Proton Beam Radiation Therapy*

Medical Policy #: 08.01.05
Original Effective Date: April 2001
Reviewed: August 2022
Revised: January 2023

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This Medical Policy document describes the status of medical technology at the time the document was developed. Since that time, new technology may have emerged, or new medical literature may have been published. This Medical Policy will be reviewed regularly and be updated as scientific and medical literature becomes available; therefore, policies are subject to change without notice.

DESCRIPTION

Proton beam radiation therapy (PBRT)/proton beam therapy (PBT) is a type of external beam radiotherapy that uses charged particles. These particles have unique characteristics, including limited lateral slide, scatter, and tissue in a defined range, going for maximum dose delivery over the last few millimeters of the particles' range. The maximum is called the Bragg peak. Proton beam therapy (PBT), when applied to treating cancer, uses different proton energy with Bragg peaks at various steps, enabling dose escalation to the tumor, minimizing excess dose to normal surrounding tissue.

Proton beam radiation therapy (PBRT) has been used in the treatment of two general categories of tumors. The first category includes tumors located near vital organs, such as intracranial lesions or those along the axial skeleton e.g., uveal melanoma, chordomas and other chondrosarcomas at the base of the skull and along the axial skeleton. The second category currently under investigation involves tumors with high rate of recurrence despite maximal doses of conventional radiation therapy (e.g.. locally advanced prostate cancer). There are ongoing studies of proton beam radiation therapy

(PBRT) for other malignancies including but not limited to breast cancer, genitourinary cancers, pancreatic cancer, gynecological cancers, gastrointestinal cancers, lung cancer, and head and neck cancers. Proton beam radiation therapy is not indicated for cancers that are widely disseminated or for cancers that have hematogenous (originating in the blood or spread through the blood system) metastases.

Over the years, PBRT has been applied to treating tumors or abnormalities (AVMs) that require dose escalation to achieve a higher probability of care, requiring increased precision in dose deposition while protecting normal surrounding tissue. Proton beam radiation therapy (PBRT) has an over 40- year history in treating cancer, yet to date, there have been few studies that show superiority to conventional photon beam radiation therapy such as 3-dimensional conformal radiotherapy, intensity modulated radiotherapy (IMRT) and stereotactic techniques, which allow for improved targeting of conventional radiation therapy that also minimize the dose delivery to surrounding normal tissues or organs at risk (OARs).

Proton Beam Therapy Treatment Delivery
Proton delivery methods can be described in one of two forms: passive scattering (also known as single and double scattering) or active scanning (also known as uniform and pencil beam scanning).

With passive scattering and uniform scanning, apertures and compensators are used to shape and fine tune the depth of the proton beam. With pencil beam scanning, there is generally no need for apertures and compensators, as the dose is "painted" in layers, producing more proximal conformity of the dose distribution as well as modulation of the dose within a field, referred to as intensity modulated proton therapy or IMPT.

The basic requirement for all forms of PBRT treatment delivery is that the technology must accurately produce the calculated dose distribution described by the PBRT plan. PBRT dose distributions are sensitive to changes in target depth and shape and thus, changes in patient anatomy during treatment may require repeat planning. Precise delivery is vital for proper treatment. Therefore, imaging guided radiation therapy (IGRT) should be used to verify accurate and consistent patient and target setup for every treatment fraction.
Proton beam radiation therapy (PBRT) is an outpatient procedure that is performed over the course of several days. The treatment regimen and duration vary depending on the type of cancer or abnormality being treated. Usually, treatment is given to a patient once daily, Monday through Friday, for up to eight weeks. The radiation doses are divided over this period to achieve the total dosage. After 2 initial planning sessions, each treatment session lasts between 20 to 40 minutes. Most of this time is spent aligning the patient for the prescribed treatment plan, while the actual delivery of the proton beam takes very little time.

Additional Information
In September 2013, as part of its national "Choosing Wisely" initiative, American Society for Radiation Oncology (ASTRO) listed proton beam therapy (PBT) for prostate

cancer as one of 5 radiation oncology practices that should not be routinely used because they are not supported by evidence.

The American Society for Radiation Oncology (ASTRO) updated their Model Policy in 2017 on the use of Proton Beam Therapy (PBT): The model policy update was developed by ASTRO's Payer Relations Subcommittee and states the model policies were developed to "communicate what ASTRO believes to be correct coverage policies for radiation oncology services." It also states that the ASTRO model policies (do not serve as clinical guidelines" and are "recommendations for medical insurance coverage."

Indications and Limitations of Coverage and/or Medical Necessity
PBT is considered reasonable in instances where sparing the surrounding normal tissue cannot be adequately achieved with photon- based radiotherapy and is of added clinical benefit to the patient. Examples of such an advantage might be:

- The target volume is in close proximity to one or more critical structures and a steep dose gradient outside the target must be achieved to avoid exceeding the tolerance dose to the critical structure(s).
- A decrease in the amount of dose inhomogeneity in a large treatment volume is required to avoid an excessive dose "hotspot" within the treatment volume to lessen the risk for excessive early or late normal tissue toxicity.
- A photon based technique would increase the probability of clinically meaningful normal tissue toxicity by exceeding an integral dose based metric associated with toxicity.
- The same or an immediately adjacent area has been previously irradiated, and the dose distribution within the patient must be sculpted to avoid exceeding the cumulative tolerance dose of nearby normal tissue.

Group 1
On the basis of the above medical necessity requirements and published clinical data, disease sites that frequently support the use of PBT include the following:

- Ocular tumors, including intraocular melanomas
- Tumors that approach or are located at the base of the skull, including but not limited to:
    - Chordoma
    - 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 when at least one of four criteria noted above apply
- 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 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 critical structure dose would exceed tolerance dose)

Group 2
Note: Please refer to the member's benefit certificate language regarding clinical trials.
While PBT is not a new technology, there is a need for continued clinical evidence development and comparative effectiveness analysis for the appropriate use of PBT for various disease sites. All other indications not listed in Group 1 are suitable for Coverage with Evidence Development (CED). Radiation therapy for patients treated under CED paradigm should be covered by the insurance carrier as long as the patient is enrolled in either an IRB-approved (institution review board-approved) clinical trial or in a multi-institutional patient registry adhering to the Medicare requirements for CED. At this time, no indications are deemed inappropriate for CED and therefore Group 2 includes various systems such as, but not limited to, the following:

- Non-T4 and resectable head and neck cancers
- Thoracic malignancies, including non-metastatic primary lung and esophageal cancers, and mediastinal lymphomas
- Abdominal malignancies, including non-metastatic primary pancreatic, biliary and adrenal cancers
- Pelvic malignancies, including non-metastatic rectal, anal, bladder and cervical cancers
- Non-metastatic prostate cancer
- Breast cancer

The model policy stated the following regarding PBT treatment of prostate cancer: "In the treatment of prostate cancer, the use of PBT is evolving as the comparative efficacy evidence is still being developed. In order for an informed consensus on the role of PBT for prostate cancer to be reached, it is essential to collect further data, especially to understand how the effectiveness or proton therapy compares to other radiation therapy modalities such as IMRT and brachytherapy. There is a need for more well-designed registries and studies with sizable comparator cohorts to help accelerate data collection. Proton beam therapy for primary treatment of prostate cancer should only be performed in the context of a prospective clinical trial or registry."

Coverage under CED requirements will help expedite more permanent coverage decisions for all indications. Due to the numerous studies under way, proton coverage policies need to be reviewed on a frequent basis. As additional clinical data is published, this policy will be revised to reflect appropriate coverage.

Limitations of Coverage
PBT is not considered reasonable and medically necessary unless at least one of the criteria listed in the "Indications of Coverage" section of this policy is present.

Use of PBT is not typically supported by the following clinical scenarios:

- Where PBT does not offer advantage over photon-based therapies that otherwise deliver good clinical outcomes and low toxicity
- Spinal cord compression, superior vena cava syndromes, malignant airway obstruction, poorly controlled malignant bleeding and other scenarios of clinical urgency.
- Inability to accommodate for organ motion
- Palliative treatment in a clinical situation where normal tissue tolerance would not be exceeding in previously irradiated areas

Clinical Trials and Clinical Registry Trials

- Proton beam radiation therapy (PBRT) is considered a **non-covered benefit** when it is the experimental arm or subject of the clinical trial (refer to the member's benefit certificate language regarding clinical trials coverage).
- When proton beam radiation therapy (PBRT) is studied as part of a clinical registry trial, Wellmark BCBS coverage criteria will be applied to determine the medical necessity of the proton beam radiation therapy (PBRT) services. When proton beam radiation therapy (PBRT) is part of a clinical registry trial and Wellmark BCBS criteria are not met, the proton beam radiation therapy (PBRT) will be considered **not medically necessary**.
- Clinical registry trials are observational and lack the basic underpinning of clinical equipoise as there is inherent bias among both patients and investigators.

