Clinical Policy Title: Proton beam therapy

Clinical Policy Number: 05.02.01

Effective Date: December 1, 2013
Initial Review Date: August 17, 2013
Most Recent Review Date: September 21, 2016
Next Review Date: September 2017

Policy contains:
- Proton beam therapy.
- Particle or hadron therapy.
- Cancer (adult and pediatric).
- Brain arteriovenous malformations (AVM).

About this policy: Keystone First has developed clinical policies to assist with making coverage determinations. Keystone First’s clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of “medically necessary,” and the specific facts of the particular situation are considered by Keystone First when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. Keystone First’s clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. Keystone First’s clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Keystone First will update its clinical policies as necessary. Keystone First’s clinical policies are not guarantees of payment.

Coverage Policy

Keystone First considers the use of proton beam therapy (PBT) to be clinically proven and, therefore, medically necessary when the patient record documents why PBT is considered the treatment of choice, and at least one of the following clinical conditions are present:

1. Benign or malignant conditions otherwise not suitable for intensity-modulated radiation therapy (IMRT) or three-dimensional conformal radiation (3DCR): base of skull or axial skeleton but not limited to chordoma or chondroscarcoma.
2. Solid tumors in children up to age 16: primary and variant forms of medulloblastoma; astrocytoma; glioblastoma; arteriovenous malformations (AVMs); acoustic neuroma; craniopharyngioma; benign and atypical meningiomas; pineal gland tumors; intraocular melanoma.

3. As primary therapy for melanoma of the uveal tract (iris, choroid, or ciliary body) involving tumors of up to 24 mm in largest diameter and 14 mm in height, and with no evidence of metastasis or extrascleral extension.

4. 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 (for example, skull-base chordoma or chondrosarcoma) or cervical spine and have residual, localized tumor without evidence of metastasis.

5. Pituitary adenoma when conventional stereotactic radiation is not an available option.

6. Metastatic lesions, for which expectation of long-term (≥ two years) benefit unobtainable with conventional therapy, and expectation of complete eradication of the lesion is otherwise not obtainable.

Other criteria for coverage includes, when applicable:

1. Dose constraints to normal tissues limit total dose safely deliverable to the tumor by other means.

2. There is reason to believe that doses thought to be above those attainable by other means may improve tumor control.

3. Higher precision associated with proton beam is clinically relevant.

4. Treatment of primary tumors has a curative intent.

**Background**

PBT is a form of radiotherapy that uses beams of charged subatomic particles in contrast to the photon beams of conventional radiation (X-rays). Proton beams have potential benefits for the treatment of tumors in cases where surgical excision is deemed impossible or unacceptably risky.

The first published use of PBT was in 1954; however, the extremely high cost of producing charged particles inhibited its widespread use. There are now 27 U.S. centers for PBT, 23 operating and 4 under construction (National Association of Proton Therapy, 2016), up from 11 in 2009, at a cost of $100 million to $225 million per center (Trikalinos (2009).

PBT is classified among particle or hadron therapies, which have different properties than X-rays. Theoretical advantages of particle beams include more precise delivery of higher doses of radiation to tumor targets and less exposure to surrounding tissues; in other words, more effective cancer treatment
with fewer adverse effects. Due to the large investment for building a PBT facility, treatment costs are higher than with conventional radiation. Therefore, it is important to evaluate whether the medical benefits of PBT are large enough to balance the higher costs.

PBT is not suitable to all tumor types but may be of particular benefit treating superficial lesions (such as those of the eye), intermediate-depth lesions (such as of the head and neck), and tumors where conventional radiotherapy would damage surrounding tissue to an unacceptable level (optical nerve, spinal cord, central nervous system, head, neck, and prostate). In addition, PBT may be ideal for use in pediatric patients.

PBT may be useful for treating arteriovenous malformations (AVMs). While many AVMs cause no symptoms and are discovered only at autopsy, those in the brain can be associated with headaches, epilepsy, hemorrhagic stroke, or death. They are treated by embolization (cutting off the blood supply with a coil, balloon, particle, or glue via catheter), neurosurgery, or radiation.

