Status: Reaffirmed

Effective Date: 03/13/2022

Doc ID: RAD01-0322.1-R0723

Last Review Date: 07/18/2023

Approval and implementation dates for specific health plans may vary. Please consult the applicable health plan for more details.

Clinical Appropriateness Guidelines

Radiation Oncology

Appropriate Use Criteria: Proton Beam Therapy

Table of Contents

Description and Application of the Guidelines

The Carelon Clinical Appropriateness Guidelines (hereinafter “the Carelon Clinical Appropriateness Guidelines” or the “Guidelines”) are designed to assist providers in making the most appropriate treatment decision for a specific clinical condition for an individual. As used by Carelon, the Guidelines establish objective and evidence-based criteria for medical necessity determinations where possible. In the process, multiple functions are accomplished:

- To establish criteria for when services are medically necessary (i.e., in general, shown to be effective in improving health outcomes and considered the most appropriate level of service)
- To assist the practitioner as an educational tool
- To encourage standardization of medical practice patterns
- To curtail the performance of inappropriate and/or duplicate services
- To advocate for patient safety concerns
- To enhance the quality of health care
- To promote the most efficient and cost-effective use of services

The Carelon guideline development process complies with applicable accreditation standards, including the requirement that the Guidelines be developed with involvement from appropriate providers with current clinical expertise relevant to the Guidelines under review and be based on the most up-to-date clinical principles and best practices. Relevant citations are included in the References section attached to each Guideline. Carelon reviews all of its Guidelines at least annually.

Carelon makes its Guidelines publicly available on its website twenty-four hours a day, seven days a week. Copies of the Carelon Clinical Appropriateness Guidelines are also available upon oral or written request. Although the Guidelines are publicly-available, Carelon considers the Guidelines to be important, proprietary information of Carelon, which cannot be sold, assigned, leased, licensed, reproduced or distributed without the written consent of Carelon.

Carelon applies objective and evidence-based criteria, and takes individual circumstances and the local delivery system into account when determining the medical appropriateness of health care services. The Carelon Guidelines are just guidelines for the provision of specialty health services. These criteria are designed to guide both providers and reviewers to the most appropriate services based on a patient’s unique circumstances. In all cases, clinical judgment consistent with the standards of good medical practice should be used when applying the Guidelines. Guideline determinations are made based on the information provided at the time of the request. It is expected that medical necessity decisions may change as new information is provided or based on unique aspects of the patient’s condition. The treating clinician has final authority and responsibility for treatment decisions regarding the care of the patient and for justifying and demonstrating the existence of medical necessity for the requested service. The Guidelines are not a substitute for the experience and judgment of a physician or other health care professionals. Any clinician seeking to apply or consult the Guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient’s care or treatment.

The Guidelines do not address coverage, benefit or other plan specific issues. Applicable federal and state coverage mandates take precedence over these clinical guidelines. If requested by a health plan, Carelon will review requests based on health plan medical policy/guidelines in lieu of the Carelon Guidelines. Pharmaceuticals, radiotracers, or medical devices used in any of the diagnostic or therapeutic interventions listed in the Guidelines must be FDA approved or conditionally approved for the intended use. However, use of an FDA approved or conditionally approved product does not constitute medical necessity or guarantee reimbursement by the respective health plan.

The Guidelines may also be used by the health plan or by Carelon for purposes of provider education, or to review the medical necessity of services by any provider who has been notified of the need for medical necessity review, due to billing practices or claims that are not consistent with other providers in terms of frequency or some other manner.

General Clinical Guideline

Clinical Appropriateness Framework

Critical to any finding of clinical appropriateness under the guidelines for a specific diagnostic or therapeutic intervention are the following elements:

- Prior to any intervention, it is essential that the clinician confirm the diagnosis or establish its pretest likelihood based on a complete evaluation of the patient. This includes a history and physical examination and, where applicable, a review of relevant laboratory studies, diagnostic testing, and response to prior therapeutic intervention.
- The anticipated benefit of the recommended intervention should outweigh any potential harms that may result (net benefit).
- Current literature and/or standards of medical practice should support that the recommended intervention offers the greatest net benefit among competing alternatives.
- Based on the clinical evaluation, current literature, and standards of medical practice, there exists a reasonable likelihood that the intervention will change management and/or lead to an improved outcome for the patient.

If these elements are not established with respect to a given request, the determination of appropriateness will most likely require a peer-to-peer conversation to understand the individual and unique facts that would supersede the requirements set forth above. During the peer-to-peer conversation, factors such as patient acuity and setting of service may also be taken into account.

Simultaneous Ordering of Multiple Diagnostic or Therapeutic Interventions

Requests for multiple diagnostic or therapeutic interventions at the same time will often require a peer-to-peer conversation to understand the individual circumstances that support the medical necessity of performing all interventions simultaneously. This is based on the fact that appropriateness of additional intervention is often dependent on the outcome of the initial intervention.

Additionally, either of the following may apply:

- Current literature and/or standards of medical practice support that one of the requested diagnostic or therapeutic interventions is more appropriate in the clinical situation presented; or
- One of the diagnostic or therapeutic interventions requested is more likely to improve patient outcomes based on current literature and/or standards of medical practice.

Repeat Diagnostic Intervention

In general, repeated testing of the same anatomic location for the same indication should be limited to evaluation following an intervention, or when there is a change in clinical status such that additional testing is required to determine next steps in management. At times, it may be necessary to repeat a test using different techniques or protocols to clarify a finding or result of the original study.

Repeated testing for the same indication using the same or similar technology may be subject to additional review or require peer-to-peer conversation in the following scenarios:

- Repeated diagnostic testing at the same facility due to technical issues
- Repeated diagnostic testing requested at a different facility due to provider preference or quality concerns
- Repeated diagnostic testing of the same anatomic area based on persistent symptoms with no clinical change, treatment, or intervention since the previous study

- Repeated diagnostic testing of the same anatomic area by different providers for the same member over a short period of time

Repeat Therapeutic Intervention

In general, repeated therapeutic intervention in the same anatomic area is considered appropriate when the prior intervention proved effective or beneficial and the expected duration of relief has lapsed. A repeat intervention requested prior to the expected duration of relief is not appropriate unless it can be confirmed that the prior intervention was never administered.

Proton Beam Therapy

General Information

Definitions

Statistical terminology

- **Confidence interval (CI)** describes the amount of uncertainty associated with a sampling method. Confidence intervals are usually reported to help explain how reliable, or precise, a result is.
- **Hazard ratio (HR)** is a measure of how often a particular event happens in one group compared to how often it happens in another group, over time. In cancer research, hazard ratios are often used in clinical trials to measure survival at any point in time in a group of patients who have been given a specific treatment compared to a control group given another treatment or a placebo. A hazard ratio of one means that there is no difference in survival between the two groups. A hazard ratio of greater than one or less than one means that survival was better in one of the groups.
- **Odds ratio (OR)** is a measure of the odds of an event happening in one group compared to the odds of the same event happening in another group. In cancer research, odds ratios are most often used in case-control (backward looking) studies to find out if being exposed to a certain substance or other factor increases the risk of cancer. For example, researchers may study a group of individuals with cancer (cases) and another group without cancer (controls) to see how many people in each group were exposed to a certain substance or factor. They calculate the odds of exposure in both groups and then compare the odds. An odds ratio of one means that both groups had the same odds of exposure and, therefore, the exposure probably does not increase the risk of cancer. An odds ratio of greater than one means that the exposure may increase the risk of cancer, and an odds ratio of less than one means that the exposure may reduce the risk of cancer. Also called relative odds.
- **Overall survival (OS)** is the length of time from either the date of diagnosis or the start of treatment for a disease, such as cancer, that patients diagnosed with the disease are still alive. In a clinical trial, measuring the overall survival is one way to see how well a new treatment works.
- **Overall survival rate** is the percentage of people in a study or treatment group who are still alive for a certain period of time after they were diagnosed with or started treatment for a disease, such as cancer. The overall survival rate is often stated as a five-year survival rate, which is the percentage of people in a study or treatment group who are alive five years after their diagnosis or the start of treatment. Also called survival rate.
- **Progression-free survival (PFS)** is the length of time during and after the treatment of a disease, such as cancer, that a patient lives with the disease but it does not get worse. In a clinical trial, measuring the progression-free survival is one way to see how well a new treatment works.
- **Relative risk (RR)** is a measure of the risk of a certain event happening in one group compared to the risk of the same event happening in another group. In cancer research, relative risk is used in prospective (forward looking) studies, such as cohort studies and clinical trials. A relative risk of one means there is no difference between two groups in terms of their risk of cancer, based on whether or not they were exposed to a certain substance or factor, or how they responded to two treatments being compared. A relative risk of greater than one or of less than one usually means that being exposed to a certain substance or factor either increases (relative risk greater than one) or decreases (relative risk less than one) the risk of cancer, or that the treatments being compared do not have the same effects. Also called risk ratio.
- **Response rate** is the percentage of patients whose cancer shrinks or disappears after treatment.

