

Charged-Particle (Proton) Radiotherapy

Effective: December 1, 2018

Next Review: June 2019

Last Review: October 2018

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Charged-particle radiation therapy conforms to the target tumor, minimizing radiation exposure to surrounding healthy tissue. Charged-particle irradiation includes both proton beam therapy (PBT) and helium ion irradiation. Helium ion irradiation is not currently available in the United States.

MEDICAL POLICY CRITERIA

- I. Charged-particle irradiation such as proton beam therapy may be considered **medically necessary** for any of the following primary or metastatic tumors, including definitive, adjuvant, or salvage treatment:
 - A. In adult patients, tumors meeting any of the following criteria:
 1. Ocular tumors including intraocular/uveal melanoma (e.g., iris, choroid, or ciliary body); or
 2. Any of the following central nervous system tumors:
 - a. Tumors invading the base of the skull, including but not limited to chordoma, chondrosarcoma, or tumors of the paranasal sinus region; or

- b. Clinical documentation by a physician that the central nervous system tumor extends to 10 mm or less from the optic chiasm, brain stem, or cervical spinal cord at or above the foramen magnum (see Policy Guidelines); or
 - 3. Reirradiation of head and neck or central nervous system tumors when the patient has had prior radiation in the expected treatment field (See Policy Guidelines for definition of head and neck cancer); or
 - B. Pediatric (less than 21 years of age) central nervous system and malignant solid tumors.
- II. Charged-particle irradiation, such as proton beam therapy, to treat local (clinical or pathological T1, T2, N0, M0) or locally advanced (clinical or pathological T3, T4, N0, N1, M0) prostate cancer has been shown to have comparable, but not superior, clinical outcomes compared to other irradiation approaches such as intensity modulated radiotherapy (IMRT) photon irradiation. Charged-particle irradiation with proton beam is generally significantly more costly than other irradiation approaches. Therefore, charged-particle irradiation with proton beam is considered **not medically necessary** in patients with local or locally advanced prostate cancer. However, given the comparable outcomes, charged-particle irradiation with proton beam to treat local or locally advanced prostate cancer may be considered **medically necessary** when the requested specific course of therapy will be no more costly than IMRT photon irradiation or other irradiation approaches.
- III. Other applications of charged-particle irradiation are considered **investigational**, including but not limited to the following:
 - A. All other tumors that do not meet Criterion I. above, including but not limited to adult solid organ tumors, primary or metastatic (e.g., liver, lung, kidney, pancreas) and metastatic prostate cancer
 - B. Choroidal neovascularization (CNV) in age-related macular degeneration (ARMD)
- IV. Use of charged-particle irradiation, such as proton beam therapy, for stereotactic radiosurgery (SRS) or stereotactic body radiotherapy (SBRT)/stereotactic ablative radiotherapy (SABR) treatment is considered **investigational**.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

SUBMISSION OF DOCUMENTATION

It is critical that the list of information below is submitted for review to determine whether the policy criteria are met. If these items are not submitted, it could impact our review and decision outcome.

All Tumors

- History and physical chart notes including information regarding specific diagnosis and any pertinent imaging results.

- Documentation of prior radiation to the treatment volume (if relevant).

Adult Central Nervous System Tumors

- When Criterion I.A.2.b. is applicable, clinical documentation must be submitted to establish proximity and must include:
 - The formal diagnostic radiology report;
 - The exact proximal distance from the tumor to any of the optic chiasm, brainstem or cervical spinal cord at or above the foramen magnum, specified by one of the following:
 - The formal diagnostic radiology report; or
 - Physician documentation in the member's clinical record.

DEFINITION OF HEAD AND NECK CANCERS

For this policy, head and neck cancers are cancers arising from the oral cavity and lip, larynx, hypopharynx, oropharynx, nasopharynx, paranasal sinuses and nasal cavity, salivary glands, and soft tissue sarcomas, unusual histologies or occult primaries in the head and neck region.

CROSS REFERENCES

1. [Intraocular Radiation Therapy for Age-Related Macular Degeneration](#). Medicine, Policy No. 134
2. [Intensity Modulated Radiotherapy \(IMRT\) of the Thorax](#), Medicine, Policy No. 136
3. [Intensity Modulated Radiotherapy \(IMRT\) of the Prostate](#), Medicine, Policy No. 137
4. [Intensity Modulated Radiotherapy \(IMRT\) for Head and Neck Cancers and Thyroid Cancer](#), Medicine, Policy No. 138
5. [Intensity Modulated Radiotherapy \(IMRT\) of the Abdomen and Pelvis](#), Medicine, Policy No. 139
6. [Radioembolization for Primary and Metastatic Tumors of the Liver](#), Medicine, Policy No. 140
7. [Intensity Modulated Radiotherapy \(IMRT\) for Central Nervous System \(CNS\) Tumors](#), Medicine, Policy No. 147
8. [Stereotactic Radiosurgery and Stereotactic Body Radiation Therapy](#), Surgery, Policy No. 16

BACKGROUND

Charged-particle beams consisting of protons or helium ions are a type of particulate radiation therapy that contrast with conventional electromagnetic (i.e., photon) radiation therapy due to the unique properties of minimal scatter as the particulate beams pass through the tissue, and deposition of the ionizing energy at a precise depth (i.e., the Bragg Peak). Thus radiation exposure to surrounding normal tissues is minimized. Helium ion irradiation is not currently available in the United States, and therefore this policy primarily focuses on proton beam therapy (PBT). Advances in photon-based radiation therapy such as 3-D conformal radiation therapy, intensity-modulated radiation therapy (IMRT), and stereotactic radiosurgery (SRS)/stereotactic body radiotherapy (SBRT) have also allowed improved targeting of conventional therapy. The theoretical advantages of protons and other charged-particle beams may improve outcomes when the following conditions apply:

- Conventional treatment modalities do not provide adequate local tumor control,
- Evidence shows that local tumor response depends on the dose of radiation delivered, and
- Delivery of an adequate radiation dose to the tumor is limited by the proximity of vital radiosensitive tissues or structures.

The use of proton or helium ion radiation therapy has been investigated in two general categories of tumors/abnormalities:

1. Tumors located next to vital structures, such as intracranial lesions, or lesions along the axial skeleton such that complete surgical excision or adequate doses of conventional radiation therapy are impossible.
2. Tumors that are associated with a high rate of local recurrence despite maximal doses of conventional radiation therapy. The most common tumor in this group is locally advanced prostate cancer (i.e., Stages C or D1 [without distant metastases], also classified as T3 or T4 and tumors with Gleason scores of 8 to 10). These patients are generally not candidates for surgical resection.

Most SRS and SBRT is carried out using photons. However, techniques to use protons for SRS and SBRT have been developed and are being tested for their safety and efficacy.

REGULATORY STATUS

Radiotherapy is a procedure and, therefore, is not subject to U.S. Food and Drug Administration (FDA) regulations. However, the accelerators and other equipment used to generate and deliver charged-particle radiation (including proton beam) are devices that require FDA oversight. Senior staff at the FDA's Center for Devices and Radiological Health have indicated that the proton beam facilities constructed in the United States prior to enactment of the 1976 Medical Device Amendments were cleared for use in the treatment of human diseases on a "grandfathered" basis, while at least one that was constructed subsequently received a 510(k) marketing clearance. There are 510(k) clearances for devices used for delivery of proton beam therapy and devices considered to be accessory to treatment delivery systems such as the Proton Therapy Multileaf Collimator (which was cleared in December 2009). Since 2001, several devices classified as medical charged-particle radiation therapy systems have received 510(k) marketing clearance. FDA Product Code LHN.

EVIDENCE SUMMARY

The principal outcomes associated with treatment of malignancies are typically measured in units of survival past treatment: disease-free survival (DFS), a period of time following treatment where the disease is undetectable; progression-free survival (PFS), the duration of time after treatment before the advancement or progression of disease; and overall survival (OS), the period of time the patient remains alive following treatment. Patient quality of life may be another primary outcome, particularly among patients living with refractory disease, or when considering treatment of slow-progressing diseases (such as prostate cancer). In order to understand the impact of charged-particle irradiation using protons on health outcomes, well-designed studies that compare the use of protons to other radiation therapies, such as external-beam radiation therapy (delivered with photons) are needed.

