Clinical Policy Bulletin:
Proton Beam and Neutron Beam Radiotherapy

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Policy

I. Aetna considers proton beam radiotherapy (PBRT) medically necessary in any of the following radiosensitive tumors:

   A. Chordomas or chondrosarcomas arising at the base of the skull or cervical spine without distant metastases; or
   B. Malignancies in children (21 years of age and younger); or
   C. Uveal melanomas confined to the globe (i.e., not distant metastases) (the uvea is comprised of the iris, ciliary body, and choroid [the vascular middle coat of the eye]).

II. Aetna considers proton beam radiotherapy for treatment of prostate cancer not medically necessary for individuals with localized prostate cancer because it has not been proven to be more effective than other radiotherapy modalities for this indication. Proton beam therapy for metastatic prostate cancer is considered experimental and investigational.

III. Aetna considers proton beam radiotherapy experimental and investigational for all other indications, including the following indications in adults (over age 21) (not an all-inclusive list) because its effectiveness for these indications has not been established:

   ■ Adenoid cystic carcinoma
   ■ Age-related macular degeneration
   ■ Bladder cancer
   ■ Brain tumors
   ■ Breast cancer
   ■ Carotid body tumor
   ■ Cavernous hemangioma
   ■ Cervical cancer
   ■ Cholangiocarcinoma
   ■ Choroidal hemangioma
   ■ Dermatofibrosarcoma protuberans
   ■ Desmoid fibrosarcoma
   ■ Ependymoma
   ■ Esophageal cancer
   ■ Ewing's sarcoma
   ■ Fibrosarcoma of the extremities
Glioma
Head and neck cancer
Hepatocellular carcinoma
Hodgkin's lymphoma
Intracranial arterio-venous malformations
Large cell lymphoma
Leiomyosarcoma of the extremities
Liver metastases
Lung cancer (including non-small-cell lung carcinoma)
Maxillary sinus tumor
Nasopharyngeal tumor
Non-Hodgkin lymphoma
Non-uveal melanoma
Oligodendroglioma
Optic nerve schwannoma
Pancreatic cancer
Parotid gland tumor
Pineal tumor
Pituitary neoplasms
Rectal cancer
Seminoma
Sino-nasal carcinoma
Small bowel adenocarcinoma
Soft tissue sarcoma
Squamous cell carcinoma of the eyelid, tongue/glottis
Submandibular gland tumor
Thymoma
Tonsillar cancer
Uterine cancer
Vestibular schwannoma.

IV. Aetna considers neutron beam therapy medically necessary for the treatment of any of the following salivary gland tumors:

- Inoperable tumor; or
- Locally advanced tumor especially in persons with gross residual disease; or
- Unresectable tumor.

V. Aetna considers neutron beam therapy experimental and investigational for all other indications including malignancies listed below (not an all inclusive list) because its effectiveness for these indications has not been established:

- Colon cancer
- Dermatofibrosarcoma protuberans
- Glioma
- Kidney cancer
- Laryngeal cancer
- Lung cancer
- Pancreatic cancer
- Prostate cancer
- Rectal cancer
- Soft tissue sarcoma.

Background
Proton Beam Therapy:

Proton beams have less scatter than other sources of energy such as gamma rays, x-rays, or electrons. Because of this feature, proton beam radiotherapy (PBRT) has been used to escalate radiation dose to diseased tissues while minimizing damage to adjacent normal tissues. Proton beams have been used in stereotactic radiosurgery of intracranial lesions; the gamma knife and linear accelerator have also been used in stereotactic radiosurgery. Proton beam radiotherapy has been shown to be particularly useful in treating radiosensitive tumors that are located next to vital structures, where complete surgical excision or administration of adequate doses of conventional radiation is difficult or impossible. Examples include uveal melanomas, chordomas and chondrosarcomas at the base of the skull, and inoperable arterio-venous malformations. There is inadequate data on the application of PBRT for the treatment of non-uveal melanoma.

The American Society of Radiation Oncology (ASTRO, 2013) has stated: “At the present time, 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.”

The emerging technology committee of the American Society of Radiation Oncology (ASTRO) concluded that current evidence provides a limited indication for proton beam therapy (Allen, et al., 2012). The ASTRO report concluded that current data do not provide sufficient evidence to recommend proton beam therapy in lung cancer, head and neck cancer, gastrointestinal malignancies, and pediatric non-CNS malignancies. The ASTRO report stated that, in hepatocellular carcinoma and prostate cancer, there is evidence for the efficacy of proton beam therapy but no suggestion that it is superior to photon based approaches. In pediatric central nervous system (CNS) malignancies, proton beam therapy appears superior to photon approaches but more data is needed. The report found that, in large ocular melanomas and chordomas, there is evidence for a benefit of proton beam therapy over photon approaches. The ASTRO report stated that more robust prospective clinical trials are needed to determine the appropriate clinical setting for proton beam therapy.

A systematic evidence review (Lodge et al, 2007) compared the efficacy and cost-effectiveness of PBRT and other types of hadron therapy (neutron and heavy and light ion therapy) with photon therapy. The authors concluded that, overall, the introduction or extension of PBRT and other types of hadron therapy as a major treatment modality into standard clinical care is not supported by the current evidence base. The authors stated, however, that the efficacy of PBRT appears superior to that of photon therapy for some ocular and skull base tumours. The authors found that, for prostate cancer, the efficacy of PBRT seems comparable to photon therapy. The authors stated that no definitive conclusions can be drawn for the other cancer types. The authors also noted that they found little evidence on the relative cost-effectiveness of PBRT and other types of hadron therapy compared to photon therapy or with other cancer treatments.

Other systematic evidence reviews of PBRT have reached similar conclusions (Lance, 2010; Brada et al, 2009; Efthathiou et al, 2009; ICER, 2008; Wilt et al, 2008; Brada et al, 2007; Olsen et al, 2007).

The only randomized controlled clinical trial comparing PBRT to conventional radiotherapy published to date found no advantage of PBRT in overall survival (OS), disease-specific survival, or total recurrence-free survival (Shipley, 1995). A total of 202 patients with stage T3-T4 prostate cancer were randomly assigned to a standard dose of conventional radiotherapy plus a 25.2 Gy equivalent PBRT boost or to a standard dose of conventional radiotherapy with a 16.8 Gy boost of conventional radiotherapy. After a median follow-up of 61 months, there were no significant differences between the 2 groups in OS, disease-specific survival, total recurrence-free survival, or local control. Local control was better with the proton beam boost only among the subgroup of patients with poorly differentiated carcinoma. Patients receiving the proton beam boost had increased rates of late radiation sequelae.
Loma Linda University’s experience with PBRT of prostate cancer was reported in an article published in 1999 by Rossi et al. These investigators reported the results of an uncontrolled study of PBRT treatment of 319 patients with biopsy-proven early-stage prostate cancer, with no patient having an initial PSA of greater than 15. Because the study was uncontrolled, one is unable to determine whether the results of PBRT are superior to conventional forms of radiation therapy. In addition, the definitions of success and failure used in this study are not comparable to those used in other recent studies of prostate cancer treatments. In the study by Rossi et al, patients were considered to have an adequate response if their PSA level fell below 1.0; most other recent studies define an adequate response as PSA level below 0.5. In the study by Rossi et al, patients were considered treatment failures if they had 3 consecutive rises of PSA of 10% or more, measured at 6-month intervals. In other words, for a patient to be considered a treatment failure, it would take at least 18 months, and patients would have to have 3 consecutive rises in PSA, each greater than 10%. By contrast, other reported studies of prostate cancer radiotherapy have defined failure as any PSA elevation over a target PSA nadir. Finally, Rossi et al defined clinical disease free survival as having “no symptoms and no evidence of disease upon physical examination or radionuclide scans”. These are very gross tests to determine success, and one would expect these tests to be negative in a high number of patients who harbored occult disease.

Of the 319 patients included in the study by Rossi et al, only 288 patients (91%) who had achieved a nadir (any nadir) or who had been followed for at least 24 months were included in the analysis. This would indicate that 31 (9%) of the patients originally included in the study either had persistently rising PSA levels without a nadir despite treatment, had dropped out of the study, or had not been followed for a sufficient length of time for some unspecified reason. Only 187 patients (59% of the original 319 patients) achieved a PSA nadir of 0.5 or less, 66 (21%) achieved a PSA nadir of 0.51 to 1.0, and 35 (11%) achieved a PSA nadir of 1.0 and above. Thus, only 59% of patients would be considered to have had an adequate response by the measure most commonly used in other recent prostate cancer treatment studies. In addition, because of the peculiar way the results are reported, there is no way of knowing how many patients’ PSA nadirs were maintained.

In a randomized, prospective, sham-controlled, double-masked study (n = 37), Ciulla et al (2002) examined the effect of PBRT on subfoveal choroidal neovascular membranes associated with age-related macular degeneration. These investigators concluded that with the acceptance of photodynamic therapy, future studies will require more complex design and larger sample size to determine whether radiation can play either a primary or adjunctive role in treating these lesions.

