Washington State Health Care Authority

Health Technology Assessment

Proton Beam Therapy

Final Evidence Report

March 28, 2014

Health Technology Assessment Program (HTA)
Washington State Health Care Authority
PO Box 42712
Olympia, WA 98504-2712
(360) 725-5126
hta.hca.wa.gov
shtap@hca.wa.go

FINAL APPRAISAL DOCUMENT

PROTON BEAM THERAPY

March 28, 2014

Daniel A. Ollendorf, MPH, ARM	Chief Review Officer
Jennifer A. Colby, PharmD	Sr. Research Associate
Steven D. Pearson, MD, MSc	President

Table of Contents

About ICER

The Institute for Clinical and Economic Review (ICER) is an independent non-profit health care research organization dedicated to improving the interpretation and application of evidence in the health care system.

There are several features of ICER's focus and methodology that distinguish it from other health care research organizations:

- Commitment to aiding patients, clinicians, and insurers in the application and use of comparative effectiveness information through various implementation avenues, including its flagship initiatives, the New England Comparative Effectiveness Public Advisory Council (CEPAC; cepac.icer-review.org) and the California Technology Assessment Forum (CTAF; www.ctaf.org).

- Focus on implementation and evaluation of ICER research to create innovative decision support tools, insurance benefit designs, and clinical/payment policy.

- Deep engagement throughout the process with all stakeholders including patients, clinicians, manufacturers, purchasers, and payers.

- Inclusion of economic modeling in our research, and use of an integrated rating system for comparative clinical effectiveness and comparative value to guide health care decisions.

ICER's independent mission is funded through a diverse combination of sources; funding is not accepted from manufacturers or private insurers to perform reviews of specific technologies. A full list of funders, as well more information on ICER's mission and policies, can be found at www.icer-review.org.

Acknowledgements

ICER would like to thank the following individuals for their expert opinion as well as peer review of draft documents:

Justin E. Bekelman, MD
Assistant Professor of Radiation Oncology, Medical Ethics and Health Policy
University of Pennsylvania Perelman School of Medicine
Senior Fellow, Leonard Davis Institute for Health Economics
Radiation Oncologist, Department of Radiation Oncology
Abramson Cancer Center
University of Pennsylvania

Thomas F. DeLaney, MD
Andres Soriano Professor of Radiation Oncology, Harvard Medical School
Radiation Oncologist, Department of Radiation Oncology
Medical Director- Francis H. Burr Proton Therapy Center
Co-Director, Center for Sarcoma and Connective Tissue Oncology
Massachusetts General Hospital

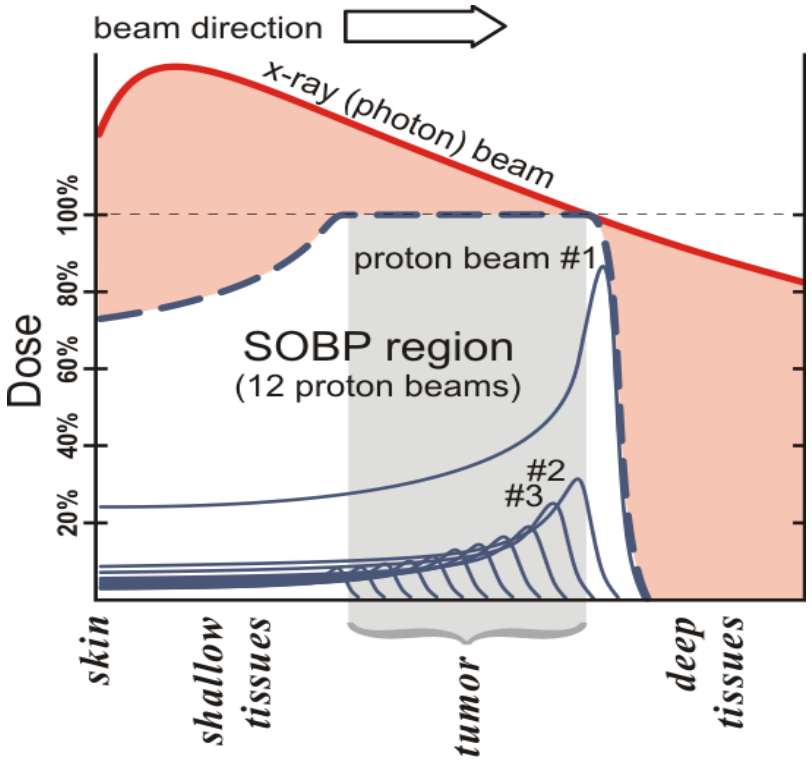
Lia M. Halasz, MD
Assistant Professor, Department of Radiation Oncology
Joint Assistant Professor, Department of Neurological Surgery
University of Washington
Radiation Oncologist, University of Washington Medicine and
Seattle Cancer Care Alliance Proton Therapy Center, a ProCure Center

Executive Summary

Introduction

Protons are positively-charged subatomic particles that have been in clinical use as a form of external beam radiotherapy for over 60 years. Compared to the photon X-ray energy used in conventional radiotherapy, proton beams have physical attributes that are potentially appealing. Specifically, protons deposit radiation energy at or around the target, at the end of the range of beam penetration, a phenomenon known as the Bragg peak (Larsson, 1958). In contrast, photons deliver radiation across tissue depths on the way toward the target tumor and beyond, as depicted in Figure ES1 below. The total radiation dose for proton therapy is delivered in the "spread out Bragg peak" (SOBP) region from multiple proton beams; proton radiation is delivered to the target tumor as well as to shallow tissue depths before the target, but not to deeper tissue depths beyond the target (Levin, 2005).

Figure ES1. Dose distribution by tissue depth for proton and photon radiation.



Source: Adapted from Levin WP, Kooy H, Loeffler, DeLaney TF. Proton beam therapy. *Br J Cancer*. 2005;93(8):849-854.

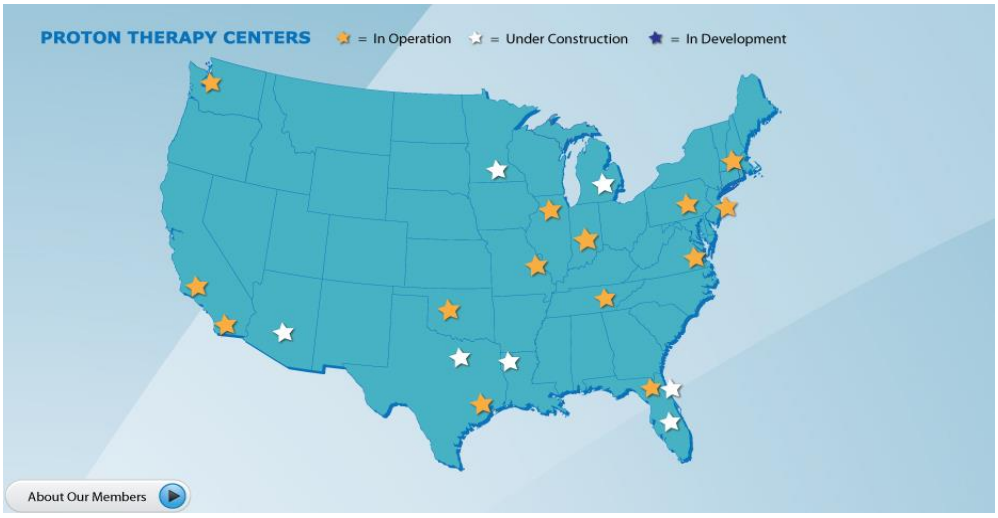
The goal of any external beam radiotherapy is to deliver sufficient radiation to the target tumor while mitigating the effects on adjacent normal tissue. As Figure ES1 demonstrates, this has been a challenge for conventional photon therapy due to the amount of radiation deposited both before and after the

target is reached. While the amount of photon radiation at entry into the body is much higher than at exit, photon beams typically "scatter" to normal tissues after leaving the target. This so-called "exit" dose is absent for protons, as tissue beyond the point of peak energy deposition receives little to no radiation (Kjellberg, 1962).

Initial use of proton beam therapy (PBT) focused on conditions where sparing very sensitive adjacent normal tissues was felt to be of utmost importance, such as cancers or noncancerous malformations of the brain stem, eye, or spinal cord. In addition, proton beam therapy was advocated for many pediatric tumors because even lower-dose irradiation of normal tissue in pediatric patients can result in pronounced acute and long-term toxicity (Thorp, 2010). There are also long-standing concerns regarding radiation's potential to cause secondary malignancy later in life, particularly in those receiving radiation at younger ages. Finally, radiation may produce more nuanced effects in children, such as neurocognitive impairment in pediatric patients treated with radiotherapy for brain cancers (Yock, 2004).

The construction of cyclotrons at the heart of proton beam facilities is very expensive ($150-$200 million for a multiple gantry facility); accordingly, as recently as 10 years ago there were fewer than 5 proton beam facilities in the United States (Jarosek, 2012). More recently, however, the use of PBT has been expanded in many settings to treat more common cancers such as those of the prostate, breast, liver, and lung. With the growth in potential patient numbers and reimbursement, the construction of proton centers has grown substantially. As depicted in Figure ES2 below, there are now 14 operating proton centers in the U.S., including one in Seattle that came online in March 2013. Eleven additional centers are under construction or in the planning stages, and many more are proposed (not shown) (Particle Therapy Co-Operative Group, 2014).

Figure ES2. Map of proton beam therapy centers in the United States.



Source: The National Association for Proton Therapy. http://www.proton-therapy.org/map.htm;
Particle Therapy Co-Operative Group. http://www.ptcog.ch/

As with pediatric and rare tumors, clinical interest in the use of PBT for more common cancers is focused on sparing adjacent tissues from excess radiation. Some of these considerations are specific to tumor type and location. For example, interest in minimizing radiation exposure in hepatocellular carcinoma stems from concerns that excess radiation to liver tissue that is uninvolved with the tumor but nonetheless cirrhotic may result in radioembolization or other serious hepatic injury (Maor, 2013).

However, while enthusiasm for expanded use of PBT has grown in recent years, there remain uncertainties regarding its use in more common conditions and even for cancer types for which its deployment has been relatively well-accepted. Some concerns have been raised about the hypothetical advantages of the radiation deposition for proton beams. The dose range is relatively certain for tumors that are close to the skin, but there is more uncertainty around the end of the dose range when deep-seated tumors such as prostate cancer are considered (Goitein, 2008). In addition, a penumbra (i.e., lateral spread or blurring of the beam as it reaches the target) develops at the end of the beam line, which can result in more scatter of the beam to adjacent normal tissue than originally estimated, particularly at deeper tissue depths (Rana, 2013). Protons are also very sensitive to tissue heterogeneity, and the precision of the beam may be disturbed as it passes through different types of tissue (Unkelbach, 2007).

Another concern is the effects of neutrons, which are produced by passively-scattered proton beams and result in additional radiation dose to the patient. The location of neutron production in a PBT patient and its biologic significance is currently a topic of significant debate (Hashimoto, 2012; Jarlskog, 2008). In addition, while it is assumed that the biologic effects of protons are equivalent to photons, specific relative biological effectiveness (RBE) values of protons in relation to photons are not known with absolute certainty for all types of tissues and fractionation schemes (Paganetti, 2002).

It is also the case that, while PBT treatment planning and delivery have evolved, so too have other approaches to radiotherapy. For example, intensity-modulated radiation therapy (IMRT) uses sophisticated treatment planning and multiple beam angles to confirm radiation delivery to the target, and has become the de facto standard of care for photon radiotherapy in the U.S. (Esiashvili, 2004). The potential for comparison of PBT and IMRT in clinical trial settings has been the subject of numerous editorials, commentaries, and bioethics exercises in recent years (Efstathiou, 2013; Nguyen, 2007; Zietman, 2007; Goitein, 2008; Combs, 2013; Glimelius, 2007; Glatstein, 2008; Hofmann, 2009; Bekelman, 2013; Bekelman, 2012). The intensity of this debate has created opportunities for the development of randomized trials, several of which are well underway (see Section 6 on page 22).

Appraisal Scope

This appraisal focuses on the use of one form of external beam radiation, proton beam therapy (PBT), to treat patients with multiple types of cancer as well as those with selected noncancerous conditions. Within each condition type, two general populations were specified as of interest for this evaluation, as noted on the following page:

- Patients receiving PBT as primary treatment for their condition (i.e., curative intent)
- Patients receiving PBT for recurrent disease or for failure of initial therapy (i.e., salvage)

All forms of PBT were considered for this evaluation, including monotherapy, use of PBT as a "boost" mechanism to conventional radiation therapy, and combination therapy with other modalities such as chemotherapy and surgery. All PBT studies that met entry criteria for this review were included, regardless of manufacturer, treatment protocol, location, or other such concerns. Key questions of interest for the appraisal can be found below.

Key Questions

1) What is the comparative impact of proton beam therapy treatment with curative intent on survival, disease progression, health-related quality of life, and other patient outcomes versus radiation therapy alternatives and other cancer-specific treatment options (e.g., surgery, chemotherapy) for the following conditions:
   a. Cancers
      I. Bone tumors
      II. Brain, spinal, and paraspinal tumors
      III. Breast cancer
      IV. Esophageal cancer
      V. Gastrointestinal cancers
      VI. Gynecologic cancers
      VII. Head and neck cancers (including skull base tumors)
      VIII. Liver cancer
      IX. Lung cancer
      X. Lymphomas
      XI. Ocular tumors
      XII. Pediatric cancers (e.g., medulloblastoma, retinoblastoma, Ewing's sarcoma)
      XIII. Prostate cancer
      XIV. Soft tissue sarcomas
      XV. Seminoma
      XVI. Thymoma

   b. Noncancerous Conditions
      i. Arteriovenous malformations
      ii. Hemangiomas
      iii. Other benign tumors (e.g., acoustic neuromas, pituitary adenomas)

2) What is the comparative impact of salvage treatment (including treatment for recurrent disease) with proton beam therapy versus major alternatives on survival, disease progression, health-related quality of life, and other patient outcomes versus radiation therapy alternatives and other cancer-specific treatment options (e.g., surgery, chemotherapy) for the condition types listed in key question 1?

3) What are the comparative harms associated with the use of proton beam therapy relative to its major alternatives, including acute (i.e., within the first 90 days after treatment) and late (>90 days) toxicities, systemic effects such as fatigue and erythema, toxicities specific to each cancer type (e.g., bladder/bowel incontinence in prostate cancer, pneumonitis in lung or breast cancer), risks of secondary malignancy, and radiation dose?

4) What is the differential effectiveness and safety of proton beam therapy according to factors such as age, sex, race/ethnicity, disability, presence of comorbidities, tumor characteristics (e.g., tumor volume and location, proliferative status, genetic variation) and treatment protocol (e.g., dose, duration, timing of intervention, use of concomitant therapy)?

5) What are the costs and cost-effectiveness of proton beam therapy relative to radiation therapy alternatives and other cancer-specific treatment options (e.g., surgery, chemotherapy)?

We focused primary attention on randomized controlled trials and comparative cohort studies that involved explicit comparisons of PBT to one or more treatment alternatives *and* measures of clinical effectiveness and/or harm. For the purposes of this review, we distinguished between comparative cohort studies that drew patients from a common pool of subjects and those that involved comparisons of non-contemporaneous case series (i.e., comparison of a current series to a series from another published study or historical control group), given the increased likelihood of selection and/or measurement biases with the latter design. Case series of PBT alone were abstracted and summarized in evidence tables, but were not the primary focus of evaluation for each key question.

Importantly, studies that involved comparisons of treatment planning algorithms or modeled simulations of outcomes were not explicitly abstracted. As noted in the Background section to this document, there are significant uncertainties that remain with the delivery of proton beams for a variety of tumor types and locations, including physical uncertainty at the end of the beam range and penumbra effects, as well as concerns regarding the effects of neutron radiation produced by PBT and a lack of precise understanding of PBT's relative biological effectiveness for all tumor types and tissue depths. Because of these concerns, we felt that any estimation of the clinical significance of PBT therapy must come from studies in which actual patient outcomes were measured. We do recognize and make explicit mention, however, of clinical areas in which simulation studies are likely to remain the cornerstone of evidence, given logistical and ethical challenges posed by conducting clinical trials in these areas (e.g., pediatric tumors, very rare cancers). One notable exception to this rule was the use of

modeling to answer questions of cost and/or cost-effectiveness, as clinical outcomes in these studies were typically derived from actual clinical outcome data from other published studies.
Uses of PBT and relevant comparators are described in detail in the sections that follow. Of note, while PBT is considered part of a "family" of heavy ion therapies that includes carbon-ion, neon-ion, and other approaches, it is the only heavy ion therapy currently in active use in the U.S. Studies that focused on these other heavy-ion therapies were therefore excluded (unless they involved comparisons to PBT).

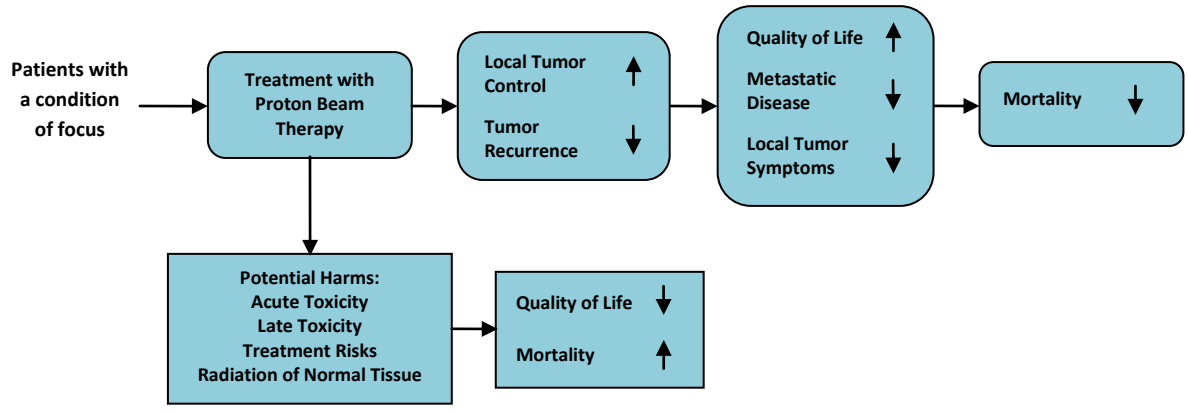
While all potential harms of PBT and its comparators were recorded, the primary focus was on adverse effects requiring medical attention (where such designations were available). Radiation-related toxicities may have also been labeled "early" (i.e., typically occurring within 90 days of treatment) or "late" (occurring >90 days after treatment or lasting longer than 90 days). In addition, because the risk of secondary malignancy is felt to be of great interest because of its link to radiation of normal tissues, these outcomes were abstracted when reported.

Finally, published studies of the economic impact of PBT are summarized in response to Key Question 5 regarding the costs and cost-effectiveness of PBT. In addition, a straightforward budget impact analysis is included that employs data from the HCA to estimate the effects of replacing existing radiation treatments with PBT for certain conditions.

Analytic Framework

The analytic framework for this review is shown in the Figure below. Note that the figure is intended to convey the conceptual links involved in evaluating outcomes of PBT and its alternatives, and is not intended to depict a clinical pathway through which all patients would flow.

Analytic Framework: Proton Beam Therapy



The available literature varies with respect to how directly the impact of PBT is measured. Some studies are randomized or observational comparisons focused directly on survival, tumor control, health-related quality of life, and long-term harms, while in other studies a series of conceptual links must be made

between intermediate effectiveness measures (e.g., biochemical recurrence in prostate cancer) or measures of harm (e.g., early toxicity) and longer-term outcomes.

Study Quality

We used criteria published by the U.S. Preventive Services Task Force to assess the quality of RCTs and comparative cohort studies, using the categories "good", "fair", or "poor". Guidance for quality rating using these criteria is presented on the following page (AHRQ, 2008).

- ***Good:*** *Meets all criteria: Comparable groups are assembled initially and maintained throughout the study (follow-up at least 80 percent); reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention to confounders in analysis. In addition, for RCTs, intention to treat analysis is used.*

- ***Fair:*** *Studies will be graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for. Intention to treat analysis is done for RCTs.*

- ***Poor:*** *Studies will be graded "poor" if any of the following fatal flaws exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied at all equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, intention to treat analysis is lacking.*

Data from all retrieved studies were included in evidence tables regardless of study quality. However, the focus of attention in presentation of results was primarily on good- or fair-quality studies.

Study quality was not assessed for single-arm case series, as the focus of quality ratings was on the level of bias in assessing the *comparative* impact of PBT versus alternatives on measures of effectiveness and harm.

The overall strength of evidence for PBT use to treat each condition type was determined primarily on the number of good- or fair-quality comparative studies available for each condition type and key question, although the totality of evidence (including case series) was considered in situations where future comparative study was unlikely (e.g., pediatrics, rare cancers). We followed the methods of the U.S. Agency for Healthcare Research and Quality (AHRQ) in assigning strength of evidence as follows: ***Low, Moderate, High, and No Evidence*** (AHRQ, 2014)**.** A "no evidence" rating is made when no studies

meeting entry criteria for the review are identified. While the remaining ratings are based on an overall value judgment, this is informed by assessment of the evidence across several domains, as listed below:

- *Risk of bias*: aspects of study design and conduct, control for confounding, etc.
- *Consistency*: direction and magnitude of findings, use of uniform outcome measures, etc.
- *Directness*: focus on most important clinical outcomes and/or comparisons to most relevant alternatives
- *Precision*: degree of certainty around estimates of treatment effect

Net Health Benefit

Because of the large number of conditions and comparators under study, a standardized system was used to describe our judgment of the overall net health benefit (that is, taking into account both clinical effectiveness and potential harms) of PBT in comparison to its major treatment alternatives. The five categories of net health benefit were derived from ICER's rating matrix for clinical effectiveness (Ollendorf, 2010), and are listed below:

- **Superior**: Evidence suggests a moderate-to-large net health benefit vs. comparator(s)
- **Incremental**: Evidence suggests a small net health benefit vs. comparators(s)
- **Comparable:** Evidence suggest that, while there may be tradeoffs in effectiveness or harms, overall net health benefit is comparable vs. comparator(s)
- **Inferior:** Evidence suggests a negative net health benefit vs. comparator(s)
- **Insufficient:** Evidence is insufficient to determine the presence and magnitude of a potential net health benefit vs. comparators(s)

When the net health benefit was rated superior, incremental, comparable, or inferior, we have provided additional information on the specific comparisons of both clinical benefits and harms. For example, if we have given an overall rating of an incremental net health benefit, we give information on whether that rating was based on evidence demonstrating small increases in effectiveness with no difference in harms, or on evidence demonstrating equivalent effectiveness and a small reduction in harms.