Proton Beam Therapy Considerations

Proton beam radiation therapy, also known as proton beam therapy (PBT), is a type of external radiation treatment. Using a stereotactic planning and delivery system, positively charged subatomic particles (protons) are targeted to a specific tissue mass. Protons behave differently than x-rays or photons in that they have a low energy deposition rate as they enter the body, followed by a steep increased energy deposition when they reach their target. Although there is essentially no energy deposited beyond the target, there is lateral scatter and some uncertainty about their physical range in tissue. Compared to x-ray treatment, surrounding healthy tissue generally receives less radiation. Despite the proliferation of proton centers in recent years, there is a lack of high-quality evidence demonstrating improved outcomes vs other forms of precision radiation therapy. Proton beam therapy remains an area of active clinical investigation, and recommendations for its use continue to evolve.

Proton beam therapy may be appropriate in circumstances where intensity modulated radiation therapy (IMRT) or stereotactic would potentially damage critical structures, particularly in patients with a history of prior irradiation. Proton beam therapy is also appropriate for pediatric patients because even low doses of scattered radiation in this population can affect growth and development and increase the risk of secondary malignancies later in life. This technique of radiation delivery is being actively studied in other clinical scenarios, and its role in these situations in many cases remains unclear. In situations where there is a lack of high-quality evidence comparing proton outcomes with photon-based therapies, proton therapy will be considered not medically necessary. In situations where proton therapy is appropriate, PBT should be administered as monotherapy.

Breast Cancer

There are no randomized trials of PBT for breast cancer. A recent systematic review discussed nine original investigations of PBT for both whole breast treatment and accelerated partial breast irradiation (APBI). Skin toxicity and esophagitis were comparable to photon therapy. None of the outcomes reported were improved with PBT. There is a randomized trial comparing PBT to photon therapy underway.

Several studies have examined the potential increase in biologic dose delivered with intensity modulated proton therapy (IMPT) compared to the doses calculated with an assumed radiobiologic equivalent (RBE) of 1.1. The variably weighted dose resulted in an increase in the biologic dose to the brachial plexus, ribs, heart, and esophagus ranging from 8%-24%. In another study, although there was significant dose improvement with protons vs photons when an RBE of 1.1 was assumed, no statistically significant difference was seen when a variable RBE was applied. The authors of these studies concluded that a variable RBE model should be considered when evaluating IMPT plans, especially for organs at risk near the end range of each proton beam. These biologic uncertainties underscore the need for further study of PBT and IMPT in this setting. They also argue against drawing conclusions about any potential dosimetric advantages of proton therapy based on historic estimations of the biologic dose.

A randomized trial comparing PBT to photon therapy for breast cancer patients requiring comprehensive nodal irradiation continues to enroll patients. The Pragmatic Randomized Trial of Proton vs. Photon Therapy for Patients With Non-Metastatic Breast Cancer: A Radiotherapy Comparative Effectiveness (RADCOMP) Consortium Trial (NCT02603341) compares multiple outcomes including quality of life (QOL), cardiovascular problems, and cancer control. As with any randomized trial, there is an assumption of equipoise.

The Particle Therapy Cooperative Group recently published a consensus statement on the use of proton beam therapy to treat breast cancer. They highlight several non-randomized trials of fewer than 100 patients which form the basis for the randomized RADCOMP trial. As a method to deliver regional nodal irradiation in high-risk patients, they advocate for proton beam therapy when target or organ at risk constraints cannot be met with a robust photon plan. The authors note that for each 1 Gy increase in mean heart dose, a 0.3%-0.6% reduction in lifetime cardiac adverse events is expected. In addition, RTOG 1304/NSAPB B-51 requires that the mean heart dose (MHD) be limited to 5 Gy or less. This can be achieved with IMRT techniques in the majority of cases. The quality of the guideline methodology is scored below passing when appraised with AGREE II.

Proton beam therapy is considered not medically necessary for the treatment of breast cancer.

Central Nervous System Lesions

Radiation therapy is commonly used to treat central nervous system (CNS) tumors and other intracranial lesions such as arteriovenous malformations (AVM). Results of proton therapy have been reported for a variety of CNS

lesions. In the treatment of gliomas, dose escalation to 68.2 centigray equivalent (CGE) did not improve outcomes in a phase I/II trial of protons in grade 2-3 astrocytoma. In another study, dose escalation to 90 CGE slightly increased median survival, but all patients had marginal failure just beyond the high-dose area and necrosis was seen in one third of patients. A more recent Japanese phase I/II study boosted glioblastomas to 96.6 CGE and reported a handful of long-term survivors, all of whom have developed necrosis. Benign tumors including meningiomas, acoustic neuromas and pituitary adenomas have also been treated with protons.

A randomized phase II trial comparing proton therapy to IMRT for newly diagnosed glioblastoma was recently reported. The primary endpoint was time to cognitive failure. Overall survival (OS), progression-free survival (PFS), and toxicity were also measured. At a median follow-up of 48 months, there were no differences in time to cognitive failure, OS, or PFS. There was less fatigue reported in the proton group. The investigators concluded that larger randomized trials are needed.

A German phase III study comparing outcomes for treatment of glioblastoma with PBT vs IMRT was recently activated. This study, known as the GRIPS trial (Glioblastoma Radiotherapy via IMRT or Proton Beams, NCT04752280), will evaluate treatment-related toxicity as its primary endpoint. Secondary endpoints include overall survival, progression-free survival, quality of life, and neurocognition.

Results of treatment are similar to those seen with non-proton techniques such as IMRT and stereotactic radiosurgery (SRS). A recent review of PBT to treat CNS lesions by Combs concluded that “no clinical data have shown superiority over advanced photon therapy.”

Use of PBT for CNS lesions is only medically necessary for specific cases where adjacent critical structures cannot be adequately spared with IMRT or SRS.

Chordoma and Chondrosarcoma

Chordomas and chondrosarcomas are rare bone and soft tissue tumors which occur along the spinal axis. The mainstay of treatment is surgery, but in many cases only biopsy or piecemeal resection is possible. Postoperative radiotherapy has been shown to improve outcomes. In the past, tumors occurring in the base of skull area were unable to be treated to high doses with conventional therapy due to the risk of damaging normal tissues. Protons were used to safely treat chordomas in this location with good results. In the most comprehensive review published to date, seven studies of proton therapy were compared to ten studies of conventional radiotherapy and reported improved local control and survival with protons compared to x-rays. The average five-year local control with protons was 69% vs only 36% with photons. The five-year survival rate was 80% with PBT vs 54% with x-rays. Chordomas and chrondrosarcoma of the spine are similarly difficult to treat given that doses above 70 Gy are given to areas in close proximity to the spinal cord and viscera. A recent prospective phase II trial of protons in this setting showed an impressive 94% five-year local control for primary tumors with acceptable late morbidity.

Results with modern radiotherapy techniques like IMRT and radiosurgery are improved compared to conventional radiotherapy, but given the excellent long-term results seen with protons, they are considered medically necessary for the treatment of base of skull and sacral chordomas and chondrosarcomas.

Head and Neck Cancer

Although several trials are underway, there are no published randomized studies comparing proton therapy to IMRT in the treatment of head and neck cancers. In 2010, the Agency for Healthcare Research and Quality (AHRQ) conducted a systematic review of radiation modalities used in the treatment of head and neck malignancies including 2D radiation, 3D conformal radiation, IMRT, and PBT. They concluded that there was insufficient evidence comparing PBT to other modalities. This report was updated in 2014 with the same conclusion.