Summary Evidence
In 2017, the American Society for Radiation Oncology (ASTRO) updated their Model Policy on the use of Proton Beam Therapy (PBT): The model policy update was developed by ASTRO's Payer Relations Subcommittee and states the model policies were developed to "communicate what ASTRO believes to be correct coverage policies for radiation oncology services." It also states that the ASTRO model policies (do not serve as clinical guidelines" and are "recommendations for medical insurance coverage."

This medical policy addresses coverage criteria for those indications for which the role of proton beam radiation therapy (PBRT) lacks high-quality evidence comparing proton beam radiation therapy (PBRT) outcomes with photon-based (3D-conformal or intensity modulated radiation therapy [IMRT]) or stereotactic techniques based on the peer reviewed published medical literature in combination with National Comprehensive Cancer Network (NCCN) guidelines. Proton beam radiation therapy (PBRT) has not been proven to be more effective than other radiotherapy modalities for the treatment of these indications and will be considered not medically necessary.

Clinical Trials and Clinical Registry Trials

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- Clinical registry trials are observational and lack the basic underpinning of clinical equipoise as there is inherent bias among both patients and investigators.

Secondary Malignancies

A common argument by advocates for use of proton beam radiation therapy (PBRT) is the potential to reduce the risk of secondary malignancies further. A larger volume of normal tissue is exposed to low dose radiation with intensity modulated radiation therapy (IMRT), and this higher integral dose theoretically could cause a higher rate of secondary malignancies. There is a large body of literature discussing the theoretical risks and benefits of proton beam radiation therapy (PBRT) with respect to secondary malignancies, based on modeling. While some studies may show promise, whether proton beam radiation therapy (PBRT) increases or reduces the risk of secondary malignancies is very much an unanswered issue, and as a result of the available published literature, the use proton beam is considered not medically necessary solely to reduce the risk of a secondary malignancy.

Practice Guidelines and Position Statements

National Comprehensive Cancer Network (NCCN)

NCCN Guideline and Version	Principles of Radiation Therapy
Anal Carcinoma Version 1.2022	The NCCN guideline does not mention or indicate the use of proton beam radiation therapy (PBRT) as a radiation treatment modality for the treatment of anal carcinoma.
Bladder Cancer Version 2.2022	The NCCN guideline does not mention or indicate the use of proton beam radiation therapy (PBRT) as a radiation treatment modality for the treatment of bladder cancer
Bone Cancer Version 1.2023	**Principles of Radiation Therapy** **General Principles** • Patients should be strongly encouraged to have RT at the same specialized center that is providing surgical and systemic interventions

	• 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. **Chrondrosarcoma**: proton and/or photon beam RT may be useful for patients with chondrosarcomas of the skull base and axial skeleton with tumors in unfavorable location not amendable to resection. **Chordomas**: For patients with resectable conventional or chondroid chordomas, wide excision with or without RT is the primary treatment option for chordomas of the sacrum and mobile spine, whereas intralesional excision with or without RT is the treatment of choice for skull base tumors. Adjuvant RT can be considered for large extracompartmental tumors or for positive surgical margins following resection. RT is the primary treatment option for patient with unresectable chordomas, irrespective of location of the tumor. **Ewing Sarcoma**: Multiagent chemotherapy is the primary treatment and patients with disease that responds to primary treatment are treated with local control therapy (wide excision, definitive RT with chemotherapy, or amputation in selected cases) followed by adjuvant chemotherapy. Progressive disease is best managed with RT with or without surgery followed by chemotherapy or best supportive care. **Osteosarcoma**: Osteosarcoma occurs mainly in children and young adults. Wide excision is the primary treatment for patients with low-grade osteosarcoma, whereas preoperative chemotherapy followed by wide excision is the preferred option for patients with high-grade

	osteosarcoma. Chemotherapy prior to wide excision can be considered for patients with periosteal lesions. Following wide excision, postoperative chemotherapy is recommended for patients with low grade or periosteal sarcomas with pathologic findings of high-grade disease and those with high grade sarcoma. RT followed by adjuvant chemotherapy is recommended if the sarcoma remains unresectable after preoperative chemotherapy. Progressive disease is managed with surgery, palliative RT, or best supportive care.
Breast Cancer Version 4.2022	The NCCN guideline does not mention or indicate the use of proton beam radiation therapy (PBRT) as a radiation treatment modality for the treatment of breast cancer .
Central Nervous System Cancers Version 1.2022	**Intracranial and Spinal Ependymomas** **Radiation Therapy** Proton beam craniospinal irradiation may be considered when clinically appropriate and when toxicity is a concern. SRS has been used as a boost after EBRT or to treat recurrent with some success, although data on long-term results are still lacking. **Adult Medulloblastoma** **Radiation Therapy** It reasonable to consider proton beam for craniospinal irradiation where available, as it is associated with less toxicity. **Meningiomas** **Radiation Therapy** Conformal fractionated RT (e.g., 3D-CRT, IMRT, VMAT, proton therapy) may be used in patients with grade I meningiomas to spare critical structures and uninvolved tissue. **Anaplastic Glioma/Glioblastoma High Grade (Grades III/IV)** • **Simulation and Treatment Planning** ▪ Tumor volumes are best defined by using pre and postoperative MRI imaging using enhanced T1

	with/without FLAIR/T2 sequences to define GTV. To account for sub-diagnostic tumor infiltration, the GTV is expanded 1-2 cm (CTV) for grade III, and up to 2-2.5 cm (CTV) for grade IV. Although trials in glioblastoma have historically used CTV expansion in the range of 2 cm, smaller CTV expansions are supported in the literature and can be appropriate. A planning target volume (PTV) of margin of 3-5 mm is typically added to the CTV to account for daily setup errors and imaging registration. Daily image guidance is required if smaller PTV margins are used (3mm or less). When edema as assessed by T2/FLAIR is included in the initial phase of treatment, fields are usually reduced for the last phase of the treatment (boost). The boost target volume will typically encompass only the gross residual tumor and the resection cavity. A range of acceptable clinical target volume margins exists. Both strategies appear to produce similar outcomes. ▪ Consider proton therapy for patients with good long-term prognosis (grade III IDH-mutant tumors and grade III 1p19q co-deleted tumors) to better spare un-involved brain and preserve cognitive function.
Cervical Cancer Version 1.2022	The NCCN guideline does not mention or indicate the use of proton beam radiation therapy (PBRT) as a radiation treatment modality for the treatment of cervical cancer.
Colon Cancer Version 1.2022	The NCCN guideline does not mention or indicate the use of proton beam radiation

	therapy (PBRT) as a radiation treatment modality for the treatment of colon cancer
Rectal Cancer Version 1.2022	The NCCN guideline does not mention or indicate the use of proton beam radiation therapy (PBRT) as a radiation treatment modality for rectal cancer.
Esophageal and Esophagogastric Junction Cancers Version 3.2022	**General Guidelines** • All available information from pre-treatment diagnostic studies should be used to determine the target volume • In general, Siewert I and II tumors should be managed with radiation therapy guidelines applicable to esophageal and EGJ cancers. Siewert III tumor patients may receive perioperative chemotherapy or preoperative chemoradiation depending on institutional preference and are generally more appropriately managed with radiation according to guidelines according to gastric cancers. These recommendations may be modified depending on the location of the bulk of the tumor. Siewert-Stein Classification of esophageal Adenocarcinoma • Type I: Adenocarcinoma of the distal esophagus (epicenter of lesion 1-5 cm above GEJ) • Type II: Adenocarcinoma of the cardia (epicenter of lesion up to 1 cm above and 2 cm below GEJ) • Type III: Sub-cardial type adenocarcinoma (epicenter of lesion 2-5 cm below GEJ) **Simulation and Treatment Planning** • CT simulation and conformal treatment planning should be used. Intensity modulated radiation therapy (IMRT) or proton beam therapy[a] is appropriate in clinical settings where reduction in dose to organs at risk (e.g., heart, lungs) is