Results

Evidence Quality & Overall Results

Our summary of the net health benefit of PBT vs. alternative treatments and the strength of available evidence on net health benefit, as well as an evaluation of consistency of these findings with clinical guideline statements and public/private coverage policy, can be found in Table ES2 on page ES-11. Detailed descriptions of the evidence base for each key question can be found in the sections that follow. The level of comparative evidence was extremely limited for certain conditions and entirely

absent for others. We identified a total of six RCTs and 37 nonrandomized comparative studies across all 19 condition types. A detailed listing of RCTs can be found in Table ES1 on the following page. Importantly, five of the six RCTs involved different treatment protocols for PBT and had no other comparison groups; while these are included for completeness, primary attention was paid to studies (RCTs and otherwise) that compared PBT to an alternative form of treatment.

Most of the comparative studies identified also had major quality concerns. For example, nearly all non-randomized comparative studies were retrospective in nature, and many involved comparisons of a PBT cohort to a non-contemporaneous group receiving alternative therapy. Major differences in patient demographics and baseline clinical characteristics as well as duration of follow-up were often noted between groups. Of the 6 RCTs identified, 1, 4, and 1 were judged to be of good, fair, and poor quality respectively. Corresponding figures for non-randomized comparative studies were 1, 20, and 16.

We also examined the possibility of publication bias by cross-referencing the results of our literature search with a list of completed randomized controlled trials of PBT available on the U.S. National Institutes of Health's clinicaltrials.gov website. A single RCT was identified on clinicaltrials.gov (NCT00388804) that has not been published, a study comparing multiple radiation modalities (including PBT) with short-course androgen suppression therapy vs. PBT alone in men with intermediate-risk prostate cancer. The study was terminated due to slower-than-expected patient accrual.

As noted on Table ES2, we judged PBT to have superior net health benefit for ocular tumors, and incremental net health benefit for adult brain/spinal tumors and pediatric cancers. We felt PBT to be comparable to alternative treatment options for patients with liver, lung, and prostate cancer as well as one noncancerous condition (hemangiomas). Importantly, however, the strength of evidence was low for all of these conditions. We determined the evidence base for all other condition types to be insufficient to determine net health benefit, including two of the four most prevalent cancers in the U.S.: breast and gastrointestinal (lung and prostate are the other two). Current authoritative guideline statements and coverage policies relevant to Washington State reflect these uncertainties through coverage restrictions or limitations on recommendations for use.

The lack of comparative data for rare and childhood cancers is not surprising, and in fact is considered appropriate by many (Macbeth, 2008). Because information from dosimetry, planning, and simulation studies indicates that the radiation dose from PBT would be consistently lower than other radiation modalities in children, and because of the increased sensitivity of children to *any* level of ionizing radiation in comparison to adults, many in the clinical community feel that there is not sufficient equipoise to ethically justify comparative study of PBT in pediatric populations (Efstathiou, 2013; Macbeth, 2008). It should be noted, however, that this opinion is not universal, and other commentators have noted that the clinical data accrued to date on PBT in pediatric cancers is lacking critical information on measures of long-term effectiveness and harm (De Ruysscher, 2012).

The situation is more complex with adult cancers, particularly those that are more prevalent. As mentioned in the Introduction, significant uncertainties remain regarding proton physics and the relative biological effectiveness of PBT in all tissues (Rana, 2013; Paganetti, 2002; Goitien, 2008). It is because of these unknowns that we opted in this review not to abstract information from dosimetry, planning, and simulation studies, as evidence on the clinical impact of these uncertainties can only be obtained by measuring patient outcomes.

Table ES1. Randomized controlled trials of proton beam therapy.

Cancer Type (Author, Year)	Comparison	N	Measurement of Clinical Outcomes	Measurement of Harms
Prostate (Kim, 2011)	Dose/fractionation comparison	82	Yes	Yes
Prostate (Zietman, 2010)	Dose/fractionation comparison	391	Yes	Yes
Uveal melanoma (Gragoudas, 2000)	Dose/fractionation comparison	188	Yes	Yes
Skull-base chordoma and chondrosarcoma (Santoni, 1998)	Dose/fractionation comparison	96	No	Yes
Uveal melanoma (Desjardins, 2006)	PBT vs. PBT + TTT	151	No	Yes
Prostate (Shipley, 1995)	PBT + photon vs. Photon	202	Yes	Yes

PBT: proton beam therapy; TTT: transpupillary thermotherapy

Table ES2. Summary table assessing strength of evidence, direction of benefit, and consistency with relevant guideline statements and coverage policy.

Condition	Incidence (per 100,000)	Net Health Benefit vs. Comparators	Type of Net Health Benefit	Strength of Evidence	Guideline Recommendations	Coverage Policies
Cancer						
Bone	1.3	Insufficient	---	+	M	M
Brain/spinal	9.6	Incremental	B: = H: ↓	+	U	U
Breast	97.7	Insufficient	---	o	NM	NR/NC
Esophageal	7.5	Insufficient	---	o	NM	NR/NC
GI	100.6	Insufficient	---	o	NM	NR/NC
Gynecologic	38.2	Insufficient	---	o	NM	NR/NC
Head/neck	17.2	Insufficient	---	+	NM	M
Liver	12.8	Comparable	B: = H: =	+	NM	M
Lung	95.0	Comparable	B: = H: =	+	M	M
Lymphomas	32.9	Insufficient	---	o	NR/NC	NR/NC
Ocular	1.2	Superior	B: ↑ H: ↓	++	U	U
Pediatric	9.1	Incremental	B: = H: ↓	+	U	U
Prostate	99.4	Comparable	B: = H: =	+	M	M
Sarcomas	4.8	Insufficient	---	o	NM	M
Seminoma	4.0	Insufficient	---	o	NM	NM
Thymoma	0.2	Insufficient	---	o	NM	NM
Noncancerous						
AVMs	1.0	Insufficient	---	o	NM	M
Hemangiomas	2.0	Comparable	B: = H: =	+	NM	NM
Other	2.0	Insufficient	---	o	NM	M

B: Benefits; H: Harms
Strength of Evidence: Low=+; Moderate=++; High=+++; No evidence=o
Legend: U = Universally recommended or covered; M=Mixed recommendations or coverage policies; NM=Not mentioned in guidelines or coverage policies; NR/NC=Not recommended or not covered

Evidence on the effects of PBT with curative intent (i.e., as a primary therapeutic option) are summarized by condition in the sections that follow. As with all of the key questions, the primary focus was on active comparisons of PBT to one or more therapeutic alternatives. ***Note that, while the detailed report summarizes the evidence base for all conditions (including case series data), the focus of this executive summary is restricted to conditions with one or more comparative studies available.***

Impact of Proton Beam Therapy with Curative Intent on Patient Outcomes for Multiple Cancers and Noncancerous Conditions (KQ1)

Cancers

Bone Cancer

We identified a single poor-quality retrospective comparative cohort study that evaluated PBT for primary and recurrent sacral chordomas in 27 patients. Among these patients 21 were treated with surgery and combination PBT /photon therapy (mean radiation dose: 72.8 Gray Equivalents [GyE]), in comparison to six patients who received PBT/photons alone (mean dose: 70.6 GyE) (Park, 2006). Two-thirds of patients in each group were male, but groups differed substantially in terms of age (mean of 68 years in the radiation-only group vs. 54 years in the radiation+surgery group) and duration of follow-up (mean of 5 and 8 years in the two groups). For patients with primary tumors, Kaplan-Meier estimates of local control, disease-free survival and overall survival exceeded 90% among those treated by surgery and radiation (n=14). Only two of the six patients with primary tumors received radiation alone, one of whom had local failure at four years, distant metastases at five years, and died at 5.5 years. (NOTE: see KQ2 on page ES-17 for discussion of results specific to recurrent cancers.)

Brain, Spinal, and Paraspinal Tumors

We identified two poor-quality retrospective comparative cohort studies of primary PBT for brain, spinal, and paraspinal tumors. One was an evaluation of PBT (mean dose: 54.6 GyE) vs. photon therapy (mean dose: 52.9 Gy) in 40 adults (mean age: 32 years; 65% male) who received surgical and radiation treatment of medulloblastoma at MD Anderson Cancer Center (Brown, 2013). PBT patients were followed for a median of 2.2 years, while photon patients were followed for a median of nearly five years. 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 (Kahn, 2011) with either PBT (n=10) or IMRT (n=22). While explicit comparisons were made between groups, the PBT 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; dose was >50 GyE or Gy in approximately 75% of patients. While the crude mortality rate was

lower in the PBT group (20% vs. 32% for IMRT, not tested), in multivariate analyses controlling for age, tumor pathology, and treatment modality, PBT was associated with significantly increased mortality risk (Hazard Ratio [HR]: 40.0, p=0.02). The rate of brain metastasis was numerically higher in the PBT group (10% vs. 5% for IMRT), but this was not statistically tested. Rates of local or regional recurrence did not differ between groups.

Head and Neck Cancers

We identified two poor-quality retrospective comparative cohorts of primary PBT in head and neck cancer. One was an evaluation of 33 patients treated with either PBT alone or PBT+photon therapy to a target dose of 76 Gy for a variety of head and neck malignancies in Japan (Tokuuye, 2004). Treatment groups differed substantially in terms of age (mean: 67 vs. 54 years for PBT and PBT+photon respectively), gender (82% vs. 44% male), and duration of follow-up (mean: 5.9 vs. 3.1 years). Numeric differences in favor of PBT+photon therapy were seen for local control, recurrence, and mortality, but these were not statistically tested, nor were multivariate adjustments made for differences between groups.

The other study was a very small (n=6) comparison of endoscopic resection followed by either PBT or IMRT as well as endoscopy alone in patients with malignant clival tumors (Solares, 2005). Limited description of the study suggests that PBT was used only in cases of residual disease, while it is unclear whether IMRT was also used in this manner or as an adjuvant modality. One of the IMRT patients died of causes unrelated to disease; no other deaths were reported.

Liver Cancer

We identified two fair-quality prospective comparative cohort studies from Japan with evidence of the clinical effectiveness of primary use of PBT in liver cancer. One was an evaluation of 35 patients with unresectable hepatocellular carcinoma (HCC) who were treated with PBT (mean dose: 76.5 GyE) either alone or in combination with chemotherapy and were followed for up to 4 years (Matsuzaki, 1995). While statistical testing was not performed, rates of local tumor control and the proportion of patients experiencing reductions in tumor volume were nearly identical between groups.

The other study was also prospective but compared PBT to another heavy-ion modality not in circulation in the U.S. (carbon ion). In this study, a fair-quality comparison of 350 patients (75% male; age ≥70: 50%) with HCC who received PBT (53-84 GyE) or carbon-ion (53-76 GyE) therapy and were followed for a median of 2.5 years (Komatsu, 2011), no statistically-significant differences were observed in 5-year Kaplan-Meier estimates of local control, no biological evidence of disease, or overall survival between treated groups.

Lung Cancer

We identified three fair-quality comparative cohort studies examining the clinical effectiveness of PBT in lung cancer. Two studies retrospectively compared outcomes with PBT to those with IMRT or older three-dimensional conformal radiotherapy (3D-CRT) at MD Anderson Cancer Center (Lopez Guerra,

2012; Sejpal, 2011). The Lopez Guerra study involved 250 patients with non-small-cell lung cancer (NSCLC) (median age 71.5 years, 57% male) who were treated with 66 Gy of photons or 74 GyE of protons and followed for up to one year to assess a key measure of lung function known as diffusing capacity of lung for carbon monoxide (DLCO). While this measure did not differ between PBT and IMRT at 5-8 months after treatment, DLCO declined significantly more in the 3D-CRT group as compared to PBT after adjustment for pretreatment characteristics and other lung function measures (p=0.009).

The study by Sejpal and colleagues focused on survival in 202 patients (median age 64 years, 55% male) with locally-advanced, unresectable NSCLC who were followed for a median of 1.5 years and treated with 74 GyE of PBT or 63 Gy of either IMRT or 3D-CRT (Sejpal, 2011). Actuarial estimates of median overall survival were 24.4, 17.6, and 17.7 months for PBT, IMRT, and 3D-CRT respectively, although these differences were not statistically significant (p=0.1061).

A third study was a prospectively-measured cohort but, as with the study of liver cancer mentioned above, compared PBT to carbon ion therapy, evaluating 111 Japanese NSCLC patients (median age 76 years, 67% male) over a median of 3.5 years (Fujii, 2013). No statistically-significant differences between groups were observed in three-year actuarial estimates of local control, progression-free survival, or overall survival.

Ocular Tumors

In comparison to other cancer types, the evidence base for ocular tumors was relatively substantial. A total of seven comparative studies were identified of the clinical benefits of primary PBT in such cancers—a single RCT, four retrospective cohort studies, a comparison of a recent case series to the treatment groups from the RCT, and a comparison of noncontemporaneous case series. 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 (Desjardins, 2006). 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, poor-quality comparison of these findings to a separate series of patients undergoing PBT with endoresection of the scar (Cassoux, 2013), 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 (Mosci, 2012; Bellman, 2010; Seddon, 1990). PBT was associated with statistically-significant improvements in overall survival rates relative to enucleation at 2-5 years in two of these studies (Bellman, 2010; Seddon, 1990). 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 (n=1,051), but were nonsignificant at later timepoints (Seddon, 1990).

The 5-year metastasis-free survival rate in the Bellman study (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 (Mosci, 2012). Metastasis-free survival also did not differ in Cox regression adjusting for age, sex, and tumor thickness.

Another fair-quality 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 (Voelter, 2008). Five-year overall survival rates did not statistically differ between groups on either an unadjusted or Cox regression-adjusted basis.

Finally, a poor-quality comparison of noncontemporaneous case series evaluated treatment with PBT + laser photocoagulation or PBT alone in 56 patients with choroidal melanoma (Char, 2003). At one year, there were no differences in visual acuity between groups.

Prostate Cancer

The largest evidence base available was for prostate cancer (10 studies). However, only 6 of these studies reported clinical outcomes *and* compared PBT to alternative treatments. These included an RCT, a prospective comparative cohort, and four comparisons of noncontemporaneous case series. (*NOTE: comparisons of different dose levels of PBT are reported as part of the evidence base for Key Question 4 on patient subgroups.*)

The included RCT was a fair-quality comparison of 202 patients (median age 69 years) with advanced (stages T3-T4) prostate cancer who were randomized to receive either photon therapy with a proton boost (total dose: 75.2 GyE) or photons alone (67.2 Gy) and were followed for a median of five years (Shipley, 1995). Kaplan-Meier estimates of local tumor control, disease-specific survival, and overall survival were similar at both 5- and 8-year timepoints among the entire intent-to-treat population as well as those completing the trial (n=189). However, in patients with poorly-differentiated tumors (Gleason grades 4 or 5), local control at 8 years was significantly better in patients receiving PBT+photons (85% vs. 40% for photons alone, p=0.0014).

The prospective cohort study was a fair-quality comparison of patient-reported health-related QoL at multiple timepoints among 185 men (mean age: 69 years) with localized prostate cancer who were treated with PBT, PBT+photons, photons alone, surgery, or watchful waiting (Galbraith, 2001). Overall QoL, general health status, and treatment-related symptom scales were employed. No differences in overall QoL or general health status were observed at 18 months of follow-up, although men treated with PBT monotherapy reported better physical function in comparison to surgery (p=0.01) or photon radiation (p=0.02), and better emotional functioning in relation to photon radiation (p<0.001). Men receiving PBT+photons also reported significantly fewer urinary symptoms at 18 months in comparison to watchful waiting (p<0.01).

Outcomes were also assessed in three comparisons of noncontemporaneous case series. One was a fair-quality evaluation of high-dose PBT+photons (79.2 GyE) in 141 patients enrolled in a clinical trial at MGH and Loma Linda University who were matched on clinical and demographic criteria to 141 patients treated with brachytherapy at MGH (Coen, 2012). Patients were followed for a median of eight years. Eight-year actuarial estimates of overall survival, freedom from metastasis, and biochemical failure did not statistically differ between groups. The proportion of patients achieving a nadir PSA level of ≤0.5 ng/mL as of their final measurement was significantly higher in the brachytherapy group (92% vs. 74% for PBT, p=0.0003).

Two additional studies were deemed to be of poor quality due to a lack of control for confounding between study populations. One was a comparison of a cohort of 206 brachytherapy patients treated at the University of California San Francisco compared with same MGH/Loma Linda PBT+photon group described above (Jabbari, 2010). The difference in the percentage of patients achieving nadir PSA after a median of 5.4 years of follow-up was similar to that reported in the Coen study above (91% vs. 59%), although statistical results were not reported. Five-year estimates of disease-free survival (using biochemical failure definitions) did not statistically differ between groups. The other study involved comparisons of bowel- and urinary-related QoL in three distinct cohorts receiving PBT (n=95; 74-82 GyE), IMRT (n=153; 76-79 Gy), or 3D-CRT (n=123; 66-79 Gy) (Gray, 2013). Statistical changes were assessed within (but not between) each cohort immediately following treatment as well as at 12 and 24 months of follow-up, and were also assessed for whether the change was considered "clinically meaningful" (>0.5 SD of baseline values). Some differences in QoL decrements were seen at earlier timepoints. However, at 24 months, all groups experienced statistically and clinically significant decrements in bowel QoL, and none of the groups had significant declines in urinary QoL.

A fourth, poor-quality comparison of case series (Hoppe, 2013) involved an evaluation of patient-reported outcomes on the Expanded Prostate Cancer Index Composite (EPIC) questionnaire among a cohort of 1,243 patients receiving PBT for prostate cancer at the University of Florida and a group of 204 patients receiving IMRT from a previous multicenter study (Sandler, 2010). Statistically-significant differences between treatment groups were observed for many baseline characteristics, only some of which were adjusted for in multivariate analyses. No differences were observed in summary scores for bowel, urinary, and sexual QoL at two years, although more IMRT patients reported specific bowel frequency (10% vs. 4% for PBT, p=0.05) and urgency (15% vs. 7%, p=0.02) problems at two years.

Noncancerous Conditions

Hemangiomas

We identified a single comparative study of PBT's clinical effectiveness in hemangiomas, a poor-quality retrospective cohort study of 44 patients (mean age 41 years, gender unreported) with diffuse or circumscribed choroidal hemangiomas who were treated with either PBT (20-23 GyE) or photon therapy

(16-20 Gy) and followed for an average of 2.5 years (Höcht, 2006). Unadjusted outcomes were reported for the entire cohort only; reduction in tumor thickness, resolution of retinal detachment, and stabilization of visual acuity were observed in >90% of the overall sample. In Kaplan-Meier analysis of outcomes adjusting for differential follow-up between treatment groups, therapeutic modality had no statistically-significant effects on stabilization of visual acuity (p=0.43).

Other Benign Tumors

We identified two comparative studies of PBT's clinical effectiveness in other benign tumors, both of poor quality. One was a retrospective cohort of consisting of 20 patients with giant-cell bone tumors (mean age: 40 years; 35% male) who were treated with PBT+photon therapy (mean: 59 GyE) or photons alone (mean: 52 Gy) and followed for median of 9 years (Chakravati, 1999). Patients could also have received partial tumor resection. Of note, however, the PBT population consisted entirely of young adults (mean age: 23 years), while the photon-only population was much older (mean: 46 years); no attempt was made to control for differences between treatment groups. Rates of disease progression, progression-free survival, and distant metastases were numerically similar between groups, although these rates were not statistically tested.

The other study was a small cohort study comparing PBT alone, photon therapy alone, or PBT + photons in 25 patients with optic nerve sheath meningioma (ONSM) (Arvold, 2009). On an overall basis, visual acuity improved in most patients. Rates did not numerically differ between treatment groups, although these were not tested statistically.

NO COMPARATIVE STUDIES IDENTIFIED FOR KEY QUESTION 1: breast, esophageal, gastrointestinal, gynecologic, and pediatric cancers; lymphomas, sarcomas, seminomas, and thymomas; arteriovenous malformations.

Impact of Proton Beam Therapy on Outcomes in Patients with Recurrent Cancer or Noncancerous Conditions (KQ2)

Cancers

Bone Cancer

In a previously-described study of 27 patients with sacral chordomas who were treated with PBT/photon radiation alone or in combination with surgery (Park, 2006), seven radiation/surgery patients and four radiation-only patients had recurrent disease. Among patients in the radiation/surgery group, four patients died of disease 4-10 years after treatment; the remainder was alive with disease at last follow-

up. In the radiation-only group, two of four patients died of disease at 4-5 years of follow-up; the other two were alive with disease at last follow-up.

Head and Neck Cancers

In a previously-described study comparing PBT with or without photon radiation in 33 patients with a variety of head and neck cancers (Tokuuye, 2004), four patients were identified as having recurrent disease, three of whom received PBT alone. Two of the three PBT-only patients were alive with local tumor control at last follow-up (5 and 17 years respectively); one patient had their cancer recur three months after PBT and died in month 7 of follow-up. The one PBT+photon patient died at 2.5 years of follow-up, but was described as having local tumor control.

Liver Cancer

Two studies were identified with information on recurrent disease. One was a poor-quality comparison of PBT to conventional photon radiation in eight patients with recurrent HCC after hepatectomy (Otsuka, 2003). Five patients were treated with PBT (68.8-84.5 GyE), and three with photons (60-70 Gy). Seven of eight patients died of liver failure or lung metastasis a median of 1.5 years after radiation; the one patient alive at the end of follow-up was a photon patient. The rate of local tumor control was 78%, and did not differ between treatment groups.

The other study was a previously-described prospective comparison of PBT to carbon-ion therapy in 350 patients with primary or recurrent HCC (Komatsu, 2011). No subgroup analyses were performed, but prior treatment history for HCC was found not to have a statistically-significant impact on local tumor control (p=0.73). Prior treatment was not examined as a risk factor for overall survival, however.

Lung Cancer

In a previously-described study of patients with locally-advanced, unresectable NSCLC who were treated with PBT, IMRT, or 3D-CRT (Sejpal, 2011), 22% of the study sample was identified as having a prior malignancy of any type. The effects of prior malignancy on overall survival were not reported, however.

