



Louisiana

Proton Beam Therapy

Policy # 00187

Original Effective Date: 01/26/2006

Current Effective Date: 03/11/2024

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services Are Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Base of Skull Tumors

Chordoma, Chondrosarcoma

Based on review of available data, the Company may consider proton beam therapy (PBT) for chordoma, or chondrosarcoma to be **eligible for coverage**.**

Patient Selection Criterion

Coverage eligibility for PBT for chordoma, or chondrosarcoma may be considered when the following criterion 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

Based on review of available data, the Company may consider proton beam therapy (PBT) for locally advanced sinonasal carcinoma to be **eligible for coverage**.**

Patient Selection Criterion

Coverage eligibility for PBT for locally advanced sinonasal carcinoma may be considered when the following criterion is met:

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

©2024 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Proton Beam Therapy

Policy # 00187

Original Effective Date: 01/26/2006

Current Effective Date: 03/11/2024

optic chiasm, or brainstem.

Central Nervous System

Arteriovenous Malformation (AVM)

Based on review of available data, the Company may consider proton beam therapy (PBT) for arteriovenous malformation (AVM) to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for PBT for AVM may be considered when **ANY** of the following criteria 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 (in adults age 21 and older)

Based on review of available data, the Company may consider proton beam therapy (PBT) for central nervous system (CNS) tumors to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for CNS tumors in adults may be considered when **ALL** of the following criteria are met:

- CNS tumors, 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 intensity-modulated radiotherapy (IMRT) or standard stereotactic modalities would not reduce the risk of radiation damage to the critical structure.

©2024 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Proton Beam Therapy

Policy # 00187

Original Effective Date: 01/26/2006

Current Effective Date: 03/11/2024

Hepatobiliary Cancer

Hepatocellular Carcinoma and Intrahepatic Cholangiocarcinoma

Based on review of available data, the Company may consider proton beam therapy (PBT) for hepatocellular cancer or intrahepatic cholangiocarcinoma to be **eligible for coverage.****

Patient Selection Criterion

Coverage eligibility for PBT for hepatocellular cancer or intrahepatic cholangiocarcinoma may be considered when the following criterion is met:

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

Melanoma

Ocular Melanoma

Based on review of available data, the Company may consider proton beam therapy (PBT) for ocular melanoma to be **eligible for coverage.****

Patient Selection Criterion

Coverage eligibility for PBT for ocular melanoma may be considered when the following criterion is met:

- As primary therapy for melanoma of the uveal tract (including the iris, choroid, or ciliary body) and with no evidence of metastasis or extrascleral extension.

Pediatric Patients

All Tumor Types

Based on review of available data, the Company may consider proton beam therapy (PBT) for all tumor types in pediatric patients to be **eligible for coverage.****

Patient Selection Criterion

Coverage eligibility for PBT may be considered for all tumor types in pediatric patients (age < 21) when the following criterion is met:

©2024 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Proton Beam Therapy

Policy # 00187

Original Effective Date: 01/26/2006

Current Effective Date: 03/11/2024

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

Re-irradiation

Based on review of available data, the Company may consider PBT for re-irradiation to be **eligible for coverage.****

Patient Selection Criterion

Coverage eligibility for PBT for re-irradiation may be considered when the following criterion is met:

- For previously treated fields where the dose tolerance of surrounding normal structures would be exceeded with 3D conformal radiation or IMRT.

When Services Are Considered Not Medically Necessary

The use of PBT is considered to be **not medically necessary**** when patient selection criteria are not met and for all other conditions including, but not limited to the following:

- 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.

Policy Guidelines

Evidence is lacking on the definition of age parameters for the use of proton beam therapy in pediatric patients. Some studies using proton beam therapy in pediatric central nervous system tumors have mostly included patients younger than 3 years of age. However, experts cite the benefit of proton beam therapy in pediatric patients of all ages (<21 years of age).

©2024 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Proton Beam Therapy

Policy # 00187

Original Effective Date: 01/26/2006

Current Effective Date: 03/11/2024

Organs at risk are defined as normal tissues whose radiation sensitivity may significantly influence treatment planning and/or prescribed radiation dose. These organs at risk may be particularly vulnerable to clinically important complications from radiation toxicity. Table PGI outlines radiation doses that are generally considered tolerance thresholds for these normal structures in various organ regions. Clinical documentation based on dosimetry plans may be used to demonstrate that radiation by conventional or advanced photon-based radiotherapy, including intensity-modulated radiotherapy (IMRT), volume-modulated arc therapy (VMAT), stereotactic radiosurgery (SRS), or stereotactic body radiation therapy (SBRT), would exceed tolerance doses to structures at risk. For patients with radiation-sensitizing genetic syndromes such as neurofibromatosis type 1 (NF-1) or retinoblastoma, clinical documentation of the condition may be used to demonstrate increased risk from exposure during treatment.

