Regence

Charged-Particle (Proton) Radiotherapy

Effective: September 1, 2024

Next Review: June 2025
Last Review: April 2024

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 proton beam therapy (PBT), carbon, and helium ion irradiation. Helium and carbon ion irradiation are 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

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.

LIST OF INFORMATION NEEDED FOR REVIEW

REQUIRED 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.

Prostate Cancer

When Criterion II is applicable, provider attestation that proposed therapy will not be more costly than intensity modulated radiotherapy (IMRT) or other irradiation approaches is required.

CROSS REFERENCES

1. Radioembolization, Transarterial Embolization (TAE), and Transarterial chemoembolization (TACE), Medicine, Policy No. 140
2. Intensity Modulated Radiotherapy (IMRT) of the Central Nervous System (CNS), Head, Neck, and Thyroid, Medicine, Policy No. 164
3. Intensity Modulated Radiotherapy (IMRT) of the Thorax, Abdomen, and Pelvis, Medicine, Policy No. 165
4. Intensity Modulated Radiotherapy (IMRT) for Breast Cancer, Medicine, Policy No. 166
5. Intensity Modulated Radiotherapy (IMRT) for Tumors in Close Proximity to Organs at Risk, Medicine, Policy No. 167
6. Stereotactic Radiosurgery and Stereotactic Body Radiation Therapy for Intracranial, Skull Base, and Orbital Sites, Surgery, Policy No. 213
7. Stereotactic Radiosurgery and Stereotactic Body Radiation Therapy for Tumors Outside of Intracranial, Skull Base, or Orbital Sites, Surgery, Policy No. 214

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 photons 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 and systematic reviews 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.

Hwang (2020) published a systematic review of toxicity outcomes following particle therapy.[1] A total of 52 studies reporting on toxicity only and 127 studies reporting on tumor and toxicity outcomes met inclusion criteria. No new studies were identified since the search dates of the 2019 WA HCA technology assessment discussed below. Protons were evaluated in 132, carbon ions in 29, and mixed therapy in 18. Two of the included proton therapy studies were RCTs, 24 were comparative cohort studies, and the rest were observational case series. In order of number of studies, the assessed indications were pediatrics, CNS, prostate, head and neck, ocular, sarcoma, gastrointestinal, thoracic, breast, mixed tumor types, and re-irradiation. Overall, the quality of evidence was low, with the majority of studies being case series, often with low patient numbers, and many of the findings were not statistically significant.

In August 2019, the Washington State Health Care Authority (HCA) published a technology assessment by Aggregate Analytics addressing the effectiveness, safety, and harms of proton beam therapy.[2, 3] This was an update to a 2014 technology assessment contracted by the HCA and conducted by the Institute for Clinical and Economic Review (ICER). The updated review included 56 publications on pediatric tumors and 155 on adult tumors. None of the pediatric studies were RCTs, 13 were retrospective comparative cohort studies, 41 were case series, and 2 were cost-effectiveness studies. Of the studies of adult tumors, there were two RCTs, one quasi-RCT, 33 retrospective comparative cohorts, 115 case series, and 4 cost effectiveness studies. The overall quality of evidence was rated as poor. Most evidence identified was retrospective and at moderately high risk of bias. Overall, this assessment concluded that for most conditions, the evidence is insufficient to recommend PBT over a comparator. Exceptions for which there is evidence of incremental net health benefit over comparators are adult esophageal (low SOE), ocular (in limited scenarios; low SOE), and liver cancer (low to moderate SOE), and pediatric brain cancer (low SOE).

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.[4] 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.[5] Of the 25 comparative studies included in this review, 22 were included in the 2014 version of the Institute for Clinical and Economic Review (ICER) technology assessment discussed above. 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.

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.[4] 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. The 2019 updated assessment included three retrospective cohort studies with photon treatment comparators. The studies were all rated as poor quality. Two assessed patients with uveal melanoma and one with choroid melanoma. One retrospective propensity-score matched comparative cohort study with 226 patients per treatment group compared the effectiveness of proton beam therapy to brachytherapy. This study reported statistically significant difference in probability of OS at five years, with PBT associated with lower OS. The other two studies, with SRS and adjuvant brachytherapy comparators, reported effectiveness and safety. Compared with brachytherapy, PBT was associated with statistically significantly lower rates of local recurrence at 3, 5, and 10 years. The second study reported local recurrence at three years, at which time there was no statistically significant difference. No statistically significant differences in adverse events were reported. Overall, the assessment concluded that based on low SOE, PBT provides inferior net health benefit versus brachytherapy and incremental health benefit when combined with TSR versus brachytherapy plus TSR. The assessment authors concluded there was insufficient evidence to determine the net health benefit of PBT versus SRS.

Verma and Mehta published a systematic review of fourteen studies reporting clinical outcomes of proton beam radiotherapy (PBT) for uveal melanoma in 2016.[6] 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.[7] 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 five-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

Pahwa (2022) conducted a systematic review and meta-analysis to assess outcomes from primary and adjuvant PBT for skull base chordomas.[8] The review included 16 studies involving 752 patients (673 adults and 79 pediatric patients). Tumor volume heterogeneity was high (3.5 to 35.4 cm^3). The majority of patients (n=715, 95%) were treated with surgery prior to PBT. Median follow-up time was 21 to 52 months, and the mean radiation dose was 74.02 cobalt grey equivalent (cGe). Tumor shrinkage was seen on MRI in 80% of patients (n=537). Tumor recurrence occurred in 17.56% (n=118) patients and 2.53% (n=17) patients experienced tumor progression or metastasis. Four patients died due to tumor progression, 21 died from unknown causes and data was not reported for 80 patients. Data on complications was limited to 83 patients. There were no statistically significant associations between 5-year local control rate with median age (p=0.75), female percentage (p=0.70), median tumor volume (p=0.80), or mean PBT dose (0.28). Limitations of the review include the heterogeneous and

incomplete data. The authors conclude that while PBT use in the treatment of skull base chordomas is becoming more common, concerns about complication rates and cost effectiveness persist, especially for pediatric patients.

El Sayed (2021) published a systematic review of protons versus photons for the treatment of chordomas in adults.[9] A total of six studies met inclusion criteria, of which four were included in the meta-analysis. All included studies were rated as high risk of bias. The evaluated outcomes were local control (HR 5.34; 95% CI 0.66 to 43.43), mortality (HR 0.44; 95% CI 0.13 to 1.57), recurrence (HR 0.34; 95% CI 0.10 to 1.17), and treatment-related toxicity (RR 1.28; 0.17 to 9.86). All outcomes were given a certainty of evidence rating using GRADE of very low. The authors concluded that there is very low-certainty evidence to show an advantage for proton therapy compared to photon therapy for local control, mortality, recurrence, and treatment related toxicity.

In 2019, Alahmari and Temel published a systematic review of proton therapy treatment for skull base chordoma.[10] A total of 11 studies with 511 patients met inclusion criteria. During the mean follow-up of 45.0 months, 26.8% of patients experienced recurrence. The authors reported substantial variation in the methods of data reporting. No calculation of local control rate or association between recurrence and gross residual tumor volume, radiotherapy type, radiation dose, or gender could be conducted due to information missing in the dataset. Early toxicities reported included two grade 4 toxicities and over 300 grade 1 or 2 toxicities. Late toxicities reported included two grade 5 toxicities, nine grade 4 toxicities, 43 grade 2 or 3 toxicities, and eight grade 1 toxicities.

A 2016 systematic review by Matloob evaluated the literature on proton beam therapy for skull-based chordomas.[11] 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

Wang (2023) published a systematic review of the safety, efficacy, and dosimetry of charged particle therapy for adults with high grade glioma (HGG).[12] Eight clinical studies and three dosimetry comparison studies were included. The eight clinical studies involved 350 participants with newly diagnosed HGG. Follow-up times ranged from 14.3 to 48.7 months. All studies were deemed of low quality. There was much heterogeneity of treatments that included carbon-ion related treatment, and proton and/or photon-based combinations along with surgical procedures and chemotherapy. In six studies involving proton and/or photon therapy there was no significant difference compared to IMRT in PFS (6.6 months vs. 8.9 months) or OS (24.5 months vs. 21.2 months). The authors conclude that proton therapy is not superior to other therapies and there is inadequate evidence to validate the effectiveness of various treatment approaches for HGG.

Santacroce (2023) conducted a systematic review and meta-analysis comparing PBT to stereotactic radiosurgery in the treatment of vestibular schwannomas.[13] The primary aim was to evaluate tumor control, with a secondary aim that assessed cranial nerve preservation/hearing. Eight studies involving 585 participants were included. Two studies were prospective and six were retrospective. Overall rates of tumor control, cranial nerve

preservation, and facial nerve preservation were high (95.4%, 93.7%, 95.6%) with PBT, but the rate of hearing preservation was 40.6%. Heterogeneity related to follow-up time, treatment techniques, outcome reporting, dose selection, and tumor sizes was high. The authors conclude that while high tumor control rates were achieved with PBT, hearing preservation was not better than reported rates from stereotactic radiosurgery.

The 2019 Washington Technology Assessment included five retrospective cohorts and six case series that evaluated various brain and spinal tumors.   All comparative studies were considered to be at moderately high risk of bias. Patients were treated with curative intent in three studies and for salvage in two. Effectiveness was reported in two of the three studies of curative intent while the third reported only safety outcomes. In a study of high-grade glioblastoma, no statistically significant differences in OS was reported. In a study of primary glioma, PBT was associated with greater OS in a multivariate analysis compared with photons. A comparative cohort study reported rates of pseudoprogression following PBT versus IMRT for low grade and anaplastic glioma. The difference between groups was not statistically significant. The study of safety outcomes in high-grade glioblastoma reported no significant differences in any outcomes except acute grade 3 toxicity at three months (p=0.02). For salvage therapy, only one study (of CNS metastases form hematological malignancies) reported safety outcomes. No statistically significant differences were reported. Regarding the case series, the authors conclude that they do not provide sufficient information to evaluate effectiveness or radiation safety of PBT. Overall, the assessment concluded that based on low SOE, compared to photons, PBT provides unclear net health benefit, and PBT boost plus photons provides comparable health benefits when used with curative intent. When used for salvage, the evidence was insufficient to evaluate the net health benefit of PBT boost plus photon versus photon alone.