In a phase II clinical study (n = 30), Kawashima and colleagues (2005) assessed the safety and effectiveness PBRT for patients with hepatocellular carcinoma (HCC). Eligibility criteria for this study were: solitary HCC; no indication for surgery or local ablation therapy; no ascites; age of 20 years or older; Zubrod performance status of 0 to 2; no serious co-morbidities other than liver cirrhosis; written informed consent. Proton beam radiotherapy was administered in doses of 76 cobalt gray equivalent in 20 fractions for 5 weeks. No patients received transarterial chemoembolization or local ablation in combination with PBRT. All patients had liver cirrhosis, the degree of which was Child-Pugh class A in 20, and class B in 10 patients. Acute reactions of PBRT were well-tolerated, and PBRT was completed as planned in all patients. Four patients died of hepatic insufficiency without tumor recurrence at 6 to 9 months; 3 of these 4 patients had pre-treatment indocyanine green retention rate at 15 minutes of more than 50%. After a median follow-up period of 31 months (range of 16 to 54 months), only 1 patient experienced recurrence of the primary tumor, and 2-year actuarial local progression-free rate was 96%. Actuarial overall survival rate at 2 years was 66%. These investigators concluded that PBRT showed excellent control of the primary tumor, with minimal acute toxicity. They stated that further study is warranted to scrutinize adequate patient selection in order to maximize survival benefit of this promising modality.

In a phase II prospective trial, Bush et al (2011) evaluated the safety and effectiveness of PBRT for HCC. Patients with cirrhosis who had radiological features or biopsy-proven HCC were
included in the study. Patients without cirrhosis and patients with extra-hepatic metastasis were excluded. The mean age was 62.7 years. The mean tumor size was 5.5 cm. Eleven patients had multiple tumors, and 46 % were within the Milan criteria. Patients received 63 Gy delivered over a 3-week period with PBRT. A total of 76 patients were treated and followed prospectively. Acute toxicity was minimal; all patients completed the full course of treatment. Radiation-induced liver disease was evaluated using liver enzyme, bilirubin, and albumin levels; no significant change supervened 6 months post-treatment. Median progression-free survival for the entire group was 36 months, with a 60 % 3-year progression-free survival rate for patients within the Milan criteria. Eighteen patients subsequently underwent liver transplantation; 6 (33 %) explants showed pathological complete response and 7 (39 %) showed only microscopic residual. The authors concluded that PBRT was found to be a safe and effective local-regional therapy for inoperable HCC. They noted that a randomized controlled trial to compare its efficacy to a standard therapy has been initiated.

Olfactory neuroblastoma (ONB) is a rare disease, and a standard treatment strategy has not been established. Radiation therapy for ONB is challenging because of the proximity of ONB to critical organs. Nishimura et al (2007) analyzed the feasibility and effectiveness of PBRT for ONB. A retrospective review was performed on 14 patients who underwent PBRT for ONB as definitive treatment. The total dose of PBRT was 65 cobalt Gray equivalents (Gy(E)), with 2.5-Gy (E) once-daily fractionations. The median follow-up period for surviving patients was 40 months. One patient died from disseminated disease. There were 2 persistent diseases, 1 of which was successfully salvaged with surgery. The 5-year overall survival rate was 93 %, the 5-year local progression-free survival rate was 84 %, and the 5-year relapse-free survival rate was 71 %. Liquorrhea was observed in 1 patient with Kadish’s stage C disease (widely destroying the skull base). Most patients experienced grade 1 to 2 dermatitis in the acute phase. No other adverse events of grade 3 or greater were observed according to the RTOG/EORTC acute and late morbidity scoring system. The authors concluded that these preliminary findings of PBRT for ONB achieved excellent local control and survival outcomes without serious adverse effects. They stated that PBRT is considered a safe and effective modality that warrants further study.

Proton beam radiotherapy represents a special case for children for several reasons (Wilson et al, 2005; Hall, 2006; Merchant, 2009). It has been shown in dosimetric planning studies to have a potential advantage over conventional photon therapy because of the ability to confine the high-dose treatment area to the tumor volume and minimize the radiation dose to the surrounding tissue. This especially important in children, as children are more sensitive to radiation-induced cancer than adults. An increased risk of second cancers in long-term survivors is more important in children than older adults. In addition to second malignant neoplasms, late effects of radiation to normal tissue can include developmental delay. Also, radiation scattered from the treatment volume is more important in the small body of the child. Finally, the question of genetic susceptibility arises because many childhood cancers involve a germline mutation.

An assessment of proton beam radiotherapy by the Veterans Health Administration Technology Assessment Program (VATAP) (Flynn, 2010) found that available English-language reviews for proton therapy generally concur on the state of the literature as consisting primarily of observational studies from which conclusions about the relative effectiveness of proton therapy versus alternatives cannot validly be made. The assessment reported that available reviews reflect the state of the literature in that they attempt to cover so much territory (multiple poor-prognosis inoperable tumors in both children and adults) that the reviews themselves are cumbersome to read, not well organized, and provide only diffuse or equivocal conclusions by individual diagnoses. "In other words, the literature reflects the early clinical investigation status of proton therapy, where observational studies are framed in terms of potential benefits, reasoning from pathophysiology, dose-finding, refinement of treatment protocols, and baseline safety of the entire approach" (Flynn, 2010). The assessment noted that only prostate cancer is represented by randomized controlled clinical trials, and in that case two small ones primarily concerned with refinement of protocol/dose escalation.

Regarding cost-effectiveness analyses of PBRT, the VATAP assessment found that the availability of studies titled by their authors as "economic evaluations" is misleading (Flynn,
The assessment stated that such studies require cost and efficacy data about both the intervention and its alternatives (costs and consequences of alternative interventions), hence should be conducted only after efficacy data from randomized controlled trials are available. The assessment noted that, in the case of proton therapy, the economic studies are premature, really should be labeled simple cost rather than cost-effectiveness analyses, and their conclusions based on unwarranted efficacy assumptions. Cost data have been carefully collected and reported, but these are only one element of decision making about investment in proton therapy. The VATAP assessment concluded that there are no indications for which proton therapy has been shown unequivocally to be effective, or more effective than its alternatives. The VATAP assessment also concluded that no research published subsequent to the searches conducted for available systematic reviews has changed the conclusions of those reviews.

Regarding research implications, the VATAP assessment concluded that, in order to obtain the next generation of data, explicit decisions need to be made about which malignancies are amenable to/should require randomized trials (e.g., prostate cancer is sufficiently common) and which malignancies are sufficiently rare or difficult to treat with surgery or conventional radiotherapy (e.g., ocular tumors, tumors of the optical nerve, spinal cord, or central nervous system) that observational studies with larger cohorts than studies to date are the best approach (Flynn, 2010). The VATAP assessment also concluded that future studies should strongly consider valid and reliable embedded collection of cost data in order to inform better quality economic evaluation than currently available.

An assessment prepared for the Agency for Healthcare Research and Quality (Trikalinos, et al., 2009) found that a large number of scientific papers on charged particle radiotherapy for the treatment of cancer currently exist. However, these studies do not document the circumstances in contemporary treatment strategies in which radiotherapy with charged particles is superior to other modalities. Comparative studies in general, and randomized trials in particular (when feasible), are needed to document the theoretical advantages of charged particle radiotherapy to specific clinical situations. The assessment noted that most eligible studies were noncomparative in nature and had small sample sizes. The report stated that it is likely that focused systematic reviews will not be able to provide a definitive answer on the effectiveness and safety of charged particle beam radiotherapies compared with alternative interventions. This is simply because of the relative lack of comparative studies in general, and randomized trials in particular. The report stated that comparative studies (preferably randomized) are likely necessary to provide meaningful answers on the relative safety and effectiveness of particle beam therapy versus other treatment options in the context of current clinical practice. This is especially true for the treatment of common cancers. The report stated that, especially for many common cancers, such as breast, prostate, lung, and pancreatic cancers, it is essential that the theorized advantages of particle beam therapy versus contemporary alternative interventions are proven in controlled clinical trials, along with concomitant economic evaluations.

An assessment of the comparative effectiveness and value of management options in low-risk prostate cancer by the Institute for Clinical and Economic Review (ICER) (Ollendorf et al, 2008) found that the evidence on the comparative effectiveness and harms of proton beam therapy is limited to relatively small, highly selective case series of short duration, making any judgments about its relative benefit or inferiority to other options premature. The uncertainty regarding PBRT is accentuated because this technology involves delivery of a novel form of radiation, and there remain important questions about the full spectrum of possible effects. ICER rated PBRT’s comparative clinical effectiveness as "insufficient", indicating that there is not enough evidence to allow a reasonable judgment of the likely balance of harms and benefits of PBRT in comparison to radical prostatectomy or other management options. ICER judged the comparative value of PBRT to be low compared to other options. The ICER reported explained, that, while ICER does not always provide a comparative value rating for technologies with insufficient evidence on comparative clinical effectiveness, the decision was made to rate the comparative value of PBRT as "low" relative to radical prostatectomy, based on current levels of reimbursement that are more than 3-fold higher for PBRT.
The Blue Cross and Blue Shield Association Medical Advisory Panel (BCBSA, 2010) concluded that proton beam radiation therapy for treatment of non-small-cell lung cancer at any stage or for recurrent non-small-cell lung cancer does not meet the Technology Evaluation Center criteria. The TEC assessment stated that, overall, evidence is insufficient to permit conclusions about the results of proton beam therapy for any stage of non-small-cell lung cancer. The report found that all proton beam therapy studies are case series; there are no studies directly comparing proton beam therapy and stereotactic body radiotherapy. Among study quality concerns, no study mentioned using an independent assessor of patient reported adverse events, adverse events were generally poorly reported, and details were lacking on several aspects of proton beam therapy treatment regimens. The proton beam therapy studies had similar patient ages, but there was great variability in percent within stage Ia, sex ratio, and percent medically inoperable. There is a high degree of treatment heterogeneity among the proton beam therapy studies, particularly with respect to planning volume, total dose, number of fractions, and number of beams. Survival results are highly variable. It is unclear if the heterogeneity of results can be explained by differences in patient and treatment characteristics. Indirect comparisons between proton beam therapy and stereotactic body radiotherapy, comparing separate sets of single-arm studies on proton beam therapy and stereotactic body radiotherapy, may be distorted by confounding. In the absence of randomized, controlled trials, the comparative effectiveness of proton beam therapy and stereotactic body radiotherapy is uncertain.