Table P1. Radiation Tolerance Doses for Normal Tissues

Site	TD 5/5 (Gray) ^a			TD 50/5 (Gray) ^b			Complication End Point
	Portion of Organ Involved			Portion of Organ Involved			
	1/3	2/3	3/3	1/3	2/3	3/3	
Heart	60	45	40	70	55	50	Pericarditis
Lung	45	30	17.5	65	40	24.5	Pneumonitis
Spinal cord	50	50	47	70	70	NP	Myelitis/necrosis
Salivary glands	32	32	32	46	46	46	Xerostomia
Kidney	50	30	23	NP	40	28	Clinical nephritis
Liver	50	35	30	55	45	40	Liver failure
Esophagus	60	58	55	72	70	68	Stricture, perforation
Stomach	60	55	50	70	67	65	Ulceration, perforation
Small intestine	50	NP	40	60	NP	55	Obstruction, perforation

©2024 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Proton Beam Therapy

Policy # 00187

Original Effective Date: 01/26/2006

Current Effective Date: 03/11/2024

Site	TD 5/5 (Gray) ^a			TD 50/5 (Gray) ^b			Complication End Point
Colon	55	NP	45	65	NP	55	Obstruction, perforation, ulceration, fistula
Rectum	NP	NP	60	NP	NP	80	Severe proctitis, necrosis, stenosis, fistula
Femoral head	NP	NP	52	NP	NP	65	Necrosis

Compiled from 2 sources: (1) Morgan MA (2011). Radiation Oncology. In DeVita, Lawrence, and Rosenberg, Cancer (p.308). Philadelphia: Lippincott Williams and Wilkins; and (2) Kehwar TS, Sharma SC. Use of normal tissue tolerance doses into linear quadratic equation to estimate normal tissue complication probability. Available online at:

<http://www.rooj.com/Radiation%20Tissue%20Tolerance.htm>.

NP: not provided; TD: tolerance dose.

^a TD 5/5 is the average dose that results in a 5% complication risk within 5 years.

^b TD 50/5 is the average dose that results in a 50% complication risk within 5 years.

For charged-particle radiotherapy (proton or helium ion) therapy to provide outcomes superior to photon-based radiotherapy, there must be a clinically meaningful decrease in the radiation exposure to normal structures. There is no standard definition for a clinically meaningful decrease in radiation dose. In principle, a clinically meaningful decrease would signify a significant reduction in anticipated complications of radiation exposure. To document a clinically meaningful reduction in dose, dosimetry planning studies should demonstrate a significant decrease in the maximum dose of radiation delivered per unit of tissue, and/or a significant decrease in the volume of normal tissue exposed to potentially toxic radiation doses. While radiation tolerance dose levels for normal tissues are well-established, the decrease in the volume of tissue exposed that is needed to provide a clinically meaningful benefit has not been standardized. Therefore, precise parameters for a clinically meaningful decrease cannot be provided.

Background/Overview

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

©2024 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Proton Beam Therapy

Policy # 00187

Original Effective Date: 01/26/2006

Current Effective Date: 03/11/2024

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 protontherapy (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

©2024 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Proton Beam Therapy

Policy # 00187

Original Effective Date: 01/26/2006

Current Effective Date: 03/11/2024

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.

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.

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.”

©2024 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Proton Beam Therapy

Policy # 00187

Original Effective Date: 01/26/2006

Current Effective Date: 03/11/2024

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 there are several trials currently underway, there are currently no published randomized studies comparing proton therapy to IMRT in the treatment of head and neck cancers. In 2010, the AHRQ conducted a systematic review of different 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

©2024 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Proton Beam Therapy

Policy # 00187

Original Effective Date: 01/26/2006

Current Effective Date: 03/11/2024

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 and weight loss greater than 20% or 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. conclude 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

©2024 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Proton Beam Therapy

Policy # 00187

Original Effective Date: 01/26/2006

Current Effective Date: 03/11/2024

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 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 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

©2024 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Proton Beam Therapy

Policy # 00187

Original Effective Date: 01/26/2006

Current Effective Date: 03/11/2024

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

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 ($P < 0.001$). 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%.