Ocular Tumors

We identified a single comparative study of PBT in recurrent ocular cancer. In this fair-quality, comparative cohort study, a total of 73 patients with uveal melanoma had recurrence of disease following an initial course of PBT at Massachusetts General Hospital (Marucci, 2011). Patients (mean age: 58 years) were treated with either a second course of PBT (70 GyE) in five fractions or surgical enucleation and followed for 5-7 years. The likelihood of overall survival at five years was significantly (p=0.04) longer in the PBT group (63% vs. 36% for enucleation), as was the probability of being free of metastasis at this timepoint (66% vs. 31% respectively, p=0.028). Findings were similar after Cox proportional hazards regression adjusting for tumor volume and year of retreatment as well as patient age. The likelihood of local tumor recurrence at five years was 31% in the PBT group. No local

recurrences were found in the enucleation group, which is not surprising given the nature of the treatment.

Noncancerous Conditions

Other Benign Tumors

In a previously-described retrospective cohort of consisting of 20 patients with giant-cell bone tumors who were treated with PBT+photon therapy or photons alone (Chakravati, 1999), five of 20 were identified as having recurrent disease. Two of the five were treated with PBT+photon therapy, one of whom had progression of disease at eight months but no further progression after retreatment at five years of follow-up. The other patient was free of local progression and metastases as of 9 years of follow-up. In the three photon patients, one had local progression at 12 months but no further progression as of year 19 of follow-up, one patient was free of progression and metastases as of five years of follow-up, and one patient had unknown status.

NO COMPARATIVE STUDIES IDENTIFIED FOR KEY QUESTION 2: brain/spinal/paraspinal, breast, esophageal, gastrointestinal, gynecologic, pediatric, and prostate cancers; lymphomas, sarcomas, seminomas, and thymomas; arteriovenous malformations and hemangiomas.

Comparative Harms of Proton Beam Therapy in Patients with Multiple Cancers or Noncancerous Conditions (KQ3)

As with information on clinical effectiveness, data on potential harms of PBT come from RCTs, comparative cohort studies, and case series, although comparative harms data are still lacking for many condition types. Across all condition types, a total of 25 studies reported comparative information on treatment-related harms; differences in the types of harms relevant to each condition, as well as variability in harms classification even within conditions, precludes any attempt to summarily present harms data across all 19 condition categories. However, summary statements regarding our overall impression of the effects of PBT on patient harms are provided within each condition type in the sections that follow.

Secondary Malignancy

Of note, observational data on secondary malignancy with PBT are generally lacking. Two studies were identified with comparative information. One was a fair-quality matched retrospective cohort study comparing 1,116 patients in a linked Medicare-SEER database who received either PBT or photon

radiation for a variety of cancers and were followed for a median of 6.4 years (Chung, 2013). On an unadjusted basis, the incidence rates of any secondary malignancy and malignancies occurring in the prior radiation field were numerically lower for PBT, but not statistically-significantly so. After adjustment for age, sex, primary tumor site, duration of follow-up, and year of diagnosis, PBT was associated with a risk of secondary malignancy approximately one-half that of photon therapy (HR=0.52; 95% CI: 0.32, 0.85; p=0.009). There are challenges with these findings, however. First and foremost, the lower rate of secondary malignancy with PBT appeared to be manifested almost entirely in the first five years after radiotherapy, a time period in which a second cancer event is not typically attributed to prior radiation (Bekelman, 2013). In addition, patients were accrued over a very long time period (1973-2001), only the very end of which included highly conformal photon techniques like IMRT.

The second study was a poor-quality retrospective cohort study comparing PBT to photon radiotherapy in 86 infants who were treated for retinoblastoma and followed for a median of 7 years (PBT) or 13 years (photon radiotherapy) (Sethi, 2013). Therapy was received at two different centers (PBT at MGH and photon radiotherapy at Children's Hospital Boston). Kaplan-Meier analyses were conducted to control for differential follow-up but no adjustments were made for other differences between groups. Ten-year estimates of the cumulative incidence of secondary malignancy were numerically lower for PBT, but not statistically-significantly so (5% vs. 14% for photon, p=0.12). However, when malignancies were restricted to those occurring in-field or thought to be radiation-induced, a significant difference in favor of PBT was observed (0% vs. 14%, p=0.015). In addition, significant differences in favor of PBT in both cumulative incidence and radiotherapy-related malignancy were observed for the subgroup of patients with hereditary disease.

Other harms are presented in detail for each condition type in the sections that follow.

Cancers

Bone Cancer

Evidence is limited and inadequate to compare the potential harms of PBT relative to other radiation modalities in patients with bone cancer.

In a previously-described study of 27 patients with sacral chordomas who were treated with PBT/photon radiation alone or in combination with surgery (Park, 2006), multiple descriptive harms were reported. Patients receiving radiation alone reported numerically lower rates of abnormal bowel or bladder function as well as difficulty ambulating in comparison to those receiving combination therapy, but rates were not statistically tested. PBT patients also reported higher rates of return to work, although this was also not tested statistically.

Brain, Spinal, and Paraspinal Tumors

Limited, low-quality evidence suggests that PBT is associated with reductions in acute radiation-related toxicity relative to photon radiation in patients with brain and spinal tumors.

In a previously-described study comparing PBT to photon therapy in 40 adult patients treated for medulloblastoma (Brown, 2013), PBT was associated with statistically-significantly lower rates of weight loss (median % of baseline: -1.2% vs. 5.8% for photon, p=0.004) as well as requirements for medical management of esophagitis (5% vs. 57% respectively, p<0.001). PBT patients also experienced less RTOG grade 2 or greater nausea and vomiting (26% vs. 71%, p=0.004).
In a second poor-quality study comparing primarily 10 pediatric patients (mean age: 14 years) receiving PBT for spinal cord gliomas to 22 adults receiving IMRT for the same condition (mean age: 44 years) (Kahn, 2011), no cases of long-term toxicity or myelopathy were reported in either group. Minor side-effect rates were reported for the overall cohort only.

Esophageal Cancer

Evidence is limited and inadequate to compare the potential harms of PBT relative to other radiation modalities in patients with esophageal cancer, particularly in comparison to IMRT.

Two studies were identified that examined comparative harms in patients treated with PBT for esophageal cancer. One was a relatively large, fair-quality, retrospective comparative cohort study of 444 patients (median age: 61 years; 91% male) who were treated with chemotherapy and radiation (PBT, IMRT, or 3D-CRT) followed by surgical resection (Wang, 2013). Patients were followed for up to 60 days after hospital discharge. After adjustment for patient characteristics and clinical variables, 3D-CRT was associated with a significantly greater risk of postoperative pulmonary complications vs. PBT (Odds Ratio [OR]: 9.13, 95% CI: 1.83, 45.42). No significant differences were observed between PBT and IMRT, however. No differences in the rate of gastrointestinal complications were observed for any treatment comparison.

In addition, a fair-quality comparative study was identified that examined early impact on lung inflammation and irritation in 75 patients receiving PBT, IMRT, or 3D-CRT for esophageal cancer (McCurdy, 2013); patients were followed for up to 75 days following radiation. Nearly all outcome and toxicity measures were reported for the entire cohort only. However, the rate of pneumonitis was found to be significantly higher among PBT patients (33% vs. 15% for IMRT/3D-CRT, p=0.04).

Head and Neck Cancers

Evidence is limited and inadequate to compare the potential harms of PBT relative to other radiation modalities in patients with head and neck cancer.

In a previously-described study comparing PBT with versus without photon radiation in 33 patients with a variety of head and neck cancers (Tokuuye, 2004), rates of tongue ulceration, osteonecrosis, and esophageal stenosis differed somewhat between treatment groups, but were not statistically tested. Overall toxicity rates were estimated to be 22.8% at both three and five years, but were not stratified by treatment modality.

In a separate, fair-quality study comparing rates of vision loss from radiation-induced optic neuropathy in 75 patients treated with PBT or carbon-ion therapy for head and neck or skull base tumors (Demizu, 2009), unadjusted rates of vision loss were similar between modalities (8% and 6% for PBT and carbon-

ion respectively, not statistically tested). In multivariate analyses controlling for demographic and clinical characteristics, treatment modality had no effect on rates of vision loss (p=0.42). Another comparison of PBT and carbon-ion therapy in 59 patients with head and neck or skull base tumors (Miyawaki, 2009) was of poor quality (due to no control for differences between patient groups) and focused on the incidence of radiation-induced brain changes. The incidence of CTCAE brain injury of any grade was significantly (p=0.002) lower in the PBT group. MRI-based assessment of brain changes showed a lower rate in the PBT group (17% vs. 64% for carbon-ion), although this was not tested statistically.

Liver Cancer

Limited, low-quality evidence suggests that PBT is associated with comparable rates of toxicity to other radiation modalities in patients with liver cancer.

Two comparative studies were identified with comparative information on radiation-related harms. In a previously-described study of eight patients with recurrent HCC after hepatectomy (Otsuka, 2003), there were no instances of bone marrow depression or gastrointestinal complications in either group. Serum aspartate aminotransferase (AST) level s increased in the three photon patients and 4/5 PBT patients, although this was not tested statistically.

In the other study, a previously-described comparison of PBT to carbon-ion therapy in 350 patients with primary or recurrent HCC (Komatsu, 2011), rates of toxicities as graded by the Common Terminology Criteria for Adverse Events (CTCAE) framework were comparable between groups, including dermatitis, GI ulcer, pneumonitis, and rib fracture. The rate of grade 3 or higher toxicities was similar between groups (3% vs. 4% for PBT and carbon-ion respectively), although this was not statistically tested.

Lung Cancer

Moderate evidence suggests that rates of treatment-related toxicities with PBT are comparable to those seen with other radiation modalities in patients with lung cancer.

A total of three comparative studies assessed harms in patients with lung cancer. One was a study of severe radiation-induced esophagitis (within six months of treatment) among 652 patients treated for NSCLC with PBT, IMRT, or 3D-CRT at MD Anderson Cancer Center (Gomez, 2012). Rates of grade 3 or higher esophagitis were 6%, 8%, and 28% for PBT, 3D-CRT, and IMRT respectively (p<.05 for PBT and 3D-CRT vs. IMRT).

In a previously-described noncontemporaneous case series comparison of patients with locally-advanced, unresectable NSCLC who were treated with PBT, IMRT, or 3D-CRT (Sejpal, 2011), hematologic toxicity rates did not differ by radiation modality. Significant differences in favor of PBT were seen in rates of grade 3 or higher esophagitis (5%, 39%, and 18% for PBT, IMRT, and 3D-CRT respectively, p<0.001) as well as pneumonitis (2%, 6%, and 30%, p<0.001), while rates of grade 3 or higher dermatitis were significantly greater in the PBT group (24% vs. 17% and 7% for IMRT and 3D-CRT, p<0.001).

Finally, in a previously-described comparison of PBT to carbon-ion therapy in 111 patients in Japan (Fujii, 2013), rates of pneumonitis, dermatitis, and rib fracture did not differ statistically between radiation modalities across all toxicity grades.

Ocular Tumors

Limited, low-quality evidence suggests comparable rates of harm for PBT relative to treatment alternatives in patients with ocular tumors.

We identified two comparative studies assessing the harms of PBT for ocular cancers. In the previously-described Desjardins RCT comparing PBT with thermotherapy to PBT alone in 151 patients with uveal melanoma (Desjardins, 2006), no statistically-significant differences were observed between groups in rates of cataracts, maculopathy, pappilopathy, glaucoma, or intraocular pressure. The combination therapy group had a significantly lower rate of secondary enucleation (p=0.02), although actual figures were not reported.

In a previously-described comparison of PBT to enucleation in 132 patients treated for unilateral choroidal tumors (Mosci, 2012), rates of eye loss in the PBT arm were assessed and estimated to be 26% at five years of follow-up.

Pediatric Cancers

PBT's theoretical potential to lower radiation-induced toxicity in children serves as the comparative evidence base. Comparative studies are lacking, most likely due to a lack of clinical equipoise.

Other than the study of secondary malignancy described above, we identified no comparative studies of the potential harms of PBT in patients with pediatric cancers.

Prostate Cancer

Moderate evidence suggests that rates of major harms are comparable between PBT and photon radiation treatments, particularly IMRT.

We identified four comparative studies of the harms associated with PBT and alternative treatments in patients with prostate cancer. The previously-described RCT of PBT+photon therapy vs. photons alone (Shipley, 1995) examined rates of rectal bleeding, urethral stricture, hematuria, incontinence, and loss of full potency; no patients in either arm had grade 3 or higher toxicity during radiation therapy. Actuarial estimates of rectal bleeding at eight years were significantly higher in the PBT+photon arm (32% vs. 12% for photons alone, p=0.002), although this was primarily grade 2 or lower toxicity. Rates of urethral stricture, hematuria, incontinence, and loss of potency did not differ between groups.

Three additional studies involved retrospective comparisons using available databases. The most recent was a matched comparison of 314 PBT and 628 IMRT patients treated for early-stage prostate cancer using the linked Chronic Condition Warehouse-Medicare database with a focus on complications occurring within 12 months of treatment (Yu, 2013). At six months, rates of genitourinary toxicity were significantly lower in the PBT arm (5.9% vs. 9.5%, p=0.03). This difference was not apparent after 12

months of follow-up, however (18.8% vs. 17.5%, p=0.66). Rates of gastrointestinal and other (e.g., infection, nerve damage) complications did not statistically differ at either timepoint.

Another recent study compared matched cohorts of men with prostate cancer in the linked Medicare-SEER database who were treated with PBT or IMRT (684 patients in each arm) and followed for a median of four years (Sheets, 2012). IMRT patients had a statistically-significantly lower rate of gastrointestinal morbidity (12.2 vs. 17.8 per 100 person-years, p<0.05). No other statistical differences were noted in genitourinary morbidity, erectile dysfunction, hip fracture, or use of additional cancer therapy.

Finally, Kim and colleagues conducted an analysis of nearly 30,000 men in the Medicare-SEER database who were treated with PBT, IMRT, 3D-CRT, brachytherapy, or conservative management (observation alone) and evaluated for gastrointestinal toxicity (Kim, 2011). All forms of radiation had higher rates of GI morbidity than conservative management. In pairwise comparisons using Cox proportional hazards regression, PBT was associated with higher rates of GI morbidity than conservative management (HR: 13.7; 95% CI: 9.1, 20.8), 3D-CRT (HR: 2.1; 95% CI: 1.5, 3.1), and IMRT (HR: 3.3; 95% CI: 2.1, 5.2).

Noncancerous Conditions

Hemangiomas

Limited evidence suggests comparable rates of harm for PBT relative to treatment alternatives in patients with hemangiomas.

A single, previously-described retrospective comparative cohort study assessed outcomes in patients with circumscribed or diffuse hemangiomas treated with PBT or photon radiation (Höcht, 2006). Small differences in unadjusted rates of optic nerve/disc atrophy, lacrimation (formation of tears) and ocular pressure as well as effects on the retina, lens, and iris were observed between groups, but most side effects were grade 1 or 2. The rate of retinopathy was substantially higher in PBT patients (40% vs. 16% for photons). However, in Cox proportional hazards regression adjusting for between-group differences, no effect of radiation modality on outcomes was observed, including retinopathy (p=0.12).

Other Benign Tumors

Evidence is limited and inadequate to compare the potential harms of PBT relative to other radiation modalities in patients with other benign tumors.

The previously-described Arvold study comparing PBT, PBT+photon, and photon therapy alone in 25 patients treated for optic nerve sheath meningiomas (Arvold, 2009) showed numerically lower rates of acute orbital pain and headache for both PBT groups compared to photon therapy, and numerically higher rates of late asymptomatic retinopathy. None of these comparisons were tested statistically, however.

NO COMPARATIVE STUDIES IDENTIFIED FOR KEY QUESTION 3: gastrointestinal and gynecologic cancers; lymphomas, sarcomas, seminomas, and thymomas; arteriovenous malformations.

Differential Effectiveness and Safety of Proton Beam Therapy in Key Patient Subgroups (KQ4)

The sections below summarize available information on how the effectiveness and safety of PBT differs relative to treatment alternatives in specific patient subgroups as delineated in Key Question 4. Because the focus of this question is on differential effects of PBT in key subgroups, the focus of this section is on comparative studies only.

Patient Demographics

Limited comparative subgroup data are available on the differential impact of PBT according to patient demographics. In a retrospective comparison of PBT and surgical enucleation in uveal melanoma, the rate of death due to metastatic disease through two years of follow-up increased with older age in the surgical group but not in the PBT group (Seddon, 1990). In a retrospective analysis of secondary malignancy with PBT vs. photon radiation in multiple cancer types (Chung, 2013), reductions in malignancy rates with PBT of 5% were seen with each year of increasing age (mean age was 59 years in both groups). In other comparative studies, patient demographics had no impact on the effect of treatment (Tokuuye, 2004; Marucci, 2011).

Clinical Characteristics

In a comparison of secondary malignancy rates in 86 infants with retinoblastoma treated with PBT or photon radiation (Sethi, 2013), statistically-significant reductions in the estimated incidence of secondary malignancy at 10 years were observed in favor of PBT for the subset of patients with hereditary disease (0% vs. 22% for photons, p=0.005). No significant differences were observed in the overall cohort, however. In other comparative studies, clinical characteristics, including prior therapy received, had no effect on treatment outcomes (Brown, 2013; Tokuuye, 2004).

Tumor Characteristics

The impact of tumor characteristics on estimates of treatment effect was measured in six comparative studies. In one study comparing PBT to carbon-ion therapy in liver cancer (Komatsu, 2011), larger tumor

sizes were associated with a greater risk of cancer recurrence in PBT patients but not in those receiving carbon-ion therapy. In the Shipley RCT comparing PBT+photon therapy to photons alone in men with prostate cancer (Shipley, 1995), the 8-year estimate of local control was significantly higher in patients receiving PBT among those with poorly-differentiated tumors (85% vs. 40% for photons, p=0.0014). No differences were observed among those with well- or moderately-differentiated tumors. In the other studies, tumor characteristics (e.g., volume, thickness, level of prostate cancer risk) had no differential impact on outcomes (Tokuuye, 2004; Sejpal, 2011; Mosci, 2012; Coen, 2012).

Treatment Protocol

Four RCTs were identified that involved comparisons of different dosing regimens for PBT. Two of these were in men with prostate cancer (Kim, 2013; Zietman, 2010). In the more recent study, five different fractionation schemes were compared in 82 men with stage T1-T3 prostate cancer, with total doses ranging from 35-60 GyE (Kim, 2013); patients were followed for a median of approximately 3.5 years. Rates of biochemical failure using two different definitions did not differ statistically between treatment groups. Similarly, no significant differences were observed in rates of acute and late skin, gastrointestinal, or genitourinary toxicity between arms.

In another RCT conducted at MGH and Loma Linda University, 395 men with stage T1b-T2b prostate cancer were randomized to receive a conventional dose of combination PBT+photon therapy (70.2 GyE total dose) or a "high dose" of combination therapy (79.2 GyE) (Zietman, 2010). Patients were followed for a median of 9 years. Significant differences in favor of the high-dose group were seen for disease control as measured by a PSA nadir value <0.5 ng/mL (59.8% vs. 44.7% for high and conventional dose respectively, p=0.003) and 10-year estimates of biochemical failure (16.7% vs. 32.3%, p=0.0001). Survival and mortality rates did not differ. Acute GI toxicity was significantly more frequent in the high-dose group (63% vs. 44% for conventional, p=0.0006); no differences were observed in other measures of toxicity. A quality-of-life subset analysis of this RCT found no differences between groups in patient-reported measures of urinary obstruction and irritation, urinary incontinence, bowel problems, or sexual dysfunction (Talcott, 2010).

Gragoudas and colleagues examined the impact of two different total doses of PBT (50 vs. 70 GyE) on clinical outcomes and potential harms in 188 patients with melanoma of the choroid or ciliary body (Gragoudas, 2006). Patients were followed for up to five years. No statistical differences were observed in any measure of effectiveness (visual acuity, vision preservation, local recurrence, death from metastases) or harm (hemorrhage, subretinal exudation, glaucoma, uveitis, secondary enucleation).

The fourth RCT involved 96 patients with chordomas and skull base tumors who received combination PBT and photon therapy at total doses of either 66.6 or 72 GyE (Santoni, 1998). Patients were followed for a median of 3.5 years. This RCT focused on harms alone. No significant differences were observed in

the rate of temporal lobe damage between groups or in grade 1, 2, or 3 clinical symptoms such as headache and motor function.

Finally, in a previously-described comparative cohort study assessing outcomes for both PBT and carbon-ion therapy (Fujii, 2013), no differences were observed in estimates of local control, progression-free survival, or overall survival when stratified by number of fractions received or total radiation dose.

Costs and Cost-Effectiveness of Proton Beam Therapy in Patients with Multiple Cancers and Noncancerous Conditions (KQ5)

A total of 16 studies were identified that examined the costs and cost-effectiveness of PBT in a variety of settings and perspectives (see Appendix E for study details). Studies are organized by cancer type in the sections that follow. Five of the 16 studies focused attention on the operating costs, reimbursement, and/or viability of proton treatment centers for multiple types of cancer, and are summarized at the end of this section.

Breast Cancer

Three studies modeled the costs and cost-effectiveness of PBT in breast cancer. One U.S.-based study examined reimbursement for treatment with 3D-conformal partial breast irradiation using protons or photons vs. traditional whole breast irradiation (Taghian, 2004). Payments included those of treatment planning and delivery as well as patient time and transport. Total per-patient costs were substantially higher for PBT vs. photon partial irradiation ($13,200 vs. $5,300) but only modestly increased relative to traditional whole breast irradiation ($10,600), as the latter incurred higher professional service fees and involved a greater amount of patient time.

Two additional studies from the same group assessed the cost-effectiveness of PBT vs. photon radiation among women with left-sided breast cancer in Sweden (Lundkvist, 2005a and 2005c). In the first of these, photon radiation was assumed to increase the risk of ischemic and other cardiovascular disease as well as pneumonitis relative to PBT (Lundkvist, 2005a); clinical effectiveness was assumed to be identical. Reductions in adverse events led to a gain in quality-adjusted life years (QALYs) equivalent to approximately one month (12.35 vs. 12.25 for photon). Costs of PBT were nearly triple those of photon therapy, however ($11,124 vs. $4,950), leading to an incremental cost-effectiveness ratio (ICER) of $65,875 per QALY gained. The other study used essentially the same model but focused attention only on women at high risk of cardiac disease (43% higher than general population) (Lundkvist, 2005c). In this instance, a lower ICER was observed ($33,913 per QALY gained).