Coggins (2019) reported a systematic review of local control of atypical and anaplastic meningiomas treated with ion radiotherapy.[14] The mean five-year local control rate reported in proton therapy studies was 59.62%. Two-year local control rates following carbon ion radiotherapy were 95% for grade II and 63% for grade III meningiomas. In studies of carbon ion radiotherapy that did not differentiate between atypical and anaplastic meningiomas, two-year local control rate was 33%.

Lesueur (2019) reported a systematic review of PBT for benign intracranial tumors in adults. A total of 24 studies were included, none of which were comparative.[15] Tumors treated were low grade meningiomas (n = 9), neurinoma (n = 4), pituitary adenoma (n = 5), paraganglioma (n = 5), or craniopharyngioma (n = 1). Nine studies used active pencil beam scanning or raster scanning and the rest used passive scattering. Approximately half of the studies used proton radiosurgery or stereotactic hypofractionated proton therapy. Every study had over 90% local control at last follow-up except two studies of pituitary adenomas. Of these, one reported five-year local control of 84% and the other reported 10-year local control of 87%.

The 2017 CADTH Tech Assessment included SRs that analyzed studies on medulloblastoma, meningioma, and intramedullary spinal cord glioma.[4] 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.[16] 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

Gamez (2021) performed a systematic review of re-irradiation using charged particles for definitive treatment of recurrent or second primary skull base and head and neck tumors.[17] A total of 15 studies of protons, 10 of carbon ions, and 1 of helium/neon were included, all of which were retrospective. Two-year local control and overall survival rates were 50 to 86% and 33 to 80%, respectively, for protons and 41 to 92% and 50 to 85%, respectively for carbon ions. Late grade 3 or higher toxicities ranged from 0 to 37%, with the most frequent complications being brain necrosis, ototoxicity, visual deficits, and bleeding. Grade 5 toxicities occurred in 1.4% (16/1118 patients) of all treated patients, with fatal bleeding as the leading cause.

Verma published a systematic review of 16 studies reporting clinical outcomes of PBT for reirradiation in 2017.[18] 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 grad 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.

A more recent systematic review, published by Barsky in 2020, included two studies published since the Verma systematic review.[19] One was a report of three patients with recurrent or second primary esophageal cancer. Median time to reirradiation was 30 years (range 5 to 41 years). Acute toxicity outcomes reported were mild/moderate odynophagia in two patients and esophageal stricture, hematemesis, and moderate/severe esophagitis in one patient each. One late toxicity was reported (intra-operative cardiac arrest). Another report was of 49 patients with recurrent or second primary liver tumors, with 10% (n=5) receiving protons. Median time to reirradiation was 9.1 months (range 6.7 to 14.9 months). For the whole cohort, the median OS was 14 months (interquartile range 7 to 22 months). Two patients who received photons and none who received protons experienced classic radiation-induced liver disease.

NONRANDOMIZED STUDIES

A 2017 case series reported by Guttmann enrolled 23 patients undergoing proton reirradiation for soft tissue sarcoma in a previously-irradiated field.[20] 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.[21] 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 to 45 Gy in the absence of chemotherapy and the risk of ototoxicity is increased in children who receive ototoxic platinum-based chemotherapy regimens.[22] 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

Wilson (2024) published a systematic review assessing safety of proton beam therapy in children and young adults with central nervous system tumors.[23] No RCTs were identified. Thirty-one studies involving 1730 children were included. Overall survival, the most common reported outcome, ranged from 68-100%, but the absence of comparator groups limited the author's ability to draw meaningful conclusions. Limitations of the review include high heterogeneity in the studies related to objectives, diagnoses and outcome and lack of long-term follow-up data. The authors identify the need for higher quality data, especially regarding long-term outcomes and late treatment effects to better understand the benefits of PBT.

The 2019 Washington Technology Assessment reviewed 11 case-control studies and 25 case series of pediatric CNS tumors.[2] The SOE for all cohort studies was low and for case series was insufficient. Six publications based on four small comparative studies reported on

effectiveness. There were no statistically significant differences in OS at any time point. Ten publications based on seven comparative studies reported on toxicity. Statistically significant differences were generally not observed. The authors suggest that this may be due to small sample sizes and/or residual confounding. Regarding the case series, the authors conclude that the limited information they contain does not provide sufficient information to evaluate effectiveness or radiation safety of PBT. Overall, the assessment concluded that based on low SOE, PBT provides incremental net health benefit.

The 2017 CADTH TEC Assessment included one study on children with craniopharyngioma that compared PBT and IMRT.[4] 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.[24] 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.[25] 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[26] and a 2012 five-year updated systematic review[27] 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:[28]

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.[29] 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.[30]

Massachusetts General Hospital reported on the use of protons in 17 children with ependymoma.[31] 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.[32] 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.[33] 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.[34] 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).[35] 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.[36] 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 and 2009.[37] 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 one-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 to 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 to 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.[4]

> 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.[38] 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.[39] 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.[40] 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.[41]

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[42] and late toxicity outcomes in other solid tumors of childhood.[43, 44]

PROSTATE CANCER

The published literature indicates that dose escalation is an accepted concept in treating organ-confined prostate cancer.[45] 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.[46]

SYSTEMATIC REVIEWS AND TECHNOLOGY ASSESSMENTS

For locally advanced prostate cancer, the 2019 Washington Technology Assessment included one quasi-RCT and three retrospective comparative cohort studies that compared PBT with photon radiation and 11 case series that reported outcomes of PBT with curative intent.[2] Low SOE was reported for all outcomes. The quasi-RCT reported no statistically significant differences in the probabilities of 5- and 10-year OS and biochemical relapse-free survival. Results regarding toxicities were mixed. The quasi-RCT reported statistically significant differences in acute and late grade 2 gastrointestinal, but not genitourinary, toxicity (lower following photons plus PBT boost). Two retrospective cohort studies reported no statistically significant differences in acute or late toxicity between PBT and IMRT, while one large database study reported lower cumulative incidences with PBT compared to IMRT. Regarding the case series, the authors conclude that the limited information they contain does not provide sufficient information to evaluate effectiveness or radiation safety of PBT. Overall, the assessment concluded that based on low SOE, PBT provides comparable net health benefit.

The 2017 CADTH Tech Assessment addressed the use of proton beam therapy for prostate cancer.[4] 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.[47] 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.[48-51] They do not include the newer comparative studies that have been done on this technology.

NONRANDOMIZED STUDIES

Barsky (2021) reported a comparison of five-year outcomes and patterns of failure in patients who received postoperative proton beam therapy or IMRT for the treatment of prostate cancer. A case-matched cohort analysis was performed for 260 men (65 PBT, 195 IMRT). No statistically significant association between radiotherapy modality and biochemical, local, regional, or distant failure was identified using multivariable Cox proportional hazards modeling (MVA). The locations of distant failure were similar between therapy modalities.

Lee (2019) reported gastrointestinal toxicity rates in 192 prostate adenocarcinoma patients

treated with PBT.[52] Median follow-up was 1.7 years and minimum follow-up was one year. Grade 2+ GI toxicity actuarial rate was 21.3% at two years. There was one event of grade 3 toxicity and no grade 4 or 5 toxicity. A multivariate analysis for predicting grade 2+ rectal bleeding identified anticoagulation as the only predicting factor, with a concordance index of 0.59 (95% CI 0.48 to 0.68; p=0.088).

Dutz (2019) reported the results of a matched pair analysis of outcomes in localized prostate cancer patients receiving IMRT or PBT.[53] A total of 31 patients received definitive PBT and 57 received IMRT. Propensity score matching resulted in 29 matched pairs based on the following parameters: PCA risk group, transurethral resection of the prostate, prostate volume, diabetes mellitus and administration of anticoagulants. Outcomes were collected prospectively up to 12 months following radiotherapy. Global health status was superior in the IMRT group at 12 months (p=0.040) and change of constipation was significantly better in the PBT group at three months (p=0.034). Late urinary urgency was significantly lower in the PBT group (IMRT: 25.0%, PBT: 0%; p=0.047). Other outcomes reported, including other measures of early and late genitourinary and gastrointestinal toxicities and quality of life, were not significantly different between groups.

BREAST CANCER

SYSTEMATIC REVIEWS AND TECHNOLOGY ASSESSMENTS

The 2019 Washington Technology Assessment included one retrospective comparative cohort study, one retrospective comparative database study, and four case series of protons for breast cancer.[2] Similar five-year probabilities of OS were reported in the database study, the only comparison of OS reported. The cohort study reported quality of life survey data collected more than five years post-diagnosis. Of 22 domains of the Breast Cancer Treatment Outcome Scale, nine were statistically significant in favor of PBT, though no correction for multiple comparisons was reported. The assessment authors concluded that the case series did not provide sufficient information to evaluate radiation safety or effectiveness of PBT. Overall, the assessment concluded that based on low SOE, PBT provides unclear net health benefit for the treatment of breast cancer.

Kammerer (2018) published a systematic review of studies evaluating the use of PBT for locally advanced breast cancer.[54] 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 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 patients with 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.[4]

NONRANDOMIZED STUDIES

Jimenez (2019) evaluated the safety and efficacy of PBT for regional nodal irradiation in patients with nonmetastatic breast cancer.[55] A total of 70 patients were evaluated and 69 were included in the analysis. Sixty-three patients had left-sided breast cancer, two had bilateral breast cancer, and five had right-sided breast cancer. Of the 62 surviving patients, the five-year locoregional failure and overall survival (OS) rates were 1.5% and 91%, respectively. One case of grade 2 radiation pneumonitis was reported, and there were no occurrences of grade 3 radiation pneumonitis or grade 4 toxicities. The rate of unplanned surgical reintervention at five years was 33%. Strain echocardiography and cardiac biomarkers were obtained before and after RT. No significant changes were reported.

ESOPHAGEAL CANCER

SYSTEMATIC REVIEWS AND TECHNOLOGY ASSESSMENTS

A 2021 systematic review published by Nicolas evaluated dosimetric and clinical outcomes of PBT for esophageal cancer.[56] A total of 32 studies were included. Only a qualitative analysis was completed. Heterogeneity was identified in treatment protocols, including treatment intent (neoadjuvant or definitive), dose, fractionation and additional treatment modalities. Although toxicity outcomes were reported to be reduced with proton compared to photon therapy, the authors noted the lack of high-quality evidence.