	required that cannot be achieved by 3-D techniques. [a]Data regarding proton beam therapy are early and evolving. Ideally, patients should be treated with proton beam therapy with a clinical trial. **Radiation Therapy** An emerging RT technique that may offer further sparing of normal tissues is proton beam therapy (PBT). Protons have a minimal exit dose beyond the target volume, which limits exposure of adjacent organs to radiation. Therefore, the use of PBT may improve the therapeutic ratio by limiting cardiopulmonary toxicities while simultaneously delivering high radiation doses to the target area. A direct comparison between IMRT, 3D-CRT and PBT in 10 patients with esophageal cancer showed that PBT significantly reduced radiation doses to various volumes of the heart and lungs. Furthermore, PBT was shown to be consistently superior to IMRT in lowering mean lung/heart radiation doses, especially when certain parameters such a beam arrangements and weighting were optimized to enhance normal tissue sparing. A phase IIb trial that randomized 145 patients to receive IMRT or PBT reported that PBT reduced the risk of severity of adverse events while maintain similar rates of 3-year PFS (50.8 % for IMRT and 51.2% for PBT) and a 3-year OS (44.5% for both). PBT is also associated with lower rates of postoperative complications, including pulmonary, cardiac, GI and wound complications, as well as reduced length of hospital stays. However, data regarding PBT are early and evolving. Therefore, the NCCN guidelines recommend that patients with esophageal cancer be treated with PBT within a clinical trial. An ongoing phase III study comparing PBT to photon therapy for esophageal cancer patients is current recruiting patients (Clinical Trial ID: NCT03801876)

	Normal Tissue Tolerance and Dose Limits Treatment planning is essential to reduce unnecessary RT doses to organs a risk (liver, kidneys, spinal cord, heart, and lungs) and to limit the volume of organs at risk receiving high RT doses. Particular effort should be made to keep RT doses to the left ventricle of the heart to a minimum.
Gastric Cancer Version 2.2022	The NCCN guideline does not mention or indicate the use of proton beam radiation therapy (PBRT) as a radiation treatment modality for the treatment of gastric cancer.
Head and Neck Cancers Version 2.2022	Proton Beam Therapy (PBT) • Achieving highly conformal dose distributions is especially important for patients whose primary tumors are periocular in location and/or invade the orbit, skull base, and/or cavernous sinuses; extend intracranially or exhibit extensive perineural invasion; and who are being treated with curative intent and/or who have long life expectancies following treatment. Nonrandomized single institution clinical reports and systematic comparisons demonstrate safety and efficacy of PBT in the above mentioned specific clinical scenarios. • Proton therapy can be considered when normal tissue constraints cannot be met by photon-based therapy. **Cancer of the Oropharynx** **Principles of Radiation Therapy** **Definitive and Concurrent Systemic Therapy/RT**: Either IMRT (preferred) or 3D conformal RT is recommended for cancers of the oropharynx in order to minimize dose to critical structures. Use of proton therapy is an area of active investigation. Proton therapy may be considered when normal tissue constraints cannot be met by photon-based therapy. **Postoperative**: RT or concurrent systemic therapy. Either IMRT (preferred) or 3D conformal is recommended for cancers of the

	oropharynx in order to minimize does to critical structures. Use of proton therapy is an area of active investigation. Proton therapy may be considered when normal tissue constraints cannot be met by photon-based therapy. **Cancer of the Nasopharynx** **Principles of Radiation Therapy** IMRT is recommended for cancers of the nasopharynx to minimize dose to critical structures. Proton therapy can be considered when normal tissue constraints cannot be met by photon-based therapy. **Cancers of the Supraglottic Larynx** **Principles of Radiation Therapy** Either IMRT or 3D conformal RT is recommended. Use of proton therapy is an area of active investigation. Proton therapy may be considered when normal tissue constraints cannot be met by photon-based therapy. **Ethmoid Sinus Tumors** **Principles of Radiation Therapy** Either IMRT or proton therapy is recommended for maxillary sinus or paranasal/ethmoid sinus tumors to minimize dose to critical structures. **Maxillary Sinus Tumors** **Principles of Radiation Therapy** Either IMRT or proton therapy is recommended for maxillary sinus or paranasal/ethmoid sinus tumors to minimize dose to critical structures. **Occult Primary** **Principles of Radiation Therapy** Either IMRT or 3D conformal RT is recommended when targeting the pharyngeal axis to minimize the dose to critical structures. Use of proton therapy is an area of active investigation. Proton therapy may be considered when normal tissue constraints cannot be met by photon-based therapy. **Salivary Glands**

	Principles of Radiation Therapy Either IMRT or 3D conformal RT is recommended. Proton therapy can be considered when normal tissue constraints cannot be met by photon-based therapy **Mucosal Melanoma (MM)** **Principles of Radiation Therapy** Either IMRT or 3D conformal RT is recommended. Proton therapy can be considered when normal tissue constraints cannot be met by photon-based therapy.
Hepatobiliary Cancers Version 2.2022	Hepatocellular Carcinoma (HCC) • Proton beam therapy (PBT) may be appropriate in specific situations. In 2014, ASTRO released model policy supporting the use of proton beam therapy (PBT) in some oncology populations. In a recent phase II study 94.8% of patients with unresectable HCC who received high dose hypofractionated PBT demonstrated > 80% local control after two years, as defined by RECIST criteria. The panel advises that PBT may be considered and appropriate in select settings for treating HCC. Several ongoing studies are continue to investigate the impact of hypofractionated PBT on HCC outcomes (e.g. NCT02395523, NCT02632864) including randomized trials comparing PBT to RFA (NCT02640924) and PBT to TACE (NCT00857805). NCCN guideline mentions the use of PBT in unresectable HCC but does not indicate or define what specific situations or select settings PBT should be utilized in unresctable HCC or the dosing. Biliary Tract Cancers Hypofractionated proton therapy may also be considered with patients with unresectable intrahepatic cholangiocarcinoma, but this treatment should only be administered at experienced centers.

Hodgkin Lymphoma Version 2.2022	• Treatment with photons, electrons, or protons may all be appropriate depending on clinical circumstances. • Advanced radiation therapy (RT) technologies such as IMRT, breath hold or respiratory gating, image-guided RT or proton therapy may offer significant and clinically relevant advantages in specific instances to spare important OARs (organs at risk) such as the heart (including coronary arteries, valves, and left ventricle). Lungs, kidneys, spinal cord, esophagus, carotid artery, bone marrow, breasts, stomach, muscle/soft tissues, and salivary glands and decrease the risk for late, normal tissue damage while still achieving the primary goal of local tumor control. • The demonstration of significant dose sparing for these OARs reflects best clinical practice. Achieving highly conformal dose distributions is especially important for patients who are being treated with curative intent or who have long life expectations following therapy. • In mediastinal Hodgkin lymphoma (HL) the use of 4D-CT for simulation and the adoption of strategies to deal with respiratory motion and minimize dose to OARs are essential, especially deep inspiration breath hold techniques, respiratory gating, and image guided RT during treatment delivery. • Randomized studies to test these concepts are unlikely to be done since these techniques are designed to decrease late effects, which take 10 + years to develop. In light of that, the modalities and techniques that are found to best reduce the doses to the OARs in a clinically meaningful way without compromising target coverage should be considered.

	Volumes OARs should be outlined for optimizing treatment plan decisions. • The treatment plan is designed using conventional 3-D conformal, proton therapy, or IMRT techniques using clinical treatment planning considerations of coverage and dose reductions for OAR. **Principles of Radiation Therapy** RT can be delivered with photons, electrons, or protons, depending upon clinical circumstances. Although advanced RT techniques emphasize tightly conformal doses and steep gradients adjacent to normal tissues, the "low dose bath" to normal structures such as the breasts must be considered in choosing the final radiation therapy (RT) techniques. Therefore, target definition, delineation and treatment delivery verification require careful monitoring to avoid the risk of tumor geographic miss and subsequent decrease in tumor control. Initial diagnostic imaging with contrast enhanced CT, MRI, PET, ultrasound and other imaging modalities facilitate target definition. Preliminary results from single institution studies have shown that significant dose reduction to organs at risk (OARs; e.g. lungs, heart, breasts, kidneys, spinal cord, esophagus, carotid artery, bone marrow, stomach, muscle, soft tissue, salivary glands) can be achieved with advanced RT planning and delivery techniques such as four dimensional CT (4D-CT) simulation, intensity modulated RT (IMRT), image guided RT, respiratory gating, or deep inspiration breath hold. These techniques offer significant and clinically relevant advantages in specific instances to spare OARs and decrease the risk for normal tissue damage and late effects without compromising the primary goal of local tumor control. For optimal mediastinal treatment planning, organs or tissues to be contoured should include the lungs, heart, coronary

