Anthem.

Subject: Proton Beam Radiation Therapy
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Description/Scope

This document addresses different applications of proton beam radiation therapy (PBRT) in the treatment of benign and malignant tumors and arteriovenous malformation.

Note: Please see the following related documents for additional information:
•THER-RAD.00001 Brachytherapy for Oncologic Indications
•THER-RAD.00007 Intensity Modulated Radiation Therapy (IMRT)
•THER-RAD.00010 Stereotactic Radiosurgery (SRS) and Stereotactic Body Radiotherapy (SBRT)

Position Statement

Medically Necessary:

Proton beam radiation therapy, with or without stereotactic techniques, is considered medically necessary for any of the following conditions:
A.As primary therapy for melanoma of the uveal tract (iris, choroid, or ciliary body) involving tumors of up to 24 mm in largest diameter and 14 mm in height, and with no evidence of metastasis or extrascleral extension; or
B.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 (for example, skull-base chordoma or chondrosarcoma) or cervical spine and have residual, localized tumor without evidence of metastasis; or
C.Pituitary adenoma when conventional stereotactic radiation is not an available option; or
D.Intracranial arteriovenous malformation (AVM) not amenable to surgical excision or other conventional forms of treatment; or
E.Central nervous system (CNS) lesions including but not limited to, primary or metastatic CNS malignancies or AVM, adjacent to critical structures such as the optic nerve, brain stem or spinal cord; or
F.Primary or benign solid tumors in children treated with curative intent.

Not Medically Necessary:

Proton beam radiation therapy is considered not medically necessary for the treatment of choroidal neovascularization secondary to age-related macular degeneration (AMD).

Investigational and Not Medically Necessary:

Proton beam radiation therapy is considered investigational and not medically necessary when criteria are not met and for all other indications, including, but not limited to, the treatment of localized prostate cancer.

Rationale

Proton beam radiation therapy (PBRT), also known as proton beam therapy (PBT) or proton radiotherapy, is a type of external beam radiation treatment in which positively charged subatomic particles (protons) are targeted to a specific tissue mass by using a stereotactic planning and delivery system. A focused dose of radiation is delivered to the target area while surrounding healthy tissue receives minimal radiation.

PBRT as Treatment for CNS Lesions, Intracranial AVM, Pituitary Adenoma, Skull-based Tumors and Uveal (Ocular) Melanoma

The use of proton beam radiation (PBRT) therapy has been studied most extensively in terms of clinical effectiveness and safety for the treatment of CNS lesions, including but not limited to malignancies or arteriovenous malformations adjacent to critical structures such as the optic nerve, brain stem or spinal cord. Examples of such conditions include uveal melanoma, pituitary adenoma, and intracranial arteriovenous malformations where open surgery is not an option and conventional radiation therapy may not be appropriate (Barker, 2003; Dunavoelgyi, 2010; Hattangadi-Gluth, 2014; Kjellberg, 1986; Lin, 2000; Merchant, 2008; Noël, 2003; Ronson, 2006; Seifert, 1994). Additionally, the use of a stereotactic approach to PBRT for CNS and uveal tumors has been shown to further improve lesion targeting.

The National Comprehensive Cancer Network® (NCCN®) Clinical Practice Guidelines (CPGs) in Oncology® for CNS cancers (V1.2016), principles of brain tumor radiation therapy, state it is reasonable in adults with brain tumors at standard risk and high risk for recurrence (that is, ependymoma and medulloblastoma) to consider

...protons over photons (if available) for craniospinal irradiation" (Brown, 2013; Roa, 2004). For adults with medulloblastoma or supratentorial primitive neuroectodermal tumors (PNET) at standard risk for recurrence, the NCCN recommends a conventional dose of "...30-36 Gy craniospinal irradiation (CSI) and boosting the primary brain site to 54-55.8 Gy with or without adjuvant chemotherapy." For medulloblastoma or supratentorial PNET at high risk for recurrence, the NCCN recommends "36 Gy CSI with boosting primary brain site to 54-55.8 Gy with adjuvant chemotherapy.

The focus of treatment for uveal tract melanomas has been to provide adequate local control while still preserving vision. Pooling data from three centers, Suit and Urie (1992) reported local control in 96% and 5-year survival of 80% in individuals who received PBRT, results considered equivalent to enucleation. In a randomized controlled trial, Gragoudas and colleagues (2000) reported the efficacy and safety of lower doses of PBRT as improving visual prognosis, without compromising local tumor control for individuals with uveal melanoma at high risk for radiation-induced complications. A decreased dose of 50 cobalt Gy equivalents (CGE) proton beam was compared to 70 CGE proton beam (each delivered in 5 fractions, usually within a 7-day period). Persons (n=188) with tumors smaller than 15 millimeters in diameter and smaller than 5 millimeters in height that were located near the optic disc or macula were randomly assigned to the two doses. At 5 years, there were no statistically significant

differences in local tumor control, rate of metastasis, visual acuity, or complication rates. However, the visual fields were better in the 50 CGE group. A large, single-center, single-surgeon series of 2069 individuals treated with PBRT had an actuarial local control rate of 95% (95% confidence interval [CI], 93% to 96%) at 15 years. The cumulative rate of enucleation was 16% (95% CI, 13% to 20%), most frequently as a result of neovascular glaucoma, blind uncomfortable eyes, or local recurrence (46%, 31%, and 23% of enucleations, respectively). As with plaque radiation, risk factors for deterioration in visual acuity after PBRT were tumor size, location near the fovea or optic disc, baseline acuity, and underlying diabetes (Gragoudis, 2002). A summary of results from the United Kingdom reports 5-year actuarial rates of 3.5% for local tumor recurrence, 9.4% for enucleation, 61.1% for conservation of vision of 20/2000 or better, and 10.0% death from metastasis (Damato, 2005). Other systematic reviews and retrospective case series have reported similar outcomes in terms of maintenance of vision, local control, metastasis-free survival rates, and metastasis-related deaths (Aziz, 2009; Caujolle, 2010; Lodge, 2007; Mosci, 2009; Olsen 2007; Vavva, 2010; Wang, 2013b).

A systematic review of the peer-reviewed literature, including a review of PBRT for uveal melanoma, was conducted by the American Society for Therapeutic Radiology and Oncology (ASTRO) Evaluation Subcommittee of Emerging Technologies (Allen, 2012). Therapeutic treatment options range from locally ablative treatments to enucleation of the eye, depending on the size and location of the tumor. The authors state the use of PBRT has 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.

The available evidence also suggests PBRT is at least as effective as, and may be superior to, alternative therapies including conventional radiation or resection, as treatment for chordomas or chondrosarcoma of the skull base or cervical spine (Hug, 2000; Hug, 2002; Igaki, 2004; Noël, 2003; Rombi, 2013; Rutz, 2008; Yasuda, 2012). This is based on evidence that demonstrates that PBRT is able to deliver higher doses of radiation to a targeted area while decreasing exposure to adjacent healthy tissue (Gridley, 2010).

The NCCN CPG for bone cancer (V2.2017) states:

Specialized techniques such as intensity-modulated RT (IMRT), particle beam RT with protons...should be considered in order to allow high-dose therapy while maximizing normal tissue sparing. Proton beam RT alone or in combination with photon beam RT has been associated with an excellent local tumor control and long-term survival in the treatment of patients with low grade skull-base and cervical spine chondrosarcomas...Postoperative treatment with proton and/or photon beam RT may be useful for patients with tumors in an unfavorable location not amenable to resection, especially in chondrosarcomas of the skull base and axial skeleton...Combined photon/proton or proton beam RT has been shown to be effective for local control in some patients with unresectable or incompletely resected osteosarcoma.

In May 2014, ASTRO published a model policy addressing treatment planning, indications (and limitations), and medical necessity criteria for PBRT. 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 defined medical necessity requirements along with consideration of the individuals clinical scenario should assist "...the treating radiation oncologist in determining the appropriateness and medical necessity for PBT."

ASTRO has structured their recommendations for the appropriate use of PBRT 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, ASTRO states the following disease sites that frequently support the use of PBRT include, but are not limited to, 1) ocular tumors (including intraocular melanomas), 2) chordomas and chondrosarcomas (tumors that approach or are located at the skull base), 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," and 4) "primary or benign solid tumors in children treated with curative intent..."

PBRT as Treatment for Primary or Benign Solid Tumors in Children

PBRT has been utilized to treat numerous pediatric solid tumors because it can precisely target the tumor near or within sensitive organs while minimizing radiation exposure to healthy tissue, thus reducing the risk of both short- and long-term side effects. Children who are cured of their tumor may experience long-term sequelae of conventional radiotherapy, which may include developmental, neurocognitive, neuroendocrine, and hearing late effects. In addition, children who receive radiation at a young age are at an increased risk of developing radiation-induced second tumors compared with their adult counterparts (Cotter, 2012; Rombi, 2014). Primary solid tumors (including bone, CNS, and soft tissue malignancies) that generally develop in children and may respond to PBRT include, but are not limited to, ependymoma (Amsbaugh, 2012; MacDonald, 2008; Mizumoto, 2015), Ewing sarcoma (Lee, 2005; Rombi, 2012), intracranial germ cell tumors, medulloblastoma (Jimenez, 2013), neuroblastoma (Hattangadi, 2012; Hill-Kayser, 2013), nephroblastoma (Wilms' tumor), PNETs of the CNS, pineoblastoma, osteosarcoma (for example, Ewing sarcoma), retinoblastoma, and rhabdomyosarcoma (Childs, 2012; Cotter, 2011; De Amorim, 2013). PBRT has also been utilized with curative intent in the treatment of children with benign solid tumors (for example, craniopharyngiomas, meningiomas and pituitary tumors) (Bishop, 2014).

PBRT as Treatment for Prostate Cancer

PBRT as Initial Mono-Radiation Treatment for Localized Prostate Cancer

PBRT has been investigated as an option for the initial treatment of localized prostate cancer, used as the sole radiation modality, or combined with other external beam radiotherapy. In the latter role, PBRT functions as a radiation "boost" designed to increase the total radiation dose in an effort to improve disease-free survival while minimizing acute and chronic toxicities related to the gastrointestinal (GI) and genitourinary (GU) tracts.

The majority of the early peer-reviewed published literature on PBRT for localized prostate cancer consists of treatment planning studies, non-randomized prospective studies (Yonemoto, 1997), retrospective analyses, and one randomized controlled trial comparing photon therapy with and without a proton boost published as two separate analyses (Benk, 1993; Shipley, 1995). These studies suggest that PBRT, either as a sole or boost modality, has acceptable complication rates and potentially improves disease-free survival compared to historical or non-randomized controls. It was reported in the study by Shipley and colleagues (1995), however, that late harm (that is, GI and GU toxicities) was significantly more frequent among individuals who had proton boost therapy. In addition, the lack of well-designed trials directly comparing PBRT with contemporary techniques using photons, such as IMRT or advanced 3-dimensional conformal radiation therapy (3D-CRT), limits any conclusions regarding the potential superiority of PBRT, either at equivalent or higher doses of radiation therapy. Definitive

selection criteria for appropriate candidates for PBRT and other conformal radiotherapy techniques for those individuals with prostate cancer have not been established.

