Molina Clinical Policy
Proton and Neutron Beam Radiation Therapy Services
Policy No. 464
Last Approval: 10/14/2026
Next Review Due By: October 2027

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STATEMENT

General Information

- *It is an expectation that all patients receive care/services from a licensed clinician. All appropriate supporting documentation, including recent pertinent office visit notes, laboratory data, and results of any special testing must be provided. If applicable: All prior relevant imaging results and the reason that alternative imaging cannot be performed must be included in the documentation submitted.*
- *Where a specific clinical indication is not directly addressed in this guideline, medical necessity determination will be made based on widely accepted standard of care criteria. These criteria are supported by evidence-based or peer-reviewed sources such as medical literature, societal guidelines and state/national recommendations. This guideline is not a prescription for treatment. All individual treatment decisions are the responsibility of the treating physician.*
- *The guideline criteria in the following sections were developed utilizing evidence-based and peer-reviewed resources from medical publications and societal organization guidelines as well as from widely accepted standard of care, best practice recommendations.*

Purpose

This guideline provides indications for the use of Proton Beam Radiation Therapy (PBRT) and Neutron Beam Radiation Therapy (NBRT).

Clinical Reasoning

This guideline considers treatment endorsed by professional organizations (i.e. the American Society for Radiation Oncology and the National Comprehensive Cancer Network). It approves many treatment regimens that fall within that guidance, but it is also modified by significant factors such as the level of evidence.

INDICATIONS

Proton Beam Radiation Therapy

Specific Cancer Types

Proton beam radiation therapy is considered medically necessary for the following conditions:

- Acoustic Neuroma [1–3]
- Arteriovenous Malformations (AVM) [4,5]

- Base of skull tumors with no metastatic disease, including but not limited to [6–8]:
  - Chordoma
  - Chondrosarcoma
  - Other histologies arising in this site
- Cavernous sinus cancer with no metastatic disease [6,7]
- Ethmoidal, frontal maxillary and sphenoidal (paranasal) sinus cancers with no metastatic disease [6,7,9]
- Intraocular (uveal) melanoma with no metastatic disease [10,11]
- Kidney-adjacent target volume in a patient with single or transplanted pelvic kidney, when maximal avoidance of the organ is critical [12]
- Liver (Hepatocellular Carcinoma) and intrahepatic biliary cancers with no metastatic disease [13], including:
  - Localized, unresectable hepatocellular carcinoma or intrahepatic cholangiocarcinoma [14]
  - Previously untreated hepatocellular carcinoma [15]
  - Recurrent hepatocellular carcinoma [16]
- Meningioma, benign and malignant [8,17–19]
- Nasal cavity cancer with no metastatic disease [20]
- Nasopharyngeal cancer with no metastatic disease [21,22]
- Pituitary adenoma [19,24]
- Primary central nervous system tumors, benign and malignant [25]
- Primary tumors of the mediastinum with no metastatic disease, including [26–29]:
  - Hodgkin and non-Hodgkin lymphomas
  - Thoracic sarcomas
  - Thymoma and thymic carcinomas

PBRT Indications for Pediatric Cancers

- PBRT will be approved for pediatric cancer patients with tumors in which radiation therapy is required. A pediatric cancer patient is defined as ≤ 18 years old or < 21 years old with cancers that display the same histology as common pediatric cancers.
- Please refer to NCCN Clinical Practice Guidelines in Oncology for cancer specific information.

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Cases of Re-Irradiation

- PBRT will be approved for **all** patients who have received any previous radiation to an anatomic location and now require an additional course of radiation to that same anatomic area. [32,33]
  - The radiation dose and the number of fractions prescribed for each patient receiving re-irradiation will be based on that patient's prior treatment history.
  - The dose and the number of fractions will be left to the discretion of the treating physician and, when possible, based on peer reviewed literature.

