

CLINICAL APPROPRIATENESS GUIDELINES

RADIATION ONCOLOGY

Appropriate Use Criteria: Proton Beam Therapy

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Description and Application of the Guidelines

The AIM Clinical Appropriateness Guidelines (hereinafter “the AIM 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 AIM, 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
- 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 AIM 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. AIM reviews all of its Guidelines at least annually.

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

AIM 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 AIM 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, AIM will review requests based on health plan medical policy/guidelines in lieu of the AIM Guidelines.

The Guidelines may also be used by the health plan or by AIM 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.

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Proton Beam Therapy

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.

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. 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 chondrosarcoma 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.

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.

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%, $p=0.06$) 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 ($p<0.001$).

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

Other Gastrointestinal Cancers

There have been few reports of PBT to treat esophageal and gastroesophageal junction tumors. There are no prospective randomized trials. 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. Several phase II trials are underway but there is insufficient evidence to draw conclusions on how PBT compares to photon based therapy for esophageal cancer.

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 investigational 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 in 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.

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 study 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.”

The body of evidence on PBT for prostate cancer largely consists of retrospective studies performed at tertiary centers. The evidence quality is low and there are insufficient data 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 ($p=0.29$). 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 ($p=0.085$). 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, as there is inherent bias among both patients and investigators that favors proton therapy. 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 **OR**
- 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 **AND**
 - 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

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

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 cancer
- Lung cancer
- Lymphoma (Hodgkin and non-Hodgkin)
- Pancreatic cancer
- Prostate cancer

Coding

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The following codes for treatments and procedures applicable to this document are included for informational purposes. Inclusion or exclusion of a procedure, diagnosis, or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

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

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)

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

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

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History

Status	Review Date	Effective Date	Action
Archived	n/a	03/14/2021	Archived.
Revised	03/25/2019	11/10/2019	Independent Multispecialty Physician Panel (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.

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