©2024 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Proton Beam Therapy

Policy # 00187

Original Effective Date: 01/26/2006

Current Effective Date: 03/11/2024

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 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 stereotactic body radiotherapy (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.

©2024 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Proton Beam Therapy

Policy # 00187

Original Effective Date: 01/26/2006

Current Effective Date: 03/11/2024

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 non-small 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.

©2024 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Proton Beam Therapy

Policy # 00187

Original Effective Date: 01/26/2006

Current Effective Date: 03/11/2024

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 were 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.

©2024 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Proton Beam Therapy

Policy # 00187

Original Effective Date: 01/26/2006

Current Effective Date: 03/11/2024

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.

©2024 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Proton Beam Therapy

Policy # 00187

Original Effective Date: 01/26/2006

Current Effective Date: 03/11/2024

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 Agency for Healthcare Research and Quality (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 (RP), brachytherapy (BT) and external beam radiotherapy (EBRT). The risk of developing bladder or

©2024 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Proton Beam Therapy

Policy # 00187

Original Effective Date: 01/26/2006

Current Effective Date: 03/11/2024

colorectal cancer was 3% for RP, 2% for BT and 4% for EBRT 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. have 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 the proton-treated patients were lost to follow up and second malignancy information was not available for this group. The authors conclude 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 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. 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

©2024 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Proton Beam Therapy

Policy # 00187

Original Effective Date: 01/26/2006

Current Effective Date: 03/11/2024

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 the PBT is the experimental arm of a clinical trial or when used as part of a clinical registry unless criteria above are otherwise met.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Radiotherapy is a procedure and, therefore, not subject to U.S. Food and Drug Administration (FDA) regulations. However, the accelerators and other equipment used to generate and deliver charged-particle radiation (including proton beam) are devices that require FDA oversight. The FDA's Center for Devices and Radiological Health has indicated that the proton beam facilities constructed in the United States prior to enactment of the 1976 Medical Device Amendments were cleared for use in the treatment of human diseases on a "grandfathered" basis, while at least one that was constructed subsequently received a 510(k) marketing clearance. There are 510(k) clearances for devices used for delivery of proton beam therapy and devices considered to be accessory to treatment delivery systems, such as the Proton Therapy Multileaf Collimator (which was cleared in December 2009). Since 2001, several devices classified as medical charged-particle radiation therapy systems have received 510(k) marketing clearance. FDA product code LHN.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

©2024 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Proton Beam Therapy

Policy # 00187

Original Effective Date: 01/26/2006

Current Effective Date: 03/11/2024

Supplemental Information

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

International Particle Therapy Co-operative Group

A 2016 consensus statement by the International Particle Therapy Co-operative Group (PTCOG) offered the following conclusion about proton therapy for non-small-cell lung cancer (NSCLC): "...Promising preliminary clinical outcomes have been reported for patients with early-stage or locally advanced NSCLC who receive proton therapy. However, the expense and technical challenges of proton therapy demand further technique optimization and more clinical studies...."

In 2021, PTCOG published consensus guidelines on particle therapy for the management of head and neck cancer. The following recommendations were made:

- Nasopharynx: "Consider proton therapy whenever feasible. Most advanced treatment, imaging, and adaptation techniques should be used to minimize risk of neurotoxicity, given anatomic location."
- Reirradiation: "Careful evaluation required for each patient to determine risks/benefits of reirradiation. Enrollment in clinical trial encouraged whenever possible."
- Sinonasal: "Consider proton therapy whenever feasible. Most advanced treatment, imaging, and adaptation techniques should be used to minimize risk of neurotoxicity, given anatomic location."
- Postoperative: "Consider proton therapy whenever feasible. Enrollment in clinical trial encouraged whenever possible."
- Oropharynx: "Consider proton therapy whenever feasible. Enrollment in clinical trial encouraged whenever possible."

American College of Radiology

The 2014 guidelines from the American College of Radiology on external-beam radiotherapy in stage T1 and T2 prostate cancer stated:

©2024 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Proton Beam Therapy

Policy # 00187

Original Effective Date: 01/26/2006

Current Effective Date: 03/11/2024

- "There are only limited data comparing proton-beam therapy to other methods of irradiation or to radical prostatectomy for treating stage T1 and T2 prostate cancer. Further studies are needed to clearly define its role for such treatment.
- There are growing data to suggest that hypofractionation at dose per fraction <3.0 Gy per fraction is reasonably safe and efficacious, and although the early results from hypofractionation/SBRT [stereotactic body radiation therapy] studies at dose per fraction >4.0 Gy seem promising, these approaches should continue to be used with caution until more mature, ongoing phase II and III randomized controlled studies have been completed."