Neutron Beam Radiation Therapy (NBRT)

Specific Cancer Types

- Salivary gland cancers that are:
  - Unresectable or recurrent [34]

CODING AND STANDARDS

Codes

Code	Description
32701	Thoracic target(s) delineation for stereotactic body radiation therapy (SRS/SBRT), (photon or particle beam), entire course of treatment
61796	Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); 1 simple cranial lesion
61798	Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); 1 complex cranial lesion
63620	Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); 1 spinal lesion
77261	Therapeutic radiology treatment planning; simple
77262	Therapeutic radiology treatment planning; intermediate
77263	Therapeutic radiology treatment planning; complex

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Code	Description
77280	Therapeutic radiology simulation-aided field setting; simple
77285	Therapeutic radiology simulation-aided field setting; intermediate
77290	Therapeutic radiology simulation-aided field setting; complex
77295	3-dimensional radiotherapy plan, including dose-volume histograms
77299	Unlisted procedure, therapeutic radiology clinical treatment planning
77300	Basic radiation dosimetry calculation, central axis depth dose calculation, TDF, NSD, gap calculation, off axis factor, tissue inhomogeneity factors, calculation of non-ionizing radiation surface and depth dose, as required during course of treatment, only when prescribed by the treating physician
77301	Intensity modulated radiotherapy plan, including dose-volume histograms for target and critical structure partial tolerance specifications
77321	Special teletherapy port plan, particles, hemibody, total body
77331	Special dosimetry (e.g., TLD, microdosimetry) (specify), only when prescribed by the treating physician
77332	Treatment devices, design and construction; simple (simple block, simple bolus)
77333	Treatment devices, design and construction; intermediate (multiple blocks, stents, bite blocks, special bolus)
77334	Treatment devices, design and construction; complex (irregular blocks, special shields, compensators, wedges, molds or casts)
77336	Continuing medical physics consultation, including assessment of treatment parameters, quality assurance of dose delivery, and review of patient treatment documentation in support of the radiation oncologist, reported per week of therapy
77338	Multi-leaf collimator (MLC) device(s) for intensity modulated radiation therapy (IMRT), design and construction per IMRT plan
77370	Special medical radiation physics consultation

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Code	Description
77372	Radiation treatment delivery, stereotactic radiosurgery (SRS), complete course of treatment of cranial lesion(s) consisting of 1 session; linear accelerator based
77373	Stereotactic body radiation therapy, treatment delivery, per fraction to 1 or more lesions, including image guidance, entire course not to exceed 5 fractions
77387	Guidance for localization of target volume for delivery of radiation treatment, includes intrafraction tracking, when performed
77399	Unlisted procedure, medical radiation physics, dosimetry and treatment devices, and special services
77423	High energy neutron radiation treatment delivery, 1 or more isocenter(s) with coplanar or non-coplanar geometry with blocking and/or wedge, and/or compensator(s)
77427	Radiation treatment management, 5 treatments
77432	Stereotactic radiation treatment management of cranial lesion(s) (complete course of treatment consisting of 1 session)
77435	Stereotactic body radiation therapy, treatment management, per treatment course, to 1 or more lesions, including image guidance, entire course not to exceed 5 fractions
77470	Special treatment procedure (e.g., total body irradiation, hemibody radiation, per oral or endocavitary irradiation)
77499	Unlisted procedure, therapeutic radiology treatment management
77520	Proton treatment delivery; simple, without compensation
77522	Proton treatment delivery; simple, with compensation
77523	Proton treatment delivery; intermediate
77525	Proton treatment delivery; complex

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Code	Description
G0339	Image guided robotic linear accelerator-based stereotactic radiosurgery, complete course of therapy in one session or first session of fractionated treatment
G0340	Image guided robotic linear accelerator-based stereotactic radiosurgery, delivery including collimator changes and custom plugging, fractionated treatment, all lesions, per session, second through fifth sessions, maximum five sessions per course of treatment
+61797	Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); each additional cranial lesion, simple (List separately in addition to code for primary procedure)
+61799	Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); each additional cranial lesion, complex (List separately in addition to code for primary procedure)
+61800	Application of stereotactic headframe for stereotactic radiosurgery (List separately in addition to code for primary procedure)
+63621	Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); each additional spinal lesion (List separately in addition to code for primary procedure)
+77293	Respiratory motion management simulation (List separately in addition to code for primary procedure)

BACKGROUND

Definitions

Re-irradiation is defined as the use of additional radiation treatment to treat an area of the body that has already received prior radiation to that same area. The term "re-irradiation" does not apply to situations where a patient has received radiation treatment to one area of the body (i.e. the lung) and now requires radiation to a completely separate area of the body (i.e. the brain).