The 2019 Washington Technology Assessment included five retrospective comparative cohort studies addressing the safety and effectiveness of PBT compared with photon RT for esophageal cancer.[2] All were considered to be at moderately high risk of bias. Two comparative studies reported both OS and progression-free (PFS) or disease-free survival. In only one of the two studies, the difference between groups for OS and PFS across one to five years was statistically significant, favoring PBT. The other reported similar results, but the difference between groups was not statistically significant. The two studies that reported mortality found no statistically significant differences between PBT and photons (low SOE for the larger study, insufficient SOE for the smaller study). Most toxicities did not differ significantly between proton- and photon-treated patients. Exceptions were statistically significant differences in grade 4 radiation-induced lymphopenia favoring PBT in two studies and statistically fewer pulmonary and cardiac adverse events compared with 3DCRT and XRT but not with IMRT. Two case series, which provided insufficient information to evaluate radiation safety or effectiveness, were included in the analysis. Overall, based on results from two retrospective studies, only one of which reported statistically significant differences in OS, the assessment concluded PBT provides incremental net health benefit for the treatment of esophageal cancer (low SOE).

The 2017 CADTH TEC Assessment, included two unique studies that reported on benefits and four on harms of PBT in esophageal cancer.[4] These were assessed 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 for 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.

RANDOMIZED STUDIES

Wang (2024) compared the incidence of grade 4 lymphopenia (G4L) in people receiving proton beam therapy versus IMRT during chemoradiation therapy for esophageal cancer delivered within a RCT.[57] Patients were randomized to either IMRT (n=61) or PBT (n=44). After chemoradiotherapy induction 44 of 105 participants (42%) experienced G4L at a median of 28 days. Significantly fewer participants receiving PBT experienced G4L (p=0.002). The benefit was largest in those with an intermediate baseline absolute lymphocyte count and large planning treatment volume (p=0.011). The authors conclude that the dose scatter limiting effect of PBT reduces the incidence of G4L in patients undergoing chemoradiation for esophageal cancer.

Lin (2020) reported results of a randomized trial comparing proton beam therapy with IMRT for locally advanced esophageal cancer.[58] Patients were randomized to receive IMRT or PBT, stratified for histology, resectability, induction chemotherapy, and stage. Initially, 72 patients were randomized to the IMRT group and 73 were randomized to the PBT group. A total of 61 IMRT patients and 46 PBT patients were available for evaluation. The posterior mean total toxicity burden (a composite score of 11 distinct adverse events) was 39.9 for the IMRT group and 17.4 for the PBT group. Fifty-one patients (30 IMRT, 21 PBT) underwent esophagectomy. The mean postoperative complication score was 19.1 (7.3 to 32.3) and 2.5 (0.3 to 5.2) for IMRT and PBT, respectively. The three-year PFS rate (50.8% vs. 51.2%) and overall survival rates (44.5% vs. 44.5%) were not significantly different.

NONRANDOMIZED COMPARATIVE STUDIES

Routman (2019) assessed 144 patients receiving curative-intent radiotherapy and concurrent chemotherapy for esophageal cancer.[59] A total of 79 received photon RT (27% 3D-CRT and 73% IMRT) and 65 received PBT (100% pencil-beam scanning PBT). Grade 4 lymphopenia was significantly different between groups (photons 56% vs protons 22%; p<0.01). Results of a multivariate analysis indicated associations between photon radiotherapy and grade 4 lymphopenia (OR 5.13; 95% CI 2.35 to 11.18 p<0.001) and between stage II/IV and grade 4 lymphopenia (OR 4.54; 95% CI 1.87 to 11.00; p<0.001). In a propensity-matched analysis of 50 photon- and 50 proton-treated patients, grade 4 lymphopenia occurred in 60% of the photon group and 24% of the proton group and a multivariate analysis indicated associations between photon radiotherapy and grade 4 lymphopenia (OR: 5.28; 95% CI 2.14 to 12.99 p<0.001) and between stage II/IV and grade 4 lymphopenia (OR: 3.77; 95% CI 1.26 to 11.30; p<0.02).

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 2019 Washington Technology Assessment included seven comparative cohort studies that compared PBT with alternative therapies with curative intent in adult patients with head and neck cancers.[2] Three retrospective cohort studies reported no statistically significant differences in probabilities of one- to three-year OS or PFS or all-cause mortality over a median 24 months (Low SOE for primary oropharyngeal and nasopharyngeal cancer; Insufficient SOE for primary or metastatic salivary gland cancer). Three retrospective comparative studies reported no statistically significant differences in frequency of grade three or higher acute or late toxicities or the incidence of ED visits/unplanned hospitalizations (Low SOE based on largest, best quality study). Several case series were also identified, though the assessment concluded that the limited information they provide does not provide sufficient information to evaluate radiation safety or effectiveness of PBT. Overall, the assessment concluded that based on low SOE, PBT provides comparable net health benefit.

The 2017 CADTH TEC Assessment found no relevant SRs reporting on benefits of PBT for head and neck cancer.[4] 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.[60] 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 five-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

Alterio (2020) published a series of 27 patients with locally advanced nasopharyngeal cancer treated with IMRT followed by proton therapy boost (mixed beam), as well as a historical cohort of patients treated with IMRT only.[61] Mixed beam patients received a first phase of IMRT consisting of up to 54 to 60 Gy followed by a second phase delivered with a proton therapy boost up to 70 to 74 Gy (RBE). For patients treated with IMRT-only, the total dose was 69.96 Gy. Of mixed beam and IMRT-only patients, 59 and 88%, respectively, received induction chemotherapy and 88 and 100%, respectively received concurrent chemoradiotherapy. The mixed beam approach resulted in a significantly higher median total dose to target volumes (p=0.02). Statistically significant differences between the historical IMRT group and the mixed beam group were reported for acute toxicities, with acute grade 3 mucositis reported in 11 and 76% (p=0.0002) of patients treated with the mixed beam and IMRT-only approach, respectively, and grade 2 xerostomia reported in 7 and 35% (p=0.02) of

patients treated with mixed beam and IMRT-only, respectively. There were no statistical differences reported in late toxicities. Local progression-free survival (PFS) and progression-free survival curves were similar between the two cohorts of patients (p=0.17 and p=0.40, respectively) and local control rates were 96% and 81% for patients treated with mixed beam and IMRT-only, respectively.

Chuong (2019) reported on acute toxicities in 105 patients with salivary gland tumors who received PBT treatment.[62] Tumors were in the parotid gland in 90 patients and in the submandibular gland in 15 patients. The treatment was postoperative in 70.5 and definitive in 29.5%. Twenty percent of patients received concurrent chemotherapy. Median follow-up was 14.3 months. Acute grade 2 or higher toxicities were reported. These included nausea (1.5%), dysgeusia (4.8%), xerostomia (7.6%), mucositis (10.5%), and dysphagia (10.5%).

In 2014, Zenda reported on late toxicity in 90 patients after PBT for nasal cavity, paranasal sinuses, or skull base malignancies.[63] 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.

LIVER CANCER

SYSTEMATIC REVIEWS AND TECHNOLOGY ASSESSMENTS

The 2019 Washington Technology Assessment included one RCT, one retrospective comparative study, and seven case series on protons treatment of the liver.[2] SOE was low (based on the retrospective comparative cohort study) to moderate (based on the RCT) for benefits and harms. Although the assessment states that based on moderate SOE, PBT provides incremental net health benefit compared to TACE and based on low SOE, PBT provides incremental net health benefit compared to IMRT, it also states in the summary table that net health benefit vs. comparators across both reports is unclear. The summary is based on the following studies:

- A 2016 report of interim results from a small, ongoing RCT (moderate quality) compared passive scatter PBT (n=33) with TACE (n=36). This study was considered at moderately low risk of bias. The use of TACE, rather than radiation, as a comparator limits the conclusions that can be drawn. Limited information was provided on acute toxicity. Hospitalization was reported as a surrogate for treatment related toxicities, though hospitalization is routinely higher following TACE than following radiation. Fewer proton patients required hospitalization and the proton-treated group had fewer total hospital days. Both of these differences reached statistical significance. Based on the reduced hospitalization, the assessment authors concluded that PBT may have incremental net health benefits versus TACE (moderate SOE). There was no statistically significant difference between groups in the probability of two-year OS, PFS, or local control.
- A retrospective cohort study (PBT n=49, photon n=84) reported on effectiveness and safety. This study was considered at moderately high risk of bias. Four PBT patients and 17 IMRT patients developed nonclassic radiation-induced liver disease (RILD) three months post-treatment which translated to a statistically significant lower incidence of RILD following PBT, odds ratio (OR) 0.26 (95% CI 0.08 to 0.86). The probability of two-year OS was statistically higher in the PBT group compared with the IMRT group:

59.1% versus 28.6% (adj. HR 0.47; 95% CI 0.27 to 0.82). No statistically significant differences in local or regional control between groups.
- The case series reported survival outcomes and toxicity, but were considered insufficient to evaluate safety or effectiveness of PBT.

A 2019 systematic review published by Spychalski identified 16 studies including 1,516 hepatocellular carcinoma patients who were treated with charged particle therapy.[64] The quality of included studies was limited by incomplete reporting and retrospective design. Mean biologically equivalent dose ranged from 68.75 to 122.5 GyE. Weighted means were calculated across studies for overall survival (86%, 62%, 59% and 35% at one, two, three, and five years, respectively) and local control (86%, 89%, 87% and 89% at one, two, three, and five years, respectively). Acute grade 1 to 2 toxicities were reported in 54% of patients and acute grade 3 and above were reported in 6%. Late grade 1 to 2 toxicities were reported in 9% of patients and late grade 3 and above toxicities were reported in less than 4%. No treatment related mortality was reported.

In 2018, Igaki published a systematic review of charged-particle therapy for hepatocellular carcinoma.[65] 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 publications 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 to 95%, respectively. Overall survival among studies that reported five-year results was 25 to 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 sever 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.[4] 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.

RANDOMIZED CONTROLLED TRIALS

Bush (2023) conducted a RCT comparing proton beam radiotherapy (PBT) to transarterial chemoembolization (TACE) for previously untreated hepatocellular carcinoma (HCC).[66] The primary endpoint was overall survival (OS). Secondary endpoints were progression-free survival (PFS), local control (LC), toxicity, and cost of treatment. Seventy-six participants were randomized to either PBT (n=36) or TACE (n=40) and information from 74 participants was available for analysis. Two-year OS was not significantly different (p=0.80). Median OS for all subjects was 32 months. OS for the TACE group was 65% and OS for the PBT group was 68%. PFS was significantly better in the PBT group (p=0.002), as was LC (p=0.003). Adverse events included higher rates of grade 1, 2, and 3 abdominal pain in the TACE group (p<0.001) as well as higher rates of hospitalization within 30 days of treatment (p<0.001). Grade I nausea, skin erythema, and fatigue were higher in the PBT group (p=0.05, p<0.001, p<0.01). Costs of inpatient care and treatment delivery were 28% lower in the PBT group. The authors concluded that while OS was not different, the improved rates of PFS and LC, and lower rates of hospitalization with corresponding lower cost indicate further study of PBT for HCC is

warranted.