A 2016 single institution report retrospectively compared intensity modulated proton therapy (IMPT) to IMRT in the treatment of oropharyngeal cancer. There was no difference in progression-free survival between the modalities. IMRT-treated patients were more likely to have a gastrostomy tube (G-tube) placed than proton-treated patients, but this was not statistically significant. Outcomes meeting statistical significance were patient-reported xerostomia at three months, weight loss greater than 20%, and G-tube presence one year after treatment. The authors concluded that prospective multicenter randomized trials are needed to validate these findings.

This hypothesis-generating report forms the basis for an NCI-sponsored, phase II/III, randomized clinical trial comparing IMRT and PBT in the treatment of oropharynx cancer (NCT01893307). In a recent review, Leeman et al. concluded that “ultimately, such trials will help establish the clinical usefulness of proton beam therapy and will be necessary to provide sufficient evidence regarding toxicity benefits to support wider adoption.”

A recent publication describes the final selection of primary and secondary endpoints to be used for NCT01893307 as this study transitions from phase II to phase III. NRG Oncology, a non-profit research organization formed to conduct clinical research in oncology and to broadly disseminate study results to inform clinical decision-making and health policy, was brought in as a partner and expressed concerns about the proposed endpoints of the study. The initial primary endpoint of physician scored, late onset, grade ≥3 toxicity was scrapped due to a perceived lack of objectivity in physician ratings using the Common Terminology Criteria for Adverse Events (CTCAE) and insufficient sensitivity to account for other forms of toxicity. The study has now been redesigned as a non-inferiority trial using progression-free survival as the primary endpoint and using an expanded group of toxicity measurements as secondary endpoints.

A systematic review and meta-analysis of charged particle therapy vs x-ray based therapy for treatment of paranasal sinus and nasal cancers was published by Patel et al. There were no head-to-head comparison trials, so their analysis consisted of 41 observational studies. Of these, there were 13 reports for charged particle therapy and 30 cohorts treated with photons. In the meta-analysis of these reports, treatment with charged particle therapy was associated with higher survival at five years. Neurologic toxicity was significantly higher in the charged particle group as well. The studies reviewed included a very heterogeneous group. For photon therapy, treatment techniques included 2D, 3D, IMRT, and brachytherapy. The charged particle cohorts included both protons and carbon ions with most patients being treated with passively scattered protons. A similar proportion of patients in both groups had advanced disease but the photon-treated patients were more likely to have a high-risk histology. The heterogeneity of both the patient populations and treatment techniques as well as the inclusion of inadequate treatment techniques such as 2D and 3D conformal radiotherapy in the photon group make it impossible to draw meaningful conclusions for the entire group. Proton beam therapy may be appropriate to treat certain locally advanced sinonasal cancers involving the base of skull when adjacent critical structures are unable to be adequately spared with IMRT.

A systematic review of proton therapy for nasopharyngeal cancer was reported by Lee et al. The authors used PRISMA guidelines and identified 9 relevant studies. They found that oncologic outcomes were similar compared to IMRT treated patients. The main differences noted were lower rates of feeding tubes and lower incidence of mucositis compared to photon-treated patients. No significant differences were found in other acute and late radiation effects.

A retrospective series of 68 patients treated with PBT for major salivary gland tumors was recently reported. Proton beam treatment showed favorable short-term local control and survival rates. There was no comparison group reported.

Proton beam therapy is considered medically necessary to treat locally advanced sinonasal cancers involving the base of skull. Proton beam therapy is not medically necessary for the treatment of other head and neck cancers.

Hepatocellular Cancer

Hepatocellular carcinomas (HCC) are aggressive primary malignancies of the liver. All patients should be evaluated for potentially curative therapies including resection, transplantation and ablative treatment. Ablative therapies include radiofrequency ablation, microwave therapy, and alcohol injection. Radiation therapy is considered for patients who are not candidates for resection. There is growing evidence for the use of stereotactic body radiation therapy (SBRT). Charged particle therapy such as proton therapy has also been used in the treatment of hepatocellular carcinoma.

There are no randomized trials comparing PBT to other forms of external radiation. A systematic review and meta-analysis comparing charged particle therapy to conventional radiation and SBRT has been reported. Overall survival, progression-free survival, and local control were equivalent for particle therapy and SBRT. Both charged particle therapy and SBRT were superior to conventional radiation.

A single institution retrospective study compared ablative photon vs proton therapy in patients with unresectable hepatocellular carcinoma. The majority of the proton beam patients were treated as part of a phase II single arm clinical trial (NCT 00976898). The primary endpoint was overall survival. Proton therapy was associated with an

improved overall survival of 31 months vs 14 months with photons. The proton-treated patients had a significantly lower risk of nonclassic radiation induced liver disease (RILD) (OR 0.26, P = .03) and development of RILD at 3 months was significantly associated with worse overall survival. There was no difference in local failure between the two treatments suggesting that the improved survival is related to the decrease in post-treatment liver decompensation.

Proton therapy has been compared to transarterial chemoembolization (TACE) for HCC in a randomized trial. A total of 69 subjects were reported. The primary endpoint was progression-free survival. There was a trend toward improved progression-free survival (48% vs 31%; P = .06) favoring protons but no significant difference in overall survival with a median overall survival of 30 months. Total days of hospitalization within 30 days of treatment was 166 days for the 36 TACE patients and 24 days for the proton patients (P < .001).

Another randomized trial compared radiofrequency ablation (RFA) to proton beam therapy for unresectable hepatocellular carcinoma. One hundred forty-four patients were randomly assigned to receive either RFA or PBT. There was significant crossover to the other modality affecting 6 patients assigned to PBT and 19 patients assigned to RFA. For the patients treated per protocol, the two-year local progression-free survival rate was 94.8% in the PBT patients vs 83.9% for RFA (P < .001). The authors concluded that PBT is non-inferior to RFA in this setting.

Proton beam therapy is considered medically necessary for the treatment of unresectable HCC with curative intent when there is no evidence of metastatic disease.

Other Gastrointestinal Cancers

There have been few reports of PBT to treat esophageal and gastroesophageal junction tumors. Wang et al. published a retrospective report of complications after trimodality therapy looking at IMRT and PBT compared to 3D conformal radiation. A total of 444 patients were reported. Both IMRT and PBT were associated with reduced risk of complications compared to 3D conformal radiation. No direct comparison of IMRT vs PBT was performed.

Lin et al. recently published a small, phase IIB, randomized, study comparing proton beam therapy to IMRT in patients with locally advanced esophageal cancer. A total of 145 patients were enrolled and 107 of these were evaluable. The IMRT group had 61 patients and the proton group had 46 patients. Median follow-up was 44 months. Three-year progression-free survival was 50.8% for IMRT and 51.2% for protons. Overall survival was identical in both arms at 44.5%.

Quality of life (QOL) was assessed at multiple time points during the study and there were no QOL differences between the two treatment arms. The main finding of the study was an improvement in what the authors term “total toxicity burden” or TTB. The TTB score is a composite of numerous possible treatment related events and/or postoperative complications, with the majority of the TTB benefit attributed to asymptomatic pleural effusion, asymptomatic pericardial effusion and atrial fibrillation. The physicians scoring the TTB were not blinded as to the treatment received, leading to possible bias. This endpoint has not been validated for this use.

In a recent editorial highlighting randomized trials for gastrointestinal cancers, Hallemeier et al. state:

> *Many questions remain unanswered regarding the utility of PBT for esophageal cancer. Importantly, does reduction in radiation doses to organs at risk lead to improved survival, quality of life, or cost savings?*

There is an ongoing NRG Oncology trial (GI006) which randomizes patients to PBT or IMRT. The primary endpoints of this investigation are overall survival and grade 3+ cardiopulmonary toxicity as measured by the Common Toxicity Criteria for Adverse Events (CTCAE).

There are no moderate or high-quality studies comparing PBT to 3D conformal radiotherapy or IMRT for gastric or pancreatic cancer.

Proton beam therapy is considered not medically necessary for the treatment of esophageal, gastric or pancreatic cancer.

Lung Cancer

Radiotherapy is used as a primary treatment for early-stage non-small cell lung cancer (NSCLC), particularly when surgical resection is not an option. In the treatment of stage I medically inoperable NSCLC, a meta-analysis of studies of PBT and SBRT has been reported. Two-year survival rates for stage I NSCLC treated with SBRT

were 70% vs 61% for PBT. The five-year survival rates were similar. Both SBRT and proton therapy were significantly better than conventional radiotherapy for stage I disease. Proton beam therapy is considered not medically necessary for small cell lung cancer and stage I NSCLC.