Mizumoto et al (2010) evaluated the efficacy and safety of PBRT for locoregionally advanced esophageal cancer. The subjects were 51 patients with esophageal cancer who were treated between 1985 and 2005 using proton beams with or without X-rays. All but 1 had squamous cell carcinoma. Of the 51 patients, 33 received combinations of X-rays (median of 46 Gy) and protons (median of 36 GyE) as a boost. The median total dose of combined X-rays and proton radiation for these 33 patients was 80 GyE (range of 70 to 90 GyE). The other 18 patients received PBRT alone (median of 79 GyE, range of 62 to 98 GyE). Treatment interruption due to radiation-induced esophagitis or hematologic toxicity was not required for any patient. The overall 5-year actuarial survival rate for the 51 patients was 21.1 % and the median survival time was 20.5 months (95 % confidence interval [CI]: 10.9 to 30.2). Of the 51 patients, 40 (78 %) showed a complete response within 4 months after completing treatment and 7 (14 %) showed a partial response, giving a response rate of 92 % (47/51). The 5-year local control rate for all 51 patients was 38.0 % and the median local control time was 25.5 months (95 % CI: 14.6 to 36.3). The authors concluded that these findings suggested that PBRT is an effective treatment for patients with locally advanced esophageal cancer. Moreover, they stated that further studies are needed to determine the optimal total dose, fractionation schedules, and best combination of PBRT with chemotherapy. Furthermore, the National Comprehensive Cancer Network (NCCN) guideline on esophageal cancer (2011) does not mention the use of PBRT as a therapeutic option for this condition.

Bassim et al (2010) reviewed the literature on radiation therapy for the treatment of vestibular schwannoma (VS). PubMed searches for English language articles on radiation treatment of VS published from January 2002 to July 2007 were conducted. Studies presenting outcomes were selected, yielding 56 articles (58 studies) in journals of neurosurgery (30), oncology (18), otolaryngology (6), and other (2). Data included type of study, number of subjects, demographics, follow-up times, type of radiation, tumor size, tumor control definition, control rates, facial nerve function measure and outcome, type of hearing and vestibular testing and outcomes, and complications. Descriptive statistics were performed. Studies (72.9 %) were retrospective reviews with stated sample sizes ranging from 5 to 829. Gamma-knife (49.2 %), linear accelerator (35.6 %), and proton beam (6.8 %) were used with various doses. Average follow-up was less than 5 years in 79.6 % of studies, and 67.4 % included patients at less than or equal to 1 year. Tumor size was reported as diameter (23.7 %), volume (49.2 %), both (11.9 %), other (3.4 %), or not reported (11.9 %). Definition of tumor control varied: less than or equal to 2 mm growth (22.0 %), no visible/measurable change (16.9 %), required surgery (10.2 %), other (17.0 %), and not clearly specified (33.9 %). Facial nerve outcome was reported as House-Brackmann (64.4 %), normal/abnormal (11.9 %), other (1.7 %), or was not reported (22 %). The
authors concluded that the lack of uniform reporting criteria for tumor control, facial function and hearing preservation, and variability in follow-up times make it difficult to compare studies of radiation treatment for VS. They recommended consideration of reporting guidelines such as those used in otology for reporting VS resection results.

Mizumoto et al (2011) evaluated the safety and effectiveness of hyper-fractionated concomitant boost proton beam therapy (PBT) for patients with esophageal cancer. The study participants were 19 patients with esophageal cancer who were treated with hyperfractionated photon therapy and PBT between 1990 and 2007. The median total dose was 78 GyE (range of 70 to 83 GyE) over a median treatment period of 48 days (range of 38 to 53 days). Ten of the 19 patients were at clinical T Stage 3 or 4. There were no cases in which treatment interruption was required because of radiation-induced esophagitis or hematologic toxicity. The overall 1- and 5-year actuarial survival rates for all 19 patients were 79.0 % and 42.8 %, respectively, and the median survival time was 31.5 months (95 % limits: 16.7 to 46.3 months). Of the 19 patients, 17 (89 %) showed a complete response within 4 months after completing treatment and 2 (11 %) showed a partial response, giving a response rate of 100 % (19/19). The 1- and 5-year local control rates for all 19 patients were 93.8 % and 84.4 %, respectively. Only 1 patient had late esophageal toxicity of Grade 3 at 6 months after hyperfractionated PBT. There were no other non-hematologic toxicities, including no cases of radiation pneumonia or cardiac failure of Grade 3 or higher. The authors concluded that these findings suggested that hyperfractionated PBT is safe and effective for patients with esophageal cancer. They stated that further studies are needed to establish the appropriate role and treatment schedule for use of PBT for esophageal cancer.

In a phase I clinical study, Hong et al (2011) evaluated the safety of 1 week of chemo-radiation with proton beam therapy and capecitabine followed by early surgery on 15 patients with localized resectable, pancreatic ductal adenocarcinoma of the head. Patients received radiation with proton beam. In dose level 1, patients received 3 GyE x 10 (week 1, Monday to Friday; week 2, Monday to Friday). Patients in dose levels 2 to 4 received 5 GyE x 5 in progressively shortened schedules: level 2 (week 1, Monday, Wednesday, and Friday; week 2, Tuesday and Thursday), level 3 (week 1, Monday, Tuesday, Thursday, and Friday; week 2, Monday), level 4 (week 1, Monday through Friday). Capecitabine was given as 825 mg/m(2) b.i.d. Weeks 1 and 2 Monday through Friday for a total of 10 days in all dose levels. Surgery was performed 4 to 6 weeks after completion of chemotherapy for dose levels 1 to 3 and then after 1 to 3 weeks for dose Level 4. Three patients were treated at dose levels 1 to 3 and 6 patients at dose level 4, which was selected as the MTD. No dose limiting toxicities were observed. Grade 3 toxicity was noted in 4 patients (pain in 1; stent obstruction or infection in 3). Eleven patients underwent resection. Reasons for no resection were metastatic disease (3 patients) and unresectable tumor (1 patient). Mean post-surgical length of stay was 6 days (range of 5 to 10 days). No unexpected 30-day post-operative complications, including leak or obstruction, were found. The authors concluded that pre-operative chemo-radiation with 1 week of PBRT and capecitabine followed by early surgery is feasible. A phase II study is underway.

UpToDate reviews on “Management of locally advanced and borderline resectable exocrine pancreatic cancer” (Ryan and Mamon, 2012) and “Surgery in the treatment of exocrine pancreatic cancer and prognosis” (Fernandez-del Castillo et al, 2012) do not mention the use of proton beam therapy. Furthermore, the NCCN’s clinical practice guideline on “Pancreatic adenocarcinoma” (2011) does not mention the use of proton beam.

Available peer-reviewed published evidence does not support the use of PBRT for squamous cell carcinomas of the head and neck. There is a lack of clinical outcome studies comparing PBRT to stereotactic radiosurgery or other photon-based methods. What few comparative studies exist are limited to dosimetric planning studies and not studies of clinical outcomes. Current guidelines from the NCCN and the National Cancer Institute (PDQ) include no recommendation for use of PBRT for squamous cell carcinoma of the head and neck. A report from the American Society for Therapeutic and Radiation Oncology (ASTRO) (2012) concludes that there is insufficient evidence to support the use of proton beam therapy for head and neck cancers, and conclude that “current data do not provide sufficient evidence to recommend PBT in ... head and
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neck cancer... " An AHRQ comparative effectiveness review (2010) on radiotherapy for head and neck cancer reached the following conclusions regarding proton beam therapy versus other radiotherapy treatments for head and neck cancer: "The strength of evidence is insufficient as there were no studies comparing proton beam therapy to any other radiotherapy modality. Therefore, no conclusions can be reached regarding the comparative effectiveness of proton beam therapy for any of the four key questions."

An UpToDate review on "Clinical presentation and management of thymoma and thymic carcinoma" (Salgia, 2012) does not mention the use of proton beam therapy. Also, the NCCN's clinical practice guideline on "Thymoma and thymic carcinomas" (2011) does not mention the use of proton beam therapy.

Guidelines on soft tissue sarcoma from the National Comprehensive Cancer Network (2012) indicate a potential role for proton therapy in retroperitoneal soft tissue sarcomas in persons who did not receive preoperative radiotherapy. The guidelines state: "Postoperative RT using newer techniques such as IMRT, 3D conformal proton therapy, and intensity modulated proton therapy (IMPT) may allow tumor target coverage and acceptable clinical outcomes within normal tissue dose constraints to adjacent organs at risk in some patients with retroperitoneal STS who did not receive pre-operative radiotherapy. Multicenter randomized controlled trials are needed to address the toxicities and therapeutic benefits of adjuvant RT techniques in patients with retroperitoneal STS."