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SUMMARY OF EVIDENCE

Proton Beam Radiation Therapy (PBRT) [32]: PBRT is indicated for specific cancer types due to its precision in targeting tumors while minimizing damage to surrounding healthy tissues. This therapy is particularly beneficial for cancers located near critical structures that cannot be sufficiently spared using other radiation treatments like intensity modulated radiation therapy (IMRT) or stereotactic radiosurgery (SRS). [12]

PBRT is also approved for all pediatric patients (≤18 years old) and for patients <21 years old with cancers that display the same histology as common pediatric cancers. Additionally, PBRT is indicated for cases of re-irradiation, where additional radiation treatment is required for an area that has already received prior radiation.

Neutron Beam Radiation Therapy (NBRT) [34]: NBRT is indicated for salivary gland cancers that are unresectable or recurrent. This therapy is beneficial due to its ability to deliver high-energy neutrons that can effectively target and destroy cancer cells.

ANALYSIS OF EVIDENCE

Proton Beam Radiation Therapy

Acoustic Neuroma

Multiple studies have demonstrated that PBRT achieves higher tumor control rates than photon therapy, with a similar toxicity profile. Local tumor control (LTC) rates varied from 85-100% across studies, with the median follow-up for those values ranging from 2.2 to 7.4 years. [3] Additionally, Barnes et al [35] demonstrated that hearing preservation rates were greater for lower doses (44% at 54 Gy, 64% at 50.4Gy).

Arteriovenous Malformations (AVM)

Experience with hypofractionated stereotactic PBRT demonstrated that large intracranial arteriovenous malformations (AVMs) can be safely treated with clinically meaningful rates of obliteration and low complication risk, offering an effective noninvasive alternative when surgical or endovascular options are limited. In this series of 64 patients with confirmed AVMs treated since 1993, lesions were stratified by volume (<14 cc vs. ≥14 cc) and irradiated under stereotactic guidance using a 200 MeV fixed, horizontal proton beam. The mean minimum target dose was 17.37 single-fraction equivalent cobalt Gray equivalent (SFE cGyE), delivered predominantly in two or three fractions. [36] Angiographic obliteration was achieved in 67% of AVMs smaller than 14 cc and 43% of those 14 cc or larger, confirming a strong volume–response relationship. Treatment was well tolerated: Grade IV acute toxicity occurred in 3%, transient delayed effects in 23%, and permanent neurological changes in only 3 patients.

Among the 1329 patients treated at the Harvard Cyclotron Laboratory for AVMs, follow-up was available for 1250 individuals (94%). [37] The median radiation dose was 10.5 Gy and the

median target volume 33.7 cm³. The analysis revealed that complication risk correlated strongly with radiation dose, target volume, patient age, and AVM location, particularly for thalamic and brainstem lesions. Of the 1043 patients treated with a dose predicted by the Kjellberg isoeffective centile curve to have a less than 1% complication risk, 1.8% experienced radiation-related complications. The actual complication rates were 4.7% for 128 patients treated at Kjellberg risk centile doses of 1 to 1.8%, and 34% for 61 patients treated at risk centile doses of 2 to 2.5%. These findings underscore the necessity of modern dose–volume modeling and individualized treatment planning in PBRT for AVMs, emphasizing that risk escalates nonlinearly with increasing dose and target size.