Most of the early studies of PBRT for prostate cancer were conducted at two treatment centers in the United States (Loma Linda Medical Center and Massachusetts General Hospital) and report on overlapping study populations over time. These retrospective, noncomparative studies reported by Slater and colleagues (1998, 1999, 2004) concluded that proton beam therapy for individuals with predominately stage I or II prostate cancer was associated with relatively low morbidity and toxicity and good long-term survival rates. Other studies consisted of small retrospective case series (Rossi, 1999) and treatment planning/dose escalation studies comparing proton therapy or 3D conformal proton therapy (3D-CPT) to IMRT for early stage cancer (Trofimov, 2007; Vargas, 2008). Uncertainty remains with regard to the comparative effectiveness and harms of the different treatments for localized prostate cancer. According to Sun and colleagues (2014):

...the amount of evidence from well-designed RCTs that directly compare different treatments, particularly emerging technologies (e.g., proton beam therapy, high-intensity focused ultrasound [HIFU]), is still small...Because evidence based on dated medical techniques may not apply to current practice, future studies are required for validating the comparative effectiveness and safety of the current and emerging treatment techniques (e.g., robotic-assisted surgery, proton beam therapy, stereotactic body radiation therapy).

Brada and colleagues (2009) reported on a systematic review of the peer-reviewed published literature for PBRT and concluded it was lacking in any clinical data demonstrating benefit in terms of survival, tumor control, or toxicity in comparison with best conventional treatment for any of the tumors so far treated including prostate cancer. They note that the current lack of evidence for benefit of protons should provide a stimulus for continued research with well-designed clinical trials.

Zietman and colleagues (2010) reported on a randomized controlled trial of individuals with prostate tumor stages between T1b and T2b and clinically node-negative disease. All study participants received conformal photon (x-ray) therapy to a fixed dose of 50.4 Gy to the prostate and seminal vesicles. The difference in the study treatment arms was in the dose of PBRT delivered as boost radiotherapy. Subjects were randomly assigned to receive conformal PBRT to the prostate alone with the dose corrected to a photon equivalent using a radiobiologic effectiveness ratio, expressed as Gray equivalent (GyE). The conventional dose PBRT group received an additional 19.8 GyE boost (n=197) while the high-dose PBRT group received an additional 28.8 GyE boost (n=197). Outcome data, reported as local failure (LF), biochemical failure (BF), and overall survival (OS), were analyzed on 197 conventional dose subjects and 196 high dose subjects with a median follow-up of 8.9 years. The investigators reported a significantly improved intermediate outcome (that is, freedom from or incidence of BF) favoring high dose boost PBRT over conventional dose boost PBRT. Grade 2 acute GI toxicity was significantly more frequent in the high dose PBRT group than in the conventional dose group (65% vs. 44%, respectively; p=0.0006). Acute GU toxicity at grade 2 in the acute period was more frequent in the high dose PBRT group than in the conventional dose PBRT group, but statistical significance was not observed (60% vs. 51%, respectively; p=0.0754). No significant differences were seen between groups in late grade 2 GI and GU toxicity. The OS rates for the conventional dose versus the high dose PBRT groups were 78.4% (n=196) and 83.4% (n=195), respectively. This trial is limited in drawing further conclusions as no significant differences were reported in long-term health outcomes and the study was not designed to evaluate whether PRBT was more or less efficacious when compared to other conformal radiotherapy techniques for prostate cancer.

Sheets and colleagues (2012) retrospectively examined the comparative morbidity and disease control outcomes for a cohort of men with prostate cancer treated with PBRT, IMRT and conformal radiation techniques. The authors compared outcomes of 684 men with nonmetastatic prostate cancer treated with PBRT (from 2002 to 2007) to 9437 men treated with IMRT using the Surveillance, Epidemiology, and End Results (SEER)-Medicare-linked database (2000 through 2009). To balance analysis of the 2 treatment groups, propensity score matched rates were calculated for each outcome due to a lack of overlap in baseline characteristics between men treated with either PBRT or IMRT. Because of the unequal distribution of men treated with PBRT across institutional-level variables, the authors performed sensitivity analysis with the Radiation Therapy Oncology Group affiliation "as an instrumental variable to assess potential unmeasured confounding." Median follow-up for the comparison was 50 months for PBRT (range, 0.3-90.2 months) and 46 months for IMRT (range, 0.4-88.3 months). Morbidity outcomes included conditions associated with radiation therapy for prostate cancer, including GI morbidity, urinary incontinence, non-incontinence urinary morbidity, sexual dysfunction, and hip fractures. When comparing men treated with PBRT to those treated with IMRT, the IMRT group had a lower rate of GI morbidity (absolute risk, 12.2 vs. 17.8 per 100 person-years; relative risk [RR], 0.66; 95% CI, 0.55-0.79). There were no significant differences in rates of the other morbidities or additional cancer-related therapies between PBRT and IMRT. Despite some limitations cited with the use of SEER-Medicare data for the assessment of clinical outcomes, the authors suggested "...that IMRT may be associated with improved disease control without compromising morbidity compared with conformal radiation therapy, although proton therapy does not appear to provide additional benefit."

Three noncomparative trials conducted by the University of Florida Proton Therapy Institute included 211 individuals with low-, intermediate-, and high-risk prostate cancer (n=89, n=82, and n=40, respectively) in which all subjects received PBRT without photon external beam radiotherapy (Mendenhall, 2012). At the minimum follow-up of 2 years, OS pooled across the 3 risk groups was 96% and PSA progression-free survival (PFS) was 99%. Late grade 2 or higher GU toxicity was reported in 44% of low-risk subjects, 37% of intermediate-risk subjects, and 49% of high-risk subjects. A total of 84 grade 2 late GU symptoms and 4 grade 3 symptoms were reported across all risk groups with 10% of all subjects experiencing late grade 2 or higher GU toxicity. Mendenhall and colleagues (2014) subsequently reported on the 5-year outcomes of subjects in these three noncomparative trials. The 5-year OS rates for the low-risk, intermediate-risk, and high-risk subjects were 93%, 88%, and 86 %, respectively. A total of 23 subjects died of intercurrent disease (n=20) or prostate cancer (n=3). Disease progression occurred in 10 subjects, with 8 of the 10 in the high-risk group. Actuarial 5-year rates of late grade 3 GU and GI events were 5.4% and 1.0%, respectively. Limitations of this study include the small sample size, and use of concomitant weekly docetaxel and 6 months of androgen deprivation in the high-risk group of subjects. In addition, the authors did not describe how risk group status was determined and did not identify the participants' prostate TNM stage and tumor grade. Further study of a larger population of subjects with homogenous prognostic factors and longer follow-up is needed to determine the clinical efficacy of PBRT for the management of individuals with low-, intermediate-, and high-risk prostate cancer.

Concerning dosimetric considerations to determine the optimal technique for the treatment of localized prostate cancer, the current NCCN CPGs for prostate cancer (V2.2017) states:

Numerous dosimetric studies have been performed trying to compare x-ray-based IMRT plans to proton therapy plans to illustrate how one or the other type of treatment can be used to spare the bladder or rectum from the higher dose parts of the exposure. These studies suffer from the biases and talents of

the investigators who plan and create computer models of dose deposition for one therapy over the other (Georg, 2014).

A phase II dose escalation trial of 85 subjects with localized prostate cancer evaluated the acute and late toxicity of conformal PBRT alone to a total dose of 82 GyE (Coen, 2011). At the median follow-up of 31.6 months, treatment-related acute grade 1, 2 and 3 toxicity was reported in 39 (46%), 19 (23%), and 2 (2%) of subjects, respectively. Combined GU and GI grade 1, 2, and 3 toxicity was reported in 42 (50%), 12 (14%), and 1 (1%) subjects, respectively. There were 28 (33%), 22 (26%), 6 (7%), and 1 (1%) grade 1, 2, 3, and 4 cases of late toxicity, respectively. Rates of late GI and GU toxicity were the same. The authors suggested that dose escalation with conformal PBRT for localized prostate cancer may only be delivered safely with hypofractionation to a maximal total dose of 82 GyE.

Two comparative effectiveness studies between men treated with PBRT and external beam radiotherapy report similar early toxicity rates (Coen, 2012; Yu, 2013). Coen and colleagues (2012) prospectively collected quality of life data for individuals treated with PBRT monotherapy for localized prostate cancer at 3 months, 12 months, and > 2 years after treatment. Significant problems with bowel dysfunction, impotence, and incontinence were reported at all 3 timeframes, with only 28% of men maintaining normal erectile function after therapy. Yu and colleagues (2013) retrospectively compared patterns of PBRT use, cost, and early toxicity among Medicare beneficiaries with prostate cancer with those of IMRT; the main outcome measures included early GU, GI, and other toxicity. Although PBRT was associated with a statistically significant reduction in GU toxicity at 6 months compared with IMRT (5.9% vs. 9.5%; odds ratio [OR], 0.60; 95% CI, 0.38 to 0.96; p=0.03), at 12 months post-treatment there was no difference in GU toxicity (18.8% vs. 17.5%; OR, 1.08, 95% CI, 0.76 to 1.54; p=0.66). There was no statistically significant difference in GI or other toxicity at 6 months or 12 months post-treatment.

Other published studies have prospectively evaluated patient-reported quality of life outcomes using an Expanded Prostate Cancer Index Composite (EPIC) questionnaire at a median follow-up of 24 months following PBRT (Hoppe, 2012) and PBRT (n=1234) or IMRT (n=204) (Hoppe, 2014) for prostate cancer. These studies report favorable short-term outcomes with respect to urinary incontinence and erectile function for individuals treated with PBRT (Hoppe, 2012); however, no significant differences were reported in quality of life outcomes "...for changes in bowel, urinary incontinence, urinary irritative/obstructive, and sexual domains..." between the PBRT and IMRT cohorts with the exception of some clinically relevant decline in sexual function and potency attributed to factors other than increasing age (Hoppe, 2014). Limitations of these studies include the subjective, variably defined outcome measures (with respect to erectile dysfunction and other non-treatment related factors), use of concomitant hormone therapy, and the presence of other medical comorbidities.

ASTRO's model policy for PBRT (2014) addresses indications and limitations of coverage and/or medical necessity for PBRT for 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.

PBRT as Salvage Therapy for Locally Recurrent Prostate Cancer

The NCCN CPGs for prostate cancer (V2.2017) states, "Most patients who have undergone radical prostatectomy are cured of prostate cancer. However, some men will suffer pathologic or biochemical failure. Selecting men appropriately for adjuvant or salvage radiation is difficult." Choo (2010) reviewed the issues and challenges in the management of individuals with post-RP PSA relapse, stating that although RP is performed with a curative intent, a significant proportion of surgically treated individuals face the risk of prostate cancer recurrence, as evidenced by a progressively rising PSA. PSA relapse after RP can be attributed to:

local tumor recurrence at the prostate bed, occult nodal or distant metastasis, or the combination of both. The optimal management for patients with post-RP PSA relapse has remained unclear. This stems from the inability to separate patients whose recurrent disease is confined to the prostate bed from those that have already developed occult metastasis. Furthermore, the clinical course of patients with post-RP PSA relapse is highly variable. As a result, management options are diverse, ranging from salvage radiotherapy, either alone or in combination with androgen ablation therapy, as a definitive therapy to expectant management or androgen ablation therapy alone as a palliative therapy.

The author states there have been no published outcomes from randomized clinical trials addressing the efficacy of salvage therapeutic modalities; however, radiotherapy has been the main salvage therapeutic modality with a curative potential for individuals with post-RP PSA relapse. Additional studies have suggested disease-specific survival benefit from salvage radiotherapy (for example IMRT), following RP using the PSA level as a prognostic indicator of recurrence (Stephenson, 2007; Trock, 2008).

A search of the peer-reviewed medical literature has failed to identify any randomized controlled trials, comparative studies or case series where PBRT has been investigated as salvage therapy for locally recurrent prostate cancer. In addition, the NCCN CPGs for prostate cancer (V2.2017) does not recommend routine use of PBRT as salvage therapy for locally recurrent prostate cancer, either as adjuvant or salvage therapy post-RP.