A BCBS TEC assessment found insufficient evidence for PBRT in the treatment of non-small-cell lung cancer. In addition, the American Society for Radiation Oncology (ASTRO) guidelines (Allen et al, 2012) found insufficient evidence for PBRT in lung cancer.

An UpToDate review on "Malignant salivary gland tumors: Treatment of recurrent and metastatic disease" (Laurie, 2012) stated that "The most common malignant salivary gland tumors include mucoepidermoid carcinoma, adenoid cystic carcinoma, polymorphous low grade adenocarcinoma, carcinoma ex pleomorphic adenoma, acinic cell carcinoma, and adenocarcinoma not otherwise specified". However, it does not mention the use of PBRT as a therapeutic option.

UpToDate reviews on "Treatment of early (stage I and II) head and neck cancer: The larynx" (Koch and Machtay, 2012) and "Treatment of locoregionally advanced (stage III and IV) head and neck cancer: The larynx and hypopharynx" (Brockstein et al, 2012) do not mention the use of NBT.

Given concerns of excess malignancies following adjuvant radiation for seminoma, Efstathiou et al (2012) evaluated photon beam therapy and PBRT treatment plans to assess dose distributions to organs at risk and model rates of second cancers. A total of 10 stage I seminoma patients who were treated with conventional para-aortic AP-PA photon radiation to 25.5 Gy at Massachusetts General Hospital had PBRT plans generated (AP-PA, PA alone). Dose differences to critical organs were examined. Risks of second primary malignancies were calculated. Proton beam radiotherapy plans were superior to photons in limiting dose to organs at risk; PBRT decreased dose by 46 % (8.2 Gy) and 64 % (10.2 Gy) to the stomach and large bowel, respectively (p < 0.01). Notably, PBRT was found to avert 300 excess second cancers among 10,000 men treated at a median age of 39 and surviving to 75 (p < 0.01). The authors concluded that in this study, the use of protons provided a favorable dose distribution with an ability to limit unnecessary exposure to critical normal structures in the treatment of early-stage seminoma. It is expected that this will translate into decreased acute toxicity and reduced risk of second cancers, for which prospective studies are warranted. Furthermore, UpToDate reviews on "Treatment of stage I seminoma" (Beard, 2012) and "Treatment of stage II seminoma" (Beard and Oh, 2012) do not mention the use of PBRT.

Proton beam radiotherapy has been used as therapeutic option for choroidal hemangiomas. However, available evidence on its effectiveness for this indication is mainly in the form of retrospective reviews with small sample size and a lack of comparison to standard therapies.
Furthermore, a review on “Choroidal hemangioma” (Finger, 2013) from the Eye Cancer Network’s website does not mention PBRT as a therapeutic option. Thus, PBRT is not an established treatment for patients with choroidal hemangiomas.

In a retrospective study, Hocht et al (2006) compared the results of therapy in patients with uveal hemangioma treated with photon or proton irradiation at a single center. From 1993 to 2002, a total of 44 patients were treated. Until 1998 radiotherapy was given with 6 MV photons in standard fractionation of 2.0 Gy 5 times per week. In 1998 PBRT became available and was used since then. A dose of 20 to 22.5 Cobalt Gray Equivalent (CGE; CGE = proton Gy x relative biological effectiveness 1.1) 68 MeV protons was given on 4 consecutive days. Progressive symptoms or deterioration of vision were the indications for therapy. Of the 44 patients treated, 36 had circumscribed choroidal hemangiomas (CCH) and 8 had diffuse choroidal hemangiomas (DCH) and Sturge-Weber syndrome. Of the patients, 19 were treated with photons with a total dose in the range of 16 to 30 Gy. A total of 25 patients were treated with PBRT. All patients with DCH but 1 were treated with photons. Stabilization of visual acuity was achieved in 93.2 % of all patients. Tumor thickness decreased in 95.4 % and retinal detachment resolved in 92.9 %. Late effects, although generally mild or moderate, were frequently detected. In all, 40.9 % showed radiation-induced optic neuropathy, maximum Grade I. Retinopathy was found in 29.5 % of cases, but only 1 patient experienced more than Grade II severity. Retinopathy and radiation-induced optic neuropathy were reversible in some of the patients and in some resolved completely. No differences could be detected between patients with CCH treated with protons and photons; treatment was less effective in DCH patients (75 %). The authors concluded that radiotherapy is effective in treating choroidal hemangiomas with respect to visual acuity and tumor thickness; but a benefit of PBRT could not be detected.

In a retrospective review, Levy-Gabriel et al (2009) evaluated the long-term effectiveness and outcome of low-dose PBRT in the treatment of symptomatic CCH. A total of 71 patients with symptomatic CCH were treated by PBRT between September 1994 and October 2002 using a total dose of 20 CGE. The median follow-up was 52 months (range of 8 to 133 months). Retinal re-attachment was obtained in all cases. Tumor thickness decreased in all cases and a completely flat scar was obtained in 65 patients (91.5 %). Visual acuity was improved by 2 lines or more in 37 of the 71 patients (52 %), and in 30 of the 40 patients (75 %) treated within 6 months after onset of the first symptoms. The main radiation complications detected during follow-up were cataract (28 %) and radiation-induced maculopathy (8 %). None of the 71 patients developed eyelid sequelae or neovascular glaucoma. The authors concluded that PBRT with a total dose of 20 CGE appeared to be a valid treatment for CCH, inducing definitive retinal re-attachment and decreasing tumor thickness. However, delayed radiation-induced maculopathy may occur. A successful functional outcome is dependent on a short interval between onset of the first symptoms and initiation of therapy.

In a retrospective chart review, Chan et al (2010) described the clinical outcomes of patients (n = 19) with CCH and DCH treated by PBRT using a non-surgical light-field technique. Choroidal hemangiomas were treated with PBRT using a light-field technique and doses ranging from 15 to 30 CGE in 4 fractions. Patients with at least 6 months’ follow-up were included in the study. Tumor regression, visual acuity, absorption of sub-retinal fluid, and treatment-associated complications were evaluated by clinical examination and ultrasonography. Visual acuity improved or remained stable in 14 of 18 eyes (78 %). Sub-retinal fluid was initially present in 16 of 19 eyes (84 %), and completely resolved in all 16 eyes. Tumor height, as measured by B-scan ultrasonography, decreased in 18 of 19 eyes and remained stable in 1 of 19, as of the last examination. Complications of radiation developed in 9 of 19 eyes (47 %) with the total applied dose ranging from 15 to 30 CGE for these 9 eyes. The authors concluded that PBRT using a light-field technique without surgical tumor localization is an effective treatment option in managing both CCH and DCH associated with Sturge-Weber syndrome. A total proton dose as low as 15 CGE applied in 4 fractions appeared to be sufficient to reduce tumor size, promote absorption of sub-retinal fluid, and improve or stabilize vision in most patients.

Published studies of proton beam therapy for Hodgkin lymphoma are limited to dosimetric planning studies; there is a lack of published clinical outcome studies of proton beam therapy.
demonstrating improvements over photon therapy modalities. Guidelines on Hodgkin Lymphoma from the National Comprehensive Cancer Network state, in under the section Principles of Radiation Therapy, “RT can be delivered with photons or protons. Preliminary results from single-institution studies have shown that significant dose reduction to organs at risk (OAR; e.g., lung, heart, breasts) can be achieved with proton beam RT, which can reduce the risk of late effects. Long-term follow-up is needed to confirm the efficacy of proton beam RT.” Guidelines on radiation therapy for Hodgkin lymphoma from the International Lymphoma Radiation Oncology Group (2014) state: “The role of proton therapy has not yet been defined, and it is not widely available.” National Cancer Institute Guidelines (2014) and American College of Radiology Appropriateness Criteria (2010) for adult Hodgkin lymphoma have no recommendation for proton beam therapy in Hodgkin lymphoma. European Society for Medical Oncology guidelines on Hodgkin disease (Eichenauer, et al., 2014) have no recommendation for proton beam therapy. Other international Hodgkin disease guidelines (British Committee for Standards in Haematology, 2014; BC Cancer Agency, 2013; Alberta Health Services, 2013) have no recommendation for proton beam radiation therapy. Guidelines on proton beam therapy from Alberta Health Services (2013) do not recommend proton beam therapy for lymphomas in adults “due to an insufficient evidence base.”

A technology assessment of proton beam therapy for the Washington State Health Care Authority (2014) found no comparative studies of proton beam therapy for lymphomas that met inclusion criteria for the systematic evidence review. The assessment concluded that the evidence for proton beam therapy for lymphomas was “insufficient” based on no evidence, and reported that their review of guidelines and coverage policies on proton beam found lymphoma was not recommended or not covered.