Base of Skull Tumors

For patients with skull base chondrosarcoma, combining maximal safe surgical resection with high-dose PBRT achieves exceptional long-term tumor control and survival, confirming its role as the reference standard for curative treatment. In a cohort of 159 patients treated with either protons alone or a proton–photon combination to a median total dose of 70.2 Gy relative biologic effectiveness, outcomes demonstrated 5-year local control (LC) of 96.4% and 10-year LC of 93.5%, alongside 5-year overall survival (OS) of 94.9% and 10-year OS of 87%. [38] Local relapse occurred in only five cases, and multivariate analysis identified younger age (<40 years) and primary presentation as independent favorable prognostic factors for progression-free survival (PFS) and OS. Importantly, extent of surgery, dosimetric parameters, and proximity to critical organs at risk (OARs) did not adversely impact LC or OS, reflecting the precision and conformality of proton therapy in this anatomically complex region. These results establish that systematic high-dose postoperative PBRT provides durable tumor control with a low toxicity profile.

Evidence synthesized from a systematic review of the literature demonstrates that PBRT, when administered following maximal safe resection, achieves durable long-term tumor control and a favorable safety profile in patients with skull base chondrosarcoma, a rare, slow-growing but potentially lethal malignancy. Across four institutional series encompassing 254 patients, postoperative or definitive PBRT provided sustained LC and long-term cure rates, even in advanced or incompletely resected disease, with relatively low incidence of significant toxicity. [39]

Delivering curative radiation doses for spine sarcomas requires advanced modalities capable of respecting spinal cord and nerve tolerance. In a Phase II clinical trial enrolling 50 patients with thoracic, lumbar, and sacral spine or paraspinal sarcomas, including chordoma and chondrosarcoma, treatment achieved 5-year LC of 78%, recurrence-free survival (RFS) of 63%, and OS of 87%. [40] Among patients treated at initial presentation, local recurrence occurred in only 5.6%, compared to 50% in those treated for recurrence ($p < 0.001$), confirming superior outcomes when PBRT is integrated early. No radiation-induced myelopathy occurred despite spinal cord dose limits of 63 Gy RBE to surface and 54 Gy RBE to center, demonstrating the safety of high-dose proton-based therapy in close proximity to neural structures. These findings reinforce that PBT enables safe escalation beyond conventional photon tolerances, achieving durable tumor control in anatomically constrained spine sarcomas where surgical margins are often positive or unresectable.

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In the management of chordoma and chondrosarcoma, outcomes are significantly enhanced when PBRT is used to safely deliver high-dose radiation (≥70 Gy) in either definitive or perioperative settings. In a national database analysis of 1,578 patients (863 with chondrosarcoma and 715 with chordoma) treated with nonpalliative PBRT or conventional radiotherapy (RT) between 2003 and 2014, PBRT and dose escalation were both associated with improved OS. [41] For chondrosarcoma, patients receiving definitive (RT) with higher dose levels had superior 5-year OS (40.6% vs. 16.9%, p = 0.006), while those treated with PBRT demonstrated a significant survival benefit (75.0% vs. 19.1%, p = 0.046). Among chordoma patients, PBRT was likewise associated with markedly improved 5-year OS (100% vs. 34.1%, p = 0.031). Higher doses correlated with superior outcomes in both definitive (79.0% vs. 54.1%, p = 0.027) and perioperative (83.3% vs. 77.4%, p = 0.007) settings. These results suggest that proton therapy enables safe and effective dose escalation, while minimizing radiation-induced morbidity.

Intraocular (Uveal) Melanoma

Evidence from a matched comparative study demonstrated that both fractionated stereotactic photon beam radiotherapy (fSRT) and PBRT provide excellent long-term tumor control in uveal melanoma, with PBRT achieving significantly lower ocular morbidity and fewer vision-threatening complications. [11] In a cohort of 306 matched patients (153 per group) treated in the Netherlands and the United Kingdom, 5-year LTC rates were equivalent at 96.1%, confirming that eye-sparing RT is highly effective for small- and medium-sized uveal melanoma. However, PBRT demonstrated a superior safety profile. The incidence of vitreous hemorrhage was significantly lower with PBRT (3.3%) compared to fSRT (18.3%) ($p < 0.001$). Neovascular glaucoma occurred in 8.5% of patients after PBT vs. 17.6% after fSRT (p = 0.027), and secondary enucleation rates were 5.9% for PBT vs. 12.4% for fSRT at 5 years. Rates of optic neuropathy (7–9%) and maculopathy (11–12%) were similar between modalities, but tumor size and proximity to the optic disc or fovea remained key predictors of complications.

