BSC8.04	Charged-Particle (Proton or Helium Ion) Radiotherapy for Neoplastic Conditions		
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Section:	8.0 Therapy	**Page:**	Page 1 of 92

Policy Statement

I. Charged-particle irradiation with proton or helium ion beams may be considered **medically necessary** for treatment in **any** of the following clinical situations:
   A. Primary therapy for melanoma of the uveal tract (iris, choroid, or ciliary body) and **both** of the following:
      1. No evidence of metastasis or extrascleral extension
      2. Tumors up to 24 millimeters (mm) in largest diameter and 14 mm in height
   B. Postoperative therapy (with or without conventional high-energy x-rays) in patients who have undergone biopsy or partial resection of chordoma or low-grade (I or II) chondrosarcoma of the basisphenoid region (e.g., skull-base chordoma or chondrosarcoma) or cervical spine. Patients eligible for this treatment have residual localized tumor without evidence of metastasis
   C. Pediatric central nervous system tumors

II. Charged-particle irradiation with proton or helium ion beams may be considered **medically necessary** for treatment in **any** of the following clinical situations:
   A. Where treatment planning with conventional or advanced photon-based radiotherapy (see Policy Guidelines section) cannot meet dose-volume constraints for normal tissue radiation tolerance (see Policy Guidelines section)
   B. In tumors requiring reirradiation where cumulative critical structure dose would exceed normal tissue tolerance
   C. In patients with tumors who also have radiation-sensitizing genetic syndromes (including but not limited to mutations in NF1 in neurofibromatosis type 1, RB1 in retinoblastoma, TP53 in Li-Fraumeni, or WT1 in Wilms tumors] where total volume of radiation minimization is critical. Radiation therapy of the existing tumor may put these patients at higher risk for secondary malignant tumors due to the radiation exposure from treatment

III. The following are considered **investigational**:
   A. Use of charged-particle irradiation with proton or helium ion beams as a Non-curative (palliative) treatment of cancer
   B. Other applications of charged-particle irradiation with proton or helium ion beams

Note: Although charged-particle irradiation with proton or helium beams may be **medically necessary** for the treatment of clinically localized prostate cancer, Intensity Modulated Radiation Therapy (IMRT) is also an effective treatment for this diagnosis and **medically necessary**. When there are **two medically necessary** procedures for the treatment of clinically localized prostate cancer, Blue Shield will consider the relative cost of each and provide coverage for the procedure that is most cost effective. The other procedure will be denied as **not cost effective**, and therefore **not medically necessary** under the circumstances.

Image Guided Radiation Therapy (IGRT)

IV. IGRT may be considered **medically necessary** as an approach to delivering radiotherapy when combined with **any** of the following treatments (see Policy Guidelines):
   A. Intensity-modulated radiotherapy (IMRT)
   B. Stereotactic body radiation therapy (SBRT)
   C. Proton delivery

V. IGRT is considered **investigational** as an approach to delivering radiotherapy when combined with **any** of the following treatments:
   A. Conventional three-dimensional conformal radiation therapy (3D CRT) (see Policy Guidelines for considerations)
   B. Stereotactic radiosurgery (SRS)
   C. Electronic brachytherapy

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

Pediatric Central Nervous System Tumors

Evidence is lacking on the definition of age parameters for the use of proton beam therapy in pediatric patients. Some studies using proton beam therapy in pediatric central nervous system (CNS) tumors have mostly included patients younger than 3 years of age. However, experts cite the benefit of proton beam therapy in pediatric patients of all ages (less than 21 years of age).

Organs at Risk

Organs at risk are defined as normal tissues whose radiation sensitivity may significantly influence treatment planning and/or prescribed radiation dose. These organs at risk may be particularly vulnerable to clinically important complications from radiation toxicity. Table PG1 outlines radiation doses that are generally considered tolerance thresholds for these normal structures in various organ regions. Clinical documentation based on dosimetry plans may be used to demonstrate that radiation by conventional or advanced photon-based radiotherapy, including intensity-modulated radiotherapy (IMRT), volume-modulated arc therapy (VMAT), stereotactic radiosurgery (SRS), or stereotactic body radiation therapy (SBRT), would exceed tolerance doses to structures at risk. For patients with radiation-sensitizing genetic syndromes such as neurofibromatosis type 1 (NF-1) or retinoblastoma, clinical documentation of the condition may be used to demonstrate increased risk from exposure during treatment.

For charged-particle radiotherapy (proton or helium ion) therapy to provide outcomes superior to photon-based radiotherapy, there must be a clinically meaningful decrease in the radiation exposure to normal structures. There is no standard definition for a clinically meaningful decrease in radiation dose. In principle, a clinically meaningful decrease would signify a significant reduction in anticipated complications of radiation exposure. To document a clinically meaningful reduction in dose, dosimetry planning studies should demonstrate a significant decrease in the maximum dose of radiation delivered per unit of tissue, and/or a significant decrease in the volume of normal tissue exposed to potentially toxic radiation doses. While radiation tolerance dose levels for normal tissues are well-established, the decrease in the volume of tissue exposed that is needed to provide a clinically meaningful benefit has not been standardized. Therefore, precise parameters for a clinically meaningful decrease cannot be provided.

The following Normal Tissue Constraint Guidelines are derived from the textbook: Radiation Oncology: A Question-Based Review published by Lippincott Williams & Wilkins, 2010 (author: Hristov et al., 2010). According to the author, most dosages were derived from randomized studies or consensus guidelines; however, pediatric dose constraints will vary greatly from protocol to protocol. Sources used in the development of the guidelines included the American Brachytherapy Society (ABS); Clinical practice guidelines from Johns Hopkins Hospital (JHH); the International Journal of Radiation Oncology *Biology* Physics (IJROBP); the National Comprehensive Cancer Network (NCCN), Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC); and the Radiation Therapy Oncology Group (RTOG) protocols at the time of publication.

The following guidelines shown in Table PG1, are only intended to serve as a guide and may not be applicable to all clinical scenarios.

Table PG1. Normal Tissue Constraint Guidelines

Organ	Constraints
Central Nervous System (1.8-2.0 Gray/fraction [Gy/fx])	
• Spinal Cord	max 50 Gy (full cord cross-section); tolerance increases by 25% 6 mo after 1st course (for re-irradiation)
• Brain	max 72 Gy (partial brain); avoid >2 Gy/fx or hyperfractionation
• Chiasm/Optic Nerves	max 55 Gy
• Brainstem	Entire brainstem <54 Gy, V59 Gy <1–10 cc
• Eyes (globe)	mean <35 Gy, max 54 Gy
• Lens	max 7 Gy
• Retina	max 50 Gy
• Lacrimal Gland	max 40 Gy
• Inner ear/cochlea	mean </=45 Gy (consider constraining to </=35 Gy with concurrent cisplatin)
• Pituitary gland	max 45 Gy (for panhypopituitarism, lower for GH deficiency)
• Cauda equina	max 60 Gy
Central Nervous System (single fraction)	
• Spinal Cord	max 13 Gy (if 3 fxs, max 20 Gy)
• Brain	V12 Gy <5–10 cc
• Chiasm/Optic Nerves	max 10 Gy
• Brainstem	max 12.5 Gy
• Sacral plexus	V18 <0.035 cc, V14.4 <5 cc
• Cauda equina	V16 <0.035 cc, V14 <5 cc
Head and Neck (1.8–2.0 Gy/fx)	
• Parotid gland(s)	mean <25 Gy (both glands) or mean <20 Gy (1 gland)
• Submandibular gland(s)	mean <35 Gy
• Larynx	mean </=44 Gy, V50 </=27%, max 63–66 Gy (when risk of tumor involvement is limited)
• TMJ/mandible	max 70 Gy (if not possible, then V75 <1 cc)
• Oral cavity	Non-oral cavity cancer: mean <30 Gy, avoid hot spots >60 Gy Oral cavity cancer: mean <50 Gy, V55 <1 cc, max 65 Gy
• Esophagus (cervical)	V45 <33%
• Pharyngeal constrictors	mean <50 Gy
• Thyroid	V26 <20%
Thoracic (1.8–2.0 Gy/fx)	
• Brachial plexus	max 66 Gy, V60 <5%
• Lung (combined lung for lung cancer treatment)	mean <20–23 Gy, V20 <30%–35%
• Lung (ipsilateral lung for breast cancer treatment)	V25 <10%
• Single lung (after pneumonectomy)	V5 <60%, V20 <4–10%, MLD <8 Gy
• Bronchial tree	max 80 Gy
• Heart (lung cancer treatment)	Heart V45 <67%; V60 <33%
• Heart (breast cancer treatment)	V25 <10%
• Esophagus	V50 <32% ;V60 <33%
Thoracic (hypofractionation) Note: the max dose limits refer to volumes >0.035 cc (~3 mm^3).	

Organ	Constraints
• Spinal cord	1 fraction: 14 Gy 3 fractions: 18 Gy (6 Gy/fx) 4 fractions: 26 Gy (6.5 Gy/fx) 5 fractions: 30 Gy (6 Gy/fx)
• Esophagus	1 fraction: 15.4 Gy 3 fractions: 30 Gy (10 Gy/fx) 4 fractions: 30 Gy (7.5 Gy/fx) 5 fractions: 32.5 Gy (6.5 Gy/fx)
• Brachial plexus	1 fraction: 17.5 Gy 3 fractions: 21 Gy (7 Gy/fx) 4 fractions: 27.2 Gy (6.8 Gy/fx) 5 fractions: 30 Gy (6 Gy/fx)
• Heart/Pericardium	1 fraction: 22 Gy 3 fractions: 30 Gy (10 Gy/fx) 4 fractions: 34 Gy (8.5 Gy/fx) 5 fractions: 35 Gy (7 Gy/fx)
• Great vessels	1 fraction: 37 Gy 3 fractions: 39 Gy (13 Gy/fx) 4 fractions: 49 Gy (12.25 Gy/fx) 5 fractions: 55 Gy (11 Gy/fx)
• Trachea/Large Bronchus	1 fraction: 20.2 Gy 3 fractions: 30 Gy (10 Gy/fx) 4 fractions: 34.8 Gy (8.7 Gy/fx) 5 fractions: 40 Gy (8 Gy/fx)
• Rib	1 fraction: 30 Gy 3 fractions: 30 Gy (10 Gy/fx) 4 fractions: 32 Gy (7.8 Gy/fx) 5 fractions: 32.5 Gy (6.5 Gy/fx)
• Skin	1 fraction: 26 Gy 3 fractions: 30 Gy (10 Gy/fx) 4 fractions: 36 Gy (9 Gy/fx) 5 fractions: 40 Gy (8 Gy/fx)
• Stomach	1 fraction: 12.4 Gy 3 fractions: 27 Gy (9 Gy/fx) 4 fractions: 30 Gy (7.5 Gy/fx) 5 fractions: 35 Gy (7 Gy/fx)
Gastrointestinal (GI) (1.8–2.0 Gy/fx)	
• Stomach	TD 5/5 whole stomach: 45 Gy
• Small bowel	V45 <195 cc
• Liver (metastatic disease)	mean liver <32 Gy (liver = normal liver minus gross disease)
• Liver (primary liver cancer)	mean liver <28 Gy (liver = normal liver minus gross disease)
• Colon	45 Gy, max dose 55 Gy
• Kidney (bilateral)	mean <18 Gy, V28 <20%, V23 Gy <30%, V20 <32%, V12 <55%. If mean kidney dose to 1 kidney >18 Gy, then constrain remaining kidney to V6 <30%.
Gastrointestinal (GI) (single fraction)	
• Duodenum	V16 <0.035 cc, V11.2 <5 cc
• Kidney (Cortex)	V8.4 <200 cc
• Kidney (Hilum)	V10.6 <66%
• Colon	V14.3 <20 cc, V18.4 <0.035 cc
• Jejunum/Ileum	V15.4 <0.035 cc, V11.9 <5 cc
• Stomach	V16 <0.035 cc, V11.2 <10 cc
• Rectum	V18.4 <0.035 cc, V14.3 <20 cc
Genitourinary (GU) (1.8-2.0 Gy/fx)	
• Femoral heads	V50 <5%

Organ	Constraints
• Rectum	V75 <15% , V70 <20%, V65 <25%, V60 <35%, V50 <50%
• Bladder	V80 <15%, V75 <25%, V70 <35%, V65 <50%
• Testis	V3 <50%
• Penile bulb	Mean dose to 95% of the volume <50 Gy. D70 </=70 Gy, D50 </=50 Gy
Genitourinary (GU) (LDR prostate brachytherapy)	
• Urethra	Volume of urethra receiving 150% of prescribed dose (Ur150) <30%
• Rectum	Volume of rectum receiving 100% of prescribed dose (RV100) <0.5 cc
Gynecological (GYN)	
• Bladder point (cervical brachytherapy)	Max 80 Gy (LDR equivalent dose)
• Rectal point (cervical brachytherapy)	Max 75 Gy (LDR equivalent dose)
• Proximal vagina (mucosa) (cervical brachytherapy)	Max 120 Gy (LDR equivalent dose)
• Distal vagina (mucosa) (cervical brachytherapy)	Max 98 Gy (LDR equivalent dose

Coding

Image Guided Radiation Therapy (IGRT) Considerations:

The following codes are for proton therapy delivery use. The CPT codes do not include image guidance in the delivery code for the facility (technical, or -TC modifier) component. In addition, the professional component (-26 modifier) is also allowed for payment for IGRT services.

When proton beam therapy is used, the following specific CPT codes are available for delivery:

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

The following codes are typical for IGRT. Up to one unit per session can be allowed (although balanced by additional radiation for the imaging, so IGRT may not take place with every treatment session).

- **77014**: Computed tomography guidance for placement of radiation therapy fields
- **G6001**: Ultrasonic guidance for placement of radiation therapy fields
- **G6002**: Stereoscopic x-ray guidance for localization of target volume for the delivery of radiation therapy
- **77387**: Guidance for localization of target volume for delivery of radiation treatment, includes intrafraction tracking, when performed
- **G6017**: Intra-fraction localization and tracking of target or patient motion during delivery of radiation therapy (e.g., 3D positional tracking, gating, 3D surface tracking), each fraction of treatment

77387 and G6017 do not have a technical component (facility) but can be used for professional services. 77387 is preferred for use over G6017. Intra-fraction tracking is often done by the technician employed by the hospital which would be included in the delivery fee. Professional services performed by the physician should be documented if billed.

There is no specific CPT code for MRI guidance. 77387 is the preferred code for that professional service.

77387 does not have a recognized technical (facility) component and therefore would not require the -26 modifier to indicate professional (physician) services (as opposed to 77014, G6001 and G6002 which have both, and should be billed with the appropriate modifiers -TC or -26).

Image-Guided Radiation Therapy Background

Image-Guided Radiation Therapy (IGRT) is a method by which image guidance is applied to place the isocenter for the upcoming treatment appropriately. This technology typically is applied for an individual undergoing charged particle/proton beam therapy. If the isocenter placement is the primary concern, then IGRT is typically the method utilized. Multiple publications have documented the additional radiation exposure which occurs in with the use of IGRT. Patient doses range from 1-3 mGy for gantry mounted kV systems to between 10 and 50 mGy per image for cone beam and fan beam CT scans. The risks of radiation exposure must be weighed against the benefits of daily imaging. In clinical scenarios where IGRT is considered medically necessary, the technique chosen should expose the patient to the minimum amount of radiation needed to achieve adequate visualization. IGRT, when used, is considered a component of simulation and radiation delivery for the technical (facility) portion of the work for IMRT and SBRT based on the CPT code descriptions.

The use of proton beam or helium ion radiotherapy typically consists of a series of CPT codes that describe the individual steps required:

- Medical radiation physics
- Clinical treatment planning
- Treatment delivery
- Clinical treatment management

The following CPT codes have been used:

Medical Radiation Physics

- **77399**: Unlisted procedure, medical radiation physics, dosimetry and treatment devices, and special services

Clinical Treatment Planning

- **77261**: Therapeutic radiology treatment planning; simple (Includes planning for single treatment area included in a single port or simple parallel opposed ports with simple or no blocking)
- **77262**: Therapeutic radiology treatment planning; intermediate (Includes planning for three or more converging ports, two separate treatment sites, multiple blocks, or special time dose constraints)
- **77263**: Therapeutic radiology treatment planning; complex (Includes planning for very complex blocking, custom shielding blocks, tangential ports, special wedges or compensators, three or more separate treatment areas, rotational or special beam considerations, combination of treatment modalities)
- **77299**: Unlisted procedure, therapeutic radiology clinical treatment planning

Simulation

- **77280**: Therapeutic radiology simulation-aided field setting; simple (includes Simulation of a single treatment site)
- **77285**: Therapeutic radiology simulation-aided field setting; intermediate (includes Two different treatment sites)
- **77290***: Therapeutic radiology simulation-aided field setting; complex (includes all of the following):

- Brachytherapy
- Complex blocking
- Contrast material
- Custom shielding blocks
- Hyperthermia probe verification
- Rotation
- Arc or particle therapy
- Simulation for 3 or more treatment sites

Radiation Therapy Planning

- **77295:** 3-dimensional radiotherapy plan, including dose-volume histograms
- **77301*:** Intensity modulated radiotherapy plan, including dose-volume histograms for target and critical structure partial tolerance specifications

*Note: Simulation (CPT code 77290) is considered to be included in the fee paid for an IMRT radiotherapy plan (CPT code 77301) and is not covered as a separate procedure.

Treatment Delivery

Codes used for treatment delivery will depend on the energy source used, typically either photons or protons. For photon (i.e., with a Gamma Knife or LINAC device) nonspecific radiotherapy treatment delivery, CPT codes may be used based on the voltage of the energy source (i.e., codes 77402-77412).

When proton beam therapy is used, the following specific CPT codes are available:

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

Note: Codes for treatment delivery primarily reflect the costs related to the energy source used—and not physician work.

Clinical Treatment Management

- **77499**: Unlisted procedure, therapeutic radiology treatment management

Table PG2. Allowable Codes and Frequencies for IMRT/Proton

Description	Code	Maximum per course of treatment	Notes
For IMRT: IGRT (Image Guided Radiation Therapy)	77014 (CT) 77387 (any) G6001 (stereotactic) G6002 (US) G6017	Professional portion allowed for up to 1 unit for each delivery session when provided	Facility fee (TC) included with delivery codes 77385/ 77386/ 77373 for IMRT/ SBRT. 77387 and G6017 are for pro fee only. Others need -26 modifier for approval
For Proton: IGRT (Image Guided Radiation Therapy)	77014, 77387, G6001, G6002, G6017	Up to 1 unit per delivery session when provided	Facility fee (TC) not included with delivery codes for proton so they can be billed. 77387 and G6017 are for pro fee only. Others need -26 or TC modifiers.
Clinical Treatment Planning	77261, 77262 or 77263	1	
Simulation	77280, 77285, 77290	0	May not be billed with 77301. 1 unit of 77290 + 1 boost is allowed for proton therapy when using 77295 instead
Verification Simulation	77280	0	One per simulation allowed
Respiratory Motion Management	77293	0	1 for breast, lung, and upper abdominal or thoracic cancer areas

Description	Code	Maximum per course of treatment	Notes
3D CRT Plan	77295	0	May not be billed with 77301. 1 unit may be allowed for proton therapy.
IMRT Plan	77301	1	If comparison 3D plan is generated, it is included in 77301
Basic Dosimetry	77300	4+ 1 boost, up to a max of 10 with documentation	0 if billed with 77306, 77307, 77321, 0394T or 0395T
Teletherapy Isodose Plan, Simple	77306	1 for mid-Tx change in volume/contour	Not on the same day as 77300; may not bill 77306 and 77307 together; documentation of medical necessity is required for more than 1
Teletherapy Isodose Plan, Complex	77307	1 for mid-Tx change in volume/contour	Not on the same day as 77300; may not bill 77306 and 77307 together; documentation of medical necessity is required for more than 1
Special Dosimetry Calculation	77331	0	Needs documentation for review
Treatment Devices, Designs, and Construction	77332, 77333, 77334	1, 5 or 10	-If billed w/ MLC (77338): 1 -If billed w/o MLC: 5 (any combination) -More may be allowed when documentation of medical necessity is provided (such as additional beams), maximum of 10
Multi-leaf Collimater (MLC)	77338	1	MLC may not be reported in conjunction with HCPCS G6016
Special Radiation Physics Consult	77370	0	May allow x 1; documentation of medical necessity required
Special MD Consultation (Special Tx Procedure)	77470	0	May allow x 1; documentation of medical necessity required
Medical Physics Management	77336	8	Allowed once per 5 courses of therapy
Radiation Treatment Management	77427	8	Allowed once per 5 courses of therapy
Radiation (IMRT or Proton) Delivery, prostate and breast cancer	IMRT 77385 or G6015; Proton 77520, 77522, 77523	Using IMRT or Proton: 28 for prostate cancer Using IMRT only: -16 for breast cancer without boost -24 for breast cancer with boost (IMRT only)	Prostate cancer: Documentation of medical necessity needed for more than 28 treatments Breast cancer: documentation of medical necessity needed for treatments beyond 16 IMRT delivery sessions without boost and/or 24 IMRT delivery sessions with boost.
Radiation (IMRT or Proton) Delivery, all other cancers	IMRT 77385, 77386; or G6015-G6016: Proton 77520, 77522, 77523, 77525	No limit	All cancers other than hypofractionated prostate or breast

Description

Charged-particle beams consisting of protons or helium ions are a type of particulate radiotherapy. Treatment with charged-particle radiotherapy is proposed for a large number of tumors that would benefit from the delivery of a high dose of radiation with limited scatter, minimizing the radiation dose to surrounding normal tissues and critical structures.

Related Policies

- Intensity-Modulated Radiotherapy of the Breast and Lung
- Intensity-Modulated Radiotherapy of the Prostate
- Intensity-Modulated Radiotherapy: Abdomen and Pelvis
- Intensity-Modulated Radiotherapy: Cancer of the Head and Neck or Thyroid
- Radiation Oncology
- Stereotactic Radiosurgery and Stereotactic Body Radiotherapy

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

Radiotherapy is a procedure and, therefore, 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. The FDA's Center for Devices and Radiological Health has 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.

Rationale

Background
Charged-particle beams consisting of protons or helium ions are a type of particulate radiotherapy. They have several unique properties that distinguish them from conventional electromagnetic (i.e., photon) radiotherapy, including minimal scatter as particulate beams pass through tissue, and deposition of ionizing energy at precise depths (i.e., the Bragg peak). Thus, radiation exposure of surrounding normal tissues and critical structures is minimized. 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 adequate radiation doses to the tumor is limited by the proximity of vital radiosensitive tissues or structures.

Literature Review

The following conclusions are based on a review of the evidence, including but not limited to, published evidence and clinical expert opinion, solicited via Blue Cross Blue Shield Association's (BCBSA) Clinical Input Process.

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function- including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, two domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Charged-Particle (Proton or Helium Ion) Radiotherapy for Uveal Melanomas

Clinical Context and Therapy Purpose

The purpose of charged-particle (proton or helium ion) radiotherapy (RT) in patients who have uveal melanoma(s) is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does charged-particle RT improve the net health outcome in patients who have uveal melanoma(s)?

The following PICO was used to select literature to inform this review.

Patients

The relevant population of interest is individuals with uveal melanoma(s). Uveal melanoma, although rare, is the most common primary intraocular malignancy in adults. Mean age-adjusted incidence of uveal melanoma in the United States is 6.3 per million people among whites, 0.9 among Hispanics, and 0.24 among blacks. Uveal melanoma has a progressively rising, age-specific, incidence rate that peaks near age 70.[1,]

Interventions

The therapy being considered is charged-particle (proton or helium ion) RT. Charged-particle therapy is administered in specially equipped treatment centers. PBT can be administered with or without stereotactic techniques.

Comparators

The following practices are currently being used to make decisions about the treatment of uveal melanoma(s): plaque RT, surgical resection, and transpupillary thermotherapy. Primary, localized uveal melanoma can be treated by surgery or RT. In general, larger tumors require enucleation surgery and smaller tumors can be treated with RT, but specific treatment parameters are lacking. The most common treatment of localized uveal melanoma is RT, which is preferred because it can spare vision in most cases. For smaller lesions, RCTs have shown that patients receiving RT or

enucleation progress to metastatic disease at similar rates after treatment.[2,] RT can be delivered by various mechanisms, most commonly brachytherapy and proton beam therapy (PBT). Treatment of primary uveal melanoma improves local control and spares vision, however, the 5-year survival rate (81.6%) has not changed over the last 3 decades, suggesting that life expectancy is independent of successful local eye treatment.[3,]

Outcomes

The general outcomes of interest are overall survival (OS), disease-free survival, change in disease status (local recurrence), and treatment-related morbidity. RT is used as part of first-line treatment for uveal melanoma. One- and 5-year outcomes are indicators of successful treatment.

Systematic Reviews

This section was informed by a Blue Cross Blue Shield Association Technology Evaluation Center (TEC) Assessment (1996) that concluded proton therapy was at least as effective as alternative therapies for treating uveal melanoma.[4,]

More recently, Wang et al (2013) published a systematic review of the literature on charged-particle (proton, helium, carbon ion) RT for uveal melanoma.[5,] Reviewers included 27 controlled and uncontrolled studies that reported health outcomes (e.g., mortality, local recurrence). Three studies were RCTs. One RCT compared helium ion therapy with an alternative treatment (brachytherapy). The other 2 RCTs compared different proton beam protocols and so cannot 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-naive patients (all but one of the identified studies). In a pooled analysis of data from 9 studies, there was no statistically significant difference in mortality rates with charged-particle therapy compared with brachytherapy (odds ratio, 0.13; 95% confidence interval [CI], 0.01 to 1.63). However, there was a significantly lower rate of local recurrence with charged-particle therapy compared with brachytherapy in a pooled analysis of 14 studies (odds ratio, 0.22; 95% CI, 0.21 to 0.23). There were also significantly lower rates of radiation retinopathy and cataract formation in patients treated with charged-particle therapy than brachytherapy (pooled rates of 0.28 vs 0.42 and 0.23 vs 0.68, respectively). Reviewers concluded there was low-quality evidence that charged-particle therapy is at least as effective as alternative therapies for the primary treatment of uveal melanoma and is better at preserving vision.

Randomized Controlled Trials

An RCT by Mishra et al (2015) compared charged-particle therapy using helium ions and iodine 125 (I-125) plaque therapy in 184 patients with uveal melanoma.[6,] The primary end point was local tumor control. Median follow-up was 14.6 years in the charged-particle therapy group and 12.3 years in the I-125 plaque therapy group. The rate of local control at 12 years was significantly higher in the helium ion group (98%; 95% CI, 88% to 100%) than in the I-125 plaque therapy group (79%; 95% CI, 68% to 87%; p=0.006). The OS rate at 12 years was 67% (95% CI, 55% to 76%) in the helium ion group and 54% (95% CI, 43% to 63%) in the I-125 plaque therapy group (p=0.02).

Comparative Observational Studies

Lin et al (2017) published a retrospective review of 1224 patients in the National Cancer Data-base who had choroid melanoma and were treated with brachytherapy (n=996) or proton therapy (n=228) between 2004 and 2013.[7,] For the brachytherapy group, median follow-up was 37 months; for proton-treated patients, median follow-up was 29 months. Proton-treated patients were propensity-matched with a smaller cohort of brachytherapy-treated patients (n=228 each). The OS rate at 2 years was 97% for brachytherapy-treated patients and 93% for proton-treated patients. The 5-year OS rates were 77% and 51% for brachytherapy- and proton-treated groups, respectively (p=0.008). Factors likely to predict poorer survival rates included the following: older age (hazard ratio [HR], 1.06; 95% CI, 1.03 to 1.09; p<0.02); tumor diameter of 12 to 18 mm (HR=2.48; 95% CI, 1.40 to 4.42; p<0.02);

tumor diameter greater than 18 mm (HR=6.41; 95% CI, 1.45 to 28.35; p<0.02); and proton treatment (HR=1.89; 95% CI, 1.06 to 3.37; p<0.02).

Long-Term Studies

Toutee et al (2019) reported 5-year visual outcomes for patients with stage T1 uveal melanoma (N = 424) treated by proton therapy, as a function of their distance to the fovea-optic disc in a long-term retrospective study.[8,] With a mean follow-up duration of 122 months, no tumor recurrences were observed. Mean baseline and final best corrected visual acuities were measured for patients with posterior edge of tumor located at ≥3mm (N = 75) or <3mm (N = 317) as 20/25 & 20/32 and 20/40 & 20/80. The frequency of a 20/200 or greater conservation was 93.2% and 60.1%, respectively (p < 0.001). Thus, proton beam therapy for stage T1 uveal melanoma was shown to yield excellent tumor control and good long-term visual outcomes, particularly for tumors located ≥3mm from the fovea-optic disc.

Section Summary: Uveal Melanoma

Systematic reviews, including a 1996 TEC Assessment, have concluded that charged-particle RT is at least as effective as alternative therapies for treating uveal melanomas and is better at preserving vision. A 2013 systematic review of charged-particle therapy for uveal melanoma identified 3 RCTs and a number of observational studies. This systematic review found that charged-particle therapy was associated with a significantly lower rate of local recurrence than brachytherapy and fewer adverse events to vision. A 2017 database review found comparable 2-year OS rates but lower 5-year OS rates for PBT than for brachytherapy.

Charged-Particle (Proton or Helium Ion) RT for Individuals with Skull-Based Tumors

Clinical Context and Therapy Purpose

The purpose of charged-particle (proton or helium ion) RT in patients who have skull-based tumors is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does charged-particle RT improve the net health outcome in individuals with skull-based tumors?

The following PICO was used to select literature to inform this review.

Patients

The relevant population of interest is individuals with skull-based tumors. The skull base is the anatomic area that supports the brain and includes the entry and exit passages for nerve and vascular bundles. Tumors located near these vital structures such as chordoma and chondro-sarcoma that arise in the skull base may not be amenable to complete surgical excision or adequate doses of conventional RT are impossible.

Interventions

The therapy being considered is charged-particle (proton or helium ion) RT. Charged-particle irradiation theoretically affords protection from radiation damage to surrounding structures. Charged-particle therapy is administered in specially equipped treatment centers. PBT can be administered with or without stereotactic techniques.

Comparators

The following practices are currently being used to make decisions about skull-based tumors: other types of RT including conventional and high-dose photon therapies, surgical resection, and other therapeutic modalities for localized tumor control.

Outcomes

The general outcomes of interest are OS, disease-free survival, change in disease status (local recurrence), and treatment-related morbidity. Local control and survival outcomes for charged-particle therapy for skull-base tumors have been reported at 1 year and 5 years.

Systematic Reviews

This section was informed by a TEC Assessment (1996) that concluded, compared with treatment using conventional RT after partial resection or biopsy, charged-particle irradiation yields greater rates of local control, OS, and disease-free survival at 5 years after therapy.[4,] More recently, Lodge et al (2007) published a systematic review of charged-particle therapy and found local tumor control and 5-year OS rates of 63% and 81%, respectively, for skull-based chordomas treated with surgery and PBT.[9,] Comparable local tumor control and 5-year OS rates were 25% and 44% for postsurgical photon therapy. For chondrosarcomas of the skull-base, proton therapy achieved a 5-year tumor control rate of 95% and photon therapy a rate of 100%.

Ameta-analysis by Zhou et al (2018) compared the effectiveness of photon- and particle-based radiotherapy (RT) for the treatment of chordoma after surgery.[10,] A fixed-effects model was used to perform an analysis of 3-, 5-, and 10-year overall survival (OS) rates. A total of 25 studies were included, x on the use of conventional RT (CRT), x on the use of stereotactic RT (SRT), 9 on the use of proton beam therapy (PBT), and 5 on the use of carbon-ion RT (CIRT). A total of 21 studies reported 3-yr OS data, 15 studies reported 5-yr OS data, and 9 studies reported 10-yr OS data. Characteristics and results are summarized in Tables 1 and 2. PBT was found to have a statistically significant benefit on 10-yr OS rates compared to both CRT ($p < 0.001$) and SRT ($p = 0.004$).

Table 1. SR & M-A Characteristics

Study	Dates	Trials	Participants[1]	N (Range)	Design	Duration (Range)
Zhou et al (2018)[10,]	1983-2016 (All) 1995-2016 (Proton) 2003-2014 (Carbon)	25 (All) 9 (Proton) 5 (Carbon)	Studies containing overall survival rates for patients with chordoma. Patients with chordoma that received at least one surgery prior to RT. Exact RT type used is described.	N = 996 (All) N = 351 (13-100) (Proton) N = 361 (32-155) (Carbon)	Single-arm trials	15 – 72 months

M-A: meta-analysis; RT: radiotherapy; SR: systematic review
[1] Key eligibility criteria.

Table 2. SR & M-A Results

Study	3-yr Outcomes		5-yr Outcomes		10-yr Outcomes	
Zhou et al (2018)[10,]	OS, % (95% CI)	P-value[1]	OS, % (95% CI)	P-value[1]	OS, % (95% CI)	P-value[1]
CRT	70 (60-81)	---	46 (36-56)	---	21 (10-33)	---
SRT	92 (88-96)	<0.001	81 (75-86)	<0.001	40 (30-55)	0.004
PBT	89 (85-93)	<0.001	78 (23-84)	<0.001	60 (43-77)	<0.001
CIRT	93 (90-95)	<0.001	87 (84-91)	<0.001	45 (36-55)	<0.001

CI: confidence interval; CIRT: carbon-ion radiotherapy; CRT: conventional radiotherapy; PBT: proton beam therapy; SRT: stereotactic radiotherapy.
[1] P-value indicates significance for difference compared to CRT.