American Urological Association et al

In 2022, the American Urological Association (AUA) and American Society for Radiation Oncology (ASTRO) published evidence-based guidelines for the management of clinically localized prostate cancer. Part III of the guideline discusses principles of radiation therapy. Regarding the use of proton therapy, the guidelines state the following: "Clinicians may counsel patients with prostate cancer that proton therapy is a treatment option, but it has not been shown to be superior to other radiation modalities in terms of toxicity profile and cancer outcomes. (Conditional Recommendation; Evidence Level: Grade C)" The guidelines additionally note that while dosimetric planning studies have indicated that proton therapy can deliver lower integral and mean doses to normal tissues, it has not been established whether these dosimetric differences translate in fewer side effects or improvements in quality of life.

National Comprehensive Cancer Network

Uveal Melanoma

National Comprehensive Cancer Network (NCCN) guidelines for uveal melanoma (v.2.2022) support the use of particle beam therapy for definitive radiotherapy of the primary tumor and that its use is appropriate as upfront therapy after diagnosis, after margin-positive enucleation, or for intraocular or orbital recurrence. Treatment recommendations for intraocular tumors include:

- "Using protons, 50-70 cobalt Gray equivalent (CGyE) in 4-5 fractions should be prescribed to encompass the planning target volume surrounding the tumor.
- Using carbon ions, 60-85 CGyE in 5 fractions should be prescribed to encompass the planning target volume surrounding the tumor."

©2024 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Proton Beam Therapy

Policy # 00187

Original Effective Date: 01/26/2006

Current Effective Date: 03/11/2024

Prostate Cancer

NCCN guidelines for prostate cancer (v.5.2023) offer the following conclusion on proton therapy: "The NCCN panel believes no clear evidence supports a benefit or decrement to proton therapy over IMRT [intensity-modulated radiotherapy] for either treatment efficacy or long-term toxicity. Conventionally fractionated prostate proton therapy can be considered a reasonable alternative to x-ray-based regimens at clinics with appropriate technology, physics, and clinical expertise." The NCCN adds that a prospective randomized trial comparing prostate PBT with x-ray-based IMRT is ongoing and may help to elucidate outcomes, as the evidence to date has not demonstrated a significant difference in benefit, particularly in regard to short and long-term toxicities. The NCCN acknowledges that PBT may deliver less radiation to surrounding tissues (eg, muscle, bone, vessels, fat), but that these tissues do not routinely contribute to the morbidity of prostate radiation. Of greater clinical relevance, is the volume of rectum and bladder that is exposed to radiation. Higher volume, lower dose exposures may minimize risk of long-term treatment morbidity. While in silico dosimetric studies have suggested that the right treatment planning can make an IMRT plan more favorable compared to a proton therapy plan or vice versa, these studies often do not accurately predict clinically meaningful endpoints.

Non-Small-Cell Lung Cancer

NCCN guidelines for non-small cell lung cancer (NSCLC) (v.1.2024) offer the following recommendations: "[Radiation therapy] has a potential role in all stages of NSCLC as either definitive or palliative therapy... More advanced techniques are appropriate when needed to deliver curative [radiation therapy] safely. These techniques include (but are not limited to) 4D-CT and/or PET/CT stimulation, IMRT/VMAT, [image-guided radiation therapy], motion management, and proton therapy... Image-guided radiation therapy is recommended when using proton with steep dose gradients around the target, when [organs at risk] are in close proximity to high-dose regions, and when using complex motion management techniques." NCCN recommends that highly conformal radiation therapies such as proton therapy be used in the setting of prior radiation therapy, potentially with hyperfractionation, to reduce risk of toxicity.

Head and Neck Cancer

NCCN guidelines for head and neck cancers (v.1.2023) indicate that proton therapy may be used per the discretion of the treating physician but is an active area of investigation. Proton therapy may be considered when normal tissue constraints cannot be met by photon-based therapy. Otherwise, IMRT or 3D conformal RT is recommended. The safety and efficacy of PBT when highly conformal

©2024 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Proton Beam Therapy

Policy # 00187

Original Effective Date: 01/26/2006

Current Effective Date: 03/11/2024

dose distributions are important has been established, and is particularly important for patient with primary periocular tumors, tumors invading the orbit, skull base, cavernous sinus, and for patients with intracranial extension or perineural invasion. These treatment approaches are recommended for those being treated with curative intent and/or those with long life expectancies following treatment. However, NCCN adds that without "high-quality prospective comparative data, it is premature to conclude that proton therapy has been established as superior to other established radiation techniques such as IMRT, particularly with regard to tumor control."