Radiation therapy, usually delivered with concurrent chemotherapy, is the standard of care for the treatment of unresectable stage III NSCLC. In specific cases, IMRT is needed to achieve adequate sparing of organs at risk such as the normal lung. Significant lung and esophageal toxicity are common and these toxicities have hampered attempts at dose escalation.

Proton beam therapy has been used for NSCLC in an attempt to allow dose escalation while minimizing lung and esophageal toxicity. Several institutions have reported on their experience. A systematic review by Widesott examined 17 studies. There were no prospective reports. Nine single institution studies reported on a total of 214 patients, most with stage I or II disease. Several studies focused on dose distributions and technical issues associated with PBT. They concluded that it was impossible to draw definitive conclusions about the superiority of PBT for NSCLC. A subsequent phase II trial by Chang reported encouraging results for unresectable stage III disease. A prospective randomized trial comparing PBT with photon therapy was completed at MD Anderson Cancer Center, and final results were published in 2018. A total of 255 patients were enrolled and 149 of these were randomized. Proton therapy did not improve local control nor did it improve survival compared to IMRT. The rate of pneumonitis was higher in the proton therapy arm (11%) vs the IMRT arm (7%). This study reinforces the importance of level 1 evidence in the study of proton therapy. NRG/RTOG protocol 1308 is a randomized trial of PBT vs IMRT both with concurrent platinum-based chemotherapy in stage II-IIIB non-small cell lung cancer which should provide additional data on how proton therapy compares to standard treatment.

ASTRO has published a clinical practice guideline on the use of radiation therapy for small cell lung cancer which states:

> *However, unlike nonsmall cell lung cancer (NSCLC), there are limited data on advanced RT techniques in SCLC treatment. Proton therapy could potentially further decrease normal tissue toxicities, but there are limited prospective data on its role in SCLC treatment. Generation of evidence is encouraged through treatment of patients in prospective clinical trials or multi-institutional registries.*
>
> *There are limited data on the role of postoperative RT for SCLC, so the recommendation on indications for RT in this setting is based on NSCLC.*

Proton beam therapy is considered not medically necessary in the treatment of lung cancer.

Lymphoma

Data on PBT for treatment for lymphoma are limited. A recent review examined the use of consolidative PBT after chemotherapy for patients with Hodgkin lymphoma. A total of 138 patients enrolled on tracking protocols or registry studies were reviewed. Forty-two percent of the patients were pediatric and received a median dose of 21 Gy equivalent. Adult patients received a median dose of 30.6 Gy equivalent. With a median follow-up of 32 months, three-year relapse-free survival was 92%. The authors concluded that early survival rates are similar to photon-based therapy and the continued follow-up to assess for late effects is needed.

Data on proton therapy for non-Hodgkin lymphoma are limited. A small retrospective cohort has been reported. Eleven patients were treated between 2008 and 2014. Follow-up was 38 months. Two-year local control was 91%. Toxicities were grade 2 or less. The authors concluded that longer-term follow-up and more patients were needed to confirm their findings.

Proton beam therapy is considered not medically necessary for the treatment of Hodgkin lymphoma and non-Hodgkin lymphoma.

Ocular (Uveal) Melanoma

Curative treatment for ocular melanoma with preservation of vision can be achieved with either plaque brachytherapy or with PBT. A systematic review and meta-analysis of charged particle radiation therapy for uveal melanoma demonstrated that charged particle therapy (most commonly PBT) resulted in a lower local recurrence rate than plaque brachytherapy. Proton beam therapy also showed better outcomes in terms of retinopathy and cataract formation. Enucleation and survival were similar with PBT and brachytherapy.

Boker et al. recently compared neoadjuvant proton therapy with adjuvant ruthenium brachytherapy together with transscleral resection for large uveal melanomas. The five-year recurrence rate was 9% for proton-treated patients vs 27.5% in the ruthenium brachytherapy-treated cohort. Metastatic rates were similar as was the risk of enucleation.

Proton therapy is considered medically necessary for the treatment of uveal melanoma.

Prostate Cancer

Historically, PBT was used as a boost technique for prostate cancer due to the ability to deliver a higher dose than could be safely delivered with 2D and 3D techniques. Single institution reports of PBT dose escalation showed favorable disease-free survival and acceptable toxicity in this era. Over the past two decades, there have been significant improvements in technology allowing similar dose escalation to be achieved with IMRT.

The only randomized trial of PBT compared low dose proton boost (19.8 CGE) with high dose proton boost (28.8 CGE) after a dose of 50.4 Gy to the pelvis with x-rays. In that study, the higher dose proton boost improved biochemical recurrence-free survival but also increased the frequency of acute gastrointestinal (GI) and genitourinary (GU) toxicity. There were no significant differences in late toxicity. The study did not evaluate whether proton therapy is more efficacious or less toxic than other forms of conformal radiation.

Although there are no reports from randomized trials comparing proton therapy with IMRT and 3D conformal radiation, there have been retrospective comparative studies. In a large-scale review of outcomes based on Medicare claims data, 684 patients treated with PBT were compared with 9,437 men treated with IMRT. Follow-up was 46 to 50 months and the results were propensity score matched to account for baseline characteristics. Rates of urinary incontinence, other urinary morbidity and sexual dysfunction were similar for PBT and IMRT. Compared to IMRT, patients treated with PBT had a higher rate of GI morbidity (17.8 vs 12.2 per 100 person-years). In terms of disease control, IMRT was shown to be better than conformal therapy. Proton therapy did not provide additional benefit over IMRT.

Patient-reported outcomes for 3D conformal radiotherapy, IMRT and PBT have also been reported. Using validated quality of life (QOL) instruments, a 2013 study looked at scores in the immediate post-treatment period and at 12- and 24-month follow-up visits. In the immediate post-treatment interval, bowel QOL decreased for both 3D and IMRT treated patients but not the PBT group. At 12 and 24 months, all three groups showed decreased bowel/rectal QOL. With regard to urinary toxicity, IMRT treated patients showed decreased GU QOL in the immediate period but this had disappeared by 12 months. At 12 months, the PBT cohort demonstrated decreased urinary QOL while 3D and IMRT patients had returned to baseline. No meaningful urinary QOL changes were seen in any group at 24 months. Although timing of toxicity varied between cohorts, patients reported similar long-term QOL decrements irrespective of modality.

There is significant consensus among radiation oncologists that there is a lack of comparative effectiveness research on PBT for prostate cancer. Multiple evidence-based reviews of this topic have concluded that no clear evidence supports a benefit of proton therapy over IMRT in terms of efficacy or long-term toxicity. These include reports from the AHRQ, Hayes, the American Urologic Association, the American College of Radiology, and the ASTRO Subcommittee on Emerging Technology. In their 2017 update of the model policy on PBT, ASTRO maintains:

“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 of proton therapy compares to other radiation 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 within the context of a prospective clinical trial or registry.”

Li et al. published a systematic review and meta-analysis of efficacy and safety of carbon ion therapy and proton beam therapy in the treatment of prostate cancer. A total of 33 studies were reviewed. Both proton beam therapy and carbon ion therapy had favorable efficacy and safety compared to photon therapy. GRADE assessment of the results indicated that the certainty of evidence was very low. On meta-analysis, treatment with protons or carbon ions did not significantly affect the outcomes. Authors concluded that the quantity and quality of the evidence are insufficient, and that more high-quality controlled studies are needed in the future.

The body of evidence on PBT for prostate cancer largely consists of retrospective studies performed at tertiary centers. The evidence quality is low, and data are insufficient to determine how PBT compares to standard of care photon-based therapies, which are able to achieve excellent outcomes with low toxicity.

Proton beam therapy is considered not medically necessary for the treatment of prostate cancer.

Risk Reduction

There have been multiple publications theorizing a reduced risk of second malignancies with the use of proton therapy. These generally compare dosimetric data from proton plans compared to IMRT plans and use mathematical modeling to predict the cancer risk. These models are largely untested and there is a dearth of actual data reporting on the risk posed by scattered radiation, especially in adults.