Summary of PBRT for Prostate Cancer

In February 2008, the Agency for Healthcare Research and Quality (AHRQ) published a systematic appraisal of the existing scientific evidence regarding treatments for prostate cancer titled, Comparative Effectiveness of Therapies for Clinically Localized Prostate Cancer: Executive Summary (Wilt, 2008). In summarizing the comparative risks, benefits, and outcomes of therapies in the available randomized controlled trials, when comparing external beam radiotherapy (EBRT) regimens, the report states:

It is not known if using higher doses of EBRT by increasing either the total amount or type of radiation (e.g., via high-dose IMRT or proton beam or by adding brachytherapy) improves overall or disease-specific survival compared with other therapies. No EBRT regimen, whether conventional, high-dose conformal, dose fractionation, or hypofractionation, was superior in reducing overall or disease-specific mortality.

For PBRT, the report states that based on comparative outcomes from nonrandomized trials, the rates of clinical outcomes and toxicity after proton therapy may be comparable with conformal radiation. It concludes "there was no direct evidence that proton EBRT results in better overall or disease-free survival than other therapies" (Wilt, 2008).

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:

...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.

In 2009, the AHRQ published a technical brief, Particle Beam Radiation Therapies for Cancer, surveying the evidence around the use of particle (mainly proton) beam therapy for some cancers, including prostate cancer. The technical brief states a large number of scientific papers exist:

However, these studies do not document the circumstances in contemporary treatment strategies in which radiotherapy with charged particles is superior to other modalities. Comparative studies, in general, and randomized trials in particular (when feasible), are likely needed to document the theorized incremental advantages of particle beam therapy over other radiotherapies (e.g. IMRT, conventional radiotherapy or stereotactic photon radiosurgery) in many cancers. In addition, incremental benefits should be considered and interpreted with respect to corresponding incremental costs (and risks) (Trikalinos, 2009).

The American Urological Association (AUA, 2007) states in their Guideline for the Management of Clinically Localized Prostate Cancer: 2007 Update (reviewed and validity confirmed in 2011), that "the highest quality evidence to identify a superior treatment modality for a particular patient is lacking, but there is some high-quality evidence to support various modifications within treatment modalities." Additional clinical trials are needed to properly define the role of external beam radiotherapy along with the precise dosage and dose escalation parameters to be administered in the clinical subgroups, to further define prognostic parameters, and to develop a consistent practice strategy for the implementation of external beam radiotherapy for the treatment of prostate cancer.

An American College of Radiology (ACR) Appropriateness Criteria® guideline (Nguyen, 2014) on external beam irradiation in stage T1 and T2 prostate cancer states:

•There are only limited data comparing proton-beam therapy to other methods of irradiation or to radical prostatectomy for treating stage T1 and T2 prostate cancer. Further studies are needed to clearly define its role for such treatment.
•There are growing data to suggest that hypofractionation at dose per fraction <3.0 Gy per fraction is reasonably safe and efficacious, and although the early results from hypofractionation/ SBRT (stereotactic body radiation therapy) studies at dose per fraction >4.0 Gy seem promising, these approaches should continue to be used with caution until more mature, ongoing phase II and III randomized controlled studies have been completed.

The ACR Appropriateness Criteria for external beam radiation therapy treatment planning for clinically localized prostate cancer states that PBRT delivery is an "evolving technology" for prostate cancer treatment and is "...controversial, and recommendations for proton RT reflect controversy within radiation oncology. If protons are used, treatment on a protocol is encouraged" (Zaorsky, 2016). Considering the clinical evidence to support the use of various treatment approaches for prostate cancer, the ACR states:

Although there is limited evidence that directly compares 3D-CRT to IMRT or proton beam therapy, the available comparative data suggest that higher EBRT doses are more effective at achieving PSA failure-free survival for localized prostate cancer and that safe dose escalation can be more readily achieved with the increased conformity of IMRT relative to 3D-CRT (Zaorsky, 2016).

In addition, the ACR Appropriateness Criteria does not include PBRT as a treatment option for locally advanced, high-risk prostate cancer (McLaughlin, 2016) or for node-positive prostate cancer or following radical prostatectomy (Gustafson, 2014).

An evidence-based systematic review by ASTRO's Evaluation Subcommittee of Emerging Technologies (Allen, 2012) states there is evidence for the efficacy and sparing of normal tissue when conformal PBRT in the "low to moderate range (< 60-70Gy)" is used as treatment for localized prostate cancer; however, the report did not suggest that PBRT is superior to photon-based approaches. Recognizing that PBRT (conformal proton therapy) has treated more individuals with prostate cancer than any other disease site, ASTRO's review states:

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 proton beam therapy. 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, proton therapy is an option for prostate cancer, but no clear benefit over the existing therapy of IMRT photons has been demonstrated.

To summarize, while much of the evidence suggests that PBRT is safe and may provide effective tumor control in men with prostate cancer, this evidence is derived from retrospective analyses conducted at a limited number of research centers or from studies with a low level of evidence and other methodological limitations. There is insufficient evidence from the available clinical trials to determine whether PBRT is equal or superior to conventional photon radiation therapy, 3D-CRT or IMRT, and who would benefit most from each type or combination of radiotherapy for the treatment of prostate cancer. Meaningful comparisons between treatments are also hindered by inconsistencies between studies of characteristics of the individual such as age, tumor grade, and pelvic lymph node status. Except for GI morbidity, the data presented by Sheets and colleagues (2012) in the cohort study using

administrative and cancer registry data suggests little outcome difference between men treated with either PBRT or IMRT. Because of its retrospective design and other limitations of a study using administrative data, conclusions cannot be drawn at this time that PBRT or IMRT is superior in improving health outcomes for the treatment of localized prostate cancer.

A search of the ClinicalTrials.gov database has identified two ongoing studies comparing the use of PBRT to IMRT in individuals with stages T1c to T2b prostate cancer, and PBRT as sole radiotherapy compared to IMRT with PBRT as boost therapy in individuals with node negative prostate cancer following RP. The first study is a prospective, phase III randomized clinical trial (NCT01617161) comparing PBRT to IMRT for individuals with low- or intermediate-risk prostate cancer with the primary outcome measure to compare the reduction in mean EPIC bowel scores at 24 months following radiation. The estimated final data collection date for the primary outcome measure is December 2018. The second non-randomized, phase II clinical trial (NCT00969111) is recruiting participants with the purpose of evaluating the safety and efficacy of postoperative or salvage radiotherapy for node negative prostate cancer following RP. The four-arm study will treat: 1) postoperative, non-high risk participants with PBRT to 66.CGE; 2) postoperative high- risk subjects with IMRT to 45 Gy and proton boost (21.6 CGE) to the prostate bed; 3) salvage non-high risk subjects with PBRT to 70.2 CGE; and, 4) salvage high-risk subjects with IMRT to 45 Gy and proton boost (25.2 CGE) to the prostate bed. The primary outcome measure is the 6 months post-treatment rate of acute grade 3 GI and GU toxicity following treatment with proton-based therapy. Secondary outcomes will analyze quality of life, treatment-related morbidity, disease control, and survival outcome parameters after radiation every 6 months for 3 years, then annually for 20 years. The estimated final data collection date for the primary outcome measure is August 2031 (NIH, 2017).

PBRT as Treatment for Lung Cancer

Widesott and colleagues (2008) completed a systematic review to determine the safety and efficacy of PBRT in the treatment of non-small cell lung cancer (NSCLC). Of the 17 studies included in the analysis, there were no randomized or non-randomized prospective trials. A total of nine uncontrolled single-arm studies were available from three proton beam centers, providing clinical outcomes for a total of 214 subjects. The studies were mainly related to stage I-II tumors, with results comparable to those obtained with surgery and without significant toxicity. Two documents compared photon and proton dose distributions, which showed a potential for dose escalation and/or a sparing of the organ at risk with the use of proton radiotherapy. Finally, six studies analyzed dosimetric and technical issues related with proton radiotherapy, mainly underlining the difficulties in designing dose distributions that are representative of the dose actually delivered during treatment. Limited data are available on the application of proton radiotherapy for NSCLC in the clinical practice. In addition, the application of proton radiotherapy to lung cancer presents technical challenges. This systematic review concludes that because of the small number of institutions involved in the treatment of this disease, the number of subjects, and methodological weaknesses of the trials, it is not possible to draw definitive conclusions about the superiority of proton radiotherapy compared to photon techniques currently available for the treatment of NSCLC.

Bush and colleagues (2013) analyzed treatment outcome data on a large series of individuals (n=111) with inoperable (or had refused surgery) NSCLC treated at Loma Linda University Medical Center over 12 years with high-dose hypofractionated proton beam therapy to the primary tumor. A total of 64% of the group had stage II disease and the remainder had stage I disease. The minimum follow-up on all individuals was 3 years, with a median follow-up duration of 48 months. A significant improvement in OS was noted with an increasing dose of proton therapy up to 70 Gy. The 4-year actuarial OS and disease-

specific survival rates were 51% and 74%, respectively. Larger tumors displayed a trend toward improved local control with a higher dose regimen, with the 4-year local control improving from 45% with 60 Gy to 74% when treated with 70 Gy (p=0.1). A subgroup analysis of individuals with peripheral stage I tumors treated with either 60 Gy or 70 Gy had an OS of 60% at 4 years. Treatment-related toxicities during the follow-up period included 4 individuals with rib fractures that occurred with tumors treated adjacent to the chest wall. Limitations of this study include the retrospective design and lack of a randomized comparison group.

McAvoy and colleagues (2014) evaluated the use of PBRT and IMRT for reirradiation of intrathoracic recurrence of NSCLC, focusing on patterns of failure, criteria for appropriate selection of candidates, and predictors of toxicity. A total of 102 participants received radiation therapy for NSCLC (median initial dose of 70 EQD2 Gy), with median interval to reirradiation of 17 months and median reirradiation dose of 60.48 EQD2 Gy. The median follow-up time was 6.5 months (range, 0-72 months). A total of 99 of 102 participants (97%) completed reirradiation with median local failure-free survival, distant metastasis-free survival (DMFS), and OS times reported as 11.43 months (range, 8.6-22.66 months), 11.43 months (range, 6.83-23.84 months), and 14.71 months (range, 10.34-20.56 months), respectively. Rates of grade ≥ 3 esophageal toxicity of 7% and grade ≥ 3 pulmonary toxicity of 10% were reported as acceptable. A total of 88% of participants who developed local failure after reirradiation had failure in either the original or the reirradiation field. Participants with poor local control had associated T4 disease, squamous histology, and Eastern Cooperative Oncology Group performance status score > 1. The authors concluded that the high rates of locoregional recurrence and distant metastasis in individuals with recurrent NCSLC following reirradiation with PBRT suggest that appropriate candidates "should be selected carefully to maximize the benefit of additional aggressive local therapy while minimizing the risk of adverse side effects."

Other Considerations for PBRT for Lung Cancer

A Blue Cross Blue Shield Association Technology Evaluation Center Assessment (BCBSA TEC, 2010) addresses the key question of how health outcomes (that is, OS, disease-specific survival, local control, disease-free survival, and adverse events) with PBRT compare with outcomes observed for SBRT which is an accepted approach for using radiation therapy to treat for NSCLC. Eight case series were identified that included a total of 340 individuals (Nakayama, 2010). No comparative studies, randomized or nonrandomized, were found. There was a high degree of treatment heterogeneity among the PBRT studies, particularly with respect to planning volume, total dose, number of fractions and number of beams. For these studies, stage I comprised 88.5% of all individuals and only 39 individuals were in other stages or had recurrent disease. Survival results were highly variable. Among seven studies reporting 2-year OS, probabilities ranged between 39% and 98%. At the 5-year OS, the range across 5 studies was 25% to 78%. It is unclear if the heterogeneity of results can be explained by differences in subjects and treatment characteristics. A meta-analysis reviewed in the assessment found a nonsignificant difference of 9 percentage points between pooled 2-year OS estimates favoring SBRT over PBRT (Grutters, 2010). The nonsignificant difference of 2.4 percentage points at 5 years also favored SBRT over PBRT. Based on separate groups of single-arm studies on SBRT and PBRT, it is unclear if this meta-analysis adequately addressed the possible influence of confounding on the comparison of SBRT and PBRT. The technology report concluded that the evidence is insufficient to permit conclusions about the results of PBRT for any stage of NSCLC.