TECHNOLOGY ASSESSMENTS AND SYSTEMATIC REVIEWS ADDRESSING MULTIPLE INDICATIONS

Several technology assessments have surveyed the spectrum of uses for PBT. Overall methods and conclusions are included here and specific indications from these technology assessments are discussed in the relevant sections below.

In August 2017, the Canadian Agency for Drugs and Technology in Health (CADTH) published a technology assessment addressing the use of proton beam therapy for the treatment of cancer in children and adults.^[1] Nine SRs met the criteria for review. They were analyzed and conclusions of the SRs and the included primary studies were reported. The authors concluded that PBT is comparable to other types of RT in most types of cancer, while a few had greater benefits (meningioma, subgroups of malignant meningioma, and poorly-differentiated tumors of prostate cancer in adults), lower benefits (some intramedullary spinal cord glioma in both children and adults, analyzed together), both greater benefits and lower benefits (eye cancer in adults), greater harms (breast cancer and prostate cancer in adults), lower harms (retinoblastoma in children and medulloblastoma in adults), or both greater harms and lower harms in adults in several other cancers. They caution that the included studies are generally of too low quality to make definitive conclusions.

In 2015, the Department of Veterans Affairs' Quality Enhancement Research Initiative's (QUERI) Evidence-based Synthesis Program (ESP) published a systematic review on the Comparative Effectiveness of Proton Irradiation Treatment.^[2] Of the 25 comparative studies included in this review, 22 were included in the Institute for Clinical and Economic Review (ICER) technology assessment discussed below. Studies were rated as fair to poor and the majority were retrospective. The conclusions of this systematic review were that comparative studies have not demonstrated long-term benefits of PBT for any indication, although there is potential for increased late toxicity from PBT compared with IMRT and 3D-CRT for breast, esophageal, prostate, and spinal cord glioma cancers.

In 2014, the Washington State Health Care Authority published a technology assessment by the ICER addressing the effectiveness, safety, and harms of proton beam therapy.^[3] Six RCTs and 37 nonrandomized comparative studies across 19 conditions met the criteria for review. Five of the six RCTs only compared variations of PBT protocols and included no other treatment conditions. The assessment noted major quality concerns in most of the comparative studies. The above-mentioned 2017 CADTH Technology Assessment referenced the ICER assessment, and included the primary studies within that met the CADTH assessment's criteria. Therefore, only nonoverlapping studies will be discussed from the ICER assessment. Overall, this assessment concluded that for most conditions, the evidence is insufficient to recommend PBT over a comparator. Exceptions are ocular tumors, for which there is evidence of health benefit, brain/spinal and pediatric tumors, for which there is evidence of incremental health benefit, and hemangiomas and liver, lung, and prostate cancer, for which PBT is comparable to comparators.

UVEAL MELANOMAS AND SKULL-BASE TUMORS

UVEAL MELANOMA

Systematic Reviews

The 2017 CADTH Technology Assessment included two unique primary studies, analyzed in two SRs, reporting on PBT for treatment of uveal melanoma.^[1] In one study, statistically significantly lower rates of local recurrence and higher mortality rate were reported for PBT in comparison to brachytherapy for choroidal melanoma. In the other study, there were late recurrences following brachytherapy but not after PBT or helium ion RT, but statistical results were not reported. The assessment authors concluded that there were both greater and lower benefits of PBT for eye cancers.

The 2014 Washington Technology Assessment reviewed two studies on the use of PBT for ocular tumors that compared PBT alone to combination therapy including PBT.^[3] PBT was compared to PBT plus chemotherapy for uveal melanoma. Overall survival was reported and there was no statistically significant difference between groups. PBT was compared to PBT plus laser photocoagulation for choroidal melanoma. Visual acuity was reported and there was no statistically significant difference between groups.

Verma and Mehta published a systematic review of fourteen studies reporting clinical outcomes of proton beam radiotherapy (PBT) for uveal melanoma in 2016.^[4] Studies occurring between 2000 and 2015 were included; review was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Meta-analyses were not conducted due to substantial methodological heterogeneity between studies. Included studies enrolled 59 to 3088 patients, median follow-up ranged from 38 to 148 months, and most tumors were choroidal and medium to medium-large-sized, and received 50-70 Cobalt Gray equivalent dose (studies conducted more recently reported lower doses). Five-year local control, overall survival, and metastasis-free survival and disease-specific survival rates were > 90% (persisting at ten and fifteen years), 75 to 90%, and between 7 and 10%. The authors concluded that although PBT is associated with low toxicity and enucleation rates, recent developments to support radiation toxicity will aid in decreasing clinical adverse events, and overall, PBT is an excellent treatment for uveal melanomas.

In 2013 Wang published a systematic review on charged-particle (proton, helium or carbon ion) radiation therapy for uveal melanoma.^[5] The review included 27 controlled and uncontrolled studies that reported health outcomes e.g., mortality, local recurrence. Three of the studies were randomized controlled trials (RCTs). One of the RCTs compared helium ion therapy brachytherapy. The other two RCTs compared different proton beam protocols so could not be used to draw conclusions about the efficacy of charged-ion particle therapy relative to other treatments. The overall quality of the studies was low; most of the observational studies did not adjust for potential confounding variables. The analysis focused on studies of treatment-naïve patients (all but one of the identified studies). In a pooled analysis of data from nine studies, there was not a statistically significant difference in mortality with charged-particle therapy compared with brachytherapy (odds ratio [OR], 0.13; 95% confidence interval [CI], 0.01 to 1.63). However, there was a significantly lower rate of local control with charged-particle therapy compared with brachytherapy in a pooled analysis of 14 studies (OR=0.22; 95% CI, 0.21 to 0.23). There were significantly lower rates of radiation retinopathy and cataract formation in patients treated with charged-particle therapy compared with brachytherapy (pooled rates of 0.28 vs 0.42 and 0.23 vs 0.68, respectively). According to this review, there is low-quality evidence that charged-particle therapy was at least as effective as alternative therapies as primary treatment of uveal melanoma and was superior in preserving vision. The review included controlled trials and case series with more than five patients. Twelve studies met eligibility criteria. The authors did not report study type, but they did not appear to identify only controlled trials, only case series. Sample sizes ranged from 9 to 367 patients. Six studies reported a 5-year survival rates that ranged from 67% to 94%.

Randomized Controlled Trials

No randomized controlled trials not already addressed in the above systematic reviews were identified.

SKULL BASED TUMORS

A 2016 systematic review by Matloob evaluated the literature on proton beam therapy for skull-based chordomas.^[6] The review included controlled trials and case series with more than five patients. Twelve studies met eligibility criteria. The authors did not report study type, but they did not appear to identify any controlled trials, only case series. Sample sizes ranged from 9 to 367 patients. Six studies reported a five-year survival rates that ranged from 67% to 94%.

CENTRAL NERVOUS SYSTEM TUMORS

SYSTEMATIC REVIEWS AND TECHNOLOGY ASSESSMENTS

The 2017 CADTH Tech Assessment included SRs that analyzed studies on medulloblastoma, meningioma, and intramedullary spinal cord glioma.^[1] One poor quality non-randomized study compared PBT with photon RT for the treatment of medulloblastoma in adults. Low-strength evidence indicated no statistically significant differences in locoregional failure at two or five years or in progression-free survival at two years, but there was statistically significantly lower risk of one-month acute toxicity. Two poor quality non-randomized studies reported on meningioma and one on recurrent malignant brain tumors. Five-year local control was significantly higher in cases of meningioma or malignant meningioma and there were no significant differences in harms, but SR authors reported that evidence was insufficient and thus results were not definitive. A single poor-quality non-randomized study on adults and children with intramedullary spinal cord glioma reported significantly lower chances of five-year survival with PBT over IMRT but no statistically significant difference in local recurrence or metastases at a 24-month follow-up. No long-term toxicity from either treatment modality was reported.