Several studies have looked at the actual risk of second malignancy following radiotherapy and have compared this to patients who have not been irradiated. Zelefsky reported on the 10-year risk of second cancer among men with prostate cancer treated with radical prostatectomy, brachytherapy, and external beam radiotherapy. The risk of developing bladder or colorectal cancer was 3% for radical prostatectomy, 2% for brachytherapy, and 4% for external beam radiotherapy at 10 years (P = .29). For all second cancers, there was a slightly higher risk in the irradiated patients but on multivariate analysis this difference was found to be attributable to age and smoking history rather than treatment received. Another report examined the risk of second cancers after radiotherapy in three randomized trials and compared this to patients randomized to no radiotherapy. A total of 2,554 patients were analyzed who had participated in the TME trial for rectal cancer, the PORTEC-1 and PORTEC-2 trials in endometrial cancer. Although all patients in these trials were at somewhat higher risk of second malignancy than the general population, the patients who received radiotherapy had no higher probability of developing second cancers than those treated with surgery alone.

Chung et al. reported on the incidence of second malignancy in 558 patients treated with proton therapy at the Harvard Cyclotron facility and compared this to matched controls in the Surveillance, Epidemiology, and End Results (SEER) database. The incidence of second cancers in the proton group was approximately 7 per 1000 person-years vs approximately 10 per 1000 person-years in the matched photon group (P = .085). Limitations include different methods of data collection, lack of radiation field size and dose, and the fact that 26% of proton-treated patients were lost to follow-up and second malignancy information was not available for this group. The authors concluded that the results are hypothesis generating and warrant further study.

Uncertainties of Proton Beam Therapy

The longest experience with protons has been using passively scattered beams. This technique, known as passively scattered proton therapy (PSPT), is a robust method of proton delivery which is less sensitive to treatment and patient variables. Passive scattered protons produce neutrons and these affect surrounding tissues negatively. Newer proton beam centers use pencil beam scanning technology. This allows for more conformal treatment delivery and has been also termed intensity modulated proton therapy (IMPT). Long-term follow-up with this technology is lacking. A recent review summarizes the status of IMPT declaring “currently, it is still unclear which patients will exhibit a significantly enhanced therapeutic ratio with IMPT over PSPT or IMRT.” Additionally, there are significant uncertainties about the physics and biology of protons in this setting. These include the complex interaction of scanning beams with moving tissues of different densities, less predictable dose distributions during treatment of radiosensitive HPV-positive tumors, and questions about the variable radiobiologic effectiveness of protons in situ. Proton plans generally assume a uniform relative biological effectiveness (RBE) of 1.1 compared to photons. The actual RBE is dependent on the fractionation and depth. At the distal edge of the Bragg peak, RBE has been measured at more than 5 times the assumed value. The existence of this uncertainty highlights the need for further prospective study of proton therapy, especially as treatment techniques such as pencil beam scanning continue to evolve.

Clinical Trials and Registries

There have been calls to cover the costs of PBT for patients enrolled in registry trials, but these studies lack the basic underpinning of clinical equipoise. Proton beam therapy will not be covered when it is the experimental arm of a clinical trial or when used as part of a clinical registry unless criteria above are otherwise met.

Clinical Indications

This guideline outlines different applications of proton beam therapy in the treatment of malignant and benign tumors and arteriovenous malformations.

Base of Skull Tumors

Chordoma, Chondrosarcoma

Proton beam is appropriate for chordoma or chondrosarcoma when the following condition is met:

- As postoperative therapy for individuals who have undergone biopsy or partial resection of a chordoma or low-grade (I or II) chondrosarcoma of the basisphenoid region (e.g., skull-base chordoma or chondrosarcoma), cervical spine, or sacral/lower spine and have residual, localized tumor without evidence of metastasis

Sinonasal Cancer

Proton beam is appropriate for locally advanced sinonasal carcinoma when the following condition is met:

- Tumor involves the base of skull and proton therapy is needed to spare the orbit, optic nerve, optic chiasm, or brainstem

Central Nervous System

Arteriovenous Malformation (AVM)

Proton beam is appropriate for AVM when **ANY** of the following conditions are met:

- Intracranial AVM not amenable to surgical excision or other conventional forms of treatment
- Adjacent to critical structures such as the optic nerve, brain stem or spinal cord

Central Nervous System (CNS) Tumors

Proton beam is appropriate for CNS tumors when **ALL** the following conditions are met:

- Including, but not limited to, primary or metastatic CNS malignancies, such as gliomas (both must be met)
    - When adjacent to critical structures such as the optic nerve, brain stem, or spinal cord
    - When other standard radiation techniques such as IMRT or standard stereotactic modalities would not sufficiently reduce the risk of radiation damage to the critical structure

Hepatobiliary cancer

Hepatocellular Carcinoma and Intrahepatic Cholangiocarcinoma

Proton beam is appropriate for hepatocellular cancer or intrahepatic cholangiocarcinoma when the following condition is met:

- To treat unresectable, non-metastatic hepatocellular cancer or intrahepatic cholangiocarcinoma with curative intent

Melanoma

Ocular Melanoma

Proton beam is appropriate for ocular melanoma when the following condition is met:

- To treat melanoma of the uveal tract (including the iris, choroid, or ciliary body) and no evidence of metastasis or extrascleral extension

Pediatric patients

All Tumor Types

Proton beam is appropriate for pediatric patients (age less than 21) when the following condition is met:

- To treat all pediatric tumors in which radiation therapy is required

Re-irradiation

Proton beam is appropriate for the repeat irradiation of previously treated fields where the dose tolerance of surrounding normal structures would be exceeded with 3D conformal radiation or IMRT.

Exclusions

Proton beam therapy is **not medically necessary** for the treatment of all other conditions including:

- Breast cancer
- Esophageal cancer
- Gastric cancer
- Gynecologic cancer
- Head and neck cancer
- Hepatobiliary cancers not listed above
- Lung cancer
- Lymphoma (Hodgkin and non-Hodgkin)
- Pancreatic cancer
- Prostate cancer

Codes

The following code list is not meant to be all-inclusive. Authorization requirements will vary by health plan. Please consult the applicable health plan for guidance on specific procedure codes.

Specific CPT codes for services should be used when available. Nonspecific or not otherwise classified codes may be subject to additional documentation requirements and review.

CPT/HCPCS

Proton Delivery	
77520	Proton treatment delivery; simple, without compensation
77522	Proton treatment delivery; simple, with compensation
77523	Proton treatment delivery; intermediate
77525	Proton treatment delivery; complex
Planning	
77301	Intensity modulated radiation therapy plan, including dose volume histogram for target and critical structure partial tolerance specifications (IMRT treatment plan)

77295	3-dimensional radiotherapy plan, including dose-volume histograms (3D conformal treatment plan)

Proton Beam Groupers

Grouper Type	Grouper ID	Grouper Name	Grouper included on order when submitted Dx/Anatomy	Included Codes	Qty Sent
Primary	77520	Delivery	N/A	77520, 77522, 77523, 77525	*n*
Common	61796		N/A	61796, 61797, 61798, 61799	5
Common	63620		N/A	63620, 63621	5
Common	61800		N/A	61800	3
Common	77432		N/A	77432	5
Common	77435		N/A	77435	5
Common	S8030		N/A	S8030	5
Common	77301		N/A	77301	2
Common	77338		N/A	77338	3
Common	77295		N/A	77295	2

ICD-10 Diagnoses

Base of Skull Tumors

Chordoma, chondrosarcoma

C41.2	Malignant neoplasm of vertebral column
C41.4	Malignant neoplasm of pelvic bones, sacrum and coccyx
C41.9	Malignant neoplasm of bone and articular cartilage, unspecified

Sinonasal cancers

C11.0 - C11.9	Malignant neoplasm of nasopharynx
C30.0	Malignant neoplasm of nasal cavity
C31.0 – C31.9	Malignant neoplasm of accessory sinuses

Central Nervous System

Arteriovenous malformation

Q28.2	Arteriovenous malformation of cerebral vessels
Q28.3	Other malformations of cerebral vessels

Central nervous system tumors (excludes pituitary)