**Searches**

Keystone First searched PubMed and the databases of:

- UK National Health Services Center for Reviews and Dissemination.
- Agency for Healthcare Research and Quality’s National Guideline Clearinghouse and other evidence-based practice centers.
- The Centers for Medicare & Medicaid Services (CMS).

We conducted searches on August 16, 2016. Search terms were “PBT (MeSH)” and the free text term “proton beam.”

We included:

- **Systematic reviews**, which pool results from multiple studies to achieve larger sample sizes and greater precision of effect estimation than in smaller primary studies. Systematic reviews use predetermined transparent methods to minimize bias, effectively treating the review as a scientific endeavor, and are thus rated highest in evidence-grading hierarchies.
- **Guidelines based on systematic reviews**.
- **Economic analyses**, such as cost-effectiveness, and benefit or utility studies (but not simple cost studies), reporting both costs and outcomes — sometimes referred to as efficiency studies — which also rank near the top of evidence hierarchies.

**Findings**

Professional medical societies have reviewed the literature to determine the efficacy of PBT, especially compared to other types of radiation therapy for cancer. The American Society of Radiation Oncology assembled a Proton Task Force, and found that efficacy of the treatment depended on the condition. Specifically, PBT demonstrated clearly superior outcomes for pediatric central nervous system cancers, large ocular melanomas, and chordomas; less convincing superiority for hepatocellular and prostate cancer;
and no superiority for lung, head/neck, gastrointestinal, and non-central nervous system pediatric cancers (Allen, 2012).

PBT has also been the subject of a number of meta analyses and systematic reviews, often based on particular conditions, especially cancer types.

One systematic review of 76 studies found PBT efficacy of management of skull base chordomas, specifically local control and survival appeared to be superior compared to other treatment modalities (Matloob, 2016). Another review of 47 studies found PBT had better outcomes than did photon irradiation over 10 years, with few significant complications (Amichetti, 2009).

Other reviews concluded that PBT produced similar outcomes to other radiation techniques for cancer treatment. In a review of 23 studies on cranial-based chordomas, outcomes for PBT patients were equal to those treated with carbon ion and photon radiation therapy, in terms of progression-free survival and overall survival (DiMaio, 2011). Another systematic review of five-year survival rates for Stage I inoperable non-small cell lung cancer found that five-year survival rates for PBT exceeded conventional radiation therapy (40% to 20%), but were no different than stereotactic radiation therapy and carbon-ion therapy, each at 42% (Grutters, 2010a). A systematic review of 86 observational studies and 8 comparative studies found that tumor control and survival for head and neck cancer patients were similar for patients in the PBT and IMRT groups (Raemakers, 2011).

A combination of PBT and IMRT was found to produce significantly higher disease free survival (RR=1.44) and locoregional control (RR=1.26) than did other interventions for patients with paranasal sinus and nasal cavity malignancies, in a systematic review of 41 observational studies (Patel, 2014).

Flynn (2010) cataloged systematic reviews published through April 2010, excluding Trikalinos (2009), and concluded evidence to that date did not definitively support efficacy or comparative effectiveness (versus other interventions) of PBT for any cancer indication. The evidence picture has not changed substantively since these reviews concluded searches.

There is still a lack of standards for determining whether the outstanding dose distribution and conformity achieved with proton irradiation translates into improved clinical outcome with respect to increased tumor control and/or reduced treatment-associated complications (Bekelman, 2013).

A Cochrane review found no randomized trials to confirm the superiority of any AVM treatment over alternatives (Ross, 2010).

Cost-effectiveness of PBT has also been assessed. A recent systematic review of eight studies found that while PBT is as efficacious and has similar levels of toxicity as brachytherapy and stereotactic body radiation therapy, is more costly and thus less cost-effective than the other two therapies (Muralid, 2016). This finding was similar to a comparison of various radiation therapies for prostate cancer from 2000-2013 (Amin, 2014). A comparison of Medicare patients treated for prostate cancer in 2008-2009 found that reimbursement for PBT greatly exceeded that for IMRT ($32,428 vs. $18,575), even though there was no difference in genito-urinary toxicity for the two groups 12 months post-operatively (Yu, 2013).
Policy updates:

In the September, 2016 update, nine (9) additional references have been added, three (3) of which are included in the Summary of Clinical Evidence section.