	arteries (including the left main, circumflex, left anterior descending and right coronary arteries with the priority placed on sparing the proximal over distal portions of the arteries) and left ventricle. Randomized prospective studies to test these concepts are unlikely to be done since these techniques are designed to decrease late effects, which usually develop ≥ 10 years after completion of treatment. Therefore, the guidelines recommend the RT delivery techniques that are found to best reduce the doses to the OARs in a clinically meaningful manner without compromising target coverage should be considered in these patients, who are likely to enjoy long life expectancies following treatment. Involved- site RT (ISRT) and involved -node RT (INRT) are being used as alternatives to involved -field RT (IFRT) in an effort to restrict the size of the RT fields and to further minimize the radiation exposure to adjacent uninvolved organs and the potential long-term toxicities associated with radiation exposures. ISRT targets the originally involved nodal sites and possible extranodal extensions which generally defines a smaller field than the classical IFRT. ISRT targets the initially involved nodal and extranodal sites as defined by the pre-treatment evaluation (physical examination, CT and PET imaging). However, it is intended to spare the adjacent uninvolved organs (such as lungs, bone, muscle, or kidney) when lymphadenopathy regresses following chemotherapy. Treatment planning for ISRT requires the use of CT-based simulation. The incorporation of additional imaging techniques such as PET and MRI often enhances the treatment planning. The optimized treatment plan for ISRT is designed using conventional 3-D conformal RT, proton therapy, or IMRT techniques using clinical treatment planning

	considerations of coverage and dose reductions for OARs.
Kidney Cancer Version 2.2023	The NCCN guideline does not mention or indicate the use of proton beam radiation therapy (PBRT) as a radiation treatment modality or the treatment of kidney cancer.
Malignant Pleural Mesothelioma Version 1.2022	• Use of conformal radiation technology intensity modulated radiation therapy (IMRT) is the preferred choice based on comprehensive consideration of target coverage and clinically relevant normal tissue tolerance. • CT simulation guided planning using either IMRT or conventional photon/electron RT is acceptable. IMRT is a promising treatment technique that allows for more conformal high dose RT and improved coverage to hemithorax. 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. Special attention should be paid to minimize radiation to the contralateral lung, as the risk of fatal pneumonitis with IMRT is excessively high when strict limits are not applied. NCCN guideline does not indicate or define what specific situations or select settings proton beam radiation therapy (PBRT) should be utilized or the dosing.
Melanoma Cutaneous Version 3.2022	The NCCN guideline does not mention or indicate the use of proton beam radiation therapy (PBRT) as a treatment modality for cutaneous melanoma.
Melanoma Uveal Version 2.2022	**Principles of Radiation Therapy** **Particle Beam Therapy** **Treatment Information**

	• Particle beam therapy is a common form of definitive radiotherapy for the primary tumor. A prospective trial found no difference in cause-specific survival among patients with tumors ≤ 15 mm in maximum basal diameter and ≤ 11 mm in apical height randomized to plaque brachytherapy or particle beam therapy • Particle beam therapy is appropriate as upfront therapy after initial diagnosis, after margin positive enucleation or for intraocular or orbital recurrence • Particle beam therapy should be performed by an experienced multidisciplinary team including an ophthalmic oncologist, radiation oncologist, and particle beam physicist • Tumor localization for particle beam therapy may be performed using indirect ophthalmoscopy, transillumination and/or ultrasound (intraoperative and/or preoperative) MRI and/or CT • Treatment Dosing Information: For intraocular tumors ▪ Using protons 50-70 cobalt Gray equivalent (CGyE) in 4-5 fractions should be prescribed to encompass the planning target volume surrounding the tumor ▪ Using carbon ions 60-85 CGyE in 5 fractions should be prescribed to encompass the planning target volume surrounding the tumor ▪ Volumetric planning in 3 dimensions with or without CT and/or MRI is encouraged to maximize radiation delivery to tumor and minimize radiation delivery to organs and tissues at risk of injury from radiation Discussion section is remains under development.

Neuroendocrine and Adrenal Tumors Version 1.2022	The NCCN guideline does not mention or indicate the use of proton beam radiation therapy (PBRT) as a radiation treatment modality for the treatment of neuroendocrine and adrenal tumors.
B-Cell Lymphomas Version 5.2022 (Also known has non-Hodgkin Lymphoma)	• Treatment with photons, electrons or protons may all be appropriate, depending on clinical scenario • Advanced radiation therapy technologies such as intensity modulated radiation therapy (IMRT)/VMAT, proton therapy, breath hold, or respiratory gating and/or image guided therapy may offer significant and clinically relevant advantages in specific instances to spare important organs at risk such as the heart (including coronary arteries and valves), 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. • Reducing dose to normal tissues reduces the risk of late complications. Achieving highly conformal dose distribution is especially important for patients who are being treated with curative intent or who have long life expectancies following therapy. For mediastinal and abdominal lymphoma, respiratory motion management such as gating or breath hold techniques may be advantageous. Breath-hold techniques have been shown to decrease incidental dose to the heart and lungs in many disease presentations. Similarly, for abdominal lymphomas, reduction in radiation exposures to liver and kidneys may be achieved by motion management techniques. • Randomized studies to test these concepts are unlikely to be done since

	these techniques are designed to decrease late effects, which take 10+ years to evolve. In light of that, the modalities and techniques that are found to best reduce the doses to the organs at risk (OAR) in a clinically meaningful way without compromising target coverage should be considered. Volumes Involved Site Radiation Therapy (ISRT) for Nodal Disease • ISRT is recommended as the appropriate field for NHL. Planning for ISRT requires modern CT based simulation and planning capabilities. Incorporating other modern imaging like PET and MRI often enhances treatment volume determination • ISRT targeting the site of the originally involved lymph nodes. The volume encompasses the original suspicious volume prior to chemotherapy or surgery. Yet, it spares adjacent uninvolved organs (like lungs, bone, muscle, or kidney) when lymphadenopathy regresses following chemotherapy. • The OAR (organs at risk) should be outlined by optimizing treatment plan decisions • The treatment plan is designed using conventional 3D conformal, or IMRT/VMAT, or proton therapy techniques using clinical treatment planning considerations of target coverage and dose reductions for OAR. ISRT for Exrtranodal Disease • Similar principles as for ISRT nodal sites above • For most organs and particularly for indolent disease, the whole organ comprises the CT (e.g. stomach, salivary gland, thyroid). For other

	organs, including orbit, lung, bone, localized skin and in some cases when RT is consolidation after chemotherapy partial organ RT may be appropriate • For most NHL subtypes no radiation is required for uninvolved lymph nodes **Principles of Radiation Therapy** Radiation therapy (RT) can be delivered with photons, electrons or protons depending upon clinical circumstances. Advanced RT techniques emphasize tightly conformal doses and steep gradients next to normal tissues. Therefore, target definition and delineation and treatment delivery verification require careful monitoring to avoid the risk of missing geographic location of the tumor and subsequent decrease in tumor control. Image guidance may be required to facilitate target definition. Preliminary results from single institution studies have shown that significant dose reduction to organs at risk (OAR; e.g. lungs, heart, breasts, kidneys, spinal cord, esophagus, carotid artery, bone marrow, stomach, muscle, soft tissue and salivary glands) can be achieved with advanced RT planning and delivery techniques such as 4D-CT simulation, intensity modulated RT (IMRT), image guided RT, respiratory gating or deep inspiration breath hold. These techniques offer significant and clinically relevant advantages in specific instances to spare OAR and reduce the risk of late complications from normal tissue damage. This is especially important for patients being treated with curative intent or how have long life expectancies following therapy. In mediastinal lymphoma the use of 4D-CT simulation and the adoption of strategies to deal with respiratory motion such as inspiration breath hold techniques, and image guided RT during treatment delivery is also important. Randomized prospective studies to test these concepts are unlikely to be done since these

	techniques are designed to decrease late effects, which usually develop ≥ 10 years after completion of treatment. Therefore, the guidelines recommend that RT delivery techniques that are found to best reduce the doses to the OAR in a clinically meaningful manner without compromising target coverage should be considered. Involved-site RT (ISRT) is recommended as the appropriate field for NHL as it limits the radiation exposure to adjacent uninvolved organs such as lungs, bone, muscle or kidney) when lymphadenopathy regresses following chemotherapy, thus minimizing the potential long term complications. ISRT targets the initially involved nodal and extra-nodal sites detectable at presentation. Larger RT fields should be considered for limited stage indolent NHL often treated with RT alone. Treatment planning for ISRT requires the use of CT based simulation. The incorporation of additional imaging techniques such as PET and MRI often enhances the treatment planning. The OAR should be outlined for optimizing treatment plan decisions. The treatment plan is designed using conventional, 3D conformal, or IMRT techniques using clinical treatment planning considerations of coverage and dose reduction for OAR. In the case of extranodal disease, particularly for indolent lymphoma, in most cases, the whole organ comprises the CTV (e.g. stomach, salivary gland and thyroid). For other organs, including orbit, breast, lung, bone, localized skin, and in some cases when RT is consolidation after chemotherapy, partial organ RT may be appropriate. No radiation is required for uninvolved lymph nodes for most NHL subtypes.
Pediatric Aggressive Mature B-Cell Lymphomas Version 1.2022	Pediatric Burkitt lymphoma and Pediatric diffuse large lymphoma