C71.0 - C71.9	Malignant neoplasm of brain
C72.0 - C72.9	Malignant neoplasm of spinal cord, cranial nerves, and other parts of central nervous system
C79.31	Secondary malignant neoplasm of brain
C79.49	Secondary malignant neoplasm of other parts of nervous system
D09.8	Carcinoma in situ of other specified sites
D33.0 - D33.9	Benign neoplasm of brain and other parts of central nervous system
D42.0 - D42.9	Neoplasm of uncertain behavior of meninges
D43.0 - D43.9	Neoplasm of uncertain behavior of brain and central nervous system
D49.6	Neoplasm of unspecified behavior of brain

Melanoma

Ocular melanoma

C69.30	Malignant neoplasm of unspecified choroid
C69.40	Malignant neoplasm of unspecified ciliary body
C69.90	Malignant neoplasm of unspecified site of unspecified eye

Pediatric patients

All tumor types

All ICD-10 diagnoses when age less than 21 years

References

1. Allen AM, Pawlicki T, Dong L, et al. An evidence based review of proton beam therapy: the report of ASTRO's emerging technology committee. Radiother Oncol. 2012;103(1):8-11.
2. American Society for Radiation Oncology (ASTRO). ASTRO model policies: proton beam therapy (PBT). Approved 2017 [20 p.]. Available from: https://www.astro.org/Daily-Practice/Reimbursement/Model-Policies.
3. Badiyan SN, Rutenberg MS, Hoppe BS, et al. Clinical outcomes of patients with recurrent lung cancer reirradiated with proton therapy on the Proton Collaborative Group and University of Florida Proton Therapy Institute Prospective Registry studies. Pract Radiat Oncol. 2019;9(4):280-8.
4. Bahn E, Bauer J, Harrabi S, et al. Late contrast enhancing brain lesions in proton-treated patients with low-grade glioma: clinical evidence for increased periventricular sensitivity and variable RBE. Int J Radiat Oncol Biol Phys. 2020;107(3):571-8.
5. Bekelman JE, Lu H, Pugh S, et al. Pragmatic randomised clinical trial of proton versus photon therapy for patients with non-metastatic breast cancer: the Radiotherapy Comparative Effectiveness (RadComp) Consortium trial protocol. BMJ Open. 2019;9(10):e025556.
6. Blue Cross and Blue Shield Association, Evidence-based Practice Center. Radiotherapy treatments for head and neck cancer update. Comparative effectiveness review. Number 144. 2014. Effective Health Care Program, Agency for Healthcare Research and Quality (AHRQ). Available from: https://effectivehealthcare.ahrq.gov/sites/default/files/pdf/head-neck-cancer-update_research.pdf.
7. Boker A, Pilger D, Cordini D, et al. Neoadjuvant proton beam irradiation vs. adjuvant ruthenium brachytherapy in transscleral resection of uveal melanoma. Graefes Arch Clin Exp Ophthalmol. 2018;256(9):1767-75.
8. Brada M, Pijls-Johannesma M, De Ruysscher D. Current clinical evidence for proton therapy. Cancer J. 2009;15(4):319-24.
9. Brown PD, Chung C, Liu DD, et al. A prospective phase II randomized trial of proton radiotherapy vs intensity-modulated radiotherapy for patients with newly diagnosed glioblastoma. Neuro Oncol. 2021;23(8):1337-47.
10. Bush DA, Smith JC, Slater JD, et al. Randomized clinical trial comparing proton beam radiation therapy with transarterial chemoembolization for hepatocellular carcinoma: results of an interim analysis. Int J Radiat Oncol Biol Phys. 2016;95(1):477-82.
11. Chang JY, Verma V, Li M, et al. Proton beam radiotherapy and concurrent chemotherapy for unresectable stage III non-small cell lung cancer: final results of a phase 2 study. JAMA Oncol. 2017;3(8):e172032.
12. Chen YL, Liebsch N, Kobayashi W, et al. Definitive high-dose photon/proton radiotherapy for unresected mobile spine and sacral chordomas. Spine. 2013;38(15):E930-6.
13. Cheng JY, Liu CM, Wang YM, et al. Proton versus photon radiotherapy for primary hepatocellular carcinoma: a propensity-matched analysis. Radiat Oncol. 2020;15(1):159.
14. Chung CS, Yock TI, Nelson K, et al. Incidence of second malignancies among patients treated with proton versus photon radiation. Int J Radiat Oncol Biol Phys. 2013;87(1):46-52.
15. Combs SE. Does proton therapy have a future in CNS tumors? Curr Treat Options Neurol. 2017;19(3):article 12.
16. Cuaron JJ, Chang C, Lovelock M, et al. Exponential increase in relative biological effectiveness along distal edge of a proton Bragg peak as measured by deoxyribonucleic acid double-strand breaks. Int J Radiat Oncol Biol Phys. 2016;95(1):62-9.
17. Dagan R, Bryant C, Li Z, et al. Outcomes of sinonasal cancer treated with proton therapy. Int J Radiat Oncol Biol Phys. 2016;95(1):377-85.
18. DeLaney TF, Liebsch NJ, Pedlow FX, et al. Long-term results of phase II study of high dose photon/proton radiotherapy in the management of spine chordomas, chondrosarcomas, and other sarcomas. J Surg Oncol. 2014;110(2):115-22.
19. ECRI Institute–Penn Medicine Evidence-based Practice Center. Therapies for clinically localized prostate cancer: update of a 2008 systematic review. Comparative effectiveness review. Number 146. 2014. Agency for Healthcare Research and Quality

(AHRQ). Available from: https://effectivehealthcare.ahrq.gov/sites/default/files/pdf/prostate-cancer-therapies-update_research.pdf.