Section Summary: Skull-Based Tumors

Several systematic reviews, including a TEC Assessment, have been published. A 2007 systematic review found 5-year OS rates of 81% with PBT compared with 44% with surgery and photon therapy.

A 2016 systematic review of observational studies found 5-year survival rates after PBT ranging from 67% to 94%. In 2018, a meta-analysis found 5-year and 10-year overall survival rates for proton beam therapy of 78% and 60% compared with 46% and 21% for conventional radiotherapy. The published evidence supports a meaningful improvement in the net health outcome. Evidence reported through clinical input further supports that this use provides a clinically meaningful improvement in net health outcome and is consistent with generally accepted medical practice. Further details from clinical input are included in the Clinical Input section and the Appendix.

Charged-Particle (Proton or Helium Ion) RT for Pediatric Central Nervous System Tumors

Clinical Context and Therapy Purpose

The purpose of charged-particle (proton or helium ion) RT in children who have CNS tumors is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does charged-particle RT improve the net health outcome in children with CNS tumors?

The following PICO was used to select literature to inform this review.

Patients

The relevant population of interest is individuals with pediatric CNS tumors. Primary malignant tumors of the CNS are the second most common childhood malignancies after hematologic malignancies. Specific types include craniopharyngioma, astrocytoma, ependymoma, glioblastoma, and medulloblastoma. There are multiple genetic syndromes that confer additional risk for the development of CNS tumors: neurofibromatosis, tuberous sclerosis, as well as von Hippel-Lindau, basal cell nevus and Li Fraumeni and Turcot syndromes.

Interventions

The therapy being considered is charged-particle (proton or helium ion) RT. Charged-particle therapy is administered in specially equipped treatment centers. PBT can be administered with or without stereotactic techniques.

Comparators

The following practices are currently being used to make decisions about pediatric CNS tumors: other types of RT, surgical resection, and other therapeutic modalities for localized tumor control.

Outcomes

The general outcomes of interest are OS, disease-free survival, change in disease status (local recurrence), and treatment-related morbidity. Local tumor control and OS would be assessed at 1 and 3 years.

Systematic Reviews

Leroy et al (2016) published a systematic review of the literature on PBT for the treatment of pediatric cancers.[11,] Their findings included the following:

- For craniopharyngioma, three studies were identified- two retrospective case series and one retrospective comparative study of PBT and intensity-modulated radiotherapy (IMRT). They found very low level evidence that survival outcomes with PBT and IMRT are similar.
- For ependymoma, 1 prospective case series and another retrospective case series were identified. They concluded that the evidence did not support or refute the use of PBT for this condition.
- For medulloblastoma, 1 prospective case series and 2 retrospective case series were identified. They concluded that the evidence did not support or refute the use of PBT for this condition.

- For CNS germinoma, 1 retrospective case series was identified. They concluded that the evidence did not support or refute the use of PBT for this condition.

Huynh et al (2018) recently published a systematic review of the literature on PBT for the treatment of pediatric central nervous system cancers.[12,] A total of 74 studies was included. However, treatment outcomes are difficult to summarize as study findings were not pooled. Only a subset of studies was described narratively.

Case Series

Representative case series of PBT used to treat multiple pediatric CNS tumor types are described next. For example, Bishop et al (2014) reported on 52 children with craniopharyngioma treated at 2 centers; 21 received PBT and 31 received IMRT.[13,] Patients received a median dose of 50.4 gray (Gy). At 3 years, the OS rate 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. Based on imaging, 17 (33%) patients had cyst growth within 3 months of RT, and 14 patients had late cyst growth (>3 months after therapy); rates did not differ significantly between groups. In 14 of the 17 patients with early cyst growth, enlargement was transient.

MacDonald et al (2011) reported on the use of protons to treat germ cell tumors in 22 patients, 13 with germinoma and 9 with nongerminomatous germ cell tumors.[14,] Radiation doses ranged from 30.6 to 57.6 cobalt Gray equivalents (CGE). All nongerminomatous germ cell tumor patients also received chemotherapy before RT. Median follow-up was 28 months. There were no CNS recurrences or deaths. Following RT, 2 patients developed growth hormone deficiency and 2 other patients developed central hypothyroidism. The authors indicated that longer follow-up was necessary to assess the neurocognitive effects of therapy. In the same study, a dosimetric comparison of photons and protons was performed. PBT provided substantial sparing to the whole brain and temporal lobes, and reduced doses to the optic nerves.

Moeller et al (2011) reported on 23 children enrolled in a prospective series and treated with PBT for medulloblastoma between 2006 and 2009.[15,]Because hearing loss is common after chemoradiotherapy for children with medulloblastoma, the authors evaluated whether PBT led to a clinical benefit in audiometric outcomes (because, compared with photons, protons reduce radiation dose to the cochlea for these patients). The children underwent pre- and 1-year post-RT pure-tone audiometric testing. Ears with moderate-to-severe hearing loss before therapy were censored, leaving 35 ears in 19 patients available for analysis. The predicted mean cochlear radiation dose was 30 CGE (range, 19-43 CGE). Hearing sensitivity significantly declined following RT across all frequencies analyzed (p<0.05). There was partial sparing of mean post-radiation hearing thresholds at low- to mid-range frequencies; the rate of high-grade (grade 3 or 4) ototoxicity at 1 year was 5%, which compared favorably to the rate of grade 3 or 4 toxicity following IMRT (18%) reported in a separate case series.

Hug et al (2002) reported on proton radiation in the treatment of low-grade gliomas in 27 pediatric patients.[16,] Six patients experienced local failure; acute adverse events were minimal. After a median follow-up of 3 years, all children with local control maintained performance status. In a dosimetric comparison of protons to photons for 7 optic pathway gliomas treated, Fuss et al (1999) showed a decrease in radiation dose to the contralateral optic nerve, temporal lobes, pituitary gland, and optic chiasm with the use of protons.[17,]

Section Summary: Pediatric Central Nervous System Tumors

A 2016 systematic review identified several case series evaluating PBT for several types of pediatric CNS tumors including craniopharyngioma, ependymoma, medulloblastoma, and CNS germinoma. One small comparative observational study was identified. It compared PBT with IMRT for children with craniopharyngioma and found similar outcomes with both types of treatment. The current evidence base is not sufficiently robust to draw conclusions about the efficacy of PBT for pediatric

CNS tumors. Limitations of the published evidence preclude determining the effects of the technology on net health outcome. Evidence reported through clinical input supports that this use provides a clinically meaningful improvement in net health outcome and is consistent with generally accepted medical practice. This modality of treatment has the potential to reduce toxicity to organs at risk and may minimize the development of radiation-induced secondary malignancies, particularly in individuals with radiation-sensitizing genetic syndromes that are highly correlated with these tumor types. Further details from clinical input are included in the Clinical Input section and the Appendix.

Charged-Particle (Proton or Helium Ion) RT for Pediatric Non-CNS Tumors

Clinical Context and Therapy Purpose

The purpose of charged-particle (proton or helium ion) RT in children who have non-CNS tumors is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does charged-particle RT improve net health outcomes in children with non-CNS tumors?

The following PICO was used to select literature to inform this review.

Patients

The relevant population of interest is individuals with pediatric non-CNS tumors. Tumors of the axial skeleton require conformal radiotherapy with the intent of avoiding damage to vital structures.

Interventions

The therapy being considered is charged-particle (proton or helium ion) RT. Charged-particle therapy is administered in specially equipped treatment centers. PBT can be administered with or without stereotactic techniques.

Comparators

The following practices are currently being used to make decisions about pediatric non-CNS tumors: other types of RT, surgical resection, and other types of therapy for localized tumor control.

Outcomes

The general outcomes of interest are OS, disease-free survival, change in disease status (local recurrence), and treatment-related morbidity. Local control and OS would be assessed at 1 and 3 years.

Case Series

There are scant data on the use of PBT in pediatric non-CNS tumors. Data include dosimetric planning studies in a small number of pediatric patients with parameningeal rhabdomyo-sarcoma[18,] and late toxicity outcomes in other solid tumors of childhood.[19,20,]

Vogel et al (2018) published a retrospective case series of proton-based radiotherapy to treat nonhematologic head and neck malignancies in 69 pediatric patients.[21,] Thirty-five of the patients had rhabdomyosarcoma and were treated with a median dose of 50.4 Gy (range 36.0-59.4 Gy) in 1.8 Gy fractions. A number of patients had Ewing sarcoma (n=10; median dose, 55.8 Gy; range, 55.8-65.6 Gy), and there were other histologies (n=24; median dose, 63.0 Gy). For the overall cohort, 92% (95% CI, 80% to 97%) were free from local recurrence at 1 year; at 3 years, 85% (95% CI, 68% to 93%). The OS rate at 1 year was 93% (95% CI, 79% to 98%); at 3 years, it was 90% (95% CI, 74% to 96%). Incidences of grade 3 toxicities were as follows: oral mucosities (4%), anorexia (22%), dysphagia (7%), dehydration (1%), and radiation dermatitis (1%). Despite the small and heterogenous sample, and the varying dosages and modalities administered, reviewers concluded that PBT was safe for the population in question, given the low rates of toxicity.

Section Summary: Pediatric Non-CNS Tumors

There are few data on charged-particle therapy for treating pediatric non-CNS tumors. A 2018 case series evaluated pediatric patients treated with PBT for rhabdomyosarcoma and Ewin sarcoma, in addition to other histologies. The current evidence base is not sufficiently robust to draw conclusions about the efficacy of PBT for pediatric non-CNS tumors. Limitations of the published evidence preclude determining the effects of the technology on net health outcome. Evidence reported through clinical input supports that this use provides a clinically meaningful improvement in net health outcome and is consistent with generally accepted medical practice. This modality of treatment has the potential to reduce toxicity to organs at risk and may minimize the development of radiation-induced secondary malignancies. This intervention may be most suitable for patients treated with curative intent. Further details from clinical input are included in the Clinical Input section and the Appendix.

Charged-Particle (Proton or Helium Ion) RT for Central Nervous System Tumors, Tumors of the Spine, or Tumors Requiring Craniospinal Irradiation

Clinical Context and Therapy Purpose

The purpose of charged-particle (proton or helium ion) RT in patients who have central nervous system tumors, tumors of the spine, or tumors requiring craniospinal irradiation is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does charged-particle RT improve the net health outcome in individuals with central nervous system tumors, tumors of the spine, or tumors requiring craniospinal irradiation?

The following PICO was used to select literature to inform this review.

Patients

The relevant population of interest is patients who have central nervous system (CNS) tumors, tumors of the spine, or tumors requiring craniospinal irradiation. Specific types of CNS tumors include glioma, astrocytoma, glioblastoma, ependymoma, medulloblastoma, and meningioma.

Interventions

The therapy being considered is charged-particle (proton or helium ion) RT. Charged-particle therapy is administered in specially equipped treatment centers. PBT can be administered with or without stereotactic techniques.

Comparators

The following practices are currently being used to make decisions about central nervous system tumors, tumors of the spine, or tumors requiring craniospinal irradiation: other types of radiotherapy, surgical resection, and other types of therapy for localized tumor control.

Outcomes

The general outcomes of interest are OS, disease-free survival, change in disease status (local recurrence), and treatment-related morbidity. Local control and OS would be assessed at 1 and 3 years.

Systematic Reviews

Lesueur et al (2019) published a systematic review of 24 studies on the use of PBT in the treatment of intracranial benign tumors in adults, including meningioma, neurinoma, pituitary adenoma, paraganglioma, and craniopharyngioma.[22,]For meningioma and neurinoma, five year local control rates ranged between 88-100% and 87-98%, respectively. Additional outcomes were not pooled in this review.

Observational Studies

Jhaveri et al (2018) published the results of a large retrospective study investigating the impact of PBT on overall survival (OS) in patients with gliomas registered in the National Cancer Data Base (NCDB).[23,] Outcomes for patients treated with photon radiotherapy (N = 49,405) and proton beam therapy (N = 170) were assessed with a mean follow-up time of 62.1 months. All patients treated with PBT were found to have superior median and 5 year OS compared to patients receiving photon radiotherapy at 45.9 vs 29.7 months (p = 0.009) and 46.1 vs 35.5% (p = 0.0160), respectively.

Craniospinal Irradiation

Gunther et al (2017) retrospectively evaluated outcomes of proton- (N = 14) or photon-based (N = 23) craniospinal irradiation (CSI) in patients with leukemia or lymphoma performed prior to stem cell transplantation.[24,] Median radiation dose was 24 Gy for photons and 21.8 Gy for protons (p = 0.03). Proton CSI was associated with lower rates of grade 1-3 mucositis compared to photon CSI (7% vs 44%; p = 0.03). Other toxicities such as infections or gastrointestinal systems did not differ between groups. Median follow-up was 8 months (interquartile range [IQR]: 6-17.5 months) for all patients and 16 months (IQR: 9-32 months) for surviving patients (N = 20). Six-month OS after CSI was 69.6% for photon-based therapy and 78.6% for proton-based (p = 0.15).

Brown et al (2013) retrospectively evaluated efficacy and acute toxicity of proton CSI compared with conventional photon CSI for adults with medulloblastoma (N = 40) treated at the MD Anderson Cancer Center from 2003 to 2011.[25,] The median follow-up duration was 57.1 months (range: 4-103 months) for patients treated with photons and 26.3 months (range: 11-63 months) for patients treated with protons. Patients treated with proton CSI lost less weight (1.2% vs 5.8%; p = 0.004), had lower rates of >5% weight loss (16% vs 64%; p = 0.004), experienced less grade 2 nausea and vomiting (26% vs 71%; p = 0.004), and were less likely to receive medical management for esophagitis (5% vs. 57%; p < 0.001). The 2-year OS and progression-free survival (PFS) were both 94% compared to 90% and 85%, respectively, for patients treated with photon-based CSI.

Section Summary: CNS Tumors, Tumors of the Spine, and Tumors Requiring Craniospinal Irradiation

A systematic review and a several retrospective studies have been published. The 2019 systematic review reported five year local control rates for meningioma and neurinoma ranging between 87-100%. A large retrospective study utilizing glioma patient OS data from the National Cancer Data Base found superior median and 5 year OS outcomes compared to patients receiving photon radiotherapy at 45.9 months and 35.5%, respectively. Retrospective, comparative studies comparing outcomes between proton- and photon-based CSI have been published. Studies have demonstrated a statistically significant reduction in CSI-related acute toxicities in patients with hematologic malignancies and medulloblastoma treated with proton-based radiotherapy. Overall survival was 78.6% after 6-months and 94% after 2-years, respectively. These rates were not statistically different from proton-based treatments. Limitations of the published evidence preclude determining the effects of the technology on net health outcome. Evidence reported through clinical input supports that this use provides a clinically meaningful improvement in net health outcome and is consistent with generally accepted medical practice. This modality of treatment has the potential to reduce toxicity to healthy tissues, organs at risk (OAR), and may minimize the development of radiation-induced secondary malignancies. Further details from clinical input are included in the Clinical Input section and the Appendix.

Charged-Particle (Proton or Helium Ion) RT for Localized Prostate Cancer

Clinical Context and Therapy Purpose

The purpose of charged-particle (proton or helium ion) RT in patients who have locally advanced prostate cancer is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does charged-particle RT improve the net health outcome in individuals with localized prostate cancer?

The following PICO was used to select literature to inform this review.

Patients
The relevant population of interest is patients who have locally advanced prostate cancer (i.e., stages C or D1 [without distant metastases], also classified as T3 or T4). These tumors may be associated with a high rate of local recurrence despite maximal doses of conventional RT.

Interventions
The therapy being considered is charged-particle (proton or helium ion) RT. Charged-particle therapy is administered in specially equipped treatment centers. PBT can be administered with or without stereotactic techniques.

Comparators
The following practices are currently being used to make decisions about localized prostate cancer: other types of radiotherapy, surgical resection, and other types of therapy for localized tumor control.

Outcomes
The general outcomes of interest are OS, disease-free survival, change in disease status (local recurrence), and treatment-related morbidity. Local control and OS would be assessed at 1 and 5 years.

Systematic Reviews
A Blue Cross Blue Shield Association Technology Evaluation Center (TEC) Assessment (2010) addressed the use of PBT for prostate cancer and concluded that it had not been established whether PBT improves outcomes in any setting for clinically localized prostate cancer.[26,] Nine studies were included in the review; 4 were comparative and 5 were noncomparative. There were 2 RCTs, and only one included a comparison group that did not receive PBT. This trial, by Shipley et al (1995), compared treatment with external-beam radiotherapy (EBRT) using photons and either a photon or proton beam boost.[27,] After a median follow-up of 61 months, the investigators found no statistically significant differences in OS, disease-specific survival, or recurrence-free survival. In a subgroup of patients with poorly differentiated tumors, there was superior local control with PBT vs photon boost, but survival outcomes did not differ. Actutimes incidence of urethral stricture and freedom from rectal bleeding were significantly better in the photon boost group. The TEC Assessment noted that higher doses were delivered to the proton beam boost group and, thus, better results on survival and tumor control outcomes would be expected. Moreover, the trial was published in the mid-1990s and used 2-dimensional methods of RT, which are now outmoded. The other RCT, known as Proton Radiation Oncology Group, was reported by Zietman et al (2005).[28,] They compared conventional- and high-dose conformal therapy using both conformal proton beams, proton boost, and EBRT. After a median follow-up of 8.9 years, there was no statistically significant difference between groups in survival. Biochemical failure (an intermediate outcome) was significantly lower in the high-dose proton beam group than in the conventional-dose proton beam group. The TEC Assessment noted that the outcome (biochemical failure) has an unclear relation to the more clinically important outcome, survival. The rate of acute gastrointestinal tract toxicity was worse with the high-dose proton beam boost.

Kim et al (2013), reported on an RCT of men with androgen-deprivation therapy-naive stage T1, T2, and T3 prostate cancer that compared different protocols for administering hypofractionated PBT.[29,] However, without an alternative intervention, conclusions cannot be drawn about the efficacy and safety of PBT. The 5 proton beam protocols used were as follows: arm 1, 60 CGE in 20 fractions for 5 weeks; arm 2, 54 CGE in 15 fractions for 5 weeks; arm 3, 47 CGE in 10 fractions for 5 weeks; arm 4, 35 CGE in 5 fractions for 2.5 weeks; or arm 5, 35 CGE in 5 fractions for 5 weeks. Eighty-two patients were

randomized, with a median follow-up of 42 months. Patients assigned to arm 3 had the lowest rate of acute genitourinary toxicity, and those assigned to arm 2 had the lowest rate of late gastrointestinal toxicity. However, without an alternative intervention, conclusions cannot be drawn about the efficacy and safety of PBT.

Sun et al (2014) assessed therapies for localized prostate cancer, for the Agency for Healthcare Research and Quality.[30,] Reviewers compared the risk and benefits of a number of treatments, including: radical prostatectomy, EBRT (standard therapy as well as PBT, 3-dimensional conformal radiotherapy, IMRT, stereotactic body radiotherapy [SBRT]), interstitial brachytherapy, cryotherapy, watchful waiting, active surveillance, hormonal therapy, and high-intensity focused ultrasound. They concluded that the evidence for most treatment comparisons was inadequate to draw conclusions about comparative risks and benefits. Limited evidence appeared to favor surgery over surveillance or EBRT, and RT plus hormonal therapy over RT alone. Reviewers noted that advances in technologies for many of the treatment options for clinically localized prostate cancer (e.g., current RT protocols permit higher doses than those administered in many of the trials included in the report). Moreover, the patient population had changed since most of the studies were conducted. More recently, most patients with localized prostate cancer have been identified using prostate-specific antigen testing and may be younger and healthier than prostate cancer patients identified before such testing existed. Thus, reviewers recommended additional studies to validate the comparative effectiveness of emerging therapies such as PBT, robotic-assisted surgery, and SBRT.

From the published literature, it appears as if dose escalation is an accepted treatment strategy for organ-confined prostate cancer.[31,] PBT, using CRT planning or IMRT, is used to provide dose escalation to a more well-defined target volume. However, dose escalation is more commonly offered with conventional EBRT using 3-dimentional conformal radiotherapy or IMRT. Morbidity related to RT 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 IMRT or 3- dimensional conformal radiotherapy permits improved delineation of the target volume, if the dose is not accurately delivered, perhaps due to movement artifact, the complications of dose escalation can be serious, because the bladder and rectal tissues are exposed to even higher doses. The accuracy of dose delivery applies to both conventional and PBT.[32,]

Section Summary: Localized Prostate Cancer

The evidence on PBT for treating localized prostate cancer includes 2 RCTs and systematic reviews. A 2010 TEC Assessment addressed the use of PBT for prostate cancer and concluded that it had not been established whether PBT improves outcomes in any setting for clinically localized prostate cancer. The TEC Assessment included 2 RCTs, only one of which included a comparison group that did not receive PBT. A 2014 comparative effectiveness review concluded that the evidence on PBT for prostate cancer is insufficient. Limitations of the published evidence preclude determining the effects of the technology on net health outcome. Evidence reported through clinical input suggests a possible role for prostate cancer. However, support for its use is pending and a large, ongoing phase III RCT comparing proton therapy to IMRT in prostate cancer may alter the conclusions of the TEC Assessment. Further details from clinical input are included in the Clinical Input section and the Appendix.

Charged-Particle (Proton or Helium Ion) RT for Non-Small-Cell Lung Cancer

Clinical Context and Therapy Purpose

The purpose of charged-particle (proton or helium ion) RT in patients who have non-small-cell lung cancer (NSCLC) is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does charged-particle RT improve the net health outcome for patients with NSCLC?

The following PICO was used to select literature to inform this review.

Patients
The relevant population of interest is individuals with NSCLC. NSCLC is the most common cause of lung cancer, and RT is an essential component of treatment for many patients. The potential benefit of PBT is to reduce radiation toxicity to normal lung tissue and the heart.

Interventions
The therapy being considered is charged-particle (proton or helium ion) RT. Charged-particle therapy is administered in specially equipped treatment centers. PBT can be administered with or without stereotactic techniques.

Comparators
The following practices are currently being used to make decisions about NSCLCs: other types of radiotherapy, surgical resection, or other types of therapy for localized tumor control.

Outcomes
The general outcomes of interest are OS, disease-free survival, change in disease status (local recurrence), and treatment-related morbidity. Local control and OS would be assessed at 1 and 5 years.

Systematic Reviews
A TEC Assessment (2010) assessed the use of PBT for NSCLC.[33,] This Assessment compared health outcomes (OS, disease-specific survival, local control, disease-free survival, adverse events) between PBT and SBRT, which is an accepted approach for using RT to treat NSCLC. Eight PBT case series were identified (total N=340 patients). No comparative studies, randomized or nonrandomized, were found. For these studies, stage I comprised 88.5% of all patients, and only 39 patients had other stages or recurrent disease. Among 7 studies reporting 2-year OS rates, probabilities ranged between 39% and 98%. At 5 years, the range across 5 studies was 25% to 78%.

The review concluded that the evidence was insufficient to permit conclusions about PBT outcomes for any stage of NSCLC. All PBT studies were case series; no studies directly compared PBT with SBRT. Among study quality concerns, no study mentioned using an independent assessor of patient-reported adverse events; adverse events were generally poorly reported, and details were lacking on several aspects of PBT regimens. The PBT studies were similar in patient age, but there was great variability in percentages with stage IA cancer, the sex ratio, and the percentage of medically inoperable tumors. There was a high degree of treatment heterogeneity among the PBT studies, particularly with respect to planning volume, total dose, the number of fractions, and the number of beams. Survival results were highly variable. It is unclear whether the heterogeneity of results could be explained by differences in patient and treatment characteristics. In addition, indirect comparisons between PBT and SBRT (e.g., comparing separate sets of single-arm studies on PBT and SBRT) might have been distorted by confounding. Absent RCTs, the comparative effectiveness of PBT and SBRT was found to be uncertain. The Assessment noted that adverse events reported after PBT generally fell into several categories: rib fracture, cardiac, esophageal, pulmonary, skin, and soft tissue. Adverse events data in PBT studies are difficult to interpret due to lack of consistent reporting across studies, lack of detail about observation periods, and lack of information about rating criteria and grades.

An indirect meta-analysis by Grutters et al (2010) reviewed in the TEC Assessment found a nonsignificant difference of 9 percentage points between pooled 2-year OS estimates favoring SBRT over PBT for the treatment of NSCLC.[34,] The nonsignificant difference of 2.4 percentage points at 5 years also favored SBRT over PBT. Based on separate groups of single-arm studies on SBRT and PBT, it is unclear whether this indirect meta-analysis adequately addressed the possible influence of confounding on the comparison of SBRT and PBT.

Pijls-Johannesma et al (2010) conducted a systematic literature review examining the use of particle therapy in lung cancer.[35,] Study selection criteria included having at least 20 patients and a follow-up of 24 months or more. Eleven studies, all dealing with NSCLC, were selected, 5 investigating protons (n=214 patients) and 6, C-ions (n=210 patients). The proton studies included 1 phase 2 study, 2 prospective studies, and 2 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 I disease, but because a wide variety of radiation schedules were used, comparisons of results were difficult, and local control rates were defined differently across studies. For proton therapy, 2-year local control rates were 74% and 85%, respectively, in the 2 studies reporting this outcome; 5-year local control rates ranged from 57% to 96% (4 studies). The 2-year OS rates ranged from 31% to 74%, and the 5-year OS rates ranged from 31% to 50% (2- and 5-year OS each reported in 4 studies). These local control and survival rates are equivalent or inferior to those achieved with SBRT. Radiation-induced pneumonitis was observed in about 10% of patients. For C-ion therapy, the overall local tumor control rate was 77%, and it was 95% when using a hypofractionated dosing schedule. The 5-year OS and cause-specific survival rates with C-ion therapy were 42% and 60%, respectively. Slightly better results were reported when using hypofractionation (50% and 76%, respectively). Reviewers concluded that, although the results with protons and heavier charged particles were promising, additional well-designed trials would be needed.

Nonrandomized Studies

To date, no RCTs comparing health outcomes in patients treated with PBT or with an alternative treatment have been identified.

Chang et al (2017) published final results from an open-label phase 2 study of 64 patients with stage III unresectable NSCLC treated with PBT plus concurrent chemotherapy (carboplatin and paclitaxel).[36,] Median OS was 26.5 months; at 5 years, the OS rate was 29% (95% CI, 18% to 41%). Median progression-free survival was 12.9 months; the 5-year progression-free survival rate was 22% (95% CI, 12% to 32%). At 5 years, 54% of patients had distant metastasis, 28% had loco-regional recurrence, and 64% had a recurrence of any type. No grade 5 adverse events were observed, and grade 3 or 4 adverse events were rare. Poor OS was predicted by Karnofsky Performance Status score of 70 to 80, compared with of 90 to 100 (HR=2.48; 95% CI, 1.33 to 4.65; p=0.004). Other predictors of poor OS were stage III cancer (p=0.03), the presence of a tumor in the left lung or right lower lobe (p=0.04), and a pretreatment tumor size greater than 7 cm (p=0.03). The use of nonstandardized induction and adjuvant chemotherapy as well as the heterogeneity across study populations limit conclusions about treatment efficacy.

Ono et al (2017) published a retrospective case series of 20 patients with lung cancer treated with PBT at a single center between 2009 and 2015.[37,] In 14 (70%) patients, tumors were clinically inoperable; overall median tumor diameter was 39.5 mm (range, 24-81 mm). PBT was administered 3.2 Gy per fraction. Median follow-up as 27.5 months (range, 12-72 months), and the 1-year OS rate was 95.0% (95% CI, 87.7% to 100%). At 2 years, the OS rate was 73.8% (95% CI, 53.9% to 93.7%); no statistically significant difference was found between operable (n=6) and inoperable patients (n=14) for 2-year OS (p=0.109), although operable patients had better survival rates. At 2 years, local control rate was 78.5% (95% CI, 59.5% to 97.5%), and there were no reported toxicities of grade 3 or higher. The study was limited by small sample size and retrospective design.

Section Summary: Non-Small-Cell Lung Cancer

A 2010 TEC Assessment, which included 8 case series, concluded that the evidence was insufficient to permit conclusions about PBT for any stage of NSCLC. Another systematic review, also published in 2010, only identified case series. No subsequent randomized or nonrandomized comparative studies have been published. Final results from a 2017 open-label phase 2 study included 5-year survival rates for patients who had PBT with concurrent chemotherapy. Limitations of the published evidence preclude determining the effects of the technology on net health outcome. Evidence reported

through clinical input supports that this use provides a clinically meaningful improvement in net health outcome and is consistent with generally accepted medical practice. This modality of treatment has the potential to reduce toxicity to healthy tissues and organs at risk (OAR), with optimal outcomes observed for patients who are treated with curative intent. Further details from clinical input are included in the Clinical Input section and the Appendix.

Charged-Particle (Proton or Helium Ion) RT for Head and Neck Tumors, Other Than Skull-Based

Clinical Context and Therapy Purpose

The purpose of charged-particle (proton or helium ion) RT in patients who have head and neck tumors, other than skull-based, is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does charged-particle RT improve the net health outcome in patients with head and neck tumors, other than skull-based?

The following PICO was used to select literature to inform this review.

Patients

The relevant population of interest is patients who have head and neck malignancies. The histology of the malignancies are predominantly of squamous cell type and may arise from, and involve multiple regions, including the oral cavity, pharynx, larynx, nasal cavity and paranasal sinuses, and the major salivary glands.

Interventions

The therapy being considered is charged-particle (proton or helium ion) RT. Charged-particle therapy is administered in specially equipped treatment centers. PBT can be administered with or without stereotactic techniques.

Comparators

The following practices are currently being used to make decisions about head and neck tumors, other than skull-based: other types of radiotherapy, surgical resection, or other types of therapy for localized tumor control.

Outcomes

The general outcomes of interest are OS, disease-free survival, change in disease status (local recurrence), and treatment-related morbidity. Local control and OS would be assessed at 1 and 5 years.

Systematic Reviews

A systematic review by Patel et al (2014) evaluated the literature comparing charged-particle therapy with PBT in the treatment of paranasal sinus and nasal cavity malignant disease.[38,] Reviewers identified 41 observational studies that included 13 cohorts treated with charged-particle therapy (n=286 patients) and 30 cohorts treated with PBT (n=1186 patients). There were no head-to-head trials. In a meta-analysis, the pooled OS event rate was significantly higher with charged-particle therapy than with photon therapy at the longest duration of follow-up (relative risk, 1.27; 95% CI, 1.01 to 1.59). Findings were similar for 5-year survival outcomes (relative risk, 1.51; 95% CI, 1.14 to 1.99). Findings were mixed for the outcomes of locoregional control and disease-free survival; photon therapy was significantly better for one of the 2 timeframes (longest follow-up or 5-year follow-up). In terms of adverse events, there were significantly more neurologic toxic effects with charged-particle therapy than with photon therapy ($p<0.001$), but other toxic adverse event rates (e.g., eye, nasal, hematologic) did not differ significantly between groups. Reviewers noted that the charged-particle studies were heterogeneous (e.g., type of charged particles [carbon ion, proton], delivery techniques). In addition, comparisons were indirect, and none of the studies selected actually compared the 2 types of treatment in the same patient sample.

Case-Matched Cohort Studies

Blanchard et al (2016) case-matched 50 patients treated with intensity-modulated proton therapy (IMPT) with 100 patients treated with intensity-modulated radiotherapy (IMRT) who were receiving treatment for oropharyngeal carcinoma.[39,] Patients were followed-up for a median of 32 months. No statistically significant differences in OS (hazard ratio [HR]: 0.55; 95% confidence interval [CI]: 0.12-2.50; p = 0.44) or PFS (HR: 1.02; 95% CI: 0.41-2.54; p = 0.96) were observed. A pre-planned composite endpoint demonstrated reduced risks of grade 3 weight loss or G-tube presence at 3 months (odds ratio [OR]: 0.44; 95% CI: 0.19-1.0; p = 0.05) and 1-year after treatment (OR: 0.23; 95% CI: 0.07-0.73; p = 0.01).

Adverse Events

Zenda et al (2015) reported on late toxicity in 90 patients after PBT for nasal cavity, paranasal sinuses, or skull-based malignancies.[40,] 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 (19%) patients, and grade 4 occurred in 6 (7%) patients. Five patients developed cataracts, and 5 developed optic nerve disorders. Late toxicities (other than cataracts) developed a median of 39.2 months after PBT.

Section Summary: Head and Neck Tumors, Other Than Skull-Based

A 2014 systematic review identified only case series and noted that the studies of charged-particle therapy were heterogenous in terms of the types of particle and delivery techniques used. No studies identified compared charged-particle therapy with other treatments. A case-matched cohort study compared outcomes for oropharyngeal cancer patients receiving intensity-modulated proton therapy (IMPT) or intensity-modulated photon-based radiotherapy. No statistically significant differences in OS or PFS were observed, however, a lower risk for treatment-related adverse events was noted with IMPT. Limitations of the published evidence preclude determining the effects of the technology on net health outcome. Evidence reported through clinical input supports that this use provides a clinically meaningful improvement in net health outcome and is consistent with generally accepted medical practice. This modality of treatment has the potential to reduce toxicity to healthy tissues in cases with documented risk to uninvolved organs as demonstrated by dosimetric treatment plans utilizing conventional or advanced photon-based radiotherapy. For patients with complex and difficult to treat advanced, very advanced, and/or unresectable head and neck cancers, proton therapy may offer a high therapeutic index while managing treatment-related toxicities. Further details from clinical input are included in the Clinical Input section and the Appendix.