RANDOMIZED STUDIES

Sanford (2017) randomized 47 meningioma patients (with 44 in the final analysis) to receive 55.8 Gy or 63.0 Gy of combined proton photon radiation therapy.^[7] Median follow-up was 17.1 years. At 10 years and 15 years, local control was 98% and 90%, respectively. Five patients experienced local recurrence, of which four occurred after 10 years and three received 55.8 Gy. There was no statistically significant difference between groups in progression-free survival or overall survival. Grade 2 or higher late toxicity was reported in 59% of patients. Nine of these patients incurred a cerebrovascular incident, of which seven were deemed at least possibly attributable to irradiation.

REIRRADIATION

While research is limited supporting reirradiation overall, there is a growing body of evidence supporting the ability of PBT to reduce toxicity from head and neck and CNS reirradiation. These are the most promising areas compared to historical controls.

SYSTEMATIC REVIEWS

Verma published a systematic review of 16 studies reporting clinical outcomes of PBT for reirradiation in 2017.^[8] Studies published through June 2017 were included; review was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. There were no comparative trials. Meta-analyses were not conducted due to substantial heterogeneity between studies. The following is a summary of the key findings and conclusions:

Ocular: One case series evaluated re-irradiation with PBT for uveal melanoma in 31 patients and five-year results were reported. Verma concluded that re-irradiation was well-tolerated with no major complications, but patients experienced a greater incidence of cataracts.

Adult CNS: Three case series addressed chordomas, CNS tumors broadly, and gliomas. The studies had small sample sizes with eight, 16, and 20 patients respectively in each study. The patients were re-irradiated with follow-up outcomes reported at two years, 19.4 months, and eight months. Authors of the studies concluded that results were comparable to existing data using photons. However, the three studies were non-comparative and had small sample sizes.

Pediatric CNS: Two case series were reported on pediatric CNS tumors, including ependymomas (n = 20) and a group of diverse CNS tumors (n = 12, six of which received re-irradiation with PBT). Median follow-up was 31 months and 42 months, respectively. At follow-up, four patients from the ependymoma study had recurrences. In the second case series, only half of the patients received PBT for re-irradiation but results were not reported separately by RT modality. Overall, treatment was tolerated well and toxicities were mild.

Head and Neck: Four case series were identified. One study included cancer of the oral cavity, and three studies were a variety of head and neck tumors with 34, 92, 60, and 61 patients, respectively. Grade three toxicities were observed in all four studies. Follow-up times were two years, 10 months, two years, and 15 months. Treatment-related deaths were reported in three studies.

Lung: Two case series of NSCLC were reported. In one, median time to re-irradiation was 36 months, and follow-up was 11 months. Nearly one-quarter of the 33 patients received concurrent chemotherapy. Grade 3 esophagitis, pneumonitis, and pericarditis were reported in 9, 21, and 3% of patients, respectively, and grade 4 tracheoesophageal fistula and tracheal necrosis were reported in 3 and 6% of patients, respectively. A second study reported a median time to re-irradiation of 19 months and a median follow-up of eight months. Of the 57 patients, 68% received concurrent chemotherapy. Greater toxicities were observed in this study, including 39% of patients experiencing acute grade 3+ toxicities, 12% experiencing late grade 3+ toxicities, and 10% of patients dying from toxicity, half of which were estimated to be re-irradiation related.

Gastrointestinal: Four case series of gastrointestinal neoplasms were reported. One included 14 esophageal cancer patients with a median follow-up of 10 months. Four patients experienced grade three toxicities. A seven-patient case series of re-irradiation for recurrent rectal cancer (14-month follow-up) and a 15-patient study of pancreatic cancer (16-month follow-up) were identified and both reported grade three and four toxicities. Finally, a study of 83 hepatocellular carcinoma patients with an unspecified follow-up time reported no grade three or higher toxicities.

The overall conclusions of the SR were that PBT has promise for use in reirradiation but further studies of outcomes and toxicities are needed.

NONRANDOMIZED STUDIES

A 2017 case series reported by Guttman enrolled 23 patients undergoing proton reirradiation for soft tissue sarcoma in a previously-irradiated field.^[9] For inclusion, patients' tumors were required to overlap the 50% isodose level or higher from the prior course of radiotherapy. Median time to reirradiation was 40.7 months (range 10-272). Median follow-up was 36 months. The three-year cumulative incidence of local failure was 41% (95% CI [20-63%]). Median OS and progression-free survival were 44 and 29 months, respectively. Acute grade 2 toxicities reported were fatigue (26%), anorexia (17%), and urinary incontinence (13%). One acute grade 3 dysphagia was reported. Late toxicities reported included grade 2 lymphedema (10%), fracture (5%), and fibrosis (5%), and grade 3 late wound infections (10%) and wound complications (5%). Amputation was spared in 7 of 10 extremity patients.

PEDIATRIC TUMORS

PEDIATRIC CENTRAL NERVOUS SYSTEM TUMORS

Radiation therapy is an integral component of the treatment of many pediatric central nervous system (CNS) tumors including high-grade gliomas, primitive neuroectodermal tumors (PNETs), medulloblastomas, ependymomas, germ cell tumors, some craniopharyngiomas, and subtotally resected low-grade astrocytomas.^[10] Children who are cured of their tumor experience long-term sequelae of radiation treatment, which may include developmental, neurocognitive, neuroendocrine, and hearing late effects. Radiation to the cochlea may lead to loss of hearing at doses greater than 35-45 Gy in the absence of chemotherapy and the risk of ototoxicity is increased in children who receive ototoxic platinum-based chemotherapy regimens.^[11] Craniospinal irradiation, most commonly used in the treatment of medulloblastoma, has been reported to lead to thyroid dysfunction and damage to the lungs, heart and gastrointestinal tract. In addition, patients who receive radiation at a young age are at an increased risk of developing radiation-induced second tumors compared to their adult counterparts.

The development of more conformal radiation techniques has decreased inadvertent radiation to normal tissues; however, while intensity-modulated radiation therapy (IMRT) decreases high doses to nearby normal tissues, it delivers a larger volume of low- and intermediate-dose radiation. Proton beam radiotherapy eliminates the exit dose to normal tissues and may eliminate ~50% of radiation to normal tissue.

Systematic Reviews and Technology Assessments

The 2017 CADTH TEC Assessment included one study on children with craniopharyngioma that compared PBT and IMRT.^[1] The evidence was very low quality and indicated no statistically significant differences in three-year overall or disease-free survival. No differences were reported for treatment-related harms.

A 2017 systematic review of craniospinal irradiation in pediatric medulloblastoma was reported by Ho.^[12] The fifteen studies that met inclusion criteria were rated for quality using the Downs & Black checklist. One study was rated as good, two were rated as poor, and the rest were rated as fair quality. A meta-analysis was not conducted due to small sample size, heterogeneity in study objectives, and differences in included analyses. Eight studies reporting comparisons of dose distribution between protons and photons all reported better overall dose distribution for protons. Results regarding target conformity and homogeneity were mixed. All seven studies that examined sparing of out-of-field organs reported superiority of PBT, with the exception of lung doses. This lack of difference in lungs was driven by girls, and the authors

suggested that this is due to the smaller size of girls, resulting in a larger proportion of their lungs being irradiated. Normal organ dysfunction risks were reported to be lower for protons than photons. Risk of second malignancy was also reported to be lower for protons than photons for most organs.

In 2016, Leroy published a systematic review of the literature on PBT for treatment of pediatric cancers.^[13] Their findings on pediatric CNS tumors include the following:

Craniopharyngioma: Three studies were identified, two retrospective case series and one retrospective comparative study of PBT versus IMRT. They concluded that there is very low level evidence that survival outcomes are similar with PBT and IMRT.

Ependymoma: One prospective case series and one retrospective case series were identified. They concluded that the evidence is insufficient to support or refute the use of PBT for this condition.

Medulloblastoma: One prospective case series and two retrospective case series were identified. They concluded that the evidence is insufficient to support or refute the use of PBT for this condition.

CNS germinoma: One retrospective case series was identified. They concluded that the evidence is insufficient to support or refute the use of PBT for this condition.

An initial systemic review^[14] and a 2012 5-year updated systematic review^[15] drew similar conclusions, that except for rare indications such as childhood cancer, the gain from proton radiation therapy (RT) in clinical practice remains controversial.