The ACR Appropriateness Criteria discussing the optimal strategy for the non-surgical definitive treatment of individuals with good performance status and NSCLC (mostly with locally advanced disease) states:

...due to physical characteristics, protons can spare more normal tissues and may allow further dose escalation/acceleration. However, there are more uncertainties about proton therapy in lung cancer, and much improvement and optimization is still needed. Protons may not be suitable for all lung cancer patients, and proper case selection and proper proton techniques based on motion and anatomy are crucial to improve the therapeutic ratio. Hopefully, larger prospective controlled trials that are underway will clarify the role of proton beam for lung cancer in the near future (Chang, 2014).

Regarding the use of proton therapy for lung cancer, ASTRO's Evaluation Subcommittee of Emerging Technologies (Allen, 2012) concludes:

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 in other clinical scenarios remain limited and does not provide sufficient evidence to recommend PBT for lung cancer outside of clinical trials. In addition, unlike in some other disease sites, the issue of organ motion in lung cancer is critical and adds an additional challenge in the use of PBT.

ASTRO's model policy for PBRT (2014) has structured their recommendations for the appropriate use of PBRT for various disease sites into 2 groups (Group 1 and Group 2 indications). For Group 2 disease sites, ASTRO states there is a need for comparative effectiveness analyses and continued clinical evidence development (CED) (that is, only cover for evidence development) for PBRT for NSCLC (thoracic malignancies). Individuals treated with PBRT for NSCLC should be "...enrolled in either an IRB-approved clinical trial or in a multi-institutional patient registry..."

The current NCCN CPGs for NSCLC (V5.2017) states that "More advanced technologies are appropriate when needed to deliver curative RT safely. These technologies include (but are not limited to)...proton therapy. Nonrandomized comparisons of using advanced technologies versus older techniques demonstrate reduced toxicity and improved survival." This category 2A recommendation for PBRT for NSCLC points only to ASTRO's model policy for PBRT (2014), which is a Group 2 recommendation for use (that is, the need for continued CED). For individuals with advanced stage NSCLC, the NCCN CPG for NSCLC (V5.2017) includes a category 2A recommendation (based on consensus) for use of proton therapy as palliative radiation therapy, stating:

The dose and fractionation of palliative RT should be individualized based on goals of care, symptoms, performance status, and logistical considerations. Shorter courses of RT provide similar pain relief as longer courses, but a higher potential need for retreatment, and are preferred for patients with poor performance status and/or shorter life expectancy. For palliation of thoracic symptoms, higher dose/longer-course thoracic RT (eg, ≥ 30 GY in 10 fractions) is associated with modestly improved survival and symptoms, particularly in patients with good performance status. When higher doses (> 30 Gy) are warranted, technologies to reduce normal tissue irradiation (at least 3d-CRT and including IMRT and proton therapy as appropriate) should be used.

At this time, the strength of this evidence is insufficient to determine the net health benefit of delivering PBRT safely for NSCLC. Limitations of these studies include, but are not limited to, their nonrandomized design, use of retrospective data for comparisons, substantial differences in pretreatment assessments

(such as imaging) and treatment-planning capabilities over the periods of study, and heterogeneous study populations (in terms of stage of disease).

A search of the ClinicalTrials.gov database has identified an ongoing prospective, phase II randomized clinical trial (NCT00495040) of individuals with inoperable stage I NSCLC and selected stage II NSCLC. The trial is evaluating the therapeutic efficacy and toxicities of PBRT to identify if escalated/accelerated doses can improve 2-year PFS at the primary site and reduce acute and chronic toxicity. The estimated final data collection date for the primary outcome measure is May 2018. Another phase III randomized, open label clinical trial (NCT01993810) of individuals with inoperable stage II-III NSCLC is evaluating the therapeutic efficacy of proton chemoradiotherapy compared to photon chemoradiotherapy to identify PFS and OS survival rates as well as quality of life measures. The estimated final data collection date for the primary outcome measure is December 2020.

PBRT as Treatment for Head and Neck Cancer

An AHRQ (Samson, 2010) report titled Comparative Effectiveness and Safety of Radiotherapy Treatments for Head and Neck Cancer, addresses four key questions comparing four alternative radiotherapy modalities including IMRT, 3D-CRT, 2D radiotherapy (2DRT), and PBRT. Effectiveness is compared in regards to adverse events and quality of life, tumor control and survival, specific characteristics of the individual and the tumor, and differences in user experience, target volume delineation, or dosimetric parameters. When comparing PBRT to other techniques for head and neck cancer, the report states:

The strength of evidence is insufficient as there were no studies comparing proton beam therapy to any other radiotherapy modality. Therefore, no conclusions can be reached regarding the comparative effectiveness of proton beam therapy for any of the four key questions. The available evidence on proton beam therapy in head and neck cancer is further weakened by the small sample size and mix of tumor locations in the single study (Slater, 2005) ... and by the lack of additional studies. Thus, insufficient data are available on combined photon-proton treatment of head and neck cancer to draw any conclusions regarding its effectiveness or likely adverse effects.

A 2014 update to this AHRQ comparative effectiveness review has not identified any new evidence to draw conclusions on the comparative effectiveness of PBRT to 3D-CRT or IMRT for the treatment of head and neck cancers (Ratko, 2014).

Patel and colleagues (2014) performed a systematic review and meta-analysis evaluating the peer-reviewed published medical literature on charged-particle therapy versus photon therapy for the treatment of paranasal sinus and nasal cavity malignant disease. The review included a total of 41 observational studies of 13 cohorts treated with charged-particle therapy (n=286 individuals) and 30 cohorts treated with photon therapy (n=1186 individuals). There were no head-to-head comparison trials. In the meta-analysis, the pooled event rate of OS was significantly higher with charged-particle therapy than photon therapy at the longest duration of follow-up (risk ratio [RR], 1.27; 95% CI, 1.01 to 1.59). At 5 years, findings were similar for the outcome survival (RR=1.51; 95% CI, 1.14 to 1.99). Photon therapy was significantly better for only 1 of the 2 timeframes (longest follow-up or 5-year follow-up) for locoregional control and disease-free survival. There were significantly more neurologic toxic effects with charged-particle therapy compared with photon therapy ($p<0.001$) but other toxic adverse event rates (for example, eye, nasal, and hematologic) did not differ significantly between groups. The studies for charged-particle therapy were heterogeneous (that is, type of charged particles [carbon ion,

proton]), and delivery techniques. Because the comparisons were indirect, none of the studies included in the review actually compared the two types of treatment in the same sample populations.

Zenda and colleagues (2015) retrospectively reported on the late toxicity of PBRT for persons with nasal cavity, paranasal sinus, or skull-based malignancy. Over a 10-year period, 90 individuals were treated with definitive or postoperative PBRT (> 50 GyE) and followed for more than 1 year. Late toxicities were graded according to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE v4.0). The median observation period was 57.5 months (range, 12.4-162.7 months), median time to onset of grade 2 or greater late toxicity except cataract was 39.2 months (range, 2.7-99.8 months). Grade 3 late toxicities occurred in 17 individuals (19%), with 19 events, and grade 4 late toxicities in 6 individuals (7%), with 6 events (n=2, encephalomyelitis infection; n=4 optic nerve disorder). A total of 3 individuals had toxicities that occurred more than 5 years after PBRT. The results of this review suggest that late toxicity in individuals treated with PBRT for nasal cavity, paranasal sinus or skull-based malignancy can occur at 5 years post-treatment; therefore, additional study is needed to evaluate the long-term effects of PBRT for these conditions.

Jakobi and colleagues (2015a; 2015b) conducted two treatment planning studies evaluating the feasibility of dose escalation in advanced head and neck cancer using intensity-modulated photon (IMXT) and intensity modulated proton therapy (IMPT) therapy. The treatment plans compared differences in toxicity risk reduction in 45 individuals with head and neck squamous cell carcinoma (HNSCC) when PBRT was used for complete treatment or sequential boost treatment only, based on normal tissue complication probability (NTCP) models for mucositis, xerostomia, aspiration, dysphagia, larynx edema and trismus. The use of IMPT was predicted to reduce the expected toxicity risk while maintaining good tumor coverage in the study population; however, these results are limited in drawing meaningful conclusions as both studies used NTCP models that were not specifically validated for the study cohorts and treatment techniques.

Sio and colleagues (2016) evaluated registry data for individuals treated for oropharyngeal cancer from 2006 to 2015 with concurrent chemotherapy and IMPT or chemotherapy and IMRT using the MD Anderson Symptom Inventory for Head and Neck Cancer (MDASI-HN) module at various times before treatment (baseline), during treatment (acute phase), within the first 3 months after treatment (subacute phase), and afterward (chronic phase). Individual symptoms and the top 5 and top 11 most severe symptoms were summarized and compared between the radiation therapy modalities for 35 individuals treated with chemotherapy and IMPT and for 46 treated with chemotherapy and IMRT. The baseline symptom burdens were similar between both groups. The overall top five symptoms on a scale of 0-10 were food taste problems (mean score [MS], 4.91), dry mouth (MS, 4.49), swallowing/chewing difficulties (MS, 4.26), lack of appetite (MS, 4.08), and fatigue (MS, 4.00). No differences in symptom burden were detected between modalities during the acute and chronic phases by top-11 symptom scoring. During the subacute phase, the mean (± standard deviation) top five MDASI scores were 5.15 ± 2.66 for IMPT compared to 6.58 ± 1.98 for IMRT (p=0.013). Limitations of this study include the retrospective analysis of registry data, different periods of diagnosis and treatment for the 2 groups, missing data during the chronic posttreatment phase (due to the shorter follow-up times), and more individuals received induction chemotherapy in the IMPT group (77% vs. 24% in the IMPT and IMRT groups, respectively).