	Radiation therapy rarely has a role in pediatric aggressive mature B-cell lymphomas due to the rapid lysis of tumor to chemotherapy and the avoidance of long-term side effects in children.
Pediatric Central Nervous System Cancers Version 1.2023	**Principles of Radiation Therapy Management** **Pediatric Diffuse High-Grade Glioma (except diffuse midline glioma and diffuse intrinsic pontine glioma)** • Proton therapy may be considered for patients with better prognoses (e.g., IDH1-mutated tumors, 1p/19q-codeleted, younger age).
Pediatric Hodgkin Lymphoma Version 1.2022	**Principles of Radiation Therapy** **General Principles** • Treatment with photons, electrons, or protons may all be appropriate, depending on the clinical circumstances. • In specific instances, advanced RT technologies may be used to spare important organs at risk (OARs) and decrease the risk for late normal tissue damage while still achieving the primary goal of local tumor control. ▪ Advanced technologies include intensity modulated RT (IMRT)/volumetric modulated arc therapy (VMAT), breath hold or respiratory gating and/or image-guided RT (IGRT), or proton therapy may offer significant and clinically relevant advantages. ▪ OARS: heart (including coronary arteries, valves, and left ventricle), lungs, kidneys, spinal cord, esophagus, carotid arteries, bone marrow, breasts, stomach, muscle/soft tissues, and salivary glands.
Primary Cutaneous B-Cell Lymphomas Version 2.2022	**Principles of Radiation Therapy**

	The general intent of RT is to treat the evident skin disease with adequate margin both circumferentially and in depth. **Target Volumes** • Involved-site radiation therapy (ISRT) for cutaneous lesions ▪ ISRT is recommended as the appropriate field for treating primary cutaneous lymphomas • Involved-site radiation therapy (ISRT) for nodal disease ▪ See Principals of Radiational Therapy for T-Cell lymphomas (Target Volumes: ISRT for nodal disease) ▪ See Principals of Radiation Therapy for B-Cell lymphomas (Target Volumes: ISRT for nodal disease) PBRT may be appropriate depending on clinical circumstances for ISRT and nodal disease
T-Cell Lymphomas Version 2.2022	• Advanced radiation therapy technologies such as IMRT, breath hold, or respiratory gating, image guided RT (IGRT), or proton therapy may offer significant and clinically relevant advantages in specific instances to spare important organs at risk such as the heart (including coronary arteries and valves), 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. Achieving highly conformal dose distributions is especially important for patients who are being treated with curative intent or who have long life expectancies following therapy

	• The demonstration of significant dose sparing for these organs at risk reflects best clinical practice • In mediastinal lymphoma the use of 4D-CT for simulation and the adoption of strategies to deal with respiratory motion such as inspiration breath hold techniques, and image guided RT during treatment delivery is also important • Randomized studies to test these concepts are unlikely to be done since these techniques are designed to decrease late effects, which take 10+ years to evolve. In light of that, the modalities and techniques that are found to best reduce the doses to the organs at risk (OARs) in a clinically meaningful way without compromising target coverage should be considered. Involved site Radiation Therapy (ISRT) for Nodal Disease • ISRT is recommended as the appropriate field for NHL. Planning for ISRT requires modern CT based simulation and planning capabilities. • ISRT targets the site of the originally involved lymph node(s). The volume encompasses the original suspicious volume prior to chemotherapy or surgery. Yet, it spares adjacent uninvolved organs (like lungs, bone, muscle, or kidney) when lymphadenopathy regresses following chemotherapy. • Possible movement of the target by respiration is determined by 4D-CT or fluoroscopy (internal target volume ITV) should also influence the final CTV. • The OAR should be outlined for optimizing treatment plan decisions. • The treatment plan is designed using conventional, 3-D conformal, or IMRT techniques using clinical treatment

	planning considerations of coverage and dose reductions for OAR. ISRT for Extranodal Disease (excluding NK/T-cell lymphoma) • **ISRT for extranodal disease (excluding NK/T-cell lymphoma)** ▪ Similar principles for ISRT nodal sites above ▪ For most organs and particularly for indolent disease, the whole organ comprises the CT (e.g. stomach, salivary gland, thyroid). For other organs, including orbit, lung, bone, localized skin and in some cases when RT is consolidation after chemotherapy partial organ RT may be appropriate ▪ Prophylactic irradiation is not required for uninvolved lymph nodes • **ISRT for extranodal NK/T-Cell Lymphoma** ▪ For optimal treatment planning, both contrast enhanced CT and contrast enhanced MRI are essential. A PET/CT scan is necessary for defining the presence of nodal disease ▪ The OARs should be outlined for optimizing treatment plan decisions ▪ The treatment plan is designed using conventional 3-D conformal, or IMRT techniques using clinical treatment planning considerations of coverage and dose reductions for OARs **Treatment Modalities** **ISRT for Extranodal NK/T -Cell Lymphoma**

	• Treatment with photons, electrons or protons may all be appropriate, depending on clinical circumstances **Principles of Radiation Therapy** Radiation therapy (RT) can be delivered with photons, electrons or protons depending on clinical circumstances. Advanced RT techniques emphasize tightly conformal doses and steep gradients next to normal tissues. Therefore, target definition and delineation and treatment delivery verification require careful monitoring to avoid the risk of missing geographic location of the tumor and subsequent decrease in tumor control. Image guidance may be required to facility target definition. Significant dose reduction to organs at risk (OAR; e.g. lungs, heart, breasts, kidneys, spinal cord, esophagus, carotid artery, bone marrow, stomach, muscle, soft tissue and salivary glands) can be achieved with advanced RT planning and delivery techniques such as 4D-CT simulation, intensity modulated RT (IMRT), image guided RT (IGRT), respiratory gating, or deep inspiration breath hold. These techniques offer significant and clinically relevant advantages in specific instances to spare OAR and decrease the risk for normal tissue damage and late effects without compromising the primary goal of local tumor control. Randomized prospective studies to test these concepts are unlikely to be done since these techniques are designed to decrease late effects, which usually develop $\geq$ 10 years after completion of treatment. Therefore, the guidelines recommend that RT delivery techniques that are found to best reduce the doses to the OAR in a clinically meaningful manner without compromising target coverage should be considered. Involved site RT (ISRT) is intended to limit radiation exposure to adjacent uninvolved

	organs (such as lungs, bone, muscle or kidney) when lymphadenopathy regresses following chemotherapy, thus minimizing the potential long- term complications. Extended field RT (EFRT) and involved field RT (IFRT) techniques have now been replaced by ISRT in an effort to restrict the size of the RT fields to smaller volumes. ISRT targets the initially involved nodal and extra-nodal sites detectable at presentation. Larger RT fields should be considered for limited stage indolent NHL often treated with RT alone. Treatment planning for ISRT requires the use of CT- based simulation. The incorporation of additional imaging techniques such as PET and MRI often enhances the treatment planning. The OAR should be outlined for optimizing treatment plan decisions. The treatment plan is designed using conventional, 3D conformal, or IMRT techniques using clinical treatment planning considerations of coverage and dose reduction for OAR. In the case of extranodal disease, (e.g. stomach, salivary gland and thyroid) comprises the CVT in most cases. For other organs, including orbit, breast, lung, bone, localized skin, and in some cases when RT is consolidation after chemotherapy, partial organ RT may be appropriate. No radiation is required for uninvolved lymph nodes for most NHL subtypes.
Basal Cell Skin Cancer Version 2.2022	The NCCN guideline does not mention or indicate the use of proton beam radiation therapy (PBRT) as a radiation treatment modality for the treatment of basal cell skin cancer.
Dermatofibrosarcoma Protuberans Version 2.2022	The NCCN guideline does not mention or indicate the use of proton beam radiation therapy (PBRT) as a radiation treatment modality for the treatment of Dermatofibrosarcoma Protuberans
Merkel Cell Carcinoma Version 2.2022	The NCCN guideline does not mention or indicate the use of proton beam radiation