The Coverage section has been expanded to include patients:

1. Given photon beam therapy as primary therapy for melanoma of the uveal tract
2. Who have had biopsy or chordoma/chondrosarcoma resection
3. With pituitary adenoma when stereotactic radiation is not an option
4. With metastatic lesions for which other therapies are not expected to exceed two years of benefits.

The policy title has been changed from “proton therapy” to “proton beam therapy” since it is often interchangeably used as “proton therapy,” “beam therapy” and “proton beam therapy.”

Summary of clinical evidence:

<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verma (2016)</td>
<td>Key points:</td>
</tr>
</tbody>
</table>
| Cost effectiveness of proton beam radiotherapy (PBT) for various conditions | • Systematic review, 18 studies, PBT compared to other treatments  
  • PBT cost-effective for regional/advanced, but not early stage lung cancer  
  • Cost-effective in selected head/neck cancer patients at high risk for mucosal toxicity, patients with uveal melanoma, several pediatric brain tumors  
  More costly for breast cancer patients, cost-effective for those at high risk for accelerated partial breast irradiation |
| Dionisi (2014)    | Key points:                       |
| Effectiveness of PBT for hepatocellular carcinomas | • 5 articles; one nonrandomized controlled study, four case series; low-quality evidence.  
  • 900+ patients with heterogeneous disease stages treated with fractionation schedules.  
  • Local control 80% at 3-5 years; average 5 year overall survival = 32%; data comparable to surgery in the most favorable groups. Toxicity was low (mainly gastrointestinal).  
  • Normal liver V0Gy < 30%volume and V30Gy < 18 – 25%volume suggested as cut-off values for hepatic toxicity. |
| Allen (2012)      | Key points:                       |
| Establishment of effectiveness of PBT vs. other treatments for various cancers | • American Society of Radiation Oncology, Proton Task Force  
  • PBT not superior for lung, head/neck, GI, pediatric non-central nervous system cancers  
  • PBT superior for pediatric CNS cancer, large non-ocular melanomas, chordomas  
  • PBT somewhat superior for hepatocellular, prostate cancer |
| DeMaio (2011)     | Key points:                       |
| Survival among patients given various treatments for cranial base chordomas | • 23 studies, 807 patients, progression free survival (PFS) and overall survival (OS)  
  • No difference in five-year OS by type of adjuvant radiation, including PBT  
  • PFS lower only for Gamma Knife surgery |
### Citation | Content, Methods, Recommendations
---|---
**Verma (2016)** Cost effectiveness of proton beam radiotherapy (PBT) for various conditions

**Key points:**
- Systematic review, 18 studies, PBT compared to other treatments
- PBT cost-effective for regional/advanced, but not early stage lung cancer
- Cost-effective in selected head/neck cancer patients at high risk for mucosal toxicity, patients with uveal melanoma, several pediatric brain tumors
- More costly for breast cancer patients, cost-effective for those at high risk for accelerated partial breast irradiation

**Ramaekers (2011)** Outcomes for various types of radiotherapy in head and neck cancers

**Key points:**
- 86 observational, 8 comparative studies, 1990 – 2010
- Carbon ions associated with longer survival for mucosal melanoma vs. protons.
- Tumor control and survival similar for IMRT and protons except for para- and sino-nasal.
- Carbon ions and protons associated with lower toxicity rates than IMRT.

**Flynn (2010)** Research on effectiveness of PBT therapy for various cancers

**Key points:**
- Systematic reviews, guidelines, or technology assessments: searches to April 2010
- 12 reviews, lung, base of skull, ocular, prostate, head and neck cancers, brain AVMs.
- Only prostate cancer and uveal melanoma represented by CCTs, with serious methodological weaknesses.
- Economic evaluations premature, overall insufficient evidence for effectiveness

**Grutters (2010a)** Mortality for therapies for Stage I inoperable non-small cell lung cancer

**Key points:**
- 30 studies (n=2611), 1994 – 2008, five-year survival rates
- Lowest was conventional radiation therapy (20%)
- Equal survival for PBT (40%), stereotactic radiotherapy, and carbon-ion therapy (42%).