Long term follow-up from a large single-institution series of 336 patients provides robust support for PBT as a medically necessary and clinically effective globe-sparing alternative to enucleation for large choroidal melanomas. [42] At a median follow-up approaching 10 years, LTC was achieved in 87.5% of patients, and eye retention was maintained in 70.4%, confirming durable disease management despite inclusion of large and optic nerve–adjacent tumors. Visual function was preserved in a subset of patients, with visual acuity ≥20/200 in 8.7% and counting-fingers vision in 22.4% at 10 years. Tumor recurrence occurred in 12.5% of patients, with larger basal diameter significantly associated with recurrence (p = .02). Despite this, melanoma-related mortality (48.5% at 10 years) was comparable to outcomes after enucleation, with no evidence that globe preservation compromised survival.

A large cohort of 1,406 patients treated at the Orsay Proton Therapy Center demonstrates that PBRT achieves durable tumor control, high eye preservation, and favorable survival outcomes in uveal melanoma. [43] At a median follow-up of 73 months, LC at 5 years reached 96%, underscoring the efficacy of PBRT for achieving durable tumor eradication. The 5-year OS rate was 79%, while the 5-year metastasis-free survival rate was 80.6%, indicating robust long-term disease control and survival outcomes. The 5-year enucleation rate for treatment-related

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complications was 7.7%, emphasizing PBRT's ocular-sparing advantage. On multivariate analysis, tumor diameter ($p = 0.003$) and macular dose exposure ($p = 0.01$) were independently associated with LC. However, small macular areas receiving 30 GCE are associated with worse LC. Prognostic factors for OS included age ($p < 0.0001$), gender ($p = 0.0003$), tumor site ($p < 0.0001$), tumor thickness ($p = 0.02$), and tumor diameter ($p < 0.0001$). Large retinal areas receiving 30 GCE and tumor sites (median and anterior) are prognostic factors for survival outcomes. Determinants of metastasis-free survival were age ($p = 0.0042$), retinal detachment ($p = 0.01$), tumor site ($p < 0.0001$), tumor volume ($p < 0.0001$), local recurrence ($p < 0.0001$), and retinal dose >30 CGE ($p = 0.002$). The risk of enucleation was strongly correlated with tumor thickness ($p < 0.0001$) and lens dose ($p = 0.0002$). [43]

Liver (Hepatocellular Carcinoma) and Intrahepatic Bile Duct Cancers

In a large single-institution study of previously untreated hepatocellular carcinoma (HCC) (ECOG 0–2, Child-Pugh grade A/B), 129 patients were treated with PBRT. At 5 years, LTC remained high across subgroups—94% (stage 0/A), 87% (stage B), and 75% (stage C) - with corresponding OS rates of 69%, 66%, and 25%, respectively. Notably, among 15 patients with tumor thrombi in major vessels, PBRT achieved 5-year LTC of 90% and OS of 34%, underscoring disease control in a population typically unsuitable for other local therapies. Performance status (PS 0 vs 1–2) emerged as a significant prognostic factor for OS ($p < .05$). Treatment tolerance was excellent, with no grade ≥3 adverse effects observed, confirming the superior hepatic sparing of PBRT. [15]

Clinical evidence demonstrates that PBRT provides safe, durable, and effective tumor control for patients with unresectable HCC and intrahepatic cholangiocarcinoma (ICC). In a phase II, multi-institutional trial, patients treated with high-dose, hypofractionated proton therapy achieved a two-year LC rate of 94.8% and a two-year OS of 63.2% for HCC. They also achieved a two-year LC rate of 94.1% and a two-year OS of 46.5% for ICC. Importantly, these outcomes were achieved without significant hepatic toxicity. [44]