In 2012 Cotter published a review of the literature on the use of proton radiotherapy for solid tumors of childhood, the most common of which are CNS tumors, offered the following summaries of studies and conclusions:^[16]

Experience with the use of proton beam therapy for medulloblastoma, the most common malignant CNS tumor in the pediatric population, is relatively large. Although data on the late effects comparing proton to photon therapy are still maturing, dosimetric studies suggest that proton therapy in medulloblastoma should lead to decreased long-term toxicity.

Gliomas in locations where surgical resection can lead to unacceptable morbidity (e.g. optic nerves or chiasm, brainstem, diencephalon, cervical-medullary junction), are often treated with chemotherapy in young patients in order to delay radiation, with radiation to a dose of 54 Gy being reserved for unresectable lesions.

Loma Linda University Medical Center reported on proton radiation in the treatment of low-grade gliomas in 27 pediatric patients.^[17] Six patients experienced local failure; acute side effects were minimal. After a median follow-up of three years, all of the children with local control maintained performance status.

A dosimetric comparison of protons to photons for seven optic pathway gliomas treated at Loma Linda showed a decrease in radiation dose to the contralateral optic nerve, temporal lobes, pituitary gland and optic chiasm with the use of protons.^[18]

Massachusetts General Hospital reported on the use of protons in 17 children with ependymoma.^[19] Radiation doses ranged from 52.2 to 59.4 cobalt Gy equivalent. Median follow-up was 26 months, and local control, progression-free survival, and overall survival rates were 86%, 80%, and 89%, respectively. Local recurrences were seen in patients who had undergone subtotal resections. No deleterious acute effects were noted; the authors stated that longer follow-up was necessary to assess late effects. In the same study, two IMRT plans were generated to measure for dosimetric advantages with the use of protons for the treatment of infratentorial and supratentorial ependymomas. In both locations, the use of proton radiation provided significant decrease in dose to the whole brain, and specifically the temporal lobes. In addition, as compared to IMRT, proton radiation better spared the pituitary gland, hypothalamus, cochlea, and optic chiasm, while providing equivalent target coverage of the resection cavity.

Craniopharyngiomas are benign lesions, which occur most commonly in children in the late first and second decades of life.

MD Anderson Cancer Center and Methodist Hospital in Houston reported on 52 children treated at two centers in Texas; 21 received PBT and 31 received IMRT.^[20] Patients received a median dose of 50.4 Gy. At three years, OS was 94.1% in the PBT group and 96.8% in the IMRT group ($p=0.742$). Three-year nodular and cystic failure-free survival rates were also similar between groups. Seventeen patients (33%) were found on imaging to have cyst growth within three months of RT and 14 patients had late cyst growth (more than three months after therapy); rates did not differ significantly between groups. In 14 of the 17 patients with early cyst growth, enlargement was transient.

Massachusetts General Hospital reported on five children treated with combined photon/proton radiation or proton radiation alone with a median follow-up of 15.5 years.^[21] All five patients achieved local control without evidence of long-term deficits from radiation in endocrine or cognitive function.

Loma Linda reported on the use of proton radiation in 16 patients with craniopharyngioma who were treated to doses of 50.4-59.4 cobalt Gy equivalent.^[22] Local control was achieved in 14 of the 15 patients with follow-up data. Follow-up was five years; three patients died, one of recurrent disease, one of sepsis, and one of a stroke. Among the survivors, one patient developed panhypopituitarism 36 months after debulking surgeries and radiation, a second patient had a cerebrovascular accident 34 months after combined primary treatment, and a third patient developed a meningioma 59 months after initial photon radiation, followed by salvage resection and proton radiation.

Massachusetts General Hospital reported on the use of protons in the treatment of germ cell tumors in 22 patients, 13 with germinoma and nine with non-germinomatous germ cell tumors (NGGCTs).^[23] Radiation doses ranged from 30.6 to 57.6 cobalt Gray equivalents. All of the NGGCT patients received chemotherapy prior to radiation therapy. Twenty-one patients were treated with cranial spinal irradiation, whole ventricular radiation therapy, or whole brain radiation followed by an involved field boost; one patient received involved field alone. Median follow-up was 28 months. There were no central nervous system (CNS) recurrences and no deaths. Following radiation therapy, two patients developed growth hormone deficiency, and two patients

developed central hypothyroidism. The authors stated that longer follow-up was necessary to assess the neurocognitive effects of therapy. In the same study, a dosimetric comparison of photons and protons for representative treatments with whole ventricular and involved field boost was done. Proton radiotherapy provided substantial sparing to the whole brain and temporal lobes, and reduced doses to the optic nerves.

Merchant sought to determine whether proton radiotherapy has clinical advantages over photon radiotherapy in childhood brain tumors.^[24] Three-dimensional imaging and treatment-planning data, which included targeted tumor and normal tissues contours, were acquired for 40 patients. Histologic subtypes in the 40 patients were 10 each with optic pathway glioma, craniopharyngioma, infratentorial ependymoma, or medulloblastoma. Dose-volume data were collected for the entire brain, temporal lobes, cochlea, and hypothalamus, and the data were averaged and compared based on treatment modality (protons vs. photons) using dose-cognitive effects models. Clinical outcomes were estimated over five years. With protons (compared to photons), relatively small critical normal tissue volumes (e.g. cochlea and hypothalamus) were spared from radiation exposure when not adjacent to the primary tumor volume. Larger normal tissue volumes (e.g. supratentorial brain or temporal lobes) received less of the intermediate and low doses. When these results were applied to longitudinal models of radiation dose-cognitive effects, the differences resulted in clinically significant higher IQ scores for patients with medulloblastoma and craniopharyngioma and academic reading scores in patients with optic pathway glioma. There were extreme differences between proton and photon dose distributions for the patients with ependymoma, which precluded meaningful comparison of the effects of protons versus photons. The authors concluded that the differences in the overall dose distributions, as evidenced by modeling changes in cognitive function, showed that these reductions in the lower-dose volumes or mean dose would result in long-term, improved clinical outcomes for children with medulloblastoma, craniopharyngioma, and glioma of the optic pathway.

One additional published study was not addressed in the Cotter systematic review. Moeller reported on 23 children who were enrolled in a prospective observational study and treated with proton beam therapy for medulloblastoma between the years 2006-2009.^[25] As hearing loss is common following chemoradiotherapy for children with medulloblastoma, the authors sought to compare whether proton radiotherapy led to a clinical benefit in audiometric outcomes (since compared to photons, protons reduce radiation dose to the cochlea for these patients). The children underwent pre- and 1-year post-radiotherapy pure-tone audiometric testing. Ears with moderate-to-severe hearing loss prior to therapy were censored, leaving 35 ears in 19 patients available for analysis. The predicted mean cochlear radiation dose was 30 60Co-Gy Equivalents (range 19-43). Hearing sensitivity significantly declined following radiotherapy across all frequencies analyzed ($p < 0.05$). There was partial sparing of mean post-radiation hearing thresholds at low-to-midrange frequencies; the rate of high-grade (grade 3 or 4) ototoxicity at one year was 5%. The authors compared this to a rate of grade 3-4 toxicity following IMRT of 18% in a separate case series. The authors concluded that preservation of hearing in the audible speech range, as observed in their study, may improve both quality of life and cognitive functioning for these patients.

RETINOBLASTOMA

Retinoblastoma is a rare (approximately 300 new cases per year in the U.S.) childhood malignancy that usually occurs in children under five years of age. External beam radiation

therapy (EBRT) is an effective treatment for retinoblastoma, but had fallen out of favor due to the adverse effects on adjacent normal tissue. With the increasing availability of more conformal EBRT techniques, there has been renewed interest in EBRT for retinoblastoma. As noted previously, proton therapy eliminates the exit dose of radiation to normal tissues and may eliminate ~50% of radiation to normal tissue.

Current evidence from small studies has consistently reported decreased radiation exposure with proton therapy compared to other EBRT. Because this tumor is rare, it seems unlikely that large comparative trials will ever become available. The following is a summary of currently available published evidence:

The 2017 CADTH Tech Assessment included an SR that reported that very low-quality evidence from one poor-quality non-randomized study indicated that PBT was associated with statistically significantly lower 10-year RT-induced or in-field secondary malignancy than photon RT, with the caveat that longer follow-up was needed.^[1]

Lee reported on a small retrospective study of eight children with malignancies, including three cases of retinoblastoma, comparing proton therapy with 3D-CRT, IMRT, single 3D lateral beam, and 3D anterolateral beam with and without lens block.^[26] Proton therapy resulted in better target coverage and less orbital bone radiation exposure (10%, 25%, 69%, 41%, 51%, and 65%, respectively). The authors concluded that proton therapy should be considered as the preferred technique for radiation therapy.