Kim (2021) published a randomized controlled trial of 144 patients who received PBT or radiofrequency ablation (RFA) for the treatment of recurrent/residual hepatocellular carcinoma (HCC).[67] After random assignment to RFA or PBT, if the assigned treatment was not technically feasible, patients were allowed to crossover. The intention-to-treat (ITT) population was 144 patients total, 72 each in the PBT and RFA groups. Six patients switched from the PBT arm to the RFA arm and 19 patients switched from the RFA arm to the PBT arm, resulting in 56 patients in RFA arm and 80 patients in the PBT arm in the per-protocol analysis. In the per-protocol population, the primary outcome of two-year local progression-free survival (LPFS) rate was 94.8% and 83.9%, for PBT (n=80) and RFA (n=56), respectively, with a between-group difference of 10.9 percentage points (90% CI 1.8 to 20.0; p<0.001). In the ITT population, the two-year LPFS rate was 92.8% and 83.2% for PBT and RFA, respectively, with a between-group difference of 9.6 percentage points (90% CI 0.7 to 18.4; p<0.001). PBT met the criteria for non-inferiority in both analyses. For PBT, the most common adverse events were radiation pneumonitis (32.5%) and decreased leukocyte counts (23.8%) and for RFA the most common were increased alanine aminotransferase levels (96.4%) and abdominal pain (30.4%). Overall, Grade 3 adverse events were significantly more frequent in the RFA arm (16.1% vs. 0%, p <0.001), but all were transient and all patients recovered. No Grade 4 adverse events or mortality were reported in either arm.

NONRANDOMIZED STUDIES

A 2019 case series published by Chadha reported outcomes in localized unresectable hepatocellular carcinoma patients treated with PBT. Inclusion criteria were Child-Pugh class A or B, no prior radiotherapy, and ECOG performance status of 0 to 2. Of the 46 patients, 83% had Child-Pugh class A, 22% had multiple tumors, and 54% received prior treatment. PBT (median BED dose of 97.7 GyE) was administered in 15 fractions. The actuarial two-year LC rate was 81% and the actuarial OS rate was 62%. According to the multivariate analysis, higher BED significantly improved OS (p=0.023; hazard ratio=0.308) Acute grade 3 toxicity was reported in six (13%) of patients.

NON-SMALL CELL LUNG CANCER (NSCLC)

SYSTEMATIC REVIEWS AND TECHNOLOGY ASSESSMENTS

Chen (2023) conducted a systematic review and meta-analysis on the safety and efficacy of particle therapy for locally advanced, inoperable NSCLC.[68] Particle therapy included carbon-ion radiotherapy (CIRT) and PBT. Nineteen studies involving 851 patients were included. No studies were phase III or IV RCTs. Three studies included 119 patients receiving PBT, and 11 studies described 452 patients who received PBT and concurrent chemotherapy (CCRT). Outcomes included pooled data on OS, PFS and LC rates at 2- and 5-years. At two years, the CCRT group had the highest OS (67.3%, 95% CI-58.0-78%, I^2=69.7%, p=0.002) and highest PFS (40.8%, 95%CI=34.0-48.8%). The PBT group had the lowest OS (49.1%, 95%CI=39.3-61.4%, I^2=11.1%, p=0.325) and PFS (24.6%, 95%CI=16.8-36.0%) at two years. LC at 2 years was also highest in the CCRT group (85.0% and lowest in the PBT group (61.9%). For the CIRT group, two-year OS was 57.8%, PFS was 38.7%, and LC was 79.1%. Five-year survival and LC rates were limited to data from five studies, all involving CCRT. OS was 41.3%, PFS was 25.3% and LC was 61.5% at five years. The CCRT and PBT groups had similar rates of pneumonitis (grade 2 PBT, 14.6%, grade 2 CCRT, 14.7%) which were higher than CIRT (6.5%). Rates of grade 3-4 pneumonitis were low overall (3.4%) and similar among the groups.

Esophagitis (grade 2/3/4) rates were highest in the CCRT group (33.1%) and lower in the PBT (6%) and CIRT (2.3%) groups. The overall incidence of side effects above grade 3 was less than 4%. The authors concluded that particle therapy shows promise for locally advanced NSCLC, but large prospective studies that compare particle therapy to photon therapy are necessary.

Volpe (2022) published a systematic review and meta-analysis of hypofractionated PBT for early stage NSCLC.[69] The review assessed eight studies with 401 patients who were treated with PBT with curative intent. Median follow-up was 32.8 months. The aims of the study included determining whether fractionation schedule/biologically effective dose (BED) are associated with better outcomes. Outcomes of interest were overall survival (OS), cancer-specific survival (CSS), progression-free survival (PFS) and local control (LC). The review also assessed treatment toxicity. Four studies were prospective and four were retrospective. Heterogeneity in radiation dosage among the studies was seen. The median radiation dose was 105.6 Gy. The meta-analysis found that OS was associated with higher radiation BED (2-, 3-, 4-year OS with BED<105.6 Gy: 0.75 [95% CI: 0.57-0.87], 0.64 [0.40-0.82], 0.56 [0.34-0.76] versus 0.86 [0.81-0.90], 0.83 [0.77-0.88], 0,78 [0.64-0.88] for BED $\geq$105.6 Gy). CSS was based on three studies (157 patients) and found BED>105.6 Gy was associated with 2-year CSS of 0.95 [0.86-0.98] and 3-year CSS of 0.90 [0.81-0.94]. CSS of BED <105.6 Gy was 0.89 [0.79-0.94] at 2 years and 0.86 [0.76-0.92] at 3 years. Four-year follow-up data was not presented, but the authors state the advantage of higher BED in CSS was not maintained at 4 years. PFS data was limited in that only one study with BED <105.6 Gy reported PFS. The three studies that reported BED >105.6 Gy had higher 2, 3, and 4-year PFS (0.75, 0.71, 0.68) than the one study with BED <105.6 Gy (0.58, 0.52, 0.50). LC was high in both groups at 2-, 3-, and 4-years, but dosage above 105.6 Gy was associated with higher rates of LC (2-year: 0.93 [0.85-0.97], 3-year 0.91 [0.82-0.96], 4-year 0.90 [0.75-0.97] vs. BED<105.6 Gy; 2-year 0.85 [0.77-0.90], 3-year 0.83 [0.75-0.88], and 4-year 0.82 [0.74-0.88]). Overall, the incidence of acute toxicity >grade 2 was 10% and the difference between BED >105.6 Gy (18/32) and <105.6 Gy (14/32) was small. However, BED >105.6 Gy was associated with a nearly three times higher rate of grade $\geq$2 late toxicity (0.35 [0.28-0.44] vs. 0.14 [0.02-0.52]). The authors conclude that hypofractionated PBT is safe and effective in the treatment of early stage NSCLC, but acknowledge the analysis did not establish PBT as an alternative to stereotactic body radiation therapy (SBRT) for early stage NSCLC.

For the evaluation of PBT for lung cancer, the 2019 Washington Technology Assessment included one RCT, five retrospective comparative cohorts, and 11 case series that evaluated PBT used with curative intent and one prospective comparative cohort and one case series that evaluated PBT for salvage therapy.[2] Based on the RCT, which was considered fair quality, there was moderate strength of evidence for no statistically significant differences between PBT and IMRT in the probability of OS at any time up to five years or in the cumulative incidence of local failure in patients with non-small cell lung cancer when treated with curative intent. Similar results were reported by the four retrospective cohort studies that compared the effectiveness of PBT with photon when used with curative intent. Toxicities were reported in the RCT and two retrospective cohort studies and no statistically significant differences between PBT and IMRT were reported. The case series were to have insufficient information to evaluate the radiation safety or effectiveness of PBT. Overall, the assessment concluded that based on moderate SOE, PBT provides comparable net health benefit.

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.[4] 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.[70] 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.[71] 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% to 87%. The two- and five-year overall survival (OS) rates were 31%to 74% and 23%, respectively, and two- and five-year cause-specific survival (CSS) rates were 58% to 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.[72] 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.[73] 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).[74] 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 2021, Jongen reported an analysis of a multi-institutional prospective registry of patients treated with PBT for locally advanced NSCLC.[75] A total of 195 patients with stage III de novo or recurrent locally advanced NSCLC were included in the analysis, 20% of whom received pencil beam scanning PBT. Median follow-up for living patients was 37.1 months. Six occurrences of treatment-related grade 3 and no grade 4 adverse events were reported. Median OS was 19.0 months.

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.[76] 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% to 41%), five-year PFS was 22% (95% CI 12% to 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.[77] 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 1 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.

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.[78-96]

The 2017 CADTH TEC Assessment included limited evidence from comparative studies regarding bone cancer.[4] 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,[97] liver metastases,[98] pediatric patients with AVMs,[99] and high-risk cerebral AVMs.[100]

PRACTICE GUIDELINE SUMMARY

NATIONAL COMPREHENSIVE CANCER NETWORK

The National Comprehensive Cancer Network (NCCN) Guidelines for Bone Cancer (2.2024) state "specialized techniques such intensity-modulated radiotherapy (IMRT), particle beam RT with protons, carbon ions or other heavy ions; stereotactic radiosurgery (SRS) should be considered as indicated in order to allow high-dose therapy while maximizing normal tissue sparing."[101]

The NCCN Guidelines for Prostate Cancer (3.2024) state "Photon or proton EBRT are both effective at achieving highly conformal radiotherapy with acceptable and similar biochemical control and long-term side effect profiles."[102] 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 regiments at clinics with appropriate technology, physics, and clinical expertise."