A phase III randomized non-inferiority trial demonstrated that PBRT provides LTC and PFS that are non-inferior to radiofrequency ablation in patients with recurrent or residual HCC. In this study of patients with limited recurrent disease (tumor size less than 3 centimeters and two or fewer lesions), the two-year local progression-free survival (LPFS) in the per-protocol population was 94.8% for PBRT versus 83.9% for RFA ($p < 0.001$). In the intention-to-treat population, the two-year LPFS was 92.8% for PBRT compared to 83.2% for RFA ($p < 0.001$), meeting pre-specified non-inferiority criteria. No Grade 4 toxicities or treatment-related deaths were reported. Adverse events were mild and manageable. [16]

Meningioma, Benign and Malignant

Comparative long-term data indicate that PBRT is associated with a lower incidence of radiation-induced second malignancies compared to conventional photon-based RT, supporting its role as a safer modality for curative treatment. [45] In a matched retrospective cohort study of 1,116 patients (558 treated with PBRT at the Harvard Cyclotron and 558 photon-treated controls from the Surveillance, Epidemiology, and End Results registry), secondary cancers developed

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in 29 proton patients (5.2%) and 42 photon patients (7.5%). After adjusting for sex, age, primary site, and year of diagnosis, PBRT was associated with a significantly reduced risk of secondary malignancy (p = 0.009), yielding an adjusted hazard ratio of 0.52, or approximately half the relative risk compared to photons. Median follow-up durations were 6.7 years for the PBRT group and 6.0 years for the photon cohort, confirming adequate observation for secondary outcomes.

In a single-institution series of 96 patients (World Health Organization [WHO] grade 1, 63.5%; grade 2, 34.4%; grade 3, 2.1%), pencil beam scanning PBT delivered with a median follow-up of 56.9 months resulted in 5-year LC of 86.4% and OS of 88.2%, with grade ≥3 toxicity-free survival of 89.1%. [46] Most treatment failures (69%) occurred in non-benign histologies, confirming dose-responsiveness by tumor grade. On univariate analysis, LC was significantly worse for higher-grade tumors (p ≤ 0.001), previously recurrent disease (p = 0.006), non–skull base locations (p = 0.014), and male sex (p = 0.032). OS was significantly influenced by LC (p ≤ 0.001), age (p = 0.002), and timing of PBT (initial vs. recurrence, p = 0.002), with up-front treatment yielding superior outcomes. Treatment of intracranial meningiomas with pencil beam scanning PBT achieved durable tumor control and survival while maintaining a favorable toxicity profile by minimizing exposure to adjacent brain, optic nerve, and cranial nerve structures.

Paranasal Sinus, Nasal Cavity, Nasopharynx, Oropharynx, Maxillary Sinus, Ethmoid Sinus, and Cavernous Sinus cancers

PBRT significantly reduces acute treatment-related toxicity compared with IMRT for patients undergoing comprehensive head and neck irradiation for cancers of the nasopharynx, nasal cavity, and paranasal sinuses. In a comparative cohort analysis, PBRT was associated with a statistically lower mean radiation doses to the oral cavity, esophagus, larynx, and parotid glands. These dosimetric advantages translated into significantly lower rates of gastrostomy tube dependence both at the completion of RT and three months post-treatment, as well as a reduced need for opioid pain medication, even after controlling for concurrent chemotherapy and nodal disease. [47]

Long-term outcomes from multimodal management of locally advanced squamous cell carcinoma of the nasal cavity and paranasal sinuses demonstrate that incorporating PBRT yields substantial survival and tumor control benefits. In a retrospective analysis of 37 patients with T3–T4 tumors and no distant metastases, PBRT was delivered either postoperatively following surgery (Group A), radically in patients who declined surgery (Group B), or radically for unresectable tumors (Group C). The 4-year OS, PFS, and LC rates were 90%, 70%, and 80% in Group A, 89%, 78%, and 89% in Group B, and 24%,11%, and 24% in Group C, respectively. Statistically significant differences were observed in OS (p = 0.0028) and PFS (p = 0.009) between Groups A and C, and in OS (p = 0.0027), PFS (p = 0.0045), and LC (p = 0.0075) between Groups B and C. These findings confirm that PBT, when used postoperatively or as definitive therapy, achieves durable survival and LTC, particularly when combined with concurrent chemotherapy. [6]

