Proton Beam radiotherapy (PBT) is a form of conformal external beam radiation treatment. Protons are positively charged atomic particles and have similar biological effects as conventional x-ray beams, but have very different energy disposition or physics profiles. Proton particles deliver a smaller amount of radiation energy as they enter the body (lower entrance dose) culminating in an intensity dose peak (e.g. Bragg Peak) therefore depositing 100% of the dosage at the targeted tissue. There is no further energy deposition beyond the Bragg peak (no exit dose). Proton beams typically deposit less radiation in normal non-targeted tissues than conventional radiation therapy and have been used to escalate the radiation dose to diseased tissues while minimizing damage to adjacent normal tissues. Proton beam therapy will typically have a significantly lower integral dose (dose to the whole body of the patient) compared to conventional x-ray therapy. In contrast, conventional external beam radiation therapy (EBRT) delivers radiation to all involved tissue, diseased and normal, and targeted tissue receives 60–70% of the intended dose.

Proton beam therapy is typically performed on an outpatient basis. For most tumor sites, a standard course of treatment is five to seven weeks, with treatments delivered five days per week. The length of each treatment will vary depending upon the tumor type and stage. The delivery of the proton beam to the patient lasts only a few minutes, although the total time spent in the treatment room will be longer (about 15 to 20 minutes) for positioning and adjustments to the equipment settings.

**Recommendation**

Medically Necessary Indications:

- Proton beam radiation therapy may be considered medically necessary and may be authorized for the following conditions when sparing the surrounding normal tissue cannot be adequately achieved with surgical excision, conventional photon beam radiation or IMRT:
  - As primary therapy for the following ocular tumors:
    - Melanoma of the uveal tract: includes iris, choroid, or ciliary body tumors; and [ALL]
      - no evidence of metastasis or extrascleral extension; and
      - tumor size diameter ≤ 24 mm; and
      - tumor size height ≤ 14 mm
  - As postoperative therapy for the following skull base tumors:
    - Chordoma at the base of the skull and: [ALL]
      - no distal metastasis; and
b. residual localized tumor after resection

- Chondrosarcoma at the base of the skull and: [ALL]
  a. no distal metastases; and
  b. grade I or II chondrosarcoma; and
  c. residual localized tumor after resection

Not Medically Necessary Conditions

- Proton beam therapy (PBT) is considered not medically necessary and may not be authorized for the treatment of the following conditions because clinical outcomes of this treatment have not been shown to be superior to other approaches:
  o Abdominal tumors
  o Age-related macular degeneration (AMD)
  o Brain and spinal cord tumors
  o Choroidal Hemangiomas
  o Head and neck tumors (other than skull base)
  o Hepatocellular carcinoma
  o Intracranial arteriovenous malformations
  o Pelvic tumors including genitourinary, gynecologic, and gastrointestinal
  o Pituitary tumors
  o Prostate Cancer: Please reference Proton Beam Therapy for prostate Cancer MCG-153
  o Thoracic tumors
  o Vestibular tumors

SUMMARY OF MEDICAL EVIDENCE

Skull base tumors

The published evidence consisting of systematic reviews, retrospective studies, and uncontrolled single arm studies is sufficient and supports that PBT is effective in the treatment of skull base tumors. A systematic review concluded that there is evidence for a benefit of proton beam therapy over photon approaches in treating chordomas. Another systematic review of seven uncontrolled single-arm studies concluded that the use of protons has shown better results in comparison to the use of conventional photon irradiation, resulting in the best long-term (10 years) outcome for skull-based chordomas with relatively few significant complications. A second systematic review by the same author reported that studies of proton beam therapy for skull-based chondrosarcoma resulted in local control ranging from 75% to 99% at 5 years. A retrospective review of 29 patients with skull base chordomas (n=18) and low-grade chondrosarcomas (CS) (n=11) assessed the clinical results of spot scanning proton beam radiation therapy (PT). Median follow-up time was 29 months (range, 6-68 months). Three year local control rates were 87.5% and 100% for chordoma and CS, respectively. According to this small study spot-scanning PT offers high tumor control rates of skull base chordoma and chondrosarcomas. A single center case series of 40 patients with chordomas of the skull base and cervical spine reviewed the outcomes of surgery and proton radiotherapy. The median follow-up was 56.5 months. The 5-year PFS and OS
rates were 70% and 83.4%, respectively. Another single center case series evaluated the clinical results of fractionated spot-scanning proton radiation therapy (PT) in 26 pediatric patients treated at Paul Scherrer Institute for chordoma (CH) or chondrosarcoma (CS) of the skull base or axial skeleton. Mean follow-up was 46 months. Actuarial 5-year local control (LC) rates were 81% for CH and 80% for CS. Actuarial 5-year overall survival (OS) was 89% for CH and 75% for CS.

Uveal Melanomas

The published evidence consisting of a RCT, comparative studies, retrospective cohort studies, and case series is sufficient and supports that PBT is effective in the treatment of uveal melanomas. A systematic review was conducted by the American Society for Therapeutic Radiology and Oncology (ASTRO) Evaluation Subcommittee of Emerging Technologies. The review noted that the use of PBRT has been reported in thousands of cases of ocular melanoma, with combined results of leading centers in the United States and Europe showing 95% control rate and 90% eye retention rate. The technique was noted as especially useful in large and posteriorly located melanomas that are unapproachable by other techniques such as brachytherapy. This review concluded that there is evidence for a benefit of proton beam therapy over photon approaches in treating large ocular melanomas.