Head and Neck Cancer

Two studies modeled the cost-effectiveness of PBT in head and neck cancers. In one study, Ramaekers and colleagues used a Markov model to assess the cost-effectiveness of intensity-modulated PBT (IMPT) or IMRT therapy among patients with locally-advanced, Stage III-IV head and neck cancers in the Netherlands (Ramaekers, 2013). IMPT and IMRT were assumed to result in equivalent rates of disease

progression and survival, but IMPT was assumed to result in lower rates of significant dysphagia (difficulty swallowing) and xerostomia (dry mouth syndrome). IMPT was found to result in one additional month of quality-adjusted survival (6.62 vs. 6.52 QALYs for IMRT), but treatment costs were estimated to be 24% higher. The resulting ICER was estimated to be $159,421 per QALY gained vs. IMRT. Use of IMPT only in patients at high risk of radiation toxicity (and IMRT in all others) resulted in an ICER that was approximately half of the base case ($75,106 per QALY gained).

Head and neck cancer was also evaluated in the above-mentioned Swedish model (Lundkvist, 2005c). The base case involved a 65 year-old cohort with head and neck cancers of all stages. PBT was assumed not only to reduce the risk of xerostomia and acute mucositis (ulceration of mucous membranes), but also to reduce overall mortality at 8 years by 25% based on modeled delivery of a higher curative dose. As a result, PBT generated an additional 1.02 QALYs over photon radiation at an additional cost of approximately $4,000, resulting in an ICER of $3,769 per QALY gained.

Lung Cancer

Two studies from the same center estimated the economic impact of PBT in lung cancers among patients in the Netherlands (Grutters, 2011; Grutters, 2010). One was a Markov model comparing PBT to carbon-ion therapy, stereotactic radiation therapy, and conventional radiation in patients with stage 1 non-small-cell lung cancer (NSCLC) over a 5-year time horizon (Grutters, 2010). Effects of therapy included both overall and disease-related mortality as well as adverse events such as pneumonitis and esophagitis. For inoperable NSCLC, PBT was found to be both more expensive and less effective than either carbon-ion or stereotactic radiation and was therefore not included in subsequent analyses focusing on inoperable disease. While not reported in the paper, PBT's derived cost-effectiveness relative to conventional radiation (based on approximately $5,000 in additional costs and 0.35 additional QALYs) was approximately $18,800 per QALY gained.

The second study was a value of information analysis that examined the implications of adopting PBT for Stage I NSCLC in three scenarios: (a) without further research; (b) along with the conduct of a clinical trial; and (c) delay of adoption while a clinical trial is conducted (Grutters, 2011). Costs included those of treatment (currently abroad, as the Netherlands has no proton facilities), the clinical trial vs. conventional radiation, and adverse events due to suboptimal care. These were calculated and compared to the expected value of sampling information (reduced uncertainty), obtained through simulation modeling of uncertainty in estimates both before and after the trial. The analysis found that adoption of PBT along with conduct of a clinical trial produced a net gain of approximately $1.9 million for any trial with a sample size <950, while the "delay and trial" strategy produced a net loss of ~$900,000. Results were sensitive to a number of parameters, including treatment costs abroad and costs of suboptimal treatment.

Pediatric Cancers

Three decision analyses were available in pediatric cancers, all of which focused on a lifetime time horizon in children with medulloblastoma who were treated at 5 years of age (Mailhot Vega, 2013;

Lundkvist, 2005b; Lundkvist, 2005c). In a US-based model that incorporated costs and patient preference (utility) values of treatment as well as management of adverse events such as growth hormone deficiency, cardiovascular disease, hypothyroidism, and secondary malignancy (Maillhot Vega, 2013), PBT was found to generate lower lifetime costs ($80,000 vs. $112,000 per patient for conventional radiation) and a greater number of QALYs (17.37 vs. 13.91). Reduced risks for PBT were estimated based on data from dosimetric and modeling studies. Sensitivity analyses on the risk of certain adverse events changed the magnitude of PBT's cost-effectiveness, but it remained less costly and more effective in all scenarios.

The same Swedish group that examined breast and head/neck cancer also assessed medulloblastoma in two modeling studies (Lundkvist, 2005b; Lundkvist, 2005c). As with the analysis above, PBT was assumed to reduce both mortality and nonfatal adverse events relative to conventional photon therapy. On a per-patient basis, PBT was assumed to reduce lifetime costs by approximately $24,000 per patient and increase quality-adjusted life expectancy by nearly nine months (12.8 vs. 12.1 QALYs) (Lundkvist, 2005b). On a population basis, 25 medulloblastoma patients treated by PBT would have lifetime costs reduced by $600,000 and generate an additional 17.1 QALYs relative to conventional photon radiation (Lundkvist, 2005c).

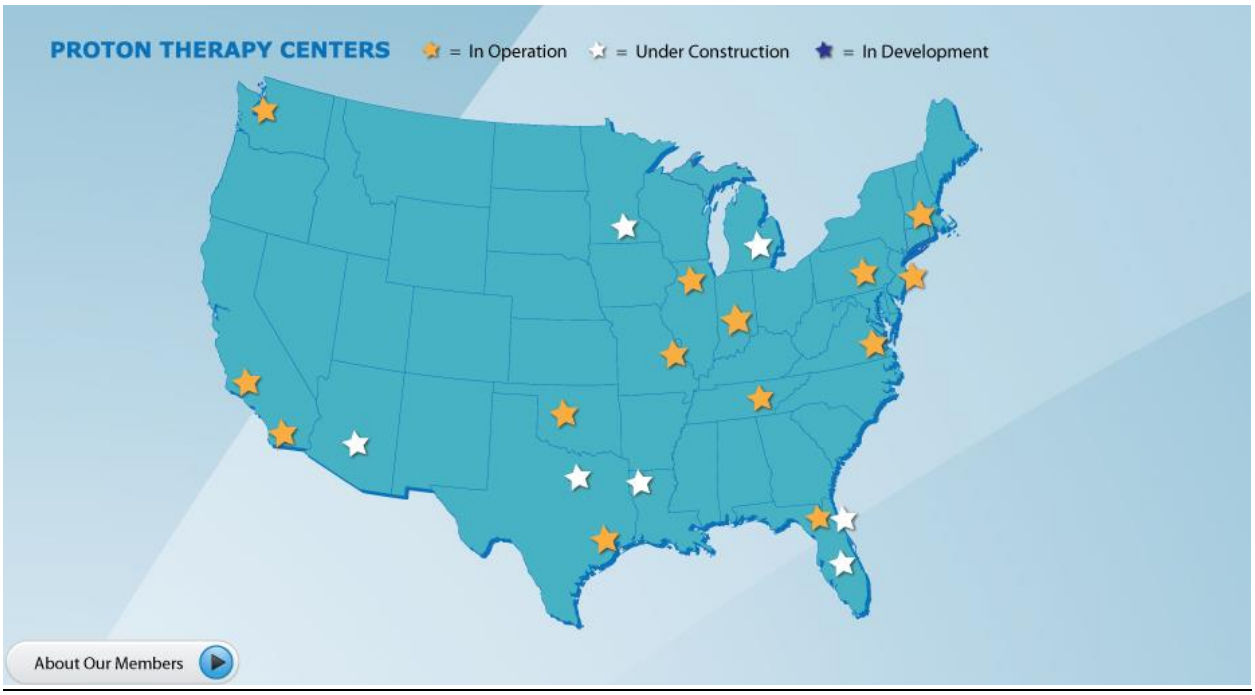
Prostate Cancer

We identified four studies examining the costs and cost-effectiveness of PBT for prostate cancer. The analysis of the 2008-2009 Chronic Condition Warehouse previously reported under KQ 3 (harms) also examined treatment costs for matched Medicare beneficiaries with prostate cancer who received PBT or IMRT (Yu, 2013). Median Medicare reimbursements were $32,428 and $18,575 for PBT and IMRT respectively (not statistically tested).

A relatively recent Markov decision analysis estimated the lifetime costs and effectiveness of PBT, IMRT, and stereotactic body radiation therapy (SBRT) for localized prostate cancer (Parthan, 2012). Clinical effectiveness and impact on mortality were assumed to be equivalent across all three groups. SBRT was found to have the lowest treatment costs and shortest time in treatment of the three modalities, and produced slightly more QALYs (8.11 vs. 8.05 and 8.06 for IMRT and PBT respectively) based on an expected rate of sexual dysfunction approximately half that of IMRT or PBT. SBRT was cost-saving or cost-effective vs. PBT in 94% of probabilistic simulations.

An earlier decision analysis estimated the potential cost-effectiveness of a hypothetically-escalated PBT dose (91.8 GyE) vs. 81 Gy delivered with IMRT over a 15-year time horizon (Konski, 2007). The model focused on mortality and disease progression alone (i.e., toxicities were assumed to be similar between groups), and assumed a 10% reduction in disease progression from PBT's higher dose. This translated into QALY increases of 0.42 and 0.46 years in 70- and 60-year-old men with intermediate-risk disease respectively. Costs of PBT were $25,000-$27,000 higher in these men. ICERs for PBT vs. IMRT were $63,578 and $55,726 per QALY for 70- and 60-year-old men respectively.

Finally, the Lundkvist model also evaluated costs and outcomes for a hypothetical cohort of 300 65 year-old men with prostate cancer (Lundkvist, 2005, e30). PBT was assumed to result in a 20% reduction in cancer recurrence relative to conventional radiation as well as lower rates of urinary and gastrointestinal toxicities. PBT was estimated to be approximately $8,000 more expensive than conventional radiation over a lifetime but result in a QALY gain of nearly 4 months (0.297). The resulting cost-effectiveness ratio was $26,481 per QALY gained.



Facility-based Analyses

Two recent U.S.-based studies modeled the case distribution necessary to service the debt incurred from the construction of new proton facilities (Elnahal, 2013; Johnstone, 2012). The more recent of these examined the impact of accountable care organization (ACO) Medicare reimbursement scenarios on debt servicing, by assessing the potential mix of complex or pediatric cases along with noncomplex and prostate cases that could be delivered with session times <30 minutes (Elnahal, 2013). Overall, replacing fee-for-service reimbursement with ACO payments would be expected to reduce daily revenue by 32%. Approximately one-quarter of complex cases would need to be replaced by noncomplex cases simply to cover debt, and PBT facilities would need to operate 18 hours per day.

The earlier study assessed the fee-for-service case distribution required to service debt in PBT facilities of various sizes (Johnstone, 2012). A single-room facility would be able to cover debt while treating only complex and pediatric cases if 85% of treatment slots were filled, but could also achieve this by treating four hours of noncomplex (30 minutes per session) and prostate (24 minutes) cases. Three- and four-room facilities could not service debt by treating complex and pediatric cases alone; an estimated 33-

50% of volume would need to be represented by simple/prostate cases to service debt in larger facilities.

An additional U.S. study examined the potential impact on reimbursement of replacing 2007 radiation therapy volume at Rhode Island Hospital (i.e., IMRT, stereotactic radiation, GammaKnife®) with PBT in all instances, based on Medicare reimbursement rates (Dvorak, 2010). No impact on capital expenditures was assumed. A total of 1,042 patients were treated with other radiation modalities, receiving nearly 20,000 treatment fractions. Estimated Medicare reimbursement was approximately $6 million at baseline. Replacing all of these fractions with PBT would increase reimbursement to approximately $7.3 million, representing a 22% increase. It was further estimated that 1.4 PBT gantries would be necessary to treat this patient volume.

Two additional studies modeled the costs of new construction of proton facilities in Europe (Peeters, 2010; Goitien, 2003). Both assumed a 30-year facility lifetime and 13-14 hours of daily operation. Taking into account both construction and daily operating costs, the total institutional costs to deliver PBT was estimated to be 2.4-3.2 times higher than that of conventional photon radiation in these studies. The Peeters study also estimated the costs to operate a combined proton-carbon ion facility, and estimated these costs at approximately 5 times higher than that of a photon-only facility (Peeters, 2010).

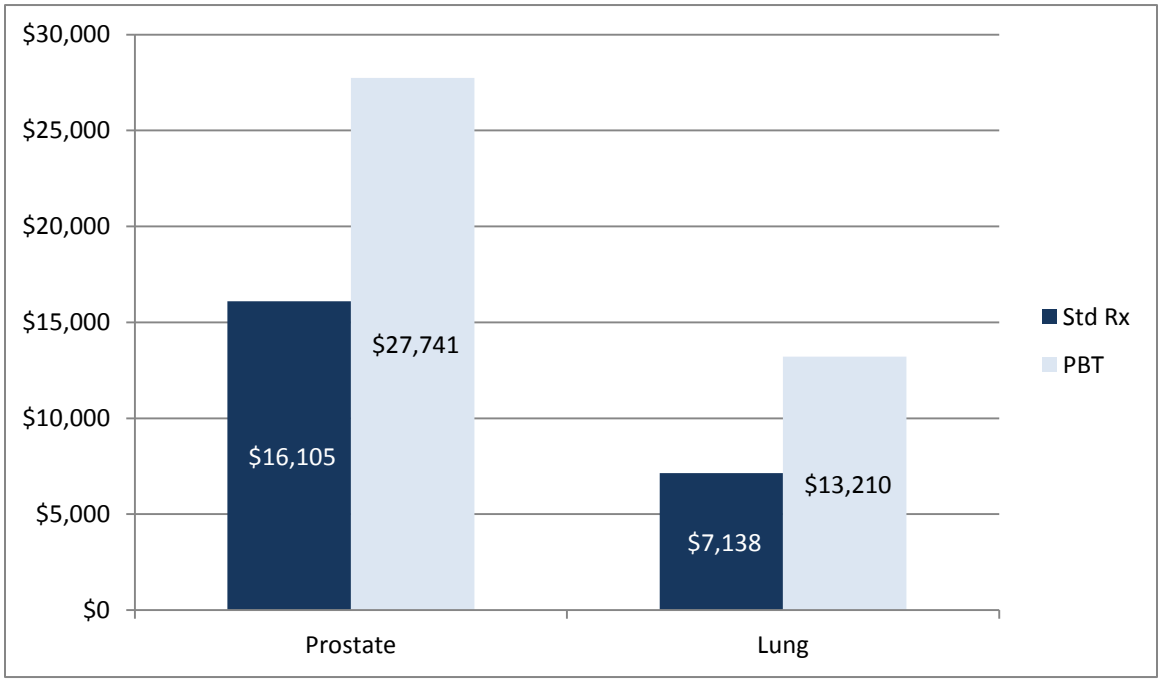
NO ECONOMIC STUDIES IDENTIFIED FOR KEY QUESTION 5: Bone, brain/spinal/paraspinal, esophageal, gastrointestinal, gynecologic, and liver cancers; lymphomas, sarcomas, seminomas, and thymomas; arteriovenous malformations, hemangiomas, and other benign tumors.

Budget Impact Analysis: Prostate and Lung Cancer

To provide additional context for an understanding of the economics of PBT, we performed a simple budget impact analysis based on 2012 radiation therapy volume within the Public Employees Benefits Board (PEBB) at the HCA. We focused on prostate and lung cancer as two common cancers for which treatment with PBT would be considered.

In 2012, 110 prostate cancer patients received treatment with IMRT or brachytherapy. Considering only the costs of treatment delivery (i.e., not of planning or follow-up), allowed payments averaged $19,143 and $10,704 for IMRT and brachytherapy respectively, and totaled approximately $1.8 million for the population. A single PEBB prostate cancer patient was referred for PBT; in this patient, allowed payments totaled $27,741 for 21 treatment encounters ($1,321 per encounter). Applying this payment level to all 110 patients would result in a total of approximately $3.1 million, or a 73% increase. Comparisons of weighted average payments per patient can be found in Figure ES3 below.

Figure ES3. Comparisons of average per-patient payments in PEBB plan based on current radiation therapy volume and expected payments for proton beam therapy.



NOTE: "Std Rx" refers to the current mix of radiation treatments used in each population (IMRT and brachytherapy for prostate cancer, IMRT and radiosurgery for lung cancer)

In 2012, 33 PEBB patients received radiation treatment for lung cancer. Allowed payments for treatment delivery averaged $15,963 and $4,792 for IMRT and radiosurgery respectively, and totaled approximately $240,000 for the population. Because PEBB had no lung cancer referrals for PBT, we assumed that treatment with 10 fractions would cost the same per fraction as for prostate cancer ($1,321), summing to a total cost of $13,210. Based on these assumptions, converting all 33 patients to PBT would raise total payment to approximately $440,000 annually, or an 84% increase.

Because volume of radiation treatments in the PEBB plan for these cancers was relatively low, and a single case was referred out of state for PBT, these payment estimates might be considered too variable for comparison. We conducted an additional analysis for prostate cancer patients using national Medicare payment estimates from a publicly-available analysis of changes in Hospital Outpatient Prospective Payment System (HOPPS) rates conducted by Revenue Cycle, Inc. for Varian Medical Systems (Varian, Inc., 2014). We used 2013 payment estimates for HDR brachytherapy, IMRT, and PBT. We assumed 40 fractions were delivered each for IMRT and PBT. Payment estimates, including simulation, planning, and treatment, were $8,548, $21,884, and $30,270 for brachytherapy, IMRT, and PBT respectively. Based on the 2012 mix of treatments in the PEBB plan (70 IMRT, 40 brachytherapy), expected Medicare HOPPS payments would total approximately $1.9 million. If all 110 patients were treated instead with PBT, expected payments would be approximately $3.3 million. This represents a 78% increase, which is similar in magnitude to that estimated using actual PEBB payments.

There are clear limitations to this analysis in that we do not know whether patients treated by PBT would have the same severity mix as the existing population, or whether some of these patients would not even be candidates for PBT. We also did not estimate total costs of care for these patients, so any potential cost-offsets are not represented here. Nevertheless, this analysis represents a reasonable estimate of the treatment expenditures the PEBB plan could expect to incur if current radiation treatment approaches were replaced by PBT.

Summary and Recommendations for Future Research

Proton beam therapy (PBT) has been used for clinical purposes for over 50 years and has been delivered to tens of thousands of patients with a variety of cancers and noncancerous conditions. Despite this, evidence of PBT's comparative clinical effectiveness and comparative value is lacking for nearly all conditions under study in this review. As mentioned previously, it is unlikely that significant comparative study will be forthcoming for childhood cancers despite uncertainty over long-term outcomes, as the potential benefits of PBT over alternative forms of radiation appear to be generally accepted in the clinical and payer communities. In addition, patient recruitment for potential studies may be untenable in very rare conditions (e.g., thymoma, arteriovenous malformations). In other areas, however, including common cancers such as breast and prostate, the poor evidence base and residual uncertainty around the effects of PBT is highly problematic.

We rated the net health benefit of PBT relative to alternative treatments to be "Superior" (moderate-large net health benefit) in ocular tumors and "Incremental" (small net health benefit) in adult brain/spinal and pediatric cancers. We judged the net health benefit to be "Comparable" (equivalent net health benefit) in several other cancers, including liver, lung, and prostate cancer, as well as hemangiomas. It should be noted, however, that we made judgments of comparability based on a limited evidence base that provides relatively low certainty that PBT is roughly equivalent to alternative therapies. While further study may reduce uncertainty and clarify differences between treatments, it is currently the case that PBT is far more expensive than its major alternatives, and evidence of its short or long-term relative cost-effectiveness is lacking for many of these conditions. It should also be noted that we examined evidence for 11 cancers and noncancerous conditions not listed above, and determined that there was insufficient evidence to obtain even a basic understanding of PBT's comparative clinical effectiveness and comparative value.

For relatively common cancers, the ideal evidence of PBT's clinical impact would come from randomized clinical trials such as those currently ongoing in liver, lung, and prostate cancer. To allay concerns regarding the expense and duration of trials designed to detect survival differences, new RCTs can focus on validated intermediate endpoints such as tumor progression or recurrence, biochemical evidence of disease, development of metastases, and near-term side effects or toxicities. In any event, overall and disease-free survival should be included as secondary measures of interest.

In addition, the availability of large, retrospective databases that integrate clinical and economic information should allow for the development of robust observational studies even as RCTs are being conceived of and designed. Advanced statistical techniques and sampling methods have been used to create observational datasets of patients treated with PBT and alternative therapies using national databases like the Medicare-SEER database and Chronic Conditions Warehouse used in some of the studies summarized in this review. These studies will never produce evidence as persuasive as randomized comparisons because of concerns regarding selection and other biases, and administrative databases lack the clinical detail necessary to create rigorously-designed observational datasets.

The continued growth of electronic health records from integrated health systems may allow for the creation of more detailed clinical and economic comparisons in large, well-matched patient groups receiving alternative radiation modalities. Use of clinical records-based registries and other observational datasets may therefore yield substantial information on PBT's benefits and harms under typical-practice conditions, as well as an indication of whether RCTs should be considered in the first place. Use of available clinical and administrative datasets also represents an opportunity for the payer and clinical communities to collaborate in setting standards for study design, identifying the outcomes of most interest, and sharing resources so that evidence can be generated in the most efficient manner possible.

Appraisal Report

Final Scope

It is estimated that nearly 14 million Americans are cancer survivors and that 1.7 million new cases will be diagnosed in 2013 (American Cancer Society, 2013). Among the treatment options for cancer, radiation therapy is commonly employed; an estimated 50% of patients receive radiation therapy at some point during the course of their illness (Delaney, 2005). This appraisal focuses on the use of one form of external beam radiation, proton beam therapy (PBT), to treat patients with multiple types of cancer as well as those with selected noncancerous conditions. The final scope of the appraisal, described using the Populations, Interventions, Comparators, Outcomes, Timeframe, and Study Designs (PICOTS) format (Counsell, 1997) is described in detail in the sections that follow. Within each condition type, two general populations were specified as of interest for this evaluation:

- Patients receiving PBT as primary treatment for their condition (i.e., curative intent)
- Patients receiving PBT for recurrent disease or for failure of initial therapy (i.e., salvage)

All forms of PBT were considered for this evaluation, including monotherapy, use of PBT as a "boost" mechanism to conventional radiation therapy, and combination therapy with other modalities such as chemotherapy and surgery. All PBT studies that met entry criteria for this review were included, regardless of manufacturer, treatment protocol, location, or other such concerns.

Objectives and Methods

The objective of this review was to appraise the comparative clinical effectiveness and comparative value of proton beam therapy in a variety of cancers and noncancerous conditions. To support this appraisal we report the results of a systematic review of published randomized controlled trials, comparative observational studies, and case series on clinical effectiveness and potential harms, as well as any published studies examining the costs and/or cost-effectiveness of proton beam therapy.