Romesser and colleagues (2016) compared dosimetry and treatment-related toxicities between individuals treated with either ipsilateral PBRT or IMRT for major salivary gland cancer or cutaneous squamous cell carcinoma. A total of 41 individuals were treated with IMRT (n=23, 56.1%) or PBRT (n=18,

43.9%) Organs at risk (OAR) were contoured, including the parotid glands, submandibular glands, cochleas, oral cavity, larynx, esophagus, brachial plexus, brain stem, and spinal cord. A dose volume histogram was constructed to evaluate target coverage and the doses to the surrounding OAR. The median age of participants was 60.9 years with an overall median follow-up of 8.7 months. Participants were assessed weekly by the treating radiation oncologist during the radiation course and in post-treatment follow up visits jointly by head and neck surgery, radiation oncology, and/or medical oncology at approximate intervals of 4, 8, and 12 weeks after completion of treatment, then every 3 months for 2 years, followed by every 6 months thereafter. There was a significant difference in the median follow-up between IMRT (16.1 months; interquartile range, 8.7-24.4 months) and PBRT participants (4.7 months; interquartile range 1.6-7.9 months) ($p<0.001$). Acute toxicities were assessed using the CTCAE v4.0. The IMRT treatment plans had a greater median maximum brainstem (29.7 Gy vs. 0.62 Gy; $p<0.001$), maximum spinal cord (36.3 Gy vs. 1.88 Gy; $p<0.001$), mean oral cavity (20.6 Gy vs. 0.94 Gy; $p<0.001$), mean contralateral parotid (1.4 Gy vs. 0.0 Gy; $p<0.001$), and mean contralateral submandibular (4.1 Gy vs. 0.0 Gy; $p<0.001$) dose when compared to PBRT plans. PBRT had significantly lower rates of grade 2 or greater acute dysgeusia (5.6% vs. 65.2%; $p<0.001$), mucositis (16.7% vs. 52.2%; $p=0.019$), and nausea (11.1% vs. 56.5%; $p=0.003$); however, the PBRT group had higher grade 2 or greater acute dermatitis compared to the IMRT group (100.0% vs.73.9%; $p=0.019$). The 1-year actuarial locoregional control rate was 92.8% with no difference between PBRT and IMRT participants (80.0% vs. 95.5%; $p=0.473$). One participant in the PBRT cohort developed an in-field local recurrence in the parotid bed at 7.7 months, while 2 participants in the IMRT cohort developed local recurrences at 2.1 and 14.7 months. The 1-year actuarial OS was 89.4% with no difference between PBRT and IMRT participants (83.3% vs. 93.3%; $p=0.083$).

Limitations of this study include the retrospective design and small number of participants. While PBRT resulted in lower acute toxicity (except for dermatitis), a large prospective, randomized study of longer follow-up is needed to evaluate the impact of PBRT on adequate tumor control, OS, quality of life outcomes, and late radiation therapy-associated morbidity.

Other Considerations

The ACR's Appropriateness Criteria® for retreatment of recurrent head and neck cancer after prior definitive radiation (McDonald, 2014) states that "newer conformal radiation modalities, including stereotactic body radiation therapy and proton therapy, may be appropriate in select cases. Additional data are needed to determine which patient subsets will most likely benefit from these modalities."

Regarding the use of PBRT for head and neck cancer, ASTRO's Evaluation Subcommittee of Emerging Technologies (Allen, 2012), states the malignancies encompass "a variety of carcinomas from multiple subsites in the upper aerodigestive tract from the nasopharynx through the hypopharynx." Even though PBRT has been shown to be well suited to treat target areas near critical structures, especially skull-based tumors, current data do not provide sufficient evidence to recommend PBRT outside of clinical trials for routine head and neck radiation therapy.

As previously stated, ASTRO's model policy for PBRT (2014) has structured their recommendations for the appropriate use of PBRT for various disease sites into 2 groups (Group 1 and Group 2 indications). For Group 2 disease sites, ASTRO states there is a need for comparative effectiveness analyses and continued CED (that is, only cover for evidence development) for PBRT for head and neck malignancies. Individuals treated with PBRT for head and neck malignancies should be "...enrolled in either an IRB-approved clinical trial or in a multi-institutional patient registry..."

The current NCCN CPG for head and neck cancers (V1.2017), principles of radiation therapy for paranasal/ethmoid or maxillary sinus tumors, states "the role of proton therapy is being investigated." In addition, the NCCN CPG states that "palliative radiation should be considered in the advanced cancer setting when curative-intent treatment is not appropriate. No general consensus exists for appropriate palliative RT regimens in head and neck cancer." For reirradiation with PBRT, "It is strongly recommended that patients be evaluated by a multidisciplinary team at a high-volume head and neck center before irradiation. Research opportunities for reirradiation should be strongly considered in patients with unresectable head and neck cancer."

The NCCN CPG (V1.2017) for head and neck cancers states that PBRT "...may be used as appropriate depending on the stage, tumor location, physician training/experience, and available physics support." The CPG includes a category 2A recommendation for PBRT as a radiation technique for select head and neck cancers, stating:

Advanced radiation therapy technologies such as IMRT, IGRT and PBT may offer clinically relevant advantages in specific instances to spare important organs at risk (OARs) such as the brain, brain stem, cochlea, semicircular canals, optic chiasm and nerves, other cranial nerves, retina, lacrimal glands, cornea, spinal cord, brachial plexus, mucosa, salivary glands, bone (skull base and mandible), pharyngeal constrictors, larynx and esophagus; and decrease the risk for late, normal tissue damage while still achieving the primary goal of local tumor control. The demonstration of significant dose-sparing of these OARs reflects best clinical practice.

A number of ways exist to integrate IMRT or PBT, target volume dosing, and fractionation.

Achieving highly conformal dose distributions is especially important for patients whose primary tumors are periocular in location and/or invade the orbit, skull base, and/o cavernous sinus; extend intracranially or exhibit extensive perineural invasion; and who are being treated with curative intent and/or who have long life expectancies following treatment.

The evidence in support of these recommendations includes "Nonrandomized single institution clinical reports and systematic comparisons demonstrate safety and efficacy of proton beam therapy in the above mentioned specific clinical scenarios." However, the NCCN noted that randomized studies to test the concepts of advanced radiation techniques, including PBRT, "...are unlikely to be done since the above clinical scenarios are relatively rare."

A search of the ClinicalTrials.gov database had identified an ongoing phase II/III randomized trial (NCT01893307) of IMPT versus IMRT for the treatment of oropharyngeal cancer of the head and neck. The primary outcome measures are rates and severity of late grade 3-5 toxicity between radiation therapies at 90 days to 2 years following radiation therapy and cumulative incidence of late onset grade 3+ toxicity anytime during the 2 years following completion of radiation therapy where late onset toxicity occurs 90 days or more following completion of radiation therapy. The estimated final data collection date for the primary outcome measure is August 2023. Other phase II studies comparing PBRT to IMRT in the treatment of adenoid cystic carcinoma, sinonasal carcinoma, mucoepidermoid carcinoma, and other head and neck cancers are currently recruiting participants.

PBRT as Treatment for Esophageal and Esophagogastric Junction Cancers

PBRT has been evaluated in the treatment of esophageal and esophagogastric junction cancers in a small, nonrandomized prospective study (Fernandez, 2016), a trimodality (chemoradiation and surgery) feasibility study (Zeng, 2016), and retrospective case series (Ishikawa, 2015; Lin, 2012; Takada, 2016). Limitations of these studies include, but are not limited to, small sample sizes, reports of preliminary outcomes, and short follow-up time.

Wang and colleagues (2013a) retrospectively analyzed a large case series of 444 individuals with esophageal cancer treated with surgical resection after chemoradiation therapy. Subjects were included in the analysis if they had no distant metastases at presentation and were treated with preoperative concurrent chemoradiation therapy with or without induction chemotherapy followed by surgery. A total of 208, 164, and 72 subjects received 3D-CRT, IMRT, and PBRT, respectively. The authors reported that IMRT or PBRT significantly reduced postoperative pulmonary and gastrointestinal complication rates compared to 3D-CRT in esophageal cancer subjects. Limitations of this study include the retrospective design and treatment of all subjects at a single institution.

There is currently insufficient evidence in the peer-reviewed published medical literature comparing the potential harms of PBRT relative to other radiation modalities, particularly in comparison to IMRT, in individuals with esophageal cancer (Mizumoto, 2010; Zhang, 2008). Well-designed prospective studies are needed to confirm the clinical utility of PBRT in the treatment of these conditions.

A search of the ClinicalTrials.gov database has identified two ongoing studies evaluating PBRT in the treatment of esophageal cancer. The first study is a prospective, open label, single group phase II trial (NCT01684904) being conducted at Loma Linda Medical Center is evaluating the efficacy and safety of combined chemoradiation with carboplatin/paclitaxel and PBRT followed by definitive surgery in a targeted population of 38 individuals with esophageal or esophagogastric junction cancer. The primary outcome measure is OS; secondary outcomes include the rate of adverse events as a measure of safety and tolerability. The estimated final data collection date for the primary outcome measure is August 2018. A second randomized, phase II clinical trial (NCT01512589) being led by MD Anderson Cancer Center is evaluating the efficacy and safety of PBRT compared to IMRT in combination with chemotherapy in a targeted population of 180 individuals with resectable or unresectable esophageal cancer. The primary outcome measures are PFS and "total toxicity burden," defined as a composite score from serious adverse events and, among those who undergo surgery, postoperative complications (from the time of randomization to 12 months after randomization). The estimated final data collection date for the primary outcome measure is April 2019 (NIH, 2017).

The current NCCN CPG for esophageal and esophagogastric junction cancers (V1.2017) states that "Data regarding proton beam therapy are early and evolving. Ideally, patients should be treated with proton beam therapy within a clinical trial."

PBRT as Treatment for Hepatocellular Cancer (HCC)

Small retrospective studies, case series, and phase I/II clinical trials in the medical literature provide some but limited evidence suggesting that PBRT may be relatively safe and effective in providing local tumor control for some individuals with HCC (Bush, 2011; Fukumitsu, 2009; Hata, 2006; Nakayama, 2011; Sugahara, 2009; Sugahara, 2010).

A systematic review of the peer-reviewed literature, including a review of PBRT for HCC conducted by ASTRO's Evaluation Subcommittee of Emerging Technologies concluded that there is evidence for the

efficacy of PBRT for treating HCC, but no suggestion that it is superior to photon-based approaches (Allen, 2012).

An AHRQ comparative effectiveness review of 13 local hepatic therapies and combinations of therapies in the treatment of unresectable HCC concluded "...there is insufficient evidence to permit conclusions on the comparative effectiveness of PBRT. Additional randomized controlled trials are necessary for all comparisons" (Belinson, 2013).

Qi and colleagues (2015) 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 (that is, PBRT) or conventional radiotherapy. A total of 73 cohorts from 70 non-comparative observational studies were included in the analysis. 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 was identified as "fair." The clinical evidence for HCC suggests that the OS rates for charged particle therapy were significantly higher than those for conventional radiotherapy at 1 year, but similar to SBRT. High-grade acute and late toxicity associated with charged particle therapy was lower than that of conventional radiotherapy and SBRT. The authors concluded that "...the overall quantity and quality of data regarding carbon-ion and proton therapy is poor and there might be potential risk of bias in comparisons between observation studies. Thus, the reported results do not allow for definite conclusions." The authors "strongly" encourage conducting prospective randomized studies that compare survival and toxicity rates between charged particle therapy and photon radiotherapy in the treatment of HCC.

The NCCN CPG for hepatobiliary cancers (V1.2017) states that "proton beam [PBT] may be appropriate in specific situations (Qi, 2015)." The citation to support this category 2A recommendation is ASTRO's model policy for PBT (2014). No specific peer-reviewed evidence is discussed in detail in the NCCN CPG.

PBRT as Treatment for Thymoma and Thymic Carcinomas

According to the NCI (2015), thymoma and thymic carcinomas are relatively rare epithelial tumors of the thymus. Thymomas are customarily described as neoplasms that show no overt atypia of the epithelial component. A thymic carcinoma is a thymic epithelial tumor that exhibits clear-cut cytologic atypia and histologic features no longer specific to the thymus (also known as type C thymoma). Thymomas have an overall incidence of 0.15 cases per 100,000 based on data from the National Cancer Institute Surveillance, Epidemiology and End Results (SEER) Program. Thymic carcinomas have been reported to account for only 0.06% of all thymic neoplasms. "In general, thymomas are indolent tumors with a tendency toward local recurrence rather than metastasis. Thymic carcinomas, however, are typically invasive, with a higher risk of relapse and death" (NCI, 2015).