Krengli compared various intraocular retinoblastoma locations and proton beam arrangements.^[27] Only 15% of orbital bone received doses higher than 20 Gy, with no appreciable dose to the contralateral eye, brain, or pituitary gland.

Chang reported on proton beam therapy in three children with retinoblastomas that were resistant to chemotherapy and focal treatment.^[28] All three showed tumor regression with proton therapy, though two eventually had recurrence resulting in enucleation.

Munier reported successful outcomes in six patients who received proton therapy as second-line or salvage therapy.^[29]

Since retinoblastoma is sensitive to radiation therapy, EBRT may eliminate or delay the need for enucleation and improve survival, particularly in patients who have not responded adequately to chemotherapy. Due to the close proximity of these tumors to vital eye structures, the orbital bone, and the brain, inadvertent radiation to normal tissues must be minimized. Proton therapy has the potential to reduce long-term side effects, as dosimetric studies of proton therapy compared with best available photon-based treatment have shown significant dose-sparing to normal tissue.

OTHER PEDIATRIC TUMORS

There is scant data on the use of proton beam therapy in other pediatric tumors and includes dosimetric planning studies in a small number of pediatric patients with parameningeal rhabdomyosarcoma^[30] and late toxicity outcomes in other solid tumors of childhood.^[31,32]

PROSTATE CANCER

The published literature indicates that dose escalation is an accepted concept in treating organ-confined prostate cancer.^[33] The morbidity related to radiation therapy of the prostate is focused on the adjacent bladder and rectal tissues; therefore, dose escalation is only possible if these tissues are spared. Even if intensity modulated radiation therapy (IMRT) or three-dimensional conformal radiotherapy (3D-CRT) permits improved delineation of the target volume, if the dose is not accurately delivered, the complications of dose escalation can be serious, as the bladder and rectal tissues would be exposed to even higher radiation doses. The accuracy of dose delivery applies to both conventional and proton beam therapy.^[34]

SYSTEMATIC REVIEWS AND TECHNOLOGY ASSESSMENTS

The 2017 CADTH Tech Assessment addressed the use of proton beam therapy for prostate cancer.^[1] Results were reported on survival and quality of life from seven non-randomized studies of poor-quality or fair quality comparing PBT with 3DCRT, IMRT, photon RT, PBT in combination with photon RT, and brachytherapy. One included study was also analyzed in the 2014 AHRQ assessment discussed below. Statistically significant decreases in bowel, but not urinary, quality of life (QoL) from baseline after PBT or 3DCRT were reported. Compared to other treatment modalities, no statistically significant differences were reported in two-year bowel, urinary, or sexual QoL or four-year QoL associated with urinary incontinence or erectile dysfunction diagnosis, or distant metastases. Eight-year local control was statistically significantly greater in poorly-differentiated tumors when treated with PBT in combination with photon as compared to photon RT alone. Statistical testing results were not always provided.

Seven unique primary studies were included reporting on toxicities. Quality of the studies was judged to be fair, low, and very low. The statistically significant differences reported were: one-year adjusted gastrointestinal toxicity rate, which was significantly higher with PBT compared with 3D-CRT; eight-year rates of rectal bleeding and urethral stricture, which were higher with PBT in combination with photon RT compared to photon RT alone; lower 46- to 50- month gastrointestinal procedures and diagnoses rates and significantly higher five-year adjusted gastrointestinal toxicity with PBT compared with IMRT; and higher rates of gastrointestinal toxicity with PBT compared with brachytherapy. Toxicities reported as not statistically significant between RT modalities included gastrointestinal and genitourinary toxicity, erectile dysfunction, hip fracture, and urinary incontinence procedures or diagnoses rates (versus IMRT) and gastrointestinal, sexual, rectal or urinary toxicity, gross hematuria (PBT plus photon versus photon RT alone). The assessment authors concluded that for PBT there were greater harms for prostate cancer and greater benefits for poorly-differentiated tumors of the prostate.

In 2014, the Agency for Healthcare Research and Quality (AHRQ) published an updated review of the risk and benefits of a number of therapies for localized prostate cancer.^[35] The authors compared risk and benefits of a number of treatments for localized prostate cancer including radical prostatectomy, EBRT (standard therapy as well as PBT, 3D conformal RT, IMRT and stereotactic body radiotherapy [SBRT]), interstitial brachytherapy, cryotherapy, watchful waiting, active surveillance, hormonal therapy, and high-intensity focused ultrasound. The review concluded that the evidence for most treatment comparisons is inadequate to draw conclusions about comparative risks and benefits. Limited evidence appeared to favor surgery over watchful waiting or EBRT, and RT plus hormonal therapy over RT alone. The authors noted that there are advances in technology for many of the treatment options for clinically localized prostate cancer; for example, current RT protocols allow higher doses than those administered in many of the trials included in the report. Moreover, the patient population has changed since most of the studies were conducted. In recent years, most patients with

localized prostate cancer are identified via prostate-specific antigen (PSA) testing and may be younger and healthier than prostate cancer patients identified in the pre-PSA era. Thus, the authors recommend additional studies to validate the comparative effectiveness of emerging therapies such as PBT, robotic-assisted surgery and SBRT.

There are several older systematic reviews and technology assessments on PBT for prostate cancer.^[36-39] They do not include the newer comparative studies that have been done on this technology.

NONRANDOMIZED STUDIES

No nonrandomized studies not addressed in the above systematic reviews were identified.

HEAD AND NECK TUMORS OTHER THAN SKULL-BASE TUMORS

In treating head and neck cancer other than skull-based tumors, the data from comparative studies are lacking and noncomparative data are insufficient.

SYSTEMATIC REVIEWS AND TECHNOLOGY ASSESSMENTS

The 2017 CADTH TEC Assessment found no relevant SRs reporting on benefits of PBT for head and neck cancer.^[41] A single fair quality unique primary study on harms was identified. It reported that PBT and carbon ion RT resulted in similar rates of vision loss, but statistical testing results were not provided.

A 2014 systematic review evaluated the literature on charged-particle therapy versus photon therapy for the treatment of paranasal sinus and nasal cavity malignant disease.^[40] The authors identified 41 observational studies that included 13 cohorts treated with charged-particle therapy (total N=286 patients) and 30 cohorts treated with photon therapy (total N=1186 patients). There were no head-to-head trials. In a 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 (RR=1.27; 95% CI, 1.01 to 1.59). Findings were similar for the outcome survival at five years (RR=1.51; 95% CI, 1.14 to 1.99). Findings were mixed for the outcomes locoregional control and disease-free survival; photon therapy was significantly better for only one of the two timeframes (longest follow-up or 5-year follow-up). In terms of adverse effects, there were significantly more neurologic toxic effects with charged-particle therapy compared with photon therapy ($p<0.001$) but other toxic adverse event rates e.g., eye, nasal and hematologic did not differ significantly between groups. The authors noted that the charged-particle studies were heterogeneous, e.g., type of charged-particles (carbon ion, proton), delivery techniques. It should also be noted that comparisons were indirect, and none of the studies included in the review compared the two types of treatment in the same patient sample.

NONRANDOMIZED STUDIES

A 2017 analysis reported by Lin utilized data from 580 esophageal cancer patients receiving neoadjuvant chemoradiation.^[41] These data included outcomes from 214 3D-CRT-treated patients, 255 IMRT-treated patients, and 111 PBT-treated patients. Statistical analyses, including multivariate analysis, indicated that RT modality was significantly associated with the incidence of pulmonary, cardiac, and wound complications, with better outcomes associated with PBT. Mean length of stay was also significantly associated with treatment modality (13.2 days for 3D [95%CI 11.7-14.7], 11.6 days for IMRT [95%CI 10.9-12.7], and 9.3 days for PBT

[95%CI 8.2-10.3], $p < 0.0001$), but 90-day postoperative mortality rates were not (4.2%, 4.3%, and 0.9%, respectively, for 3D, IMRT and PBT, $p = 0.264$).