20. Efstathiou JA, Trofimov AV, Zietman AL. Life, liberty, and the pursuit of protons: an evidence-based review of the role of particle therapy in the treatment of prostate cancer. Cancer J. 2009;15(4):312-8.
21. El Sayed I, Trifiletti DM, Lehrer EJ, et al. Protons versus photons for the treatment of chordoma (review). Cochrane Database Syst Rev. 2021(7):article number CD013224.
22. Fitzek MM, Thornton AF, Harsh Gt, et al. Dose-escalation with proton/photon irradiation for Daumas-Duport lower-grade glioma: results of an institutional phase I/II trial. Int J Radiat Oncol Biol Phys. 2001;51(1):131-7.
23. Fitzek MM, Thornton AF, Rabinov JD, et al. Accelerated fractionated proton/photon irradiation to 90 cobalt gray equivalent for glioblastoma multiforme: results of a phase II prospective trial. J Neurosurg. 1999;91(2):251-60.
24. Frank SJ, Blanchard P, Lee JJ, et al. Comparing intensity-modulated proton therapy with intensity-modulated photon therapy for oropharyngeal cancer: the journey from clinical trial concept to activation. Semin Radiat Oncol. 2018;28(2):108-13.
25. Gamez ME, Patel SH, McGee LA, et al. A systematic review on re-irradiation with charged particle beam therapy in the management of locally recurrent skull base and head and neck tumors. Int J Part Ther. 2021;8(1):131-54.
26. Gray PJ, Paly JJ, Yeap BY, et al. Patient-reported outcomes after 3-dimensional conformal, intensity-modulated, or proton beam radiotherapy for localized prostate cancer. Cancer. 2013;119(9):1729-35.
27. Grutters JP, Kessels AG, Pijls-Johannesma M, et al. Comparison of the effectiveness of radiotherapy with photons, protons and carbon-ions for non-small cell lung cancer: a meta-analysis. Radiother Oncol. 2010;95(1):32-40.
28. Gunn GB, Blanchard P, Garden AS, et al. Clinical outcomes and patterns of disease recurrence after intensity modulated proton therapy for oropharyngeal squamous carcinoma. Int J Radiat Oncol Biol Phys. 2016;95(1):360-7.
29. Hahn C, Eulitz J, Peters N, et al. Impact of range uncertainty on clinical distributions of linear energy transfer and biological effectiveness in proton therapy. Med Phys. 2020;47(12):6151-62.
30. Hallemeier CL, Huguet F, Tait D, et al. Randomized trials for esophageal, liver, pancreas, and rectal cancers. Int J Radiat Oncol Biol Phys. 2021;1(2):305-11.
31. Hattangadi-Gluth JA, Chapman PH, Kim D, et al. Single-fraction proton beam stereotactic radiosurgery for cerebral arteriovenous malformations. Int J Radiat Oncol Biol Phys. 2014;89(2):338-46.
32. Hoppe BS, Hill-Kayser CE, Tseng YD, et al. Consolidative proton therapy after chemotherapy for patients with Hodgkin lymphoma. Ann Oncol. 2017;28(9):2179-84.
33. Indelicato DJ, Bradley JA, Rotondo RL, et al. Outcomes following proton therapy for pediatric ependymoma. Acta Oncol. 2018;57(5):644-8.
34. Indelicato DJ, Rotondo RL, Uezono H, et al. Outcomes following proton therapy for pediatric low-grade glioma. Int J Radiat Oncol Biol Phys. 2019;104(1):149-56.
35. Jett JR, Schild SE, Kesler KA, et al. Treatment of small cell lung cancer: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013;143(5 Suppl):e400S-e19S.
36. Kahalley LS, Douglas Ris M, Mahajan A, et al. Prospective, longitudinal comparison of neurocognitive change in pediatric brain tumor patients treated with proton radiotherapy versus surgery only. Neuro Oncol. 2019;21(6):809-18.
37. Kim TH, Koh YH, Kim BH, et al. Proton beam radiotherapy vs. radiofrequency ablation for recurrent hepatocellular carcinoma: a randomized phase trial. J Hepatol. 2020;74(3):603-12.
38. Kong FS. What happens when proton meets randomization: is there a future for proton therapy? J Clin Oncol. 2018;36(18):1777-9.
39. Konig L, Jakel C, von Knebel Doeberitz N, et al. Glioblastoma radiotherapy using intensity modulated radiotherapy (IMRT) or proton radiotherapy-GRIPS trial (Glioblastoma Radiotherapy via IMRT or Proton BeamS): a study protocol for a multicenter, prospective, open-label, randomized, two-arm, phase III study. Radiat Oncol. 2021;16(1):240.
40. Lee A, Kitpanit S, Chilov M, et al. A systematic review of proton therapy for the management of nasopharyngeal cancer. Int J Part Ther. 2021;8(1):119-30.
41. Leeman JE, Romesser PB, Zhou Y, et al. Proton therapy for head and neck cancer: expanding the therapeutic window. Lancet Oncol. 2017;18(5):e254-e65.
42. Lewis GD, Holliday EB, Kocak-Uzel E, et al. Intensity-modulated proton therapy for nasopharyngeal carcinoma: decreased radiation dose to normal structures and encouraging clinical outcomes. Head Neck. 2016;38 Suppl 1:E1886-95.
43. Li M, Li X, Yao L, et al. Clinical efficacy and safety of proton and carbon ion radiotherapy for prostate cancer: a systematic review and meta-analysis. Front Oncol. 2021;11(article 709530):15 pp.
44. Liao Z, Lee JJ, Komaki R, et al. Bayesian adaptive randomization trial of passive scattering proton therapy and intensity-modulated photon radiotherapy for locally advanced non-small-cell lung cancer. J Clin Oncol. 2018;36(18):1813-22.
45. Lin SH, Hobbs BP, Verma V, et al. Randomized phase IIB trial of proton beam therapy versus intensity-modulated radiation therapy for locally advanced esophageal cancer. J Clin Oncol. 2020;38(14):1569-79.

46. Liu C, Zheng D, Bradley JA, et al. Incorporation of the LETd-weighted biological dose in the evaluation of breast intensity-modulated proton therapy plans. Acta Oncol. 2021;60(2):252-9.
47. Macomber MW, Bowen SR, Gopan O, et al. Heart dose and outcomes in radiation treatment for esophageal cancer. Cureus. 2018;10(3):e2378.
48. Manzar GS, Lester SC, Routman DM, et al. Comparative analysis of acute toxicities and patient reported outcomes between intensity-modulated proton therapy (IMPT) and volumetric modulated arc therapy (VMAT) for the treatment of oropharyngeal cancer. Radiother Oncol. 2020;147:64-74.
49. Marshall TI, Chaudhary P, Michaelidesova A, et al. Investigating the implications of a variable RBE on proton dose fractionation across a clinical pencil beam scanned spread-out Bragg peak. Int J Radiat Oncol Biol Phys. 2016;95(1):70-7.
50. Marteinsdottir M, Wang CC, McNamara A, et al. The impact of variable relative biological effectiveness in proton therapy for left-sided breast cancer when estimating normal tissue complications in the heart and lung. Phys Med Biol. 2021;66(3):035023.
51. McDonald MW, Liu Y, Moore MG, et al. Acute toxicity in comprehensive head and neck radiation for nasopharynx and paranasal sinus cancers: cohort comparison of 3D conformal proton therapy and intensity modulated radiation therapy. Radiat Oncol. 2016;11(32):[10 p.].
52. McDonald MW, Zolali-Meybodi O, Lehnert SJ, et al. Reirradiation of recurrent and second primary head and neck cancer with proton therapy. Int J Radiat Oncol Biol Phys. 2016;96(4):808-19.
53. Mishra MV, Aggarwal S, Bentzen SM, et al. Establishing evidence-based indications for proton therapy: an overview of current clinical trials. Int J Radiat Oncol Biol Phys. 2017;97(2):228-35.
54. Mizumoto M, Tsuboi K, Igaki H, et al. Phase I/II trial of hyperfractionated concomitant boost proton radiotherapy for supratentorial glioblastoma multiforme. Int J Radiat Oncol Biol Phys. 2010;77(1):98-105.
55. Mizumoto M, Yamamoto T, Takano S, et al. Long-term survival after treatment of glioblastoma multiforme with hyperfractionated concomitant boost proton beam therapy. Pract Radiat Oncol. 2015;5(1):e9-16.
56. Moreno AC, Frank SJ, Garden AS, et al. Intensity modulated proton therapy (IMPT) - the future of IMRT for head and neck cancer. Oral Oncol. 2019;88:66-74.
57. Mutter RW, Choi JI, Jimenez RB, et al. Proton therapy for breast cancer: a consensus statement from the Particle Therapy Cooperative Group Breast Cancer Subcommittee. Int J Radiat Oncol Biol Phys. 2021;111(2):337-59.
58. Nakajima K, Iwata H, Ogino H, et al. Clinical outcomes of image-guided proton therapy for histologically confirmed stage I non-small cell lung cancer. Radiat Oncol. 2018;13(1):[9 p.].
59. National Cancer Institute (NCI). NCI dictionary of cancer terms [Internet]. [cited 2022 July 20]. Available from: https://www.cancer.gov/publications/dictionaries/cancer-terms.
60. National Institutes of Health (NIH). U.S. National Library of Medicine (NLM). Finding and using health statistics: glossary [Internet]. [Last Reviewed: April 3, 2019] [cited 2022 July 20]. Available from: https://www.nlm.nih.gov/nichsr/usestats/glossary.html.
61. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer (Version 4.2022). Available at http://www.nccn.org. ©National Comprehensive Cancer Network, 2022.
62. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Small Cell Lung Cancer (Version 3.2022). Available at http://www.nccn.org. ©National Comprehensive Cancer Network, 2022.
63. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Prostate Cancer (Version 4.2022). Available at http://www.nccn.org. ©National Comprehensive Cancer Network, 2022.
64. Olsen DR, Bruland OS, Frykholm G, et al. Proton therapy - a systematic review of clinical effectiveness. Radiother Oncol. 2007;83(2):123-32.
65. Pan HY, Jiang J, Hoffman KE, et al. Comparative toxicities and cost of intensity-modulated radiotherapy, proton radiation, and stereotactic body radiotherapy among younger men with prostate cancer. J Clin Oncol. 2018;36(18):1823-30.
66. Pasalic D, Ludmir EB, Allen PK, et al. Patient-reported outcomes, physician-reported toxicities, and treatment outcomes in a modern cohort of patients with sinonasal cancer treated using proton beam therapy. Radiother Oncol. 2020;148:258-66.
67. Patel S, Nunna RS, Ryoo JS, et al. Outcomes and patterns of care in adult skull base chondrosarcoma patients in the United States. World Neurosurg. 2021;150:71-83.
68. Patel SH, Wang Z, Wong WW, et al. Charged particle therapy versus photon therapy for paranasal sinus and nasal cavity malignant diseases: a systematic review and meta-analysis. Lancet Oncol. 2014;15(9):1027-38.
69. Paulino AC, Mahajan A, Ye R, et al. Ototoxicity and cochlear sparing in children with medulloblastoma: proton vs. photon radiotherapy. Radiother Oncol. 2018;128(1):128-32.
70. Phan J, Sio TT, Nguyen TP, et al. Reirradiation of head and neck cancers with proton therapy: outcomes and analyses. Int J Radiat Oncol Biol Phys. 2016;96(1):30-41.
71. Pompos A, Durante M, Choy H. Heavy ions in cancer therapy. JAMA Oncol. 2016;2(12):1539-40.
72. Qi WX, Fu S, Zhang Q, et al. Charged particle therapy versus photon therapy for patients with hepatocellular carcinoma: a systematic review and meta-analysis. Radiother Oncol. 2015;114(3):289-95.