Key Questions

1) What is the comparative impact of proton beam therapy treatment with curative intent on survival, disease progression, health-related quality of life, and other patient outcomes versus radiation therapy alternatives and other cancer-specific treatment options (e.g., surgery, chemotherapy) for the following conditions:
   a. Cancers

i. Bone tumors
ii. Brain, spinal, and paraspinal tumors
iii. Breast cancer
iv. Esophageal cancer
v. Gastrointestinal cancers
vi. Gynecologic cancers
vii. Head and neck cancers (including skull base tumors)
viii. Liver cancer
ix. Lung cancer
x. Lymphomas
xi. Ocular tumors
xii. Pediatric cancers (e.g., medulloblastoma, retinoblastoma, Ewing's sarcoma)
xiii. Prostate cancer
xiv. Soft tissue sarcomas
xv. Seminoma
xvi. Thymoma

b. Noncancerous Conditions
   i. Arteriovenous malformations
   ii. Hemangiomas
   iii. Other benign tumors (e.g., acoustic neuromas, pituitary adenomas)

2) What is the comparative impact of salvage treatment (including treatment for recurrent disease) with proton beam therapy versus major alternatives on survival, disease progression, health-related quality of life, and other patient outcomes versus radiation therapy alternatives and other cancer-specific treatment options (e.g., surgery, chemotherapy) for the condition types listed in key question 1?

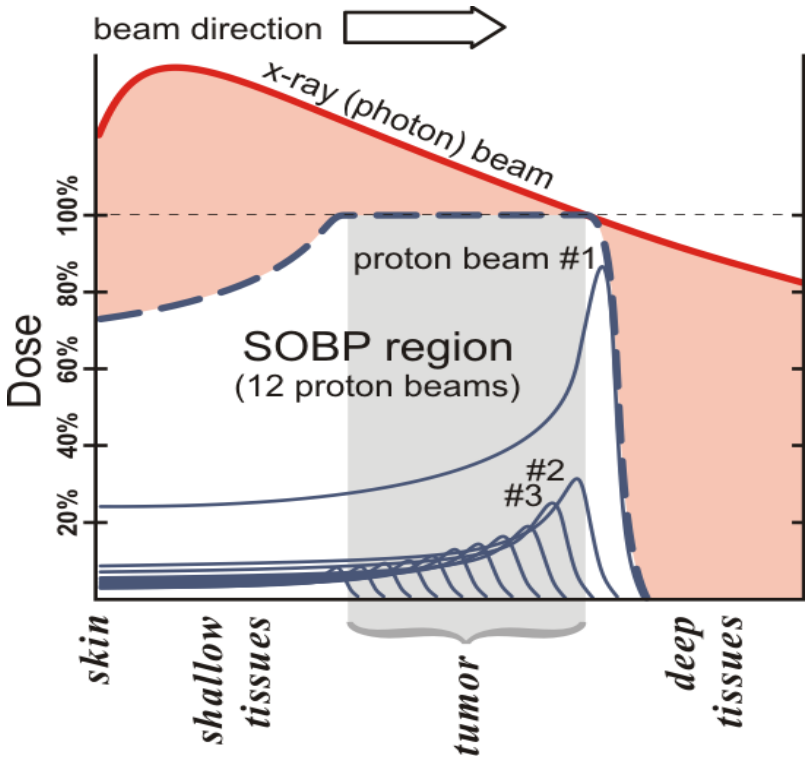
3) What are the comparative harms associated with the use of proton beam therapy relative to its major alternatives, including acute (i.e., within the first 90 days after treatment) and late (>90 days) toxicities, systemic effects such as fatigue and erythema, toxicities specific to each cancer type (e.g., bladder/bowel incontinence in prostate cancer, pneumonitis in lung or breast cancer), risks of secondary malignancy, and radiation dose?

4) What is the differential effectiveness and safety of proton beam therapy according to factors such as age, sex, race/ethnicity, disability, presence of comorbidities, tumor characteristics (e.g., tumor volume and location, proliferative status, genetic variation) and treatment protocol (e.g., dose, duration, timing of intervention, use of concomitant therapy)?
5) What are the costs and cost-effectiveness of proton beam therapy relative to radiation therapy alternatives and other cancer-specific treatment options (e.g., surgery, chemotherapy)?

1. Background

Protons are positively-charged subatomic particles that have been in clinical use as a form of external beam radiotherapy for over 60 years. Compared to the photon X-ray energy used in conventional radiotherapy, proton beams have physical attributes that are potentially appealing. Specifically, protons deposit radiation energy at or around the target, at the end of the range of beam penetration, a phenomenon known as the Bragg peak (Larsson, 1958). In contrast, photons deliver radiation across tissue depths on the way toward the target tumor and beyond, as depicted in Figure 1 below. The total radiation dose for proton therapy is delivered in the "spread out Bragg peak" (SOBP) region from multiple proton beams; proton radiation is delivered to the target tumor as well as to shallow tissue depths before the target, but not to deeper tissue depths beyond the target (Levin, 2005).

Figure 1. Dose distribution by tissue depth for proton and photon radiation.



Source: Adapted from Levin WP, Kooy H, Loeffler, DeLaney TF. Proton beam therapy. *Br J Cancer*. 2005;93(8):849-854.

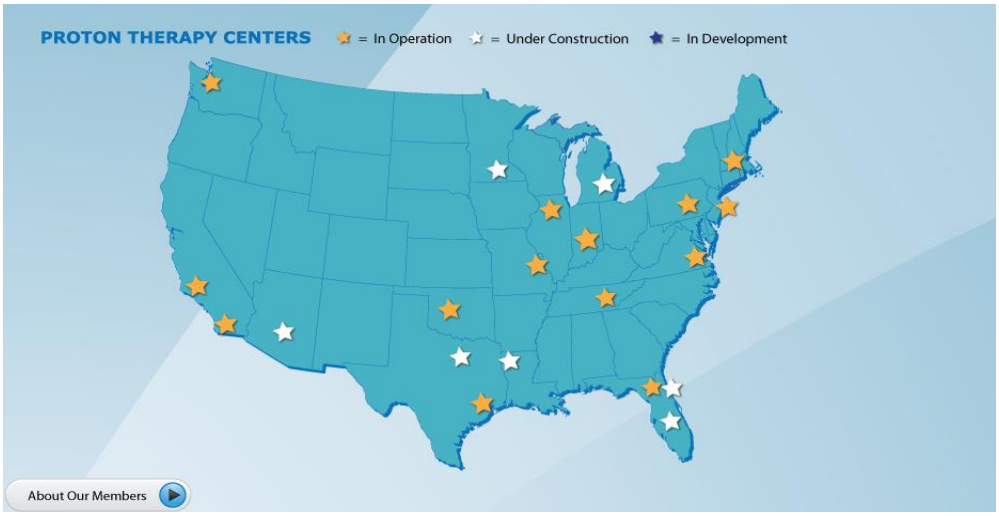
The goal of any external beam radiotherapy is to deliver sufficient radiation to the target tumor while mitigating the effects on adjacent normal tissue. As Figure 1 demonstrates, this has been a challenge for

conventional photon therapy due to the amount of radiation deposited both before and after the target is reached. While the amount of photon radiation at entry into the body is much higher than at exit, photon beams typically "scatter" to normal tissues after leaving the target. This so-called "exit" dose is absent for protons, as tissue beyond the point of peak energy deposition receives little to no radiation (Kjellberg, 1962).

Initial use of proton beam therapy (PBT) focused on conditions where sparing very sensitive adjacent normal tissues was felt to be of utmost importance, such as cancers or noncancerous malformations of the brain stem, eye, or spinal cord. In addition, proton beam therapy was advocated for many pediatric tumors because even lower-dose irradiation of normal tissue in pediatric patients can result in pronounced acute and long-term toxicity (Thorp, 2010). There are also long-standing concerns regarding radiation's potential to cause secondary malignancy later in life, particularly in those receiving radiation at younger ages. Finally, radiation may produce more nuanced effects in children, such as neurocognitive impairment in pediatric patients treated with radiotherapy for brain cancers (Yock, 2004).

The construction of cyclotrons at the heart of proton beam facilities is very expensive ($150-$200 million for a multiple gantry facility); accordingly, as recently as 10 years ago there were fewer than 5 proton beam facilities in the United States (Jarosek, 2012). More recently, however, the use of PBT has been expanded in many settings to treat more common cancers such as those of the prostate, breast, liver, and lung. With the growth in potential patient numbers and reimbursement, the construction of proton centers has grown substantially. As depicted in Figure 2 below, there are now 14 operating proton centers in the U.S., including one in Seattle that came online in March 2013. Eleven additional centers are under construction or in the planning stages, and many more are proposed (not shown) (Particle Therapy Co-Operative Group, 2014).

Figure 2. Map of proton beam therapy centers in the United States.



Source: The National Association for Proton Therapy. http://www.proton-therapy.org/map.htm; Particle Therapy Co-Operative Group. http://www.ptcog.ch/

Several approaches to reduce the costs of delivering PBT are being explored. One is the use of "hypofractionation", a process of delivering higher-dose fractions of radiation that has the potential to reduce the frequency of radiation delivery and shorten the overall treatment course (Nguyen, 2007). Another is the construction of compact, single-gantry proton facilities that have been estimated to cut the construction cost of a proton facility to the range of $15-$25 million. Some commentators believe that lower construction costs will reduce the debt incurred by medical institutions and therefore lead to the ability to reduce the price charged to payers for each treatment course (Smith, 2009).

As with pediatric and rare tumors, clinical interest in the use of PBT for more common cancers is focused on sparing adjacent tissues from excess radiation. Some of these considerations are specific to tumor type and location. For example, interest in minimizing radiation exposure in hepatocellular carcinoma stems from concerns that excess radiation to liver tissue that is uninvolved with the tumor but nonetheless cirrhotic may result in radioembolization or other serious hepatic injury (Maor, 2013).

However, while enthusiasm for expanded use of PBT has grown in recent years, there remain uncertainties regarding its use in more common conditions and even for cancer types for which its deployment has been relatively well-accepted. Some concerns have been raised about the hypothetical advantages of the radiation deposition for proton beams. The dose range is relatively certain for tumors that are close to the skin, but there is more uncertainty around the end of the dose range when deep-seated tumors such as prostate cancer are considered (Goitein, 2008). In addition, a penumbra (i.e., lateral spread or blurring of the beam as it reaches the target) develops at the end of the beam line, which can result in more scatter of the beam to adjacent normal tissue than originally estimated, particularly at deeper tissue depths (Rana, 2013). Protons are also very sensitive to tissue heterogeneity, and the precision of the beam may be disturbed as it passes through different types of tissue (Unkelbach, 2007).

Another concern is the effects of neutrons, which are produced by passively-scattered proton beams and result in additional radiation dose to the patient. The location of neutron production in a PBT patient and its biologic significance is currently a topic of significant debate (Hashimoto, 2012; Jarlskog, 2008). In addition, while it is assumed that the biologic effects of protons are equivalent to photons, specific relative effectiveness (RBE) values of protons in relation to photons are not known with absolute certainty for all types of tissues and fractionation schemes (Paganetti, 2002).

It is also the case that, while PBT treatment planning and delivery have evolved, so too have other approaches to radiotherapy. For example, intensity-modulated radiation therapy (IMRT) uses sophisticated treatment planning and multiple beam angles to confirm radiation delivery to the target, and has become the de facto standard of care for photon radiotherapy in the U.S. (Esiashvili, 2004). The potential for comparison of PBT and IMRT in clinical trial settings has been the subject of numerous editorials, commentaries, and bioethics exercises in recent years (Efstathiou, 2013; Nguyen, 2007; Zietman, 2007; Goitein, 2008; Combs, 2013; Glimelius, 2007; Glatstein, 2008; Hofmann, 2009; Bekelman,

2013; Bekelman, 2012). The intensity of this debate has created opportunities for the development of randomized trials, several of which are well underway (see Section 6 on page 22).

Due to the growth in popularity of proton beam therapy as well as concerns regarding its use in certain patient populations, there is interest in understanding the clinical benefits, potential harms, and costs associated with proton beam therapy relative to treatment alternatives in multiple types of cancer as well as certain noncancerous conditions. Accordingly, a review of the available evidence on PBT was conducted under the auspices of the Washington Health Care Authority's health technology assessment program.

Washington State Agency Utilization Data

Figure 1. Proton Beam Therapy Patients 2009-2012, Patient Counts and Costs (Paid $)

PEB Proton Beam Patients	2009	2010	2011	2012	4 Yr Overall Total**	Avg Annual % Chnge	
PEB Average Annual Members	210,501	213,487	212,596	212,684		0.3%	
Total Proton Beam Patients	7	5	7	4	20	-10.6%	*
Proton Beam Patients by Diagnosis Category Patient Counts (Medicare primary patients)							
Brain cancer	1		1		2		
Eye cancer		1		1	2		
Lung cancer				1 (1)	1 (1)		
Prostate Cancer	6 (4)	3 (3)	5 (5)	2 (2)	14 (12)		
Spinal cord cancer		1	1		1		
Total Paid (PEB Primary only) (Imaging and planning included)	**$290,083**	**$53,639**	**$37,133**	**$83,088**	**$463,943**	**3.8%**	*
% of total for direct day of treatment costs)	**94.3%**	**62.4%**	**98.2%**	**90.6%**	**90.2%**		
Average Paid per Patient, PEB Primary	$96,694	$26,820	$18,567	$83,088†	$66,278		
Total treatment day counts	**255**	**105**	**208**	**87**	**655**	-6.2%	*
Average treatment days per patient (4-134 range)	36.4	21.0	29.7	21.8	32.8	-9.2%	
Proton Beam Patients by Diagnosis Category - treatment counts (average where possible)							
Brain cancer	31†		5†		18.0		
Eye cancer		4†		24†	28.0		
Lung cancer				30†	30.0†		
Prostate Cancer	74.7	31.7	38.4	16.5	41.8		
Spinal cord cancer		6†	11†		17.0†		

*Average annual % change adjusted for population

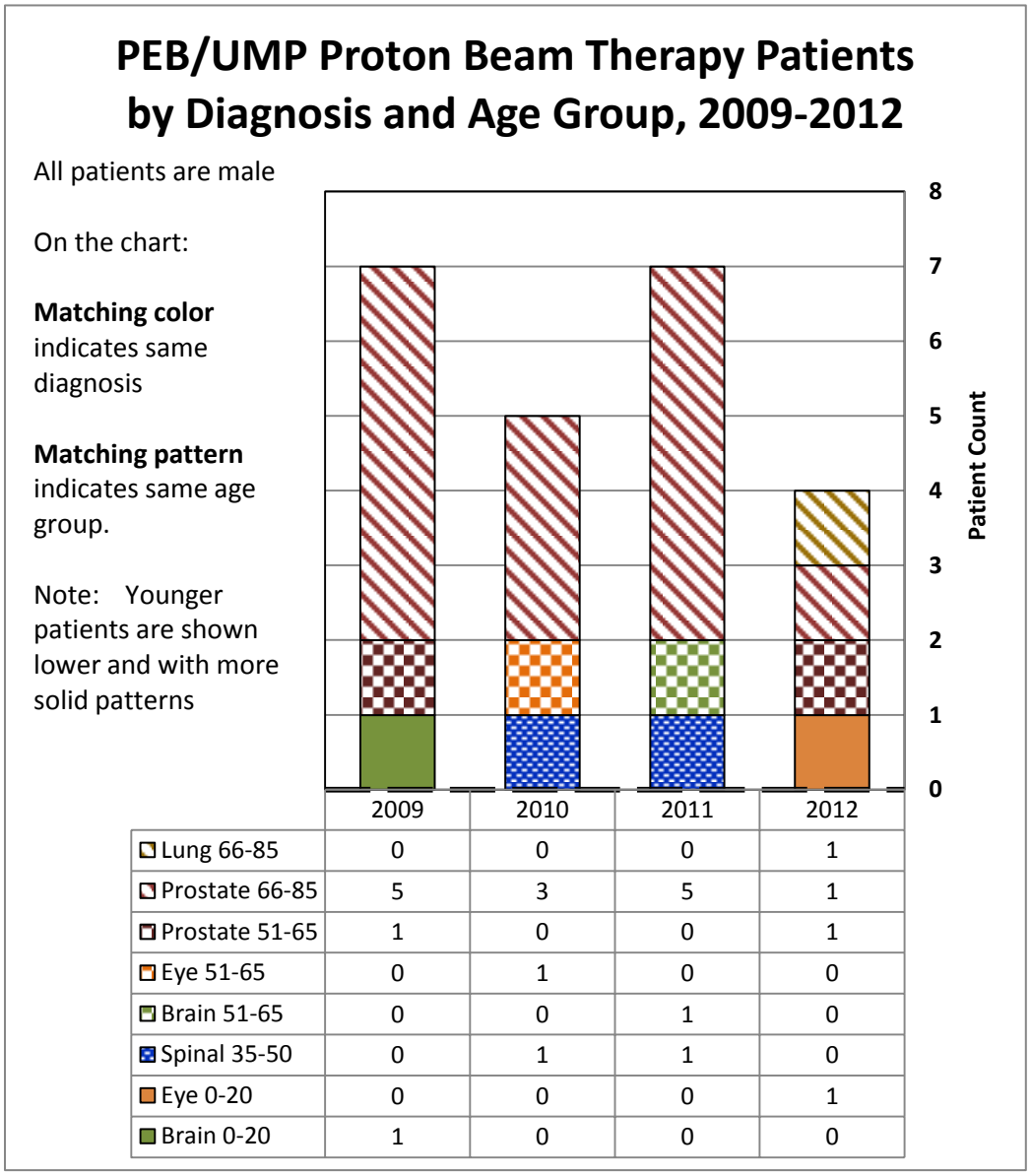
**Unique patients are counted over the 4 year period

† Single value - not average

‡ Total paid includes imaging and planning up to 21 days ahead of first treatment and surveillance imaging to 7 days after last treatment.

Note: L&I and Medicaid reported no Proton Beam Therapy in the 2009-2012 timeframe. Seventy percent of PEB/UMP proton beam treatments were for prostate cancer, and 10% were pediatric patients.

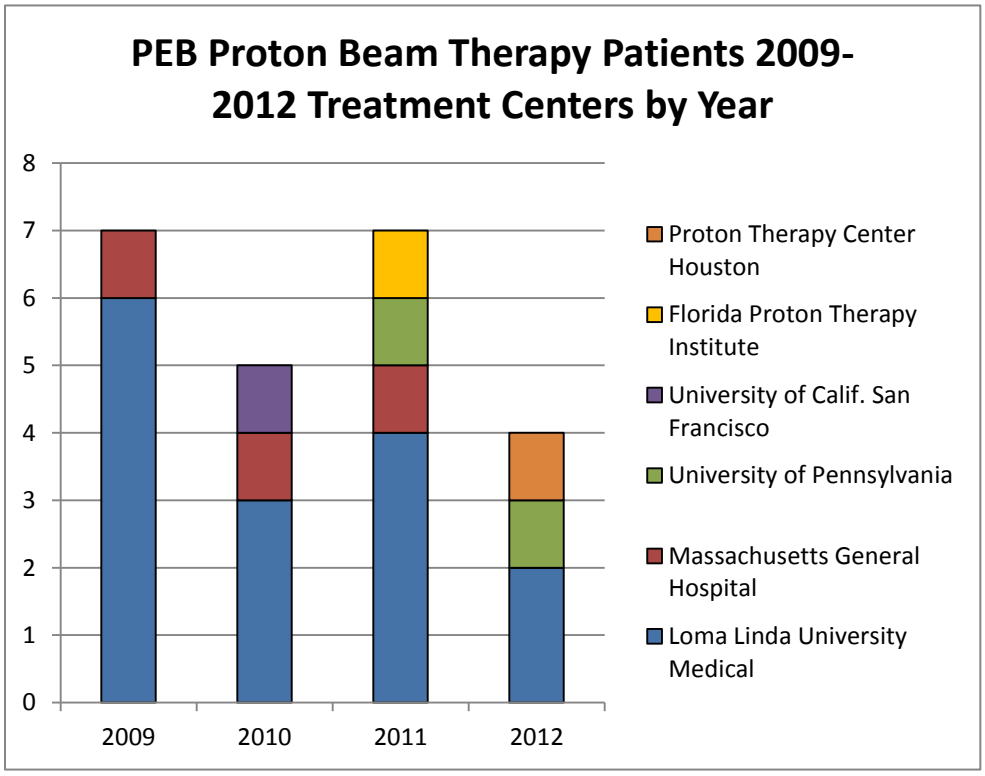
Figure 2. PEB/UMP Proton Beam Therapy Patients by Diagnosis and Age Group, 2009-2012

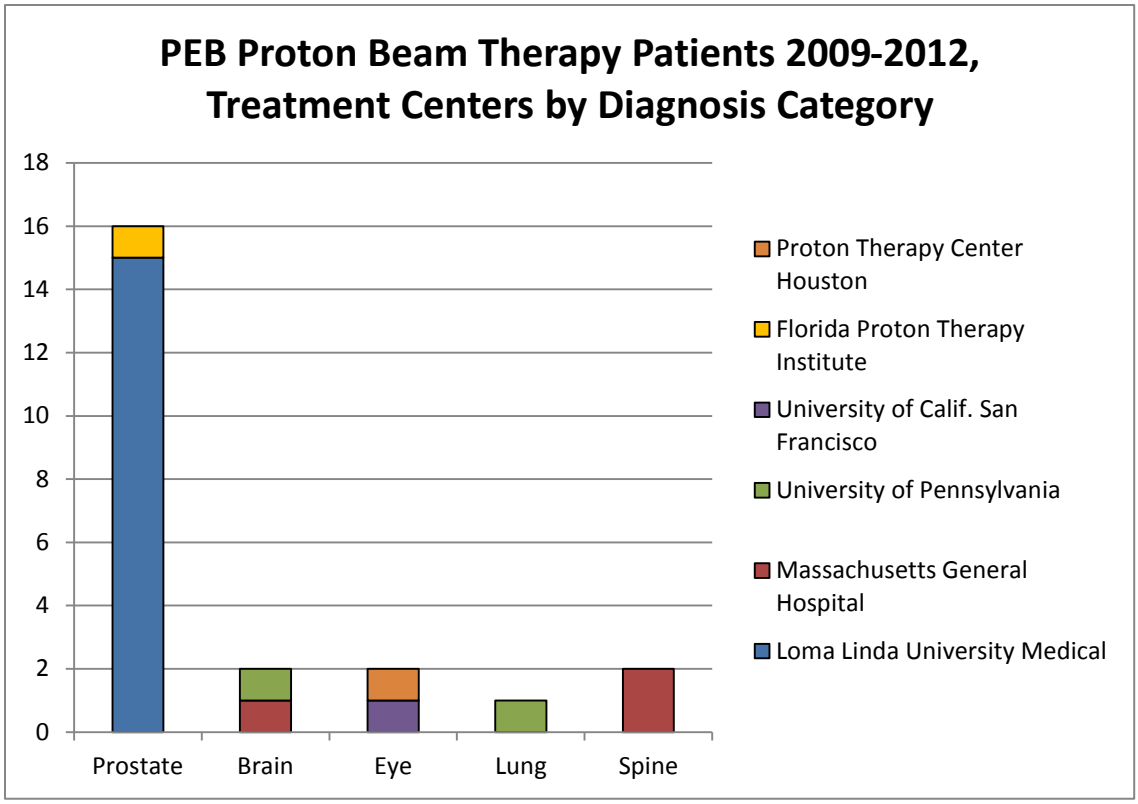


	2009	2010	2011	2012
Lung 66-85	0	0	0	1
Prostate 66-85	5	3	5	1
Prostate 51-65	1	0	0	1
Eye 51-65	0	1	0	0
Brain 51-65	0	0	1	0
Spinal 35-50	0	1	1	0
Eye 0-20	0	0	0	1
Brain 0-20	1	0	0	0

Note: Patients were clustered in younger and older age groups. The prostate patients (all red patterned areas above) were between 63 and 79 years old.