In 2014, Zenda reported on late toxicity in 90 patients after PBT for nasal cavity, paranasal sinuses, or skull base malignancies.^[42] Eighty seven of the 90 patients had paranasal sinus or nasal cavity cancer. The median observation period was 57.5 months. Grade 3 late toxicities occurred in 17 patients (19%) and grade 4 occurred in six patients (7%). Five patients developed cataracts, and five had optic nerve disorders. Late toxicities (other than cataracts) developed a median of 39.2 months after PBT.

NON-SMALL CELL LUNG CANCER (NSCLC)

SYSTEMATIC REVIEWS AND TECHNOLOGY ASSESSMENTS

The 2017 CADTH TEC Assessment included two unique primary studies reporting on PBT for treatment of NSCLC, one of them specifically addressing locally advanced, unresectable NSCLC.^[1] Tumour or cancer control, overall survival, and progression-free survival between PBT and carbon ion RT were reported as well as toxicities, including acute severe esophagitis, pneumonitis, dermatitis, fatigue, and rib fracture. No statistically significant differences were reported. The assessment concluded that PBT was comparable to alternative forms of RT for the treatment of NSCLC.

In 2017, Chi published a systematic review that assessed the efficacy of hypo-fractionated particle beam therapy compared to photon SBRT for early stage NSCLC.^[43] Included in the systematic review and meta-analysis were 72 SBRT studies and nine hypo-fractionated PBT studies. Included studies were not rated for quality. A statistically significant association was reported between PBT and improved OS ($p = 0.005$) and between PBT and PFS ($p = 0.01$). In an analysis of the influence of study characteristics on study outcome, OS was shown to be significantly influenced by treatment type and functional performance status. However, when operability was included in the analysis, the OS benefit was not statistically significant.

Pijls-Johannesma conducted a 2010 systematic literature review examining the evidence on the use of charged-particle therapy in lung cancer.^[44] Study inclusion criteria included series with at least 20 patients and a minimum follow-up period of 24 months. Eleven studies all dealing with NSCLC, mainly stage I, were included in the review, five investigating protons ($n = 214$) and six investigating C-ions ($n = 210$). The proton studies included one phase 2 study, two prospective studies, and two retrospective studies. The C-ion studies were all prospective and conducted at the same institution in Japan. No phase 3 studies were identified. Most patients had stage 1 disease; however, a wide variety of radiation schedules, along with varied definitions of control rates were used, making comparisons of results difficult. For proton therapy, two- to five-year local tumor control rates varied in the range of 57%–87%. The two- and five-year overall survival (OS) rates were 31%–74% and 23%, respectively, and two- and five-year cause-specific survival (CSS) rates were 58%–86% and 46%, respectively. These local control and survival rates are equivalent to or inferior to those achieved with stereotactic radiation therapy. Radiation-induced pneumonitis was observed in about 10% of patients. For C-ion therapy, the overall local tumor control rate was 77%, but it was 95% when using a hypofractionated radiation schedule. The five-year OS and CSS rates were 42% and 60%, respectively. Slightly better results were reported when using hypofractionation, 50% and 76%, respectively. The authors concluded that the results with protons and heavier charged particles are promising, but that because of the lack of evidence, there is a need for further investigation in an adequate manner with well-designed trials.

A 2010 BCBSA TEC Assessment concluded there was insufficient evidence to make conclusions about the use of PBT for NSCLC, citing a lack of randomized controlled trials.^[45] More recent evidence is included in the CADTH assessment above.

NONRANDOMIZED STUDIES

Few studies have been published that directly compare health outcomes in patients with NSCLC treated with PBT versus an alternative treatment. A 2017 study by Niedzielski retrospectively reviewed data from a randomized trial to analyze toxicity from radiation therapy in NSCLC patients.^[46] Of the 134 patients in the study, 49 were treated with protons and 85 were treated with IMRT. Inter-group comparisons were made for a previously validated esophageal toxicity imaging biomarker, esophageal expansion quantified during radiation therapy, and esophagitis grade. No statistically significant differences were reported.

In another 2017 study, Remick reported a comparison of 27 patients receiving PBT and 34 receiving IMRT as postoperative radiation therapy for locally advanced NSCLC with positive microscopic margins and/or positive N2 lymph nodes (stage III).^[47] Median follow-up time was 23.1 and 27.9 months for PBT and IMRT, respectively. There was not a statistically significant difference between groups for one-year median overall survival (PBT 85.2%; IMRT 82.4%) or local recurrence-free survival (PBT 92.3%; IMRT 93.3%). Grade 3 radiation esophagitis was reported in one PBT patient and four IMRT patients. Grade 3 radiation pneumonitis was reported in one patient in each group.

Other studies have reported outcomes following PBT without comparisons to alternative treatments. In 2018, Chang reported five-year results of a prospective single-arm study of concurrent chemotherapy (carboplatin-paclitaxel) and high-dose passively scattered PBT (74-Gy relative biological effectiveness) for unresectable stage III NSCLC.^[48] A total of 64 patients were enrolled and analyzed. Median follow-up was 27.3 months for all patients and 79.6 months for survivors. Median OS was 26.5 months (five-year OS, 29%; 95% CI, 18%-41%), five-year PFS was 22% (95% CI, 12%-32%), and five-year actuarial distant metastasis and locoregional recurrence were 54% (n = 36) and 28% (n = 22), respectively. Rates of crude local and regional recurrences were 15% and 14%, respectively. Acute toxicities reported were grade 2 and 3 acute esophagitis (28 and 8%, respectively) and acute pneumonitis (2%). Late toxicities reported were grade 2 and 3 pneumonitis (16% and 12%, respectively), grade 2 bronchial stricture (3%) and grade 4 bronchial fistula (2%). No grade 5 toxicities were reported.

In 2013, Bush published data on a relatively large series of patients (n=111) treated at one U.S. facility over 12 years.^[49] Patients had NSCLC that was inoperable (or refused surgery) and were treated with high-dose hypofractionated PBT to the primary tumor. Most patients (64%) had stage II disease and the remainder had stage I disease. The four-year actuarial OS rate was 51% and the CSS rate was 74%. The subgroup of patients with peripheral stage I tumors treated with either 60 or 70 Gy had an OS of 60% at four years. In terms of adverse events, four patients had rib fractures determined to be related to treatment; in all cases, this occurred in patients with tumors adjacent to the chest wall. The authors noted that a 70-Gy regimen is now used to treat stage I patients at their institution. The lack of comparison group does not permit conclusion about the effectiveness and toxicity of PBT compared with alternative therapies.

BREAST CANCER

SYSTEMATIC REVIEWS

Kammerer (2018) published a systematic review of studies evaluating the use of PBT for locally advanced breast cancer.^[50] Of the 13 articles that met inclusion criteria, six used passive double scatter, five used pencil beam scanning, and two used a combination of both. Study quality was not assessed. Two studies, with 20 and 11 patients, compared target planned target coverage between proton therapy, IMRT, and 3D. IMRT and PBT had better target coverage than 3D. Three studies with 10 patients each and one case report were included comparing sparing of organs at risk using dosimetry. In these studies, PBT resulted in superior sparing of organs at risk. Three studies, with 12, 93 (21 of whom received protons), and 30 patients, compared acute toxicities in patients receiving irradiation of chest wall/ breast, and nodal areas. One study using passive proton therapy for adjuvant treatment of chest wall and nodal areas reported no grade III, nine patients with grade II, and three patients with grade I skin toxicity. A second study using pencil beam scanning and passive proton therapy compared to 3D radiotherapy for adjuvant breast and chest wall radiotherapy. This study reported grade I, II, and III toxicities but did not report statistical comparisons. A third study using passive proton therapy for post-operative irradiation of breast and chest wall with regional lymph nodes reported one grade III toxicity. No studies assessing late cardiac toxicity were identified.

The CADTH TEC assessment reported one study with low-strength evidence indicating statistically significant higher risk of seven-year skin toxicity associated with PBT over 3D-CRT, and no statistically significant differences in seven-year local recurrences between PBT and 3D-CRT in adults with stage I breast cancer or in occurrences of fat necrosis or moderate/severe fibrosis, moderate/severe breast pain, or rib fracture.