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Improved radiation precision has enabled PBRT to deliver curative-intent treatment for nasopharyngeal carcinoma (NPC) while substantially reducing dose to the surrounding normal tissues compared to IMRT. In a systematic review conducted under Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, 9 studies evaluating PBRT for NPC demonstrated several oncologic outcomes that were similar to IMRT, with 2-year local and regional PFS ranging from 84% to 100%, 2-year PFS from 75% to 88.9%, and 2-year OS from 88% to 95%. [21] In 4 comparative studies however, PBT was superior and achieved significantly lower rates of toxicity such as feeding tube dependence (20% vs. 65%, $p = 0.015$; 14% vs. 85%, $p < 0.001$) and mucositis (Grade 2: 46% vs. 70%, $p = 0.019$; Grade 3: 11% vs. 76%, $p = 0.0002$) compared to IMRT, with additional improvements noted in other acute and late toxicity endpoints.

In treating oropharyngeal cancers, PBRT demonstrated non-inferior PFS and improved OS when compared to IMRT, with reduced high-grade toxicity. [23] Across 440 patients, OS with PBRT was 90.9% at 5 years, whereas IMRT OS at 5 years was 81.05%. [23]

Pituitary Adenoma and Primary CNS Tumors

Clinical evidence from a single-institution series of 165 patients demonstrated that PBRT provides excellent long-term tumor control and meaningful biochemical response in patients with functional pituitary adenomas, confirming its role as an effective and medically necessary treatment for hormonally active sellar tumors refractory to surgery. [51] Nearly all patients (162/165) had undergone prior resection, and 14 had received prior photon irradiation, highlighting the complex, recurrent nature of this population. At a median follow-up of 4.3 years, tumor control reached 98% among 140 patients with imaging follow-up. The actuarial 3-year biochemical complete response (CR) rates were 54% for Cushing disease, 63% for Nelson syndrome, 26% for acromegaly, and 22% for prolactinomas. Median times to CR were 32, 27, 62, and 60 months, respectively. Corticotroph adenomas (Cushing/Nelson) demonstrated significantly faster CR compared with other tumor types ($p = 0.001$). The primary adverse effect was hypopituitarism, developing in 45% at 3 years and 62% at 5 years, with a median onset of 40 months. Larger radiosurgical target volumes predicted higher risk (adjusted HR 1.3, $p = 0.004$). Other late effects were infrequent, with no radiation-induced tumors observed and only 4 cases of post-treatment seizures, primarily in patients with generously defined target margins.

Contemporary evidence demonstrates that modern RT, particularly PBRT, achieves durable LC, long-term survival, and favorable safety in patients with pituitary adenomas, especially following incomplete resection or tumor recurrence. In a retrospective series of 122 patients treated at a single tertiary center between 1992 and 2023, with a median follow-up of 107 months, fSRT was used in 96% of cases, and single-session radiosurgery in 4%. [52] LC was maintained in 95% at 5 years and 75% at 20 years, confirming the long-term efficacy of RT for benign pituitary tumors. Importantly, PBRT significantly improved both LC and OS compared to photon-based modalities ($p < 0.01$), underscoring the benefit of Bragg peak–guided dose precision in sparing adjacent optic and hypothalamic structures. Hypopituitarism occurred in 40% of patients, representing the most common late effect, while visual toxicity was rare (<3%).

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PBRT allows for precise dose delivery that spares adjacent normal tissues, reducing radiation-induced lymphopenia, secondary malignancies, and loss of cognitive function for adult patients with gliomas and meningiomas. [25]

Primary Tumors of the Mediastinum

The importance of sparing adjacent tumors from radiation in the mediastinum makes PBRT especially valuable in treating Hodgkin lymphoma, as well as thymic carcinoma and other primary mediastinal tumors. The effect of radiation on heart and lung tissues and coronary vessels can be especially damaging. Hodgkin lymphoma frequently affects younger patients, and major late toxicities have been shown to result in valvular disease and cardiovascular ischemia. Secondary cancers, including breast, lung, and thyroid cancers, as well as soft-tissue sarcomas, have an increased incident in patients given traditional RT for Hodgkin lymphoma. [27] A randomized controlled trial of 10 patients showed that PBRT reduced radiation exposure to cardiac tissues by an average of 50% when compared to IMRT. [27] A larger study of 162 patients demonstrated high rates of disease-free survival, OS, and LC. Over a 4-year observation period post-treatment, the most frequent late toxicity observed was grade 2 hypothyroidism (23% of patients). Only 3 grade 2 coronary events were recorded, and these all occurred in patients with pre-existing cardiovascular risk factors. [26]