The NCCN Guidelines for Central Nervous System Cancers (1.2023) state in The Principles of Radiation Therapy for Brain and Spinal Cord:[103]

- For High-Grade Glioma: Glioblastoma, WHO Grade 3 Oligodendroglioma (IDH-mutant, 1p19q codeleted), WHO Grade 3 or 4 IDH-Mutant Astrocytoma Simulation and Treatment Planning: "Consider proton therapy for patients with good long-term prognosis (grade 3 IDH-mutant tumors5 and 1p19q codeleted tumors6) to better spare uninvolved brain and preserve cognitive function."
- Reirradiation for Gliomas:
  - "Highly focal techniques like intensity-modulated RT (IMRT), proton therapy, or SRS may be required in these reirradiation settings in order to improve dose distribution to critical structures, and reduce overlap with prior radiation fields."
  - "…Treatment may be performed with highly focused modern SRS techniques for lower volume disease10; fractionated IMRT, including doses of 35 Gy in 10 fractions for recurrent glioblastoma, and proton therapy to help spare previously irradiated normal brain…"
- Craniospinal: "To reduce toxicity from CSI (craniospinal irradiation) in adults, consider the use of IMRT or protons if available (for patients with positive CSF or known metastatic disease)."

- Adult Medulloblastoma: "To reduce toxicity from CSI in adults, consider the use of IMRT or protons if available."
- Primary spinal cord tumors: "Proton therapy may also be helpful in the setting of primary spinal cord tumors to better spare surrounding normal tissues, uninvolved cord, and nerve roots."
- Meningiomas, general treatment information: "Highly conformal fractionated RT techniques (eg, 3D conformal RT [3D-CRT], IMRT, volumetric modulated arc therapy [VMAT], proton therapy) are recommended to spare critical structures and uninvolved tissue."

The NCCN Guidelines for Pediatric Central Nervous System Cancers (1.2024) state, "Proton therapy may be considered for patients with better prognoses (e.g., IDH1-mutated tumors, 1p/19q-codeleted, younger age)."[104] Also, "Proton therapy should be considered for potential tissue sparing, if available in a timely manner. In the context of avoiding delays in therapy or logistical consideration, photon therapy is an acceptable treatment modality for situations in which proton therapy is not available such as recurrence and logistical situations (such as travel delays)."

The NCCN Guidelines for Non-Small Cell Lung Cancer (4.2024) state, "In retrospective studies, intensity-modulated proton therapy (IMPT) has also been shown to reduce the toxicities as compared with 3D-based passive scattering proton therapy in stage III NSCLC."[105]

The NCCN Guidelines for Pleural Mesothelioma (1.2024) state that more advanced technologies, including proton therapy, "are appropriate when needed to deliver curative RT safely."[106]

The NCCN Guidelines for Head and Neck Cancer (3.2024), in the Principles of Radiation Techniques states, "Proton therapy can be considered when normal tissue constraints cannot be met by photon-based therapy, or when photon-based therapy causes compromise of standard radiation dosing to tumor or postoperative volumes."[107]

For specific head and neck cancers:

- Maxillary sinus or paranasal/ethmoid sinus tumors: Either IMRT or proton therapy is recommended for maxillary sinus or paranasal/ethmoid sinus tumors to minimize dose to critical structures.
- Oropharynx: Either IMRT (preferred) or 3D-CRT is recommended for cancers of the oropharynx in order to minimize dose to critical structures. Use of proton therapy is an area of active investigation. Proton therapy may be considered when normal tissue constraints cannot be met by photon-based therapy, or when photon-based therapy causes compromise of standard radiation dosing to tumor or postoperative volumes.
- Supraglottic larynx: Either IMRT (preferred) or 3D-CRT is recommended. Use of proton therapy is an area of active investigation. Proton therapy may be considered when normal tissue constraints cannot be met by photon-based therapy, or when photon-based therapy causes compromise of standard radiation dosing to tumor or postoperative volumes.
- Occult primary: Either IMRT (preferred) or 3D-CRT is recommended when targeting the pharyngeal axis to minimize the dose to critical structures. Use of proton therapy is an area of active investigation. Proton therapy may be considered when normal tissue

constraints cannot be met by photon-based therapy, or when photon-based therapy causes compromise of standard radiation dosing to tumor or postoperative volumes.

- Nasopharynx: IMRT is recommended for cancers of the nasopharynx to minimize dose to critical structures. Proton therapy can be considered when normal tissue constraints cannot be met by photon-based therapy, or when photon-based therapy causes compromise of standard radiation dosing to tumor or postoperative volumes.
- Very advanced head and neck cancer: Proton therapy can be considered when normal tissue constraints cannot be met by photon-based therapy, or when photon-based therapy causes compromise of standard radiation dosing to tumor or postoperative volumes.
- Salivary gland tumors: Either IMRT (preferred) or 3D-CRT is recommended. Proton therapy can be considered when normal tissue constraints cannot be met by photon-based therapy, or when photon-based therapy causes compromise of standard radiation dosing to tumor or postoperative volumes.
- Mucosal melanoma: Either IMRT (preferred) or 3D-CRT is recommended. Proton therapy can be considered when normal tissue constraints cannot be met by photon-based therapy, or when photon-based therapy causes compromise of standard radiation dosing to tumor or postoperative volumes.

The NCCN Guidelines for Uveal Melanoma (1.2023) state that "particle beam therapy is appropriate as upfront therapy after initial diagnosis, after margin-positive enucleation, or for intraocular or orbital recurrence."[108]

The NCCN Guidelines for Esophageal and Esophagogastric Junction Cancers (1.2024) states, Proton beam therapy is appropriate in clinical settings where reduction in dose to organs at risk (e.g., heart, lungs) is required that cannot be achieved by 3-D techniques, ideally within a clinical trial or registry study."[109]

The NCCN Guidelines for B-Cell Lymphomas (1.2024) states, "Treatment with photons, electrons, or protons is appropriate depending upon clinical scenario", and "Advanced RT technologies such as intensity-modulated RT (IMRT)/volumetric modulated arc therapy (VMAT), proton therapy, breath hold or respiratory gating, and/or image-guided therapy may offer significant and clinically relevant advantages in specific instances to spare organs at risk (OARs) such as the heart (including coronary arteries and valves), lungs, kidneys, liver, spinal cord, esophagus, bone marrow, breasts, stomach, muscle/soft tissue, and salivary glands to decrease the risk for late, normal tissue toxicity while still achieving the primary goal of local tumor control."[110]

The NCCN Guidelines for Soft Tissue Sarcoma (3.2023) state that for soft tissue sarcoma on the extremity/body wall/head and neck, and for retroperitoneal/intra-abdominal sarcoma: "When EBRT is used, sophisticated treatment planning with intensity-modulated RT (IMRT) and/or protons should be used to improve the therapeutic ratio."[111]

The NCCN Guidelines for Thymomas and Thymic Carcinomas (1.2024) state, "A minimum technological standard for RT is CT-planned 3D conformal RT (3D-CRT).[112] More advanced technologies are appropriate when needed to deliver curative RT safely. These technologies include (but are not limited to) 4D-CT and/or PET/CT simulation, intensity modulated RT (IMRT)/volumetric modulated arc therapy (VMAT), image-guided RT (IGRT), motion management, and proton therapy. In particular, IMRT is preferred over 3D-CRT. Compared to IMRT, proton therapy has been shown to improve dosimetry, thus allowing for better sparing of

normal organs (lungs, heart, and esophagus) with favorable local control and toxicity, and is appropriate."

The NCCN Guidelines for Biliary Tract Cancers (1.2024) states, "Hypofractionation: Doses ranging between 58–67.5 Gy (in 15 fractions; median EQD2 80.5 Gy) using photons or protons are recommended at centers with experience."[113]

The NCCN Guidelines for Hepatocellular Carcinoma (1.2024) state that for unresectable tumors, "Hypofractionation with photons or protons is an acceptable option for intrahepatic tumors, although treatment at centers with experience is recommended." and "Proton beam therapy (PBT) may be appropriate in specific situations."

The NCCN Guidelines for Breast Cancer (2.2024), Kidney Cancer (3.2024), Pancreatic Adenocarcinoma (1.2024), and Rectal Cancer (1.2024) do not address the use of proton beam or charged particle radiotherapy.[114-117]

AMERICAN SOCIETY OF RADIATION ONCOLOGY

The American Society of Radiation Oncology (ASTRO) published an updated Proton Beam Therapy Model Policy in 2022 which is not a clinical practice guideline.[118] 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:

General

- Benign or malignant tumors or hematologic malignancies in children aged 21 years and younger treated with curative intent and occasionally palliative intent treatment of childhood tumors when at least one of the three criteria noted above under "indications for coverage" apply.
- Benign or malignant tumors or hematologic malignancies in the adolescent/young adult (AYA) population aged 22 years to 39 years treated with curative intent when at least one of the three criteria noted above under "indications for coverage" apply.
- Patients with genetic syndromes making total volume of radiation minimization crucial, such as but not limited to NF-1 patients, deleterious ATM mutations, Li-Fraumeni, retinoblastoma patients, and patients with known or suspected genetic mutations. In addition, patients with other genetic mutations who are at increased risk of developing second cancers at or near the same body location such as but not limited to BRCA 1/2, Lynch syndrome, etc.
- Medically inoperable patients with a diagnosis of cancer typically treated with surgery where dose escalation is required due to the inability to receive surgery.
- Re-irradiation cases (where cumulative critical structure dose would exceed tolerance dose).
- Primary malignant or benign bone tumors.

Central Nervous System

- Ocular tumors, including intraocular melanomas.
- Tumors that approach or are located at the base of skull, including but not limited to:
  - Chordoma
  - Chondrosarcomas

- Other histologies arising in this site
- Malignant and benign primary CNS tumors excluding IDH wild-type GBM, that are treated with curative intent and with potential for long term prognosis.
- Primary spine or spinal cord tumors or metastatic tumors to the spine or spinal cord where organ at risk tolerance may be exceeded with photon treatments.
- Primary and metastatic tumors requiring craniospinal irradiation

Head and Neck

- Cancers of the nasopharynx, nasal cavity, paranasal sinuses and other accessory sinuses
- Advanced stage and unresectable head and neck cancers

Thoracic

- Primary cancers of the esophagus
- Primary tumors of the mediastinum, including thymic tumors, mediastinal tumors, mediastinal lymphomas and thoracic sarcomas
- Malignant pleural mesothelioma

Abdominal

- Hepatocellular cancer and intra-hepatic biliary cancers
- Non-metastatic retroperitoneal sarcomas

Pelvic

- Advanced and unresectable pelvic tumors with significant pelvic and/or peri-aortic nodal disease
- Patient with a single kidney or transplanted pelvic kidney with treatment of an adjacent target volume and in whom maximal avoidance of the organ is critical

The 2022 guidelines from ASTRO on radiation therapy for IDH-Mutant Grade 2 and Grade 3 diffuse glioma conditionally recommend proton beam therapy (low quality of evidence).[119]

Also in 2022, ASTRO published guidelines on clinically localized prostate cancer.[120] These guidelines, co-published by the American Urological Society and endorsed by the Society of Urologic Oncology state that "Clinicians may counsel patients with prostate cancer that proton therapy is a treatment option, but it has not been shown to be superior to other radiation modalities in terms of toxicity profile and cancer outcomes. (Conditional Recommendation; Evidence Level: Grade C)."