The NCCN CPG for thymomas and thymic carcinomas (V1.2017) has updated a recommendation for use of PBRT as a radiation technique for the treatment of thymomas and thymic cancer, stating:

Proton beam therapy (PBT) has been shown to improve the dosimetry compared to IMRT allowing better sparing of the normal organs (lungs, heart, and esophagus) (Parikh, 2016). Additionally, favorable results in terms of both local control and toxicity have been obtained with PBT (Vogel, 2016). Based on these data, PBT may be considered in certain circumstances.

The evidence in support of this category 2A recommendation includes a small case series reported by Parikh and colleagues (2016) that evaluated treatment planning differences (dosimetric differences) between PBRT and IMRT, and early clinical outcomes and potential toxicities in those undergoing PBRT in the treatment of resected thymoma. A total of 4 participants completed adjuvant PBRT to a median dose of 57.0 CGE; (range, 50.4-66.6 CGE) after definitive resection. Adjuvant radiation was administered for positive (n=3) or close margin (n=1). Disease stages included II (n=2), III (n=1), and IVA (n=1). Equivalent IMRT treatment plans were generated for each participant for comparison with an evaluation of preset dosimetric endpoints. Compared with IMRT, PBRT was associated with lower mean doses to the lung (4.6 vs. 8.1 Gy; p=0.02), esophagus (5.4 vs. 20.6 Gy; p=0.003), and heart (6.0 vs. 10.4 Gy; p=0.007). Percentages of lung, esophagus, and heart receiving radiation were consistently lower in the PBRT plans over a wide range of radiation doses. There was no difference in mean breast dose (2.68 vs. 3.01 Gy; p=0.37). On retrospective chart review, 3 of 4 participants experienced grade 1 radiation dermatitis, and 1 participant experienced grade 2 dermatitis, which resolved after treatment. At a median follow-up of 5.5 months, there were no additional grade ≥ 2 acute or subacute toxicities, including radiation pneumonitis. Limitations of this study include the small sample size, lack of an active IMRT treatment group, and short-term follow-up.

Vogel and colleagues (2016) retrospectively evaluated early response and toxicity of double scattering proton therapy (DS-PT) for adjuvant and definitive treatment of thymoma and thymic carcinoma in 27 individuals enrolled in a registry between 2011 and 2015. Individuals were a median of 56 years and treated with definitive (n=6; 22%), salvage (n=4; 15%) or adjuvant (n=17; 63%) DS-PT to a median of 61.2/1.8 Gy CGE. The median clinical follow-up was 2.0 years (range, 0.2-4.1 years). No individual experienced grade ≥ 3 acute or late toxicity. Acute grade 2 toxicities included dermatitis (37%), fatigue (11%), esophagitis (7%), and pneumonitis (4%). Late grade 2 toxicity was limited to a single individual with chronic dyspnea after neoadjuvant chemotherapy, surgical resection, and concurrent chemoradiation. At a median follow-up of 2 years, 100% local control was achieved. Three-year regional control, distant control, and OS rates were 96% (95% CI, 76%-99%), 74% (95% CI, 41%-90%), and 94% (95% CI, 63%-99%), respectively. Limitations of this study include the retrospective design (analysis of registry data), small numbers of participants, and short follow-up. In addition, the population of individuals treated was heterogeneous, as some received definitive, salvage, or adjuvant radiation therapy with a variety of systematic chemotherapy regimens and radiation doses. The authors noted, however, that thymoma and thymic carcinomas are rare conditions and homogeneous study populations of larger sample size and long-term follow-up may not be feasible.

PBRT as Treatment for Other Malignancies

Other small retrospective studies, case series, and phase I/II clinical trials in the medical literature provide some but limited evidence suggesting that PBRT may be relatively safe and effective in providing local tumor control for the treatment of other cancers, including cancer of the bladder, breast (Bush, 2007; Bush, 2010; Kozak, 2006; MacDonald, 2013a; MacDonald, 2013b; Taghian, 2006; Xu, 2014), cervix (Georg, 2008), Hodgkin lymphoma (Andolini, 2011; Hoppe, 2012a; Hoppe, 2012b; Li, 2011), localized resectable adenocarcinoma of the pancreas (Hong, 2010), squamous cell carcinoma of the tongue (Takayama, 2016) and soft tissue sarcomas (other than primary solid tumors in children) (Chung, 2006; Yoon, 2010). Some of the studies primarily focus on treatment planning and dosimetric data comparing tumor coverage and tissue sparing; others compared high-tech external-beam therapy (IMRT and proton therapy) to high-tech brachytherapy. Comparison with published survival rates for these conditions and the difference between overall and cause-specific survival suggests that PBRT, as used in some of these studies, had a positive treatment effect. However, the magnitude of effect of PBRT on local tumor

control or survival cannot be determined because the studies lacked control or comparison groups. Furthermore, PBRT was used in combination with other therapies in several studies, so results do not reflect the outcome of PBRT alone. Other methodological limitations of the reviewed studies included small sample sizes, changes in protocol or treatment site over time, and heterogeneous study groups. A systematic review of charged-particle radiation therapy for these and other cancers concluded "evidence on the comparative effectiveness and safety of charged-particle radiation therapy in cancer is needed to assess the benefits, risks, and costs of treatment alternatives" (Terasawa, 2009).

In the systematic review by ASTRO's Evaluation Subcommittee of Emerging Technologies (Allen, 2012) regarding the use of PBRT for GI malignancies, the authors' state:

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 rectal and gastric cancers there appears to be little role for PBT, in esophageal and pancreatic cancers there may be a rationale for PBT, as these are two sites often with localized unresectable disease near critical organs at risk, but almost no clinical data exist. In hepatocellular cancer there appears to be the most data and perhaps promise for PBT as an alternative to photon based approaches, but more rigorous study and prospective clinical trials are necessary to define the differences in toxicity and efficacy between protons and photons.

ASTRO's model policy for PBRT (2014) includes "limitations of coverage" for uses considered not "reasonable and medically necessary" unless one of the criteria listed in their indications of coverage is present. ASTRO's model policy states:

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.

The NCCN CPG for Hodgkin lymphoma (V1.2017) states that "treatment with photons, electrons, or protons may all be appropriate, depending upon the clinical circumstances." Advanced radiation therapy technologies such as proton therapy "...may offer significant and clinically relevant advantages in specific instances to spare important organs at risk (OARs)...and decrease the risk for late, normal tissue damage while still achieving the primary goal of late tumor control (Hoppe, 2012b; Li, 2011)." The recommendation does not include a discussion of specific dose or length of treatment considering the disease stage.

The NCCN CPG for soft tissue sarcoma (in adults) (V2.2017) states that "newer RT techniques such as IMRT and 3D-CRT using protons or photons may allow tumor target coverage and acceptable clinical outcomes within normal tissue dose constraints to adjacent organs at risk." EBRT can be used with or without proton therapy to improve therapeutic effect. However, the guideline concludes that "...the safety and efficacy of adjuvant RT techniques is yet to be evaluated in multicenter randomized controlled studies."

PBRT for Choroidal Neovascularization

The use of PBRT for choroidal neovascularization (CN) secondary to age-related macular degeneration (AMD) has been the subject of several randomized controlled trials. Ciulla and colleagues (2002) examined the effect of PBRT on CN membranes associated with AMD in a randomized, prospective, sham-controlled, double-blind study (n=37). The authors concluded that with the acceptance of photodynamic therapy, future studies will require more complex design and larger sample size to determine whether radiation can play either a primary or adjunctive role in treating these lesions. A randomized controlled trial (n=166) conducted by Zambarakji and colleagues (2006) evaluated the safety and visual outcomes after PBRT for subfoveal neovascular AMD. Subjects were assigned randomly (1:1) to receive 16-CGE or 24-CGE PBRT in 2 equal fractions. Visual acuity was measured before treatment and 3-, 6-, 12-, 18-, and 24 months after treatment using Early Treatment Diabetic Retinopathy Study charts, best-corrected visual acuity measurement, ophthalmological examinations, color fundus photography, and fluorescein angiography. The authors reported no significant differences in rates of visual acuity or complications between the 2 groups, but suggested that PBRT may be useful as an adjuvant therapy or as an alternative for individuals who decline or are not appropriate for approved therapies for AMD. PBRT was proposed as a treatment for wet AMD based on the results from another small, industry sponsored clinical trial (n=21) which suggested that proliferating vascular cells are sensitive to low-dose radiation, thereby destroying the abnormal blood vessels and allowing retinal reattachment and stabilization or restoration of vision (Yonemoto, 1996). These studies as designed (that is, small sample population, no significant differences reported) have failed to demonstrate any significant benefit of the use of PBRT when compared to placebo. The American Academy of Ophthalmology (AAO) guidelines for the treatment of AMD include surgical and postoperative care of individuals receiving thermal laser surgery, photodynamic therapy or intravitreal injections. PBRT is not discussed as a treatment option for AMD (AAO, 2015).

Background/Overview

Description of Proton Beam Radiation Therapy

PBRT is a type of external radiation treatment that uses electrically charged atomic particles (protons or helium ions) to target a given area (for example, tumor or blood vessel malformation). PBRT differs from conventional electromagnetic (that is, photon) radiation therapy in several respects including less scatter as the particle beams pass through tissue with deposition of the ionizing energy at precise depths (Bragg peak). A theoretical advantage of proton beam therapy over photon therapies is its ability to deliver higher and more effective radiation dose to the tumor without harm to adjacent normal tissue.

PBRT has been found be useful in the treatment of tumors that are not amenable to surgical excision or other conventional forms of radiation treatment. This includes specific types of tumors that are in close proximity to the brain stem or other nervous system structures, such as the optic nerve or spinal cord, which make surgery or other forms of radiation therapy difficult. Since PBRT can be used to precisely focus radiation on specific areas with little exposure to adjacent tissues, PBRT may be very useful for treatment of tumors located near radio-sensitive structures, where even low doses of radiation could cause significant damage.

Age-Related Macular Degeneration (AMD)

AMD is the leading cause of vision loss in people older than age 60. The greatest risk factor for AMD is age; other risk factors include smoking, obesity, family history, female gender, and race (Caucasian). The main symptom of AMD is a gradual to rapid loss of vision, especially the centrally focused vision required for reading and driving, that eventually leads to blindness. There are 2 types of AMD, wet and dry. Wet AMD, also known as advanced AMD, occurs when abnormal blood vessels posterior to the retina grow under the macula, leak blood and fluid, and displace the macula. Damage to the macula begins and loss of central vision can occur quickly. An early symptom of wet AMD is the change in appearance of straight lines to wavy lines. Dry AMD occurs when the light-sensitive cells in the macula slowly break down, gradually blurring central vision in the affected eye. Over time, as less of the macula functions, central vision is gradually lost in the affected eye. The most common symptom of dry AMD is slightly blurred vision. Dry AMD generally affects both eyes, but vision may be lost in one eye while the other eye seems unaffected. AMD is detected during a comprehensive eye exam that includes a visual acuity test, a dilated eye exam, and tonometry. Treatments for wet AMD include laser surgery, photodynamic therapy or anti-vascular endothelial growth factor (anti-VEGc) therapy.

Central Nervous System (CNS) Lesions

Treatment of intracranial and skull base tumors depends on the location, size, and grade of the tumor, the individual's age and general health status. These tumors may be surgically excised with follow-up treatment involving chemotherapy, radiation therapy, or both. CNS tumors include the general category called gliomas. Gliomas can be benign or malignant, high-grade or low-grade, and include astrocytomas (that is, pilocytic, low-grade, anaplastic and glioblastoma multiforme), primitive neuroectodermal tumors, oligodendrogliomas, ependymomas, subependymoma, brain stem gliomas, optic gliomas and mixed gliomas. Gliomas can be a single tumor cell type, such as in astrocytoma, ependymoma, or oligodendroglioma, or a mixed tumor containing more than one type of cell. Children with CNS tumors may be treated with surgery, radiation therapy, chemotherapy, or a combination of these therapies. Generally, the standard treatment for low-grade CNS tumors (that is, astrocytomas, infiltrating or diffuse) in children is surgical resection and chemotherapy if the tumor cannot be completely removed or reoccurs; however, treatment varies for different types of tumors. In younger children, radiation therapy, which can cause developmental delay and problems with intellectual development, may postpone this treatment approach until the child is older. Surgery alone or combined with radiation therapy may cure many other childhood CNS tumors. Survival rates depend on the age of the individual, the type of tumor (grade and location), and status of metastasis.