Charged-Particle (Proton or Helium ion) RT for Thymoma and Thymic Carcinoma

Clinical Context and Therapy Purpose

The purpose of charged-particle (proton or helium ion) RT in patients who have thymoma or thymic carcinoma is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does charged-particle RT improve the net health outcome in individuals with thymoma or thymic carcinoma?

The following PICO was used to select literature to inform this review.

Patients

The relevant population of interest is patients who have thymic malignancies, including thymoma and thymic carcinoma. The relative occurrence of these malignancies is rare, with 0.13 cases per 100,000 person years, based on data from the National Cancer Institute (NCI) Surveillance, Epidemiology, and End Results (SEER) Program.

Interventions
The therapy being considered is charged-particle (proton or helium ion) RT. Charged-particle therapy is administered in specially equipped treatment centers. PBT can be administered with or without stereotactic techniques.

Comparators
The following practices are currently being used to make decisions about thymoma and thymic carcinoma: other types of radiotherapy, surgical resection, and other types of therapy for localized tumor control.

Outcomes
The general outcomes of interest are OS, disease-free survival, change in disease status (local recurrence), and treatment-related morbidity. Local control and OS would be assessed at 1 and 5 years.

Prospective Studies
Mercado and coworkers (2019) reported on 30 patients with thymic malignancies who originally enrolled for study between 2008 and 2017.[41,] Patients received proton radiotherapy postoperatively (91%) or definitively (9%). Median follow-up duration was 13 months (range: 2-59 months). Five patients relapsed and three patients died of disease progression. No treated patients experience grade 3 or higher toxicities.

Section Summary: Thymoma or Thymic Carcinoma
A prospective study reports a favorable toxicity profile and a low rate of recurrence with proton radiotherapy in patients with thymic malignancies. Studies with longer follow-up durations and comparative data are lacking. Limitations of the published evidence preclude determining the effects of the technology on net health outcome. Evidence reported through clinical input supports that this use provides a clinically meaningful improvement in net health outcome and is consistent with generally accepted medical practice. This modality of treatment has the potential to reduce toxicity to healthy tissues and organs at risk. The likelihood of additional published evidence or larger studies is unlikely due to the rarity of thymic malignancies. Further details from clinical input are included in the Clinical Input section and the Appendix.

Charged-Particle (Proton or Helium Ion) RT for Lymphomas
Clinical Context and Therapy Purpose
The purpose of charged-particle (proton or helium ion) RT in patients who have lymphoma is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does charged-particle RT improve the net health outcome in individuals with lymphoma?

The following PICO was used to select literature to inform this review.

Patients
The relevant population of interest is patients who have lymphoma, including Hodgkin or non-Hodgkin lymphomas.

Interventions
The therapy being considered is charged-particle (proton or helium ion) RT. Charged-particle therapy is administered in specially equipped treatment centers. PBT can be administered with or without stereotactic techniques.

Comparators
The following practices are currently being used to make decisions about lymphoma: other types of radiotherapy, surgical resection, and other types of therapy for localized tumor control.

Outcomes
The general outcomes of interest are OS, disease-free survival, change in disease status (local recurrence), and treatment-related morbidity. Local control and OS would be assessed at 1 and 3 years.

Efficacy Trials
Hoppe et al (2014) conducted a prospective phase II trial of consolidative involved-node proton therapy (INPT) in patients with Hodgkin lymphoma and mediastinal involvement. Median follow-up was 37 months (range: 26-55 months). The 3-yr relapse-free survival rate was 93%. No acute or late grade 3 nonhematologic adverse events were observed. [42,]

Prospective Studies
Hoppe and coworkers (2017) also conducted a prospective registry study for patients with Hodgkin lymphoma (HL) receiving consolidative proton therapy.[43,] Patients with relapsed or refractory disease were excluded. The 3-yr relapse-free survival rate was 92% for all patients (N = 138). No grade 3 treatment-related toxicities were reported. Survival outcomes are similar to those reported for photon-based treatments.

Section Summary: Lymphomas
Observational studies and efficacy trials support a favorable toxicity profile to organs at risk in the chest and suggest that proton radiotherapy may improve survival outcomes for patients receiving consolidative therapy. Studies with longer follow-up durations assessing late effects and comparative data are lacking. Limitations of the published evidence preclude determining the effects of the technology on net health outcome. Evidence reported through clinical input supports that this use provides a clinically meaningful improvement in net health outcome and is consistent with generally accepted medical practice. This modality of treatment has the potential to reduce toxicity to healthy tissues and organs at risk. Further details from clinical input are included in the Clinical Input section and the Appendix.

Charged-Particle (Proton or Helium Ion) RT for Tumors near Organs at Risk or Where Photon-Based RT Planning Does Not Meet Dose-Volume Constraints for Normal Tissue Radiation Tolerance

Clinical Context and Therapy Purpose
The purpose of charged-particle (proton or helium ion) RT in patients who have tumors near organs at risk that require reirradiation, or where conventional or advanced photon-based radiotherapy planning does not meet dose-volume constraints for normal tissue radiation tolerance, is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does charged-particle RT improve the net health outcome in individuals with tumors near organs at risk that require reirradiation, or where conventional or advanced photon-based radiotherapy planning does not meet dose-volume constraints for normal tissue radiation tolerance?

The following PICO was used to select literature to inform this review.

Patients
The relevant population of interest is patients who have tumors near organs at risk that require reirradiation, or where conventional or advanced photon-based radiotherapy planning does not meet dose-volume constraints for normal tissue radiation tolerance.

Interventions
The therapy being considered is charged-particle (proton or helium ion) RT. Charged-particle therapy is administered in specially equipped treatment centers. PBT can be administered with or without stereotactic techniques. Due to the distinct energy deposition profile at a near-fixed point (termed the Bragg peak), PBT may be an attractive modality of therapy for sparing radiation dose to uninvolved tissues and organs at risk.

Comparators
The following practices are currently being used to make decisions about tumors near organs at risk that require reirradiation, or where conventional or advanced photon-based radiotherapy planning does not meet dose-volume constraints for normal tissue radiation tolerance: other types of radiotherapy, surgical resection, and other types of therapy for localized tumor control.

Outcomes
The general outcomes of interest are OS, disease-free survival, change in disease status (local recurrence), and treatment-related morbidity. Radiation exposure to organs at risk exceeding tolerable radiation dose limits for normal tissues is a major concern of treatment. Further details regarding dose-volume constraints are provided in Table PG1.

Systematic Reviews
Verma et al (2017) performed a systematic review assessing clinical outcomes and toxicities of proton RT used for reirradiation of CNS, head & neck, lung, and gastrointestinal malignancies.[44,] Favorable survival rates were noted for chordoma and head & neck cancers. For head & neck cancers, low rates (9-10%) of feeding tube placement were reported compared to historical photon-treated patients. Gastrointestinal malignancies induced few high-grade complications. The authors conclude that proton-based radiotherapy appears to be a safe treatment modality for effective salvage of recurrent disease.

Breast Cancer
Kammerer and coworkers (2018) conducted a systematic review evaluating clinical outcomes of proton therapy for locally advanced breast cancer.[45,] Thirteen studies met inclusion criteria. Studies comparing dosimetric treatment plans demonstrated better target coverage with IMRT or PBT compared to 3D-CRT. Volumes receiving 105% or more of the prescribed dose were minimized with the use of PBS. Mean heart and lung doses were reduced with PBT, providing support for organ at risk (OAR) sparing.

Verma et al (2016) performed a systematic review assessing clinical outcomes and toxicity of PBT in breast cancer.[46,] PBT was found to contribute to rates of grade 1 and 2 dermatitis at rates of 25% and 71-75%, respectively. These rates were reported to be comparable or improved over historical rates for photon-based therapies.

Esophageal Cancer
Xi et al (2017) published outcomes from a retrospective study assessing definitive chemoradiotherapy in esophageal cancer patients (N = 343) with PBT (N = 132) compared to IMRT. (N = 211).[47,] Compared to IMRT, PBT dosimetric plans provided significant improvements in planning target volume dose coverage (93.6% vs 94.8%; $p < 0.001$). The mean doses to heart and lung were 19.9 Gy and 10 Gy for IMRT compared to 11.6 Gy and 6.5 Gy for PBT, respectively ($p < 0.001$). Significantly lower V5 and V20 of the lung and V30 of the heart were also observed for PBT ($p < 0.001$). No significant differences in the rates of treatment-related toxicities were observed between groups. Grade 3 or 4 toxicities were observed in 45.0% of patients receiving IMRT and 37.9% of patients receiving PBT ($p = 0.192$). Four patients (1.9%) receiving IMRT and 1 patient (0.8%) receiving PBT ($p = 0.653$) experienced grade 5 toxicities. At 5 years, patients receiving PBT had significantly higher OS (41.6% vs 31.6%; $p = 0.011$) and progression-free survival (34.9% vs 20.4%; $p = 0.001$).

Pancreatic Cancer

Jethwa et al (2018) assessed outcomes for 13 patients with intact and clinically localized pancreatic cancer undergoing concurrent capecitabine or 5-fluorouracil chemoradiation therapy incorporating intensity-modulated proton therapy (IMPT).[48,] A matched volumetric modulated arc therapy (VMAT) radiation treatment plan was generated for each patient for dosimetric comparison. Patients were prospectively followed and assessed for adverse events and patient-reported outcomes (PRO). These outcomes were collected with the Functional Assessment of Cancer Therapy PRO questionnaire for hepatobiliary cancers at baseline and following chemoradiation. IMPT was demonstrated to offer significant reductions in radiation dose to organs at risk, including the stomach, bowel, duodenum, liver, and kidneys ($p < 0.05$). No grade 3 or greater treatment-related adverse events were reported. Changes in baseline PRO were not statistically significant.

Hitchcock et al (2017) conducted a retrospective study assessing the feasibility of pancreatectomy following proton therapy with concomitant capecitabine treatment with initially unresectable pancreatic cancer in 15 patients.[49,] Six patients achieved radiographic response sufficient to justify surgical exploration, and 5 underwent resection. Median OS for the 5 resected patients was 24 months (range: 10-30).

Rectal and Anal Cancers

Ojerholm and coworkers (2015) conducted a dosimetric comparison between IMRT and pencil-beam scanning proton therapy which had been utilized in patients undergoing chemo-radiotherapy for anal cancer.[50,] Compared to IMRT treatment plans, PBT reduced low dose radiation (≤ 30 Gy) to the bowel, pelvic bone marrow, external genitalia, femoral heads, and bladder (all $p < 0.05$) without compromising planned target coverage. For PBT vs IMRT, mean organ volume receiving ≥15 Gy (V15)), V20, and V15 was 81 vs 151 cm^3 in the small bowel, 14 vs 40% in the external genitalia, and 66 vs 83% in the total pelvic bone marrow, respectively (all $p = 0.008$).

Section Summary: Tumors near Organs at Risk or Where Photon-Based RT Planning Does Not Meet Dose-Volume Constraints for Normal Tissue Radiation Tolerance

Systematic reviews, observational studies, and dosimetric comparison studies report a favorable toxicity profile and reductions of radiation dose to organs at risk with the use of proton beam radiotherapy for a variety of neoplastic conditions and for patients with tumors requiring reirradiation. Studies with optimal follow-up durations assessing long-term clinical outcomes and randomized, comparative data are lacking. Limitations of the published evidence preclude determining the effects of the technology on net health outcome. Evidence reported through clinical input along with NCCN and ASTRO guidelines supports that this use provides a clinically meaningful improvement in net health outcome and is consistent with generally accepted medical practice for selected cases when therapeutic goals and radiation dose constraints for critical organs at risk (i.e., surrounding normal tissue) cannot be met by other advanced conformal, fractionated photon-based radiotherapy techniques (i.e., including intensity modulated radiotherapy [IMRT], volume-modulated arc therapy [VMAT], stereotactic radiosurgery [SRS], or stereotactic body radiation therapy [SBRT]) for patients with indications such as breast cancer, esophageal cancer, resectable head & neck cancer, seminomas, pancreatic or hepatobiliary cancers, pelvic or genitourinary cancers, and soft tissue sarcomas. Further details from clinical input are included in the Clinical Input section and the Appendix.

Summary of Evidence

The following conclusions are based on a review of the evidence, including but not limited to, published evidence and clinical expert opinion, solicited via BCBSA's Clinical Input Process.

For individuals who have uveal melanoma(s) who receive charged-particle (proton or helium ion) radiotherapy, the evidence includes long-term studies, randomized controlled trials, and systematic reviews. Relevant outcomes are overall survival, disease-free survival, change in disease status, and

treatment-related morbidity. Systematic reviews, including a 1996 TEC Assessment and a 2013 review of randomized and nonrandomized studies, concluded that the technology is at least as effective as alternative therapies for treating uveal melanomas and is better at preserving vision. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have a skull-based tumor(s) (i.e., cervical chordoma, chondrosarcoma) who receive charged-particle (proton or helium ion) radiotherapy, the evidence includes observational studies and systematic reviews. Relevant outcomes are overall survival, disease-free survival, change in disease status, and treatment-related morbidity. A 2007 systematic review found a 5-year overall survival rate of 81% with proton beam therapy (PBT) compared with 44% with surgery plus photon therapy. In2018, a meta-analysis found 5-year and 10-year overall survival rates for proton beam therapy of 78% and 60% compared with 46% and 21% for conventional radiotherapy. The published evidence supports a meaningful improvement in the net health outcome. Evidence reported through clinical input further supports that this use provides a clinically meaningful improvement in net health outcome and is consistent with generally accepted medical practice. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have pediatric central nervous system tumor(s) who receive charged-particle (proton or helium ion) radiotherapy, the evidence includes case series, nonrandomized comparative studies, and systematic reviews. Relevant outcomes are overall survival, disease-free survival, change in disease status, and treatment-related morbidity. There are few comparative studies, and they tend to have small sample sizes. The available observational studies do not provide sufficient evidence on the efficacy of charged-particle therapy compared with other treatments (e.g., intensity-modulated radiotherapy). Limitations of the published evidence preclude determining the effects of the technology on net health outcome. Evidence reported through clinical input supports that this use provides a clinically meaningful improvement in net health outcome and is consistent with generally accepted medical practice. This modality of treatment has the potential to reduce toxicity to organs at risk and may minimize the development of radiation-induced secondary malignancies, particularly in individuals with radiation-sensitizing genetic syndromes that are highly correlated with these tumor types. The evidence is sufficient to determine the effects of the technology on health outcomes.

For individuals who have pediatric non-central nervous system tumor(s) who receive charged-particle (proton or helium ion) radiotherapy, the evidence includes dosimetric planning studies in a small number of patients. Relevant outcomes are overall survival, disease-free survival, change in disease status, and treatment-related morbidity. For this population, there is a lack of randomized and observational studies evaluating the efficacy and safety of this technology. Limitations of the published evidence preclude determining the effects of the technology on net health outcome. Evidence reported through clinical input supports that this use provides a clinically meaningful improvement in net health outcome and is consistent with generally accepted medical practice. This modality of treatment has the potential to reduce toxicity to organs at risk and may minimize the development of radiation-induced secondary malignancies. This intervention may be most suitable for patients treated with curative intent. The evidence is sufficient to determine the effects of the technology on health outcomes.

For individuals with central nervous system tumors, tumors of the spine, or with tumors requiring craniospinal irradiation, and where conventional or advanced photon-based radiotherapy may cause toxicity to organs at risk who receive charged-particle (proton or helium ion) radiotherapy, the evidence includes a systematic review and retrospective studies. Relevant outcomes are overall survival, disease-free survival, change in disease status, and treatment-related morbidity. For this population, there is a lack of randomized and comparative studies evaluating safety and efficacy. Limitations of the published evidence preclude determining the effects of the technology on net health outcome. Evidence reported through clinical input supports that this use provides a clinically meaningful improvement in net health outcome and is consistent with generally accepted medical

practice. This modality of treatment has the potential to reduce toxicity to healthy tissues, organs at risk, and may minimize the development of radiation-induced secondary malignancies. The evidence is sufficient to determine the effects of the technology on health outcomes.

For individuals who have localized prostate cancer who receive charged-particle (proton or helium ion) radiotherapy, the evidence includes two randomized controlled trials and systematic reviews. Relevant outcomes are overall survival, disease-free survival, change in disease status, and treatment-related morbidity. A 2010 TEC Assessment addressed the use of PBT for prostate cancer and concluded that it had not been established whether PBT improves outcomes in any setting for clinically localized prostate cancer. The TEC Assessment included 2 randomized controlled trials, only one of which had a comparison group of patients that did not receive PBT. Limitations of the published evidence preclude determining the effects of the technology on net health outcome. Evidence reported through clinical input suggests a possible role for prostate cancer. However, support for its use is pending and a large, ongoing phase III RCT comparing proton therapy to IMRT in prostate cancer may alter the conclusions of the TEC Assessment. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have non-small cell lung cancer who receive charged-particle (proton or helium ion) radiotherapy, the evidence includes case series and systematic reviews. Relevant outcomes are overall survival, disease-free survival, change in disease status, and treatment-related morbidity. A 2010 TEC Assessment, which included 8 case series, concluded that the evidence was insufficient to permit conclusions about PBT for any stage of non-small-cell lung cancer. No subsequent randomized or nonrandomized comparative studies were identified that would alter the conclusions of the TEC Assessment. Limitations of the published evidence preclude determining the effects of the technology on net health outcome. Evidence reported through clinical input supports that this use provides a clinically meaningful improvement in net health outcome and is consistent with generally accepted medical practice. This modality of treatment has the potential to reduce toxicity to healthy tissues and organs at risk, with optimal outcomes observed for patients who are treated with curative intent. The evidence is sufficient to determine the effects of the technology on the health outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have head and neck tumors other than skull-based who receive charged-particle (proton or helium ion) radiotherapy, the evidence includes case series, a case-matched cohort study, and a systematic review. Relevant outcomes are overall survival, disease-free survival, change in disease status, and treatment-related morbidity. The systematic review noted that the studies on charged-particle therapy were heterogenous in terms of the types of particles and delivery techniques used; further, there are no head-to-head trials comparing charged-particle therapy with other treatments. The evidence is insufficient to determine the effects of the technology on health outcomes. Limitations of the published evidence preclude determining the effects of the technology on net health outcome. Evidence reported through clinical input supports that this use provides a clinically meaningful improvement in net health outcome and is consistent with generally accepted medical practice. This modality of treatment has the potential to reduce toxicity to healthy tissues in cases with documented risk to uninvolved organs as demonstrated by dosimetric treatment plans utilizing conventional or advanced photon-based radiotherapy. For patients with complex and difficult to treat advanced, very advanced, and/or unresectable head and neck cancers, proton therapy may offer a high therapeutic index while managing treatment-related toxicities. The evidence is sufficient to determine the effects of the technology on the health outcomes.

For individuals who have thymomas or thymic carcinoma who receive charged-particle (proton or helium ion) radiotherapy, the evidence includes a prospective study. Relevant outcomes are overall survival, disease-free survival, change in disease status, and treatment-related morbidity. For this population, there is a lack of randomized and comparative studies assessing safety and efficacy. Limitations of the published evidence preclude determining the effects of the technology on net health outcome. Evidence reported through clinical input supports that this use provides a clinically

meaningful improvement in net health outcome and is consistent with generally accepted medical practice. This modality of treatment has the potential to reduce toxicity to healthy tissues and organs at risk. The likelihood of additional published evidence or larger studies is unlikely due to the rarity of thymic malignancies. The evidence is sufficient to determine the effects of the technology on the health outcomes.

For individuals with lymphomas who receive charged-particle (proton or helium ion) radiotherapy, the evidence includes prospective studies and a phase II trial. Relevant outcomes are overall survival, disease-free survival, change in disease-status, and treatment-related morbidity. For this population, there is a lack of randomized and comparative studies assessing safety and efficacy compared to other treatments. Limitations of the published evidence preclude determining the effects of the technology on net health outcome. Evidence reported through clinical input supports that this use provides a clinically meaningful improvement in net health outcome and is consistent with generally accepted medical practice. This modality of treatment has the potential to reduce toxicity to healthy tissues and organs at risk. The evidence is sufficient to determine the effects of the technology on the health outcomes.

For individuals with tumors near organs at risk that require reirradiation, or where conventional or advanced photon-based radiotherapy planning does not meet dose-volume constraints for normal tissue radiation tolerance, who receive charged-particle (proton or helium ion) radiotherapy, the evidence includes a systematic review. Relevant outcomes are overall survival, disease-free survival, change in disease-status, and treatment-related morbidity. Studies with optimal follow-up durations assessing long-term clinical outcomes and randomized, comparative data are lacking. Limitations of the published evidence preclude determining the effects of the technology on net health outcome. Evidence reported through clinical input along with NCCN and ASTRO guidelines supports that this use provides a clinically meaningful improvement in net health outcome and is consistent with generally accepted medical practice for selected cases when therapeutic goals and radiation dose constraints for critical organs at risk (i.e., surrounding normal tissue) cannot be met by other advanced conformal, fractionated photon-based radiotherapy techniques (i.e., including intensity modulated radiotherapy [IMRT], volume-modulated arc therapy [VMAT], stereotactic radiosurgery [SRS], or stereotactic body radiation therapy [SBRT]) for patients with indications such as breast cancer, esophageal cancer, resectable head & neck cancer, seminomas, pancreatic or hepatobiliary cancers, pelvic or genitourinary cancers, and soft tissue sarcomas. The evidence is sufficient to determine the effects of the technology on the health outcomes.

Clinical Input

CI Objective

In 2019, clinical input was sought to help determine whether the use of charged-particle (proton or helium ion) beam therapy (PBT) for various tumor indications would provide a clinically meaningful improvement in net health outcome and whether the use is consistent with generally accepted medical practice.

Respondents

Clinical input was provided by the following specialty societies and physician members identified by a specialty society or clinical health system:

- American Society for Radiation Oncology (ASTRO)
- Massachusetts Society of Clinical Oncology (MSCO)
- Anonymous, MD, Radiation Oncology, identified by an academic medical center (AMC)

*Indicates that no response was provided regarding conflicts of interest related to the topic where clinical input is being sought.

** Indicates that conflicts of interest related to the topic where clinical input is being sought were identified by this respondent (see Appendix).

Clinical Input Responses

Clinical Indication	Respondent	Identified by	Confidence Level That PBT Provides a Clinically Meaningful Improvement in Net Health Outcome That Is **Superior** to Other Advanced Conformal, Fractionated Photon-Based Radiotherapy Techniques[1] for **Most Patients** With This Indication										Confidence Level That PBT Provides a Clinically Meaningful Improvement in Net Health Outcome That Is **Superior ONLY** When Radiation Dose Constraints For Critical Organs At Risk (i.e., Surrounding Normal Tissue) Cannot Be Met By Other Conformal, Fractionated Photon-based Radiotherapy Techniques[1] for Patients With This Indication										Confidence Level that PBT for This Indication is Consistent with Generally Accepted Medical Practice									
			Yes or No	5	4	3	2	1	1	2	3	4	5	Yes or No	5	4	3	2	1	1	2	3	4	5	Yes or No	5	4	3	2	1	1	2	3	4	5
				NO (High)					YES (Low)						NO (High)					YES (Low)						NO (High)					YES (Low)				
				High				Low	Low				High		High				Low	Low				High		High				Low	Low				High
Pediatric central nervous system (CNS) tumor(s)	ASTRO		Yes									■		No		■									Yes								■	
	Anonymous	AMC	Yes									■		No	■										Yes									■
	MSCO		Yes									■		Yes								■			Yes							■		
Pediatric primary or benign solid non-CNS tumors treated with curative intent	ASTRO		Yes								■			No			■								Yes							■		
	Anonymous	AMC	Yes									■		No	■										Yes									■
	MSCO		No	NR										No	NR										No	NR								
Palliative treatment of childhood tumors	ASTRO		Yes								■			No			■								Yes							■		
	Anonymous	AMC	No	■										Yes								■			No		■							
	MSCO		No	NR										No	NR										No	NR								
Adult CNS malignant and benign tumors (e.g., intracranial and spinal ependymoma, medulloblastoma, meningioma)	ASTRO		Yes								■			No			■								Yes							■		
	Anonymous	AMC	Yes									■		No			■								Yes								■	
	MSCO		No	NR										No	NR										No	NR								
Adult primary or metastatic tumors of the spine where the spinal cord tolerance may be exceeded with conventional treatment or where the spinal cord has previously been irradiated	ASTRO		Yes									■		No		■									Yes	NR								
	Anonymous	AMC	Yes									■		No			■								Yes								■	
	MSCO		No	NR										No	NR										No	NR								
Oropharyngial cancer	ASTRO		Yes								■			Yes								■			Yes							■		
	Anonymous	AMC	Yes									■		No		■									Yes								■	
	MSCO		No	NR										No	NR										No	NR								
Nasopharyngial cancer	ASTRO		No			■								Yes									■		Yes								■	
	Anonymous	AMC	Yes									■		No		■									Yes								■	
	MSCO		No	NR										No	NR										No	NR								
Supraglottic laryngeal cancer	ASTRO		No					■						Yes								■			No				■					
	Anonymous	AMC	No	■										Yes								■			No			■						
	MSCO		No	NR										No	NR										No	NR								
Sinonasal tumors (e.g., ethmoid or maxillary sinus tumor)	ASTRO		No			■								Yes								■			No			■					
	Anonymous	AMC	Yes									■		No		■									Yes								■	
	MSCO		No	NR										No	NR										No	NR								
Very advanced head and neck cancer	ASTRO		NR	NR										NR	NR										NR	NR								
	Anonymous	AMC	Yes								■			No			■								Yes							■		
	MSCO		No	NR										No	NR										No	NR								
Occult primary tumor of head and neck	ASTRO		Yes									■		No		■									Yes	NR								
	Anonymous	AMC	No	■										Yes								■			No			■						
	MSCO		No	NR										No	NR										No	NR								
Salivary gland tumor	ASTRO		Yes									■		No		■									Yes								■	
	Anonymous	AMC	Yes								■			No			■								Yes							■		
	MSCO		No	NR										No	NR										No	NR								
Mucosal melanoma	ASTRO		Yes								■			No			■								Yes							■		
	Anonymous	AMC	No	■										Yes							■				No		■							
	MSCO		No	NR										No	NR										No	NR								
Non-small-cell lung cancer (curative treatment)	ASTRO		No			■								Yes								■			No			■					
	Anonymous	AMC	No			■								Yes									■		Yes							■		
	MSCO		No	NR										No	NR										No	NR								

ASTRO: American Society for Radiation Oncology; AMC: Academic medical center; MSCO: Massachusetts Society of Clinical Oncology; NR: Not reported
[1] Advanced conformal, fractionated photon-based radiotherapy techniques include intensity modulated radiotherapy (IMRT), volume-modulated arc therapy (VMAT), stereotactic radiosurgery (SRS), or stereotactic body radiation therapy (SBRT).

Clinical Indication	Respondent	Identified by	Confidence Level That PBT Provides a Clinically Meaningful Improvement in Net Health Outcome That Is **Superior** to Other Advanced Conformal, Fractionated Photon-Based Radiotherapy Techniques[1] for **Most Patients** With This Indication										Confidence Level That PBT Provides a Clinically Meaningful Improvement in Net Health Outcome That Is **Superior ONLY** When Radiation Dose Constraints For Critical Organs At Risk (i.e., Surrounding Normal Tissue) Cannot Be Met By Other Conformal, Fractionated Photon-based Radiotherapy Techniques[1] for Patients With This Indication										Confidence Level that PBT for This Indication is Consistent with Generally Accepted Medical Practice									
			NO					YES					NO					YES					NO					YES							
			High				Low	Low				High	High				Low	Low				High	High				Low	Low				High		
			Yes or No	5	4	3	2	1	1	2	3	4	5	Yes or No	5	4	3	2	1	1	2	3	4	5	Yes or No	5	4	3	2	1	1	2	3	4	5
Thymomas and thymic carcinoma	ASTRO		No			■								Yes									■		No			■							
	Anonymous	AMC	Yes								■			Yes									■		Yes									■	
	MSCO		No	NR										No	NR										No	NR									
Esophageal cancer	ASTRO		Yes									■		No		■									Yes									■	
	Anonymous	AMC	Yes									■		No		■									Yes									■	
	MSCO		No	NR										No	NR										No	NR									
Hepatocellular cancer	ASTRO		Yes									■		No		■									Yes									■	
	Anonymous	AMC	No					■						Yes									■		Yes										■
	MSCO		No	NR										No	NR										No	NR									
Intrahepatic cholangiocarcinoma	ASTRO		Yes								■			No			■								Yes								■		
	Anonymous	AMC	No					■						Yes									■		Yes										■
	MSCO		No	NR										No	NR										No	NR									
Gallbladder cancer	ASTRO		NR	NR										NR	NR										NR	NR									
	Anonymous	AMC	No		■									No			■								No				■						
	MSCO		No	NR										No	NR										No	NR									
Abdominal malignancies, including non-metastatic primary pancreatic and adrenal cancers	ASTRO		Yes								■			No			■								Yes								■		
	Anonymous	AMC	Yes								■			No			■								Yes									■	
	MSCO		No	NR										No	NR										No	NR									
Prostate cancer	ASTRO		No		■									Yes									■		Yes								■		
	Anonymous	AMC	No	■										No	■										Yes										■
	MSCO		No	NR										No	NR										No	NR									
Pelvic malignancies, including non-metastatic rectal, anal, bladder and cervical cancers	ASTRO		No				■							Yes									■		No	NR									
	Anonymous	AMC	No			■								Yes									■		Yes							■			
	MSCO		No	NR										No	NR										No	NR									
Stage IIA seminoma	ASTRO		Yes									■		No		■									Yes									■	
	Anonymous	AMC	Yes	NR										No	■										Yes										■
	MSCO		No	NR										No	NR										No	NR									
Lymphoma (e.g., Hodgkin lymphoma, non-Hodgkin lymphoma, or extranodal NK/T-Cell Lymphoma, nasal type)	ASTRO		Yes									■		No		■									Yes									■	
	Anonymous	AMC	Yes									■		No		■									Yes									■	
	MSCO		No	NR										No	NR										No	NR									
Ewing Sarcoma	ASTRO		No			■								Yes							■				Yes								■		
	Anonymous	AMC	Yes									■		No		■									Yes									■	
	MSCO		No	NR										No	NR										No	NR									
Soft tissue sarcoma (e.g., soft tissue sarcoma of extremity/superficial trunk, head/neck, or non-metastatic retroperitoneal sarcoma (non-metastatic)	ASTRO		Yes									■		No		■									Yes									■	
	Anonymous	AMC	No		■									Yes								■			No			■							
	MSCO		No	NR										No	NR										No	NR									
Breast cancer	ASTRO		Yes									■		No		■									Yes									■	
	Anonymous	AMC	No		■									Yes								■			No			■							
	MSCO		No	NR										No	NR										No	NR									
Re-irradiation tumor cases	ASTRO		Yes									■		No		■									Yes									■	
	Anonymous	AMC	No			■								Yes							■				Yes										■
	MSCO		No	NR										No	NR										No	NR									
Patients with genetic syndromes making total volume of radiation minimization crucial such as but not limited to NF-1 patients and retinoblastoma patients	ASTRO		Yes								■			No			■								Yes								■		
	Anonymous	AMC	No	■										No	■										Yes										■
	MSCO		No	NR										No	NR										No	NR									

ASTRO: American Society for Radiation Oncology; AMC: Academic medical center; MSCO: Massachusetts Society of Clinical Oncology; NR: Not reported

[1] Advanced conformal, fractionated photon-based radiotherapy techniques include intensity modulated radiotherapy (IMRT), volume-modulated arc therapy (VMAT), stereotactic radiosurgery (SRS), or stereotactic body radiation therapy (SBRT).

Supplemental Information

Clinical Input From Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

2019

In response to requests from Blue Cross Blue Shield Association in 2019, clinical input on use of charged-particle (proton or helium ion) beam therapy (PBT) for various tumor indications was received from 3 respondents, including 2 specialty society-level responses and 1 physician-level response identified by an academic health system. In addition, the specialty society responses included multiple physicians with academic medical center affiliations.

Evidence from clinical input is integrated within the Rationale section summaries and the Summary of Evidence.

2013

In response to requests from Blue Cross Blue Shield Association, input was received from 2 physician specialty societies (4 responses) and 4 academic medical centers in 2013. There was uniform support for the use of proton beam therapy in pediatric central nervous system tumors. Two reviewers supported the use of proton beam therapy in pediatric non-central nervous system tumors; data for this use are scant. Input on head and neck tumors (non-skull-based) was mixed.