Figure 3a, 3b. PEB Proton Beam Therapy Patients – Treatment Center Location by Year and Diagnosis, 2009-2012



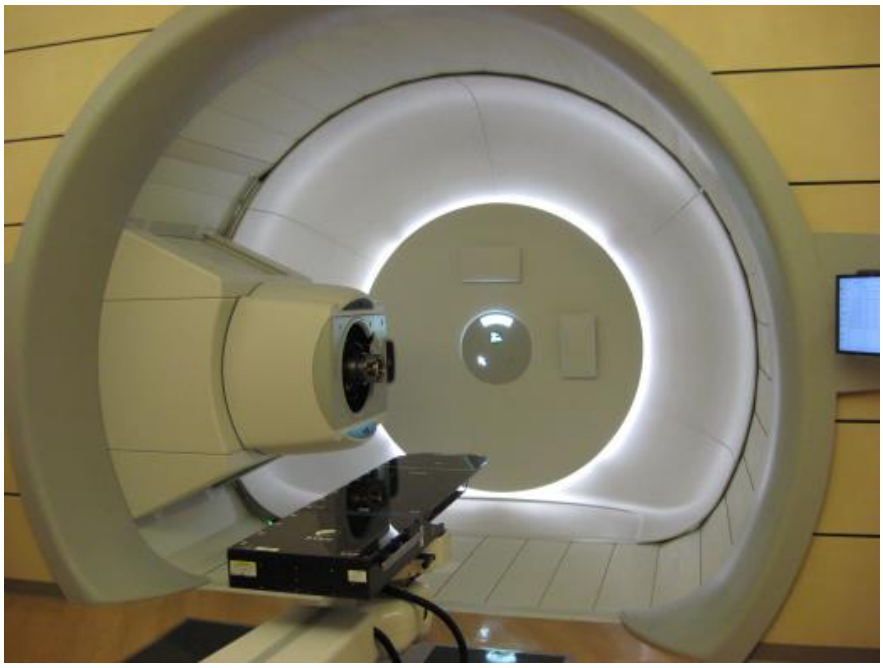


2. Proton Beam Therapy: What Patients Can Expect

Following an initial consultation with the treatment team, patients are then scheduled for a pretreatment planning and simulation session. At this session, any required immobilization devices are provided. These devices are customized to the patient and to the site of PBT treatment. The skin is also marked to identify the site of beam entry. Treatment simulation is performed with the patient immobilized, using one of several imaging systems to develop a precise treatment plan—computed tomography (CT), magnetic resonance imaging (MRI), and/or positron emission tomography (PET).

Proton treatments themselves are typically delivered in daily fractions (Monday through Friday). Each treatment session may take 15-60 minutes, depending on the type and location of the tumor. The total duration of the treatment course also will vary by type and location of the tumor, and may last up to 8 weeks. A depiction of a typical PBT treatment room can be found in Figure 3 below.

Figure 3. Proton beam therapy treatment room.



Source: ProCure Proton Therapy Centers. http://www.procure.com/Portals/1/Media/Gantry-New_1_display.jpg

Potential systemic side effects of any course of PBT include fatigue, skin irritation, and hair loss. Other side effects vary by type of condition. For example, PBT for prostate cancer may be associated with bladder and bowel dysfunction as well as sexual side effects. The risks of PBT in breast cancer, on the other hand, include cardiotoxicity and pneumonitis (inflammation of lung tissue). Finally, as previously mentioned, all forms of radiotherapy including PBT pose a risk of secondary malignancy.

3. Clinical Guidelines and Training Standards

Major guideline statements as well as competency and/or accreditation standards regarding proton beam therapy can be found in the sections that follow below. Documents are organized by the organization or association.

National Comprehensive Cancer Network (NCCN) (2013 – 2014)

http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#site

PBT is considered appropriate for use in the treatment of non-small-cell lung cancer (NSCLC). For unresectable high- and low-grade chondrosarcomas of the skull base and axial skeleton, PBT may be indicated to allow for high-dose treatment. PBT may be appropriate for patients with Hodgkin and Non-Hodgkin lymphoma as well as soft tissue sarcomas; however, long-term studies are necessary to confirm benefits and harms.

Currently, PBT is not recommended for use in prostate cancer, as superior or equivalent effects have not been demonstrated in comparison to conventional external-beam therapy. For ethmoid and maxillary sinus tumors, PBT is an investigative therapeutic technique only.

Guidelines for treatment options in ocular tumors are under development. No other cancer types of interest for this review are described in NCCN guidelines.

American Society for Radiation Oncology (ASTRO) (2013)

https://www.astro.org/Practice-Management/Reimbursement/Proton-Beam-Therapy.aspx
http://www.choosingwisely.org/doctor-patient-lists/american-society-for-radiation-oncology/

In a position statement, ASTRO concludes that the evidence supporting the use of PBT in prostate cancer continues to develop and define its role among current alternate treatment modalities. ASTRO strongly supports the provision of coverage with evidence development to evaluate the comparative effectiveness of PBT relative to other options including IMRT and brachytherapy.

As part of the Choosing Wisely® campaign, ASTRO provided a list of items that physicians and patients should discuss, including the topic of PBT, listed below:

“Don’t routinely recommend proton beam therapy for prostate cancer outside of a prospective clinical trial or registry.”

American College of Radiology (ACR) (2011-2013)

http://www.acr.org/Quality-Safety/Appropriateness-Criteria

The ACR Appropriateness Criteria® consider PBT for treatment planning in T1 and T2 prostate cancer to be appropriate but with lower ratings than for IMRT (6-7 versus 8-9, based on a 1-9 scale). PBT-based treatment plans are considered inappropriate (rated 1-2) in spinal and non-spinal bone metastases, and for NSCLC patients with poor performance status or requirements for palliative treatment. The use of PBT as boost therapy in cervical cancer is not considered to be appropriate by the ACR. The ACR appropriateness criteria do not evaluate PBT in the treatment of other cancers or noncancerous conditions.

American Cancer Society (ACS) (2013)

In a detailed patient guide, the ACS concludes that use of protons in prostate cancer may theoretically cause less damage to normal tissue surrounding the area of focus, but no current studies demonstrate the advantages of PBT over photon therapy. More comparative studies are necessary to evaluate the outcomes between the different modalities, with identification of the appropriate therapy for different kinds of cancer.

http://www.cancer.org/cancer/prostatecancer/detailedguide/prostate-cancer-treating-radiation-therapy
http://www.cancer.org/treatment/treatmentsandsideeffects/treatmenttypes/radiation/radiationtherapyprinciples/radiation-therapy-principles-how-is-radiation-given-external-beam-rad

Alberta Health Services (2013)

http://www.albertahealthservices.ca/hp/if-hp-cancer-guide-rt002-proton-beam-RT.pdf

PBT is recommended as a therapeutic option in patients with ocular melanoma, CNS lesions (including craniopharyngioma, germ cell tumors and low-grade gliomas), sarcomas (including chordoma and chondrosarcoma), and benign conditions such as arteriovenous malformations (AVMs) and meningiomas. Additional pediatric conditions that may be considered for PBT are ependymomas, rhabdomyosarcoma, Ewing's sarcoma, pineal tumors, and patients requiring craniospinal irradiation. Treatment with PBT for adults with acoustic neuromas, and paranasal sinus and nasal cavity tumors is recommended, as well as for lymphoma in patients less than 30 years of age. PBT is not recommended for the treatment of prostate cancer, NSCLC or other lymphomas.

Training Standards

In documents published by the ACR, and in joint publications with ASTRO and the American Association of Physicists in Medicine (AAPM), qualifications for radiation oncologists and qualified medical physicists are specified. Specific criteria are described below:

- Radiation oncologist
  - certification in Radiology by the American Board of Radiology (ABR); or
  - certification in Radiation Oncology or Therapeutic Radiology by the ABR, the American Osteopathic Board of Radiology, the Royal College of Physicians and Surgeons of Canada (RCPSC) or the Collège des Médecins du Québec; or
  - satisfactory completion of a radiation oncology residency program approved by the American Council of Graduate Medicine Education, the RCPSC, the Collège des Médecins du Québec or the American Osteopathic Association; and
  - specific training in proton therapy; and
  - completion of continuing medical education

- Qualified medical physicist
  - certification in Therapeutic Medical Physics by the ABR, the Canadian College of Physicists in Medicine, or the American Board of Medical Physics; and
  - meet state/local radiation control agency qualifications to practice radiation oncology physics and/or provide oversight of a facility; and
  - specific training in proton therapy including treatment planning, quality assurance and equipment configuration; and
  - completion of continuing medical education

http://www.acr.org/~/media/ACR/Documents/PGTS/guidelines/Radiation_Oncology.pdf
http://www.acr.org/~/media/ACR/Documents/PGTS/guidelines/Rad_Onc_Proton_Therapy.pdf
http://www.acr.org/~/media/ACR/Documents/PGTS/standards/ProtonTherapy.pdf

ProCure, a company that develops and manages proton therapy centers in the U.S., operates a Training and Development Center in Bloomington, IN. Clinical and technical training programs focused on proton therapy are offered for radiation oncologists, medical physicists, dosimetrists, radiation therapists and other support staff.

http://www.procure.com/Media/SeattleCenterMedia/ProCureTrainingandDevelopmentCenter.aspx

4. Medicare and Representative Private Insurer Coverage Policies

Centers for Medicare and Medicaid Services (CMS)

Local Coverage Determination (LCD)

While there is no current National Coverage Determination (NCD) for PBT, an LCD involving Washington State provides coverage of PBT for treatment with curative intent or for advanced disease (if life expectancy is greater than two years) for the following indications (Group 1):

- Unresectable benign or malignant tumors of the CNS, including glioblastoma, acoustic neuroma and arteriovenous malformations
- Intraocular melanomas
- Pituitary neoplasms
- Chordomas and chondrosarcomas
- Advanced, unresectable tumors of the head and neck
- Malignant tumors of the paranasal and other accessory sinuses
- Unresectable retroperitoneal sarcoma
- Solid tumors in children

Coverage of PBT is provided for the following investigational conditions (Group 2) as long as patients are enrolled in a clinical trial or registry:

- Unresectable lung cancers, upper abdominal cancers, and left breast tumors
- Advanced, unresectable pelvic tumors, pancreatic and adrenal tumors
- Skin cancer with nerve innervation of the skull base
- Unresectable lesions of the liver, biliary tract, anal canal and rectum
- Non-metastatic prostate cancer, with documented clinical staging and demonstration of clinical necessity of PBT

Representative Regional Private Insurer Policies

The Regence Group

http://blue.regence.com/trgmedpol/medicine/med49.pdf

The Regence Group provides coverage of PBT for primary therapy of uveal melanoma, postoperative therapy in patients with non-metastatic chordoma or low-grade (I or II) chondrosarcoma, and treatment of CNS tumors and retinoblastoma in pediatric patients (<21 years). PBT is considered investigational in the treatment of other benign and malignant conditions including acoustic neuroma, brain tumors, breast tumors, head and neck tumors (other than skull-base), olfactory neuroblastoma, and primary or

metastatic disease in solid organs. PBT is not considered medically necessary for the treatment of clinically localized prostate cancer.

Premera Blue Cross
https://www.premera.com/medicalpolicies/CMI_056943.htm

Premera provides coverage of PBT for primary therapy of uveal melanoma, postoperative therapy in patients with non-metastatic chordoma or low-grade (I or II) chondrosarcoma, and treatment of CNS tumors and retinoblastoma in pediatric patients (<21 years). Use of PBT for all other conditions is considered investigational, including NSCLC. PBT is not considered medically necessary for the treatment of clinically localized prostate cancer.

Blue Shield of California
https://www.blueshieldca.com/provider/content_assets/documents/download/public/bscpolicy/ChrgPart_RadThpy.pdf

Blue Shield of California provides coverage of PBT for primary therapy of uveal melanoma, postoperative therapy in patients with non-metastatic chordoma or low-grade (I or II) chondrosarcoma, and treatment of CNS tumors and retinoblastoma in pediatric patients. Use of PBT for all other conditions is considered investigational, including NSCLC. Blue Shield will provide coverage of 3D-CRT or IMRT for clinically localized prostate cancer, but does not cover PBT, as it is not considered to be cost-effective for this condition.

Representative National Private Insurer Policies

Aetna
http://www.aetna.com/cpb/medical/data/200_299/0270.html

Aetna considers the use of PBT to be medically necessary in the treatment of uveal melanomas, skull-base chordomas or chondrosarcomas, CNS lesions adjacent to critical structures, pediatric malignancies (≤21 years), pituitary neoplasms and retroperitoneal soft tissue sarcomas. PBT is not considered to be medically necessary in clinically-localized prostate cancer as its effectiveness has not been proven over radiation alternatives. PBT is considered investigational in the treatment of all other conditions including lung cancer.

Anthem Blue Cross Blue Shield
http://www.anthem.com/medicalpolicies/policies/mp_pw_a053258.htm
Anthem provides coverage of PBT for primary therapy of uveal melanoma, postoperative therapy in patients with non-metastatic chordoma or low-grade (I or II) chondrosarcoma, CNS lesions adjacent to critical structures, and pituitary adenomas and intracranical arteriovenous malformations lacking

alternate treatment options. PBT is covered as initial monotherapy in the treatment of localized prostate cancer. The use of PBT is considered investigational and not medically necessary in all other conditions.

Humana
http://apps.humana.com/tad/tad_new/Search.aspx?searchtype=beginswith&docbegin=P&policyType=medical

Humana provides coverage of PBT in the treatment of uveal melanoma that is not amenable to other treatment options and inoperable intracranial arteriovenous malformations. PBT may be used to treat tumors close to vital structures of the brain including CNS tumors, chordomas, meningiomas and pituitary tumors. PBT may be medically necessary for treatment of prostate cancer in patients with comorbid inflammatory bowel disease or with a history of pelvic radiation therapy.

UnitedHealthcare
https://www.unitedhealthcareonline.com/ccmcontent/ProviderII/UHC/en-US/Assets/ProviderStaticFiles/ProviderStaticFilesPdf/Tools%20and%20Resources/Policies%20and%20Protocols/Medical%20Policies/Medical%20Policies/Proton_Beam_Radiation_Therapy.pdf

UnitedHealthcare considers PBT to be preferential treatment for uveal melanomas, primary intracranial and skull base tumors, spinal cord tumors and intracranial arteriovenous malformations. PBT is not covered for other indications, including NSCLC and prostate cancer.

5. Previous Health Technology Assessments

Recent technology assessments focusing on the use of PBT were identified from national and international organizations as described below.

Agency for Healthcare Research and Quality (AHRQ)

Comparative Effectiveness of Therapies for Clinically Localized Prostate Cancer: An Update of a 2008 Comparative Effectiveness Review (draft – 2013)
http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=1434

Overall, the evidence supporting the comparative effectiveness of external beam radiation therapy for the treatment of prostate cancer remains inadequate. Contemporary RCTs are important for the evaluation of benefits and harms among the available treatment modalities, including PBT.

Local Therapies for Unresectable Primary Hepatocellular Carcinoma (2013)
http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=1511

Moderate strength of evidence was found to support better survival in patients undergoing radiofrequency ablation compared to percutaneous injections. Evidence for the comparative effectiveness of other local therapies is insufficient, and no studies evaluating PBT were included in the assessment.

Local Nonsurgical Therapies for Stage I and Symptomatic Obstructive Non-Small-Cell Lung Cancer (2013)
http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=1532

Data supporting the use of PBT in medically operable and unresectable stage I NSCLC were insufficient to evaluate the comparative effectiveness of treatment. Future clinical comparative studies are necessary to determine appropriate localized therapy in this patient population.

Comparative Effectiveness and Safety of Radiotherapy Treatments for Head and Neck Cancer (2010)
http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=1766

No comparative data evaluating PBT and alternate therapies were identified for the treatment of head and neck cancers. The evidence is insufficient to draw conclusions about the benefits and harms of PBT.

Particle Beam Radiation Therapies for Cancer (2009)
http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=174

Overall, charged particle therapy (including PBT) did not lead to significantly improved patient outcomes compared to alternate treatment modalities. RCTs and non-randomized comparative studies with appropriate statistical adjustment are important to assess the comparative benefits and harms of charged particle therapy with other treatments. Further research regarding treatment planning and therapy delivery to inform treatment protocols is also necessary.

BlueCross BlueShield Technology Assessment Center (BCBS-TEC)

Proton Beam Therapy for Non-Small-Cell Lung Cancer (2011)
http://www.bcbs.com/blueresources/tec/press/proton-beam-therapy-for.html

Overall, the data were insufficient to compare PBT to stereotactic body radiotherapy (SBRT) in the treatment of NSCLC. With only case series data identified, the comparative effectiveness of PBT is unknown.

Proton Beam Therapy for Prostate Cancer (2011)
http://www.bcbs.com/blueresources/tec/press/proton-beam-therapy-for-1.html

BCBS-TEC found inadequate evidence to evaluate the comparative effectiveness of PBT and/or photon therapy compared to alternate treatment modalities. Based on the paucity of available data, the use of PBT alone or with photon therapy did not meet the TEC criteria.

California Technology Assessment Forum (CTAF)

Proton Therapy for Prostate Cancer (2012)
http://www.ctaf.org/assessments/proton-beam-therapy-prostate-cancer

CTAF concluded that while PBT provided a net benefit in the treatment of prostate cancer, its comparative benefit to alternate treatment modalities has not been established. Its role as a therapeutic option for localized prostate cancer remains uncertain with respect to safety, efficacy and improvement in patient outcomes.

Institute for Clinical and Economic Review

Brachytherapy & Proton Beam Therapy for Treatment of Clinically-localized, Low-risk Prostate Cancer (2008)
http://www.icer-review.org/bt-pbt/

At the time of its review, ICER determined that the data supporting the comparative clinical effectiveness of PBT versus alternative management options in clinically-localized, low-risk prostate cancer were insufficient, and the comparative value of PBT was low.

National Institute for Health and Care Excellence (NICE)

Currently, NICE has not produced any guidance on the use of PBT in the treatment of cancers, and patients residing in the UK travel abroad to obtain treatment. Utilizing a specialized program, the National Health Service (NHS) evaluates and facilitates the use of PBT for approved patients overseas. The Department of Health recently announced plans for the construction of two proton beam centers in the UK, with scheduled completion by 2017.

6. Ongoing Clinical Studies

Information on ongoing clinical studies that have been submitted to the U.S. National Institutes of Health's registry of publicly- and privately-supported studies (www.clinicaltrials.gov) is presented in the table below and on the following pages. We focused on randomized controlled trials comparing proton beam therapy alone to an alternate treatment modality with a projected study enrollment of more than 50 patients. We concentrated on trials evaluating the various conditions that are the focal point of this review, and excluded comparative studies of carbon ion therapy, as this treatment modality is not currently available in the U.S.

