was achieved in 83.3 % of patients at risk for radiation-induced injury to the optic pathways. The authors concluded that this report of late effects in children with low-grade gliomas after PBT is encouraging. Proton beam therapy appears to be associated with good clinical outcome, especially when the tumor location allows for increased sparing of the left temporal lobe, hippocampus, and hypothalamic-pituitary axis. The authors also stated that larger cohorts are likely needed to enable accurate assessment of the incidence of moyamoya disease after PBT.

In June 2017, ASTRO published an updated model policy addressing treatment planning, indications (and limitations), and medical necessity criteria for PBT. The document states that “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." ASTRO's "coverage decision may extend beyond ICD-10 codes to incorporate additional considerations of clinical scenario and medical necessity with appropriate documentation, which in certain circumstances may include comparative dose volume histograms." ASTRO has structured their recommendations for the appropriate use of PBT for various disease sites into 2 groups (Group 1 and Group 2 indications). For Group 1 disease sites, based on the defined medical necessity requirements and published clinical data, the following disease sites that frequently support the use of PBT:

1. Ocular tumors, including intraocular melanomas
2. Tumors that approach or are located at the base of skull, for example Chordomas and Chondrosarcomas
3. 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
4. Hepatocellular cancer
5. 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
6. Malignant and benign primary CNS tumors
7. Advanced (e.g., T4) and/or unresectable head and neck cancers
8. Cancers of the paranasal sinuses and other accessory sinuses
9. Non-metastatic retroperitoneal sarcomas
10. Re-irradiation cases (where cumulative critical structure dose would exceed tolerance dose)

Group 2 includes various systems including but not limited to:

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

Proton Beam Therapy is not a new technology, however there is still a need for comparative effectiveness analysis and clinical evidence development for the appropriate use on various disease sites. According to ASTRO all other indications not listed in Group 1 are acceptable for Coverage with Evidence Development (CED). Group 2 includes various systems and at this time, with no indications deemed inappropriate for CED are considered acceptable. As long as the patient is enrolled in either an institutional review board (IRB)-approved study or in a multi-institutional registry following Medicare requirements. Insurance carriers should cover radiation therapy for patients treated under the CED model.

A 2019 Hayes technology assessment on PBT for head and neck cancers, reviewed a total of 13 studies, 3 retrospective cohorts, 2 prospective cohorts and 8 retrospective uncontrolled cohorts. Ten of the studies had newly diagnosed patients (5 comparative and 5 non-comparative) and 3 studies had patients with recurrent disease that had been previously treated with radiation therapy. The quality of evidence for efficacy and safety of PBT in head and neck cancers was moderate in size with a low overall quality in patients receiving primary radiation, for reirradiation the size was small and very low in quality. In conclusion, based on the evidence evaluated in this report, PBT has potential to improve outcomes and quality of life in newly diagnosed patients with head and neck cancers due to a more targeted approach than standard EBRT. However, evidence was insufficient to evaluate adult patients previously treated with radiation therapy and in children or adolescents. Further studies are needed to evaluate this therapy for particular sites of head and neck cancers, adults needing reirradiation and using PBT in children or adolescents with standard therapies over the long term.

Coverage under CED requirements will help accelerate and establish coverage decisions for all indications. Because of the many studies under way, proton coverage policies will need to be reviewed on a continual basis.

Applicable Coding

CPT Codes

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

HCPCS Codes

S8030	Scleral application of tantalum ring(s) for localization of lesions for proton beam therapy

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