Practice Guidelines and Position Statements

International Particle Therapy Co-operative Group

A 2016 consensus statement by the International Particle Therapy Co-operative Group offered the following conclusion about proton therapy for non-small-cell lung cancer (NSCLC): "...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...."[51,]

American College of Radiology

The 2014 guidelines from the American College of Radiology on external-beam radiotherapy in stage T1 and T2 prostate cancer stated:

- "There are only limited data comparing proton-beam therapy to other methods of irradiation or to radical prostatectomy for treating stage T1 and T2 prostate cancer. Further studies are needed to clearly define its role for such treatment.
- There are growing data to suggest that hypofractionation at dose per fraction <3.0 Gy per fraction is reasonably safe and efficacious, and although the early results from hypofractionation/SBRT [stereotactic body radiation therapy] studies at dose per fraction >4.0 Gy seem promising, these approaches should continue to be used with caution until more mature, ongoing phase II and III randomized controlled studies have been completed."[52,]

National Comprehensive Cancer Network

Radiation Therapy in Oncology

The National Comprehensive Cancer Network (NCCN) regularly updates its Clinical Practice Guidelines in Oncology, which may include recommendations for the use of radiotherapy in the treatment of cancer. NCCN maintains a clinical resource known as the NCCN Radiation Therapy Compendium which includes information and recommendations to support clinical decision-making regarding the use of radiotherapy in patients with cancer, and is directly informed by NCCN oncology guidelines.[53,] A search through the NCCN Radiation Therapy Compendium for guidelines mentioning the use of particle-based therapy (PBT) revealed recommendations (Category 1, 2A, or 2B) supporting

the use of PBT in a variety of clinical settings. These recommendations are generalized in Table 3 below.

Table 3. NCCN Recommendations for the use of Particle Beam Therapy in Oncology[i,ii]

Clinical Setting	Indications	Guideline Statements
Adult Intracranial and Spinal Ependymoma (Excluding Subependymoma)	• Intracranial, Metastases • Spinal, Metastases	"To reduce toxicity from craniospinal irradiation in adults, consider the use of IMRT or protons if available."
Adult Medulloblastoma	• Standard Risk • High Risk	"To reduce toxicity from craniospinal irradiation in adults, consider the use of IMRT or protons if available."
Burkitt Lymphoma	• Bone Marrow Transplant, Prior Systemic Therapy, Recurrence	"Treatment with photons, electrons, or protons may all be appropriate depending on clinical circumstances. Advanced radiation therapy technologies such as [proton therapy] may offer significant and clinically relevant advantages in specific instances to spare important organs at risk such as the heart, lungs, kidneys, spinal cord, esophagus, bone marrow, breasts, stomach, muscle/soft tissue, and salivary glands and decrease the risk for late, normal tissue damage while still achieving the primary goal of local tumor control."
Cancer of the Glottic Larynx	• Recurrence/Persistent • Prior RT, Recurrence/Persistent • Metastases, Recurrence/Persistent	"Advanced RT techniques such as [PBT] recommended."
Cancer of the Hypopharynx	• Recurrence/Persistent • Prior RT, Recurrence/Persistent • Metastases, Recurrence/Persistent	"Advanced RT techniques such as [PBT] recommended."
Cancer of the Lip (Mucosa)	• Recurrence/Persistent • Prior RT, Recurrence/Persistent • Metastases, Recurrence/Persistent	"Advanced RT techniques such as [PBT] recommended."
Cancer of the Nasopharynx	• No resection • No resection, Induction chemotherapy • Metastases • Recurrence/Persistent • Prior RT, Recurrence/Persistent • Metastases, Recurrence/Persistent	"Advanced techniques such as [PBT] is preferred over 3D conformal EBRT. Proton therapy can be considered when normal tissue constraints cannot be met by photon-based therapy."
Cancer of the Oral Cavity	• Resected/Node positive • No resection • Recurrence/Persistent • Prior RT, Recurrence/Persistent • Metastases, Recurrence/Persistent	"Advanced RT techniques such as [PBT] recommended."
Cancer of the Oropharynx	• No resection • Resected/Node negative • Resected/Node positive • Induction chemotherapy/No resection • p 16 HPV positive • Recurrence/Persistent • Prior RT, Recurrence/Persistent • Metastases, Recurrence/Persistent	"Advanced RT techniques such as [PBT] recommended."

Clinical Setting	Indications	Guideline Statements
Cancer of the Supraglottic Larynx	• No resection • Resected/Node negative • Resected/Node positive • Induction chemotherapy/No resection • Induction chemotherapy/Node positive • Recurrence/Persistent • Prior RT, Recurrence/Persistent • Metastases, Recurrence/Persistent	"Advanced RT techniques such as [PBT] recommended."
Chondrosarcoma	• Low or high-grade, Recurrence/progression, Unresectable • Low or high-grade, Positive margins, Resectable • Extracranial, Low-grade, Unresectable • Low-grade, Recurrence/Progression • Borderline resectable, Extracranial, High-grade, Unresectable • High-grade, Positive margins • Metastatic, Oligometastatic • Chemotherapy responders, Mesenchymal • Mesenchymal, Recurrence/Progression	"Specialized techniques such as IMRT or particle beam RT with protons, carbon ions, or other heavy ions; or SRS should be considered in order to allow high-dose therapy while maximizing normal tissue sparing."
Chordoma	• Extracranial sites, Resectable or Resected or Unresectable • Cranial, Unresectable or Resected • Metastases, Recurrence/Progression	"Specialized techniques such as IMRT or particle beam RT with protons, carbon ions, or other heavy ions; or SRS should be considered in order to allow high-dose therapy while maximizing normal tissue sparing."
Classic Hodgkin Lymphoma	• Non-bulky, Stage I-II Favorable or Unfavorable • Bulky, Stage I, II Unfavorable • Stage III, IV • Bone marrow transplant and/or Refractory/Relapse	"Treatment with photons, electrons, or protons may all be appropriate depending on clinical circumstances. Advanced radiation therapy technologies such as [proton therapy] may offer significant and clinically relevant advantages in specific instances to spare important organs at risk such as the heart, lungs, kidneys, spinal cord, esophagus, bone marrow, breasts, stomach, muscle/soft tissue, and salivary glands and decrease the risk for late, normal tissue damage while still achieving the primary goal of local tumor control."
Diffuse Large B-Cell Lymphoma	• Initial therapy, Stage I-II, Non-bulky • Stage I, II, Bone marrow transplant, Partial/Non-responders to initial therapy, Prior systemic therapy • Stage III-IV, Complete response to initial chemotherapy • Relapsed/Refractory, Recurrence/Progression, Prior systemic therapy • Recurrence/Progression, Prior systemic therapy	"Treatment with photons, electrons, or protons may all be appropriate depending on clinical circumstances. Advanced radiation therapy technologies such as [proton therapy] may offer significant and clinically relevant advantages in specific instances to spare important organs at risk such as the heart, lungs, kidneys, spinal cord, esophagus, bone marrow, breasts, stomach, muscle/soft tissue, and salivary glands and decrease the risk for late, normal tissue damage while still achieving the primary goal of local tumor control."

Clinical Setting	Indications	Guideline Statements
Esophageal and Esophagogastric Junction Cancers	• Adenocarcinoma • Squamous cell carcinoma • Unresectable, Previously Resected, or Esophagectomy declined	"Advanced RT techniques such as [PBT] recommended."
Ethmoid Sinus Tumors	• Resected/Node negative or positive • No resection • Incomplete resection • Recurrence/Persistent • Prior RT, Recurrence/Persistent • Metastases, Recurrence/Persistent	"Advanced RT techniques such as [PBT] recommended."
Ewing Sarcoma	• Chemotherapy responders, Resected, Positive, Negative or Unspecified margins • Chemotherapy responders, Marginally resectable	"Specialized techniques such as intensity-modulated RT (IMRT); particle-beam RT with protons, carbon ions, or other heavy ions, or stereotactic radiosurgery (SRS) should be considered as indicated in order to allow high-dose therapy while maximizing normal tissue sparing."
Extrahepatic Cholangiocarcinoma	• Unresectable • Resected gross residual disease	"Proton beam therapy (PBT) may be appropriate in specific situations."
Extranodal NK/T-Cell Lymphoma, Nasal Type	• Stage I-II, Unfit or Fit for chemotherapy, Extranodal or nodal • Stage IV, Extranodal • Stage I-IV, Extranodal	"Advanced radiation therapy technologies such as [proton therapy] may offer significant and clinically relevant advantages in specific instances to spare important organs at risk such as the heart, lungs, kidneys, spinal cord, esophagus, bone marrow, breasts, stomach, muscle/soft tissue, and salivary glands and decrease the risk for late, normal tissue damage while still achieving the primary goal of local tumor control."
Extremity/Superficial Trunk, Head/Neck	• Recurrence • Stage I, Positive margin • Stage II-III, Node positive or negative, Resectable or Unresectable • Any stage with metastases (M1)	"When EBRT is used, sophisticated treatment planning with IMRT and/or protons can be used to improve the therapeutic ratio."
Follicular Lymphoma	• Grade 1-2 • Stage I-II, Initial therapy • Stage III-IV, Initial therapy or Non-responders/Progression to initial therapy or Prior systemic therapy • Histologic transformation to diffuse large B-cell lymphoma, Initial therapy or Non-responders/Progression to initial therapy or Prior systemic therapy or Responsive disease with multiple lines of prior therapies • Stage I-II, Pediatric-type in adults	"Treatment with photons, electrons, or protons may all be appropriate depending on clinical circumstances. Advanced radiation therapy technologies such as [proton therapy] may offer significant and clinically relevant advantages in specific instances to spare important organs at risk such as the heart, lungs, kidneys, spinal cord, esophagus, bone marrow, breasts, stomach, muscle/soft tissue, and salivary glands and decrease the risk for late, normal tissue damage while still achieving the primary goal of local tumor control."
Gastric MALT Lymphoma	• Consolidation, Stage 1-II, H. pylori positive or negative • Complete response to initial therapy, Recurrence	"Treatment with photons, electrons, or protons may all be appropriate depending on clinical circumstances. Advanced radiation therapy technologies such as [proton therapy] may offer significant and clinically relevant advantages in specific instances to spare important organs at risk such as the heart, lungs, kidneys, spinal

Clinical Setting	Indications	Guideline Statements
		cord, esophagus, bone marrow, breasts, stomach, muscle/soft tissue, and salivary glands and decrease the risk for late, normal tissue damage while still achieving the primary goal of local tumor control."
Hepatocellular Carcinoma	• Resectable or Unresectable	"Hypofractionation with photons or protons is an acceptable option for intrahepatic tumors, though treatment at centers with experience is recommended."
High-Grade B-Cell Lymphomas	• Early stage disease	"Treatment with photons, electrons, or protons may all be appropriate depending on clinical circumstances. Advanced radiation therapy technologies such as [proton therapy] may offer significant and clinically relevant advantages in specific instances to spare important organs at risk such as the heart, lungs, kidneys, spinal cord, esophagus, bone marrow, breasts, stomach, muscle/soft tissue, and salivary glands and decrease the risk for late, normal tissue damage while still achieving the primary goal of local tumor control."
Intrahepatic Cholangiocarcinoma	• Unresectable	"Hypofractionation with photons or protons is an acceptable option for intrahepatic tumors, though treatment at centers with experience is recommended."
Malignant Pleural Mesothelioma	• Medically operable, Stage I-IIIA • Recurrence	"IMRT or other modern technology (such as tomotherapy or protons) should only be used in experienced centers or on protocol. When IMRT is applied, the NCI and ASTRO/ACR IMRT guidelines should be strictly followed."
Mantle Cell Lymphoma	• Stage I-II, Initial therapy or Second-line treatment for recurrence • Stage II bulky, III, or IV and prior treatment with systemic therapy	"Treatment with photons, electrons, or protons may all be appropriate depending on clinical circumstances. Advanced radiation therapy technologies such as [proton therapy] may offer significant and clinically relevant advantages in specific instances to spare important organs at risk such as the heart, lungs, kidneys, spinal cord, esophagus, bone marrow, breasts, stomach, muscle/soft tissue, and salivary glands and decrease the risk for late, normal tissue damage while still achieving the primary goal of local tumor control."
Maxillary Sinus Tumors	• T1-2, N0, Margin negative or positive resection • T3-T4a, N0, Margin negative or positive resection • T4b, N0-3, No resection • T1-T4a, Resected/Node positive • Recurrence/Persistent • Prior RT, Recurrence/Persistent • Metastases, Recurrence/Persistent	"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."
Meningiomas	• Unresected or Resected, Grade I-II • Recurrent/Progression, Grade I-II • Grade III	"To reduce toxicity from craniospinal irradiation in adults, consider the use of IMRT or protons if available."
Mucosal Melanoma	• T3, N0, Resected • T3-T4a, Resected	"Advanced RT techniques such as [PBT] recommended."

Clinical Setting	Indications	Guideline Statements
	• T4b, N0-1, No resection • T4a, N0, Resected • Occult, Resected	
Nodal Marginal Zone Lymphoma	• Stage I-II, Symptomatic disease • No response or partial response to prior chemotherapy • Stage III-IV, No response • Histologic transformation to diffuse large B-cell lymphoma with or without prior chemotherapy	"Treatment with photons, electrons, or protons may all be appropriate depending on clinical circumstances. Advanced radiation therapy technologies such as [proton therapy] may offer significant and clinically relevant advantages in specific instances to spare important organs at risk such as the heart, lungs, kidneys, spinal cord, esophagus, bone marrow, breasts, stomach, muscle/soft tissue, and salivary glands and decrease the risk for late, normal tissue damage while still achieving the primary goal of local tumor control."
Nodular Lymphocyte-Predominant Hodgkin Lymphoma	• Stage IA, IIA, Non-bulky • Stage I-II, Bulky, Unfavorable • Stage III-IV • Stage I-IV, PET response to systemic therapy, no prior RT • Stage III-IV, Symptomatic disease • Refractory/Relapsed	"Treatment with photons, electrons, or protons may all be appropriate depending on clinical circumstances. Advanced radiation therapy technologies such as [proton therapy] may offer significant and clinically relevant advantages in specific instances to spare important organs at risk such as the heart, lungs, kidneys, spinal cord, esophagus, bone marrow, breasts, stomach, muscle/soft tissue, and salivary glands and decrease the risk for late, normal tissue damage while still achieving the primary goal of local tumor control."
Non-Small Cell Lung Cancer	• Medically inoperable, Stage I-III, Negative mediastinal nodes • Stage I-III, Positive margins • Medically inoperable, Stage III • Stage II-III, Positive mediastinal nodes • Stage III, Local recurrence • Definitive local therapy possible • Stage IV, Metastases or Local recurrence	"More advanced technologies are appropriate when needed to deliver curative RT safely. These technologies include (but are not limited to) [proton therapy]."
Nongastric MALT Lymphoma	• Stage I-II, Initial therapy • Stage I-IV, Recurrence	"Treatment with photons, electrons, or protons may all be appropriate depending on clinical circumstances. Advanced radiation therapy technologies such as [proton therapy] may offer significant and clinically relevant advantages in specific instances to spare important organs at risk such as the heart, lungs, kidneys, spinal cord, esophagus, bone marrow, breasts, stomach, muscle/soft tissue, and salivary glands and decrease the risk for late, normal tissue damage while still achieving the primary goal of local tumor control."
Occult Primary	• Recurrence/Persistent with or without prior RT • Metastases, Recurrence/Persistent • Resected/Node positive • Induction chemotherapy, No resection, Node positive	"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."

Clinical Setting	Indications	Guideline Statements
Osteosarcoma	• Unresectable • Positive margins	"Specialized techniques such as intensity-modulated RT (IMRT); particle-beam RT with protons, carbon ions, or other heavy ions, or stereotactic radiosurgery (SRS) should be considered as indicated in order to allow high-dose therapy while maximizing normal tissue sparing."
Peripheral T-Cell Lymphomas	• Stage I-IV, Extranodal or Nodal • Relapse or refractory disease, Extranodal or Nodal	"Advanced radiation therapy technologies such as [proton therapy] may offer significant and clinically relevant advantages in specific instances to spare important organs at risk such as the heart, lungs, kidneys, spinal cord, esophagus, bone marrow, breasts, stomach, muscle/soft tissue, and salivary glands and decrease the risk for late, normal tissue damage while still achieving the primary goal of local tumor control."
Retroperitoneal/Intra-Abdominal	• Unresectable or Resectable	"When EBRT is used, sophisticated treatment planning with IMRT and/or protons can be used to improve the therapeutic ratio."
Salivary Gland Tumors	• Resected, Node positive or negative • Incomplete resection	"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."
Splenic Marginal Zone Lymphoma	• Palliative	"Treatment with photons, electrons, or protons may all be appropriate depending on clinical circumstances. Advanced radiation therapy technologies such as [proton therapy] may offer significant and clinically relevant advantages in specific instances to spare important organs at risk such as the heart, lungs, kidneys, spinal cord, esophagus, bone marrow, breasts, stomach, muscle/soft tissue, and salivary glands and decrease the risk for late, normal tissue damage while still achieving the primary goal of local tumor control."
Thymomas and Thymic Carcinomas	• Stage II-IV, Resectable • Locally advanced with or without metastases, Resectable or Unresectable	"Proton beam therapy (PBT) has been shown to improve the dosimetry compared to IMRT allowing better sparing of the normal organs (lungs, heart, and esophagus). Additionally, favorable results in terms of both local control and toxicity have been obtained with PBT. Based on these data, PBT may be considered in certain circumstances."
Uveal Melanoma	• Primary tumor • Extraocular extension and enucleation • Recurrence	"Particle beam therapy is a common form of definitive radiotherapy for the primary tumor....Particle beam therapy is appropriate as upfront therapy after initial diagnosis, after margin-positive enucleation, or for intraocular or orbital recurrence...Using protons, 50-70 cobalt Gray equivalent (CGyE) in 4-5 fractions should be prescribed to encompass the planning target volume surrounding the tumor."
Very Advanced Head and Neck Cancer	• Locoregional recurrence or second primary with prior RT • Unresectable	"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."

Adapted from the NCCN Radiation Therapy Compendium.[53,] ACR: American College of Radiology; ASTRO: American Society for Radiation Oncology; EBRT: external beam radiation therapy; IMRT: intensity-modulated radiotherapy; NCI: National Cancer Institute; PBT: proton beam therapy; RT: radiotherapy; SRS: stereotactic radiosurgery.

[i] Referenced with permission from the NCCN Radiation Therapy Compendium[53,] and NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) that discuss the use of particle beam therapy (PBT) in various clinical settings. © National Comprehensive Cancer Network, Inc. 2019. All rights reserved. Accessed September 2, 2019. To view the most recent and complete version of the guideline, go online to NCCN.org. [ii] NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

Prostate Cancer

National Comprehensive Cancer Network (NCCN) guidelines for prostate cancer (v.3.2022) offer the following conclusion on proton therapy: "The NCCN panel believes no clear evidence supports a benefit or decrement to proton therapy over IMRT [intensity-modulated radiotherapy] for either treatment efficacy or long-term toxicity. Conventionally fractionated prostate proton therapy can be considered a reasonable alternative to x-ray-based regimens at clinics with appropriate technology, physics, and clinical expertise."[54,] The NCCN adds that a prospective randomized trial comparing prostate PBT with x-ray-based IMRT is ongoing and may help to elucidate outcomes, as the evidence to date has not demonstrated a significant difference in benefit, particularly in regard to short and long-term toxicities. The NCCN acknowledges that PBT may deliver less radiation to surrounding tissues (e.g., muscle, bone, vessels, fat), but that these tissues do not routinely contribute to the morbidity of prostate radiation. Of greater clinical relevance, is the volume of rectum and bladder that is exposed to radiation. Higher volume, lower dose exposures minimize risk of long-term treatment morbidity. In the clinical reports, this has been achieved with dosimetric planning and the use of hypofractionated schedules. [i,ii]

Non-Small-Cell Lung Cancer

NCCN guidelines for NSCLC (v.1.2024) have been updated.[55,] Radiation has a potential role in all stages of NSCLC as either definitive or palliative therapy. A minimum technological standard is CT-planned 3D-CRT (3-dimensional conformal radiotherapy). More advanced techniques are appropriate when needed to deliver curative RT safely. These techniques include but are not limited to IMRT and proton therapy. Image-guided radiation therapy is recommended when using proton with steep dose gradients around the target, when organs at risk are in close proximity to high-dose regions, and when using complex motion management protocols. When higher radiation doses (>30 Gy) are warranted, technologies such as proton therapy may be used to reduce normal tissue irradiation.[i,ii]

Head and Neck Cancer

NCCN guidelines for head and neck cancers (v.2.2024) indicate that proton therapy may be used per the discretion of the treating physician but is an active area of investigation.[56,] Proton therapy may be considered when normal tissue constraints cannot be met by photon-based therapy. Otherwise, IMRT or 3D conformal RT is recommended. The safety and efficacy of PBT when highly conformal dose distributions are important has been established, and is particularly important for patient with primary periocular tumors, tumors invading the orbit, skull base, cavernous sinus, and for patients with intracranial extension or perineural invasion. These treatment approaches are recommended for those being treated with curative intent and/or those with long life expectancies following treatment. However, NCCN adds that without "high-quality prospective comparative data, it is premature to conclude that proton therapy has been established as superior to other established radiation techniques such as IMRT, particularly with regard to tumor control.".[56,i,ii]

Central Nervous System Cancer

NCCN guidelines for central nervous system cancers (v.1.2023) state to consider the use of IMRT or proton therapy for the treatment of intracranial and spinal ependymoma in adults to reduce toxicity from craniospinal irradiation.[57,] This approach is also recommended for consideration for adult medulloblastoma. For meningiomas, highly conformal fractionated RT techniques, including proton therapy, are recommended to spare critical structures and uninvolved tissues. No statements regarding use in pediatric populations was available.[i,ii]

[i] Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for *Prostate Cancer* V.4.2019, *Non-Small Cell Lung Cancer* V.7.2019, *Head and Neck Cancers* V.2.2019, and *Central Nervous System Cancers* V.1.2019. © National Comprehensive Cancer Network, Inc. 2019. All rights reserved. Accessed September 2, 2019. To view the most recent and complete version of the guideline, go online to NCCN.org.

[ii] NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

American Society for Radiation Oncology

The American Society for Radiation Oncology (ASTRO) (2017) updated its model policy on the medical necessity requirements for the use of proton therapy.[58,] ASTRO deemed the following disease sites those for which the evidence frequently supports the use of proton beam therapy:

- Ocular tumors, including intraocular melanomas
- Tumors that approach or are located at the base of the skull, including but not limited to chordoma and chondrosarcomas
- Primary or metastatic tumors of the spine where the spinal cord tolerance may be exceeded with conventional treatment or where the spinal cord has previously been irradiated
- Hepatocellular cancer
- Primary or benign solid tumors in children treated with curative intent and occasional palliative treatment of childhood tumors
- Patients with genetic syndromes making total volume of radiation minimization crucial such as but not limited to NF-1 patients and retinoblastoma patients
- Malignant and benign primary central nervous system tumors
- Advanced (e.g., T4) and/or unresectable head and neck cancers
- Cancers of the paranasal sinuses and other accessory sinuses
- Nonmetastatic retroperitoneal sarcomas
- Re-irradiation cases (where cumulative critical structure dose would exceed tolerance dose).

The model policy also made a specific statement on proton beam therapy for treating prostate cancer: "…, ASTRO believes the comparative efficacy evidence of proton beam therapy with other prostate cancer treatments is still being developed, and thus the role of proton beam therapy for localized prostate cancer within the current availability of treatment options remains unclear."

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 4.

Table 4. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT01230866	Study of Hypo-fractionated Proton Radiation for Low Risk Prostate Cancer	150	Dec 2020
NCT01993810	Comparing Photon Therapy To Proton Therapy To Treat Patients With Lung Cancer	560	Dec 2020
NCT02838602	Randomized Carbon Ions vs Standard Radiotherapy for Radioresistant Tumors (ETOILE)	250	May 2024
NCT01617161	Proton Therapy vs. IMRT for Low or Intermediate Risk Prostate Cancer (PARTIQoL)	400	Dec 2026
NCT02603341	Pragmatic Randomized Trial of Proton vs. Photon Therapy for Patients With Non-Metastatic Breast Cancer: A Radiotherapy Comparative Effectiveness (RADCOMP) Consortium Trial	1720	Nov 2030

NCT: national clinical trial.

Appendix 1

Respondent Profile

	Specialty Society	
#	Name of Organization	Clinical Specialty
1	American Society for Radiation Oncology (ASTRO)	Radiation Oncology
2	Massachusetts Society of Clinical Oncology (MSCO)	Radiation Oncology, Clinical Oncology

	Physician				
#	Name	Degree	Institutional Affiliation	Clinical Specialty	Board Certification and Fellowship Training
Identified by Academic Medical Center					
3	Anonymous	MD	Academic Medical Center	Radiation Oncology	

Respondent Conflict of Interest Disclosure

#	1) Research support related to the topic where clinical input is being sought		2) Positions, paid or unpaid, related to the topic where clinical input is being sought		3) Reportable ,more than $1,000,healthcare-related assets or sources of income for myself, my spouse, or my dependent children related to the topic where clinical input is being sought		4) Reportable, more than $350, gifts or travel reimbursements for myself, my spouse, or my dependent children related to the topic where clinical input is being sought	
	YES/NO	Explanation	YES/NO	Explanation	YES/NO	Explanation	YES/NO	Explanation
3	No	Not applicable, as this response is from health system, and not from individual physicians	No	Not applicable, as this response is from health system, and not from individual physicians	No	Not applicable, as this response is from health system, and not from individual physicians	No	Not applicable, as this response is from health system, and not from individual physicians

#	Conflict of Interest Policy Statement
1	ASTRO's Payer Relations Committee provided feedback. Regarding COI: "If there is any material information that raises potential conflict of interest issues for a Committee member at any time throughout the course of our work, it should be brought to the attention of the Committee Chair." No Committee members reported any conflicts of interest.
2	No conflicts of interest reported.

Individual physician respondents answered at individual level. Specialty Society respondents provided aggregate information that may be relevant to the group of clinicians who provided input to the Society-level response. NR = not reported

Clinical Input Responses

CI- Background

Charged-particle beams consisting of protons or helium ions are a type of particulate radiotherapy. Treatment with charged-particle radiotherapy is proposed for a large number of indications, often for tumors that would benefit from the delivery of a high dose of radiation with limited scatter.

CI-Objective

clinical input is sought to help determine whether the use of charged-particle (proton or helium ion) beam therapy (PBT) for various tumor indications would provide a clinically meaningful improvement in net health outcome and whether the use is consistent with generally accepted medical practice.

The following PICO applies to this indication.

Populations	Interventions	Comparators	Outcomes
Individuals: • Various tumor indications listed in questions 1 (a) through 1 (cc)	Interventions of interest are: • Charged-particle (proton or helium ion) beam therapy (i.e., PBT)	Comparators of interest are: • Advanced conformal, fractionated photon-based radiotherapy techniques including intensity modulated radiotherapy (IMRT), volume-modulated arc therapy (VMAT), stereotactic radiosurgery (SRS), or stereotactic body radiation therapy (SBRT). • Other types of therapy for localized tumor	Relevant outcomes include: • Overall survival • Disease-free survival • Change in disease status • Treatment-related morbidity

Responses

1. We are seeking your opinion regarding whether and when clinical scenarios using charged-particle (proton or helium ion) therapy (PBT) for the tumor types highlighted below provide a clinically meaningful improvement in net health outcome that is **superior** to advanced conformal, fractionated photon-based radiotherapy including intensity modulated radiotherapy (IMRT), volume-modulated arc therapy (VMAT), stereotactic radiosurgery (SRS), or stereotactic body radiation therapy (SBRT).Please respond based on the evidence and your clinical experience. Please address these points in your narrative rationale:
   - Relevant patient inclusion/exclusion criteria or clinical context important to consider when PBT may offer superior improvement in net health outcome;
   - Relevant critical organs at risk for each clinical indication and associated thresholds for radiation dose limits; and
   - Supporting evidence from the authoritative scientific literature (please include PMID).
     a) Pediatric central nervous system (CNS) tumor(s)

#	Rationale
1	• Armstrong FD, Holtz Children's Hospital. Proton-beam radiation therapy and health-related quality of life in children with CNS tumors. J Clin Oncol. 2012;30(17):2028-2029. PMID: 2254996. • Chhabra A, Mahajan A. Treatment of common pediatric CNS malignancies with proton therapy. Chin Clin Oncol. 2016 Aug;5(4):49. PMID: 27506805. • Habrand JL, Mammar H, Ferrand R, et al. Proton beam therapy (PT) in the management of CNS tumors in childhood. Strahlenther Onkol. 1999;175(Suppl 2):91â€'94. PMID: 10394410. • MacDonald SM, Sethi R, Lavally B, et al. Proton radiotherapy for pediatric central nervous system ependymoma: clinical outcomes for 70 patients. Neuro Oncol. 2013; 15(11): 1552-9. PMID: 24101739.

#	Rationale
	• 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):121â€'129. PMID: 20452141.
2	More good quality data on the use of PBT for pediatric CNS tumors are emerging Several recent good quality publications were not cited in the 8.01.10 document and are noteworthy. 1. Review articles A. Baliga and Yock's review article Proton Beam Therapy in Pediatric Oncology (Curr Opin Pediastr 2019;31(1):28-34) showed that PBT decreased the incidence and severity of late effects with the strongest evidence in pediatric brain tumors patients. High quality data show that reduction in late effect from PBT is linked to lower doses to normal tissues such as the brainstem, compared to sophisticated photon delivery methods. PBT provided benefits in neurocognitive, hearing and endocrine outcomes. B. Mizumoto et al (Neurol Med Chir (Tokyo) 57, 343–355, 2017) published a systematic review of PBT for pediatric brain tumor. In addition to summaries on treatment efficacy for a large range of tumors, the authors also compiled data on dosimetric comparison and late toxicity of PBT in comparison to photon therapy. The authors concluded that PBT provided an equivalent therapeutic effect to that of photon radiotherapy and that many studies showed PBT to reduce dose to organs at risk compared with photon radiotherapy. Further studies such as Pulsifer et al (Int J Radiat Oncol Biol Phys 93: 400–407, 2015) demonstrated that cognitive function in children treated with PBT was superior to those treated with photon radiotherapy. 2. Case studies A couple of recent case series suggest that PBT for pediatrics CNS tumors may be associated with less cognitive impairment. A. Ventura et al (J Neurooncol. 2018 Mar;137(1):119-126. PMID: showed that children who underwent PBT had relatively intact intelligence, executive functioning, and school-based health-related quality of life, though were at risk for reduced processing speed. The authors claimed that the results with PBT "compare favorably" to photon radiation outcomes. B. Antonini et al (Radiother Oncol. 2017 Jul;124(1):89-97. doi: 10.1016/j.radonc.2017.06.010) studied attention, processing speed, and executive functioning in 39 children who received craniospinal or focal PBT, in comparison to population norms. In the focal PBT subgroup, attention, processing speed, and executive functioning remained intact and were within normal limits. In the craniospinal subgroup, patterns of cognitive dysfunction were observed. Overall, they found no evidence of profound cognitive impairment in either group. C. Gross et al (Neuro Oncol 2019:21(7):934-943) studied the intelligence and processing speed in 125 children who received PBT or photon therapy and found significantly improved outcome in the PBT group. D. Radiation plays a prominent role in the treatment of pediatric CNS tumors. The late effects of CNS radiation in the pediatric population can be devastating. There is sufficient evidence to show that 1) PBT is safe and provides equivalent therapeutic efficacy compare to photon therapy.2) PBT lowers the risk of late effects compared to photon therapy. 3) This reduction in risk is related to decrease in dose to normal tissues such as the brainstem. This reviewer would suggest BCBS to provide coverage for PBT for pediatric CNS tumors or at least consider its appropriateness on a case-by-case basis.
3	Particle and proton therapy represent enormous opportunity for normal tissue sparing in children requiring radiotherapy for central nervous system tumors. Some pediatric brain tumors, such as medulloblastoma, disseminated ependymoma, and CNS AT/RT, require radiotherapy to the entire brain and spine (craniospinal axis). When given with even the most sophisticated x-ray approach, this treatment results in exposure of the anterior, visceral organs, including the heart, lungs, liver, bowel, and organs of fertility. Numerous studies have demonstrated that proton therapy can decrease or eliminate exposure of the heart, breast tissue, bowel, and ovaries during craniospinal irradiation. For young patients, this is expected to translate to decreased risk of heart disease and second malignancies, and also spares patients from need for surgery to relocate ovaries prior to beginning radiotherapy. (Sakthivel V, Ganesh KM, McKenzie C, Boopathy R, Selvaraj J.Australas Phys Eng Sci Med. 2019 Mar;42(1):201-209. doi: 10.1007/s13246-019-00731-y. Epub 2019 Feb 6. PMID:30725439; Welch GD, Lin KY, Fisher MJ, Hill-Kayser CE. J Pediatr Hematol Oncol. 2018 Jul;40(5):e330-e333. PMID: 29200158). Other pediatric brain tumors are treated with radiotherapy to the partial brain alone (localized ependymoma, glioma) or in combination with craniospinal radiation. Proton therapy drastically reduces the amount of normal brain that receives radiation, with preliminary studies demonstrating sparing of neurocognitive damage compared to historical x-ray studies (Pulsifer MB, Duncanson H, Grieco J, Evans C,

#	Rationale
	Tseretopoulos ID, MacDonald S, Tarbell NJ, Yock TI. Int J Radiat Oncol Biol Phys. 2018 Oct 1;102(2):391-398. doi: 10.1016/j.ijrobp.2018.05.069. Epub 2018 Jun 6. PMID: 30108004). Proton therapy also provides sparing of the hypothalamic-pituitary axis and cochlea, decreasing need for long-term medical care and disability in survivors growing up after having received radiotherapy (Paulino AC, Mahajan A, Ye R, Grosshans DR, Fatih Okcu M, Su J, McAleer MF, McGovern S, Mangona VA, Chintagumpala M. Ototoxicity and cochlear sparing in children with medulloblastoma: Proton vs. photon radiotherapy. Radiother Oncol. 2018 Jul;128(1):128-132. doi: 10.1016/j.radonc.2018.01.002. Epub 2018 Jan 17. PMID:29373195).