LIVER CANCER

SYSTEMATIC REVIEWS

In 2018, Igaki published a systematic review of charged-particle therapy for hepatocellular carcinoma.^[51] Only the MEDLINE database was searched and no analysis of publication bias was performed. Included publications were not assessed for quality and no meta-analysis was conducted. Eleven papers met inclusion criteria which included 13 cohorts. Of the 13 cohorts, nine were PBT-treated and four were carbon ion-treated; 10 were prospective clinical trials and three were retrospective case series. Primary outcomes reported were local control, overall survival, and late radiation morbidities. The range of crude and actuarial local control rates at three years was 67-93% and 71.4-95%, respectively. Overall survival among studies that reported five-year results was 25-42.3%. One RCT compared PBT to transarterial chemoembolization (TACE). The interim results reported showed overall survival was not significantly different between PBT and TACE at two years. A total of 18 grade 3 or greater late adverse events were reported, although most cohorts had no severe morbidities.

The 2017 CADTH TEC Assessment included three unique primary studies of varying quality reported on PBT for treatment of adults with liver cancer and liver metastases.^[1] PBT and carbon ion RT were similar in local control and overall survival at 1.5 to 2 years, and in toxicities, but statistical testing results were not reported.

NONRANDOMIZED STUDIES

In 2004 Bush published a case series of patients with locally unresectable hepatocellular carcinoma.^[52] A total of 34 patients with a mean age of 65 years completed treatment with 63Gy over three weeks. Three patients experienced duodenal or colonic bleeding when the

bowel was immediately adjacent to the treated tumor. Additional posttreatment toxicity reported included a small but significant decline in albumin levels and increased total bilirubin. Two-year actuarial local control was 75% and two-year actuarial overall survival was 55%.

OTHER INDICATIONS

Current research on the use of charged-particle radiation therapy for other indications is limited. A number of case series describe initial results using proton beam therapy for a variety of indications including but not limited to gastrointestinal neoplasms, uterine, age-related macular degeneration, and axial skeletal tumors.^[52-68] The combination of proton beam radiotherapy with transpupillary thermotherapy in the treatment of ocular melanoma is being studied.^[69]

The 2017 CADTH TEC Assessment included limited evidence from comparative studies regarding several other cancers:^[1]

Esophageal cancer: Two unique studies reported on benefits and four on harms of PBT in esophageal cancer, reported in one and two SRs, respectively. The SRs reported no differences in benefits, with analyses of 90-day mortality, overall survival, and disease-specific survival. No statistically significant differences were reported in a number of toxicities, but PBT was associated with lower risk of 30-day pulmonary post-operative complications and higher risk of acute pneumonitis compared with 3D-CRT and 3D-CRT and IMRT analyzed together, respectively. PBT was also associated with lower risk of grade ≥ 2 nausea, fatigue, and hematologic toxicity; and pulmonary, wound, or total, but not cardiac or gastrointestinal, post-operative complications, all over an unknown duration. The data was reported to be of unknown quality.

Bone Cancer: Only one poor quality study was available, which reported no significant differences in distant metastases or progression-free survival between PBT plus photon RT and PBT alone at a median follow-up of nine years.

SRS AND SBRT/SABR USING CHARGED-PARTICLE IRRADIATION

Current research on the use of charged-particle radiation therapy for stereotactic radiosurgery (SRS) or stereotactic body radiotherapy (SBRT)/stereotactic ablative radiotherapy (SABR) is limited. Evidence includes retrospective case series of proton SRS/SBRT for brain metastases,^[70] liver metastases,^[71] pediatric patients with AVMs,^[72] and high-risk cerebral AVMs.^[73]

PRACTICE GUIDELINE SUMMARY

NATIONAL COMPREHENSIVE CANCER NETWORK

The National Comprehensive Cancer Network (NCCN) Guidelines for Bone Cancer (1.2019) state “specialized techniques such as intensity-modulated radiotherapy (IMRT), particle beam RT with protons, carbon ions or other heavy ions; stereotactic radiosurgery; or fractionated stereotactic RT should be considered as indicated in order to allow high-dose therapy while maximizing normal tissue sparing.”^[74]

The NCCN Guidelines for Prostate Cancer (4.2018) state “Photon or proton beam radiation are both effective at achieving highly conformal radiotherapy with acceptable and similar biochemical control and long-term side effect profiles.”^[75] They further state “The costs

associated with proton beam facility construction and proton beam treatment are high compared with the expense of building and using the more common photon linear accelerator based practice,” and “The NCCN panel believes no clear evidence supports a benefit or decrement to proton therapy over IMRT for either treatment efficacy or long-term toxicity. Conventionally fractionated prostate proton therapy can be considered a reasonable alternative to x-ray-based regimens at clinics with appropriate technology, physics, and clinical expertise.”

The NCCN Guidelines for Central Nervous System Cancers (1.2018) includes a footnote stating “To reduce toxicity from craniospinal irradiation in adults, consider the use of intensity-modulated radiotherapy or protons if available...”^[76]

The NCCN Guidelines for Non-Small Cell Lung Cancer (1.2019) state that, more advanced technologies, including proton therapy, “are appropriate when needed to deliver curative RT safely. . . Nonrandomized comparisons of using advanced technologies versus older techniques demonstrate reduced toxicity and improved survival.”^[77] No comparative studies are cited with this discussion point.

The NCCN Guidelines for Esophageal and Esophagogastric Junction Cancers (2.2018), B-Cell Lymphomas (4.2018), and Soft Tissue Sarcoma (2.2018) all include statements indicating that advanced conformal radiation techniques can be used in certain clinical situations to improve the therapeutic ratio or spare important organs at risk.^[78-80]

AMERICAN SOCIETY OF RADIATION ONCOLOGY

The American Society of Radiation Oncology (ASTRO) published an updated Proton Beam Therapy Model Policy in 2017 which is not a clinical practice guideline.^[81] This recommendation is not based on a systematic review of the evidence and the quality of evidence was not assessed for risk of bias. Indications for which the recommendation supports the use of PBT include the following: Malignant and benign primary central nervous system (CNS) tumors; advanced (e.g., T4) and/or unresectable head and neck cancers; cancers of the paranasal sinuses and other accessory sinuses; nonmetastatic retroperitoneal sarcomas; reirradiation cases where cumulative critical structure dose would exceed tolerance dose; hepatocellular cancer; ocular tumors, including intraocular melanomas; tumors that approach or are located at the base of skull, including but not limited to chordoma and chondrosarcomas; primary or metastatic tumors of the spine where the spinal cord tolerance may be exceeded with conventional treatment or where the spinal cord has previously been irradiated; primary or benign solid tumors in children treated with curative intent and occasional palliative treatment of childhood tumors when criteria apply; patients with genetic syndromes making total volume of radiation minimization crucial, such as but not limited to NF-1 patients and retinoblastoma patients.

A literature review with clinical recommendations from ASTRO considered the use of charged-particle therapy in several indications, including uveal melanoma.^[82] The society concluded that “[Charged particle therapy] has been shown to be effective in the treatment of large ocular melanomas not approachable via brachytherapy.” Nevertheless, due to the absence of a clear appraisal of the literature, these recommendations are considered consensus-based.

AMERICAN SOCIETY OF CLINICAL ONCOLOGY

A 2018 clinical practice guideline from the American Society of Clinical Oncology (ASCO) on the treatment of malignant pleural mesothelioma states that for adjuvant or neoadjuvant hemithoracic radiation therapy, “proton therapy may be considered in centers with significant experience, preferably in the context of a clinical trial.”^[83]

AMERICAN COLLEGE OF RADIOLOGY

The American College of Radiology (ACR) Appropriateness Criteria (2015) for induction and adjuvant therapy for N2 NSCLC state that the utility of intensity-modulated radiation therapy (IMRT) or protons to potentially reduce normal tissue toxicity remains to be explored.^[84]

The 2014 ACR Appropriateness Criteria® concluded that “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.^[85] Further studies are needed to clearly define its role for such treatment.”