Meyer et al (2012) noted that chemotherapy plus radiation treatment is effective in controlling stage IA or IIA non-bulky Hodgkin's lymphoma in 90% of patients but is associated with late treatment-related deaths. Chemotherapy alone may improve survival because it is associated with fewer late deaths. These researchers randomly assigned 405 patients with previously untreated stage IA or IIA non-bulky Hodgkin's lymphoma to treatment with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) alone or to treatment with subtotal nodal radiation therapy, with or without ABVD therapy. Patients in the ABVD-only group, those with a favorable risk profile as well as those with an unfavorable risk-profile, received 4 to 6 cycles of ABVD. Among patients assigned to subtotal nodal radiation therapy, those who had a favorable risk-profile received subtotal nodal radiation therapy alone and those with an unfavorable risk-profile received 2 cycles of ABVD plus subtotal nodal radiation therapy. The primary end-point was 12-year OS. The median length of follow-up was 11.3 years. At 12 years, the rate of OS was 94% among those receiving ABVD alone, as compared with 87% among those receiving subtotal nodal radiation therapy (hazard ratio [HR] for death with ABVD alone, 0.50; 95% CI: 0.25 to 0.99; p = 0.04); the rates of freedom from disease progression were 87% and 92% in the 2 groups, respectively (HR for disease progression, 1.91; 95% CI: 0.99 to 3.69; p = 0.05); and the rates of event-free survival were 85% and 80%, respectively (HR for event, 0.88; 95% CI: 0.54 to 1.43; p = 0.60). Among the patients randomly assigned to ABVD alone, 6 patients died from Hodgkin's lymphoma or an early treatment complication and 6 died from another cause; among those receiving radiation therapy, 4 deaths were related to Hodgkin's lymphoma or early toxic effects from the treatment and 20 were related to another cause. The authors concluded that among patients with Hodgkin's lymphoma, ABVD therapy alone, as compared with treatment that included subtotal nodal radiation therapy, was associated with a higher rate of OS owing to a lower rate of death from other causes. This study did not address the use of PBT for the treatment of Hodgkin lymphoma; in fact it argued against the combination use of chem- and radiation-therapy.

National Comprehensive Cancer Network’s clinical practice guideline on “Head and neck cancers” (Version 2.2013) stated that “the role of proton therapy is being investigated”.

The Alberta Health Services, Cancer Care’s clinical practice guideline on “Proton beam radiation therapy” (2013) noted that “Members of the working group do not currently recommend that
patients with prostate cancer, non-small cell lung cancer, or most lymphomas be referred for proton beam radiotherapy, due to an insufficient evidence base”.

The European Society for Medical Oncology’s guidelines on biliary cancers (Eckel et al, 2011) made no recommendation regarding the use of PBT in the treatment of cholangiocarcinoma. Furthermore, NCCN guidelines on “Hepatobiliary cancers” (Version 2.2013) made no recommendation for use PBT in cholangiocarcinoma.

A systematic evidence review of proton beam therapy prepared for the Washington State Healthcare Authority (2014) reviewed studies comparing proton beam therapy to photon therapies. The investigators identified two poor-quality retrospective comparative cohort studies of primary PBT for brain, spinal, and paraspinal tumors. One was an evaluation of proton beam therapy versus photon therapy in 40 adults who received surgical and radiation treatment of medulloblastoma at MD Anderson Cancer Center (citing Brown, et al., 2013). No statistical differences between radiation modalities were seen in Kaplan-Meier assessment of either overall or progression-free survival at two years. A numeric difference was seen in the rate of local or regional failure (5% for PBT vs. 14% for photon), but this was not assessed statistically. The second study involved 32 patients treated for intramedullary gliomas at Massachusetts General Hospital (citing Kahn, et al., 2011) with either proton beam therapy (n=10) or IMRT (n=22). While explicit comparisons were made between groups, the proton beam therapy population was primarily pediatric (mean age 14 years), while the IMRT population was adult (mean age 44 years). Patients in both groups were followed for a median of 24 months. While the crude mortality rate was lower in the proton beam therapy group (20% vs. 32% for IMRT), in multivariate analyses controlling for age, tumor pathology, and treatment modality, proton beam therapy was associated with significantly increased mortality risk (Hazard Ratio 40.0, p = 0.02). The rate of brain metastasis was numerically higher in the proton beam therapy group (10% vs. 5% for IMRT), but this was not statistically tested. Rates of local or regional recurrence did not differ between groups.

NCCN guidelines on central nervous system cancers (2014) have no recommendation for proton beam therapy. International guidelines on CNS malignancies (ESMO, 2010; Alberta Cancer Care, 2012; Cancer Council Australia, 2009) have no recommendation for proton beam therapy. An ASTRO Technology Review of proton beam therapy (2012) stated that, for CNS malignancies other than skull base and cervical spine chordomas and chondrosarcomas, “the potential benefit of proton beam therapy remains theoretical and deserving of further study.”

Dermatofibrosarcoma protuberans is an uncommon tumor that arises in the skin. The tumor is firm and often flesh-colored although it can be reddish, bluish, or purplish. The tumor is often found on the chest or shoulders, but it can be found on other parts of the body. Dermatofibrosarcoma protuberans may cause no symptoms, and the initial size of the tumor tends to be around 1 to 5 centimeters. This tumor has a low potential to spread to other tissues (metastasize). Treatment often involves surgery to remove the tumor, such as by Mohs’ micrographic surgery. https://rarediseases.info.nih.gov/GARD/Condition/9569/Dermatofibrosarcoma_protuberans.aspx. Moreover, NCCN's clinical practice guideline on “Dermatofibrosarcoma protuberans” (Version 1.2014) does not mention proton or neutron beam therapy as a therapeutic option.

Plastaras et al (2014) stated that the dose distributions that can be achieved with protons are usually superior to those of conventional photon external-beam radiation. There are special cases where proton therapy may offer a substantial potential benefit compared to photon treatments where toxicity concerns dominate. Re-irradiation may theoretically be made safer with proton therapy due to lower cumulative lifetime doses to sensitive tissues, such as the spinal cord. Proton therapy has been used in a limited number of patients with rectal, pancreatic, esophageal, and lung cancers. Chordomas and soft tissue sarcomas require particularly high radiation doses, posing additional challenges for re-irradiation. Lymphoma is another special case where proton therapy may be advantageous. Late toxicities from even relatively low radiation doses, including cardiac complications and second cancers, are of concern in lymphoma patients with high cure rates and long life expectancies. Proton therapy has begun to
be used for consolidation after chemotherapy in patients with Hodgkin and non-Hodgkin lymphoma. Breast cancer is another emerging area of proton therapy development and use.

Proton therapy may offer advantages compared to other techniques in the setting of breast boosts, accelerated partial breast irradiation, and post-mastectomy radiotherapy. In these settings, proton therapy may decrease toxicity associated with breast radiotherapy. The authors concluded that as techniques are refined in proton therapy, one may be able to improve the therapeutic ratio by maintaining the benefits of radiotherapy while better minimizing the risks.

Mendenhall et al (2014) reported 5-year clinical outcomes of 3 prospective trials of image-guided proton therapy for prostate cancer. A total of 211 prostate cancer patients (89 low-risk, 82 intermediate-risk, and 40 high-risk) were treated in institutional review board-approved trials of 78 cobalt gray equivalent (CGE) in 39 fractions for low-risk disease, 78 to 82 CGE for intermediate-risk disease, and 78 CGE with concomitant docetaxel therapy followed by androgen deprivation therapy for high-risk disease. Toxicities were graded according to Common Terminology Criteria for Adverse Events (CTCAE), version 3.0. Median follow-up was 5.2 years. Five-year rates of biochemical and clinical freedom from disease progression were 99%, 99%, and 76% in low-, intermediate-, and high-risk patients, respectively. Actuarial 5-year rates of late CTCAE, version 3.0 (or version 4.0) grade 3 gastrointestinal and urologic toxicity were 1.0% (0.5%) and 5.4% (1.0%), respectively. Median pre-treatment scores and International Prostate Symptom Scores at greater than 4 years post-treatment were 8 and 7, 6 and 6, and 9 and 8, respectively, among the low-, intermediate-, and high-risk patients. There were no significant changes between median pre-treatment summary scores and Expanded Prostate Cancer Index Composite scores at greater than 4 years for bowel, urinary irritation and/or obstructive, and urinary continence. The authors concluded that 5-year clinical outcomes with image-guided proton therapy included extremely high efficacy, minimal physician-assessed toxicity, and excellent patient-reported outcomes. Moreover, they stated that further follow-up and a larger patient experience are needed to confirm these favorable outcomes.

Furthermore, NCCN’s clinical practice guideline on “Prostate cancer” (Version 1.2015) states that “An ongoing prospective randomized trial is accruing patients and comparing prostate proton therapy to prostate IMRT. The NCCN panel believes that there is no clear evidence supporting a benefit or decrement to proton therapy over IMRT for either treatment efficacy or long-term toxicity”.