	therapy (PBRT) as a radiation treatment modality for the treatment of Merkel cell carcinoma.
Squamous Cell Skin Cancer Version 2.2022	The NCCN guideline does not mention or indicate the use of proton beam radiation therapy (PBRT) as a radiation treatment modality for the treatment of squamous cell skin cancer.
Non-Small Cell Lung Cancer Version 3.2022	**General Principles** • Determination of the appropriateness of radiation therapy (RT) should be made by a board -certified radiation oncologists who perform lung cancer RT as a prominent part of their practice • RT has a potential role in all stages of NSCLC, as either definitive or palliative therapy. Radiation oncology input as part of a multidisciplinary evaluation or discussion should be provided for all patients with stage IV disease that may benefit from local therapy • Critical goals of modern RT are to maximum tumor control and to minimize treatment toxicity. A minimum technologic standard is CT planned 3D-CRT • More advanced technologies are appropriate when needed to delivery curative RT safely. These technologies include (but are not limited to) 4D-CT and/or PET/CT simulation, IMRT/VMAT, IGRT, motion management, and proton therapy (https://www.astro.org/Daily-Practice/Reimbursement/Model-Policies/Model-Policies). Nonrandomized comparisons of using advanced technologies demonstrate reduced toxicity and improved survival versus older techniques. • Centers using advanced technologies should implement and document modality specific quality assurance measures. The ideal external

	credentialing of both treatment planning and delivery such as required for participation in RTOG clinical trials employing advance technologies. Useful reference include the ACR practice parameters and technical standards. **Radiation Therapy Simulation, Planning and Delivery** • IGRT including (but not limited to) orthogonal pair planar imaging and/or volumetric imaging (such as CBCT or CT on rails) is recommended when using SABR, 3D-CRT/IMRT, and proton therapy with steep dose gradients around the target, when OARs are in close proximity to high dose regions and when using complex motion management techniques. **Target Volumes, Prescription Doses and Normal Tissue Dose Constraints** • Because risk of normal organ toxicity increases with dose, doses to normal organs should be kept as low as reasonably achievable rather than simply meeting nominal constraints. This is generally facilitated by more advanced techniques to achieve better dose conformity. **Palliative RT for Advanced/Metastatic NSCLC** The dose and fractionation of palliative RT should be individualized based on goals of care, symptoms, performance status, and logistical considerations. Shorter courses of RT are preferred for patients with poor performance status and/or shorter life expectancy because they provider similar pain relive as longer courses, although there is a higher potential need for retreatment. For palliation of thoracic symptoms higher dose/longer course thoracic RT is associated with moderately improved

	survival and symptoms, particularly in patients with good performance status. When higher doses (>30 Gy) are warranted, technologies to reduce normal tissue irradiation (at least 3D-CRT and including IMRT or proton therapy as appropriate) may be used. For patients with advanced lung cancer (i.e. stage IV) with extensive metastases, systemic therapy is recommended; palliative RT can be used for symptom relief and potentially for prophylaxis at primary distant sites (such as pain. Bleeding or obstruction). Shorter courses of palliative RT are preferred for patients with symptomatic chest disease who have poor PS and/or shorter life expectancy (e.g. 17 Gy in 8.5 Gy fractions), because they provide similar pain relief as longer courses, although there is a higher potential need for retreatment. Higher doses and longer course thoracic RT (e.g. $\geq$ 30 Gy in 10 fractions) are associated with modestly improved survival and symptoms, especially in patients with good PS. When higher doses (>30 Gy) are warranted, technologies to reduce normal tissue irradiation may be used (at least 3D-CRT and including IMRT or proton therapy as appropriate)
Occult Primary (Cancer of Unknown Primary [CUP]) Version 1.2023	The NCCN guideline does not mention or indicate the use of proton beam radiation therapy (PBRT) as a radiation treatment modality for the treatment of occult primary (cancer of unknown primary [CUP]). **Note:** See Occult Primary under Head and Neck
Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer Version 4.2022	The NCCN guideline does not mention or indicate the use of proton beam radiation therapy (PBRT) as a radiation treatment modality for the treatment of ovarian cancer including fallopian tube cancer and primary peritoneal cancer.
Pancreatic Adenocarcinoma Version 1.2022	The NCCN guideline does not mention or indicate the use of proton beam radiation therapy (PBRT) as a radiation treatment

	modality for the treatment of pancreatic adenocarcinoma.
Penile Cancer Version 2.2022	The NCCN guideline does not mention or indicate the use of proton beam radiation therapy (PBRT) as a radiation treatment modality for the treatment of penile cancer.
Prostate Cancer Version 4.2022	**Principles of Radiation Therapy** **Definitive Radiation Therapy General Principles** • Highly conformal RT techniques should be used to treat localized prostate cancer. • Photon or proton EBRT are both effective at achieving highly conformal radiotherapy with acceptable and similar biochemical control and long-term side effect profiles. • Brachytherapy boost when added to EBRT plus ADT in men with NCCN intermediate and high/very high- risk prostate cancer, has demonstrated improved biochemical control over EBRT plus ADT alone in randomized trials but with higher toxicity. • SBRT is acceptable in practices with appropriate technology, physics and clinical expertise. **Proton Therapy** Proton beam RT has been used to treat patients with cancer since the 1950s. Proponents of proton therapy argue that this form of RT could have advantages over x-ray (photon) based radiation in certain clinical circumstances. Proton therapy and x-ray- based therapies like IMRT can deliver highly conformal doses to the prostate. Proton-based therapies will delivery less radiation dose to some of the surrounding normal tissues like muscle, bone, vessels and fat not immediately adjacent to the prostate. These tissues do not routinely contribute to the morbidity of prostate radiation and are relatively resilient to radiation injury, therefore, the benefit of decreased dose to these types of

	normal, non-critical tissues has not been apparent. The critical normal structures adjacent to the prostate that can create prostate cancer treatment morbidity include the bladder, rectum, neurovascular bundles and occasionally small bowel. The weight of the current evidence about prostate cancer treatment morbidity supports the notion that the volume of the rectum and bladder that receives radiobiologically high doses of radiation near the prescription radiation dose accounts for the likelihood of long term treatment morbidity, as opposed to higher volume, lower dose exposures. Numerous dosimetric studies have been performed trying to compare x-ray based IMRT plans to proton therapy plans to illustrate how one or the other type of treatment can be used to spare the bladder or rectum from higher dose parts of the exposure. These studies suffer from biases and talents of the investigators who plan and create computer models of dose deposition for one therapy or the other. Although dosimetric studies in-silico can suggest that the right treatment planning can make an IMRT plan beat a proton therapy plan and vice-versa, they do not accurately predict clinically meaningful endpoints. Comparative effectiveness studies have been published in an attempt to compare toxicity and oncologic outcomes between proton and photon therapies. Two comparisons between men treated with proton therapy or EBRT report similar toxicity rates. The largest retrospective comparative effectiveness analysis to date comparing IMRT to proton therapy was performed using SEER-Medicare claims data for the following long-term endpoints: gastrointestinal morbidity, urinary incontinence, non-incontinence urinary morbidity, sexual dysfunction, and hip fractures. With follow-up as mature as 80 months and using both propensity scoring and scoring and instrumental variable analysis, the authors concluded that

	men receiving IMRT therapy had statistically significantly lower gastrointestinal morbidity than patients receiving proton therapy, whereas rates of urinary incontinence, non-incontinence urine morbidity, sexual dysfunction, hip fractures and additional cancer therapies were statistically indistinguishable between the cohorts. However, firm conclusions regarding differences in toxicity or effectiveness of proton and photon therapy cannot be drawn because of the limitations inherent in retrospective/observational studies. The costs associated with proton beam facility construction and proton beam treatment are high compared to the expense of building and using the more common photon linear accelerator- based practice. The American Society of Radiation Oncology (ASTRO) evaluated proton therapy and created a model policy to support the society's position on payment coverage for proton beam therapy in 2014. This model policy was updated in 2017 and recommends coverage of proton therapy for the treatment of non-metastatic prostate cancer if the patient is enrolled in either an institutional review board (IRB) approved study or a multi-institutional registry that adheres to Medicare requirements for Coverage with Evidence Development (CED). The policy states "In the treatment of prostate cancer, the use of proton beam therapy is evolving as the comparative efficacy is still being developed. In order for an informed consensus on the role of proton beam therapy for prostate cancer to be reached, it is essential to collect further data, especially to understand how the effectiveness of proton therapy compares to other RT modalities such as IMRT and brachytherapy. There is a need for more well -designed registries and studies with sizeable comparator cohorts to help accelerate data collection. Proton beam therapy for primary treatment of prostate cancer should only be performed within the context of a prospective clinical trial or registry."