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."[121]

A 2021 clinical practice guideline from ASCO on the treatment of salivary gland malignancy (SGM) states that "particle therapy, including proton, neutron, and carbon ion therapy, may be used for patients with SGM; there are no indications for the use of heavy particle therapy over

photon or electron therapy (Type: evidence based; Evidence quality: low; Strength of recommendation: weak)."

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.[122]

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.[123] 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.[124-126]

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).[127] 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.

REFERENCES

1. Hwang EJ, Gorayski P, Le H, et al. Particle therapy toxicity outcomes: A systematic review. *J Med Imaging Radiat Oncol.* 2020;64(5):725-37. PMID: 32421259
2. Aggregate Analytics. Proton Beam Therapy - Re-review. Olympia (WA): Washington State Health Care Authority; 2019 April 15. [cited 4/18/2024]. 'Available from:' https://www.hca.wa.gov/assets/program/proton-beam-therapy-rr-final-report-20190418.pdf.
3. Institute for Clinical and Economic Review (ICER). Proton beam therapy: final evidence report [Internet]. Olympia (WA): Washington State Health Care Authority; 2014 Mar 28. [cited 4/18/2024]. 'Available from:' https://www.hca.wa.gov/about-hca/health-technology-assessment/proton-beam-therapy.
4. Kim J, Wells C, Khangura S, et al. CADTH Health Technology Assessments. Proton Beam Therapy for the Treatment of Cancer in Children and Adults: A Health Technology Assessment. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health. Copyright © 2017 Canadian Agency for Drugs and Technologies in Health., 2017.
5. Peterson K, McCleery E, Waldrip K, Helfand M. Comparative effectiveness of proton irradiation treatment. VA ESP Project #09-199; 2015. . PMID:
6. Verma V, Mehta MP. Clinical Outcomes of Proton Radiotherapy for Uveal Melanoma. *Clin Oncol (R Coll Radiol).* 2016. PMID: 26915706
7. Wang Z, Nabhan M, Schild SE, et al. Charged particle radiation therapy for uveal melanoma: a systematic review and meta-analysis. *Int J Radiat Oncol Biol Phys.* 2013;86(1):18-26. PMID: 23040219

8. Pahwa B, Medani K, Lu VM, et al. Proton beam therapy for skull base chordomas: a systematic review of tumor control rates and survival rates. *Neurosurg Rev.* 2022;45(6):3551-63. PMID: 36181614
9. El Sayed I, Trifiletti DM, Lehrer EJ, et al. Protons versus photons for the treatment of chordoma. *Cochrane Database of Systematic Reviews.* 2021(7). PMID: CD013224
10. Alahmari M, Temel Y. Skull base chordoma treated with proton therapy: A systematic review. *Surg Neurol Int.* 2019;10:96. PMID: 31528434
11. Matloob SA, Nasir HA, Choi D. Proton beam therapy in the management of skull base chordomas: systematic review of indications, outcomes, and implications for neurosurgeons. *British journal of neurosurgery.* 2016:1-6. PMID: 27173123
12. Wang Y, Liu R, Zhang Q, et al. Charged particle therapy for high-grade gliomas in adults: a systematic review. *Radiat Oncol.* 2023;18(1):29. PMID: 36755321
13. Santacroce A, Trandafirescu MF, Levivier M, et al. Proton beam radiation therapy for vestibular schwannomas-tumor control and hearing preservation rates: a systematic review and meta-analysis. *Neurosurg Rev.* 2023;46(1):163. PMID: 37402894
14. Coggins WS, Pham NK, Nguyen AV, et al. A Systematic Review of Ion Radiotherapy in Maintaining Local Control Regarding Atypical and Anaplastic Meningiomas. *World neurosurgery.* 2019;132:282-91. PMID: 31476452
15. Lesueur P, Calugaru V, Nauraye C, et al. Proton therapy for treatment of intracranial benign tumors in adults: A systematic review. *Cancer treatment reviews.* 2019;72:56-64. PMID: 30530009
16. Sanford NN, Yeap BY, Larvie M, et al. Prospective, Randomized Study of Radiation Dose Escalation With Combined Proton-Photon Therapy for Benign Meningiomas. *Int J Radiat Oncol Biol Phys.* 2017;99(4):787-96. PMID: 28865924
17. Gamez ME, Patel SH, McGee LA, et al. A Systematic Review on Re-irradiation with Charged Particle Beam Therapy in the Management of Locally Recurrent Skull Base and Head and Neck Tumors. *Int J Part Ther.* 2021;8(1):131-54. PMID: 34285942
18. Verma V, Rwigema JM, Malyapa RS, et al. Systematic assessment of clinical outcomes and toxicities of proton radiotherapy for reirradiation. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology.* 2017. PMID: 28941560
19. Barsky AR, Reddy VK, Plastaras JP, et al. Proton beam re-irradiation for gastrointestinal malignancies: a systematic review. *Journal of gastrointestinal oncology.* 2020;11(1):187-202. PMID: 32175122
20. Guttmann DM, Frick MA, Carmona R, et al. A prospective study of proton reirradiation for recurrent and secondary soft tissue sarcoma. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology.* 2017;124(2):271-76. PMID: 28697854
21. Hoffman KE, Yock TI. Radiation therapy for pediatric central nervous system tumors. *Journal of child neurology.* 2009;24(11):1387-96. PMID: 19841427
22. Borsting E, Mitchell GL, Kulp MT, et al. Improvement in Academic Behaviors After Successful Treatment of Convergence Insufficiency. *Optom Vis Sci.* 2012;89(1):12-18. PMID: 22080400
23. Wilson JS, Main C, Thorp N, et al. The effectiveness and safety of proton beam radiation therapy in children and young adults with Central Nervous System (CNS) tumours: a systematic review. *J Neurooncol.* 2024;167(1):1-34. PMID: 38294638
24. Ho ESQ, Barrett SA, Mullaney LM. A review of dosimetric and toxicity modeling of proton versus photon craniospinal irradiation for pediatrics medulloblastoma. *Acta Oncol.* 2017;56(8):1031-42. PMID: 28509599

25.   Leroy R, Benahmed N, Hulstaert F, et al. Proton Therapy in Children: A Systematic Review of Clinical Effectiveness in 15 Pediatric Cancers. *Int J Radiat Oncol Biol Phys.* 2016;95(1):267-78. PMID: 27084646

26.   Lodge M, Pijls-Johannesma M, Stirk L, et al. A systematic literature review of the clinical and cost-effectiveness of hadron therapy in cancer. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology.* 2007;83(2):110-22. PMID: 17502116

27.   De Ruysscher D, Mark Lodge M, Jones B, et al. Charged particles in radiotherapy: a 5-year update of a systematic review. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology.* 2012;103(1):5-7. PMID: 22326572

28.   Cotter SE, McBride SM, Yock TI. Proton radiotherapy for solid tumors of childhood. *Technology in cancer research & treatment.* 2012;11(3):267-78. PMID: 22417062

29.   Hug EB, Muenter MW, Archambeau JO, et al. Conformal proton radiation therapy for pediatric low-grade astrocytomas. *Strahlentherapie und Onkologie : Organ der Deutschen Rontgengesellschaft [et al].* 2002;178(1):10-7. PMID: 11977386

30.   Fuss M, Hug EB, Schaefer RA, et al. Proton radiation therapy (PRT) for pediatric optic pathway gliomas: comparison with 3D planned conventional photons and a standard photon technique. *Int J Radiat Oncol Biol Phys.* 1999;45(5):1117-26. PMID: 10613303

31.   MacDonald SM, Safai S, Trofimov A, et al. Proton radiotherapy for childhood ependymoma: initial clinical outcomes and dose comparisons. *Int J Radiat Oncol Biol Phys.* 2008;71(4):979-86. PMID: 18325681

32.   Bishop AJ, Greenfield B, Mahajan A, et al. Proton beam therapy versus conformal photon radiation therapy for childhood craniopharyngioma: multi-institutional analysis of outcomes, cyst dynamics, and toxicity. *Int J Radiat Oncol Biol Phys.* 2014;90(2):354-61. PMID: 25052561

33.   Fitzek MM, Linggood RM, Adams J, et al. Combined proton and photon irradiation for craniopharyngioma: long-term results of the early cohort of patients treated at Harvard Cyclotron Laboratory and Massachusetts General Hospital. *Int J Radiat Oncol Biol Phys.* 2006;64(5):1348-54. PMID: 16580494

34.   Luu QT, Loredo LN, Archambeau JO, et al. Fractionated proton radiation treatment for pediatric craniopharyngioma: preliminary report. *Cancer J.* 2006;12(2):155-9. PMID: 16630407

35.   MacDonald SM, Trofimov A, Safai S, et al. Proton radiotherapy for pediatric central nervous system germ cell tumors: early clinical outcomes. *Int J Radiat Oncol Biol Phys.* 2011;79(1):121-9. PMID: 20452141

36.   Merchant TE, Hua CH, Shukla H, et al. Proton versus photon radiotherapy for common pediatric brain tumors: comparison of models of dose characteristics and their relationship to cognitive function. *Pediatric blood & cancer.* 2008;51(1):110-7. PMID: 18306274

37.   Moeller BJ, Chintagumpala M, Philip JJ, et al. Low early ototoxicity rates for pediatric medulloblastoma patients treated with proton radiotherapy. *Radiat Oncol.* 2011;6:58. PMID: 21635776

38.   Lee CT, Bilton SD, Famiglietti RM, et al. Treatment planning with protons for pediatric retinoblastoma, medulloblastoma, and pelvic sarcoma: how do protons compare with other conformal techniques? *Int J Radiat Oncol Biol Phys.* 2005;63(2):362-72. PMID: 16168831

39. Krengli M, Hug EB, Adams JA, et al. Proton radiation therapy for retinoblastoma: comparison of various intraocular tumor locations and beam arrangements. *Int J Radiat Oncol Biol Phys.* 2005;61:583-93. PMID: 15667981