Neutron Beam Radiation Therapy

In one of the pivotal randomized clinical trials jointly conducted by the Radiation Therapy Oncology Group (RTOG) and the Medical Research Council (MRC), fast neutron beam radiation therapy (NBRT) demonstrated superior long-term local and regional control compared with conventional photon and/or electron radiotherapy for unresectable or recurrent malignant salivary gland tumors. Among 25 evaluable patients stratified by surgical status, tumor size, and histology, the study was terminated early for ethical reasons after interim analysis revealed clear efficacy advantages favoring NBRT. At 10-year follow-up, locoregional control remained significantly improved with neutrons ($p = 0.009$), confirming durable disease control. Although OS did not differ significantly (15% vs 25%, p = NS), the pattern of failure diverged: distant metastases predominated in the neutron arm, whereas local and regional recurrences were more frequent following photon therapy. Toxicity assessment revealed a higher incidence of severe (grade ≥3) morbidity with NBRT, which occurred in 9 out of 13 patients. However, life-threatening complications were observed in 2 neutron-treated patients and 1 photo-treated patient; notably, there were no fatal complications in either group, thus, demonstrating acceptable long-term tolerability given the disease's refractory nature. Collectively, these findings affirm that NBRT is an excellent choice for inoperable or recurrent malignant salivary gland tumors, providing sustained local-regional disease control and clinically beneficial in a patient population for whom photon therapy yields inadequate outcomes. [53]

A large retrospective study conducted at the University of Washington Cancer Center, one of the few centers worldwide with a dedicated clinical neutron facility, evaluated the long-term outcomes of NBRT in patients with salivary gland malignancies treated with curative intent. [54] Between the early 1980s and 1990s, 279 patients received NBRT, including 141 with tumors of the major salivary glands and 138 with tumors arising from the minor salivary glands. The vast

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majority of patients, 263 in total, had gross residual disease at the time of treatment, reflecting the advanced and often inoperable nature of this cohort. With a median follow-up of 36 months (range, 1 to 142 months), the results demonstrated durable tumor control and meaningful long-term survival. The six-year actuarial cause-specific survival rate was 67%, while local-regional control and freedom from metastasis were 59% and 64%, respectively. Patients who began treatment without evidence of gross residual disease achieved 100% six-year local-regional control, highlighting the curative potential of NBRT in selected cases. Multivariate analyses identified several favorable prognostic factors, including tumor size ≤4 cm, lack of skull base invasion, absence of prior radiotherapy, minor salivary gland origin, and presentation with primary rather than recurrent disease. Together, these findings underscore the importance of early detection and treatment at a specialized center. Toxicity outcomes were encouraging for such a challenging disease population. The six-year actuarial incidence of grade 3 or 4 late toxicity was limited to 10%, and no grade 5 (fatal) toxicities occurred. Reported adverse effects were generally manageable and did not outweigh the clear disease control benefits achieved.

In summary, the University of Washington experience confirmed that NBRT provides effective and durable local-regional control in patients with salivary gland neoplasms, including those with extensive or unresectable disease. For patients treated without residual tumor, outcomes approached cure. These data established NBRT as an evidence-based, medically appropriate treatment option in specialized centers for aggressive or photon-resistant salivary gland cancers.

APPROVAL HISTORY

10/14/2026	Added the following indications for proton beam radiation therapy: a kidney-adjacent target volume in a patient with single or transplanted pelvic kidney and primary tumors of the mediastinum with no metastatic disease
12/10/2025	Updated citations, Removed Oropharynx Cancer from Indications, Added Clinical Reasoning Section, Added Summary of Evidence and Analysis of Evidence
12/11/2024	New policy

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