A report on proton beam therapy from the Institute for Clinical and Economic Review (ICER) rated the net health benefit of PBT relative to alternative treatments to be superior in ocular tumors. The RCT compared PBT alone to a combination of PBT and transpupillary thermotherapy (TTT) in 151 patients (mean age: 58 years; 52% male) treated for uveal melanoma and followed for a median of 3 years in France. Combination therapy was associated with a statistically-significantly (p=0.02) reduced likelihood of secondary enucleation; no other outcomes differed significantly between groups. In a separate comparison of these findings to a separate series of patients undergoing PBT with endoresection of the scar rates of secondary enucleation did not differ between groups, but rates of neovascular glaucoma were significantly lower in the PBT+endoresection group vs. the groups from the RCT (7% vs. 58% and 49% for PBT alone and PBT+TTT respectively, p<0.0001). Of note, however, median follow-up was less than two years in the PBT+endoresection series vs. 9 years in the RCT. Three of the cohort studies were all fair-quality and involved comparisons to surgical enucleation in patients with uveal melanoma at single centers. PBT was associated with statistically-significant improvements in overall survival rates relative to enucleation at 2-5 years in two of these studies. Rates of metastasis-related and all cancer-related death were statistically-significantly lower among PBT patients through two years of follow-up in the Seddon study, but were nonsignificant at later timepoints. The 5-year metastasis-free survival rate (n=67) was 50% higher among PBT patients in a Cox regression model controlling for baseline characteristics (59.0% vs. 39.4% for enucleation, p=0.02). In the third study, Kaplan-Meier curves for all-cause mortality, melanoma-related mortality and metastasis-free survival did not statistically differ for 132 patients treated with PBT and enucleation. Metastasis-free survival also did not differ in Cox regression adjusting for age, sex, and tumor thickness.

Another study assessed the impact of PBT + chemotherapy vs. PBT alone in 88 patients with uveal melanoma (aged primarily between 20-55 years; 63% male) who were followed for 5-8 years. Five-year overall survival rates did not statistically differ between groups on either an unadjusted or Cox regression-adjusted basis. Lastly,
a comparison of noncontemporaneous case series evaluated treatment with PBT + laser photocoagulation or PBT alone in 56 patients with choroidal melanoma. At one year, there were no differences in visual acuity between groups. 11

Other Conditions

There is limited clinical evidence that directly compares proton beam therapy (PBT) with other types of radiation therapy for other conditions. The current published evidence is of low quality and consists of small comparative studies that are not randomized or controlled, retrospective/prospective studies and individual case series. Therefore, the current published evidence does not allow for any definitive conclusions about the safety and efficacy of proton beam therapy to treat other conditions not listed in the medically necessary recommendation section above. 4 9 17 23-26

AHRQ published a report (2009) on particle beam therapy for treating many types of cancers. AHRQ identified studies that described treatment of ocular cancers (uveal melanoma in particular), and cancers of the head and neck (brain tumors, and tumors arising from skull base, cervical spine and nearby structures). Other types of malignancies were also described that included gastrointestinal (esophageal cancer, hepatocellular carcinomas of the liver, pancreatic cancer), prostate, lung, spine and sacrum, bone and soft tissue, uterine (cervix and corpus), bladder, and skin cancers. 185 were single-arm retrospective studies, and another 35 studies were prospective single-arm trials. The number of included patients ranged from 10 to 2,645 (median 63). Seven studies (3 percent) focused on a pediatric population; most of the remaining studies reported mean or median age above 50 years. The reported follow up periods ranged from 5 to 157 months (median, 36 months) for 188 studies that commented on the pertinent data. Thirty-one studies followed patients longer than 5 years. Two studies had mean follow up longer than 10 years. All trials enrolled a relatively small sample size, ranging from 15 to 393 patients and studied different comparisons. Most trials did not compare charged particle radiotherapy with contemporary alternates. No trial reported significant differences in overall or cancer-specific survival or in total serious adverse events. Overall, no study found that charged particle radiotherapy is significantly better than alternative treatments with respect to patient-relevant clinical outcomes. Comparative effectiveness studies including randomized controlled trials are needed to document the theoretical advantages of charged particle radiotherapy to specific clinical situations. 9

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<td>Proton treatment delivery; intermediate</td>
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### ICD-9 Description

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### ICD-10 Description

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</table>

### Resource References

6. UpToDate: [website]: Gragoudas E et al. Uveal and conjunctival melanomas. 2015
7. UpToDate: [website]: Snyderman C, Lin D. Chordoma and chondrosarcoma of the skull base. 2015.


28. Advanced Medical Review: Policy reviewed by a practicing physician board certified in Radiation Oncology. 1/5/15

DISCLAIMER

This Medical Guidance is intended to facilitate the Utilization Management process. It expresses Molina’s determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (i.e., will be paid for by Molina) for a particular member. The member’s benefit plan determines coverage. Each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their providers will need to consult the member’s benefit plan to determine if there is any exclusion or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a member’s plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid members. CMS’s Coverage Database can be found on the following website: http://www.cms.hhs.gov/center/coverage.asp

CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this Molina medical coverage guidance (MCG) document and provide the directive for all Medicare members.

CMS does not have a National Coverage Determination (NCD) for Proton Beam Therapy (PBT). Local Coverage Determinations (LCDs) are available.