40. Chang JW, Yu YS, Kim JY, et al. The clinical outcomes of proton beam radiation therapy for retinoblastomas that were resistant to chemotherapy and focal treatment. *Korean journal of ophthalmology : KJO.* 2011;25(6):387-93. PMID: 22131775

41. Munier FL, Verwey J, Pica A, et al. New developments in external beam radiotherapy for retinoblastoma: from lens to normal tissue-sparing techniques. *Clin Experiment Ophthalmol.* 2008;36:78-89. PMID: 18290958

42. Kozak KR, Adams J, Krejcarek SJ, et al. A dosimetric comparison of proton and intensity-modulated photon radiotherapy for pediatric parameningeal rhabdomyosarcomas. *Int J Radiat Oncol Biol Phys.* 2009;74(1):179-86. PMID: 19019562

43. Merchant TE. Proton beam therapy in pediatric oncology. *Cancer J.* 2009;15(4):298-305. PMID: 19672146

44. Timmermann B. Proton beam therapy for childhood malignancies: status report. *Klinische Padiatrie.* 2010;222(3):127-33. PMID: 20514614

45. Nilsson S, Norlen BJ, Widmark A. A systematic overview of radiation therapy effects in prostate cancer. *Acta Oncol.* 2004;43(4):316-81. PMID: 15303499

46. Kuban D, Pollack A, Huang E, et al. Hazards of dose escalation in prostate cancer radiotherapy. *Int J Radiat Oncol Biol Phys.* 2003;57(5):1260-8. PMID: 14630260

47. Sun F, Oyesanmi O, Fontanarosa J, et al. Therapies for Clinically Localized Prostate Cancer: Update of a 2008 Systematic Review. AHRQ Comparative Effectiveness Reviews. 2014. PMID: 25610935

48. TEC Assessment 2010. "Proton Beam Therapy for Prostate Cancer." BlueCross BlueShield Association Technology Evaluation Center, Vol. 25, Tab 10.

49. Brada M, Pijls-Johannesma M, De Ruysscher D. Current clinical evidence for proton therapy. *Cancer J.* 2009;15(4):319-24. PMID: 19672149

50. Grimm P, Billiet I, Bostwick D, et al. Comparative analysis of prostate-specific antigen free survival outcomes for patients with low, intermediate and high risk prostate cancer treatment by radical therapy. Results from the Prostate Cancer Results Study Group. *BJU international.* 2012;109 Suppl 1:22-9. PMID: 22239226

51. Efstathiou JA, Trofimov AV, Zietman AL. Life, liberty, and the pursuit of protons: an evidence-based review of the role of particle therapy in the treatment of prostate cancer. *Cancer J.* 2009;15(4):312-8. PMID: 19672148

52. Lee HJ, Jr., Macomber MW, Spraker MB, et al. Analysis of Gastrointestinal Toxicity in Patients Receiving Proton Beam Therapy for Prostate Cancer: A Single-Institution Experience. *Adv Radiat Oncol.* 2019;4(1):70-78. PMID: 30706013

53. Dutz A, Agolli L, Baumann M, et al. Early and late side effects, dosimetric parameters and quality of life after proton beam therapy and IMRT for prostate cancer: a matched-pair analysis. *Acta Oncol.* 2019;58(6):916-25. PMID: 30882264

54. Kammerer E, Guevelou JL, Chaikh A, et al. Proton therapy for locally advanced breast cancer: A systematic review of the literature. *Cancer treatment reviews.* 2018;63:19-27. PMID: 29197746

55. Jimenez RB, Hickey S, DePauw N, et al. Phase II Study of Proton Beam Radiation Therapy for Patients With Breast Cancer Requiring Regional Nodal Irradiation. *J Clin Oncol.* 2019;37(30):2778-85. PMID: 31449469

56. Nicholas O, Prosser S, Mortensen HR, et al. The Promise of Proton Beam Therapy for Oesophageal Cancer: A Systematic Review of Dosimetric and Clinical Outcomes. *Clin Oncol (R Coll Radiol).* 2021;33(8):e339-e58. PMID: 33931290

57. Wang X, van Rossum PSN, Chu Y, et al. Severe Lymphopenia During Chemoradiation Therapy for Esophageal Cancer: Comprehensive Analysis of Randomized Phase 2B Trial of Proton Beam Therapy Versus Intensity Modulated Radiation Therapy. *Int J Radiat Oncol Biol Phys.* 2024;118(2):368-77. PMID: 37652304

58. Lin SH, Hobbs BP, Verma V, et al. Randomized Phase IIB Trial of Proton Beam Therapy Versus Intensity-Modulated Radiation Therapy for Locally Advanced Esophageal Cancer. *J Clin Oncol.* 2020;38(14):1569-79. PMID: 32160096

59. Routman DM, Garant A, Lester SC, et al. A Comparison of Grade 4 Lymphopenia With Proton Versus Photon Radiation Therapy for Esophageal Cancer. *Adv Radiat Oncol.* 2019;4(1):63-69. PMID: 30706012

60. Patel SH, Wang Z, Wong WW, et al. Charged particle therapy versus photon therapy for paranasal sinus and nasal cavity malignant diseases: a systematic review and meta-analysis. *The Lancet Oncology.* 2014;15(9):1027-38. PMID: 24980873

61. Alterio D, D'Ippolito E, Vischioni B, et al. Mixed-beam approach in locally advanced nasopharyngeal carcinoma: IMRT followed by proton therapy boost versus IMRT-only. Evaluation of toxicity and efficacy. *Acta Oncol.* 2020;59(5):541-48. PMID: 32090645

62. Chuong M, Bryant J, Hartsell W, et al. Minimal acute toxicity from proton beam therapy for major salivary gland cancer. *Acta Oncol.* 2020;59(2):196-200. PMID: 31805791

63. Zenda S, Kawashima M, Arahira S, et al. Late toxicity of proton beam therapy for patients with the nasal cavity, para-nasal sinuses, or involving the skull base malignancy: importance of long-term follow-up. *International journal of clinical oncology.* 2014. PMID: 25135461

64. Spychalski P, Kobiela J, Antoszewska M, et al. Patient specific outcomes of charged particle therapy for hepatocellular carcinoma - A systematic review and quantitative analysis. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology.* 2019;132:127-34. PMID: 30825961

65. Igaki H, Mizumoto M, Okumura T, et al. A systematic review of publications on charged particle therapy for hepatocellular carcinoma. *International journal of clinical oncology.* 2018;23(3):423-33. PMID: 28871342

66. Bush DA, Volk M, Smith JC, et al. Proton beam radiotherapy versus transarterial chemoembolization for hepatocellular carcinoma: Results of a randomized clinical trial. *Cancer.* 2023;129(22):3554-63. PMID: 37503907

67. Kim TH, Koh YH, Kim BH, et al. Proton beam radiotherapy vs. radiofrequency ablation for recurrent hepatocellular carcinoma: A randomized phase III trial. *J Hepatol.* 2021;74(3):603-12. PMID: 33031846

68. Chen Y, Luo H, Liu R, et al. Efficacy and safety of particle therapy for inoperable stage II-III non-small cell lung cancer: a systematic review and meta-analysis. *Radiat Oncol.* 2023;18(1):86. PMID: 37217970

69. Volpe S, Piperno G, Colombo F, et al. Hypofractionated proton therapy for non-small cell lung cancer: Ready for prime time? A systematic review and meta-analysis. *Cancer treatment reviews.* 2022;110:102464. PMID: 36194908

70. Chi A, Chen H, Wen S, et al. Comparison of particle beam therapy and stereotactic body radiotherapy for early stage non-small cell lung cancer: A systematic review and hypothesis-generating meta-analysis. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology.* 2017;123(3):346-54. PMID: 28545956

71. Pijls-Johannesma M, Grutters JP, Verhaegen F, et al. Do we have enough evidence to implement particle therapy as standard treatment in lung cancer? A systematic literature review. *Oncologist.* 2010;15(1):93-103. PMID: 20067947

72. TEC Assessment 2010. "Proton Beam Therapy for Non-Small-Cell Lung Cancer." BlueCross BlueShield Association Technology Evaluation Center, Vol. 25, Tab 7.

73. Niedzielski JS, Yang J, Mohan R, et al. Differences in Normal Tissue Response in the Esophagus Between Proton and Photon Radiation Therapy for Non-Small Cell Lung Cancer Using In Vivo Imaging Biomarkers. *Int J Radiat Oncol Biol Phys.* 2017;99(4):1013-20. PMID: 29063837

74. Remick JS, Schonewolf C, Gabriel P, et al. First Clinical Report of Proton Beam Therapy for Postoperative Radiotherapy for Non-Small-Cell Lung Cancer. *Clinical lung cancer.* 2017;18(4):364-71. PMID: 28162946

75. Jongen A, Charlier F, Baker K, et al. Clinical Outcomes After Proton Beam Therapy for Locally Advanced Non-Small Cell Lung Cancer: Analysis of a Multi-institutional Prospective Registry. *Adv Radiat Oncol.* 2022;7(1):100767. PMID: 35071826

76. Chang JY, Verma V, Li M, et al. Proton Beam Radiotherapy and Concurrent Chemotherapy for Unresectable Stage III Non-Small Cell Lung Cancer: Final Results of a Phase 2 Study. *JAMA Oncol.* 2017;3(8):e172032. PMID: 28727865

77. Bush DA, Cheek G, Zaheer S, et al. High-dose hypofractionated proton beam radiation therapy is safe and effective for central and peripheral early-stage non-small cell lung cancer: results of a 12-year experience at Loma Linda University Medical Center. *Int J Radiat Oncol Biol Phys.* 2013;86(5):964-8. PMID: 23845845

78. Miyanaga N, Akaza H, Okumura T, et al. A bladder preservation regimen using intra-arterial chemotherapy and radiotherapy for invasive bladder cancer: a prospective study. *Int J Urol.* 2000;7(2):41-8. PMID: 10710246

79. Bush DA, Hillebrand DJ, Slater JM, et al. High-dose proton beam radiotherapy of hepatocellular carcinoma: preliminary results of a phase II trial. *Gastroenterology.* 2004;127(5 Suppl 1):S189-93. PMID: 15508084

80. Kagei K, Tokuuye K, Okumura T, et al. Long-term results of proton beam therapy for carcinoma of the uterine cervix. *Int J Radiat Oncol Biol Phys.* 2003;55(5):1265-71. PMID: 12654436

81. Huang D, Xia P, Akazawa P, et al. Comparison of treatment plans using intensity-modulated radiotherapy and three-dimensional conformal radiotherapy for paranasal sinus carcinoma. *Int J Radiat Oncol Biol Phys.* 2003;56(1):158-68. PMID: 12694834