NR = not reported

Rating Questions:	#	YES / NO	Low Confidence		Intermediate Confidence		High Confidence
			1	2	3	4	5
Does the evidence show that PBT provides a clinically meaningful improvement in net health outcome that is superior to other advanced conformal, fractionated photon-based radiotherapy techniques[1] for most patients with this indication?	1	Yes				X	
	2	Yes				X	
	3	Yes					X
Does PBT provide a clinically meaningful improvement in net health outcome that is superior ONLY when radiation dose constraints for critical organs at risk (i.e., surrounding normal tissue) cannot be met by other conformal, fractionated photon-based radiotherapy techniques[1] for patients with this indication?	1	No				X	
	2	Yes				X	
	3	No					X
Is use of PBT for this indication consistent with generally accepted medical practice?	1	Yes				X	
	2	Yes			X		
	3	Yes					X

NR = not reported

b) Pediatric primary or benign solid non-CNS tumors treated with curative intent

#	Rationale
1	• 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 October 1;90(2):354-61. PMID: 25052561. • Cotter SE, McBride SM, Yock TI. Proton radiotherapy for solid tumors of childhood. Technol Cancer Res Treat. 2012;11(3):267-278. PMID: 22417062. • Eaton BR, Esiashvili N, Kim S, et al. Clinical outcomes among children with standard risk medulloblastoma treated with proton and photon radiotherapy: a comparison of disease control and overall survival. Int J Radiat Oncol Biol Phys. 2016 Jan 1;94(1):133-138. PMID: 26700707. • Haas-Kogan D, Indelicato D, Paganetti H, et al. National Cancer Institute Workshop on Proton Therapy for Children: Considerations Regarding Brainstem Injury. Int J Radiat Oncol Biol Phys. 2018;101(1):152-168. PMID: 29619963. • Mahajan A, Strother D, Pollack I, et al. ATRT -10: Early post radiation changes and efficacy in children with ATRT treated on COG ACNS 0333: A comparison of proton vs. photon therapy. Neuro Oncol. 2017;19 (suppl_4): iv3. • Yock TI, Tarbell NJ. Technology insight: proton beam radiotherapy for treatment in pediatric brain tumors. Nat Clin Pract Oncol. 2004;1(2):97â€'103.
2	There are case series showing a favorable safety profile and efficacy. However the evidence base remains not sufficiently robust to draw conclusions about the efficacy of PBT for pediatric non-CNS tumors.

#	Rationale
3	Non-CNS pediatric cancers represent a diverse group of diseases, including sarcomas, abdominal tumors (neuroblastoma and Wilms tumor), and Hodgkin lymphoma. Sarcomas of childhood include rhabdomyosarcoma (RMS), Ewing sarcoma, and osteosarcoma. Ewing sarcoma and RMS can arise anywhere in the body, and radiation is required for patients whose tumors cannot be completely resected, including those with positive surgical margins.An increasing body of literature supports use of proton therapy for treatment of these tumors, particularly when they arise in the head/neck and trunk, where significant normal tissue sparing can be achieved. Use of particle therapy can spare salivary function, reduce risk of cataract and sensorineural hearing loss, and reduce need for supplemental feeding by reducing acute toxicity for patients with parameningeal tumors. For those with pelvic and/or bladder tumors, proton therapy can reduce dose to rectum, ovaries, and pelvic bones and allow bladder preservation in some patients. (Weber DC, Ares C, Albertini F, et al. Pencil Beam Scanning Proton Therapy for Pediatric Parameningeal Rhabdomyosarcomas: Clinical Outcome of Patients Treated at the Paul Scherrer Institute. Pediatr Blood Cancer 2016;63:1731e1736. PMID: 26701148; Cotter SE, Herrup DA, Friedmann A, et al. Int J Radiat Oncol Biol Phys 2011;81: 1367-73. PMID: 20934266;Rombi B, DeLaney TF, MacDonald SM, et al. Int J Radiat Oncol Biol Phys 2012;82:1142-8. PMID: 21856094). Osteosarcoma is treated only rarely with proton therapy; however, for unresectable tumors, proton and particle therapy represent the only modality to allow delivery of very high doses required to treat this disease. This use is well-established in the literature. (DeLaney TF, Park L, Goldberg SI, et al. Int J Radiat Oncol Biol Phys 2005;61: 492-498. PMID: 15667972; Ciernik IF, Niemierko A, Harmon DC, et al. Cancer 2011;117:4522-4530. PMID: 21448934). Abdominal tumors of childhood may include sarcomas as discussed above, as well as neuroblastoma and Wilms tumor.Recent publications provide evidence regarding excellent clinical outcomes after treatment of neuroblastoma tumors with proton therapy, with this treatment allowing decreased exposure of kidneys, liver, and bowel to radiotherapy and providing extremely low toxicity risk (Hill-Kayser CE, Tochner Z, Li Y, Kurtz G, Lustig RA, James P, Balamuth N, Womer R, Mattei P, Grupp S, Mosse YP, Maris JM, Bagatell R. Int J Radiat Oncol Biol Phys. 2019 Jun 1;104(2):401-408. doi: 10.1016/j.ijrobp.2019.01.095. PMID: 30738983). Proton therapy has become accepted as a standard of care within pediatrics, and has been adopted by the Children's Oncology group for children with neuroblastoma. Although similar benefits likely exist in treatment of Wilms tumor, these have not been investigated thoroughly. It is the opinion of our center that proton therapy for Wilms tumor should be offered in the context of a clinical trial only, until further data have been published. Survivors of Hodgkin lymphoma who have received radiotherapy are well-recognized to be at risk for cardiac disease as well as secondary breast and lung cancers. These effects, particularly related to heart disease, seem to be related to dose received by heart muscles and vessels. Proton therapy has been demonstrated to be effective for treatment of Hodgkin lymphoma in the pediatric population, with decreased or eliminated dose to heart and breast tissue (Hoppe BS, Hill-Kayser CE, Tseng YD, Flampouri S, Elmongy HM, Cahlon O, Mendenhall NP, Maity A, McGee LA, Plastaras JP. Ann Oncol. 2017 Sep 1;28(9):2179-2184. doi: 10.1093/annonc/mdx287.PMID: 28911093; Andolino DL, Hoene T, Xiao L, Buchsbaum J, Chang AL. Int J Radiat Oncol Biol Phys. 2011 Nov 15;81(4):e667-71. Doi 10.1016/j.ijrobp.2011.01.061. Epub 2011 Apr 1. PMID:21459527).

NR = not reported

Rating Questions:	#	YES / NO	Low Confidence		Intermediate Confidence		High Confidence
			1	2	3	4	5
Does the evidence show that PBT provides a clinically meaningful improvement in net health outcome that is **superior** to other advanced conformal, fractionated photon-based radiotherapy techniques[1] for **most patients** with this indication?	1	Yes			X		
	2	No	Rating not provided				
	3	Yes					X
Does PBT provide a clinically meaningful improvement in net health outcome that is **superior ONLY** when radiation dose constraints for critical organs at risk (i.e., surrounding normal tissue) cannot be met by other	1	No			X		
	2	No	Rating not provided				
	3	No					X

Rating Questions:	#	YES / NO	Low Confidence		Intermediate Confidence		High Confidence
			1	2	3	4	5
conformal, fractionated photon-based radiotherapy techniques[1] for patients with this indication?							
Is use of PBT for this indication consistent with generally accepted medical practice?	1	Yes			X		
	2	No	Rating not provided				
	3	Yes					X

NR = not reported

c) Palliative treatment of childhood tumors

#	Rationale
1	Proton Beam Therapy is not typically utilized in palliative treatment.
2	Insufficient evidence
3	In general, proton therapy is not indicated for palliative treatment in pediatrics. On occasion, proton therapy may minimize acute toxicities and allow bone marrow sparing (in turn allowing delivery of systemic therapy), and thus may be deemed beneficial by the medical team. This may be particularly true in the setting of craniospinal palliative radiotherapy, when proton or particle therapy may be used to minimize acute nausea/vomiting and diarrhea accompanied by x-ray treatment of the total spine.

NR = not reported

Rating Questions:	#	YES / NO	Low Confidence		Intermediate Confidence		High Confidence
			1	2	3	4	5
Does the evidence show that PBT provides a clinically meaningful improvement in net health outcome that is **superior** to other advanced conformal, fractionated photon-based radiotherapy techniques[1] for **most patients** with this indication?	1	Yes			X		
	2	No	Rating not Provided				
	3	No					X
Does PBT provide a clinically meaningful improvement in net health outcome that is **superior ONLY** when radiation dose constraints for critical organs at risk (i.e., surrounding normal tissue) cannot be met by other conformal, fractionated photon-based radiotherapy techniques[1] for patients with this indication?	1	No			X		
	2	No	Rating not Provided				
	3	Yes			X		
Is use of PBT for this indication consistent with generally accepted medical practice?	1	Yes			X		
	2	No	Rating not Provided				
	3	No				X	

NR = not reported

d) Adult CNS malignant and benign tumors (e.g., intracranial and spinal ependymoma, medulloblastoma, meningioma)

#	Rationale
1	• Amsbaugh MJ, Grosshans DR, McAleer MF, et al. Proton therapy for spinal ependymomas: planning, acute toxicities, and preliminary outcomes. Int J Radiat Oncol Biol Phys. 2012;83(5):1419â€'1424. PMID: 22245209.

#	Rationale
	• Jhaveri J, Cheng E, Buchwald ZS, et al. Proton versus photon radiation therapy for primary gliomas: an analysis of the National Cancer Data Base. Front Oncol. 2018 Nov 28;8:440. PMID: 30547008. • Murray FR, Snider JW, Bolsi A, et al. Long-term clinical outcomes of Pencil Beam Scanning Proton Therapy for benign and non-benign intracranial meningiomas. Int J Radiat Oncol Biol Phys. 2017, doi: 10.1016/j.ijrobp.2017.08.005. PMID: 28939227. • Wilkinson B, Morgan H, Gondi V, et al. Low Levels of Acute Toxicity Associated With Proton Therapy for Low-Grade Glioma: A Proton Collaborative Group Study. Int J Radiat Oncol Biol Phys. 2016 Oct 1;96(2S):E135. • Zhu S, Rotondo R, Mendenhall WM, et al. Long-term outcomes of fractionated stereotactic proton therapy for vestibular schwannoma: a case series. Int J Part Ther. 2018.
2	Adult CNS benign tumors Lesueur et al "Proton Therapy for Treatment of Intracranial Benign Tumors in Adults: A Systematic Review" (Cancer Treat Rev 2019;72:56-64. PMID: 30530009.) provided a review of PBT for benign adult intracranial and cervical tumors. Control rates were favorable but there is insufficient evidence to show whether PBT is superior to photon therapy.
3	There are a number of reviews that have examined and summarized the use of charged particle therapy in adult intracranial tumors.One review (Lesueuer et al. Cancer Treatment Reviews 72, 56-64, 2019) examined the role of proton therapy for meningiomas, neurinomas, pituitary adenomas and paragangliomas over 24 non-randomized studies which noted long term local control of over 90% with equivalent if not decreased acute and long term toxicities. A review (Adeberg et al, Radiation Oncology, 12:193, 2017) of the use of protons and carbon ions for meningiomas and gliomas noted high rates of long term control, low rates of adverse event and maintenance of functional outcomes with implications of quality of life and cost-effectiveness measures in the long term. There is also a benefit with charged particle therapy in regards to dose escalation as well as re-irradiation. However there is still a need for long term prospective data in regards to neurocognitive decline and function over a longer period of time.

NR = not reported

Rating Questions:	#	YES / NO	Low Confidence		Intermediate Confidence		High Confidence
			1	2	3	4	5
Does the evidence show that PBT provides a clinically meaningful improvement in net health outcome that is **superior** to other advanced conformal, fractionated photon-based radiotherapy techniques[1] for **most patients** with this indication?	1	Yes			X		
	2	No	Rating not Provided				
	3	Yes				X	
Does PBT provide a clinically meaningful improvement in net health outcome that is **superior ONLY** when radiation dose constraints for critical organs at risk (i.e., surrounding normal tissue) cannot be met by other conformal, fractionated photon-based radiotherapy techniques[1] for patients with this indication?	1	No			X		
	2	No	Rating not Provided				
	3	No			X		
Is use of PBT for this indication consistent with generally accepted medical practice?	1	Yes			X		
	2	No	Rating not Provided				
	3	Yes				X	

NR = not reported

e) Adult primary or metastatic tumors of the spine where the spinal cord tolerance may be exceeded with conventional treatment or where the spinal cord has previously been irradiated

#	Rationale
1	• Demizu Y, Mizumoto M, Onoe T, et al. Proton beam therapy for bone sarcomas of the skull base and spine: a retrospective nationwide multicenter study in Japan. Cancer Sci. 2017 May;108(5):972-977 • Gentile MS, Miao R, Liebsch NJ, et al. Combined Surgical Resection and Adjuvant High Dose Photon/Proton Radiation Therapy Strategy Results in High Local Control in Cervical Spine Chordomas. Int J Radiat Oncol Biol Phys. 2017; 99(2): E752. • Indelicato DJ, Rotondo RL, Begosh-Mayne D, et al. A prospective outcomes study of proton therapy for chordomas and chondrosarcomas of the spine. Int J Radiat Oncol Biol Phys. 2016;95(1):297-303. • Kabolizadeh P, Chen YL, Liebsch N, et al. Updated outcome and analysis of tumor response in mobile spine and sacral chordoma treated with definitive high-dose photon/proton radiation therapy. Int J Radiat Oncol Biol Phys. 2017;97(2):254-262.
2	NR
3	There is no prospective study in this population of patients however there is evidence in a retrospective review of consecutively treated adult medulloblastoma patients requiring craniospinal irradiation in which patients who received proton radiotherapy lost less weight, had less grade 2 nausea and vomiting overall as well as these patients had less >5% weight loss when compared to photon craniospinal patients. Photon patients required much higher rates of medical management of esophagitis (57% vs 5%, P<.001).In addition, the patients receiving protons had a smaller reduction in blood counts which was statistically significant (Brown AP, Barney CL, Grosshans DR, et al. Proton Beam Craniospinal Irradiation Reduces Acute Toxicity for Adults with Medulloblastoma. 2013 Jun 1;86(2):277-284. PMID: 23433794).

NR = not reported

Rating Questions:	#	YES / NO	Low Confidence		Intermediate Confidence		High Confidence
			1	2	3	4	5
Does the evidence show that PBT provides a clinically meaningful improvement in net health outcome that is **superior** to other advanced conformal, fractionated photon-based radiotherapy techniques[1] for **most patients** with this indication?	1	Yes				X	
	2	No	Rating not provided				
	3	Yes				X	
Does PBT provide a clinically meaningful improvement in net health outcome that is **superior ONLY** when radiation dose constraints for critical organs at risk (i.e., surrounding normal tissue) cannot be met by other conformal, fractionated photon-based radiotherapy techniques[1] for patients with this indication?	1	No				X	
	2	No	Rating not provided				
	3	No			X		
Is use of PBT for this indication consistent with generally accepted medical practice?	1	Yes	Rating not provided				
	2	No	Rating not provided				
	3	Yes				X	

NR = not reported

f) Oropharyngeal cancer

#	Rationale
1	• Bagley AF, Ye R, Hernandez M, Frank SJ. (P30) Prospective Outcomes of Xerostomia-Related quality of Life in Oropharyngeal Carcinoma Patients Treated With Proton Therapy. Int J Radiat Oncol Biol Phys. 2018;101(2):E32-E33.

#	Rationale
	• Frank SJ, Blanchard P, Lee JJ, et al. Comparing Intensity-Modulated Proton Therapy With Intensity-Modulated Photon Therapy for Oropharyngeal Cancer: The Journey From Clinical Trial Concept to Activation. Semin Radiat Oncol. 2018;28(2):108-113. PMID: 29735186. • Gunn GB, Blanchard P, Garden AS, et al. Clinical outcomes and patterns of disease recurrence following intensity modulated proton therapy for oropharyngeal squamous carcinoma: results from single institution prospective registry studies. Int J Radiat Oncol Biol Phys. 2016 May 1;95(1):360-367. PMID: 27084653. • Sio TT, Lin HK, Shi Q, et al. Intensity modulated proton therapy versus intensity modulated photon radiation therapy for oropharyngeal cancer: first comparative results of patient-reported outcomes. Int J Radiat Oncol Biol Phys. 2016 Jul 15;95(4):1107-1114. PMID: 27354125.
2	Kim et al's review article "Proton Therapy for Head and Neck Cancer" (Curr Treat Options Oncol 2018;19(6):28. PMID: 29744681) provides a comprehensive review of the use of PBT for head and neck cancer. There are small case series on PBT for oropharyngeal cancer. Evidence is not robust enough to support PBT for this site.
3	Oropharynx cancer, given its excellent disease outcomes and long-term patient survival, is an ideal indication for consideration of proton therapy for toxicity mitigation. From a clinical standpoint, as mentioned above, the use of proton therapy for oropharynx in the postoperative setting is superior to IMRT, with gains in patients-reported outcome and quality of life (Sharma S, Zhou O, Thompson R, Gabriel P, Chalian A, Rassekh C, et al. Quality of Life of Postoperative Photon versus Proton Radiation Therapy for Oropharynx Cancer. International Journal of Particle Therapy. 2018;5(2):11-7.). A case matched analysis of 150 patients with oropharynx cancer (50 treated with IMPT versus 100 treated with IMRT) from the MD Anderson Cancer Center examined clinical outcomes of the 2 modalities (PMID 27342249). There were no differences in overall survival between the 2 modalities, while patients receiving IMPT were far less likely to require the use of a gastrostomy tube either during or up to 1 year after completion of treatment. A prospective, multi-center randomized trial of IMPT versus IMRT for oropharynx is currently underway, with another trial to be launched in late 2019. The current multi-center trial, being led out of MD Anderson (NCT 01893307), is a phase III study of 360 patients in which patients with locoregionally-advanced oropharynx cancer will receive organ-preservation chemoradiation, with RT technique randomized between IMRT and IMPT. The trial is powered for a primary outcome measure of equivalence in progression-free survival between the 2 techniques, with a secondary outcome measure of rates and severity of late grade 3-5 toxicity. In late 2019, the National Health System in England will launch their first prospective, randomized clinical trial for proton therapy (TORPeDO). TORPeDO will be a phase III, multi-center, randomized controlled study for patients with oropharyngeal cancer requiring definitive, organ-preservation chemoradiation. Patients will be randomized to IMRT versus IMPT, with primary outcome of treatment-related toxicity. In summary, given the of importance of chronic toxicity mitigation for expected long-term survivors of oropharynx cancer, proton therapy should be strongly considered when radiotherapy is indicated (either as single modality, in combination with chemotherapy for organ preservation, or in and adjuvant setting). Participation in a clinical trial, such as those mentioned above, is encouraged, whenever possible. When trial participation is not feasible, treatment with proton therapy, whenever possible, is recommended, given the existing (non-randomized) data suggesting improved therapeutic ratio.

NR = not reported

Rating Questions:	#	YES / NO	Low Confidence		Intermediate Confidence		High Confidence
			1	2	3	4	5
Does the evidence show that PBT provides a clinically meaningful improvement in net health outcome that is **superior** to other advanced conformal, fractionated photon-based radiotherapy techniques[1] for **most patients** with this indication?	1	Yes			X		
	2	No	Rating not provided				
	3	Yes				X	
	1	Yes			X		

Rating Questions:	#	YES / NO	Low Confidence		Intermediate Confidence		High Confidence
			1	2	3	4	5
Does PBT provide a clinically meaningful improvement in net health outcome that is **superior ONLY** when radiation dose constraints for critical organs at risk (i.e., surrounding normal tissue) cannot be met by other conformal, fractionated photon-based radiotherapy techniques[1] for patients with this indication?	2	No	Rating not provided				
	3	No				X	
Is use of PBT for this indication consistent with generally accepted medical practice?	1	Yes			X		
	2	No	Rating not provided				
	3	Yes				X	

NR = not reported

g) Nasopharyngeal cancer

#	Rationale
1	• Lewis GD, Holliday EB, Kocak-Uzel E, et al. Intensity-modulated proton therapy for nasopharyngeal carcinoma: decreased radiation dose to normal structures and encouraging clinical outcomes. Head Neck. 2016 Apr;38 Suppl 1:E1886-1895. • McDonald MW, Liu Y, Moore MG, Johnstone PA. Acute toxicity in comprehensive head and neck radiation for nasopharynx and paranasal sinus cancers: cohort comparison of 3D conformal proton therapy and intensity modulated radiation therapy. Radiat Oncol. 2016;11:32. • Russo AL, Adams JA, Weyman EA, et al. Long-term outcomes after proton beam therapy for sinonasal squamous cell carcinoma. Int J Radiat Oncol Biol Phys. 2016;95(1):368-376.
2	There are small case series on PBT for oropharyngeal cancer. Evidence is not robust enough
3	Advances in radiation therapy, such as with IMRT (PMID 12007936 and 15936155) and systemic therapy (such as with induction chemotherapy) (PMID 27686945), have resulted in favorable outcomes for locoregionally-advanced, non-metastatic nasopharynx cancer, with high rates of locoregional and systemic control, and long-term survival. However, these modern IMRT series report > grade 3 acute toxicities of 24-41% (PMID 12007936 and 15590175) and > grade 3 late toxicities of 12-15% (PMID 12007936, 15936155 and 15590175). Therefore, the use of proton therapy to improve normal organ sparing and improve acute and late morbidity, while maintaining favorable disease outcomes, is of significant interest and potential application. Initial studies for nasopharyngeal proton radiation focused on planning comparisons and model-based predictions of toxicity. Widesott et al. compared IMPT to helical tomotherapy in 6 patients, and found equivalent target coverage and dose homogeneity, but with significant sparing of normal structures such as parotid glands, esophagus, and larynx, with decreased normal tissue complication probability for the parotid glands with IMPT (PMID 18793962). Taheri-Kadkhoda et al. compared IMPT to IMRT in 8 patients, reporting equivalent mean dose delivered to targets between both techniques, but with improved tumor coverage and conformality with IMPT, as well as significant reductions in mean dose to several organs at risk with IMPT (PMID 18218078). Although there is no randomized data of proton therapy versus IMRT for nasopharynx cancer, there are existing clinical data comparing the 2 modalities. McDonald et al. evaluated acute toxicity in a cohort of 40 patients with either cancers of the nasopharynx or paranasal sinus, comparing 3D conformal proton radiation to IMRT (PMID 26922239). Compared to patients who received IMRT, those who received proton therapy were found to have improved normal tissue sparing to critical structures, as well as corresponding lower rates of requiring opioid pain medication at the end of RT, and lower rates of gastrostomy tube dependence at the end of RT and at 3 months post-treatment. Holliday et al. reported a case-match control study of 20 patients treated with intensity-modulated proton therapy (IMPT) matched to 10 patients treated with IMRT (Holliday EB, Garden AS, Rosenthal DI, Fuller CD, Morrison WH, Gunn GB, et al. Proton Therapy Reduces Treatment-Related Toxicities for Patients with Nasopharyngeal Cancer: A Case-Match Control Study of Intensity-Modulated Proton Therapy and Intensity-Modulated Photon

#	Rationale
	Therapy. International Journal of Particle Therapy. 2015;2(1):19-28.). Those receiving IMPT had significantly lower doses of gastrostomy tube insertion (20% versus 65%), with a reduction in mean oral cavity dose to less than 26 Gy from proton therapy associated with decreased G-tube placement. In summary, given the morbidity commonly seen with treatment of nasopharynx cancer with the most advanced, non-proton radiation techniques, proton therapy can be used to improve normal tissue sparing and therefore decrease toxicity. Prospective efforts, such as a randomized trial to compared IMPT to IMRT, or prospective collection and reporting of patient-reported outcomes, should be considered in the future.

NR = not reported

Rating Questions:	#	YES / NO	Low Confidence		Intermediate Confidence		High Confidence
			1	2	3	4	5
Does the evidence show that PBT provides a clinically meaningful improvement in net health outcome that is **superior** to other advanced conformal, fractionated photon-based radiotherapy techniques[1] for **most patients** with this indication?	1	No			X		
	2	No	Rating not provided				
	3	Yes				X	
Does PBT provide a clinically meaningful improvement in net health outcome that is **superior ONLY** when radiation dose constraints for critical organs at risk (i.e., surrounding normal tissue) cannot be met by other conformal, fractionated photon-based radiotherapy techniques[1] for patients with this indication?	1	Yes				X	
	2	No	Rating not provided				
	3	No				X	
Is use of PBT for this indication consistent with generally accepted medical practice?	1	Yes				X	
	2	No	Rating not provided				
	3	Yes				X	

NR = not reported

h) Supraglottic laryngeal cancer

#	Rationale
1	No new evidence at this time.
2	There are small case series on PBT for oropharyngeal cancer. Evidence is not robust enough
3	Considering the PICO formulation as a reference guide: there is no existing published literature directly comparing charged particle therapy to: -Advanced conformal, fractionated photon-based radiotherapy techniques including intensity modulated radiotherapy (IMRT), volume-modulated arc therapy (VMAT), stereotactic radiosurgery (SRS), or stereotactic body radiation therapy (SBRT), or - Other types of therapy for localized tumor

NR = not reported

Rating Questions:	#	YES / NO	Low Confidence		Intermediate Confidence		High Confidence
			1	2	3	4	5
	1	No	X				

Rating Questions:	#	YES / NO	Low Confidence		Intermediate Confidence		High Confidence
			1	2	3	4	5
Does the evidence show that PBT provides a clinically meaningful improvement in net health outcome that is **superior** to other advanced conformal, fractionated photon-based radiotherapy techniques[1] for **most patients** with this indication?	2	No	Rating not provided				
	3	No					X
Does PBT provide a clinically meaningful improvement in net health outcome that is **superior ONLY** when radiation dose constraints for critical organs at risk (i.e., surrounding normal tissue) cannot be met by other conformal, fractionated photon-based radiotherapy techniques[1] for patients with this indication?	1	Yes			X		
	2	No	Rating not provided				
	3	Yes			X		
Is use of PBT for this indication consistent with generally accepted medical practice?	1	No	X				
	2	No	Rating not provided				
	3	No			X		

NR = not reported

i) Sinonasal tumors (e.g., ethmoid or maxillary sinus tumor)

#	Rationale
1	• Russo AL, Adams JA, Weyman EA, et al. Long-term outcomes after proton beam therapy for sinonasal squamous cell carcinoma. Int J Radiat Oncol Biol Phys. 2016;95(1):368-376. • Dagan R, Bryant C, Li Z, et al. Outcomes of sinonasal cancer treated with proton therapy. Int J Radiat Oncol Biol Phys. 2016;95(1):377-385. • Fuji H, Yoshikawa S, Kasami M, et al. High-dose proton beam therapy for sinonasal mucosal malignant melanoma. Radiat Oncol. 2014 July 23;9:162.
2	There are small case series on PBT for oropharyngeal cancer. Evidence is not robust enough
3	Post-operative proton beam therapy is used in situations where compared with IMRT, there are dosimetric benefits (improved target volume coverage/reduction in doses to organs at risk) that translate into improved local tumour control (e.g., treatment of paranasal sinus cancers). In a systematic review and meta-analysis of 41 observational studies, subgroup analysis showed the use of proton beam therapy compared with IMRT for paranasal sinus and nasal cavity cancers, improved disease-free survival at 5 years (relative risk, 1.44, 95% CI 1.01-2.05; p=0·045) and loco-regional control at longest follow-up (relative risk, 1.26, 1.05-1.51; p=0.011) (PMID 24980873). More recent retrospective studies of proton beam therapy for sinonasal cancers report encouraging loco-regional control rates (Dagan R, Bryant C, Li Z, Yeung D, Justice J, Dzieglewiski P, et al. Outcomes of Sinonasal Cancer Treated With Proton Therapy. International journal of radiation oncology, biology, physics. 2016;95(1):377-85 and PMID 27084654). In the study from Dagan et al, 84 patients received primary (13%) or post-operative (87%) proton beam therapy with an overall 3-year local control rare of 83%; and in the 64/73 cases where gross total surgical resection was achieved, the 3-year local control rate was 90%. In summary, the use of proton therapy for adjuvant radiation, such as for sinonasal tumors, can improve patient outcomes with respect to toxicity and quality of life. Therefore, its use in the postoperative setting can and should be considered.

NR = not reported

Rating Questions:	#	YES / NO	Low Confidence		Intermediate Confidence		High Confidence
			1	2	3	4	5
Does the evidence show that PBT provides a clinically meaningful improvement in net health outcome that is **superior** to other advanced conformal, fractionated photon-based radiotherapy techniques[1] for most patients with this indication?	1	No			X		
	2	No	Rating not provided				
	3	Yes					
Does PBT provide a clinically meaningful improvement in net health outcome that is **superior ONLY** when radiation dose constraints for critical organs at risk (i.e., surrounding normal tissue) cannot be met by other conformal, fractionated photon-based radiotherapy techniques[1] for patients with this indication?	1	Yes			X		
	2	No	Rating not provided				
	3	No				X	
Is use of PBT for this indication consistent with generally accepted medical practice?	1	No			X		
	2	No	Rating not provided				
	3	Yes					

NR = not reported

j) Very advanced head and neck cancer

#	Rationale
1	• M.R.C.P. Yaacov Richard Lawrence, X. Allen Li, Ph.D. Radiation Dose–Volume Effects in the Brain. Int J Radiat Oncol Biol Phys. 2010; 76:3: S20-S27. See also, answers "G," "I," and "M."
2	There are small case series on PBT for oropharyngeal cancer. Evidence is not robust enough
3	This section will focus on reirradiation of head and neck cancer, which constitutes the most advanced and technically complex treatment for head and neck cancer with radiotherapy. Usually, options for definitive therapy are limited. Surgery can only be done for focal recurrences and are often subjected to high complication/morbidity rates and usually require further adjuvant therapy. Chemotherapy or systemic therapy alone can provide some palliation and disease control, but ultimately it is not curative. Re-irradiation is often necessary adjuvantly after surgery, as additional disease recurrences can dramatically affect quality of life and can ultimately be the cause of death with progression affecting swallowing, breathing, causing pain, bleeding and infections. Data from large cooperative groups and single institutions have demonstrated efficacy for re-irradiation in this setting. While re-irradiation can be the only curative option, the morbidity of re-irradiation in proximity to previously irradiated critical organs at risk (OAR) can be prohibitive to delivering a proper tumoricidal dose especially with photons. Thus, particle therapy may provide the proper solution. A recently published series reported clinical results of proton reirradiation in 17 patients with recurrent nasopharynx cancer (PMID 31155998). A median dose of 60 Gy RBE was delivered, with no reported > grade 3 acute toxicity, and a 23.5% rate of > late toxicity, and 1 patient with a fatal carotid blowout. At 18 months, overall survival and local control were 54.4% and 66.6%, respectively. Other recent publications from MD Anderson Cancer Center (MDACC), Indiana University Health (IUH), Memorial Sloan Kettering Cancer Center (MSKCC), and Northwestern Medicine Chicago Proton Center (NMCPC) have demonstrated preliminary data with median follow-ups of 1-2 years (PMID 27325480, 27788954, and 27084656). Locoregional control was 70-80% with overall survival rates of 65-80% at 12 months (PMID 27325480 and 27084656), but approximately 35% at 2 years (39). Grade 3+ acute and late toxicities ranged from 12-30% including approximately 2-5% treatment related mortality seen mainly from carotid hemorrhage. Long term feeding tube dependence was approximately 20-25%.These results compare favorably to historical controls from

#	Rationale
	the RTOG and University of Chicago where overall survivals were below 30%, grade 5 toxicities were 10% or higher and feeding tube dependence was over 50% with photons There are several prospective studies that are currently open and actively accruing for proton reirradiation. A Memorial Sloan Kettering Cancer Center phase II study (NCT 03217188) is comparing conventionally fractionated full dose proton re-irradiation (70 Gy in 2 Gy fractions) versus hypofractionated palliative re-irradiation (3.7 Gy bid x 2 days, followed by a 4 week break, repeated up to 4 cycles), with a primary outcome of 1 year locoregional control. A MD Anderson Cancer Center phase II study (NCT 03164460) is comparing stereotactic photon radiotherapy (SBRT) versus conventionally fractionated proton therapy, with a primary outcome measure of comparing 2-year rates of grade 3 or higher toxicity between the 2 arms. Reirradiation of recurrent head and neck cancer is necessary in many patients. Utilization of multiple treatment strategies is possible. Particle therapy may provide the least invasive and best approach in locoregional definitive therapy in this setting combined with surgical salvage and neoadjuvant or concurrent systemic therapy.