The ACR Appropriateness Criteria® for nonsurgical treatment for locally advanced non-small cell lung cancer: good performance status/definitive intent (2014); postoperative adjuvant therapy in NSCLC (2011); and nonsurgical treatment for non-small-cell lung cancer: poor performance status or palliative intent (2009) do not include charged-particle radiation therapy as an appropriate treatment for non-small cell lung cancer.^[86-88]

INTERNATIONAL PARTICLE THERAPY CO-OPERATIVE GROUP

A 2016 consensus statement by the International Particle Therapy Co-operative Group made the following conclusion about proton therapy for non-small-cell lung cancer (NSCLC).^[89] The statement is based on expert consensus opinion:

“...Promising preliminary clinical outcomes have been reported for patients with early-stage or locally advanced NSCLC who receive proton therapy. However, the expense and technical challenges of proton therapy demand further technique optimization and more clinical studies....”

SUMMARY

OCULAR TUMORS

There is enough research to show reduced harms when using charged-particle irradiation such as proton beam therapy compared to other modalities for ocular tumors. Therefore, the use of charged-particle irradiation such as proton beam therapy may be considered medically necessary to treat ocular tumors when policy criteria are met.

CENTRAL NERVOUS SYSTEM TUMORS

There is enough research to show reduced harms when using charged-particle irradiation such as proton beam therapy compared to other modalities for cervical spinal cord or skull base central nervous system tumors. Therefore, the use of charged-particle irradiation such as proton beam therapy may be considered medically necessary to treat central nervous system tumors invading the base of the skull when policy criteria are met.

Research is limited regarding the clinical benefit of charged-particle irradiation such as proton beam therapy compared to other modalities in the context of radiation treatment of other regions of the adult central nervous system. However, the optic chiasm, brainstem, and cervical spinal cord are considered well-defined on cross sectional MRI, thus allowing accurate treatment planning, of crucial importance to health outcomes. Additionally, these regions have somewhat reduced radiation tolerance compared to other brain regions. Due to these features and the potential of proton beam therapy to be more precise in delivery, treatment of tumors extending to within 10 mm or less of the optic chiasm, brainstem, or cervical spinal cord at or above the foramen magnum is considered a promising clinical context for charged-particle irradiation such as proton beam therapy and may be considered medically necessary when policy criteria are met.

There is not enough research to show an improvement in health outcomes using charged-particle irradiation such as proton beam therapy to treat central nervous system tumors not meeting criteria. Therefore, the use of charged-particle irradiation such as proton beam therapy to treat central nervous system tumors not meeting criteria is considered investigational.

PRIOR RADIATION

Research is limited supporting charged-particle irradiation such as proton beam therapy for reirradiation overall. However, there is a growing body of evidence supporting the ability of proton beam therapy to reduce toxicity from reirradiation of head and neck and the central nervous system. Therefore, charged-particle irradiation such as proton beam therapy may be considered medically necessary for head and neck or central nervous system tumors when the patient has had prior radiation in the expected treatment field and policy criteria are met.

PEDIATRIC TUMORS

For pediatric central nervous system and malignant solid tumors, there is limited research but some studies suggest reduced harms and a reduction in cancer recurrence when using charged-particle irradiation. Therefore, charged-particle irradiation such as proton beam therapy may be considered medically necessary in the treatment of pediatric central nervous system and malignant solid tumors.

There is not enough research to show an improvement in health outcomes for all other pediatric tumors. Therefore, charged-particle irradiation such as proton beam therapy is considered investigational for all other pediatric tumors when policy criteria are not met.

PROSTATE CANCER

Charged-particle irradiation, such as proton beam therapy, to treat local (clinical or pathological T1, T2, N0, M0) or locally advanced (clinical or pathological T3, T4, N0, N1, M0) prostate cancer has been shown to have comparable, but not superior, clinical outcomes compared to other irradiation approaches such as intensity modulated radiotherapy (IMRT) photon irradiation. Charged-particle irradiation with proton beam is generally significantly more costly than other irradiation approaches. Therefore, charged-particle irradiation with proton beam is considered not medically necessary in patients with local or locally advanced prostate cancer. However, given the comparable outcomes, charged-particle irradiation with proton beam to treat local or locally advanced prostate cancer may be considered medically

necessary when the requested specific course of therapy will be no more costly than IMRT photon irradiation or other irradiation approaches.

There is not enough research to show an improvement in health outcomes using charged-particle irradiation such as proton beam therapy to treat regional (locally advanced) or metastatic prostate cancer. Therefore, the use of charged-particle irradiation such as proton beam therapy to treat regional (locally advanced) or metastatic prostate cancer is considered investigational.

OTHER TUMORS

For all other tumors or indications when policy criteria are not met, there is not enough research to show improved health outcomes with charged-particle irradiation such as proton beam therapy compared to other radiotherapy techniques and therefore, are considered investigational.

PROTON BEAM FOR STEREOTACTIC RADIOSURGERY OR STEREOTACTIC BODY RADIOTHERAPY/STEREOTACTIC ABLATIVE RADIOTHERAPY

There is not enough research to show improved health outcomes with charged-particle irradiation such as proton beam therapy when used for stereotactic radiosurgery (SRS) or stereotactic body radiotherapy (SBRT)/stereotactic ablative radiotherapy (SABR) compared to other radiotherapy techniques. Therefore, charged-particle irradiation such as proton beam therapy used for SRS or SBRT/ SABR is considered investigational.

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CODES

NOTES: The use of proton beam or helium ion radiation therapy typically consists of a series of CPT codes describing the individual steps required; medical radiation physics, clinical treatment planning, treatment delivery and clinical treatment management. It should be noted that the code for treatment delivery primarily reflects the costs related to the energy source used, and not physician work. Unlisted procedure codes for medical radiation physics, clinical treatment planning and treatment management may be used.

The correct code to use for image fusion performed to provide enhanced delineation of target and normal critical structures is CPT code 77399 (Unlisted procedure, medical radiation physics, dosimetry and treatment devices, and special services); however, it is considered part of the treatment planning.

Treatment delivery:

The codes for treatment delivery will depend on the energy source used typically either photons or protons. For photons (i.e. with a gamma knife or LINAC device) nonspecific radiation therapy treatment delivery CPT codes may be used based on the voltage of the energy source (i.e. CPT codes 77402-77416). When proton therapy is used the following specific CPT codes are available:

Codes	Number	Description
CPT	32701	Thoracic target(s) delineation for stereotactic body radiation therapy (SRS/SBRT), (photon or particle beam), entire course of treatment

77371	Radiation therapy delivery, stereotactic radiosurgery (SRS), complete course of treatment of cranial lesion(s) consisting of 1 session; multi-source Cobalt 60 based
77372	Radiation therapy delivery, stereotactic radiosurgery (SRS), complete course of treatment of cranial lesion(s) consisting of 1 session; linear accelerator based
77373	Stereotactic body radiation therapy, treatment delivery, per fraction to 1 or more lesions, including image guidance, entire course not to exceed 5 fraction
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
77299	Unlisted procedure, therapeutic radiology clinical treatment planning
77399	Unlisted procedure, medical radiation physics, dosimetry and treatment devices, and special services
77520	Proton beam delivery, simple, without compensation
77522	Proton beam delivery; simple with compensation
77523	Proton beam delivery; intermediate
77525	Proton beam delivery; complex

NOTE: Codes for treatment delivery primarily reflects the costs related to the energy source used, and not physician work.

Clinical treatment management:

CPT	77432	Stereotactic radiation treatment management of cerebral lesion(s) (complete course of treatment consisting of one session.)
	61796	Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); 1 simple cranial lesion
	61797	Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); each additional cranial lesion, simple (List separately in addition to code for primary procedure)
	61798	Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); 1 complex cranial lesion
	61799	Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); each additional cranial lesion, complex (List separately in addition to code for primary procedure)
	61800	Application of stereotactic headframe for stereotactic radiosurgery (List separately in addition to code for primary procedure)
	63620	Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); 1 spinal lesion
	63621	Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); each additional spinal lesion (List separately in addition to code for primary procedure)
HCPCS	G0339	Image guided robotic linear accelerator-based stereotactic radiosurgery, complete course of therapy in one session, or first session of fractionated treatment.
	G0340	Image guided robotic linear accelerator-based stereotactic radiosurgery, delivery including collimator changes and custom plugging, fractionated treatment, all lesions, per session, second through fifth sessions, maximum five sessions per course of treatment

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