Amsbaugh (2012) reported acute toxicities and preliminary outcomes for pediatric patients with ependymomas of the spine treated with proton beam therapy at the MD Anderson Cancer Center. A total of 8 pediatric patients received proton beam irradiation between October 2006 and September 2010 for spinal ependymomas. Toxicity data were collected weekly during radiation therapy and all follow-up visits. Toxicities were graded according to the Common Terminology Criteria for Adverse Events version 3.0. All patients had surgical resection of the tumor before irradiation (7 subtotal resection and 1 gross total resection). Six patients had World Health Organization Grade I ependymomas, and 2 had World Health Organization Grade II ependymomas. Patients had up to 3 surgical interventions before radiation therapy (range of 1 to 3; median, 1). Three patients received proton therapy after recurrence and 5 as part of their primary management. The entire vertebral body was treated in all but 2 patients. The mean radiation dose was 51.1 cobalt gray equivalents (range of 45 to 54 cobalt gray equivalents). With a mean follow-up of 26 months from the radiation therapy start date (range of 7 to 51 months), local control, event-free survival, and overall survival rates were all 100%. The most common toxicities during treatment were Grade 1 or 2 erythema (75%) and Grade 1 fatigue (38%). No patients had a Grade 3 or higher adverse event. Proton therapy dramatically reduced dose to all normal tissues anterior to the vertebral bodies in comparison to photon therapy. The authors concluded that preliminary outcomes showed the expected control rates with favorable acute toxicity profiles. They noted that proton beam therapy offers a powerful treatment option in the pediatric population, where adverse events related to radiation exposure are of concern. Moreover, they stated that extended follow-up will be required to assess for late recurrences and long-term adverse effects.
The American College of Radiology’s “Appropriateness Criteria® retreatment of recurrent head and neck cancer after prior definitive radiation” (McDonald et al, 2014) stated that “Newer conformal radiation modalities, including stereotactic body radiation therapy and proton therapy, may be appropriate in select cases. Additional data are needed to determine which patient subsets will most likely benefit from these modalities”.

In a review on “Promise and pitfalls of heavy-particle therapy”, Mitin and Zietman (2014) stated that “Particle therapy [including proton beam], on a relatively thin evidence base, has established itself as the standard of care for these rare malignancies [chordoma and chondrosarcoma].”

An UpToDate review on “Ependymoma” (Kieran, 2014) does not mention proton beam as a therapeutic option.

Greenberger et al (2014) reported their experience with pediatric patients treated with PBT. A total of 32 pediatric patients with low-grade gliomas of the brain or spinal cord were treated with PBT from 1995 to 2007; 16 patients received at least 1 regimen of chemotherapy before definitive radiotherapy (RT). The median radiation dose was 52.2 GyRBE (48.6 to 54 GyRBE). The median age at treatment was 11.0 years (range of 2.7 to 21.5 years), with a median follow-up time of 7.6 years (range of 3.2 to 18.2 years). The 6-year and 8-year rates of progression-free survival were 89.7 % and 82.8 %, respectively, with an 8-year overall survival of 100 %. For the subset of patients who received serial neurocognitive testing, there were no significant declines in Full-Scale Intelligence Quotient (p = 0.80), with a median neurocognitive testing interval of 4.5 years (range of 1.2 to 8.1 years) from baseline to follow-up, but subgroup analysis indicated some significant decline in neurocognitive outcomes for young children (less than 7 years) and those with significant dose to the left temporal lobe/hippocampus. The incidence of endocrinopathy correlated with a mean dose of greater than or equal to 40 GyRBE to the hypothalamus, pituitary, or optic chiasm. Stabilization or improvement of visual acuity was achieved in 83.3 % of patients at risk for radiation-induced injury to the optic pathways. The authors concluded that this report of late effects in children with low-grade gliomas after PBT is encouraging. Proton beam therapy appears to be associated with good clinical outcome, especially when the tumor location allows for increased sparing of the left temporal lobe, hippocampus, and hypothalamic-pituitary axis. The authors also stated that larger cohorts are likely needed to enable accurate assessment of the incidence of moyamoya disease after PBT.

In a review on “Promise and pitfalls of heavy-particle therapy”, Mitin and Zietman (2014) stated that “In others, the benefits are likely to be small or non-existent such as with skin cancer; and proton beam therapy should not be considered”.

Li et al (2011) stated that the papillary tumor of the pineal region (PTPR) is a distinct entity that is particularly rare in the pediatric population. The authors documented the youngest reported patient with this clinicopathological entity to date. These researchers described the case of PTPR in a 15-month old boy. Initially thought to be a tectal glioma, the tumor was later identified as a pineal region tumor after demonstrating growth on routine imaging. Diagnosis of PTPR was established by histopathological evaluation of biopsy samples, which revealed papillary, cystic, and solid tumor components. The patient's post-operative course was complicated by tumor growth despite several debulking procedures and chemotherapy, as well as persistent hydrocephalus requiring 2 endoscopic third ventriculostomies and eventual ventriculo-peritoneal shunt placement. After a 15-month follow-up period, the patient has received proton-beam therapy (PBT) and has a stable tumor size. The PTPR is a recently described tumor of the CNS that must be included in the differential diagnosis of pineal region masses. The biological behavior, prognosis, and appropriate treatment of PTPR have yet to be fully defined.

An UpToDate review on “Pineal gland masses” (Moschovi and Chrousos, 2014) does not mention PBT as a therapeutic option.

Clivio et al (2013) evaluated intensity modulated proton therapy (IMPT) in patients with cervical cancer in terms of coverage, conformity, and DVH parameters correlated with recommendations from magnetic resonance imaging (MRI)-guided brachytherapy. A total of 11 patients with
histologically proven cervical cancer underwent primary chemo-radiation for the pelvic lymph nodes, the uterus, the cervix, and the parametric region, with a symmetric margin of 1 cm. The prescription was for 50.4 Gy, with 1.8 Gy per fraction. The prescribed dose to the parametria was 2.12 Gy up to 59.36 Gy in 28 fractions as a simultaneous boost. For several reasons, the patients were unable to undergo brachytherapy. As an alternative, IMPT was planned with 5 fractions of 6 Gy to the cervix, including the macroscopic tumor with an MRI-guided target definition, with an isotropic margin of 5 mm for PTV definition. Groupe-Europeen de Curietherapie and European society for Radiotherapy and Oncology (GEC-ESTRO) criteria were used for DVH evaluation. Reference comparison plans were optimized for volumetric modulated rapid arc (VMAT) therapy with the RapidArc (RA). The dose to the high-risk volume was calculated with $\alpha/\beta = 10$ with 89.6 Gy. For IMPT, the clinical target volume showed a mean dose of 38.2 ± 5.0 Gy (35.0 ± 1.8 Gy for RA). The D98% was 31.9 ± 2.6 Gy (RA: 30.8 ± 1.0 Gy). With regard to the organs at risk, the 2Gy Equivalent Dose (EQD2) ($\alpha/\beta = 3$) to 2 cm(3) of the rectal wall, sigmoid wall, and bladder wall was 62.2 ± 6.4 Gy, 57.8 ± 6.1 Gy, and 80.6 ± 8.7 Gy (for RA: 75.3 ± 6.1 Gy, 66.9 ± 6.9 Gy, and 89.0 ± 7.2 Gy, respectively). For the IMPT boost plans in combination with external beam radiation therapy, all DVH parameters correlated with less than 5 % risk for grades 2 to 4 late gastro-intestinal and genitourinary toxicity. The authors concluded that in patients who are not eligible for brachytherapy, IMPT as a boost technique additionally to external beam radiation therapy provides good target coverage and conformity and superior DVH parameters, compared with recommendations to MRI-guided brachytherapy. They stated that for selected patients, IMPT might be a valid alternative to brachytherapy and also superior to reference VMAT plans. (These preliminary findings from a small study [n = 11] need to be validated by well-designed studies).

UpToDate reviews on “Approach to adjuvant treatment of endometrial cancer” (Plaxe and Mundt, 2014) and “Treatment of recurrent or metastatic endometrial cancer” (Campos and Cohn, 2014) do not mention proton beam therapy as a therapeutic option.

Moreover, the National Comprehensive Cancer Network’s clinical practice guideline on “Uterine cancer” (Version 1.2015) does not list proton beam therapy as a therapeutic option.

An UpToDate review on “Management of anaplastic oligodendrogial tumors” (van den Bent, 2014) does not mention proton beam therapy as a therapeutic option.

Neutron Beam Therapy:

Most radiation therapies utilize photons -- lightweight particles that damage cancerous cells. Neutron beam therapy (NBT) uses neutrons, which are much heavier than photons and appear to be more effective in destroying very dense tumors. Compared to roentgen ray (X-ray), neutrons are characterized by several properties: (i) reduced oxygen enhancement factor, (ii) less or no repair of sub-lethal or potentially lethal cell damage, and (iii) less variation of sensitivity through cell cycle.

Neutron beam therapy entails the use of a particle accelerator; protons from the accelerator are deflected by a magnet to a target which creates the neutron beam. Neutron beam therapy has been employed mainly for the treatment of the salivary gland cancers. It has also been used to treat other malignancies such as soft tissue sarcoma (STS) as well as lung, pancreatic, colon, kidney and prostate cancers. Nevertheless, NBT has not gained wide acceptance because of the clinical difficulty in generating neutron particles. It should be noted that NBT is different from boron neutron capture therapy (BNCT), which is a radiotherapy based on the preferential targeting of tumor cells with non-radioactive isotope (10)B and subsequent activation with thermal neutrons to produce a highly localized radiation, and is often used to treat brain tumors. In BNCT, the patient is given a drink containing boron, which is taken up by tumor cells. The tumor is then irradiated with a neutron beam, causing the boron to split into two highly energetic particles (helium and lithium) that destroy the cancerous cells while largely sparing adjacent healthy cells.

Salivary Gland Cancer
In the treatment of patients with salivary gland cancer, primary radiation including NBT may play a role in certain histological types or non-operative patients (Day, 2004). Neutron beam therapy has been most extensively used either for an incompletely excised primary tumor or for recurrent disease.