NR = not reported

Rating Questions:	#	YES / NO	Low Confidence		Intermediate Confidence		High Confidence
			1	2	3	4	5
Does the evidence show that PBT provides a clinically meaningful improvement in net health outcome that is **superior** to other advanced conformal, fractionated photon-based radiotherapy techniques[1] for **most patients** with this indication?	1	NR	Rating not provided				
	2	No	Rating not provided				
	3	Yes			X		
Does PBT provide a clinically meaningful improvement in net health outcome that is **superior ONLY** when radiation dose constraints for critical organs at risk (i.e., surrounding normal tissue) cannot be met by other conformal, fractionated photon-based radiotherapy techniques[1] for patients with this indication?	1	NR	Rating not provided				
	2	No	Rating not provided				
	3	No			X		
Is use of PBT for this indication consistent with generally accepted medical practice?	1	NR	Rating not provided				
	2	No	Rating not provided				
	3	Yes			X		

NR = not reported

k) Occult primary tumor of head and neck

#	Rationale
1	• Lewis GD, Holliday EB, Kocak-Uzel E, et al. Intensity-modulated proton therapy for nasopharyngeal carcinoma: decreased radiation dose to normal structures and encouraging clinical outcomes. Head Neck. 2016 Apr;38 Suppl 1:E1886-1895. • McDonald MW, Liu Y, Moore MG, Johnstone PA. Acute toxicity in comprehensive head and neck radiation for nasopharynx and paranasal sinus cancers: cohort comparison of 3D conformal proton therapy and intensity modulated radiation therapy. Radiat Oncol. 2016;11:32. • Russo AL, Adams JA, Weyman EA, et al. Long-term outcomes after proton beam therapy for sinonasal squamous cell carcinoma. Int J Radiat Oncol Biol Phys. 2016;95(1):368-376.
2	Evidence insufficient
3	Considering the PICO formulation as a reference guide: there is no existing published literature directly comparing charged particle therapy to:

#	Rationale
	-Advanced conformal, fractionated photon-based radiotherapy techniques including intensity modulated radiotherapy (IMRT), volume-modulated arc therapy (VMAT), stereotactic radiosurgery (SRS), or stereotactic body radiation therapy (SBRT), or - Other types of therapy for localized tumor

NR = not reported

Rating Questions:	#	YES / NO	Low Confidence		Intermediate Confidence		High Confidence
			1	2	3	4	5
Does the evidence show that PBT provides a clinically meaningful improvement in net health outcome that is **superior** to other advanced conformal, fractionated photon-based radiotherapy techniques[1] for **most patients** with this indication?	1	Yes				X	
	2	No	Rating not provided				
	3	No					X
Does PBT provide a clinically meaningful improvement in net health outcome that is **superior ONLY** when radiation dose constraints for critical organs at risk (i.e., surrounding normal tissue) cannot be met by other conformal, fractionated photon-based radiotherapy techniques[1] for patients with this indication?	1	No				X	
	2	No	Rating not provided				
	3	Yes			X		
Is use of PBT for this indication consistent with generally accepted medical practice?	1	Yes	Rating not provided				
	2	No	Rating not provided				
	3	No			X		

NR = not reported

l) Salivary gland tumor

#	Rationale
1	• Grant SR, Grosshans DR, Bilton SD, et al. Proton versus conventional radiotherapy for pediatric salivary gland tumors: acute toxicity and dosimetric characteristics. Radiother Oncol. 2015 August;116(2):309-315. • Van de Water TA, Lomax AJ, Bijl HP, et al. Using a reduced spot size for intensity-modulated proton therapy potentially improves salivary gland-sparing in oropharyngeal cancer. Int J Radiat Oncol Biol Phys. 2012;82:e313–319. • Bagley AF, Ye R, Hernandez M, Frank SJ. (P30) Prospective Outcomes of Xerostomia-Related quality of Life in Oropharyngeal Carcinoma Patients Treated With Proton Therapy. Int J Radiat Oncol Biol Phys. 2018;101(2):E32-E33. • Frank SJ, Blanchard P, Lee JJ, et al. Comparing Intensity-Modulated Proton Therapy With Intensity-Modulated Photon Therapy for Oropharyngeal Cancer: The Journey From Clinical Trial Concept to Activation. Semin Radiat Oncol. 2018. doi: 10.1016/j.semradonc.2017.12.002. • Gunn GB, Blanchard P, Garden AS, et al. Clinical outcomes and patterns of disease recurrence following intensity modulated proton therapy for oropharyngeal squamous carcinoma: results from single institution prospective registry studies. Int J Radiat Oncol Biol Phys. 2016 May 1;95(1):360-367 • Sio TT, Lin HK, Shi Q, et al. Intensity modulated proton therapy versus intensity modulated photon radiation therapy for oropharyngeal cancer: first comparative results of patient-reported outcomes. Int J Radiat Oncol Biol Phys. 2016 Jul 15;95(4):1107-1114.
2	There are small case series on PBT for oropharyngeal cancer. Evidence is not robust enough
3	Post-operative proton beam therapy is used in situations where compared with IMRT, there are dosimetric benefits (improved target volume coverage/reduction in doses to organs at risk) that translate into reduced treatment related toxicities, such as the postoperative treatment of salivary gland cancers.

#	Rationale
	Romesser et al compared IMRT and proton beam therapy for the ipsilateral treatment of salivary gland cancers (PMID 26867969). For 41 consecutive patients, 37/41 received post-operative ipsilateral radiation using IMRT (23/41) or proton beam therapy (18/41). There was similar target volume coverage between modalities, but IMRT compared with proton beam therapy plans had significantly higher median maximum doses to the brainstem (29.7 Gy vs. 0.6 Gy (RBE), p<0.001), spinal cord (36.3 Gy vs. 1.9 Gy (RBE), p<0.001) and mean oral cavity (20.6 Gy vs. 0.94 Gy (RBE), p<0.001). For proton beam therapy, this corresponded with lower rates of grade 2 or above acute dysgeusia (5.6 % vs. 65.2%, p<0.001), mucositis (16.7% vs. 52.2%, p=0.019), and nausea (11.1% vs. 56.5%, p=0.003). In summary, the use of proton therapy for adjuvant radiation, even in situations where bilateral neck radiation is not required such as for salivary gland cancers, can improve patient outcomes with respect to toxicity and quality of life. Therefore, its use in the postoperative setting can and should be considered.

NR = not reported

Rating Questions:	#	YES / NO	Low Confidence		Intermediate Confidence		High Confidence
			1	2	3	4	5
Does the evidence show that PBT provides a clinically meaningful improvement in net health outcome that is **superior** to other advanced conformal, fractionated photon-based radiotherapy techniques[1] for **most patients** with this indication?	1	Yes				X	
	2	No	Rating not provided				
	3	Yes			X		
Does PBT provide a clinically meaningful improvement in net health outcome that is **superior ONLY** when radiation dose constraints for critical organs at risk (i.e., surrounding normal tissue) cannot be met by other conformal, fractionated photon-based radiotherapy techniques[1] for patients with this indication?	1	No				X	
	2	No	Rating not provided				
	3	No			X		
Is use of PBT for this indication consistent with generally accepted medical practice?	1	Yes				X	
	2	No	Rating not provided				
	3	Yes			X		

NR = not reported

m) Mucosal melanoma

#	Rationale
1	• Fuji H, Yoshikawa S, Kasami M, et al. High-dose proton beam therapy for sinonasal mucosal malignant melanoma. Radiat Oncol. 2014 July 23;9:162. • Demizu Y, Fujii O, Terashima K, et al. Particle therapy for mucosal melanoma of the head and neck. A single-institution retrospective comparison of proton and carbon ion therapy. Strahlenther Onkol. 2014;190(2):186-191.
2	small case series
3	Considering the PICO formulation as a reference guide: there is no existing published literature directly comparing charged particle therapy to: -Advanced conformal, fractionated photon-based radiotherapy techniques including intensity modulated radiotherapy (IMRT), volume-modulated arc therapy (VMAT), stereotactic radiosurgery (SRS), or stereotactic body radiation therapy (SBRT), or - Other types of therapy for localized tumor

#	Rationale
	Published literature with charged particle therapy for mucosal melanoma are limited to small, single-arm (charged particle RT alone) studies, with no comparisons to other modalities within RT or outside of RT.

NR = not reported

Rating Questions:	#	YES / NO	Low Confidence		Intermediate Confidence		High Confidence
			1	2	3	4	5
Does the evidence show that PBT provides a clinically meaningful improvement in net health outcome that is **superior** to other advanced conformal, fractionated photon-based radiotherapy techniques[1] for **most patients** with this indication?	1	Yes			X		
	2	No					
	3	No					X
Does PBT provide a clinically meaningful improvement in net health outcome that is **superior ONLY** when radiation dose constraints for critical organs at risk (i.e., surrounding normal tissue) cannot be met by other conformal, fractionated photon-based radiotherapy techniques[1] for patients with this indication?	1	No			X		
	2	No					
	3	Yes		X			
Is use of PBT for this indication consistent with generally accepted medical practice?	1	Yes			X		
	2	No					
	3	No				X	

NR = not reported

n) Non-small-cell lung cancer (curative treatment)

#	Rationale
1	• Akita K, Iwata H, Ogino H, et al. A phase II trial of S-1 plus cisplatin with concurrent proton-beam therapy for locally advanced non-small cell lung cancer. J Clin Oncol. 2017;35(15):e20070 • Bush DA, Cheek G, Zaheer S, et al. Highâ€'dose hypofractionated proton beam radiation therapy is safe and effective for central and peripheral earlyâ€'stage nonâ€'small cell lung cancer: results of a 12â€'year experience at Loma Linda University Medical Center. Int J Radiat Oncol Biol Phys. 2013;86(5):964â€'968. • 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 May; 95(1):505-16. • Cooper BT, Mah D, Chen CC, et al. Hypofractionated Proton Therapy for Early Stage Non–small Cell Lung Cancer: Clinical Outcomes and Comparative Dosimetric Analysis. Int J Radiat Oncol Biol Phys. 2017; 99(2): E449. • Gomez DR, Li H, Chang JY. Proton therapy for early-stage non-small cell lung cancer (NSCLC). Transl Lung Cancer Res. 2018;7(2):199-204. • Jeter MD, Gomez D, Nguyen Q, et al. Simultaneous Integrated Boost for Radiation Dose Escalation to the Gross Tumor Volume with Intensity-Modulated (Photon) Radiation Therapy or Intensity-Modulated Proton Therapy and Concurrent Chemotherapy for Stage II-III Non-Small Cell Lung Cancer: A Phase I Study. Int J Radiat Oncol Biol Phys. 2017; https://doi.org/10.1016/j.ijrobp.2017.10.042. • Nakajima K, Iwata H, Ogino H, et al. Clinical Outcomes of Image-Guided Proton Therapy for Stage I Non-small Cell Lung Cancer. Int J Radiat Oncol Biol Phys. 2017;99(2S):E483. • Yang P, Xu T, Gomez DR, Deng W, et al. Patterns of local-regional failure after intensity-modulated radiation therapy or passive scattering proton therapy with concurrent chemotherapy for non-small cell lung cancer. Int J Radiat Oncol Biol Phys. 2018.

#	Rationale
2	Vyfhuis et al "Advances in Proton Therapy in Lung Cancer" (Ther Adv Respir Dis 2018;12:1-16) provides a comprehensive review of this subject. There are a number of papers reporting on institutional experiences with PBT for non small cell lung cancer. The evidence is not sufficiently robust to support PBT. PBT is being evaluated in comparison to photon therapy in a number of clinical trials
3	Radiation therapy is a vital component of the curative management for patient advanced lung cancer. Unfortunately, it has become quite clear morbidity and mortality following standard treatment can limit outcomes specifically related to injuries to the esophagus, lung and heart (Bradley 2015, Khalil 2015, Graham 1999).Several large single and multi-institutional studies have demonstrated critical dosimetric cut points for each of these normal tissues. If these critical dosimetric parameters which are described below can't be achieved, Proton Beam Radiation can reduce these parameters to a safer level. Esophageal dose: Bradley et. al. (Bradley 2015) from RTOG 0617 demonstrated the development of grade 3 esophagitis was one of the variables that predicted for a detriment in survival on multivariate analysis with a hazard ratio of 1.54 (p=0.01).Based on the work by Palma et. al (Palma 2013),the volume of esophagus that receives 60 Gy was critical in predicting grade 3 or higher events where the major cut points to achieve were 0.07and 17 %. This correspond to risks of grade 3 esophagitis of 4% (< 0.07%), 10% (0.07-17%) and 22% (>17%). Heart dose: The results of RTOG 0617 (Bradley 2015) demonstrate that a higher heart dose predicted for a lower rate in survival presumably related to an increase in non-cancer related deaths. Several authors have demonstrated the importance of mean heart as the most important predictor of major/symptomatic cardiac events that are likely the cause of this decrease in survival. Chun et. al. demonstrated that an important cut point was a mean dose to the heart > 20 Gy has a 40% rate of cardiac events which can be decrease to 10%.In addition, Darby (NEJM 2013) demonstrated major coronary events continue to occur as there was no apparent threshold and that for every 1 Gy increase in dose to the heart the relative risk of major coronary events increases 7.4%. Lung Dose: The initial experience at Washington University (Graham 1999) demonstrated all of the cases of fatal pneumonitis occurred when the V20 > 35%, so this patient has substantial risks. Palma (Palma 2013) describes an odd ratio of 1.09 in fatal pneumonitis per every 1% increase in V20. • Palma, David A., et al. "Predicting radiation pneumonitis after chemoradiation therapy for lung cancer: an international individual patient data meta-analysis." International Journal of Radiation Oncology* Biology* Physics 85.2 (2013): 444-450. • Palma, David A., et al. "Predicting esophagitis after chemoradiation therapy for non-small cell lung cancer: an individual patient data meta-analysis." International Journal of Radiation Oncology* Biology* Physics 87.4 (2013): 690-696. • Khalil, Azza A., et al. "New dose constraint reduces radiation-induced fatal pneumonitis in locally advanced non-small cell lung cancer patients treated with intensity-modulated radiotherapy." Acta oncological 54.9 (2015): 1343-1349. • Bradley, Jeffrey D., et al. "Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study." The lancet oncology 16.2 (2015): 187-199. • Graham, Mary V., et al. "Clinical dose–volume histogram analysis for pneumonitis after 3D treatment for non-small cell lung cancer (NSCLC)." International Journal of Radiation Oncology* Biology* Physics 45.2 (1999): 323-329. • Darby, Sarah C., et al. "Risk of ischemic heart disease in women after radiotherapy for breast cancer." New England Journal of Medicine 368.11 (2013): 987-998. • Speirs, Christina K., et al. "Heart dose is an independent dosimetric predictor of overall survival in locally advanced non–small cell lung cancer." Journal of Thoracic Oncology12.2 (2017): 293-301. • Wang, Kyle, et al. "Cardiac toxicity after radiotherapy for stage III non–small-cell lung cancer: pooled analysis of dose-escalation trials delivering 70 to 90 Gy." Journal of Clinical Oncology 35.13 (2017): 1387. • Dess, Robert T., et al. "Cardiac events after radiation therapy: combined analysis of prospective multicenter trials for locally advanced non–small-cell lung cancer." Journal of Clinical Oncology 35.13 (2017): 1395.

NR = not reported

Rating Questions:	#	YES / NO	Low Confidence		Intermediate Confidence		High Confidence
			1	2	3	4	5
Does the evidence show that PBT provides a clinically meaningful improvement in net health outcome that is **superior** to other advanced conformal, fractionated photon-based radiotherapy techniques[1] for **most patients** with this indication?	1	No			X		
	2	No	Rating not provided				
	3	No			X		
Does PBT provide a clinically meaningful improvement in net health outcome that is **superior ONLY** when radiation dose constraints for critical organs at risk (i.e., surrounding normal tissue) cannot be met by other conformal, fractionated photon-based radiotherapy techniques[1] for patients with this indication?	1	Yes			X		
	2	No	Rating not provided				
	3	Yes				X	
Is use of PBT for this indication consistent with generally accepted medical practice?	1	No			X		
	2	No	Rating not provided				
	3	Yes			X		

NR = not reported

o) Thymomas and thymic carcinoma

#	Rationale
1	• Vogel J, Lin L, Litzky LA, et al. Predicted rate of secondary malignancies following adjuvant proton versus photon radiation therapy for thymoma. Int J Radiat Oncol Biol Phys. 2017 Oct 1;99(2):427-433. • Kojima H, Isaka M, Nagata M, et al. Preoperative proton beam therapy for thymoma: a case report. Ann Thorac Cardiovasc Surg. 2016 June;22(3):186-188.
2	NR
3	Radiation therapy is a vital component of the curative management for patients with stage II and stage III thymomas and thymic carcinomas in the adjuvant setting. It is also used in the unresectable setting. Similar to lung cancer, radiation therapy can impact morbidity and mortality following standard treatment due to the proximity of the target that needs to be treated especially in the setting of lung and heart injuries. (Bradley 2015, Khalil 2015, Graham 1999)Esophageal injuries are less likely due to the fact that systemic therapy is not needed and the target does not include the lymph nodes stations. Several large single and multi-institutional studies have demonstrated critical dosimetric cut points for each of these normal tissues in lung cancer that we use in a similar fashion for thymic malignancies. If these critical dosimetric parameters which are described below can't be achieved, Proton Beam Radiation can reduce these parameters to a safer level. Esophageal dose: Bradley et. al. (Bradley 2015) from RTOG 0617 demonstrated the development of grade 3 esophagitis was one of the variables that predicted for a detriment in survival on multivariate analysis with a hazard ratio of 1.54 (p=0.01).Based on the work by Palma et. al (Palma 2013),the volume of esophagus that receives 60 Gy was critical in predicting grade 3 or higher events where the major cut points to achieve were 0.07and 17 %. This correspond to risks of grade 3 esophagitis of 4% (< 0.07%), 10% (0.07-17%) and 22% (>17%). Heart dose: The results of RTOG 0617 (Bradley 2015) demonstrate that a higher heart dose predicted for a lower rate in survival presumably related to an increase in non-cancer related deaths. Several authors have demonstrated the importance of mean heart as the most important predictor of major/symptomatic cardiac events that are likely the cause of this decrease in survival. Chun et. al. demonstrated that an important cut point was a mean dose to the heart > 20 Gy has a 40% rate of cardiac events which can be decrease to 10%.In addition, Darby (NEJM 2013) demonstrated major coronary events continue to occur as there was no apparent threshold and that for every 1 Gy increase in dose to the heart the relative risk of major coronary events increases 7.4%.

#	Rationale
	Lung Dose: The initial experience at Washington University (Graham 1999) demonstrated all of the cases of fatal pneumonitis occurred when the V20 > 35%, so this patient has substantial risks. Palma (Palma 2013) describes an odd ratio of 1.09 in fatal pneumonitis per every 1% increase in V20. • Palma, David A., et al. "Predicting radiation pneumonitis after chemoradiation therapy for lung cancer: an international individual patient data meta-analysis." International Journal of Radiation Oncology* Biology* Physics 85.2 (2013): 444-450. • Palma, David A., et al. "Predicting esophagitis after chemoradiation therapy for non-small cell lung cancer: an individual patient data meta-analysis." International Journal of Radiation Oncology* Biology* Physics 87.4 (2013): 690-696. • Khalil, Azza A., et al. "New dose constraint reduces radiation-induced fatal pneumonitis in locally advanced non-small cell lung cancer patients treated with intensity-modulated radiotherapy." Acta oncological 54.9 (2015): 1343-1349. • Bradley, Jeffrey D., et al. "Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study." The lancet oncology 16.2 (2015): 187-199. • Graham, Mary V., et al. "Clinical dose–volume histogram analysis for pneumonitis after 3D treatment for non-small cell lung cancer (NSCLC)." International Journal of Radiation Oncology* Biology* Physics 45.2 (1999): 323-329. • Darby, Sarah C., et al. "Risk of ischemic heart disease in women after radiotherapy for breast cancer." New England Journal of Medicine 368.11 (2013): 987-998. • Speirs, Christina K., et al. "Heart dose is an independent dosimetric predictor of overall survival in locally advanced non–small cell lung cancer." Journal of Thoracic Oncology12.2 (2017): 293-301. • Wang, Kyle, et al. "Cardiac toxicity after radiotherapy for stage III non–small-cell lung cancer: pooled analysis of dose-escalation trials delivering 70 to 90 Gy." Journal of Clinical Oncology 35.13 (2017): 1387. • Dess, Robert T., et al. "Cardiac events after radiation therapy: combined analysis of prospective multicenter trials for locally advanced non–small-cell lung cancer." Journal of Clinical Oncology 35.13 (2017): 1395.

NR = not reported

Rating Questions:	#	YES / NO	Low Confidence		Intermediate Confidence		High Confidence
			1	2	3	4	5
Does the evidence show that PBT provides a clinically meaningful improvement in net health outcome that is **superior** to other advanced conformal, fractionated photon-based radiotherapy techniques[1] for most **patients** with this indication?	1	No			X		
	2	No	Rating not provided				
	3	Yes			X		
Does PBT provide a clinically meaningful improvement in net health outcome that is **superior ONLY** when radiation dose constraints for critical organs at risk (i.e., surrounding normal tissue) cannot be met by other conformal, fractionated photon-based radiotherapy techniques[1] for patients with this indication?	1	Yes				X	
	2	No	Rating not provided				
	3	Yes				X	
Is use of PBT for this indication consistent with generally accepted medical practice?	1	No			X		
	2	No	Rating not provided				
	3	Yes				X	

NR = not reported

p) Esophageal cancer

#	Rationale
1	• Fang P, Shiraishi Y, Jiang W, et al. Lymphocyte-sparing effect of proton therapy in patients with esophageal cancer. Int J Radiat Oncol Biol Phys. 2017;98(2):e6. • Haque W, Verma V, Butler EB, The BS. Utilization of neoadjuvant intensity-modulated radiation therapy and proton beam therapy for esophageal cancer in the United States. J Gastrointest Oncol. 2018. http://jgo.amegroups.com/article/view/18383. • Hirano Y, Onozawa M, Hojo H, et al. Dosimetric comparison between proton beam therapy and photon radiation therapy for locally advanced esophageal squamous cell carcinoma. Radiat Oncol. 2018;13(23). • Lester SC, Lin SH, Chuong M, et al. A Multi-institutional Analysis of Trimodality Therapy for Esophageal Cancer in Elderly Patients. Int J Radiat Oncol Biol Phys. 2017;98(4):820-828. • Lin SH, Merrell KW, Shen J, et al. Multi-institutional analysis of radiation modality use and postoperative outcomes of neoadjuvant chemoradiation for esophageal cancer. Radiother Oncol. 2017;123(3):376-381. • Warren S, Hurt CH, Crosby T, et al. The potential of proton therapy to reduce acute haematological toxicity in concurrent chemoradiotherapy for esophageal cancer. Int J Radiation Oncol Biol Phys. 2017;99(3):729-737.
2	NR
3	The rationale for using proton therapy in esophageal cancer stems from toxicity concerns when treating large target volumes in the central chest, often posterior to the heart where lung and heart dose must be balanced during photon planning. Randomized data do not yet exist, although they are being developed, notably at MDACC and through the NRG. Interestingly, there is a hint at improved survival when using proton therapy in at least the inoperable setting. At minimum, there appear to be HRQOL differences between photon and proton therapy Garant A, Whitaker TJ, Spears GM, Routman DM, Harmsen WS, Wilhite TJ, Ashman JB, Sio TT, Rule WG, Neben Wittich MA, Martenson JA, Tryggestad EJ, Yoon HH, Blackmon S, Merrell KW, Haddock MG, Hallemeier CL. A Comparison of Patient-Reported Health-Related Quality of Life During Proton Versus Photon Chemoradiotherapy for Esophageal Cancer. Pract Radiat Oncol. 2019 Jul 13. pii: S1879-8500(19)30197-3. doi: 10.1016/j.prro.2019.07.003. [Epub ahead of print] PubMed PMID: 31310815. At the Mayo Clinic, 125 patients completed a baseline and post-treatment FACT-E surveys, 63 received XRT and 62 received PRT. They found that on univariate and multivariate analyses, less mean decline in FACT-E score was observed for PRT vs XRT (-12.7 vs -20.6, p=0.026). Inoperable setting: A retrospective review of 343 pts with locally advanced esophageal cancer at MDACC, treated with either IMRT (n=211) or PBT (n=132) from 2007-2014 showed that PBT was associated with better OS, PFS, LRFFS, and distant meets (Xi et al. IJROBP. 99: 667. Comparative Outcomes After Definitive Chemoradiotherapy Using Proton Beam Therapy Versus Intensity Modulated Radiation Therapy for Esophageal Cancer: A Retrospective, Single-Institutional Analysis). Their group has hypothesized that this is due to less lymphopenia caused by proton therapy. Preoperative setting: Pulmonary complications are the most common serious morbidity after esophagectomy and are the leading cause of postoperative mortality in patients treated with surgery for esophageal cancer. The incidence of postoperative pulmonary complications is 30% and pulmonary complications are responsible for 55% of in-hospital deaths. It has been previously shown that radiation dose to lung is the most important clinical factor associated with postoperative pulmonary complications (Lee, H.K., et al., Postoperative pulmonary complications after preoperative chemoradiation for esophageal carcinoma: correlation with pulmonary dose-volume histogram parameters. Int J Radiat Oncol Biol Phys, 2003. 57(5): p. 1317-22).Pulmonary complications were noted more often (35% vs. 8%, p = 0.014) when the pulmonary V10 was > or =40% vs. <40% and when the V15 was > or /=30% vs. < 30% (33% vs. 10%, p = 0.036).Similarly, Wang et al. found that the volume of the lung spared from doses of 5 Gy or higher was the only independent predictive factor associated with postoperative pulmonary complications for patients with esophageal cancer treated with concurrent chemoradiotherapy followed by surgery (Wang, S.L., et al., Investigation of clinical and dosimetric factors associated with postoperative pulmonary complications in esophageal cancer patients treated with concurrent chemoradiotherapy followed by surgery. Int J Radiat Oncol Biol Phys, 2006. 64(3): p. 692-9.). These findings underscore the clinical importance of reducing the volume of lung that receives doses as low as 5 Gy.

#	Rationale
	Zhang et al compared IMRT and proton plans for 15 patients with distal esophageal cancer (Zhang, X., et al., Intensity-modulated proton therapy reduces the dose to normal tissue compared with intensity-modulated radiation therapy or passive scattering proton therapy and enables individualized radical radiotherapy for extensive stage IIIB non-small-cell lung cancer: a virtual clinical study. Int J Radiat Oncol Biol Phys, 2010. 77(2): p. 357-66.). For similar tumor coverage, a two-beam proton plan reduced median lung volumes exposed to 5, 10, and 20 Gy by 35.6%, 20.5%, and 5.8%. Thus, proton therapy provided significantly better sparing of lung than did IMRT. The authors calculated that the two-beam proton plan could reduce the probability of pulmonary complications from 18.5% with IMRT to 5% with proton beam therapy. In another study, Makishima et al compared standard x-ray based radiation with proton radiation therapy in 44 patients and showed that the V5 and V20 for lung was reduced significantly in the proton group and that all grade ≥ 2pulmonary toxicities were seen in the x-ray treated patients (Makishima, H., et al. Comparison of adverse effects of proton and X-ray chemoradiotherapy for esophageal cancer using an adaptive dose-volume histogram analysis. Journal of Radiation Research, 2015. 56(3): p. 568-576). In this study heart dose was also lower with protons, with grade ≥ 2 cardiac events occurring in 52.6 % of x-ray treated patients and 4 % proton treated patients.

NR = not reported

Rating Questions:	#	YES / NO	Low Confidence		Intermediate Confidence		High Confidence
			1	2	3	4	5
Does the evidence show that PBT provides a clinically meaningful improvement in net health outcome that is **superior** to other advanced conformal, fractionated photon-based radiotherapy techniques[1] for **most patients** with this indication?	1	Yes				X	
	2	No	Rating not provided				
	3	Yes				X	
Does PBT provide a clinically meaningful improvement in net health outcome that is **superior ONLY** when radiation dose constraints for critical organs at risk (i.e., surrounding normal tissue) cannot be met by other conformal, fractionated photon-based radiotherapy techniques[1] for patients with this indication?	1	No				X	
	2	No	Rating not provided				
	3	No				X	
Is use of PBT for this indication consistent with generally accepted medical practice?	1	Yes				X	
	2	No	Rating not provided				
	3	Yes				X	

NR = not reported

q) Hepatocellular cancer

#	Rationale
1	• Apisarnthanarax S, Yeung R, Bowen S, Chapman TR. Proton Beam Therapy for Hepatic Malignancies. Gastrointestinal Malignancies. 2017: 171-195. • Bush DA, Smith JC, Slater JD, et al. Randomized clinical trial comparing proton bream radiation therapy with transarterial chemoembolization for hepatocellular carcinoma: results of an interim analysis. Int J Radiat Oncol Biol Phys. 2016 May;95(1):477-82. • Chuong MD, et al. Proton beam therapy for liver cancer is well tolerated: outcomes from the Proton Collaborative Group REG001-09 trial. J Clin Oncol. 2017. • Dyer MA, McDonnell EI, Yeap BY, et al. Change in Platelet Count and Normal Liver Dosimetry in Patients Receiving Proton Radiation Therapy for Unresectable Hepatocellular Carcinoma or Intrahepatic Cholangiocarcinoma. Int J Radiat Oncol Biol Phys. 2016 Oct 1;96(2S):E174-E175.

#	Rationale
	• Hong TS, Wo JY, Yeap BY, et al. Multi-institutional phase II study of high-dose hypofractionated proton beam therapy in patients with localized, unresectable hepatocellular carcinoma and intrahepatic cholangiocarcinoma. J Clin Oncol. 2016;34(5): 460-468. • Lee CH, Hung SP, Hong JH, et al. How small is too small? New liver constraint is needed – proton therapy of hepatocellular carcinoma patients with small normal liver. PLoS One. 2018;13(9).
2	NR
3	Primary liver cancer has become one of the predominant GI indications for proton beam therapy (PBT), as evidenced by the recommendations in the ASTRO Model Policy on Proton Beam Therapy. Primary hepatocellular cancer treated with hypofractionation is considered a Group 1 recommendation, meaning PBT is medically necessary based on published clinical data. Proton beam therapy has been used in hundreds of patients in Asia and the United States and has been demonstrated to be an effective and safe method for the treatment of patients with inoperable hepatocellular cancer (1.Bush DA, Kayali Z, Grove R, et al. The safety and efficacy of high-dose proton beam radiotherapy for hepatocellular carcinoma: a phase 2 prospective trial. Cancer. 2011; 2.Nakayama H, Sugahara S, Tokita, M, et al. Proton beam therapy for hepatocellular carcinoma.Cancer.2009). The use of PBT in liver tumors has been thoroughly reviewed (Dionisi F. and Ben-Josef E. The use of proton therapy in the treatment of gastrointestinal cancers: liver. Cancer J 20(6):371-377, 2014). The decision to use PBT versus photon radiation can be aided by a clinical decision tool that modeled various tumor sizes and locations within the liver (Gandhi S.J., Liang X., Ding X., Zhu T.C., Ben-Josef E., Plastaras J.P., Metz J.M., Both S. and Apisarnthanarax S. Clinical decision tool for optimal delivery of liver stereotactic body radiation therapy: Photons versus protons. Pract Radiat Oncol 5(4):209-218, 2015.). PBT most notably outperformed photons in dome and central tumors that were >3 cm. In general, PBT was able to deliver lower MLD in tumors >5 cm, suggesting a role for PBT where the MLD threshold may limit the prescription dose. A randomized study at Loma Linda randomized HCC patients between PBT and TACE as a bridge to OLT (Bush D.A., Smith J.C., Slater J.D., Volk M.L., Reeves M.E., Cheng J., Grove R. and de Vera M.E. Randomized Clinical Trial Comparing Proton Beam Radiation Therapy with Transarterial Chemoembolization for Hepatocellular Carcinoma: Results of an Interim Analysis. Int J Radiat Oncol Biol Phys 95(1):477-482, 2016). At the interim analysis, they found that PBT trended toward increased pathologic complete responses and fewer hospital days. There are good, single arm prospective data for using proton therapy in primary liver tumors. A multi-institutional trial enrolled 83 patients (44 HCC, 37 IHCC, 2 mixed) with unresectable disease and Child-Pugh A or B liver function (Hong T.S., Wo J.Y., Yeap B.Y., Ben-Josef E., McDonnell E.I., Blaszkowsky L.S., Kwak E.L., Allen J.N., Clark J.W., Goyal L., Murphy J.E., Javle M.M., Wolfgang J.A., Drapek L.C., Arellano R.S., Mamon H.J., Mullen J.T., Yoon S.S., Tanabe K.K., Ferrone C.R., Ryan D.P., DeLaney T.F., Crane C.H. and Zhu A.X. Multi-Institutional Phase II Study of High-Dose Hypofractionated Proton Beam Therapy in Patients With Localized, Unresectable Hepatocellular Carcinoma and Intrahepatic Cholangiocarcinoma. J Clin Oncol 34(5):460-468, 2016.). They used an isotoxic dose prescription with fractionated proton therapy dose intensification trial where the prescribed dose was varied based on NTCP models. The goal was to deliver 67.5 Gy in 15 fractions for peripheral tumors (>2 cm from porta hepatis) or 58.05 Gy in 15 fractions for central tumors (within 2 cm of porta hepatis). Dose de-escalation occurred based on NTCP models, and the median delivered dose was 58 Gy. Although the median tumor size was fairly large (5 cm for HCC and 6 cm for IHCC), 2-year local control was 94.8% for HCC and 94.1% for IHCC. The mean liver-GTV dose ranged from 3.2 to 29.5 GyE (mean 19.2 GyE), and one patient developed liver failure and ascites. Primary liver tumors (both HCC and IHCC) appear to require high biologically effective doses to obtain local control. When trying to treat large or ill-located tumors in diseased livers, often proton therapy is the only possible local therapy option.