For primary or metastatic tumors that are adjacent to critical structures, PBRT, with or without stereotactic radiosurgery, may spare normal, surrounding tissue. For highly malignant gliomas, conventional external beam radiotherapy has been identified as the treatment of choice. Even though conventional radiotherapy slows progression, prolongs survival and may enhance quality of life, survival rates are only between 7 and 10 months. Given the severity of prognosis for malignant gliomas, PBRT is used as an alternative therapy. In addition to PBRT increasing survival rates up to 4 times greater than conventional radiotherapy, PBRT may improve quality of life, especially in younger individuals with a more favorable histology (for example, grade III astrocytomas).

Chordoma and Chondrosarcoma

Chordoma and chondrosarcoma are the two primary malignant tumors of the skull base. Chordoma is a rare tumor that arises from cellular remnants of the notochord within the clivus (a bone in the base of the skull), spinal vertebrae, and sacrum. The incidence of chordoma in the U.S. is approximately 1 case

per 1,000,000 people per year. Chordomas are slow-growing, life-threatening tumors that occur spontaneously. They may be present for over a year before symptoms appear. Individuals usually present with pain, with or without neurologic deficits such as cranial or other nerve symptoms. Diagnosis is straightforward when the typical physaliferous (soap-bubble-bearing) cells are present. Chordoma can cause death by direct growth or by spreading to other organs. Metastasis occurs most frequently to the lungs. Standard treatment includes radical resection, which is not commonly curative because of difficulty in obtaining clear margins, and external radiation therapy, such as PBRT. If the tumor is located in close proximity to the brain, surgery is not an option. In these cases, PBRT is more effective because of its high dose delivery and well-defined range (Hug, 2001).

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. Histiologic 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, V1.2016).

Intracranial Arteriovenous Malformations (AVM)

It is estimated that brain AVMs occur in less than 1% of the general population; each year about 1% of those with AVMs will die as a direct result of the AVM (NINDS, 2016). Although an AVM usually develops as a congenital defect, most AVM cases present during the third decade of life and can occur following trauma. Larger AVMs are more likely to exert pressure on surrounding structures of the brain, resulting in hemorrhage, seizures, headaches, and other neurological problems. Hemorrhage is the most common presentation. Other than radiosurgery, the treatment options for AVM include microsurgery, embolization, or multimodal treatment that combines one or more of these procedures with radiosurgery. Surgery is generally considered the treatment of choice in appropriate candidates, and microsurgery immediately addresses the risk of hemorrhage. Although 60% to 70% of individual's with AVM can be treated by microsurgery, the remaining individuals are considered poor candidates for traditional surgery. This includes individuals whose AVMs lie deeply in the brain or near vital areas, including the brain stem and internal capsule. For these individuals, PBRT may be a treatment option when AVMs are not amenable to surgical excision or other conventional forms of treatment.

Melanoma of the Uveal Tract

Melanoma of the uveal tract (iris, ciliary body, and choroid), also known as ocular (eye) melanoma (OM), though rare, is the most common primary intraocular malignancy in adults. Uveal melanoma is diagnosed mostly at older ages, with a progressively rising age-specific incidence rate that peaks near

the age of 70. Host susceptibility factors associated with the development of this cancer include Caucasian race, light eye color, fair skin color, the ability to tan (Singh, 2005), as well as genetic factors and environmental exposure. Uveal melanomas can arise in the anterior uveal tract (iris) or the posterior (ciliary body or choroid) uveal tract. Iris melanomas have the best prognosis, whereas melanomas of the ciliary body have the worst prognosis. Most uveal tract melanomas originate in the choroid. The ciliary body is less commonly a site of origin, and the iris is the least common. Surgical removal of the eye (enucleation) is the standard treatment for large posterior tumors. Among conservative modalities, PBRT has been suggested as an external beam radiotherapy that may provide precise tumor targeting of small tumors, thus causing less damage to healthy tissue surrounding the eye (Wilson, 1999; National Cancer Institute [NCI], 2015).

Pituitary Adenoma

Pituitary adenomas are slow growing, encapsulated tumors of epithelial origin that penetrate adjacent structures. The tumors can contain necrotic, cystic, or hemorrhagic regions. In rare cases, the tumors become calcified. The incidence of malignant degeneration among pituitary adenomas is exceedingly small. In rare cases, a pituitary adenoma may invade the orbit, with devastating consequences to the integrity of the globe and ocular structure; therefore, early recognition of this complication is of the utmost importance to begin appropriate treatment to minimize ocular and orbital damage. When indicated, surgery by means of the transsphenoidal approach is considered the technique of choice. Surgery has the advantage of rapidly lowering hormone levels. When conventional stereotactic radiation is not an available treatment option, PBRT may improve the control of disease progression.

Prostate Cancer

Determining the optimal treatment of prostate cancer is challenging, given its uncertain natural history based on the size and stage of the tumor (that is, if it has spread beyond the prostate) and characteristics of the individual, including age and other medical problems. For example, no active treatment (called watchful waiting) may be recommended if a small focus of cancer is found in a man of advancing age. Active treatment options include surgery to remove the prostate gland (radical prostatectomy) and different types of radiation therapy, delivered either externally or where radioactive seeds are implanted into the prostate.

Definitions

Biochemical no evidence of disease (bNED): Also known as biochemical disease-free survival; as it relates to prostate cancer outcomes, is defined as 3 successive rises in serum prostate specific antigen (PSA) with the date of failure being the halfway point between post-treatment nadir and the first of the consecutive rises in serum PSA.

Biopsy: The removal of a sample of tissue for examination under a microscope to check for cancer cells.

Choroidal neovascularization: A condition characterized by the growth of new blood vessels at the back portion of the eye that causes reduced visual acuity, blurred vision, visual distortion, and reading difficulty.

Conformal radiation therapy: A form of external beam radiation therapy where the beam conforms or shapes to match the 3-dimensional shape of a tumor (created by a computer), allowing delivery of

higher doses of radiation to the targeted tumor, not the surrounding normal tissue; also known as 3-dimensional conformal radiation therapy, 3-D radiation therapy, or 3D-CRT.

Conventional radiation therapy: A form of radiotherapy where the greatest energy release is at the surface of the tissue and decreases exponentially the farther the radiation travels, unavoidably at nearby healthy tissue, also known as photon radiation therapy. Photon-based radiation therapy such as 3D-CRT, IMRT, and stereotactic body radiotherapy (SBRT) allow improved targeting of conventional radiation therapy.

Intensity modulated radiation therapy (IMRT): A form of conformal radiation therapy that uses computer-generated images to match radiation beams to closely approximate the size and shape of the tumor, having the ability to deliver a higher radiation dose within the tumor; the radiation beam is modulated (varied) across the treatment field, rather than being a single, uniform intensity beam.

Localized prostate cancer: Cancer that includes T1-3a (the tumor has spread through the capsule on one or both sides but has not invaded seminal vesicles or other structures) and any N disease (either no spread to lymph nodes or there has been spread to the regional lymph nodes).

Metastasis: The process by which cancer spreads from one part of the body to another; the term "metastasis" also applies to a tumor that appears at a distant site from the primary tumor and is confirmed as the same cell type.

Photon radiation therapy: See conventional radiation therapy.

Primary tumor: The original, or first, tumor in the body. Cancer cells from a primary tumor may spread to other parts of the body and form new, or secondary, tumors called metastasis. Also called primary cancer (NCI, 2016).

Proton beam: A focused beam of high-energy positively charged particle radiation (proton particles) used in radiation therapy. Proton beam therapy can be given with or without stereotactic techniques.

Radiation: Energy carried by waves or a stream of particles; visible light, X-rays, and protons are all examples of radiation.

Radiation therapy (radiotherapy): The use of high-energy penetrating radiation or subatomic particles to treat disease; types of radiation may include X rays, electrons, protons, alpha and beta particles, and gamma rays.

Radiosurgery: A form of radiation therapy involving the use of highly focused beams of radiation that are delivered in a single dose; radiosurgery is different than radiotherapy, which is delivered in multiple fractions (doses) over several days to weeks.

Salvage therapy: Any therapy given after a cancerous tumor has failed to respond to or reoccurred after other treatments.

Solid tumor: An abnormal mass of tissue that usually does not contain cysts or liquid areas. Solid tumors may be benign (not cancer), or malignant (cancer). Different types of solid tumors are named for the

type of cells that form them. Examples of solid tumors are sarcomas, carcinomas, and lymphomas (NCI, 2016).

Stereotactic: Refers to the precise positioning of tumors and other lesions in 3-dimensional space which allows for increased accuracy of treatment; for example, radiation therapy can be done stereotactically, as a number of precisely aimed beams of ionizing radiation are aimed from several directions to converge on a tumor.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services may be medically necessary when criteria are met:

CPT
61796 Stereotactic radiosurgery (particle beam, gamma ray or linear accelerator); 1 simple cranial lesion [when specified as proton beam]
61797 Stereotactic radiosurgery (particle beam, gamma ray or linear accelerator); each additional cranial lesion, simple [when specified as proton beam]
61798 Stereotactic radiosurgery (particle beam, gamma ray or linear accelerator); 1 complex cranial lesion [when specified as proton beam]
61799 Stereotactic radiosurgery (particle beam, gamma ray or linear accelerator); each additional cranial lesion, complex [when specified as proton beam]
61800 Application of stereotactic headframe for stereotactic radiosurgery
63620 Stereotactic radiosurgery (particle beam, gamma ray or linear accelerator); 1 spinal lesion [when specified as proton beam]
63621 Stereotactic radiosurgery (particle beam, gamma ray or linear accelerator); each additional spinal lesion [when specified as proton beam]
77301 Intensity modulated radiotherapy plan, including dose-volume histograms for target and critical structure partial tolerance specifications [when specified as treatment planning for PBRT]
77432 Stereotactic radiation treatment management of cranial lesion(s) (complete course of treatment consisting of 1 session) [when specified as proton beam]
77435 Stereotactic body radiation therapy, treatment management, per treatment course, to 1 or more lesions, including image guidance, entire course not to exceed 5 fractions [when specified as proton beam]
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
S8030 Scleral application of tantalum ring(s) for localization of lesions for proton beam