	An ongoing prospective randomized trial is accruing patients to compare prostate proton therapy and prostate IMRT. The NCCN Panel believes no clear evidence supports a benefit or decrement to proton therapy over IMRT for either treatment efficacy or long- term toxicity. Conventionally fractionated prostate cancer proton therapy can be considered a reasonable alternative to x-ray- based regimens at clinics with appropriate technology, physics and clinical expertise.
Small Bowel Adenocarcinoma Version 1.2022	The NCCN guideline does not mention or indicate the use of proton beam radiation therapy (PBRT) as a radiation treatment modality for the treatment of small bowel adenocarcinoma.
Small Cell Lung Cancer Version 1.2023	The NCCN guideline does not mention or indicate the use of proton beam radiation therapy (PBRT) as a radiation treatment modality for the treatment of small cell lung cancer.
Soft Tissue Sarcoma Version 2.2022	**Overview** Sarcomas constitute a heterogenous group of rare solid tumors of mesenchymal cell origin with distinct clinical and pathologic features; they are usually divided into two broad categories. • Sarcomas of soft tissues (including fat, muscle, nerve and nerve sheath, blood vessels, and other connective tissues); and • Sarcomas of bone Sarcomas collectively account for approximately 1% of all adult malignancies and 15% of pediatric malignancies. **Radiation Therapy** RT can be administered either as primary, preoperative or postoperative treatment. Total RT doses are always determined based on the tissue tolerance. Newer RT techniques such as brachytherapy, intraoperative RT (IORT) and intensity modulated RT (IMRT) have led to the

	improvement of treatment outcomes in patients with STS. **Soft Tissue Sarcomas of the Extremities, Superficial Trunk or Head and Neck** **Radiation Therapy** Data from randomized studies and retrospective analyses support the use of preoperative and postoperative EBRT in appropriately selected patients. Brachytherapy (alone or in combination with EBRT) and IMRT have also been evaluated as an adjunct to surgery. **Panel Recommendations** When EBRT is used, sophisticated treatment planning with IMRT, tomotherapy and/or proton therapy can be used to improve therapeutic effect. RT is not a substitute for definitive surgical resection with negative margins, and re-resection to negative margins is preferable. **Retroperitoneal/Intra-abdominal Soft Tissue Sarcoma** **Radiation Therapy** RT can be administered either as preoperative treatment for patients with resectable disease or as primary treatment for those with unresctable disease. The panel discourages postoperative RT with the exception of highly selected cases of if LR would cause undue morbidity. The panel emphasizes that RT is not a substitute for definitive surgical resection with oncologically appropriate margins and re-resection may be necessary. If re-resection is not feasible, postoperative RT may be considered in highly selected patients who have not received preoperative RT, to attempt to control microscopic residual disease; however, this approach has not been validated in randomized trials. Newer RT techniques such as IMRT and 3D conformal RT using protons or photons may allow tumor target coverage and acceptable

	clinical outcomes with normal tissue dose constraints to adjacent organs at risk. When EBRT is used, sophisticated treatment planning with IMRT, tomotherapy, and/or proton therapy can be used to improve therapeutic effect. However, the safety and efficacy of adjuvant RT techniques have yet to be evaluated in multicenter randomized controlled studies.
Testicular Cancer Version 2.2022	The NCCN guideline does not mention or indicate the use of proton beam radiation therapy (PBRT) as a radiation treatment modality for the treatment of testicular cancer.
Thymomas and Thymic Carcinomas Version 2.2022	**Principles of Radiation Therapy** **General Principles** • Recommendations regarding RT should be made by a board-certified radiation oncologist with experience in managing thymomas and thymic carcinomas • Definitive RT should be given for patients with unresectable disease (if disease progresses on induction chemotherapy), incompletely resected invasive thymoma or thymic carcinoma, or as adjuvant therapy after chemotherapy and surgery for patients with locally advanced disease. • Radiation oncologists need to communicate with the surgeon to review the operative findings and to help determine the target volume at risk. They also need to communicate with the pathologist regarding the detailed pathology on histology, disease extent such as extracapsular extension, and surgical margins. • The review of preoperative imaging and co-registration of preoperative imaging into the planning system are helpful in defining treatment volumes. **Radiation Techniques** • CT based planning is highly recommended. • RT should be given by 3-D conformal technique to reduce surrounding normal

	tissue damage (e.g. heart, lungs, esophagus, spinal cord). Intensity modulated RT (IMRT) may further improve the dose distribution and decrease the dose to the normal tissue as indicated. If IMRT is applied, the ASTRO/ACR IMRT guideline should be strictly followed • In addition to following the normal tissue constraints recommendations using the Principles of Radiation Therapy in the NCCN guidelines for Non-Small Cell Lung cancer, more conservative limits are recommended to minimize the dose volumes to all the normal structures. Since these patients are younger and mostly long term survivors, the mean total dose to the heart should be as low as reasonably achievable to potentially maximize survival. • Proton beam therapy (PBT) has been shown to improve the dosimetry compared to IMRT allowing better sparing of the normal organ (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. **Thymic Masses** **Treatment** The optimal plan of care for patients with thymic malignancies should be developed before treatment after evaluation by radiation oncologists, thoracic surgeons, medical oncologists, and diagnostic imaging specialists. It is critical to determine whether the mass can be surgically resected; a board certified thoracic surgeon with primary focus on thoracic oncology should make this decision. Total thymectomy and complete surgical excision of

	the tumor are recommended whenever possible for resectable tumors. Similar to thymomas patients with completely resected thymic carcinomas have longer survival than those who are either incompletely resected or unresectable. Patients who have R0 resection have a 5 year survival of about 60%. Thus management depends on the extent of resection. Patients with thymic. Patients with thymic carcinoma have a higher risks of recurrent disease, therefore, postoperative radiation is recommended to maximize local control. After resection of thymic carcinomas, postoperative management includes RT with or without chemotherapy, depending on the completeness of resection. For unresectable or metastatic thymic carcinomas, chemotherapy with or without RT is recommended. **Thymomas** Although thymomas can be locally invasive (e.g. pleura, lung) they uncommonly spread to regional lymph nodes or extrathoracic sites. Surgery (i.e. total thymectomy and complete excision of tumor) is recommended for all resectable thymomas for patients who can tolerate surgery. Adjuvant therapy is not recommended for completely resected (R0) stage I thymomas. For incompletely resected thymomas, postoperative RT is recommended. CT based treatment planning is highly recommended before RT. RT should be given by the 3D conformal technique to reduce damage to surrounding normal tissue (e.g. heart, lungs, esophagus, spinal cord). For locally advanced thymomas, induction chemotherapy is recommended followed by an evaluation for surgery; postoperative RT can be considered after surgical resection of the primary tumor and isolated metastases. For those with solitary metastasis or ipsilateral pleural metastases, options include 1) induction

	chemotherapy followed by surgery for resectable patients; or 2) surgery alone. After induction chemotherapy, imaging recommended (e.g. chest CT, MRI, PET/CT) as clinically indicated to determine whether resection is feasible. For patients with unresectable disease in both of these settings, RT with or without chemotherapy is recommended. It is difficult to specify RT dosing regimens for metastatic disease given the very broad range of metastatic scenarios that are possible. Stereotactic body radiation therapy (SBRT) may be appropriate for limited focal metastases, whereas conventional fractionation is appropriate for larger metastases. Highly conformal techniques may be appropriate for limited volume metastases, given the relatively long natural history of even metastatic thymoma.
Thyroid Carcinoma Version 2.2022	The NCCN guideline does not mention or indicate the use of proton beam radiation therapy (PBRT) as a radiation treatment modality for the treatment of thyroid carcinoma.
Uterine Neoplasms Version 1.2022	The NCCN guideline does not mention or indicate the use of proton beam radiation therapy (PBRT) as a radiation treatment modality for uterine neoplasms.
Vulvar Cancer (Squamous Cell Carcinoma) Version 2.2022	The NCCN guideline does not mention or indicate the use of proton beam radiation therapy (PBRT) as a radiation treatment modality for the treatment of vulvar cancer.
Wilms Tumor (Nephroblastoma) Version 1.2022	Principles of Radiation Therapy • Indications: Flank RT for patients diagnosed with either local stage III or stage IV with local stage III. Local stage III refers to staging at the primary tumor regardless of metastases. • Delivery of RT is recommended with photons for flank, whole abdomen and whole lung. Boost modality should be more conformal with three-dimensional conformal RT (3D-CRT), intensity-modulated RT (IMRT), or protons.