82. Yuh GE, Loredo LN, Yonemoto LT, et al. Reducing toxicity from craniospinal irradiation: using proton beams to treat medulloblastoma in young children. *Cancer J.* 2004;10(6):386-90. PMID: 15701271

83. St Clair WH, Adams JA, Bues M, et al. Advantage of protons compared to conventional X-ray or IMRT in the treatment of a pediatric patient with medulloblastoma. *Int J Radiat Oncol Biol Phys.* 2004;58(3):727-34. PMID: 14967427

84. Hug EB, Fitzek MM, Liebsch NJ, et al. Locally challenging osteo- and chondrogenic tumors of the axial skeleton: results of combined proton and photon radiation therapy using three-dimensional treatment planning. *Int J Radiat Oncol Biol Phys.* 1995;31(3):467-76. PMID: 7852108

85. Ciulla TA, Danis RP, Klein SB, et al. Proton therapy for exudative age-related macular degeneration: a randomized, sham-controlled clinical trial. *Am J Ophthalmol.* 2002;134(6):905-6. PMID: 12470761

86. Flaxel CJ, Friedrichsen EJ, Smith JO, et al. Proton beam irradiation of subfoveal choroidal neovascularisation in age-related macular degeneration. *Eye (Lond).* 2000;14 (Pt 2):155-64. PMID: 10845009

87. Adams JA, Paiva KL, Munzenrider JE, et al. Proton beam therapy for age-related macular degeneration: development of a standard plan. *Med Dosim.* 1999;24(4):233-8. PMID: 10643731

88. Taghian AG, Kozak KR, Katz A, et al. Accelerated partial breast irradiation using proton beams: Initial dosimetric experience. *Int J Radiat Oncol Biol Phys.* 2006;65(5):1404-10. PMID: 16730137

89. Kozak KR, Smith BL, Adams J, et al. Accelerated partial-breast irradiation using proton beams: initial clinical experience. *Int J Radiat Oncol Biol Phys.* 2006;66(3):691-8. PMID: 17011445

90. Brown AP, Barney CL, Grosshans DR, et al. Proton beam craniospinal irradiation reduces acute toxicity for adults with medulloblastoma. *Int J Radiat Oncol Biol Phys.* 2013;86(2):277-84. PMID: 23433794

91. Holliday EB, Kocak-Uzel E, Feng L, et al. Dosimetric advantages of intensity-modulated proton therapy for oropharyngeal cancer compared with intensity-modulated radiation: A case-matched control analysis. *Med Dosim.* 2016. PMID: 27158021

92. Verma V, Shah C, Mehta MP. Clinical Outcomes and Toxicity of Proton Radiotherapy for Breast Cancer. *Clinical breast cancer.* 2016;16(3):145-54. PMID: 26995159

93. Verma V, Lin SH, Simone CB, 2nd, et al. Clinical outcomes and toxicities of proton radiotherapy for gastrointestinal neoplasms: a systematic review. *Journal of gastrointestinal oncology.* 2016;7(4):644-64. PMID: 27563457

94. Rwigema JM, Verma V, Lin L, et al. Prospective study of proton-beam radiation therapy for limited-stage small cell lung cancer. *Cancer.* 2017;123(21):4244-51. PMID: 28678434

95. Mukkamala LK, Mishra K, Daftari I, et al. Phase I/II randomized study of proton beam with anti-VEGF for exudative age-related macular degeneration: long-term results. *Eye (Lond).* 2020;34(12):2271-79. PMID: 32055016

96. Fok M, Toh S, Easow J, et al. Proton beam therapy in rectal cancer: A systematic review and meta-analysis. *Surg Oncol.* 2021;38:101638. PMID: 34340196

97. Atkins KM, Pashtan IM, Bussiere MR, et al. Proton Stereotactic Radiosurgery for Brain Metastases: A Single-Institution Analysis of 370 Patients. *Int J Radiat Oncol Biol Phys.* 2018;101(4):820-29. PMID: 29976494

98. Hong TS, Wo JY, Borger DR, et al. Phase II Study of Proton-Based Stereotactic Body Radiation Therapy for Liver Metastases: Importance of Tumor Genotype. *Journal of the National Cancer Institute.* 2017;109(9). PMID: 28954285

99. Walcott BP, Hattangadi-Gluth JA, Stapleton CJ, et al. Proton beam stereotactic radiosurgery for pediatric cerebral arteriovenous malformations. *Neurosurgery.* 2014;74(4):367-73; discussion 74. PMID: 24448188

100. Hattangadi JA, Chapman PH, Bussiere MR, et al. Planned two-fraction proton beam stereotactic radiosurgery for high-risk inoperable cerebral arteriovenous malformations. *Int J Radiat Oncol Biol Phys.* 2012;83(2):533-41. PMID: 22099050

101. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™. Bone Cancer. v2.2024. [cited 4/17/2024]. 'Available from:' https://www.nccn.org/professionals/physician_gls/pdf/bone.pdf.

102. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™. Prostate Cancer. v.3.2024. [cited 4/17/2024]. 'Available from:' https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf.

103. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™. Central Nervous System Cancers. v.1.2023. [cited 04/17/2024]. 'Available from:' https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf.
104. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™. Pediatric Central Nervous System Cancers. v1.2024. [cited 4/18/2024]. 'Available from:' https://www.nccn.org/professionals/physician_gls/pdf/ped_cns.pdf.
105. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™. Non-Small Cell Lung Cancer. v.4.2024. 2024. PMID:
106. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™. Mesothelioma: Pleural. v4.2024. [cited 4/17/2024]. 'Available from:' https://www.nccn.org/professionals/physician_gls/pdf/meso_pleural.pdf.
107. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™. Head and Neck Cancers. v3.2024. [cited 4/17/2024]. 'Available from:' https://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf.
108. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™. Uveal Melanoma. v1.2023. [cited 04/17/2024]. 'Available from:' https://www.nccn.org/professionals/physician_gls/pdf/uveal.pdf.
109. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™. Esophageal and Esophagogastric Junction Cancers. v1.2024. [cited 4/17/2024]. 'Available from:' https://www.nccn.org/professionals/physician_gls/pdf/esophageal.pdf.
110. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™. B-Cell Lymphomas. v1.2024. [cited 4/17/2024]. 'Available from:' https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf.
111. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™. Soft Tissue Sarcoma. v3.2023. [cited 4/17/2024]. 'Available from:' https://www.nccn.org/professionals/physician_gls/pdf/sarcoma.pdf.
112. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™. Thymomas and Thymic Carcinomas. v1.2024. [cited 4/17/2023]. 'Available from:' https://www.nccn.org/professionals/physician_gls/pdf/thymic.pdf.
113. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™. Biliary Tract Cancers. v1.2024. [cited 4/17/2024]. 'Available from:' https://www.nccn.org/professionals/physician_gls/pdf/btc.pdf.
114. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™. Breast Cancer. v2.2024. [cited 4/17/2024]. 'Available from:' https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf.
115. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™. Kidney Cancer. v3.2024. [cited 4/18/2024]. 'Available from:' https://www.nccn.org/professionals/physician_gls/pdf/kidney.pdf.
116. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™. Pancreatic Adenocarcinoma. v1.2024. [cited 4/18/2024]. 'Available from:' https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf.
117. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™. Rectal Cancer. v1.2024. [cited 4/17/2024]. 'Available from:' https://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf.
118. ASTRO Model Policies: Proton Beam Therapy. [cited 4/18/2024]. 'Available from:' https://www.astro.org/ASTRO/media/ASTRO/Daily%20Practice/PDFs/ASTROPBTModelPolicy.pdf.

119. Gondi V, Bauman G, Bradfield L, et al. Radiation Therapy for Brain Metastases: An ASTRO Clinical Practice Guideline. *Practical Radiation Oncology.* 2022;12(4):265-82. PMID:
120. Eastham JA, Boorjian SA, Kirkby E. Clinically Localized Prostate Cancer: AUA/ASTRO Guideline. *J Urol.* 2022:101097ju0000000000002854. PMID: 35830561
121. Kindler HL, Ismaila N, III SGA, et al. Treatment of Malignant Pleural Mesothelioma: American Society of Clinical Oncology Clinical Practice Guideline. *Journal of Clinical Oncology.* 2018;36(13):1343-73. PMID: 29346042
122. Willers H, Stinchcombe TE, Barriger RB, et al. ACR Appropriateness Criteria(R) induction and adjuvant therapy for N2 non-small-cell lung cancer. *Am J Clin Oncol.* 2015;38:197-205. PMID: 25803563
123. Nguyen PL, Aizer A, Assimos DG, et al. ACR Appropriateness Criteria(R) Definitive External-Beam Irradiation in stage T1 and T2 prostate cancer. *Am J Clin Oncol.* 2014;37:278-88. PMID: 25180754
124. Decker RH, Langer CJ, Rosenzweig KE, et al. ACR Appropriateness Criteria(R) Postoperative Adjuvant Therapy in Non-Small Cell Lung Cancer. *Am J Clin Oncol.* 2011;34(5):537-44. PMID: 21946673
125. Chang JY, Kestin LL, Barriger RB, et al. ACR Appropriateness Criteria(R) nonsurgical treatment for locally advanced non-small-cell lung cancer: good performance status/definitive intent. *Oncology (Williston Park).* 2014;28(8):706-10, 12, 14 passim. PMID: 25140629
126. Rosenzweig KE, Movsas B, Bradley J, et al. ACR appropriateness criteria on nonsurgical treatment for non-small-cell lung cancer: poor performance status or palliative intent. *J Am Coll Radiol.* 2009;6:85-95. PMID: 19179235
127. Chang JY, Jabbour SK, De Ruysscher D, et al. Consensus Statement on Proton Therapy in Early-Stage and Locally Advanced Non-Small Cell Lung Cancer. *Int J Radiat Oncol Biol Phys.* 2016;95(1):505-16. PMID: 27084663

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

Codes	Number	Description
	77299	Unlisted procedure, therapeutic radiology clinical treatment planning
	77301	Intensity modulated radiotherapy plan, including dose volume histograms for target and critical structure partial tolerance specification
	77338	Multi-leaf collimator (MLC) device(s) for intensity modulated radiation therapy (IMRT), design and construction per IMRT plan
	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
	77399	Unlisted procedure, medical radiation physics, dosimetry and treatment devices, and special services
	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
	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:

Codes	Number	Description
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