ICD-10 Procedure

D0004ZZ Beam radiation of brain using heavy particles (protons, ions)
D0014ZZ Beam radiation of brain stem using heavy particles (protons, ions)
D0064ZZ Beam radiation of spinal cord using heavy particles (protons, ions)
D0074ZZ Beam radiation of peripheral nerve using heavy particles (protons, ions)
D8004ZZ Beam radiation of eye using heavy particles (protons, ions)
DP004ZZ-DP0C4ZZ Beam radiation of bone using heavy particles (protons, ions) [by site; includes codes DP004ZZ, DP024ZZ, DP034ZZ, DP044ZZ, DP054ZZ, DP064ZZ, DP074ZZ, DP084ZZ, DP094ZZ, DP0B4ZZ, DP0C4ZZ]
DT004ZZ Beam radiation of kidney using heavy particles (protons, ions)
DW014ZZ Beam radiation of head and neck using heavy particles (protons, ions)
DW024ZZ Beam radiation of chest using heavy particles (protons, ions)
DW034ZZ Beam radiation of abdomen using heavy particles (protons, ions)
DW064ZZ Beam radiation of pelvic region using heavy particles (protons, ions)
D020HZZ Stereotactic particulate radiosurgery of brain
D021HZZ Stereotactic particulate radiosurgery of brain stem
D026HZZ Stereotactic particulate radiosurgery of spinal cord
D027HZZ Stereotactic particulate radiosurgery of peripheral nerve
D820HZZ Stereotactic particulate radiosurgery of eye
DG20HZZ Stereotactic particulate radiosurgery of pituitary gland
DG21HZZ Stereotactic particulate radiosurgery of pineal body
DG22HZZ Stereotactic particulate radiosurgery of adrenal glands
DT20HZZ Stereotactic particulate radiosurgery of kidney
DW21HZZ Stereotactic particulate radiosurgery of head and neck
DW22HZZ Stereotactic particulate radiosurgery of chest
DW23HZZ Stereotactic particulate radiosurgery of abdomen
DW26HZZ Stereotactic particulate radiosurgery of pelvic region

ICD-10 Diagnosis
C40.00-C41.9 Malignant neoplasm of bone and articular cartilage
C47.0-C47.9 Malignant neoplasm of peripheral nerves and autonomic nerves
C49.0-C49.9 Malignant neoplasm of other connective and soft tissue
C64.1-C64.9 Malignant neoplasm of kidney, except renal pelvis
C69.20-C69.22 Malignant neoplasm of retina
C69.30-C69.32 Malignant neoplasm of choroid
C69.40-C69.42 Malignant neoplasm of ciliary body
C70.0-C70.9 Malignant neoplasm of meninges
C71.0-C71.9 Malignant neoplasm of brain
C72.0-C72.9 Malignant neoplasm of spinal cord, cranial nerves and other parts of central nervous system
C74.00-C74.92 Malignant neoplasm of adrenal gland
C75.1-C75.3 Malignant neoplasm of pituitary gland, craniopharyngeal duct, pineal gland
C7A.8 Other malignant neuroendocrine tumors
C79.31 Secondary malignant neoplasm of brain
C79.40-C79.49 Secondary malignant neoplasm of other and unspecified parts of nervous system
D09.3 Carcinoma in situ of thyroid and other endocrine glands [pituitary]
D32.0-D32.9 Benign neoplasm of meninges
D33.0-D33.9 Benign neoplasm of brain and other parts of central nervous system
D35.2 Benign neoplasm of pituitary gland
D44.3-D44.4 Neoplasm of uncertain behavior of pituitary gland, craniopharyngeal duct

D49.7 Neoplasm of unspecified behavior of endocrine glands and other parts of nervous system [pituitary]
I67.1 Cerebral aneurysm, nonruptured
I67.89-I67.9 Other and unspecified cerebrovascular disease
Q28.2 Arteriovenous malformation of cerebral vessels

See THER-RAD.00010 for other covered indications for stereotactic radiosurgery using gamma ray or linear accelerator

When services are Not Medically Necessary:
For the procedure codes listed above for the following diagnoses:

ICD-10 Diagnosis
H35.051-H35.059 Retinal neovascularization, unspecified
H35.30 Unspecified macular degeneration (age-related)
H35.3110-H35.3194 Nonexudative age-related macular degeneration
H35.3210-H35.3293 Exudative age-related macular degeneration

When services are Investigational and Not Medically Necessary:
For the procedure codes listed above when criteria are not met or for all other diagnoses not listed, or when the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

When services are also Investigational and Not Medically Necessary:

ICD-10 Procedure
D0074ZZ-DW054ZZ Beam radiation using heavy particles (protons, ions) of all other sites; [includes codes D7004ZZ, D7014ZZ, D7024ZZ, D7034ZZ, D7044ZZ, D7054ZZ, D7064ZZ, D7074ZZ, D7084ZZ, D9004ZZ, D9014ZZ, D9034ZZ, D9044ZZ, D9054ZZ, D9064ZZ, D9074ZZ, D9084ZZ, D9094ZZ, D90B4ZZ, D90D4ZZ, D90F4ZZ, DB004ZZ, DB014ZZ, DB024ZZ, DB054ZZ, DB064ZZ,DB074ZZ, DB084ZZ, DD004ZZ, DD014ZZ, DD024ZZ, DD034ZZ, DD044ZZ, DD054ZZ, DD074ZZ, DF004ZZ, DF014ZZ, DF024ZZ, DF034ZZ, DH024ZZ, DH034ZZ, DH044ZZ, DH064ZZ, DH074ZZ, DH084ZZ, DH094ZZ, DH0B4ZZ, DM004ZZ, DM014ZZ, DT014ZZ, DT024ZZ, DT034ZZ, DU004ZZ, DU014ZZ, DU024ZZ, DV004ZZ, DV014ZZ, DW044ZZ, DW054ZZ]
D027HZZ-DV21HZZ Stereotactic particulate radiosurgery of all other sites [includes codes D720HZZ, D721HZZ, D722HZZ, D723HZZ, D724HZZ, D725HZZ, D726HZZ, D727HZZ, D728HZZ, D920HZZ, D921HZZ, D924HZZ, D925HZZ, D926HZZ, D927HZZ, D928HZZ, D929HZZ, D92BHZZ, D92CHZZ, D92DHZZ, DB20HZZ, DB21HZZ, DB22HZZ, DB25HZZ, DB26HZZ, DB27HZZ, DB28HZZ, DD20HZZ, DD21HZZ, DD22HZZ, DD23HZZ, DD24HZZ, DD25HZZ, DD27HZZ, DF20HZZ, DF21HZZ, DF22HZZ, DF23HZZ, DG24HZZ, DG25HZZ, DM20HZZ, DM21HZZ, DT21HZZ, DT22HZZ, DT23HZZ, DU20HZZ, DU21HZZ, DU22HZZ, DV20HZZ, DV21HZZ]

ICD-10 Diagnosis
All diagnoses

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Charged Particle Radiation Therapy

Document History

Status Date Action
Reviewed 05/04/2017 Medical Policy & Technology Assessment Committee (MPTAC) review.
Reviewed 05/03/2017 Hematology/Oncology Subcommittee review. Updated Description, Rationale, Background, Coding, References, and Websites for Additional Information sections.
Reviewed 11/03/2016 MPTAC review.
Reviewed 11/02/2016 Hematology/Oncology Subcommittee review. Updated formatting in Position Statement section. Updated Rationale, Background, References, and Websites for Additional Information sections. Updated Coding section with 10/01/2016 ICD-10-CM diagnosis code changes.
Revised 11/05/2015 MPTAC review.
Revised 11/04/2015 Hematology/Oncology Subcommittee review. Revised document number from RAD.00015 to THER-RAD.00002. Format changes to medically necessary statement and criteria. Removed medically necessary and investigational and not medically necessary Position Statements for Localized Prostate Cancer. Revised remaining investigational and not medically necessary statement for PBRT, adding "when criteria are not met and" for all other indications, "including, but not limited to, the treatment of localized prostate cancer." Removed Appendix tables. Updated Rationale, Background, Definitions, Coding, References, and Websites for Additional Information sections. Removed ICD-9 codes from Coding section.
Revised 11/13/2014 MPTAC review.
Revised 11/12/2014 Hematology/Oncology Subcommittee review. Added a medically necessary statement for proton beam therapy for the treatment of primary or benign solid tumors in children treated with curative intent. Updated Rationale, Background, Coding, References, and Websites for Additional Information sections.
Reviewed 05/15/2014 MPTAC review.
Reviewed 05/14/2014 Hematology/Oncology Subcommittee review. Minor format changes in Position Statements. Updated Rationale, Background, References, and Websites for Additional Information sections.
Reviewed 05/09/2013 MPTAC review.
Reviewed 05/08/2013 Hematology/Oncology Subcommittee review. Updated Rationale, Background, Definitions, References, Websites for Additional Information, and Index.
Revised 05/10/2012 MPTAC review.
Revised 05/09/2012 Hematology/Oncology Subcommittee review. Added statement and a Note to clarify medically necessary statement for localized prostate cancer. Updated Rationale, Background, Coding, References, and Websites for Additional Information.
Revised 11/17/2011 MPTAC review.
Revised 11/16/2011 Hematology/Oncology Subcommittee review. Clarified the investigational and not medically necessary statement for PBRT for all conditions other than localized prostate cancer. For Localized Prostate Cancer: 1) Revised medically necessary statement for localized prostate cancer and removed the Note; 2) Added brachytherapy to the investigational and not medically necessary statement; 3) Added an investigational and not medically necessary statement for all other indications. Updated Rationale, Background, Definitions, References, and Websites for Additional Information.
10/12/2011 Updated Coding section.
Revised 05/19/2011 MPTAC review.

Revised 05/18/2011 Hematology/Oncology Subcommittee review. Minor clarification to localized prostate cancer medically necessary statement. Updated Rationale, Discussion, Coding, References and Websites for Additional Information.
Reviewed 11/18/2010 MPTAC review.
Reviewed 11/17/2010 Hematology/Oncology Subcommittee review. Updated Rationale, Background, Definitions, References, and Appendix sections.
Reviewed 11/19/2009 MPTAC review.
Reviewed 11/18/2009 Hematology/Oncology Subcommittee review. Moved the *Note statement from the position statements for Localized Prostate Cancer to the document's Rationale section. Updated Rationale with review of References, professional society guidelines, Background, and Definitions.
Revised 11/20/2008 MPTAC review.
Revised 11/19/2008 Hematology/Oncology Subcommittee review. Revised medically necessary and investigational and not medically necessary statements for the treatment of localized prostate cancer including a Note statement. Updated Rationale and References. Updated Coding with 01/01/2009 CPT changes; removed CPT 61793 deleted 12/31/2008.
Revised 05/15/2008 MPTAC review.
Revised 05/14/2008 Hematology/Oncology Subcommittee review. Revised the medically necessary statement for CNS lesions (removed ≤3 cm size of lesion specification and base of skull). Revised Position Statements related to treatment of prostate cancer: 1) Proton beam radiation therapy is considered medically necessary if it is not more costly than intensity modulated radiation therapy (IMRT) for the treatment of localized prostate cancer as the sole modality of treatment; 2) Proton beam radiation therapy is considered not medically necessary if it is more costly than IMRT for the treatment of localized prostate cancer as the sole modality of treatment; 3) The use of proton beam radiation as dose escalation therapy, in conjunction with stereotactic radiotherapy, IMRT, or three-dimensional conformal radiation therapy (3D CRT) for the treatment of localized prostate cancer is considered investigational and not medically necessary. Updated Rationale, Definitions, Coding, and References. Expanded Background section. Added Appendix tables.
Reviewed 11/29/2007 MPTAC review. The phrase "investigational/not medically necessary" was clarified to read "investigational and not medically necessary."
Reviewed 11/28/2007 Hematology/Oncology Subcommittee review. Updated Rationale, Definitions, Index and References.
Reviewed 03/08/2007 MPTAC review. Description and References updated.
01/01/2007 Updated Coding section with 01/01/2007 CPT/HCPCS changes.
Reviewed 03/23/2006 MPTAC review. Updated References.
Revised 04/28/2005 MPTAC review. Revision based on Pre-merger Anthem and Pre-merger WellPoint Harmonization.

Pre-Merger Organizations
Last Review Date

Document Number
Title
Anthem, Inc. 01/28/2004 RAD.00015 Charged Particle Radiation Therapy
WellPoint Health Networks, Inc. 12/02/2004 4.11.07 Proton Beam Radiotherapy

Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Medical Policy, which addresses medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

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