Pediatric Central Nervous System Cancer

NCCN guidelines for pediatric central nervous system cancers (v.2.2023) indicate that proton therapy offers maximal sparing of normal tissue and may be considered for patients with better prognoses (e.g., *IDH1*-mutated tumors, 1p/19q-codeletions, or younger age) as most data are derived from studies involving pediatric cases of low-grade glioma.

American Society for Radiation Oncology

The American Society for Radiation Oncology (ASTRO) (2017) updated its model policy on the medical necessity requirements for the use of proton therapy. ASTRO deemed the following disease sites those for which the evidence frequently supports the use of proton beam therapy:

- Ocular tumors, including intraocular melanomas
- Tumors that approach or are located at the base of the skull, including but not limited to chordoma and chondrosarcomas
- Primary or metastatic tumors of the spine where the spinal cord tolerance may be exceeded with conventional treatment or where the spinal cord has previously been irradiated
- Hepatocellular cancer
- Primary or benign solid tumors in children treated with curative intent and occasional palliative treatment of childhood tumors
- Patients with genetic syndromes making total volume of radiation minimization crucial such as but not limited to NF-1 patients and retinoblastoma patients
- Malignant and benign primary central nervous system tumors
- Advanced (eg, T4) and/or unresectable head and neck cancers
- Cancers of the paranasal sinuses and other accessory sinuses
- Nonmetastatic retroperitoneal sarcomas
- Re-irradiation cases (where cumulative critical structure dose would exceed tolerance dose).

©2024 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Proton Beam Therapy

Policy # 00187

Original Effective Date: 01/26/2006

Current Effective Date: 03/11/2024

The model policy also made a specific statement on proton beam therapy for treating prostate cancer: “..., ASTRO believes the comparative efficacy evidence of proton beam therapy with other prostate cancer treatments is still being developed, and thus the role of proton beam therapy for localized prostate cancer within the current availability of treatment options remains unclear.”

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

References

1. Carelon Medical Benefits Management, Clinical Appropriateness Guidelines: Radiation Oncology, “Appropriate Use Criteria: Proton Beam Therapy”, March 13, 2022.
2. 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.
3. 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>.
4. 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.
5. 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.
6. 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.
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.

©2024 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Proton Beam Therapy

Policy # 00187

Original Effective Date: 01/26/2006

Current Effective Date: 03/11/2024

8. Brada M, Pijls-Johannesma M, De Ruyscher 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*.

©2024 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Proton Beam Therapy

Policy # 00187

Original Effective Date: 01/26/2006

Current Effective Date: 03/11/2024

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

©2024 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Proton Beam Therapy

Policy # 00187

Original Effective Date: 01/26/2006

Current Effective Date: 03/11/2024

- 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. König 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

©2024 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Proton Beam Therapy

Policy # 00187

Original Effective Date: 01/26/2006

Current Effective Date: 03/11/2024

- 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.].

©2024 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Proton Beam Therapy

Policy # 00187

Original Effective Date: 01/26/2006

Current Effective Date: 03/11/2024

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 5.2023). Available at <http://www.nccn.org>. ©National Comprehensive Cancer Network, 2023.
62. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Small Cell Lung Cancer (Version 1.2024). Available at <http://www.nccn.org>. ©National Comprehensive Cancer Network, 2024.
63. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Prostate Cancer (Version 4.2023). Available at <http://www.nccn.org>. ©National Comprehensive Cancer Network, 2023.
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

©2024 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Proton Beam Therapy

Policy # 00187

Original Effective Date: 01/26/2006

Current Effective Date: 03/11/2024

- 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

©2024 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Proton Beam Therapy

Policy # 00187

Original Effective Date: 01/26/2006

Current Effective Date: 03/11/2024

- 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.