Title/ Trial Sponsor	Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Date
Image-guided adaptive conformal photon versus proton therapy (MD Anderson Cancer Center) NCT00915005	RCT	PBT (74 Gy) PBT (66 Gy) Photon therapy	• n=250 • 18-85 years • Unresected, locoregionally advanced NSCLC (stage II-IIIb) w/out evidence of hematogenous metastases • Suitable for concurrent chemoradiation therapy • FEV1 ≥ 1 liter	Tumor recurrence, evaluated 4-8 weeks after treatment, then every 3-4 months for 3 years	June 2015
Proton therapy vs. IMRT for low or intermediate risk prostate cancer (PARTIQoL) (Massachusetts General Hospital) NCT01617161	RCT	PBT IMRT	• n=400 • ≥18 years • Histologically confirmed adenocarcinoma of the prostate • Clinical stages T1c-T2b	Reduction in mean EPIC bowel scores at 24 months	January 2016
Randomized comparison of proton and carbon ion radiotherapy w/advanced photon radiotherapy in skull base meningiomas: the PINOCCHIO Trial (University Hospital Heidelberg) NCT01795300	RCT	PBT Carbon ion therapy Hypo-fractionated photon therapy Conventional photon therapy	• n=80 • ≥18 years • Histologically or imaging confirmed skull base meningioma • Macroscopic tumor, Simpson grade 4 or 5 • Karnofsky score ≥60	Toxicity (graded by CTCAE) at 1 year	February 2016

Title/ Trial Sponsor	Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Date
Proton beam radiotherapy plus sorafenib versus sorafenib for patients w/hepatocellular carcinoma exceeding San Francisco criteria (Loma Linda University) NCT01141478	RCT	PBT + sorafenib Sorafenib	• n=220 • 18-80 years • Tumor burden exceeds San Francisco criteria	Overall survival, followed on average for 5 years	June 2016
Stereotactic body radiotherapy (SBRT) versus stereotactic proton therapy (SBPT) (MD Anderson Cancer Center) NCT01511081	RCT	SBPT SBRT	• n=120 • ≥18 years • Histological confirmation or clinically diagnosed primary NSCLC • Centrally located stage I or selective stage II primary tumors • Isolated recurrent disease • Zubrod status = 0-2	Therapy-related toxicities (including radiation-induced pneumonitis/ fibrosis/fistula, esophagitis/ stricture/fistul a	August 2016
Glioblastoma multiforme (GBM) proton vs. IMRT (MD Anderson Cancer Center) NCT01854554	RCT	IMPT IMRT	• n=80 • ≥18 years • Histological diagnosis of glioblastoma or gliosarcoma (WHO grade IV) adapted RPA class III, IV or V • Mini Mental Status Exam score ≥21 • Karnofsky score ≥70	Time to cognitive failure at 4 months	May 2017
Proton beam therapy (PBT) versus intensity-modulated radiation therapy (IMRT) trial (MD Anderson Cancer Center) NCT01512589	RCT	PBT IMRT	• n=180 • ≥18 years • Histologically confirmed adenocarcinoma or squamous cell carcinoma of the cervical or thoracic esophagus or gastroesophageal junction or cardia of stomach • Karnofsky score ≥60 • ECOG criteria = 0, 1, or 2	• Progression-free survival at 6 weeks • Total toxicity burden (composite of serious adverse events and postoperative complications) at 12 months	April 2018

Title/ Trial Sponsor	Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Date
Comparison between radiofrequency ablation and hypofractionated proton beam radiation for recurrent/residual HCC (National Cancer Center, Korea) NCT01963429	RCT	PBT RFA	• n=144 • ≥18 years • HCC patients w/recurrent or residual tumors after other treatments • No evidence of extrahepatic metastasis • Largest tumor diameter <3cm w/≤2 tumors • No previous RT to target tumors • Child-Pugh score ≤7 • ECOG criteria = 0, 1, or 2	Local progression-free survival up to 2 years	December 2018
Comparing photon therapy to proton therapy to treat patients w/lung cancer (Radiation Therapy Oncology Group) NCT01993810	RCT	PBT + chemotherapy Photon therapy + chemotherapy	• n=560 • ≥18 years • Histologically or cytologically proven NSCLC • Patients w/non-operable disease or refuse surgery • Clinical stage TII, TIIIA, TIIIB • Zubrod status = 0-1 • FEV1 ≥ 1 liter	Overall survival at last follow-up	December 2020
Intensity-modulated proton beam therapy (IMPT) versus intensity-modulated photon therapy (IMRT) (MD Anderson Cancer Center) NCT01893307	RCT	IMPT IMRT	• n=360 • ≥18 years • Histologically documented squamous cell carcinoma of the oropharynx • ECOG criteria = 0, 1, or 2	Rates and severity of late grade 3-5 toxicity between IMPT and IMRT, evaluated 90 days after treatment	August 2023

CTCAE: Common Terminology Criteria for Adverse Events; ECOG: Eastern Cooperative Oncology Group; EPIC: Expanded Prostate Cancer Index; FEV1: forced expiratory volume in 1 second; HCC: hepatocellular carcinoma; IMPT: intensity-modulated proton therapy; IMRT: intensity-modulated radiation therapy; NSCLC: non-small cell lung cancer; PBT: proton beam therapy; PSA: prostate specific antigen; RCT: randomized controlled trial; RFA: radiofrequency ablation; RPA: recursive partitioning analysis; RT: radiation therapy; SBPT: stereotactic body proton therapy; SBRT: stereotactic radiation therapy; WHO: World Health Organization

7. Methods

Objectives

The primary objectives of the systematic review were to:

- Evaluate and compare the published evidence on the impact of proton beam therapy relative to other radiotherapy modalities and non-radiation treatment alternatives on survival, control of cancerous and noncancerous tumors, health-related quality of life, and other patient outcomes for populations with both primary and recurrent disease;

- Evaluate and compare the harms of proton beam therapy and treatment alternatives, including generalized effects (e.g., fatigue), specific toxicities relative to treatment location (e.g., bladder and bowel dysfunction in prostate cancer), and secondary malignancy;

- Examine the differential effectiveness and safety of proton beam therapy according to patient subgroups of interest, including age, sex, race/ethnicity, disability, presence of comorbidities, tumor characteristics (e.g., tumor volume and location, proliferative status, genetic variation) and treatment protocol (e.g., dose, duration, timing of intervention, use of concomitant therapy); and

- Assess the published evidence on costs and cost-effectiveness of proton beam therapy in multiple patient populations.

The target populations for this appraisal included patients who received proton beam therapy (PBT) for treatment of primary or recurrent disease. A total of 19 categories (16 cancer types, three types of noncancerous tumors) of disease were selected for this review (see "Patient Populations" on page 27). We did not evaluate the use of PBT for palliative purposes only, as the expert guidance we received suggested that its use for this purpose is currently minimal.

We focused primary attention on randomized controlled trials and comparative cohort studies that involved explicit comparisons of PBT to one or more treatment alternatives ***and*** measures of clinical effectiveness and/or harm. For the purposes of this review, we distinguished between comparative cohort studies that drew patients from a common pool of subjects and those that involved comparisons of non-contemporaneous case series (i.e., comparison of a current series to a series from another published study or historical control group), given the increased likelihood of selection and/or measurement biases with the latter design. Case series of PBT alone were abstracted and summarized in evidence tables, but were not the primary focus of evaluation for each key question.

Importantly, studies that involved comparisons of treatment planning algorithms or modeled simulations of outcomes were not explicitly abstracted. As noted in the Background section to this document, there are significant uncertainties that remain with the delivery of proton beams for a variety of tumor types and locations, including physical uncertainty at the end of the beam range and penumbra effects, as well as concerns regarding the effects of neutron radiation produced by PBT and a lack of precise understanding of PBT's radiobiological effectiveness for all tumor types and tissue depths. Because of these concerns, we felt that any estimation of the clinical significance of PBT therapy must come from studies in which actual patient outcomes were measured. We do recognize and make explicit mention, however, of clinical areas in which simulation studies are likely to remain the cornerstone of evidence, given logistical and ethical challenges posed by conducting clinical trials in these areas (e.g., pediatric tumors, very rare cancers). One notable exception to this rule was the use of modeling to answer questions of cost and/or cost-effectiveness, as clinical outcomes in these studies were typically derived from actual clinical outcome data from other published studies.

Uses of PBT and relevant comparators are described in detail in the sections that follow. Of note, while PBT is considered part of a "family" of heavy ion therapies that includes carbon-ion, neon-ion, and other approaches, it is the only heavy ion therapy currently in active use in the U.S. Studies that focused on these other heavy-ion therapies were therefore excluded (unless they involved comparisons to PBT).

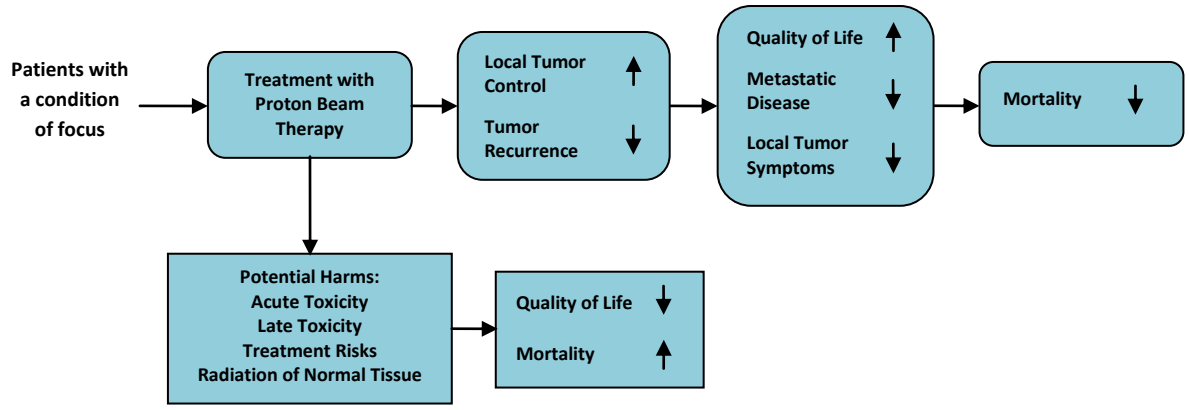
While all potential harms of PBT and its comparators were recorded, the primary focus was on adverse effects requiring medical attention (where such designations were available). Radiation-related toxicities may have also been labeled "early" (i.e., typically occurring within 90 days of treatment) or "late" (occurring >90 days after treatment or lasting longer than 90 days). In addition, because the risk of secondary malignancy is felt to be of great interest because of its link to radiation of normal tissues, these outcomes were abstracted when reported.

Finally, published studies of the economic impact of PBT are summarized in response to Key Question 5 regarding the costs and cost-effectiveness of PBT. In addition, a straightforward budget impact analysis is included that employs data from the HCA to estimate the effects of replacing existing radiation treatments with PBT for certain conditions.

Analytic Framework

The analytic framework for this review is shown in the Figure on the following page. Note that the figure is intended to convey the conceptual links involved in evaluating outcomes of PBT and its alternatives, and is not intended to depict a clinical pathway through which all patients would flow.

Analytic Framework: Proton Beam Therapy



The available literature varies with respect to how directly the impact of PBT is measured. Some studies are randomized or observational comparisons focused directly on survival, tumor control, health-related quality of life, and long-term harms, while in other studies a series of conceptual links must be made between intermediate effectiveness measures (e.g., biochemical recurrence in prostate cancer) or measures of harm (e.g., early toxicity) and longer-term outcomes.

Patient Populations

The focus of this appraisal was on children and adults treated with PBT for a variety of conditions. The condition categories of interest are listed below, and included 16 cancer types and three types of noncancerous conditions as listed in Table 1 below.

Table 1. Conditions of interest for evidence review of proton beam therapy.

Condition Category	Specific Condition Types	
Cancer	Bone cancer	Lung cancer
	Brain, spinal, & paraspinal tumors	Lymphomas
	Breast cancer	Ocular tumors
	Esophageal cancer	Pediatric cancers
	Gastrointestinal cancers	Prostate cancer
	Gynecologic cancers	Sarcomas
	Head & neck cancers	Seminoma
	Liver cancer	Thymoma
Noncancerous Conditions	Arteriovenous malformations	Other benign tumors
	Hemangiomas	

As mentioned previously, studies of the use of PBT to treat primary and recurrent cancers were included in the project scope, while studies of PBT's use in palliative care were not. All levels of disease within each condition type were considered for this evaluation.

Certain patient subpopulations were also identified as of interest in evaluating whether PBT's clinical effects and/or harms differed in these groups. These included subpopulations defined by demographic characteristics (e.g., age, sex, race/ethnicity), disability, presence of comorbidities, tumor characteristics (e.g., tumor volume and location, proliferative status, genetic variation) and treatment protocol (e.g., dose, duration, timing of intervention, use of concomitant therapy).

Intervention

For in-scope uses, all approaches to PBT were considered, including monotherapy, use of PBT as a "boost" mechanism to conventional radiation, and combination therapy with other treatment modalities such as chemotherapy and surgery. Note that comparisons of different doses of PBT were included as part of our evaluation of subgroup data (Key Question 4). As mentioned previously, studies of PBT's use for curative intent as well as its deployment for "salvage" purposes (i.e., failure of initial therapy or disease recurrence) were considered relevant.

We placed no limitations on the use of PBT by manufacturer, software system, or treatment planning protocol. However, where available, both dose and duration of therapy were recorded.

Comparators

All relevant comparators of interest were included in this evaluation. Primary comparators included other radiation alternatives such as intensity-modulated radiation therapy (IMRT), stereotactic radiation techniques and other external beam therapies, and brachytherapy. Other treatment alternatives were specific to each condition type treated, and may have included chemotherapy, surgical procedures, and other devices (e.g., laser therapy for ocular tumors).

Outcomes

A variety of patient clinical outcomes were assessed as measures of effectiveness for this evaluation, as listed below:

- Disease-free and/or overall survival
- Disease-related and/or all-cause mortality
- Measures of tumor regression and control
- Incidence of metastases

- Tumor recurrence (including intermediate measures such as biochemical recurrence)
- Health-related quality of life (HrQoL)
- Requirements for subsequent therapy

Where possible, our preference was for techniques of survival or actuarial analysis (e.g., Kaplan-Meier, Cox proportional hazards) to measure survival and/or mortality outcomes. We accepted unadjusted rates of these measures if that was the only method used to report them.

We also captured other outcomes specific to particular conditions. Examples included visual acuity for ocular tumors and shunt requirements for arteriovenous malformations.

Information on the costs and cost-effectiveness of PBT relative to treatment alternatives also was collected from available studies, including initial costs of treatment as well as downstream costs such as management of toxicity and long-term morbidity, requirements for subsequent therapy, and work or productivity loss.

Potential Harms

While the focus of attention was on adverse effects requiring medical attention, all available data on treatment-related harms were abstracted where available. These included generalized effects from treatment (e.g., fatigue, erythema) as well as more localized toxicities specific to each condition (e.g., urinary incontinence in prostate cancer, pulmonary toxicity in lung or breast cancer). Where reported as such, toxicities were separated into early (≤90 days following treatment) or late (>90 days following treatment) effects. Relevant grades on standardized toxicity scales such as those promulgated by the Radiation Therapy Oncology Group (RTOG) and the European Organization for the Research and Treatment of Cancer (EORTC) were used to determine which toxicities would require medical attention.

We also collected information on secondary malignancy risk due to treatment radiation exposure where reported. Because PBT and other radiotherapy alternatives involve delivery of a substantial radiation dose, there is concern that such exposure could lead to development of secondary malignancy in the treated field (or even outside of it), particularly in younger patients or those who have a life expectancy of 15 years or more (Bostrom, 2007).

There is considerable controversy on extrapolating cancer death risks from those experienced by adults with high radiation exposure at Hiroshima and Nagasaki to the potential risks at much lower radiation doses. Linear extrapolation has been the approach generally used, although the uncertainties inherent in this approach become progressively greater at lower doses. Also controversial is whether a natural threshold of radiation exposure exists before excess risk from specific exposures can be realized. The current guidance from a variety of regulatory authorities is that no threshold exists, but this has also been intensely debated. On the other hand, exposure to ionizing radiation has increased; a recent estimate indicates that the average per capita annual exposure in the U.S. has risen from approximately

3.6 milliSieverts (mSv) in the early 1980s to 6.25 mSv in 2006, an increase that has been attributed almost entirely to medical imaging (Schauer, 2009).

Historically, the literature on the association of radiotherapy techniques and secondary cancer risk was limited to registry-based studies or dose extrapolations combining information on planned dose with risk coefficients from standards organizations such as the National Council of Radiation Protection and Measurements (NRCP). These studies have not provided definitive answers, however, due to concerns regarding selection bias, changes in technology over long periods of follow-up, and sensitivity to assumptions made in dose-extrapolation models. As a result, there is no consensus regarding the long-term effects of radiation received during PBT or radiation alternatives. We therefore opted to abstract effective radiation dose where reported, and to include explicit measures of the incidence of secondary malignancy where available.

Timeframe

Data on all relevant measures were abstracted at all relevant timepoints, regardless of study duration.

Study Designs

Data from both RCTs and selected types of observational studies were considered for measures of effectiveness. Observational studies of interest included those making explicit prospective or retrospective comparisons of PBT to one or more treatment alternatives within the same setting as well as comparisons of non-contemporaneous series of PBT and alternative therapies from different settings. Case series of PBT were abstracted and summarized in evidence tables, but were not a primary focus of the review due to their non-comparative nature.

No limits were placed on study selection based on sample size, duration, location, or frequency of outcome measurement. As mentioned previously, studies that involved simulated outcomes only were not included in this review.

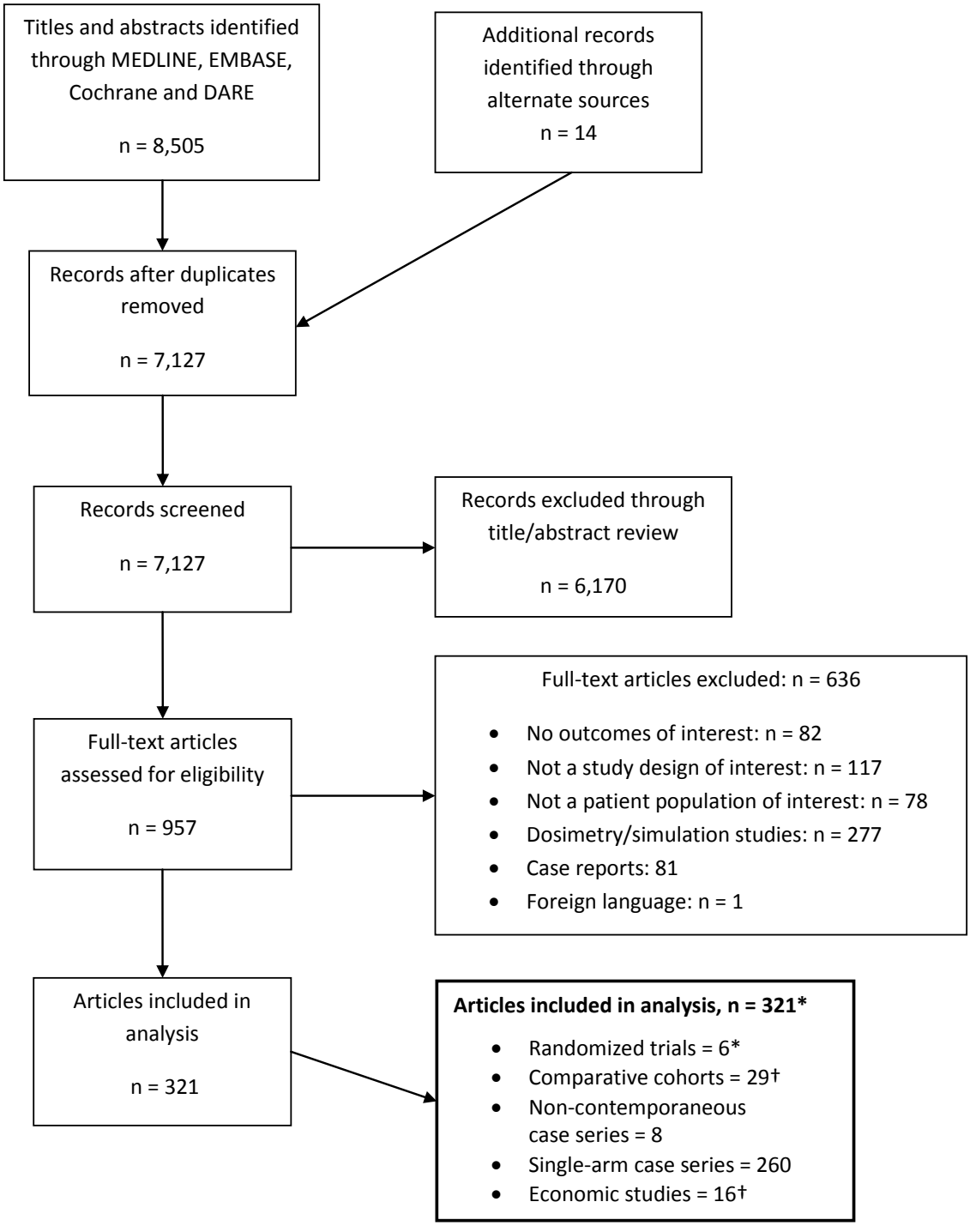
Literature Search and Retrieval

The general timeframe for literature search and retrieval was January 1990 – February 2014. We focused on English-language reports only. As noted previously, RCTs and comparative cohort studies were limited to those comparing PBT with alternative treatment strategies. The one exception was comparisons of different PBT dosing regimens, which were used to inform Key Question 4 (subgroups of interest).

The electronic databases we searched as part of the systematic review included MEDLINE, EMBASE, and *The Cochrane Library* (including the Database of Abstracts of Reviews of Effects [DARE]) for health technology assessments (HTAs), systematic reviews, and primary studies. Reference lists of all eligible studies were also searched and cross-referenced against public comments received by the HCA. The strategies used for MEDLINE, EMBASE, and *The Cochrane Library* are shown in Appendix B.

Studies were not further restricted by instrumentation, manufacturer, or testing protocol. Figure 4 on the following page shows a flow chart of the results of all searches for RCTs (n=6), comparative cohort studies (n=29), non-contemporaneous case series (n=8), and single case series (n=260).

Figure 4. PRISMA flow chart showing results of literature search.



* Nine studies evaluated six unique randomized trials.
† One study reported on clinical and economic outcomes.

Study Quality

We used criteria published by the U.S. Preventive Services Task Force to assess the quality of RCTs and comparative cohort studies, using the categories "good", "fair", or "poor". Guidance for quality rating using these criteria is presented below (AHRQ, 2008).

- ***Good:*** *Meets all criteria: Comparable groups are assembled initially and maintained throughout the study (follow-up at least 80 percent); reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention to confounders in analysis. In addition, for RCTs, intention to treat analysis is used.*

- ***Fair:*** *Studies will be graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for. Intention to treat analysis is done for RCTs.*

- ***Poor:*** *Studies will be graded "poor" if any of the following fatal flaws exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied at all equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, intention to treat analysis is lacking.*

Data from all retrieved studies were included in evidence tables regardless of study quality. However, the focus of attention in presentation of results was primarily on good- or fair-quality studies.

Study quality was not assessed for single-arm case series, as the focus of quality ratings was on the level of bias in assessing the *comparative* impact of PBT versus alternatives on measures of effectiveness and harm.

The overall strength of evidence for PBT use to treat each condition type was determined primarily on the number of good- or fair-quality comparative studies available for each condition type and key question, although the totality of evidence (including case series) was considered in situations where future comparative study was unlikely (e.g., pediatrics, rare cancers). We followed the methods of the U.S. Agency for Healthcare Research and Quality (AHRQ) in assigning strength of evidence as follows: ***Low, Moderate, High, and No Evidence*** (AHRQ, 2014)**.** A "no evidence" rating is made when no studies meeting entry criteria for the review are identified. While the remaining ratings are based on an overall value judgment, this is informed by assessment of the evidence across several domains, as listed below:

- *Risk of bias*: aspects of study design and conduct, control for confounding, etc.
- *Consistency*: direction and magnitude of findings, use of uniform outcome measures, etc.
- *Directness*: focus on most important clinical outcomes and/or comparisons to most relevant alternatives
- *Precision*: degree of certainty around estimates of treatment effect

Net Health Benefit

Because of the large number of conditions and comparators under study, a standardized system was used to describe our judgment of the overall net health benefit (that is, taking into account both clinical effectiveness and potential harms) of PBT in comparison to its major treatment alternatives. The five categories of net health benefit were derived from ICER's rating matrix for clinical effectiveness (Ollendorf, 2010), and are listed on the following page:

- **Superior**: Evidence suggests a moderate-to-large net health benefit vs. comparator(s)
- **Incremental**: Evidence suggests a small net health benefit vs. comparators(s)
- **Comparable:** Evidence suggest that, while there may be tradeoffs in effectiveness or harms, overall net health benefit is comparable vs. comparator(s)
- **Inferior:** Evidence suggests a negative net health benefit vs. comparator(s)
- **Insufficient:** Evidence is insufficient to determine the presence and magnitude of a potential net health benefit vs. comparators(s)

When the net health benefit was rated superior, incremental, comparable, or inferior, we have provided additional information on the specific comparisons of both clinical benefits and harms. For example, if we have given an overall rating of an incremental net health benefit, we give information on whether that rating was based on evidence demonstrating small increases in effectiveness with no difference in harms, or on evidence demonstrating equivalent effectiveness and a small reduction in harms.