In a randomized clinical study, Larimore and associates (1993) compared the effectiveness of fast neutron radiotherapy versus conventional photon and/or electron radiotherapy for unresectable, malignant salivary gland tumors. Eligibility criteria included either inoperable primary or recurrent major or minor salivary gland tumors. Patients were stratified by surgical status (primary versus recurrent), tumor size (less than or greater than 5 cm), and histology (squamous or malignant mixed versus other). After a total of 32 patients were entered into this study, it appeared that the group receiving fast neutron radiotherapy had a significantly improved local/regional control rate and also a borderline improvement in survival and the study was stopped earlier than planned for ethical reasons. Twenty-five patients were study-eligible and analyzable. Ten-year follow-up data for this study was presented. On an actuarial basis, there was a statistically-significant improvement in local/regional control for the neutron radiotherapy group (56% versus 25%, p = 0.009), but there was no statistically significant improvement in OS (15% versus 25%). Patterns of failure were analyzed and it was demonstrated that distant metastases account for the majority of failures on the neutron radiotherapy arm and local/regional failures account for the majority of failures on the photon/electron radiotherapy arm. Long-term, treatment-related morbidity was analyzed and while the incidence of morbidity graded "severe" was greater on the neutron arm, there was no significant difference in "life-threatening" complications. These investigators concluded that fast neutron radiotherapy appeared to be the treatment-of-choice for patients with inoperable primary or recurrent malignant salivary gland tumors.

Prott et al (2000) reported their findings of fast neutron therapy in 72 patients with adenoid cystic carcinoma (ACC) of the salivary glands. The median age was 54 years; and the median follow-up was 50 months. This study showed that 39.1% of the patients achieved a complete remission and 48.6% achieved partial remission. The survival probability was 86% after 1 year, 73% after 2 years and 53% after 5 years. The recurrence-free survival was 83% after 1 year, 71% after 2 years and 45% after 5 years. These investigators concluded that NBT appeared to have been an effective treatment in these selected patients.

Huber and colleagues (2001) compared retrospectively radiotherapy with neutrons, photons, and a photon/neutron mixed beam in patients (n = 75) with advanced ACC of the head and neck. Local control, survival, distant failure, and complications were analyzed. Follow-up ranged from 1 to 160 months (median 51 months), and the surviving patients had a minimum follow-up of 3 years at the time of analysis. The actuarial 5-year local control was 75% for neutrons, and 32% for both mixed beam and photons (p = 0.015, log-rank). This advantage for neutrons in local control was not transferred to significant differences in survival (p > 0.1). In multi-variate analysis post-operative radiotherapy (p = 0.003) and small tumor size (p = 0.01) were associated with high local control, while primary therapy (p = 0.006) and negative lymph nodes (p = 0.01) were associated with longer survival. While acute toxicity was similar in all 3 radiotherapy groups, severe late grade 3 and 4 toxicity tended to be more prevalent (p > 0.1) with neutrons (19%) than with mixed beam (10%) and photons (4%). These researchers concluded that fast neutron radiotherapy provides higher local control rates than a mixed beam and photons in advanced, recurrent or not completely resected ACC of the major and minor salivary glands. Neutron radiotherapy can be recommended in patients with bad prognosis with gross/macroscopic residual disease (R2 resection), with unresectable tumors, or inoperable tumors.

Douglas et al (2003) evaluated the effectiveness of fast neutron radiotherapy for the treatment of salivary gland neoplasms. Of the 279 patients, 263 had evidence of gross residual disease at the time of treatment, while 16 had no evidence of gross residual disease; 141 had tumors of a major salivary gland, and 138 had tumors of minor salivary glands. The median follow-up period was 36 months (range of 1 to 142 months). The main outcome measures were local-regional control, cause-specific survival, and freedom from metastasis. The 6-year actuarial cause-
specific survival rate was 67%. Multi-variate analysis revealed that low group stage (I - II) disease, minor salivary sites, lack of skull base invasion, and primary disease were associated with a statistically significant improvement in cause-specific survival. The 6-year actuarial local-regional control rate was 59%. Multi-variate analysis revealed size 4 cm or smaller, lack of base of skull invasion, prior surgical resection, and no previous radiotherapy to have a statistically significant improved local-regional control. Patients without evidence of gross residual disease had a 100% 6-year actuarial local-regional control. The 6-year actuarial freedom from metastasis rate was 64%. Factors associated with decreased development of systemic metastases included negative lymph nodes at the time of treatment and lack of base of skull involvement. The 6-year actuarial rate of development of grade 3 or 4 long-term toxicity (using the Radiation Therapy Oncology Group and European Organization for Research on the Treatment of Cancer criteria) was 10%. No patient experienced grade 5 toxic effects. The authors concluded that NBT is an effective treatment for patients with salivary gland neoplasms who have gross residual disease and achieves excellent local-regional control in patients without evidence of gross disease.

Other Types of Cancer

Russell et al (1994) evaluated the effectiveness of fast neutron radiation therapy in treatment of locally advanced carcinomas of the prostate (n = 178). Median follow-up was 68 months (range of 40 to 86 months). The 5-year actuarial clinical local-regional failure rate was significantly better for neutron-treated patients than photon-treated patients (11% versus 32%). When findings of routine post-treatment prostate biopsies were incorporated, the resulting “histological” local-regional tumor failure rates were 13% for the neutron-treated group versus 32% for the photon-treated group (p = 0.01). Moreover, actuarial survival and cause-specific survival rates were statistically indistinguishable for the 2 patient cohorts, with 32% of the neutron-treated patient deaths and 41% of the photon-treated patient deaths caused by prostate cancer. Prostate specific antigen values were elevated in 17% of neutron-treated patients and 45% of photon-treated patients at 5 years (p < 0.001). Severe late complications of treatment were higher for the neutron-treated patients (11% versus 3%), and were inversely correlated with the degree of neutron beam shaping available at the participating institutions. The authors concluded that high energy fast neutron radiotherapy is safe and effective when adequate beam delivery systems and collimation are available, and it is significantly superior to external beam photon radiotherapy in the local-regional treatment of large prostate tumors.

In a review on the use of fast neutron radiation for the treatment of prostatic adenocarcinomas, Lindsley et al (1998) stated that the Radiation Therapy Oncology Group performed a multi-institutional randomized trial comparing mixed beam (neutron plus photon) irradiation to conventional photon irradiation for the treatment of locally advanced prostate cancer. A subsequent randomized trial by the Neutron Therapy Collaborative Working Group compared pure neutron irradiation to standard photon irradiation. Both studies reported significant improvement in loco-regional control with neutron irradiation compared to conventional photon irradiation in the treatment of locally advanced prostate carcinoma. To date, only the mixed beam study has demonstrated a significant survival benefit. Future analysis of the larger Neutron Therapy Collaborative Working Group trial at the 10-year follow-up should confirm whether or not improved loco-regional control translates into a survival advantage.

Lindsley et al (1996) noted that a phase III clinical study comparing NBT to photon radiotherapy for inoperable regional non-small cell lung cancer showed no overall improvement in survival. However, a statistically significant improvement in survival was observed in the subset of patients with squamous cell histology. Engenhart-Cabillic and colleagues (1998) discussed the use of NBT in the management of locally advanced non-resectable primary or recurrent rectal cancer. They noted that the value of radiation therapy in managing such patients is being appreciated, although up to 40% of the treated patients have no symptomatic response. The authors also stated that over 350 patients were entered in studies comparing NBT alone and mixed-beam treatments. At present, no therapeutic gain for long-lasting survival has been achieved. However, local control and pain improvement seems to be better with NBT than with photon
therapy. There is insufficient evidence regarding the effectiveness of NBT for rectal and lung cancers.

Strander et al (2003) stated that there is some evidence that adjuvant radiation therapy in combination with conservative surgery improves the local control rate in the treatment of STS of extremities and trunk in patients with negative, marginal or minimal microscopic positive surgical margins. A local control rate of 90% has been achieved. Improvement is obtained with radiation therapy added in the case of intralesional surgery, but the local control rate is somewhat lower. More studies are needed on this issue. For STS in other anatomical sites, retroperitoneum, head and neck, breast and uterus, there is only weak indication of a benefit for the local control rate, with the use of adjuvant radiation therapy. There is still insufficient data to establish that pre-operative radiotherapy is favorable compared to post-operative radiotherapy for local control in patients presenting primarily with large tumors. One small study has shown a possible survival benefit for pre-operative radiotherapy. There is fairly good evidence to suggest that the pre-operative setting results in more wound complications. There is no randomized study comparing external beam radiotherapy and brachytherapy. The data suggested that external beam radiotherapy and low-dose rate brachytherapy result in comparable local control for high-grade tumors. Some patients with low-grade STS benefit from external beam radiotherapy in terms of local control. Brachytherapy with low-dose rate for low-grade tumors seems to be of no benefit, but data are sparse. The available data are inconclusive concerning the effect of intra-operative high-dose rate radiotherapy for retroperitoneal STS. Further studies are needed. Neutron radiotherapy might be beneficial for patients with low-grade and intermediate-grade tumors considered inoperable and for those operated with intralesional margins. More severe adverse effects for NBT have been reported.

Murray (2004) noted that the commonest STS of the upper extremity are the epithelioid sarcoma, synovial cell sarcoma, and malignant fibrous histiocytoma. Limb salvage surgery is the treatment of choice for STS to preserve upper extremity function. Following wide tumor resection, adjuvant therapies such as chemotherapy, external beam radiation therapy, and brachytherapy may lessen local recurrence rates, but their effect on overall survival remains unclear.