American Urological Association (AUA)
In April 2017, American Urological Association (AUA)/American Society for Radiation Oncology (ASTRO) and Society of Urologic Oncology (SUO), issued a guideline on clinically localized prostate cancer. The guideline states the following regarding radiotherapy: "Clinicians should inform localized prostate cancer patients who are considering proton beam therapy that it offers no clinical advantage over other forms of definitive treatment." (Moderate Recommendation; Evidence Level: Grade C [RTCs with serious deficiencies of procedure or generalizability or extremely small sample sizes or observational studies that are inconsistent, have small sample sizes, or have other problems that potentially confound interpretation of data]).

American College of Radiology (ACR)
The 2014 ACR Appropriateness Criteria Definitive External Beam Irradiation in Stage T1 and T2 Prostate Cancer states:

- "There are only limited data comparing proton-beam therapy to other methods of irradiation or to radical prostatectomy for treating stage T1 and T2 prostate cancer. Further studies are needed to clearly define its role for such treatment."

PRIOR APPROVAL

Prior approval is required.

POLICY

See related medical policy

- 06.01.15 Stereotactic Radiosurgery (SRS) and Stereotactic Body Radiation Therapy (SBRT)

Clinical Trials and Clinical Registry Trials
Proton beam radiation therapy (PBRT) is considered a **non-covered benefit** when it is the experimental arm or subject of the clinical trial (refer to the member's benefit certificate language regarding clinical trials coverage).

When proton beam radiation therapy (PBRT) is studied as part of a clinical registry trial, Wellmark BCBS coverage criteria will be applied to determine the medical necessity of the proton beam radiation therapy (PBRT) services. When proton beam radiation therapy (PBRT) is part of a clinical registry trial and Wellmark BCBS criteria are not met, the proton beam radiation therapy (PBRT) will be considered **not medically necessary**.

Clinical registry trials are observational and lack the basic underpinning of clinical equipoise as there is inherent bias among both patients and investigators.

Proton beam radiation therapy (PBRT) not meeting Wellmark BCBS medical necessity criteria will be considered **not medically necessary** as proton beam radiation therapy (PBRT) has not been proven effective outside of these indications**.**

Secondary Malignancies
Proton beam radiation therapy (PBRT) is considered **not medically necessary** solely to reduce the risk of secondary malignancy as the available published data on whether proton beam radiation therapy (PBRT) increases or reduces the risk of secondary malignancy remains unproven.

Prostate Cancer
Proton Beam radiation therapy (PBRT) is considered **not medically necessary** for the treatment of prostate cancer because it has not been proven to be more effective than other radiotherapy modalities for this indication.

Proton beam radiation therapy (PBRT) is considered **not medically necessary,** including but not limited to the following indications in adults (over age 21), as there is lack of high-quality evidence comparing proton beam radiation therapy (PBRT) outcomes with photon-based (3D-conformal or intensity modulated radiation therapy [IMRT]) or stereotactic techniques based on the peer reviewed published medical literature in combination with National Comprehensive Cancer Network (NCCN) guidelines. Proton beam radiation therapy (PBRT) has not been proven to be more effective than other radiotherapy modalities for the treatment of these indications:

- Anal cancer
- Basal cell skin cancer
- Bladder cancer/genitourinary cancers (upper tract tumors, urothelial carcinoma, primary carcinoma of urethra)
- Bone cancer (except the following which will require medical review: chondrosarcoma; chordoma; and osteosarcoma unresectable or incompletely resectable)
- Breast cancer (except left sided invasive breast cancer which will require medical review)
- Central nervous system (CNS) cancers (except for the following which will require medical review: Ependymoma by biopsy intracranial or spinal; Anaplastic Glioma/Glioblastoma by biopsy; Medulloblastoma by biopsy; and Meningiomas)
- Cervical cancer
- Colon cancer (includes colorectal cancer)
- Cutaneous melanoma
- Dermatofibrosarcoma Protuberans
- Esophageal and esophagogastric junction cancers (except when the Wellmark BCBS coverage criteria is met, will require medical review**)**
- Gastric cancers
- Head and neck cancers (except the following which will require a medical review: Cancers of the oropharynx; mucosal melanoma; nasopharyngeal cancer; occult primary when targeting the pharyngeal axis; paranasal sinus cancer [maxillary sinus tumor, ethmoid sinus tumor, frontal sinus tumor, sphenoid sinus tumor]; salivary gland cancer; supraglottic larynx cancer; stage T4b disease; metastatic disease; recurrent persistent disease; unresectable nodal disease; and individual unfit for surgery)

- Hepatobiliary cancers (except the following which will require a medical review Hepatocellular carcinoma (HCC) and Intrahepatic cholangiocarcinoma)
- Intracranial arteriovenous malformations (AVM) (except for the following which will require a medical review intracranial arteriovenous malformations (AVM) not amendable to surgical excision, embolization, or standard stereotactic radiosurgery)
- Kidney cancer
- Lung cancer (including non-small cell and small cell and other lung cancers)
- Lymphomas (Hodgkin's lymphoma, non-Hodgkin's lymphoma i.e. B-cell lymphomas, T-cell Lymphomas) (except when the Wellmark BCBS coverage criteria is met, will require medical review**)**
- Malignant pleural mesothelioma
- Merkel cell carcinoma
- Multiple myeloma
- Neuroendocrine and adrenal tumors
- Occult Primary – Cancer of Unknown Primary (CUP)
- Ovarian cancer including fallopian tube and primary peritoneal cancer
- Pancreatic cancer
- Penile cancer
- Rectal cancer
- Small bowel adenocarcinoma
- Soft tissue sarcomas (except the following which will require a medical review: retroperitoneal/intrabdominal soft tissue sarcoma)
- Squamous cell skin cancer
- Testicular cancer (except for Seminoma IIA which will require a medical review)
- Thymomas and thymic carcinomas (except when the Wellmark BCBS coverage criteria is met, will require medical review)
- Uterine neoplasm
- Vulvar cancer

Policy Guidelines

Documentation Requirements for Proton Beam Radiation Therapy
The documentation requirements outlined below are used to assess whether the member meets the clinical criteria for coverage but does not guarantee coverage of the service requested.

Medical notes documenting **All** of the following:
- History of medical condition requiring treatment; **and**
- Documentation that sparing the surrounding normal tissues/organs at risk (OARs) cannot be achieved with standard radiation therapy techniques; **and**
- Physician's treatment plan.

Definition

Curative Intent: treatment provided with the main intent being to improve or eliminate symptoms that the patient is experiencing and to extend the patient's overall length of life.

PROCEDURE CODES AND BILLING GUIDELINES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnosis codes.

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

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POLICY HISTORY

Date	Reason	Action
January 2023	Interim Review	Policy Revised
August 2022	Annual Review	Policy Renewed
August 2021	Annual Review	Policy Revised
August 2020	Annual Review	Policy Revised
August 2019	Annual Review	Policy Revised
November 2018	Interim Review	Policy Revised
August 2018	Annual Review	Policy Revised
August 2017	Annual Review	Policy Renewed
May 2017	Interim Review	Policy Revised
August 2016	Annual Review	Policy Revised
September 2015	Annual Review	Policy Revised
May 2015	Interim Review	Policy Revised

January 2015		Policy Revised
October 2014	Annual Review	Policy Renewed
January 2014	Annual Review	Policy Revised
January 2013	Annual Review	Policy Renewed
January 2012	Annual Review	Policy Renewed
January 2011	Annual Review	Policy Revised

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

Wellmark Blue Cross and Blue Shield
Medical Policy Analyst
PO Box 9232
Des Moines, IA 50306-9232

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