73. Romesser PB, Cahlon O, Scher E, et al. Proton beam radiation therapy results in significantly reduced toxicity compared with intensity-modulated radiation therapy for head and neck tumors that require ipsilateral radiation. Radiother Oncol. 2016;118(2):286-92.
74. Romesser PB, Cahlon O, Scher ED, et al. Proton beam reirradiation for recurrent head and neck cancer: multi-institutional report on feasibility and early outcomes. Int J Radiat Oncol Biol Phys. 2016;95(1):386-95.
75. Ronson BB, Schulte RW, Han KP, et al. Fractionated proton beam irradiation of pituitary adenomas. Int J Radiat Oncol Biol Phys. 2006;64(2):425-34.
76. Sachsman S, Flampouri S, Li Z, et al. Proton therapy in the management of non-Hodgkin lymphoma. Leuk Lymphoma. 2015;56(9):2608-12.
77. Saltzman AF, Cost NG. Current treatment of pediatric bladder and prostate rhabdomyosarcoma. Curr Urol Rep. 2018;19(1):[9 p.].
78. Sanda MG, Chen RC, Crispino T, et al. Clinically localized prostate cancer: AUA/ASTRO/SUO guideline [Internet]. American Urological Association; 2017 [cited 2022 Mar 31]. Available from: https://www.auanet.org/guidelines/prostate-cancer-clinically-localized-guideline.
79. Sanford NN, Pursley J, Noe B, et al. Protons versus photons for unresectable hepatocellular carcinoma: liver decompensation and overall survival. Int J Radiat Oncol Biol Phys. 2019;105(1):64-72.
80. Seifert V, Stolke D, Mehdorn HM, et al. Clinical and radiological evaluation of long-term results of stereotactic proton beam radiosurgery in patients with cerebral arteriovenous malformations. J Neurosurg. 1994;81(5):683-9.
81. Sheets NC, Goldin GH, Meyer AM, et al. Intensity-modulated radiation therapy, proton therapy, or conformal radiation therapy and morbidity and disease control in localized prostate cancer. JAMA. 2012;307(15):1611-20.
82. Simone CB, 2nd, Bogart JA, Cabrera AR, et al. Radiation therapy for small cell lung cancer: an ASTRO clinical practice guideline. Pract Radiat Oncol. 2020;10(3):158-73.
83. Sio TT, Lin HK, Shi Q, et al. Intensity modulated proton therapy versus intensity modulated photon radiation therapy for oropharyngeal cancer: first comparative results of patient-reported outcomes. Int J Radiat Oncol Biol Phys. 2016;95(4):1107-14.
84. Steinmeier T, Schulze Schleithoff S, Timmermann B. Evolving radiotherapy techniques in paediatric oncology. Clin Oncol. 2019;31(3):142-50.
85. Verma V, Rwigema JM, Malyapa RS, et al. Systematic assessment of clinical outcomes and toxicities of proton radiotherapy for reirradiation. Radiother Oncol. 2017;125(1):21-30.
86. Verma V, Shah C, Mehta MP. Clinical outcomes and toxicity of proton radiotherapy for breast cancer. Clin Breast Cancer. 2016;16(3):145-54.
87. Verma V, Simone CB, 2nd, Mishra MV. Quality of life and patient-reported outcomes following proton radiation therapy: a systematic review. J Natl Cancer Inst. 2018;110(4):341-53.
88. Wang J, Wei C, Tucker SL, et al. Predictors of postoperative complications after trimodality therapy for esophageal cancer. Int J Radiat Oncol Biol Phys. 2013;86(5):885-91.
89. Wang Z, Nabhan M, Schild SE, et al. Charged particle radiation therapy for uveal melanoma: a systematic review and meta-analysis. Int J Radiat Oncol Biol Phys. 2013;86(1):18-26.
90. Widesott L, Amichetti M, Schwarz M. Proton therapy in lung cancer: clinical outcomes and technical issues. a systematic review. Radiother Oncol. 2008;86(2):154-64.
91. Wiltink LM, Nout RA, Fiocco M, et al. No increased risk of second cancer after radiotherapy in patients treated for rectal or endometrial cancer in the randomized TME, PORTEC-1, and PORTEC-2 trials. J Clin Oncol. 2015;33(15):1640-6.
92. Yang P, Xu T, Gomez DR, et al. Patterns of local-regional failure after intensity modulated radiation therapy or passive scattering proton therapy with concurrent chemotherapy for non-small cell lung cancer. Int J Radiat Oncol Biol Phys. 2019;103(1):123-31.
93. Yu JB, Soulos PR, Herrin J, et al. Proton versus intensity-modulated radiotherapy for prostate cancer: patterns of care and early toxicity. J Natl Cancer Inst. 2013;105(1):25-32.
94. Zakeri K, Wang H, Kang JJ, et al. Outcomes and prognostic factors of major salivary gland tumors treated with proton beam radiation therapy. Head Neck. 2021;43(4):1056-62.
95. Zelefsky MJ, Pei X, Teslova T, et al. Secondary cancers after intensity-modulated radiotherapy, brachytherapy and radical prostatectomy for the treatment of prostate cancer: incidence and cause-specific survival outcomes according to the initial treatment intervention. BJU Int. 2012;110(11):1696-701.
96. Zhou J, Yang B, Wang X, et al. Comparison of the effectiveness of radiotherapy with photons and particles for chordoma after surgery: a meta-analysis. World Neurosurg. 2018;117:46-53.
97. Zietman AL, Bae K, Slater JD, et al. Randomized trial comparing conventional-dose with high-dose conformal radiation therapy in early-stage adenocarcinoma of the prostate: long-term results from Proton Radiation Oncology Group/American College of Radiology 95-09. J Clin Oncol. 2010;28(7):1106-11.

Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer 4.2022, Non-Small Cell Lung Cancer 3.2022, and Prostate Cancer 4.2022. Available at: http://www.nccn.org. Accessed July

20, 2022. ©National Comprehensive Cancer Network, 2022. To view the most recent and complete version of the Guidelines, go online to http://www.nccn.org.

These Guidelines are a work in progress that may be refined as often as new significant data becomes available.

The NCCN Guidelines® are a statement of consensus of its authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult any NCCN Guidelines® is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

History

Status	Review Date	Effective Date	Action
Reaffirmed	07/18/2023	Unchanged	Independent Multispecialty Physician Panel (IMPP) review. Guidelines reaffirmed.
Reaffirmed	05/09/2022	Unchanged	Independent Multispecialty Physician Panel (IMPP) review. Guidelines reaffirmed. Updated discussion and references.
Revised	05/26/2021	03/13/2022	IMPP review. Revised proton beam therapy considerations with discussion of recent clinical studies of treatments for breast cancer, CNS lesions, head and neck cancer, hepatocellular cancer, and other GI cancers. Added references.
Revised	05/11/2020	03/14/2021	IMPP review. Added new indication for Hepatocellular carcinoma and intrahepatic cholangiocarcinoma based on literature. Added grouper chart to code section.
Revised	3/25/2019	11/10/2019	IMPP review. Revised proton beam therapy considerations and indications for sinonasal cancer, melanoma of the uveal tract, and pediatric tumors. Updated references.
Revised	07/11/2018	03/09/2019	IMPP review. Added the General Clinical Guideline.
Revised	12/12/2017	03/12/2018	IMPP review. Revised proton beam therapy considerations and indications. Updated references.
Reviewed	06/13/2017	09/05/2017	IMPP review.
Reviewed	07/26/2016	02/20/2017	IMPP review.
Revised	08/27/2015	01/01/2016	IMPP review. Revised indications.
Created	05/14/2014	09/05/2014	IMPP review. Original effective date.