©2024 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Proton Beam Therapy

Policy # 00187

Original Effective Date: 01/26/2006

Current Effective Date: 03/11/2024

Policy History

Original Effective Date: 01/26/2006

Current Effective Date: 03/11/2024

10/05/2005	Medical Director review
12/20/2005	Medical Policy Committee review
01/26/2006	Quality Care Advisory Council approval
07/07/2006	Format revision, including addition of FDA and or other governmental regulatory approval and rationale/source. Coverage eligibility unchanged.
09/20/2006	Medical Policy Committee approval. Coverage eligibility changed for the treatment of prostate cancer from not medically necessary to “eligible for coverage”.
12/06/2006	Medical Director review
12/20/2006	Medical Policy Committee approval. Coverage eligibility unchanged.
02/13/2008	Medical Director review
02/20/2008	Medical Policy Committee approval
02/04/2009	Medical Director review
02/19/2009	Medical Policy Committee approval. No change to coverage eligibility.
02/04/2010	Medical Policy Committee review
02/17/2010	Medical Policy Implementation Committee approval. No change to coverage eligibility. Rationale replaced.
02/03/2011	Medical Policy Committee review
02/16/2011	Medical Policy Implementation Committee approval. New investigational statement added.
02/02/2012	Medical Policy Committee review
02/15/2012	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
02/07/2013	Medical Policy Committee review
02/20/2013	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
02/06/2014	Medical Policy Committee review
02/19/2014	Medical Policy Implementation Committee approval. Added that proton radiotherapy may be considered eligible for coverage with criteria for the treatment of pediatric central nervous system tumors. Investigational statements added for

©2024 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Proton Beam Therapy

Policy # 00187

Original Effective Date: 01/26/2006

Current Effective Date: 03/11/2024

	pediatric non-central nervous system tumors and head and neck tumors (non-skull based).
02/05/2015	Medical Policy Committee review
02/18/2015	Medical Policy Implementation Committee approval. No change to coverage.
08/03/2015	Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
02/04/2016	Medical Policy Committee review
02/17/2016	Medical Policy Implementation Committee approval. Title change
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
02/02/2017	Medical Policy Committee review
02/15/2017	Medical Policy Implementation Committee approval. No change to coverage.
09/07/2017	Medical Policy Committee review
09/20/2017	Medical Policy Implementation Committee approval. Changed policy title from "Charged-Particle (Proton or Helium Ion) Radiotherapy" to "Proton Beam Radiation Therapy" to adopt the title from AIM Guidelines. Coverage changed to follow AIM Guidelines.
11/15/2017	Coding update
09/06/2018	Medical Policy Committee review
09/19/2018	Medical Policy Implementation Committee approval. All changes adopt AIM 2018 Guidelines. Title changed from "Proton Beam Radiation Therapy" to "Proton Beam Therapy". Added a section on re-irradiation to be eligible for coverage if criterion is met. Proton beam therapy for all other conditions with some conditions specified in bullets was added to the Not Medically Necessary section.
10/03/2019	Medical Policy Committee review
10/09/2019	Medical Policy Implementation Committee approval. Added a coverage section title for "Base of Skull Tumors". Existing coverage for Chordoma, Chondrosarcoma moved under this section and conditional coverage for Sinonasal Cancer was added to this section. Removed "involving tumors of up to 24 mm in largest diameter and 14 mm in height" from the Ocular Melanoma criterion, since AIM no longer requires certain size parameters. Revised the "Pediatric Patients" section for clarity and revised criterion for proton beam therapy to treat all pediatric tumors in which radiation is required. All revisions track AIM Guidelines.
10/01/2020	Medical Policy Committee review

©2024 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Proton Beam Therapy

Policy # 00187

Original Effective Date: 01/26/2006

Current Effective Date: 03/11/2024

10/07/2020 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

02/04/2021 Medical Policy Committee review

02/10/2021 Medical Policy Implementation Committee approval. Added an eligible for coverage section for Hepatobiliary Cancer. Revised the Not Medically Necessary bullet for hepatobiliary cancers to those not listed in the coverage section.

02/03/2022 Medical Policy Committee review

02/09/2022 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

02/02/2023 Medical Policy Committee review

02/08/2023 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

02/01/2024 Medical Policy Committee review

02/14/2024 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 02/2025

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)®, copyright 2023 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

The responsibility for the content of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines is with Blue Cross and Blue Shield of Louisiana and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Blue Cross Blue Shield of Louisiana Medical Policy

©2024 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Proton Beam Therapy

Policy # 00187

Original Effective Date: 01/26/2006

Current Effective Date: 03/11/2024

Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	77520, 77522, 77523, 77525
HCPCS	S8030
ICD-10 Diagnosis	All related diagnoses

****Medically Necessary (or “Medical Necessity”)** - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

- In accordance with nationally accepted standards of medical practice;
- Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
- Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

©2024 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Proton Beam Therapy

Policy # 00187

Original Effective Date: 01/26/2006

Current Effective Date: 03/11/2024

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.

©2024 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.