### Glossary

**Arteriovenous malformation (AVM)** — An abnormal connection between arterial and venous systems that can occur anywhere in the body but is most dangerous in the brain.

**Intensity-modulated radiation therapy (IMRT)** — Along with conformal therapy (defined below), these are radiation oncology techniques developed in the 1990s to capitalize on computers’ abilities to plan radiation delivery more precisely, thus maximizing exposure of tumors while avoiding surrounding tissues.

**Proton beam therapy (PBT)** — A type of radiation treatment that uses protons rather than x-rays to treat cancer. At high energy, protons can destroy cancer cells.

### References

**Professional society guidelines/others:**


Australia and New Zealand Horizon Scanning Network (ANZHSN). Proton beam therapy for the treatment of neoplasms involving (or adjacent to) cranial structures. Royal Australasian College of Surgeons. May 2007.(a)


**Peer-reviewed references:**


Hayes, Inc., Hayes Medical Technology Report. Proton beam therapy for prostate cancer. Search & Summary. Lansdale, PA. Hayes, Inc. May 28, 2015. https://www.hayesinc.com/subscribers/displaySubscriberArticle.do?articleId=22546&searchStore=%24search_type%3Dall%24icd%3D%24keywords%3D%22proton%20beam%20therapy%22%24status%3Dall%24page%3D1%24from_date%3D%24to_date%3D%24report_type_options%3D%24technology_type_options%3D%24organ_system_options%3D%24specialty_options%3D%24order%3DasearchRelevance. Accessed August 18, 2016.

Hayes, Inc., Hayes Medical Technology Report. Proton beam therapy for medulloblastoma in children. Search & Summary. Lansdale PA. Hayes, Inc. June 27, 2015. https://www.hayesinc.com/subscribers/displaySubscriberArticle.do?articleId=16641&searchStore=%24search_type%3Dall%24icd%3D%24keywords%3D%22proton%20beam%20therapy%22%24status%3Dall%24page%3D1%24from_date%3D%24to_date%3D%24report_type_options%3D%24technology_type_options%3D%24organ_system_options%3D%24specialty_options%3D%24order%3DasearchRelevance. Accessed August 18, 2016.


**Clinical trials:**

Searched clinicaltrials.gov on August 27, 2015 using term “Proton Beam Therapy” cancer. | Open Studies. 83 studies, three (3) relevant.


Massachusetts General Hospital. Proton therapy vs. IMRT for Low or Intermediate Risk Prostate Cancer. ClinicalTrials.gov web site.

Radiation Therapy Oncology Group, National Cancer Institute. Comparing Photon Therapy To Proton Therapy To Treat Patients With Lung Cancer. ClinicalTrials.gov web site.

**CMS National Coverage Determinations (NCDs):**

No NCDs identified as of the writing of this policy.

**Local Coverage Determinations (LCDs):**

https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=34282&ver=10&CoverageSelection=Both&ArticleType=All&PolicyType=Final&s=All&Key Word=%22proton+beam+therapy%22&KeyWordLookUp=Title&KeyWordSearchType=And&bc=gAAAAACAAAA AAAAA%3d%3d&. Accessed August 18, 2016.

L34684 Proton Beam Therapy. Wisconsin Physicians Service Insurance Corporation. CMS website.
https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=34634&ver=12&CoverageSelection=Both&ArticleType=All&PolicyType=Final&s=All&Key Word=%22proton+beam+therapy%22&KeyWordLookUp=Title&KeyWordSearchType=And&bc=gAAAAACAAAA AAAAA%3d%3d&. Accessed August 18, 2016.

https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=35075&ver=5&CoverageSelection=Both&ArticleType=All&PolicyType=Final&s=All&Key
Commonly submitted codes

Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill accordingly.

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<td>Includes particle, hadron therapy</td>
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<td>77525</td>
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