NR = not reported

Rating Questions:	#	YES / NO	Low Confidence		Intermediate Confidence		High Confidence
			1	2	3	4	5
Does the evidence show that PBT provides a clinically meaningful improvement in net health outcome that is **superior** to other advanced conformal, fractionated	1	Yes				X	
	2	No	Rating not provided				
	3	No	X				

Rating Questions:	#	YES / NO	Low Confidence		Intermediate Confidence		High Confidence
			1	2	3	4	5
photon-based radiotherapy techniques[1] for **most patients** with this indication?							
Does PBT provide a clinically meaningful improvement in net health outcome that is **superior ONLY** when radiation dose constraints for critical organs at risk (i.e., surrounding normal tissue) cannot be met by other conformal, fractionated photon-based radiotherapy techniques[1] for patients with this indication?	1	No				X	
	2	No	Rating not provided				
	3	Yes					X
Is use of PBT for this indication consistent with generally accepted medical practice?	1	Yes				X	
	2	No	Rating not provided				
	3	Yes					X

NR = not reported

r) Intrahepatic cholangiocarcinoma

#	Rationale
1	• Dyer MA, McDonnell EI, Yeap BY, et al. Change in Platelet Count and Normal Liver Dosimetry in Patients Receiving Proton Radiation Therapy for Unresectable Hepatocellular Carcinoma or Intrahepatic Cholangiocarcinoma. Int J Radiat Oncol Biol Phys. 2016 Oct 1;96(2S):E174-E175. • Hong TS, Grassberger C, Yeap BY, et al. Hepatocyte Growth Factor is Associated With Liver Dysfunction and Survival: Biomarker Results of a Phase 2 Study of Proton Beam Therapy in Patients with Hepatocellular Carcinoma and Intrahepatic Cholangiocarcinoma. Int J Radiat Oncol Biol Phys. 2017 Oct 1;99(2):S89. • Hong TS, Wo JY, Yeap BY, et al. Multi-institutional phase II study of high-dose hypofractionated proton beam therapy in patients with localized, unresectable hepatocellular carcinoma and intrahepatic cholangiocarcinoma. J Clin Oncol. 2016;34(5): 460-468. • Ohkawa A, Mizumoto M, Ishikawa H, et al. Proton beam therapy for unresectable intrahepatic cholangiocarcinoma. J Gastroenterol Hepatol. 2015 May;30(5):957-63.
2	NR
3	The rationale for using proton therapy in esophageal cancer stems from toxicity concerns when treating large target volumes in the central chest, often posterior to the heart where lung and heart dose must be balanced during photon planning. Randomized data do not yet exist, although they are being developed, notably at MDACC and through the NRG. Interestingly, there is a hint at improved survival when using proton therapy in at least the inoperable setting. At minimum, there appear to be HRQOL differences between photon and proton therapy Garant A, Whitaker TJ, Spears GM, Routman DM, Harmsen WS, Wilhite TJ, Ashman JB, Sio TT, Rule WG, Neben Wittich MA, Martenson JA, Tryggestad EJ, Yoon HH, Blackmon S, Merrell KW, Haddock MG, Hallemeier CL. A Comparison of Patient-Reported Health-Related Quality of Life During Proton Versus Photon Chemoradiotherapy for Esophageal Cancer. Pract Radiat Oncol. 2019 Jul 13. pii: S1879-8500(19)30197-3. doi: 10.1016/j.prro.2019.07.003. [Epub ahead of print] PubMed PMID: 31310815. At the Mayo Clinic, 125 patients completed a baseline and post-treatment FACT-E surveys, 63 received XRT and 62 received PRT. They found that on univariate and multivariate analyses, less mean decline in FACT-E score was observed for PRT vs XRT (-12.7 vs -20.6, p=0.026). Inoperable setting: A retrospective review of 343 pts with locally advanced esophageal cancer at MDACC, treated with either IMRT (n=211) or PBT (n=132) from 2007-2014showed that PBT was associated with better OS, PFS, LRFFS, and distant meets (Xi et al. IJROBP. 99: 667. Comparative Outcomes After Definitive Chemoradiotherapy Using Proton Beam Therapy Versus Intensity Modulated Radiation Therapy for Esophageal Cancer: A Retrospective, Single-Institutional Analysis). Their group has hypothesized that this is due to less lymphopenia caused by proton therapy.

#	Rationale
	Preoperative setting: Pulmonary complications are the most common serious morbidity after esophagectomy and are the leading cause of postoperative mortality in patients treated with surgery for esophageal cancer. The incidence of postoperative pulmonary complications is 30% and pulmonary complications are responsible for 55% of in-hospital deaths. It has been previously shown that radiation dose to lung is the most important clinical factor associated with postoperative pulmonary complications (Lee, H.K., et al., Postoperative pulmonary complications after preoperative chemoradiation for esophageal carcinoma: correlation with pulmonary dose-volume histogram parameters. Int J Radiat Oncol Biol Phys, 2003. 57(5): p. 1317-22).Pulmonary complications were noted more often (35% vs. 8%, p = 0.014) when the pulmonary V10 was > or =40% vs. <40% and when the V15 was > or /=30% vs. < 30% (33% vs. 10%, p = 0.036).Similarly, Wang et al. found that the volume of the lung spared from doses of 5 Gy or higher was the only independent predictive factor associated with postoperative pulmonary complications for patients with esophageal cancer treated with concurrent chemoradiotherapy followed by surgery (Wang, S.L., et al., Investigation of clinical and dosimetric factors associated with postoperative pulmonary complications in esophageal cancer patients treated with concurrent chemoradiotherapy followed by surgery. Int J Radiat Oncol Biol Phys, 2006. 64(3): p. 692-9.). These findings underscore the clinical importance of reducing the volume of lung that receives doses as low as 5 Gy. Zhang et al compared IMRT and proton plans for 15 patients with distal esophageal cancer (Zhang, X., et al., Intensity-modulated proton therapy reduces the dose to normal tissue compared with intensity-modulated radiation therapy or passive scattering proton therapy and enables individualized radical radiotherapy for extensive stage IIIB non-small-cell lung cancer: a virtual clinical study. Int J Radiat Oncol Biol Phys, 2010. 77(2): p. 357-66.). For similar tumor coverage, a two-beam proton plan reduced median lung volumes exposed to 5, 10, and 20 Gy by 35.6%, 20.5%, and 5.8%. Thus, proton therapy provided significantly better sparing of lung than did IMRT. The authors calculated that the two-beam proton plan could reduce the probability of pulmonary complications from 18.5% with IMRT to 5% with proton beam therapy. In another study, Makishima et al compared standard x-ray based radiation with proton radiation therapy in 44 patients and showed that the V5 and V20 for lung was reduced significantly in the proton group and that all grade ≥ 2pulmonary toxicities were seen in the x-ray treated patients (Makishima, H., et al. Comparison of adverse effects of proton and X-ray chemoradiotherapy for esophageal cancer using an adaptive dose-volume histogram analysis. Journal of Radiation Research, 2015. 56(3): p. 568-576). In this study heart dose was also lower with protons, with grade ≥ 2 cardiac events occurring in 52.6 % of x-ray treated patients and 4 % proton treated patients.

NR = not reported

Rating Questions:	#	YES / NO	Low Confidence		Intermediate Confidence		High Confidence
			1	2	3	4	5
Does the evidence show that PBT provides a clinically meaningful improvement in net health outcome that is **superior** to other advanced conformal, fractionated photon-based radiotherapy techniques[1] for **most patients** with this indication?	1	Yes			X		
	2	No	Rating not provided				
	3	No	X				
Does PBT provide a clinically meaningful improvement in net health outcome that is **superior ONLY** when radiation dose constraints for critical organs at risk (i.e., surrounding normal tissue) cannot be met by other conformal, fractionated photon-based radiotherapy techniques[1] for patients with this indication?	1	No			X		
	2	No	Rating not provided				
	3	Yes					X
Is use of PBT for this indication consistent with generally accepted medical practice?	1	Yes			X		
	2	No	Rating not provided				
	3	Yes					X

NR = not reported

s) Gallbladder cancer

#	Rationale
1	No new evidence at this time.
2	NR
3	There is no prospective and little retrospective evidence for the routine use of proton radiation therapy for the treatment of patients with gallbladder cancer. Nevertheless, radiation therapy is routinely used in the adjuvant treatment of gallbladder carcinoma, with phase 2 studies showing favorable survival (Ben-Josef et al., SWOG S0809: A Phase II Intergroup Trial of Adjuvant Capecitabine and Gemcitabine Followed by Radiotherapy and Concurrent Capecitabine in Extrahepatic Cholangiocarcinoma and Gallbladder Carcinoma., J Clin Oncol. 2015 Aug 20;33(24):2617-22). The use of PBT in liver tumors has been thoroughly reviewed (Dionisi F. and Ben-Josef E. The use of proton therapy in the treatment of gastrointestinal cancers: liver. Cancer J 20(6):371-377, 2014). The decision to use PBT versus photon radiation can be aided by a clinical decision tool that modeled various tumor sizes and locations within the liver (Gandhi S.J., Liang X., Ding X., Zhu T.C., Ben-Josef E., Plastaras J.P., Metz J.M., Both S. and Apisarnthanarax S. Clinical decision tool for optimal delivery of liver stereotactic body radiation therapy: Photons versus protons. Pract Radiat Oncol 5(4):209-218, 2015.). PBT most notably outperformed photons in dome and central tumors that were >3 cm, with gallbladder carcinomas being in a central location. In general, PBT was able to deliver lower mean liver doses (MLD) in tumors >5 cm, suggesting a role for PBT where the MLD threshold may limit the prescription dose. As a result, when trying to treat large or ill-located tumors in close proximity to the liver, proton radiation therapy can be considered when traditional radiation therapy in unable to meet safe dose constraints.

NR = not reported

Rating Questions:	#	YES / NO	Low Confidence		Intermediate Confidence		High Confidence
			1	2	3	4	5
Does the evidence show that PBT provides a clinically meaningful improvement in net health outcome that is **superior** to other advanced conformal, fractionated photon-based radiotherapy techniques[1] for **most patients** with this indication?	1	NR					
	2	No	Rating not provided				
	3	No				X	
Does PBT provide a clinically meaningful improvement in net health outcome that is **superior ONLY** when radiation dose constraints for critical organs at risk (i.e., surrounding normal tissue) cannot be met by other conformal, fractionated photon-based radiotherapy techniques[1] for patients with this indication?	1	NR					
	2	No	Rating not provided				
	3	No		X			
Is use of PBT for this indication consistent with generally accepted medical practice?	1	NR					
	2	No	Rating not provided				
	3	No		X			

NR = not reported

t) Abdominal malignancies, including non-metastatic primary pancreatic and adrenal cancers

#	Rationale
1	• Hitchcock K, Nichols R, Morris C, et al. Feasibility of pancreatectomy following high-dose proton therapy for unresectable pancreatic cancer. World J Gastrointest Surg. 2017 Apr 27;9(4):103–108.

#	Rationale
	• Maemura K, Mataki Y, Kurahara H, et al. Comparison of proton beam radiotherapy and hyper-fractionated accelerated chemoradiotherapy for locally advanced pancreatic cancer. Pancreatology. 2017 Sep – Oct;17(5):833-838. • Nichols RC Jr, Morris CG, Hoppe BS, Rutenberg MS. A phase II trial of escalated dose proton radiotherapy with elective nodal irradiation and concomitant chemotherapy for patients with unresectable, borderline resectable, or medically inoperable pancreatic adenocarcinoma. J Clin Oncol. 2017;35(4). • Nichols RC Jr, Morris CG, Prabhu K, et al. Postoperative proton therapy for pancreatic cancer patients enrolled on the Proton Collaborative Group (PCG) registry. J Clin Oncol. 2018;36(4):513.
2	NR
3	There are no randomized data showing that proton therapy has less toxicity for pancreatic cancer. A review of the existing literature on non-liver GI cancers was published in 2014 detailing that bowel doses in the 15-25 Gy range correlate with acute bowel toxicity when combined with 5-FU-based chemotherapy, providing the rationale for proton therapy in many GI cancers. (Plastaras JP, Dionisi F, Wo JY. Gastrointestinal cancer: nonliver proton therapy for gastrointestinal cancers. Cancer J. 2014 Nov-Dec;20(6):378-86. doi: 10.1097/PPO.0000000000000085. Review. PubMed PMID: 25415682.) Pancreas Cancer: There are both dosimetric data and Phase I clinical data to suggest that proton radiotherapy for pancreatic cancer is feasible, tolerable, and safer than chemoradiation with photon therapy. PRT for pancreatic cancer in both the resected and unresected groups is associated with very low acute toxicity when standard dose and fractionation are used with concurrent chemotherapy (Nichols RC, Jr., George TJ, Zaiden RA, Jr., Awad ZT, Asbun HJ, Huh S, et al. Proton therapy with concomitant capecitabine for pancreatic and ampullary cancers is associated with a low incidence of gastrointestinal toxicity. Acta Oncol 2013;52(3):498-505.) and (Lukens J, Mick R, Demas K, Apisarnthanarax S, Metz J, McCall D, et al. Acute Toxicity of Proton Versus Photon Chemoradiation Therapy for Pancreatic Adenocarcinoma: A Cohort Study. American Society of Radiation Oncology Annual Meeting, Atlanta, GA, 2013). Only one grade 3 toxicity was reported out of a combined 33 patients (20 from University of Florida, 13 from University of Pennsylvania). This combined rate (3%) compares favorably to the historical control of RTOG 9704 where an acute Grade ≥ 3 non-hematologic toxicity rate of 58% was observed. An alternate preoperative strategy using 5 Gy x 5 with concurrent capecitabine has been piloted at Massachusetts General Hospital with no dose limiting toxicities (10. Hong TS, Ryan DP, Blaszkowsky LS, Mamon HJ, Kwak EL, Mino-Kenudson M, et al. Phase I study of preoperative short-course chemoradiation with proton beam therapy and capecitabine for resectable pancreatic ductal adenocarcinoma of the head. Int J Radiat Oncol Biol Phys 2011;79(1):151-7.). They reported on 15 patients with localized resectable pancreatic head cancer. The patients were treated with preoperative proton radiation and concurrent chemotherapy (capecitabine 825 mg/m2 BID x 10 days). As they treated with shortening courses of radiotherapy, they were able to shorten the course to 5 Gy x 5 fractions over 1 week and they observed no dose limiting toxicities. More recent single institution retrospective data from 42 unresectable locally advanced pancreas cancer patients treated by proton beam concurrent chemoradiation showed that all grade 3 and 4 events were hematologic and the median survival was 25.6â€¯months (Hiroshima Y, Fukumitsu N, Saito T, Numajiri H, Murofushi KN, Ohnishi K, NonakaT, Ishikawa H, Okumura T, Sakurai H. Concurrent chemoradiotherapy using proton beams for unresectable locally advanced pancreatic cancer. Radiother Oncol. 2019 Jul;136:37-43. doi:10.1016/j.radonc.2019.03.012. Epub 2019 Apr 6. PubMed PMID:31015127). An additional 13 patients with localized pancreas cancer treated with concurrent chemotherapy and proton radiation were reported from the Mayo Clinic. No patients experienced grade ≥3 treatment-related adverse events. They also reported on the dosimetric advantages of proton therapy compared with advanced photon techniques (Jethwa KR, Tryggestad EJ, Whitaker TJ, Giffey BT, Kazemba BD, Neben-Wittich MA, Merrell KW, Haddock MG, Hallemeier CL. Initial experience with intensity modulated proton therapy for intact, clinically localized pancreas cancer: Clinical implementation, dosimetric analysis, acute treatment-related adverse events, and patient-reported outcomes. Adv Radiat Oncol. 2018 Apr 13;3(3):314-321. doi: 10.1016/j.adro.2018.04.003. eCollection 2018 Jul-Sep. PubMed PMID: 30202800; PubMed Central PMCID: PMC6128024.). In summary, the single arm data treating pancreatic cancer with proton chemoradiation that have been reported thus far have shown remarkably low rates of acute non-hematologic toxicities. These data, although not randomized, provide compelling rationale for accepted medical practice when acute toxicity is a concern.

NR = not reported

Rating Questions:	#	YES / NO	Low Confidence		Intermediate Confidence		High Confidence
			1	2	3	4	5
Does the evidence show that PBT provides a clinically meaningful improvement in net health outcome that is **superior** to other advanced conformal, fractionated photon-based radiotherapy techniques[1] for **most patients** with this indication?	1	Yes			X		
	2	No	Rating not provided				
	3	Yes			X		
Does PBT provide a clinically meaningful improvement in net health outcome that is **superior ONLY** when radiation dose constraints for critical organs at risk (i.e., surrounding normal tissue) cannot be met by other conformal, fractionated photon-based radiotherapy techniques[1] for patients with this indication?	1	No			X		
	2	No	Rating not provided				
	3	No			X		
Is use of PBT for this indication consistent with generally accepted medical practice?	1	Yes			X		
	2	No	Rating not provided				
	3	Yes				X	

NR = not reported

u) Prostate cancer

#	Rationale
1	• Arimura T, Kondo N, Matsukawa K, et al. The role of proton beam therapy for patients with intermediate- and high-risk prostate cancer. J Clin Oncol. 2018;36(6):97. • Bryant C, Smith TL, Henderson RH, et al. Five-year biochemical results, toxicity, and patient-reported quality of life following delivery of dose-escalated image-guided proton therapy for prostate cancer. Int J Radiat Oncol Biol Phys. 2016;95(1):422-434. • Choi S, Blanchard P, Ye R, et al. Outcomes Following Proton Therapy for the Treatment of Prostate Cancer: Efficacy and Toxicity Results from 2 Prospective Single Institution Cohorts. Int J Radiat Oncol Biol Phys. 2017;99(2S):E221. • Ho CK, Bryant CM, Mendenhall NP, et al. Long-term outcomes following proton therapy for prostate cancer in young men with a focus on sexual health. Acta Oncol. 2018. https://doi.org/10.1080/0284186X.2018.1427886. • Jain et al. Acute and late toxicity report of post-prostatectomy proton therapy for prostate cancer patients undergoing adjuvant or salvage radiotherapy. Int J Radiat Oncol Biol Phys. 2017;98(2):e25. • Mendenhall NP, Wong W, Bryant C et al. Comparison of clinical outcomes with IMRT and proton therapy for prostate cancer. J Clin Oncol. 2017; e16555-e16555. • Walsh S, Roelofs E, Kuss P, et al. Towards a Clinical Decision Support System for External Beam Radiation Oncology Prostate Cancer Patients: Proton vs. Photon Radiotherapy? A Radiobiological Study of Robustness and Stability. Cancers. 2018;10(55):1-16.
2	NR
3	The definitive randomized trial for localized prostate cancer (NCT01617161) is near completion of enrollment and should report in a few years.

NR = not reported

Rating Questions:	#	YES / NO	Low Confidence		Intermediate Confidence		High Confidence
			1	2	3	4	5
	1	No				X	

Rating Questions:	#	YES / NO	Low Confidence		Intermediate Confidence		High Confidence
			1	2	3	4	5
Does the evidence show that PBT provides a clinically meaningful improvement in net health outcome that is **superior** to other advanced conformal, fractionated photon-based radiotherapy techniques[1] for **most patients** with this indication?	2	No	Rating not provided				
	3	No					X
Does PBT provide a clinically meaningful improvement in net health outcome that is **superior ONLY** when radiation dose constraints for critical organs at risk (i.e., surrounding normal tissue) cannot be met by other conformal, fractionated photon-based radiotherapy techniques[1] for patients with this indication?	1	Yes				X	
	2	No	Rating not provided				
	3	No					X
Is use of PBT for this indication consistent with generally accepted medical practice?	1	Yes			X		
	2	No	Rating not provided				
	3	Yes					X

NR = not reported

v) Pelvic malignancies, including non-metastatic rectal, anal, bladder and cervical cancers

#	Rationale
1	• Colaco RJ, Nichols RC, Huh S, et al. Protons offer reduced bone marrow, small bowel, and urinary bladder exposure for patients receiving neoadjuvant radiotherapy for resectable rectal cancer. J Gastrointest Oncol. 2014;5(1):3-8. • Marnitz S, Wlodarczyk W, Neumann O, et al. Which technique for radiation is most beneficial for patients with locally advanced cervical cancer? Intensity modulated proton therapy versus intensity modulated photon treatment, helical tomotherapy and volumetric arc therapy for primary radiation – an intraindividual comparison. Radiat Oncol. 2015;10:91.
2	NR
3	For bladder cancer, there is insufficient evidence on the comparative effectiveness of proton therapy. Two articles to consider are below but are combined proton/photon therapy. • Hata M, Miyanaga N, Tokuuye K, Saida Y, Ohara K, Sugahara S, Kagei K, Igaki H, Hashimoto T, Hattori K, Shimazui T, Akaza H, Akine Y Proton beam therapy for invasive bladder cancer: a prospective study of bladder preserving therapy with combined radiotherapy and intra-arterial chemotherapy. 2006 Int J Radiat Oncol Biol Phys. 2006 Apr 1;64(5):1371-9 • Takaoka EI, Miyazaki J, Ishikawa H, Kawai K, Kimura T, Ishitsuka R, Kojima T, Kanuma R, Takizawa D, Okumura T, Sakurai H, Nishiyama H. Long-term single-institute experience with trimodal bladder-preserving therapy with proton beam therapy for muscle-invasive bladder cancer. Jpn J Clin Oncol. 2017 Jan;47(1):67-73. doi: 10.1093/jjco/hyw151. Epub 2016 Oct 13 There are no randomized data showing that proton therapy has less toxicity for anal cancer or rectal cancer. A review of the existing literature on non-liver GI cancers was published in 2014 detailing that bowel doses in the 15-25 Gy range correlate with acute bowel toxicity when combined with 5-FU-based chemotherapy, providing the rationale for proton therapy in many GI cancers. (Plastaras JP, Dionisi F, Wo JY. Gastrointestinal cancer: nonliver proton therapy for gastrointestinal cancers. Cancer J. 2014 Nov-Dec;20(6):378-86. doi: 10.1097/PPO.0000000000000085. Review. PubMed PMID: 25415682.) Rectal Cancer: A comparison of intensity-modulated radiation therapy (IMRT) with pencil beam scanning (PBS) proton therapy using lateral beams in the preoperative setting showed that PBS proton therapy could deliver much lower small bowel V15 (66 cc vs. 286 cc), lower bladder and lower femoral head doses [Dionisi et al. ASTRO annual meeting , 2013]. In a retrospective series comparing 39 patients treated with IMRT and 26

#	Rationale
	patients treated with PBS proton therapy in the neoadjuvant setting with concurrent chemotherapy, there was significantly less Grade ≥ 2 diarrhea in PBS proton therapy patients (12% versus 39%, p = 0.022) [Batra, JCO 2015]. Anal Cancer: A retrospective comparative dosimetry study showed that proton therapy resulted in lower doses to bowel, bone marrow, and bladder in anal cancer (Ojerholm E, Kirk ML, Thompson RF, Zhai H, Metz JM, Both S, Ben-Josef E, Plastaras JP. Pencil-beam scanning proton therapy for anal cancer: a dosimetric comparison with intensity-modulated radiotherapy. Acta Oncol. 2015;54(8):1209-17.doi: 10.3109/0284186X.2014.1002570. Epub 2015 Mar 3. PubMed PMID: 25734796.) Since then, prospective, a multi-institutional pilot study of proton therapy with concurrent chemotherapy, showed that proton therapy in this setting was feasible, however toxicity rates were not very different from historical controls, including 2/25 who died on treatment. (Wo JY, Plastaras JP, Metz JM, Jiang W, Yeap BY, Drapek LC, Adams J, Baglini C, Ryan DP, Murphy JE, Parikh AR, Allen JN, Clark JW, Blaszkowsky LS, DeLaney TF, Ben-Josef E, Hong TS. Pencil Beam Scanning Proton Beam Chemoradiation Therapy With 5-Fluorouracil and Mitomycin-C for Definitive Treatment of Carcinoma of the Anal Canal: A Multi-institutional Pilot Feasibility Study. Int J Radiat Oncol Biol Phys. 2019 May 22. pii: S0360-3016(19)30747-3. doi: 10.1016/j.ijrobp.2019.04.040. [Epub ahead of print] PubMed PMID: 31128146.)A phase 2 study of proton beam radiation therapy for anal cancer is underway. Cervical cancer: there is no randomized data showing the superiority of one treatment modality over another for patients with cervical cancer. Dosimetric studies show that proton radiation therapy provides superior sparing of normal tissues (Hashimoto et al., J Radiat Res. Whole-pelvic radiotherapy with spot-scanning proton beams for uterine cervical cancer: a planning study. 2016 Sep;57(5):524-532) (van de Schoot AJ et al., Dosimetric advantages of proton therapy compared with photon therapy using an adaptive strategy in cervical cancer. Acta Oncol. 2016 Jul;55(7):892-9), including the small bowel, rectum, and bladder. In summary, it is reasonable to consider proton therapy for pelvic cancers such as rectal and anal cancer when critical OAR's, such as small bowel and marrow are of particular importance. When treating frail patients or those with inflammatory bowel disease, it is generally accepted medical practice to do whatever can be done to limit even modest dose (15-25 Gy) to small bowel in these special circumstances.

NR = not reported

Rating Questions:	#	YES / NO	Low Confidence		Intermediate Confidence		High Confidence
			1	2	3	4	5
Does the evidence show that PBT provides a clinically meaningful improvement in net health outcome that is **superior** to other advanced conformal, fractionated photon-based radiotherapy techniques[1] for **most patients** with this indication?	1	No		X			
	2	No	Rating not provided				
	3	No			X		
Does PBT provide a clinically meaningful improvement in net health outcome that is **superior ONLY** when radiation dose constraints for critical organs at risk (i.e., surrounding normal tissue) cannot be met by other conformal, fractionated photon-based radiotherapy techniques[1] for patients with this indication?	1	Yes				X	
	2	No	Rating not provided				
	3	Yes				X	
Is use of PBT for this indication consistent with generally accepted medical practice?	1	No	Rating not provided				
	2	No	Rating not provided				
	3	Yes		X			

NR = not reported

w) Stage IIA seminoma

#	Rationale
1	• Choo R, Kazemba B, Choo CS, Lester SC, Whitaker T. Proton therapy for stage IIA-B seminoma: a new standard of care for treating retroperitoneal nodes. Int J Part Ther. 2018. In-Press.
2	NR
3	For seminoma, Penn supports the assessment of Evicore, which can be found here:https://www.evicore.com/-/media/files/evicore/clinical-guidelines/solution/radiation-oncology/proton-beam-therapy_v302019_eff71519.pdf. We report the findings verbatim from the review as follows: "The risks of radiation-induced second malignancy in seminoma are well documented. The current NCCN Guidelines™ continue to mention the increased risk of second cancers arising in the stomach, kidney, liver, and bowels in patients treated with radiation therapy. They caution against the use of IMRT in the treatment of seminoma as the radiation doses to these organ (integral dose) is increased compared to 3DCRT fields used in anterior and posterior fashion. However, it must be recognized that use of anterior/posterior fields whether 2D or 3D are the very technique which has been the subject of these reports. IMRT might theoretically make it worse. A brief review of the literature outlines the risk. Lewinshtein et al. (2012) used SEER data between 1973 and 2000. They found a 19% increase in secondary primary malignancies in seminoma patients exposed to radiation therapy as compared to the general population including pancreas, non-bladder urothelial, bladder, thyroid, and others. The risk lasted 15 years from the time of initial diagnosis. An accompanying editorial in the journal noted an increased incidence of seminoma during the last 4 decades with improved survival, which makes the issue of radiation-induced malignancies of increasing concern. Indeed, the NCCN noted that the routine use of adjuvant therapy for Stage I seminoma is not warranted as the risk of recurrence is low compared to the potential harms of adjuvant therapy. Travis et al., reported twice on this issue in 1997 and 2005. They identified risks of lung, bladder, pancreas, stomach, and other organs, noting that secondary primary cancers are a leading cause of death in men with a history of testicular cancer. The risk may extend as long as 35 years. Patients treated with radiation therapy had the highest risk of developing cancer especially when treated at a young age. Among organs treated in a radiation field, stomach, large bowel, pancreas, and bladder stood out for the development of a later cancer. Given these findings, radiation is no longer used in early seminoma but there remains a population of patients with more advanced disease that may benefit. Although this population of patients is relatively small as 80% of seminoma, totaling approximately 8600 cases a year, is diagnosed in Stage I, the relative doses of radiation and increased field sizes pose a problem. Dose modeling by Mazonakis et al., published in 2015 showed that medically necessary abdominopelvic irradiation increased the risk for induction of secondary malignancies by as much as 3.9%. The use of protons brings a distinct advantage in lowering radiation dosed to the population at risk. Simone II, et al., writing in the International Journal of Radiation Oncology Biology Physics in 2012, showed that proton plans could reduce mean doses to the stomach to 119 cGy vs. 768 cGy for photons as well as having meaningful reductions in doses to bladder and pancreas with a subsequent theoretical expected decrease in cancers. Based on the above information documenting a higher risk of secondary malignancy unique to seminoma, the use of PBT is considered medically necessary."

NR = not reported

Rating Questions:	#	YES / NO	Low Confidence		Intermediate Confidence		High Confidence
			1	2	3	4	5
Does the evidence show that PBT provides a clinically meaningful improvement in net health outcome that is **superior** to other advanced conformal, fractionated photon-based radiotherapy techniques[1] for **most patients** with this indication?	1	Yes				X	
	2	No	Rating not provided				
	3	Yes	Rating not provided				
Does PBT provide a clinically meaningful improvement in net health outcome that is **superior ONLY** when radiation dose constraints for critical organs at risk (i.e., surrounding normal tissue) cannot be met by other	1	No				X	
	2	No	Rating not provided				
	3	No					X

Rating Questions:	#	YES / NO	Low Confidence		Intermediate Confidence		High Confidence
			1	2	3	4	5
conformal, fractionated photon-based radiotherapy techniques[1] for patients with this indication?							
Is use of PBT for this indication consistent with generally accepted medical practice?	1	Yes				X	
	2	No	Rating not provided				
	3	Yes					X

NR = not reported

x) Lymphoma (e.g., Hodgkin lymphoma, non-Hodgkin lymphoma, or extranodal NK/T-Cell Lymphoma, nasal type)

#	Rationale
1	• Hoppe BS, Hill-Kayser CE, Tseng YD, et al. Consolidative proton therapy after chemotherapy for patients with Hodgkin lymphoma. Ann Oncol. 2017 Sep 1;28(9):2179-2184. • Hoppe BS, Mendenhall NP, Louis D, et al. Comparing Breath Hold and Free Breathing during Intensity-Modulated Radiation Therapy and Proton Therapy in Patients with Mediastinal Hodgkin Lymphoma. Int J Part Ther. 2017 Spring;3(4):492-496. • Plastaras JP, Maity A, Flampouri S, et al. Bi-institutional report on consolidative proton therapy after initial chemotherapy for mediastinal diffuse large B-cell and primary mediastinal large B-cell lymphomas. Int J Radiat Oncol Biol Phys. 2018;102(3). • Ricardi U, Dabaja B, Hodgson DC. Proton therapy in mediastinal Hodgkin lymphoma: moving from dosimetric prediction to clinical evidence. Ann Oncol. 2017 Sep 1;28(9):2049-2050. • Tseng YD, Hoppe BS, Miller D, et al. Rates of Toxicity and Outcomes After Mediastinal Proton Therapy For Relapsed/Refractory Lymphoma. Int J Radiat Oncol Biol Phys 2017;99:S62-S63.
2	NR
3	Dosimetric studies comparing proton therapy to photon therapy in patients with mediastinal lymphomas have demonstrated significantly reduced radiation dose to breast, lung, heart and total body. These have been extensively reviewed by the PTCOG Lymphoma Committee (Tseng YD, Cutter DJ, Plastaras JP, Parikh RR, Cahlon O, Chuong MD, Dedeckova K, Khan MK, Lin SY, McGee LA, Shen EY, Terezakis SA, Badiyan SN, Kirova YM, Hoppe RT, Mendenhall NP, Pankuch M, Flampouri S, Ricardi U, Hoppe BS. Evidence-based Review on the Use of Proton Therapy in Lymphoma From the Particle Therapy Cooperative Group (PTCOG) Lymphoma Subcommittee. Int J Radiat Oncol Biol Phys. 2017 Nov 15;99(4):825-842. doi: 10.1016/j.ijrobp.2017.05.004. Epub 2017 Sep 21. Review. PubMed PMID: 28943076). In this review, the acceptable dose constraints when treating lymphoma patients are discussed. Namely, dose constraints listed by QUANTEC do not reflect that accepted standards for treating lymphoma patients who have a high chance of being cured with combined modality treatments, often at young ages. The time scale for developing cardiac disease, including valvular dysfunction, coronary artery disease, and second cancers are much longer for lymphoma patients. Therefore, tighter OAR constraints were adopted by the ILROG (International Lymphoma Radiation Oncology Group). These were published along with guidelines using proton therapy for mediastinal lymphoma where the indications for proton therapy were outlined (Dabaja BS, Hoppe BS, Plastaras JP, Newhauser W, Rosolova K, Flampouri S, Mohan R, Mikhaeel NG, Kirova Y, Specht L, Yahalom J. Proton therapy for adults with mediastinal lymphomas: the International Lymphoma Radiation Oncology Group guidelines. Blood. 2018 Oct 18;132(16):1635-1646. doi: 10.1182/blood-2018-03-837633. Epub 2018 Aug 14.). Because of the time scale of development of toxicities is so long, no randomized trials comparing photons and protons have been attempted yet, although there is one being developed in the UK. The recommendation for using proton therapy when OAR constraints cannot be met has been largely based on modeling studies. The concern that proton therapy results in inferior loco-regional control has been addressed by a multi-institutional collaborative study of 138 patients that showed that disease free survival in Hodgkin lymphoma patients treated with proton therapy is similar to historical studies with photon therapy (2-year progression-free survival rate 93% with a median follow-up of 24 months) (Hoppe BS, Hill-Kayser CE, Tseng YD, Flampouri S, Elmongy H, Cahlon O, Mendenhall NP, Maity

#	Rationale
	A, McGee LA, Plastaras JP. The Use of Consolidative Proton Therapy After First-Line Therapy Among Patients With Hodgkin Lymphoma at Academic and Community Proton Centers. Int J Radiat Oncol Biol Phys. 2016 Oct 1;96(2S):S39. doi: 10.1016/j.ijrobp.2016.06.107.PMID: 27675918). The use of proton therapy for non-mediastinal lymphomas is based on sparing other organs that could be sites of second cancer development and bone marrow sparing. Fewer studies have addressed non-mediastinal lymphomas, but similar principles hold for young lymphoma patients as for AYA/pediatric patients in terms of reducing integral dose and risk for second cancers. For NK/T-cell lymphoma, the rationale for using proton therapy is similar to nasopharyngeal carcinomas. The doses used are above 50 Gy and when stage I/II, these cancers are curable with radiation. In summary, most patients with curable lymphomas will benefit from proton therapy based on models of OAR and decreased integral dose, but given the wide variety of patients with lymphoma, a customized approach is appropriate.

NR = not reported

Rating Questions:	#	YES / NO	Low Confidence		Intermediate Confidence		High Confidence
			1	2	3	4	5
Does the evidence show that PBT provides a clinically meaningful improvement in net health outcome that is **superior** to other advanced conformal, fractionated photon-based radiotherapy techniques[1] for **most patients** with this indication?	1	Yes				X	
	2	No	Rating not provided				
	3	Yes				X	
Does PBT provide a clinically meaningful improvement in net health outcome that is **superior ONLY** when radiation dose constraints for critical organs at risk (i.e., surrounding normal tissue) cannot be met by other conformal, fractionated photon-based radiotherapy techniques[1] for patients with this indication?	1	No				X	
	2	No	Rating not provided				
	3	No				X	
Is use of PBT for this indication consistent with generally accepted medical practice?	1	Yes				X	
	2	No	Rating not provided				
	3	Yes				X	

NR = not reported

y) Ewing Sarcoma

#	Rationale
1	• Hattangadi J, Esty B, Winey B, et al. Radiation recall myositis in pediatric Ewing sarcoma. Pediatr Blood Cancer. 2012;59(3):570 572. • Rombi B, DeLaney TF, MacDonald SM, et al. Proton radiotherapy for pediatric Ewing's sarcoma: initial clinical outcomes. Int J Radiat Oncol Biol Phys. 2012;82(3):1142â€'1148.
2	NR
3	Ewing Sarcoma is a rare malignancy that disproportionately impacts children and young adults. Optimal management for localized disease includes aggressive chemotherapy and either surgery and/ or radiation. When radiation is indicated proton radiation is able to optimally spare uninvolved normal tissue, which is particularly important for young patients to help mitigate the risk of late complications including a secondary radiation induced malignancy. Available literature supports to utility of proton therapy in various anatomic locations. For pelvis tumors, proton therapy can better spare dose to the intestine, bladder, bone marrow and femoral head compared to photons (PMID: 12377335).For paraspinal tumors, protons permit appropriate

#	Rationale
	dosing while still sparing the spinal cord (PMID:9364633).In fact, long term outcomes of young patients with Ewing Sarcoma of a variety of anatomic locations treated with proton therapy demonstrate good tumor control outcomes with minimal late toxicity (PMID: 28627000)

NR = not reported

Rating Questions:	#	YES / NO	Low Confidence		Intermediate Confidence		High Confidence
			1	2	3	4	5
Does the evidence show that PBT provides a clinically meaningful improvement in net health outcome that is **superior** to other advanced conformal, fractionated photon-based radiotherapy techniques[1] for **most patients** with this indication?	1	No			X		
	2	No	Rating not provided				
	3	Yes				X	
Does PBT provide a clinically meaningful improvement in net health outcome that is **superior ONLY** when radiation dose constraints for critical organs at risk (i.e., surrounding normal tissue) cannot be met by other conformal, fractionated photon-based radiotherapy techniques[1] for patients with this indication?	1	Yes			X		
	2	No	Rating not provided				
	3	No				X	
Is use of PBT for this indication consistent with generally accepted medical practice?	1	Yes			X		
	2	No	Rating not provided				
	3	Yes				X	

NR = not reported

z) Soft tissue sarcoma (e.g., soft tissue sarcoma of extremity/superficial trunk, head/neck, or non-metastatic retroperitoneal sarcoma (non-metastatic)

#	Rationale
1	• Guttmann DM, Frick MA, Carmona R, et al. A prospective study of proton reirradiation for recurrent and secondary soft tissue sarcoma. Radiother Oncol. 2017 Jul 8. pii: S0167-8140(17)32444-1.
2	NR
3	Considering the PICO formulation as a reference guide: in patients with soft tissue sarcoma there is no existing published literature directly comparing charged particle therapy to: -Advanced conformal, fractionated photon-based radiotherapy techniques including intensity modulated radiotherapy (IMRT) or volume-modulated arc therapy (VMAT). However special considerations should be considered when determining the utility of proton therapy. Namely: -Young patients may benefit from the potential reduction in late toxicity and risk of secondary malignancies -Certain patients with head/ neck sarcomas may benefit as described in the other relevant sections of this document - Patients with retroperitoneal sarcoma may benefit from reduction of dose to the bowel or kidney

NR = not reported

Rating Questions:	#	YES / NO	Low Confidence		Intermediate Confidence		High Confidence
			1	2	3	4	5
Does the evidence show that PBT provides a clinically meaningful improvement in net health outcome that is **superior** to other advanced conformal, fractionated photon-based radiotherapy techniques[1] for **most patients** with this indication?	1	Yes				X	
	2	No	Rating not provided				
	3	No				X	
Does PBT provide a clinically meaningful improvement in net health outcome that is **superior ONLY** when radiation dose constraints for critical organs at risk (i.e., surrounding normal tissue) cannot be met by other conformal, fractionated photon-based radiotherapy techniques[1] for patients with this indication?	1	No				X	
	2	No	Rating not provided				
	3	Yes				X	
Is use of PBT for this indication consistent with generally accepted medical practice?	1	Yes				X	
	2	No	Rating not provided				
	3	No				X	

NR = not reported

aa) Breast cancer

#	Rationale
1	• Choi JI, Chang AL. Excellent acute toxicity outcomes with proton therapy for partial breast irradiation in early stage breast cancer: Initial results of a multi-institutional phase II trial [abstract]. Cancer Res. 2018;78(4). • Fega R, Vargas CE, Hartsell WF, et al. Clinical Outcomes of Breast Proton Radiation Therapy: A Multi-institutional Analysis of the Proton Collaborative Group Registry. Int J Radiat Oncol Biol Phys. 2017;99(2S):S214. • McGee LA, Iftekaruddin Z, Chang JHC, et al. Postmastectomy Chest Wall Reirradiation With Proton Therapy for Breast Cancer. Int J Radiat Oncol Biol Phys. 2017;99(2S):E34. • Niska JR, Thorpe C, Bruso ME, et al. Proton beam therapy for isolated locoregional recurrence of breast cancer after mastectomy without prior radiation therapy: prospective PCG registry analysis. Int J Radiat Oncol Biol Phys. 2018. • Teichman SL, Do S, Lum S, et al. Improved long-term patient-reported health and well-being outcomes of early-stage breast cancer treated with partial breast proton therapy. Cancer Medicine. 2018;7:6064-6076. • Thorpe C, Niska JR, Bruso ME, et al. Proton beam therapy reirradiation for recurrent breast cancer: multi-institutional prospective PCG registry analysis. Int J Radiat Oncol Biol Phys. 2018.
2	NR
3	Radiation therapy is associated with a local-regional control and survival benefit for most patients with breast cancer in both the lumpectomy and mastectomy settings. Organs at risk from this treatment are most prominently ipsilateral lung and heart rate cardiac morbidity and mortality have been particularly associated with radiation therapy for breast cancer. Protons have been investigated for postlumpectomy partial breast radiation, postmastectomy radiation, and comprehensive (internal mammary) regional node radiation. Individuals with breast cancer most suited for protons are those with challenging anatomy not able to meet reasonable lung and heart dose constraints with 3D conformal or IMRT photon radiation. Examples include pectus deformity of the chest wall, highly concave chest walls, postmastectomy cases with highly concave breast reconstructions, bilateral breast cancer needing simultaneous treatment, or many cases of internal mammary node radiation. Re-irradiation cases for breast cancer are also suited for protons to minimize retreatment of normal tissue.

#	Rationale
	Evidence for protons in breast cancer currently consists of a) dosimetry comparison studies of planning results for 3D, IMRT, or protons such as PMID: 28734644, PMID: 29483041, PMID: 28734644.and b) early clinical outcomes studies showing excellent local-regional control and toxicity profiles as well such as PMID: 30414757, PMID: 31338974, PMID: 31185327, PMID: 30453388.There is presently no known survival benefit to protons for breast cancer PMID: 30693271.A phase III trial of Photons versus Protons is underway RADCOMP NCT02603341. Excellent recent review articles about protons and breast cancer with more comprehensive references of dosimetry comparison studies, clinical outcomes studies, and tables of ongoing clinical trials are Corbin and Mutter DOI: 10.2217/bmt-2018-0001; and Braunstein and Cahlon https://doi.org/10.1016/j.semradonc.2017.11.009.

NR = not reported

Rating Questions:	#	YES / NO	Low Confidence		Intermediate Confidence		High Confidence
			1	2	3	4	5
Does the evidence show that PBT provides a clinically meaningful improvement in net health outcome that is **superior** to other advanced conformal, fractionated photon-based radiotherapy techniques[1] for **most patients** with this indication?	1	Yes				X	
	2	No	Rating not provided				
	3	No				X	
Does PBT provide a clinically meaningful improvement in net health outcome that is **superior ONLY** when radiation dose constraints for critical organs at risk (i.e., surrounding normal tissue) cannot be met by other conformal, fractionated photon-based radiotherapy techniques[1] for patients with this indication?	1	No				X	
	2	No	Rating not provided				
	3	Yes				X	
Is use of PBT for this indication consistent with generally accepted medical practice?	1	Yes				X	
	2	No	Rating not provided				
	3	No				X	

NR = not reported

bb) Re-irradiation tumor cases

#	Rationale
1	• McGee LA, Iftekaruddin Z, Chang JHC, et al. Postmastectomy Chest Wall Reirradiation With Proton Therapy for Breast Cancer. Int J Radiat Oncol Biol Phys. 2017;99(2S):E34. • Thorpe C, Niska JR, Bruso ME, et al. Proton beam therapy reirradiation for recurrent breast cancer: multi-institutional prospective PCG registry analysis. Int J Radiat Oncol Biol Phys. 2018. • Sheu T, Garden AS, Fuller CD, et al. Reirradiation Utilizing Proton Radiation Therapy May Improve Toxicity Free Survival in Patients With Small-Volume, Recurrent Head And Neck Cancer. Int J Radiat Oncol Biol Phys. 2016 Oct 1;96(2S):E331. • Ho JC, et al. Reirradiation of thoracic cancers with intensity modulated proton therapy. Int J Radiat Oncol Biol Phys. 2017;98(1):222.
2	Proton may provide advantage over photon radiation in a case by case basis. There is insufficient data to support broad application
3	There are not a lot of data comparing outcomes of patients treated with photon re-irradiation compared to proton re-irradiation for most body sites. This is in part due to a reluctance to re-irradiate with photons, so even historical controls are not well represented in the literature. An exception to this is head and neck re-irradiation, which has been covered above in section "j)Very advanced head and neck cancer." A systematic review of proton therapy for re-irradiation was published that summarizes the limited available evidence (1: Verma V, Rwigema JM, Malyapa RS,

#	Rationale
	Regine WF, Simone CB 2nd. Systematic assessment of clinical outcomes and toxicities of proton radiotherapy for reirradiation. Radiother Oncol. 2017 Oct;125(1):21-30. doi: 10.1016/j.radonc.2017.08.005. Epub 2017 Sep 20. Review. PubMed PMID: 28941560.) Some of the data from proton re-irradiation studies are summarized below for individual disease sites: Non-Small Cell Lung Cancer: A 57 subject multicenter study of proton re-irradiation of NSCLC showed 1-year rates of overall and progression-free survival were 59% and 58%, respectively. In total, grade 3 or higher acute and/or late toxicity developed in 24 patients (42%), acute toxicity developed in 22 (39%), and late toxicity developed in seven (12%). Overlap in the central airway region and high dose to the heart and esophagus portended worse outcomes, highlighting the importance of careful patient selection. A single-institution report from MDACC showed that local control was achievable with proton re-irradiation and median survival of the 22 NSCLC patients was 18 months (Ho JC, Nguyen QN, Li H, Allen PK, Zhang X, Liao Z, Zhu XR, Gomez D, Lin SH, Gillin M, Komaki R, Hahn S, Chang JY. Reirradiation of thoracic cancers with intensity modulated proton therapy. Pract Radiat Oncol. 2018 Jan - Feb;8(1):58-65. doi: 10.1016/j.prro.2017.07.002. Epub 2017 Jul 8. PubMed PMID:28867546). Esophageal cancer: the feasibility of re-irradiation with protons in esophageal cancer was described as a possibly safer means of re-irradiating previously-treated areas. (Fernandes A, Berman AT, Mick R, Both S, Lelionis K, Lukens JN, Ben-Josef E, Metz JM, Plastaras JP. Int J Radiat Oncol Biol Phys. 2016 May 1;95(1):483-7. doi: 10.1016/j.ijrobp.2015.12.005. Epub 2015 Dec 14. PMID: 26847847). Pancreas cancer: a 15 patient feasibility study of re-irradiation of pancreatic cancer with protons showed a median survival of 16.4 months, which is better than the previously published median survival of ~6-8 months for reirradiation with SBRT (Boimel PJ, Berman AT, Li J, Apisarnthanarax S, Both S, Lelionis K, Larson GL,Teitelbaum U, Lukens JN, Ben-Josef E, Metz JM, Plastaras JP. Proton beam reirradiation for locally recurrent pancreatic adenocarcinoma. J Gastrointest Oncol. 2017 Aug;8(4):665-674. doi: 10.21037/jgo.2017.03.04. PubMed PMID: 28890817; PubMed Central PMCID: PMC5582048.). There were 2 subjects with grade 4/5 toxicities, which were associated with stents. Sarcoma: A 23 subject study of proton re-irradiation of sarcoma showed a median overall survival and progression-free survival were 44 and 29 months, respectively. In extremity patients, amputation was spared in 7/10. (Guttmann DM, Frick MA, Carmona R, Deville C Jr, Levin WP, Berman AT, Chinniah C, Hahn SM, Plastaras JP, Simone CB 2nd. A prospective study of proton reirradiation for recurrent and secondary soft tissue sarcoma. Radiother Oncol. 2017 Aug;124(2):271-276. doi: 10.1016/j.radonc.2017.06.024. Epub 2017 Jul 8. PubMed PMID: 28697854.) As is stated in the ASTRO Model Policy, proton re-irradiation is usually considered when photon re-irradiation leads to unacceptable cumulative radiation doses to critical organs, such as spinal cord, lung, or heart. Limiting the total volume of reirradiated tissues has a potential advantage of limiting soft tissue fibrosis. Often the alternative to proton re-irradiation is NO radiation at all, consigning patients to death from untreated local recurrences where few other option exist.

NR = not reported

Rating Questions:	#	YES / NO	Low Confidence		Intermediate Confidence		High Confidence
			1	2	3	4	5
Does the evidence show that PBT provides a clinically meaningful improvement in net health outcome that is **superior** to other advanced conformal, fractionated photon-based radiotherapy techniques[1] for **most patients** with this indication?	1	Yes				X	
	2	No	Rating not provided				
	3	No			X		
Does PBT provide a clinically meaningful improvement in net health outcome that is **superior ONLY** when radiation dose constraints for critical organs at risk (i.e., surrounding normal tissue) cannot be met by other conformal, fractionated photon-based radiotherapy techniques[1] for patients with this indication?	1	No				X	
	2	No	Rating not provided				
	3	Yes			X		
	1	Yes				X	

Rating Questions:	#	YES / NO	Low Confidence		Intermediate Confidence		High Confidence
			1	2	3	4	5
Is use of PBT for this indication consistent with generally accepted medical practice?	2	No	Rating not provided				
	3	Yes					X

NR = not reported

cc) Patients with genetic syndromes making total volume of radiation minimization crucial such as but not limited to NF-1 patients and retinoblastoma patients

#	Rationale
1	• Agarwal A, Thaker NG, Tawk B, et al. The evolution of radiation therapy for retinoblastoma: the MD Anderson Cancer Center experience. Int J Part Ther. 2016;2(4):490-498. • Kim JY, Park Y. Treatment of retinoblastoma: the role of external beam radiotherapy. Yonsei Med J. 2015 November;56(6):1478-1491.
2	NR
3	Although there is no clinical data specific to genetic syndromes, it is generally accepted medical practice to do whatever can be done to limit dose as much as possible to normal tissues for these patients, as they are predisposed to short- and long-term toxicity of radiation. This is in accordance with the principal in radiation oncology to keep doses to normal tissues as low as reasonably achievable (ALARA).

NR = not reported

Rating Questions:	#	YES / NO	Low Confidence		Intermediate Confidence		High Confidence
			1	**2**	**3**	**4**	**5**
Does the evidence show that PBT provides a clinically meaningful improvement in net health outcome that is **superior** to other advanced conformal, fractionated photon-based radiotherapy techniques[1] for **most patients** with this indication?	1	Yes			X		
	2	No	Rating not provided				
	3	No					X
Does PBT provide a clinically meaningful improvement in net health outcome that is **superior ONLY** when radiation dose constraints for critical organs at risk (i.e., surrounding normal tissue) cannot be met by other conformal, fractionated photon-based radiotherapy techniques[1] for patients with this indication?	1	No			X		
	2	No	Rating not provided				
	3	No					X
Is use of PBT for this indication consistent with generally accepted medical practice?	1	Yes			X		
	2	No	Rating not provided				
	3	Yes				X	

NR = not reported

2. Additional narrative rationale or comments regarding the clinical context or specific clinical pathways for this topic and/or any relevant scientific citations (including the PMID) with evidence that demonstrates health outcomes you would like to highlight.

#	Additional Comments
1	NA
2	NR

#	Additional Comments
3	Penn Medicine has worked with commercial insurers on innovative and successful proton therapy coverage initiatives for the past 10 years. These initiatives have been described in the academic and lay literature (see below).Penn Medicine specifically has established coverage policies for proton therapy with Independence Blue Cross and Horizon that have been resoundingly successful in providing access to proton therapy while still ensuring that any necessary comparative effectiveness research is conducted. These initiatives have led to important research findings (both positive and negative) that have impacted patient care nationally and have led to large funded pragmatic trials from the NCI and PCORI. Investigators at have collaborated with BCBS Association in some of these efforts. Penn Medicine also participates in Aetna's recently announced coverage with trial participation policy for NCI and PCORI randomized trials. Penn Medicine is a national leader in innovative strategies to provide access to new medical technology while ensuring the technology is safe and effective. Clinical and managed care leaders at Penn Medicine would be delighted to meet with the BCBS Association as it conducts it review. See for example: • Bekelman JE and Hahn SM. J Clin Oncol. 2014 May 20;32(15):1540-2. Doi: 10.1200/JCO.2014.55.6613. Epub 2014 Apr 21. • Reference pricing with evidence development: a way forward for proton therapy. PMID: 24752049 PMCID: PMC4026577 DOI: 10.1200/JCO.2014.55.6613 • Bekelman JE, Denicoff A, Buchsbaum J. J Clin Oncol. 2018 Aug 20;36(24):2461-2464. Doi: 10.1200/JCO.2018.77.7078. Epub 2018 Jul 9. • Randomized Trials of Proton Therapy: Why They Are at Risk, Proposed Solutions, and Implications for Evaluating Advanced Technologies to Diagnose and Treat Cancer. PMID: 29985746 PMCID: PMC6366815 DOI: 10.1200/JCO.2018.77.7078

NR = not reported

3. Is there any evidence missing from the attached draft review of evidence that demonstrates clinically meaningful improvement in net health outcome?

#	YES / NO	Citations of Missing Evidence
1	No	NA
2	NR	NR
3	No	NR

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12. Huynh M, Marcu LG, Giles E et al. Current status of proton therapy outcome for paediatric cancers of the central nervous system - Analysis of the published literature. Cancer Treat. Rev., 2018 Oct 17;70:272-288. PMID 30326423.
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Documentation for Clinical Review

Please provide the following documentation:

- (click here >>>) Radiation Oncology – Prior Authorization fax form
- (click here >>>) Radiation Oncology – Post Service fax form

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	77014	Computed tomography guidance for placement of radiation therapy fields
	77261	Therapeutic radiology treatment planning; simple (Includes planning for single treatment area included in a single port or simple parallel opposed ports with simple or no blocking)
	77262	Therapeutic radiology treatment planning; intermediate (Includes planning for three or more converging ports, two separate treatment sites, multiple blocks, or special time dose constraints)
	77263	Therapeutic radiology treatment planning; complex (Includes planning for very complex blocking, custom shielding blocks, tangential ports, special wedges or compensators, three or more separate treatment areas, rotational or special beam considerations, combination of treatment modalities)
	77280	Therapeutic radiology simulation-aided field setting; simple (includes Simulation of a single treatment site)
	77285	Therapeutic radiology simulation-aided field setting; intermediate (includes Two different treatment sites)
	77290	Therapeutic radiology simulation-aided field setting; complex (includes all of the following): • Brachytherapy • Complex blocking • Contrast material • Custom shielding blocks • Hyperthermia probe verification • Rotation • Arc or particle therapy • Simulation for 3 or more treatment sites
	77293	Respiratory motion management simulation (List separately in addition to code for primary procedure)

Type	Code	Description
	77295	3-dimensional radiotherapy plan, including dose-volume histograms
	77299	Unlisted procedure, therapeutic radiology clinical treatment planning
	77300	Basic radiation dosimetry calculation, central axis depth dose calculation, TDF, NSD, gap calculation, off axis factor, tissue inhomogeneity factors, calculation of non-ionizing radiation surface and depth dose, as required during course of treatment, only when prescribed by the treating physician (Excludes Brachytherapy [77316-77318, 77767-77772, 0394T-0395T] and Teletherapy plan [77306-77307, 77321])
	77301	Intensity modulated radiotherapy plan, including dose-volume histograms for target and critical structure partial tolerance specifications
	77321	Special teletherapy port plan, particles, hemibody, total body
	77306	Teletherapy isodose plan; simple (1 or 2 unmodified ports directed to a single area of interest), includes basic dosimetry calculation(s) (Excludes Brachytherapy [0394T-0395T], Radiation dosimetry calculation [77300], Radiation treatment delivery [77401], and Therapy performed more than one time for treatment to a specific area)
	77307	Teletherapy isodose plan; complex (multiple treatment areas, tangential ports, the use of wedges, blocking, rotational beam, or special beam considerations), includes basic dosimetry calculation(s) (Excludes Brachytherapy [0394T-0395T], Radiation dosimetry calculation [77300], Radiation treatment delivery [77401], and Therapy performed more than one time for treatment to a specific area)
	77331	Special dosimetry (e.g., TLD, microdosimetry) (specify), only when prescribed by the treating physician
	77332	Treatment devices, design and construction; simple (simple block, simple bolus) (Excludes Brachytherapy [0394T-0395T] and Radiation treatment delivery [77401])
	77333	Treatment devices, design and construction; intermediate (multiple blocks, stents, bite blocks, special bolus) (Excludes Brachytherapy [0394T-0395T] and Radiation treatment delivery [77401])
	77334	Treatment devices, design and construction; complex (irregular blocks, special shields, compensators, wedges, molds or casts) (Excludes Brachytherapy [0394T-0395T] and Radiation treatment delivery [77401])
	77336	Continuing medical physics consultation, including assessment of treatment parameters, quality assurance of dose delivery, and review of patient treatment documentation in support of the radiation oncologist, reported per week of therapy (Excludes Brachytherapy [0394T-0395T] and Radiation treatment delivery [77401])
	77370	Special medical radiation physics consultation
	77399	Unlisted procedure, medical radiation physics, dosimetry and treatment devices, and special services
	77402	Radiation treatment delivery, =>1 MeV; simple
	77407	Radiation treatment delivery, =>1 MeV; intermediate
	77412	Radiation treatment delivery, => 1 MeV; complex
	77417	Therapeutic radiology port image(s)
	77427	Radiation treatment management, 5 treatments (Excludes High dose rate electronic brachytherapy [0394T-0395T] and Radiation treatment delivery [77401])
	77470	Special treatment procedure (e.g., total body irradiation, hemibody radiation, per oral or endocavitary irradiation)

Type	Code	Description
	77499	Unlisted procedure, therapeutic radiology treatment management
	77520	Proton treatment delivery; simple, without compensation
	77522	Proton treatment delivery; simple, with compensation
	77523	Proton treatment delivery; intermediate
	77525	Proton treatment delivery; complex
HCPCS	G6001	Ultrasonic guidance for placement of radiation therapy fields
	G6002	Stereoscopic x-ray guidance for localization of target volume for the delivery of radiation therapy
	G6017	Intra-fraction localization and tracking of target or patient motion during delivery of radiation therapy (e.g., 3D positional tracking, gating, 3D surface tracking), each fraction of treatment

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
02/02/1997	New Policy Adoption Policy Adopted
06/09/1999	Policy Title Revision, criteria revised External Review
01/24/2002	Policy Revision Eligible for coverage
04/28/2008	Policy Revision Scope of coverage expanded
07/01/2011	Policy revision without position change
03/29/2013	Policy revision with position change
08/26/2013	Administrative update for clarity of prostate cancer position statement
10/28/2013	Policy revision with position change
01/30/2015	Coding update
07/31/2015	Coding update
01/01/2016	Policy title change from Charged-Particle (Proton or Helium) Radiation Therapy Policy revision without position change
09/01/2016	Policy title change from Charged-Particle (Proton or Helium Ion) Radiotherapy Policy revision without position change
09/01/2017	Policy revision without position change
02/01/2018	Coding update
12/01/2018	Policy revision without position change
12/16/2019	Policy revision without position change. Transition to BSC Custom policy. Policy ID# changed from 8.01.10 to current one.
05/01/2020	Annual review. Policy statement and guidelines updated. Coding update.
06/01/2020	Administrative update. Policy statement and guidelines updated.
05/01/2021	Annual review. No change to policy statement. Policy guidelines updated.
12/01/2021	Administrative update. No change to policy statement. Policy guidelines updated.
05/01/2022	Annual review. Policy statement updated.
03/01/2023	Annual review. Policy statement and guidelines updated.
03/01/2024	Annual review. No change to policy statement.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to

treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT (No changes)	
BEFORE	**AFTER**
Charged-Particle (Proton or Helium Ion) Radiotherapy for Neoplastic Conditions BSC8.04 **Policy Statement:** I. Charged-particle irradiation with proton or helium ion beams may be considered **medically necessary** for treatment in **any** of the following clinical situations: A. Primary therapy for melanoma of the uveal tract (iris, choroid, or ciliary body) and **both** of the following: 1. No evidence of metastasis or extrascleral extension 2. Tumors up to 24 millimeters (mm) in largest diameter and 14 mm in height B. Postoperative therapy (with or without conventional high-energy x-rays) in patients who have undergone biopsy or partial resection of chordoma or low-grade (I or II) chondrosarcoma of the basisphenoid region (e.g., skull-base chordoma or chondrosarcoma) or cervical spine. Patients eligible for this treatment have residual localized tumor without evidence of metastasis C. Pediatric central nervous system tumors II. Charged-particle irradiation with proton or helium ion beams may be considered **medically necessary** for treatment in **any** of the following clinical situations: A. Where treatment planning with conventional or advanced photon-based radiotherapy (see Policy Guidelines section) cannot meet dose-volume constraints for normal tissue radiation tolerance (see Policy Guidelines section) B. In tumors requiring reirradiation where cumulative critical structure dose would exceed normal tissue tolerance	**Charged-Particle (Proton or Helium Ion) Radiotherapy for Neoplastic Conditions BSC8.04** **Policy Statement:** I. Charged-particle irradiation with proton or helium ion beams may be considered **medically necessary** for treatment in **any** of the following clinical situations: A. Primary therapy for melanoma of the uveal tract (iris, choroid, or ciliary body) and **both** of the following: 1. No evidence of metastasis or extrascleral extension 2. Tumors up to 24 millimeters (mm) in largest diameter and 14 mm in height B. Postoperative therapy (with or without conventional high-energy x-rays) in patients who have undergone biopsy or partial resection of chordoma or low-grade (I or II) chondrosarcoma of the basisphenoid region (e.g., skull-base chordoma or chondrosarcoma) or cervical spine. Patients eligible for this treatment have residual localized tumor without evidence of metastasis C. Pediatric central nervous system tumors II. Charged-particle irradiation with proton or helium ion beams may be considered **medically necessary** for treatment in **any** of the following clinical situations: A. Where treatment planning with conventional or advanced photon-based radiotherapy (see Policy Guidelines section) cannot meet dose-volume constraints for normal tissue radiation tolerance (see Policy Guidelines section) B. In tumors requiring reirradiation where cumulative critical structure dose would exceed normal tissue tolerance

POLICY STATEMENT (No changes)	
BEFORE	**AFTER**
C. In patients with tumors who also have radiation-sensitizing genetic syndromes (including but not limited to mutations in NF1 in neurofibromatosis type 1, RB1 in retinoblastoma, TP53 in Li-Fraumeni, or WT1 in Wilms tumors] where total volume of radiation minimization is critical. Radiation therapy of the existing tumor may put these patients at higher risk for secondary malignant tumors due to the radiation exposure from treatment	C. In patients with tumors who also have radiation-sensitizing genetic syndromes (including but not limited to mutations in NF1 in neurofibromatosis type 1, RB1 in retinoblastoma, TP53 in Li-Fraumeni, or WT1 in Wilms tumors] where total volume of radiation minimization is critical. Radiation therapy of the existing tumor may put these patients at higher risk for secondary malignant tumors due to the radiation exposure from treatment
III. The following are considered **investigational**: A. Use of charged-particle irradiation with proton or helium ion beams as a Non-curative (palliative) treatment of cancer B. Other applications of charged-particle irradiation with proton or helium ion beams	III. The following are considered **investigational**: A. Use of charged-particle irradiation with proton or helium ion beams as a Non-curative (palliative) treatment of cancer B. Other applications of charged-particle irradiation with proton or helium ion beams
Note: Although charged-particle irradiation with proton or helium beams may be **medically necessary** for the treatment of clinically localized prostate cancer, Intensity Modulated Radiation Therapy (IMRT) is also an effective treatment for this diagnosis and **medically necessary**. When there are **two medically necessary** procedures for the treatment of clinically localized prostate cancer, Blue Shield will consider the relative cost of each and provide coverage for the procedure that is most cost effective. The other procedure will be denied as **not cost effective**, and therefore **not medically necessary** under the circumstances.	Note: Although charged-particle irradiation with proton or helium beams may be **medically necessary** for the treatment of clinically localized prostate cancer, Intensity Modulated Radiation Therapy (IMRT) is also an effective treatment for this diagnosis and **medically necessary**. When there are **two medically necessary** procedures for the treatment of clinically localized prostate cancer, Blue Shield will consider the relative cost of each and provide coverage for the procedure that is most cost effective. The other procedure will be denied as **not cost effective**, and therefore **not medically necessary** under the circumstances.
Image Guided Radiation Therapy (IGRT) IV. IGRT may be considered **medically necessary** as an approach to delivering radiotherapy when combined with **any** of the following treatments (see Policy Guidelines): A. Intensity-modulated radiotherapy (IMRT) B. Stereotactic body radiation therapy (SBRT) C. Proton delivery	**Image Guided Radiation Therapy (IGRT)** IV. IGRT may be considered **medically necessary** as an approach to delivering radiotherapy when combined with **any** of the following treatments (see Policy Guidelines): A. Intensity-modulated radiotherapy (IMRT) B. Stereotactic body radiation therapy (SBRT) C. Proton delivery

POLICY STATEMENT (No changes)	
BEFORE	**AFTER**
V. IGRT is considered **investigational** as an approach to delivering radiotherapy when combined with **any** of the following treatments: A. Conventional three-dimensional conformal radiation therapy (3D CRT) (see Policy Guidelines for considerations) B. Stereotactic radiosurgery (SRS) C. Electronic brachytherapy	V. IGRT is considered **investigational** as an approach to delivering radiotherapy when combined with **any** of the following treatments: A. Conventional three-dimensional conformal radiation therapy (3D CRT) (see Policy Guidelines for considerations) B. Stereotactic radiosurgery (SRS) C. Electronic brachytherapy