A review by Hassen-Khodja and Lance (2003) stated that the efficacy of NBT is well-established only for the treatment of inoperable or unresectable salivary gland tumors, regardless of their degree of malignancy or stage of progression, and for the treatment of large residual tumors after surgical resection. The authors also examined the data on the effectiveness of for NBT in the treatment of malignant prostate tumors, STS and central nervous system tumors. However, these data are insufficient to rule on its therapeutic efficacy.

An assessment of the evidence for neutron beam radiotherapy prepared by the Australia and New Zealand Horizon Scanning Network (Purins et al, 2007) found that NBT is a promising technology. The assessment cautioned, however, that "[t]he studies identified in this prioritising summary were not of high quality and, as such, the conclusions must be taken as preliminary in nature."

In a phase I study, Kankaanranta and colleagues (2011) examined the safety of BNCT in the treatment of malignant gliomas that progress after surgery and conventional external beam radiation therapy. Adult patients who had histologically confirmed malignant glioma that had progressed after surgery and external beam radiotherapy were included in this study, provided that greater than 6 months had elapsed from the last date of radiation therapy. The first 10 patients received a fixed dose, 290 mg/kg, of l-boronophenylalanine-fructose (l-BPA-F) as a 2-hour infusion before neutron irradiation, and the remaining patients were treated with escalating doses of l-BPA-F, either 350 mg/kg, 400 mg/kg, or 450 mg/kg, using 3 patients on each dose level. Adverse effects were assessed using National Cancer Institute Common Toxicity Criteria version 2.0. A total of 22 patients entered the study. Twenty subjects had glioblastoma, and 2 patients had anaplastic astrocytoma, and the median cumulative dose of prior external beam radiotherapy was 59.4 Gy. The maximally tolerated l-BPA-F dose was reached at the 450 mg/kg level, where 4 of 6 patients treated had a grade 3 adverse event. Patients who were given more than 290 mg/kg of l-BPA-F received a higher estimated average planning target volume dose.
than those who received 290 mg/kg (median of 36 versus 31 Gy [W, i.e., a weighted dose]; p = 0.018). The median survival time following BNCT was 7 months. The authors concluded that BNCT administered with an I-BPA-F dose of up to 400 mg/kg as a 2-hour infusion is feasible in the treatment of malignant gliomas that recur after conventional radiation therapy.

CPT Codes / HCPCS Codes / ICD-9 Codes

Proton Beam Radiotherapy (PBRT):

CPT codes covered if selection criteria are met:

77520 Proton treatment delivery; simple, without compensation
77522 simple, with compensation
77523 intermediate
77525 complex

Other CPT codes related to the CPB:

61796 Stereotactic radiosurgery (particle beam, gamma ray or linear accelerator); 1 simple cranial lesion
+61797 each additional cranial lesion, simple (List separately in addition to code for primary procedure)
61798 1 complex cranial lesion
+61799 each additional cranial lesion, complex (List separately in addition to code for primary procedure)
63620 Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); 1 spinal lesion
+63621 each additional spinal lesion, complex (List separately in addition to code for primary procedure)
77432 Stereotactic radiation treatment management of cranial lesion(s) (complete course of treatment consisting of 1 session)

ICD-9 codes covered if selection criteria are met for adults:

170.0 Malignant neoplasm of bones of skull and face, except mandible
170.2 Malignant neoplasm of vertebral column, excluding sacrum and coccyx
190.0 Malignant neoplasm of eyeball, except conjunctiva, cornea, retina, and choroid (e.g., uveal tract) [confined to globe - not distant metastases]
190.6 Malignant neoplasm of choroid
225.3 Benign neoplasm of spinal cord
237.5 Neoplasm of uncertain behavior of brain and spinal cord

ICD-9 codes not covered for indications listed in the CPB for adults (not all-inclusive):

141.0 - 141.9 Malignant neoplasm of tongue [squamous cell carcinoma]
142.0 - 142.9 Malignant neoplasm of major salivary glands
146.0 - 146.20  Malignant neoplasm of tonsil
147.0 - 147.9  Malignant neoplasm of nasopharynx [adenoid cystic carcinoma]
149.0 - 149.9  Malignant neoplasm of other and ill-defined sites within the lip, oral cavity, and pharynx
150.0 - 150.9  Malignant neoplasm of esophagus
152.0 - 152.9  Malignant neoplasm of small intestine, including duodenum
154.0 - 154.8  Malignant neoplasm of rectum, rectosigmoid, rectosigmoid junction, and anus
155.0 - 155.2  Malignant neoplasm of liver and intrahepatic bile ducts [hepatocellular] [cholangiocarcinoma]
157.0 - 158.0  Malignant neoplasm of pancreas and retroperitoneum
160.0 - 160.9  Malignant neoplasm of nasal cavities, middle ear, and accessory sinuses
161.0 - 161.9  Malignant neoplasm of larynx (glottis) [squamous cell carcinoma]
162.2 - 162.9  Malignant neoplasm of bronchus and lung [including non-small-cell lung carcinoma]
164.0  Malignant neoplasm of thymus
170.0 - 170.9  Malignant neoplasm of bone and articular cartilage, site unspecified [Ewing's sarcoma]
171.0 - 171.9  Malignant neoplasm of connective and other soft tissue [soft tissue sarcoma] [desmoid fibrosarcoma] [fibrosarcoma of extremities] [squamous cell carcinoma of the head and neck][leiomyosarcoma of extremities]
172.0 - 172.9  Malignant melanoma of skin
173.02, 173.12, 173.22, 173.32, 173.42  Squamous cell carcinoma of skin of lip, eyelid including canthus, ear and external auditory canal, other and unspecified parts of face, or scalp and skin of neck
173.90  Unspecified malignant neoplasm of skin, site unspecified [Dermatofibrosarcoma protuberans]
174.0 - 174.9  Malignant Neoplasm of Female Breast
175.0 - 175.9  Malignant Neoplasm of Male Breast
180.0 - 180.9  Malignant neoplasm of cervix uteri
185  Malignant neoplasm of prostate
186.9  Malignant neoplasm of other and unspecified testes
188.0 - 188.9  Malignant neoplasm of bladder
191.0 - 191.9  Malignant neoplasm of brain
192.0 - 192.1, 192.3  Malignant neoplasm of cranial nerves, cerebral meninges, and spinal meninges
192.8 - 192.9  Malignant neoplasm of other and unspecified parts of nervous system
194.3 Malignant neoplasm of pituitary gland and craniopharyngeal duct
194.5 Malignant neoplasm of carotid body
195.0 Malignant neoplasm of head, face, and neck
197.0 Secondary malignant neoplasm of lung
197.7 Secondary malignant neoplasm of liver
198.3 - 198.4 Secondary malignant neoplasm of brain and spinal cord and other parts of nervous system
198.82 Malignant neoplasm of genital organs [prostate]
198.89 Secondary malignant neoplasm of other specified sites [carotid body] [submandibular gland]
201.00 - 201.98 Hodgkin's disease
210.2 Benign neoplasm of major salivary glands
210.7 Benign neoplasm of nasopharynx
225.0 - 225.2 Benign neoplasm of brain
227.3 Benign neoplasm of pituitary gland and craniopharyngeal duct (pouch)
227.5 Benign neoplasm of carotid body
228.02 Hemangioma of intracranial structures [cavernous hemangioma]
228.09 Hemangioma of other sites [choroid]
230.0 Carcinoma in situ of lip, oral cavity, and pharynx
235.0 Neoplasm of uncertain behavior of major salivary glands
237.3 Neoplasm of uncertain behavior of paraganglia [carotid body]
239.0 Neoplasm of unspecified nature of digestive system
239.6 Neoplasm of unspecified nature of brain
362.16 Retinal neovascularization
362.50 - 362.52 Macular degeneration (senile)
747.81 Anomalies of cerebrovascular system [arterio-venous malformations]
747.82 Spinal vessel anomaly [arterio-venous malformations]

**ICD-9 codes covered if selection criteria are met for children:**
140.0 - 209.30, 230.0 - 234.9

**Other ICD-9 codes related to the CPB:**
S8030 Scleral application of tantalum ring(s) for localization of lesions for proton beam therapy

**Neutron Beam Therapy (NBT):**
CPT codes covered if selection criteria are met:

- **61796** 61796 Stereotactic radiosurgery (particle beam, gamma ray or linear accelerator); 1 simple cranial lesion
- **+ 61797** each additional cranial lesion, simple (List separately in addition to code for primary procedure)
- **61798** 1 complex cranial lesion
- **+ 61799** each additional cranial lesion, complex (List separately in addition to code for primary procedure)
- **77422** High energy neutron radiation treatment delivery; single treatment area using a single port or parallel-opposed ports with no blocks or simple blocking
- **77423** 1 or more isocenter(s) with coplanar or non-coplanar geometry with blocking and/or wedge, and/or compensator(s)

ICD-9 codes covered if selection criteria are met:

- **142.0 - 142.9** Malignant neoplasm of major salivary glands [locally advanced, unresectable, or inoperable]

ICD-9 codes not covered for indications listed in the CPB (not all-inclusive):

- **140.0 - 141.9, 143.0 - 199.1** Malignant neoplasm [other than salivary gland]

The above policy is based on the following references:

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Neutron Beam Therapy:


