VHA Office of Integrated Veteran Care
Clinical Determination and Indication
Proton Beam Therapy

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I. Disclaimer

This document is currently in draft and is intended to be used as a reference for non-VA providers and not intended to replace clinical judgment when determining care pathways. These guidelines do not guarantee benefits or constitute medical advice.

II. Clinical Determinations and Indications

a. Indications for Proton Beam Radiation Therapy

Radiation therapy is a cancer treatment that uses ionizing radiation with charged particles (e.g., protons) with great precision to minimize the radiation dose to surrounding normal tissues. Controlling the particle energy allows the radiation beam to be stopped at a designed depth. As a result, proton beam therapy (PBT) may be considered when sparing of normal tissue offers a clinical benefit, which cannot be obtained using photon irradiation.

Determining both the risk of normal tissue injury and the ability to deliver a therapeutic dose to a tumor, in comparison to advanced photon therapies, has frequently demonstrated an advantage for PBT in clinical presentations listed below.

Proton beam therapy will be considered **medically necessary** for **ANY** of the following Group 1, non-pediatric indications from the American Society for Radiation Oncology (ASTRO):

- Certain malignant and benign primary central nervous system (CNS) tumors
- Advanced (e.g., T4) and/or unresectable head and neck cancers
- Cancers of the paranasal sinuses and other accessory sinuses
- Non-metastatic retroperitoneal sarcomas
- Re-irradiation cases where cumulative radiation doses to sensitive structures would exceed tolerance dose
- Hepatocellular cancer (whether treated in a hypofractionated or conventionally fractionated regimen)
- Ocular tumors, including intraocular melanomas

- Tumors that approach or are located at the base of skull, including but not limited to chordoma and chondrosarcomas
- Primary or metastatic tumors of the spine where the spinal cord tolerance may be exceeded with conventional treatment or where the spinal cord has previously been irradiated

Note: Veterans with certain genetic syndromes, the total volume of radiation exposure should be minimized.

- Such genetic syndromes include but are not limited to Von Recklinghausen (NF-1), Li-Fraumeni (p53), Cowden (PTEN), Peutz-Jeghers (STK11) and retinoblastoma (RB) patients

b. Limitations/Exclusions

Currently there are clinical trials comparing proton versus photon therapy for breast and prostate cancers, tumors of the head and neck, esophagus and lung. VHA, through its NROP office, will closely monitor these and other on-going investigations for any proven potential to improve cancer treatment outcomes for Veterans through PBT. Veterans with such cancers may be considered for enrollment in formal Institutional Review Board (IRB) approved, National Cancer Institute (NCI) and VA approved clinical trials.

For all conditions/indications not listed in section II.a. of this document, PBT is considered **not medically necessary** due to insufficient evidence of efficacy and safety.

Conditions/indications for which PBT is **not medically necessary** include, but are not limited to, the following:

- Prostate adenocarcinoma
- ASTRO Group 2 indications such as:
  - Non-T4 and other resectable head and neck cancers.
  - Non-metastatic prostate cancer
  - Breast cancer, especially for those with pectus excavatum and left sided tumors that would lead to increased cardiac dose
  - Thoracic malignancies, including non-metastatic primary lung and esophageal cancers that would lead to increased normal tissue lung dose
  - Abdominal malignancies, including non-metastatic primary pancreatic, biliary and adrenal cancers, where conventional radiation therapy might lead to increased small bowel, liver and stomach dose
  - Pelvic malignancies, including non-metastatic rectal, anal, bladder and cervical cancers

Note: Proton beam therapy for ASTRO Group 2 indications must be conducted as a part of a VA approved or Cancer Therapy Evaluation Program (CTEP) formal national multi-group clinical trial and will not be deemed appropriate for the routine treatment of Veterans diagnosed with ASTRO Group 2 presentations not enrolled in a prospective therapeutic clinical trial.

c. Description of Treatment

Proton Beam Therapy (PBT) is a cancer treatment that offers some advantages in very specialized circumstances because of particular dosimetric advantages (i.e., SOBP). As PBT continues to be studied and treatment options expand, proton beam facilities also continue to be built throughout the country.

The proton beam treatment plan is orchestrated by a multi-disciplinary team of providers including radiation oncologists, nurses, dosimetrists, physicists and radiation therapists. Patients are prepared for treatment with simulation planning to determine their position in relation to the proton beam treatment area. The radiation oncologist determines the proton beam radiation dose, while the dosimetrist determines the position and depth of the beam, and the physicist ensures the proton beam can be generated to the exact dose and depth ordered for treatment.

Typically, treatments are delivered on an outpatient basis and range from 15-30 minutes in length, 5 days a week, for 4-8 weeks depending on the specific cancer diagnosis.

Proton beam radiation therapy must be managed by a radiation oncologist, who ideally has prior proton beam training and/or experience. Proton beam therapy must be performed at an Imaging and Radiation Oncology Core (IROC) Houston credentialed facility. Facility list can be provided upon request via VHANROPADMIN@va.gov.

III. Background and Supporting Information

The following information is for reference purposes only in accordance with the medical benefits package outlined in 38 C.F.R. § 17.38 (b). Each subsection supports VA's determinations for medical necessity and alignment with generally accepted standards of medical practice.

a. Background Information

For radiation therapy, the treatment is precisely delivered through photon, proton, or electron beams for cancer treatment by delivering high-energy radiation to an exact location to maximize radiation targeting a tumor. All radiation therapy results in damage to cellular DNA.

Radiation therapy beams delivered by high-energy photons deliver the greatest amount of energy (that is, radiation dose) beneath the body surface

with a gradual reduction in dose along the beam path as it passes through the tumor and then an exit point. This means that a single radiation beam if given by x-ray photons, would give more dose than desirable to tissues superficial to the tumor and some unwanted dose beyond the tumor target. Therefore, when using x-ray photons, multiple beams from various angles are employed to mitigate additional tissue damage.

In contrast, external beam radiation therapy delivered by high-energy charged particles (e.g., protons or electrons) have limited range in body tissue. Electron beams are typically used to treat very superficial tumors close to the skin. Proton beams, depending on the energy chosen, can treat deep-seated tumors. A major advantage of proton beam therapy (PBT) treatment over standard x-ray photon radiation therapy is that protons slowly deposit their energy as they travel towards the tumor and deliver an intense dose distribution pattern called the Bragg peak. Beyond the Bragg peak, the energy rapidly decreases, minimizing the damage to surrounding tissue. In clinical practice, since real tumors have a definite geometry and volume (as opposed to being a mathematical point) we must use a series of Bragg peaks to cover the entire volume of tumor. This is called a “spread out Bragg peak” or SOBP to distinguish it from a solitary or pristine Bragg peak that would address a point volume. A clinically useful SOBP significantly increases the dose to superficial normal tissues before the tumor compared to a “pristine” Bragg peak. Thus, just as with x-ray photons, multiple beams of protons might be required to obtain a clinically suitable radiation dose distribution.

Maximizing dose to the tumor while minimizing healthy tissue damage continues to be a challenge in radiation therapy. Proton beam has held the clinical promise of allowing for higher doses of radiation to be delivered more safely, especially for ocular, skull base, and spinal tumors that require precise control of the exit dose. But the role of protons is less clear for more common tumors, like prostate, where the dosimetric advantages may be diminished and for which intensity-modulated radiation therapy (IMRT) can now safely deliver precise, optimally high radiation doses.

b. Research, Clinical Trials, and Evidence Summaries

Over eight hundred clinical studies have been published on PBT since its Food and Drug Administration (FDA) approval for cancer treatment in 1988. The first PBT treatments for cancer were delivered at Berkeley Radiation laboratory in 1954.

Suit et al. 2003, reviewed the outcomes and efficacy of proton beam radiation therapy as a strategy for improving success rates and reducing the planned treatment volume. The team researched and outlined the comparative depth of photon and proton beams, summarizing the closer approximation of the planning treatment volume to the grossly evident tumor volume/subclinical

tumor extensions indicates a clinical advantage with a smaller treatment volume. Additional clinical dose distributions were reviewed, highlighting the importance of intensity modulated proton beam radiation therapy, which achieves contouring of the proximal edge of the Spread Out Bragg Peak (SOBP).

Wu et al. 2022, performed a literature review of proton therapy for prostate cancer with an emphasis on dosimetric advantage, clinical outcomes, cost-effective strategies, and novel technological trends. Proton beam therapy research has proven it is safe, associated with a low risk of second cancer, does not affect testosterone levels and its efficacy is comparable to that of standard photon-based therapy or brachytherapy. The cost-effectiveness of PBT for prostate cancer indicates it is currently suboptimal but may improve as proton therapy centers are established over time.

In 2021, after reviewing all available medical literature, the VHA Health Services Research & Development Service's Evidence-based Synthesis Program recognized that proton therapy can be a valuable treatment option for some types of cancer, but acknowledged the lack of proven benefit, inability to account for organ motion, and significant costs associated with this modality. In the case of prostate cancer, there is currently a lack of clear evidence demonstrating the superiority of proton therapy over other forms of radiation therapy, such as intensity-modulated radiation therapy (IMRT) and stereotactic body radiation therapy (SBRT). Additionally, IMRT continues to evolve with moderately hypofractionated photon therapy yielding low rates of patient-reported late gastrointestinal (GI) and genitourinary (GU) toxicity with superior imaging and motion management strategies. VHA agrees with the ASTRO Proton Beam Therapy Model Policy that clinical evidence does not support proton therapy for Group 2 presentations. Proton beam therapy must not be used when it does not offer an advantage over photon-based therapies delivering good clinical outcomes and low toxicity. VHA, through its NROP will continue to closely monitor these and other on-going investigations for the potential to improve cancer related outcomes for our veterans through PBT.

The *Evidence Brief: Proton Beam Therapy for Treatment of Localized Prostate Cancer* published in August 2022 identified the following key findings supporting the exclusion of PBT for localized prostate cancer:

- Comparative evidence on GI and GU toxicity after treatment of localized prostate cancer with PBT or IMRT is low strength
- Risk of early GI and GU toxicity is possibly lower after treatment with PBT compared with IMRT (RRGI = 0.76, 95% CI [0.39, 1.50]; RRGU = 0.65, 95% CI [0.28, 1.34])
- In the first year after PBT or IMRT, GI toxicity risk may not differ between modalities, while risk of GU toxicity is possibly lower after

treatment with PBT compared with IMRT (RRGI = 1.08, 95% CI [0.68, 1.95]; RRGU = 0.82, 95% CI [0.57, 1.29])
- Low-strength evidence suggests that PBT and brachytherapy confer similar overall survival rates, and that GI and GU toxicity rates are similar for hypofractionation and conventional dosing
- Evidence is insufficient to determine whether second cancers are less likely after PBT compared with IMRT, or whether PBT has advantages over IMRT for the treatment of relapsed prostate cancer initially treated with radical prostatectomy
- Randomized controlled trials underway could provide important additions to the evidence base on the comparative effectiveness of PBT

c. U.S. Food & Drug Administration (FDA) Information

VA generally only approves use of medical devices that have received at least FDA clearance for 510(k) Premarket Notification. The FDA has determined these Class II devices are substantially equivalent (SE) to legally marketed predicate devices and may be marketed in the U.S.

To search for devices that have received FDA 510(k) clearance or Premarket Approval (PMA), please visit the FDA Devices database.

d. Medicare Coverage Determinations

Available Medicare coverage determinations are listed below as a resource. VA and Medicare are governed by separate laws and regulations; thus, VA coverage determinations may be different.

NCD Number	Name	Effective Date
None	N/A	N/A

LCD Number	Contractor	Original/Revision Effective Date
L36658	CGS Administrators, LLC	10/06/2022
L33937	First Coast Service Options, Inc	12/16/2019
L35075	National Government Services, Inc	11/07/2019

- NCD: National Coverage Determination
- LCD: Local Coverage Determination

IV. Definitions

Term	Definition
American Society for Radiation Oncology (ASTRO)	ASTRO is a radiation oncology society with 10,000+ members, including physicians, nurses, biologists, physicists, radiation therapists, dosimetrists and other health care professionals who specialize in treating patients with radiation therapies
Adenocarcinoma	A malignant tumor originating in glandular epithelium
Benign Tumor	An abnormal but noncancerous collection of cells
Chordoma	A malignant tumor that forms from the remains of the embryotic notochord and occurs along the spine
Dosimetrist	A medical professional certified to develop radiotherapy treatment plans, including calculating doses of radiation
Hepatocellular Cancer	The most common type of primary liver cancer and occurs most often in people with chronic liver diseases
Ionizing Radiation	Radiation consisting of particles, x-rays, or gamma rays with sufficient energy to cause ionization in the medium through which it passes
Malignant	A term used to refer to the presence of cancerous cells
Metastatic	A term used to describe the spread of malignant cells from the primary site of disease to another part of the body
Photon Irradiation	The use of high energy radiation from x-rays and gamma rays to kill cancer cells and shrink tumors
Photon Therapy	A type of radiation therapy that uses x-rays or gamma rays from a machine called a linear accelerator (linac) to kill tumor cells
Proton Therapy	A type of radiation therapy that uses streams of protons to kill tumor cells and may reduce the amount of radiation damage to surrounding healthy tissue
Protons	A subatomic particle with a positive charge. Protons along with neutrons (electrically neutral) make up all atomic nuclei except the hydrogen nucleus which consists of only one proton
Retinoblastoma	A malignant tumor of the retina; associated with a chromosomal abnormality
Retroperitoneal	Located behind the abdominal or peritoneal cavity
Sarcoma	A malignant tumor that begins in tissue, such as bone, muscle, fat, blood vessels, or other connective or supportive tissue

Term	Definition
Solid Tumor	Tumors that appear in body tissues other than blood, bone marrow, or the lymphatic system (e.g., lung, liver, or colon tumors)
Stereotactic Radiation Therapy (SRT)	A type of external radiation therapy that uses special equipment to position the patient and precisely delivery radiation to a tumor
Tumor	An abnormal mass of tissue that results from excessive cell division that is uncontrolled and progressive
Unresectable	Not amenable to completely remove by a surgical procedure

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VI. CDI History/Revision Information

- Explanation of changes to the CDI

Revision Type	Date of Revision	Update(s) Made to CDI
	MM/DD/YYYY	•
	MM/DD/YYYY	•