Data Synthesis

Because of an expected paucity of RCT data within any single condition type, no attempt was made to quantitatively synthesize available evidence; all analyses were qualitative in nature only. Detailed evidence tables are presented in Appendices C, D and F for all key outcomes and study designs evaluated in this review.

8. Results

Evidence Quality

Our summary of the net health benefit of PBT vs. alternative treatments and the strength of available evidence on net health benefit, as well as an evaluation of consistency of these findings with clinical guideline statements and public/private coverage policy, can be found in Table 3 on page 37. Detailed descriptions of the evidence base for each key question can be found in the sections that follow. The level of comparative evidence was extremely limited for certain conditions and entirely absent for others. We identified a total of six RCTs and 37 nonrandomized comparative studies across all 19 condition types. A detailed listing of RCTs can be found in Table 2 on the following page. Importantly, five of the six RCTs involved different treatment protocols for PBT and had no other comparison groups; while these are included for completeness, primary attention was paid to studies (RCTs and otherwise) that compared PBT to an alternative form of treatment.

Most of the comparative studies identified also had major quality concerns. For example, nearly all non-randomized comparative studies were retrospective in nature, and many involved comparisons of a PBT cohort to a non-contemporaneous group receiving alternative therapy. Major differences in patient demographics and baseline clinical characteristics as well as duration of follow-up were often noted between groups. Of the 6 RCTs identified, 1, 4, and 1 were judged to be of good, fair, and poor quality respectively. Corresponding figures for non-randomized comparative studies were 1, 20, and 16.

We also examined the possibility of publication bias by cross-referencing the results of our literature search with a list of completed randomized controlled trials of PBT available on the U.S. National Institutes of Health's clinicaltrials.gov website. A single RCT was identified on clinicaltrials.gov (NCT00388804) that has not been published, a study comparing multiple radiation modalities (including PBT) with short-course androgen suppression therapy vs. PBT alone in men with intermediate-risk prostate cancer. The study was terminated due to slower-than-expected patient accrual.

As noted on Table 3, we judged PBT to have superior net health benefit for ocular tumors, and incremental net health benefit for adult brain/spinal tumors and pediatric cancers. We felt PBT to be comparable to alternative treatment options for patients with liver, lung, and prostate cancer as well as one noncancerous condition (hemangiomas). Importantly, however, the strength of evidence was low or moderate for all of these conditions. We determined the evidence base for all other condition types to be insufficient to determine net health benefit, including two of the four most prevalent cancers in the U.S.: breast and gastrointestinal (lung and prostate are the other two). Current authoritative guideline statements and coverage policies relevant to Washington State reflect these uncertainties through coverage restrictions or limitations on recommendations for use.

The lack of comparative data for rare and childhood cancers is not surprising, and in fact is considered appropriate by many (Macbeth, 2008). Because information from dosimetry, planning, and simulation studies indicates that the radiation dose from PBT would be consistently lower than other radiation modalities in children, and because of the increased sensitivity of children to *any* level of ionizing radiation in comparison to adults, many in the clinical community feel that there is not sufficient equipoise to ethically justify comparative study of PBT in pediatric populations (Efstathiou, 2013; Macbeth, 2008). It should be noted, however, that this opinion is not universal, and other commentators have noted that the clinical data accrued to date on PBT in pediatric cancers is lacking critical information on measures of long-term effectiveness and harm (De Ruysscher, 2012).
The situation is more complex with adult cancers, particularly those that are more prevalent. As mentioned in the Background, significant uncertainties remain regarding proton physics and the relative biological effectiveness of PBT in all tissues (Rana, 2013; Paganetti, 2002; Goitien, 2008). It is because of these unknowns that we opted in this review not to abstract information from dosimetry, planning, and simulation studies, as evidence on the clinical impact of these uncertainties can only be obtained by measuring patient outcomes.

Table 2. Randomized controlled trials of proton beam therapy.

Cancer Type (Author, Year)	Comparison	N	Measurement of Clinical Outcomes	Measurement of Harms
Prostate (Kim, 2011)	Dose/fractionation comparison	82	Yes	Yes
Prostate (Zietman, 2010)	Dose/fractionation comparison	391	Yes	Yes
Uveal melanoma (Gragoudas, 2000)	Dose/fractionation comparison	188	Yes	Yes
Skull-base chordoma and chondrosarcoma (Santoni, 1998)	Dose/fractionation comparison	96	No	Yes
Uveal melanoma (Desjardins, 2006)	PBT vs. PBT + TTT	151	No	Yes
Prostate (Shipley, 1995)	PBT + photon vs. Photon	202	Yes	Yes

PBT: proton beam therapy; TTT: transpupillary thermotherapy

Table 3. Summary table assessing strength of evidence, direction of benefit, and consistency with relevant guideline statements and coverage policy.

Condition	Incidence (per 100,000)	Net Health Benefit vs. Comparators	Type of Net Health Benefit	Strength of Evidence	Guideline Recommendations	Coverage Policies
Cancer						
Bone	1.3	Insufficient	---	+	M	M
Brain/spinal	9.6	Incremental	B: = H: ↓	+	U	U
Breast	97.7	Insufficient	---	o	NM	NR/NC
Esophageal	7.5	Insufficient	---	o	NM	NR/NC
GI	100.6	Insufficient	---	o	NM	NR/NC
Gynecologic	38.2	Insufficient	---	o	NM	NR/NC
Head/neck	17.2	Insufficient	---	+	NM	M
Liver	12.8	Comparable	B: = H: =	+	NM	M
Lung	95.0	Comparable	B: = H: =	++	M	M
Lymphomas	32.9	Insufficient	---	o	NR/NC	NR/NC
Ocular	1.2	Superior	B: ↑ H: ↓	++	U	U
Pediatric	9.1	Incremental	B: = H: ↓	++	U	U
Prostate	99.4	Comparable	B: = H: =	++	M	M
Sarcomas	4.8	Insufficient	---	o	NM	M
Seminoma	4.0	Insufficient	---	o	NM	NM
Thymoma	0.2	Insufficient	---	o	NM	NM
Noncancerous						
AVMs	1.0	Insufficient	---	o	NM	M
Hemangiomas	2.0	Comparable	B: = H: =	+	NM	NM
Other	2.0	Insufficient	---	o	NM	M

B: Benefits; H: Harms
Strength of Evidence: Low=+; Moderate=++; High=+++; No evidence=o
Legend: U=Universally recommended or covered; M=Mixed recommendations or coverage policies; NM=Not mentioned in guidelines or coverage policies; NR/NC=Not recommended or not covered

Impact of Proton Beam Therapy with Curative Intent on Patient Outcomes for Multiple Cancers and Noncancerous Conditions (KQ1)

Evidence on the effects of PBT with curative intent (i.e., as a primary therapeutic option) are summarized by condition in the sections that follow and presented in Appendices C, D, and F. As with all of the key questions, the primary focus was on active comparisons of PBT to one or more therapeutic alternatives, although findings from available case series are also summarized for each topic. Note that, given the paucity of comparative studies, *all* studies are summarized regardless of quality.

Cancers

Bone Tumors

We identified a single poor-quality retrospective comparative cohort study that evaluated PBT for primary and recurrent sacral chordomas in 27 patients. Among these patients 21 were treated with surgery and combination PBT /photon therapy (mean radiation dose: 72.8 Gray Equivalents [GyE]), in comparison to six patients who received PBT/photons alone (mean dose: 70.6 GyE) (Park, 2006). Two-thirds of patients in each group were male, but groups differed substantially in terms of age (mean of 68 years in the radiation-only group vs. 54 years in the radiation+surgery group) and duration of follow-up (mean of 5 and 8 years in the two groups). For patients with primary tumors, Kaplan-Meier estimates of local control, disease-free survival and overall survival exceeded 90% among those treated by surgery and radiation (n=14). Only two of the six patients with primary tumors received radiation alone, one of whom had local failure at four years, distant metastases at five years, and died at 5.5 years. (NOTE: see KQ2 on page 44 for discussion of results specific to recurrent cancers.)

Four case series were identified involving 166 patients treated for a variety of bone cancers (Chen, 2013; Ciernik, 2011; Staab, 2011; Hug, 1995). Overall survival ranged from 50-78% in these studies.

Brain, Spinal, and Paraspinal Tumors

We identified two poor-quality retrospective comparative cohort studies of primary PBT for brain, spinal, and paraspinal tumors. One was an evaluation of PBT (mean dose: 54.6 GyE) vs. photon therapy (mean dose: 52.9 Gy) in 40 adults (mean age: 32 years; 65% male) who received surgical and radiation treatment of medulloblastoma at MD Anderson Cancer Center (Brown, 2013). PBT patients were followed for a median of 2.2 years, while photon patients were followed for a median of nearly five years. 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 (Kahn, 2011) with either PBT (n=10) or IMRT (n=22). While explicit comparisons were made between groups, the PBT 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; dose was >50 GyE or Gy in approximately 75% of patients. While the crude mortality rate was lower in the PBT group (20% vs. 32% for IMRT, not tested), in multivariate analyses controlling for age, tumor pathology, and treatment modality, PBT was associated with significantly increased mortality risk (Hazard Ratio [HR]: 40.0, p=0.02). The rate of brain metastasis was numerically higher in the PBT group (10% vs. 5% for IMRT), but this was not statistically tested. Rates of local or regional recurrence did not differ between groups.

We identified six case series of brain, spinal, and other nervous system cancers (see Appendix F, Table 2 for specific citations). Five-year overall survival ranged from 23-100% depending on disease and stage.

Breast Cancer

We identified no comparative studies of the clinical effectiveness of primary PBT in breast cancer. We identified four case series of PBT in 112 patients with breast cancer (see Appendix F, Table 3 for specific citations). Overall survival ranged from 96-100% in these studies.

Esophageal Cancer

We identified no comparative studies of the clinical effectiveness of primary PBT in esophageal cancer. There were five PBT case series comprising 208 patients with esophageal cancer (see Appendix F, Table 4 for specific citations). Overall survival ranged from 21-100% depending on disease stage.

Gastrointestinal Cancers

We identified no comparative studies of the clinical effectiveness of primary PBT in gastrointestinal cancers. We identified four case series of PBT in 180 patients with gastrointestinal cancers (three of which were in pancreatic cancer, one in cholangiocarcinoma) (see Appendix F, Table 5 for specific citations). One-year survival ranged from 36-79% depending on disease location and stage.

Gynecologic Cancers

We identified no comparative studies of the clinical effectiveness of primary PBT in gynecologic cancers. Two gynecologic case series were identified in 40 patients (see Appendix F, Table 6 for specific citations). Overall survival ranged from 59-93% in these studies.

Head and Neck Cancers

We identified two poor-quality retrospective comparative cohorts of primary PBT in head and neck cancer. One was an evaluation of 33 patients treated with either PBT alone or PBT+photon therapy to a target dose of 76 Gy for a variety of head and neck malignancies in Japan (Tokuuye, 2004). Treatment groups differed substantially in terms of age (mean: 67 vs. 54 years for PBT and PBT+photon respectively), gender (82% vs. 44% male), and duration of follow-up (mean: 5.9 vs. 3.1 years). Numeric differences in favor of PBT+photon therapy were seen for local control, recurrence, and mortality, but these were not statistically tested, nor were multivariate adjustments made for differences between groups.

The other study was a very small (n=6) comparison of endoscopic resection followed by either PBT or IMRT as well as endoscopy alone in patients with malignant clival tumors (Solares, 2005). Limited description of the study suggests that PBT was used only in cases of residual disease, while it is unclear whether IMRT was also used in this manner or as an adjuvant modality. One of the IMRT patients died of causes unrelated to disease; no other deaths were reported.

A total of 27 PBT case series were identified that involved patients with head, neck, or skull base tumors (see Appendix F, Table 7 for specific citations). Five-year survival ranged widely by and even within cancer type; for example, survival ranged from 50-100% for skull base tumors.

Liver Cancer

We identified two fair-quality prospective comparative cohort studies from Japan with evidence of the clinical effectiveness of primary use of PBT in liver cancer. One was an evaluation of 35 patients with unresectable hepatocellular carcinoma (HCC) who were treated with PBT (mean dose: 76.5 GyE) either alone or in combination with chemotherapy and were followed for up to 4 years (Matsuzaki, 1995). While statistical testing was not performed, rates of local tumor control and the proportion of patients experiencing reductions in tumor volume were nearly identical between groups.

The other study was also prospective but compared PBT to another heavy-ion modality not in circulation in the U.S. (carbon ion). In this study, a fair-quality comparison of 350 patients (75% male; age ≥70: 50%) with HCC who received PBT (53-84 GyE) or carbon-ion (53-76 GyE) therapy and were followed for a median of 2.5 years (Komatsu, 2011), no statistically-significant differences were observed in 5-year Kaplan-Meier estimates of local control, no biological evidence of disease, or overall survival between treated groups.

We identified 21 case series focusing on PBT for the treatment of liver cancer (see Appendix F, Table 8 for specific citations), almost all of which were conducted in Japan. Five-year survival estimates ranged from 21-58% in these studies.

Lung Cancer

We identified three fair-quality comparative cohort studies examining the clinical effectiveness of PBT in lung cancer. Two studies retrospectively compared outcomes with PBT to those with IMRT or older three-dimensional conformal radiotherapy (3D-CRT) at MD Anderson Cancer Center (Lopez Guerra, 2012; Sejpal, 2011). The Lopez Guerra study involved 250 patients with non-small-cell lung cancer (NSCLC) (median age 71.5 years, 57% male) who were treated with 66 Gy of photons or 74 GyE of protons and followed for up to one year to assess a key measure of lung function known as diffusing capacity of lung for carbon monoxide (DLCO). While this measure did not differ between PBT and IMRT at 5-8 months after treatment, DLCO declined significantly more in the 3D-CRT group as compared to PBT after adjustment for pretreatment characteristics and other lung function measures (p=0.009).

The study by Sejpal and colleagues focused on survival in 202 patients (median age 64 years, 55% male) with locally-advanced, unresectable NSCLC who were followed for a median of 1.5 years and treated with 74 GyE of PBT or 63 Gy of either IMRT or 3D-CRT (Sejpal, 2011). Actuarial estimates of median overall survival were 24.4, 17.6, and 17.7 months for PBT, IMRT, and 3D-CRT respectively, although these differences were not statistically significant (p=0.1061).

A third study was a prospectively-measured cohort but, as with the study of liver cancer mentioned above, compared PBT to carbon ion therapy, evaluating 111 Japanese NSCLC patients (median age 76 years, 67% male) over a median of 3.5 years (Fujii, 2013). No statistically-significant differences between groups were observed in three-year actuarial estimates of local control, progression-free survival, or overall survival.

A total of 15 case series were identified with information on outcomes in patients with lung cancer (see Appendix F, Table 9 for study citations). Overall 2-year survival (the most common measured timepoint) ranged from 64-98% depending on cancer stage.

Lymphomas

We identified no comparative studies or case series focusing on the clinical effectiveness of primary PBT in lymphomas.

Ocular Tumors

In comparison to other cancer types, the evidence base for ocular tumors was relatively substantial. A total of seven comparative studies were identified of the clinical benefits of primary PBT in such cancers—a single RCT, four retrospective cohort studies, a comparison of a recent case series to the treatment groups from the RCT, and a comparison of noncontemporaneous case series. 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 (Desjardins, 2006). 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, poor-quality comparison of these findings to a separate series of patients undergoing PBT with endoresection of the scar (Cassoux, 2013), 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 (Mosci, 2012; Bellman, 2010; Seddon, 1990). PBT was associated with statistically-significant improvements in overall survival rates relative to enucleation at 2-5 years in two of these studies (Bellman, 2010; Seddon, 1990). 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 (n=1,051), but were nonsignificant at later timepoints (Seddon, 1990). The 5-year metastasis-free survival rate in the Bellman study (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 (Mosci, 2012). Metastasis-free survival also did not differ in Cox regression adjusting for age, sex, and tumor thickness.

Another fair-quality 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 (Voelter, 2008). Five-year overall survival rates did not statistically differ between groups on either an unadjusted or Cox regression-adjusted basis.

Finally, a poor-quality comparison of noncontemporaneous case series evaluated treatment with PBT + laser photocoagulation or PBT alone in 56 patients with choroidal melanoma (Char, 2003). At one year, there were no differences in visual acuity between groups.

A total of 28 case series were identified in ocular cancers with information on the effects of PBT treatment for primary tumors (see Appendix F, Table 11 for specific citations). Estimates of 5-year overall survival ranged from 69-100% in these studies.

Pediatric Cancers

We identified no comparative studies of the clinical effectiveness of primary PBT in pediatric cancers. A total of 35 case series were identified of PBT in a variety of childhood cancers (see Appendix F, Table 12 for specific citations). Overall survival ranged from 50-100% in these series at a variety of timepoints.

Prostate Cancer

The largest evidence base available was for prostate cancer (10 studies). However, only 6 of these studies reported clinical outcomes *and* compared PBT to alternative treatments. These included an RCT, a prospective comparative cohort, and four comparisons of noncontemporaneous case series. (*NOTE: comparisons of different dose levels of PBT are reported as part of the evidence base for Key Question 4 on patient subgroups.*)

The included RCT was a fair-quality comparison of 202 patients (median age 69 years) with advanced (stages T3-T4) prostate cancer who were randomized to receive either photon therapy with a proton boost (total dose: 75.2 GyE) or photons alone (67.2 Gy) and were followed for a median of five years (Shipley, 1995). Kaplan-Meier estimates of local tumor control, disease-specific survival, and overall survival were similar at both 5- and 8-year timepoints among the entire intent-to-treat population as well as those completing the trial (n=189). However, in patients with poorly-differentiated tumors (Gleason grades 4 or 5), local control at 8 years was significantly better in patients receiving PBT+photons (85% vs. 40% for photons alone, p=0.0014).

The prospective cohort study was a fair-quality comparison of patient-reported health-related QoL at multiple timepoints among 185 men (mean age: 69 years) with localized prostate cancer who were treated with PBT, PBT+photons, photons alone, surgery, or watchful waiting (Galbraith, 2001). Overall QoL, general health status, and treatment-related symptom scales were employed. No differences in overall QoL or general health status were observed at 18 months of follow-up, although men treated with PBT monotherapy reported better physical function in comparison to surgery ($p=0.01$) or photon radiation ($p=0.02$), and better emotional functioning in relation to photon radiation ($p<0.001$). Men receiving PBT+photons also reported significantly fewer urinary symptoms at 18 months in comparison to watchful waiting ($p<0.01$).

Outcomes were also assessed in three comparisons of noncontemporaneous case series. One was a fair-quality evaluation of high-dose PBT+photons (79.2 GyE) in 141 patients enrolled in a clinical trial at MGH and Loma Linda University who were matched on clinical and demographic criteria to 141 patients treated with brachytherapy at MGH (Coen, 2012). Patients were followed for a median of eight years. Eight-year actuarial estimates of overall survival, freedom from metastasis, and biochemical failure did not statistically differ between groups. The proportion of patients achieving a nadir PSA level of ≤0.5 ng/mL as of their final measurement was significantly higher In the brachytherapy group (92% vs. 74% for PBT, $p=0.0003$).

Two additional studies were deemed to be of poor quality due to a lack of control for confounding between study populations. One was a comparison of a cohort of 206 brachytherapy patients treated at the University of California San Francisco compared with same MGH/Loma Linda PBT+photon group described above (Jabbari, 2010). The difference in the percentage of patients achieving nadir PSA after a median of 5.4 years of follow-up was similar to that reported in the Coen study above (91% vs. 59%), although statistical results were not reported. Five-year estimates of disease-free survival (using biochemical failure definitions) did not statistically differ between groups. The other study involved comparisons of bowel- and urinary-related QoL in three distinct cohorts receiving PBT (n=95; 74-82 GyE), IMRT (n=153; 76-79 Gy), or 3D-CRT (n=123; 66-79 Gy) (Gray, 2013). Statistical changes were assessed within (but not between) each cohort immediately following treatment as well as at 12 and 24 months of follow-up, and were also assessed for whether the change was considered "clinically meaningful" (>0.5 SD of baseline values). Some differences in QoL decrements were seen at earlier timepoints. However, at 24 months, all groups experienced statistically and clinically significant decrements in bowel QoL, and none of the groups had significant declines in urinary QoL.

A fourth, poor-quality comparison of case series (Hoppe, 2013) involved an evaluation of patient-reported outcomes on the Expanded Prostate Cancer Index Composite (EPIC) questionnaire among a cohort of 1,243 patients receiving PBT for prostate cancer at the University of Florida and a group of 204 patients receiving IMRT from a previous multicenter study (Sandler, 2010). Statistically-significant differences between treatment groups were observed for many baseline characteristics, only some of which were adjusted for in multivariate analyses. No differences were observed in summary scores for

bowel, urinary, and sexual QoL at two years, although more IMRT patients reported specific bowel frequency (10% vs. 4% for PBT, p=0.05) and urgency (15% vs. 7%, p=0.02) problems at two years.

We identified eight case series with information on effectiveness in prostate cancer (see Appendix F, Table 13 for specific citations). Rates of overall survival ranged from 71-100% in these studies.

Soft Tissue Sarcomas

We identified no comparative studies of the clinical effectiveness of primary PBT in sarcomas. Two case series were identified in 41 patients (see Appendix F, Table 14 for specific citations). Overall survival at 3-4 years ranged from 83-87% in these studies.

Seminomas

We identified no comparative studies or case series focusing on the clinical effectiveness of primary PBT in seminomas.

Thymomas

We identified no comparative studies or case series focusing on the clinical effectiveness of primary PBT in thymomas.

Noncancerous Conditions

Arteriovenous Malformations

We identified no comparative studies of the clinical effectiveness of primary PBT in arteriovenous malformations. We identified three case series of PBT in AVMs, totaling 78 patients (Nakai, 2012; Hattangadi, 2011; Ito, 2011). Overall survival in these studies ranged from 81-91%.

Hemangiomas

We identified a single comparative study of PBT's clinical effectiveness in hemangiomas, a poor-quality retrospective cohort study of 44 patients (mean age 41 years, gender unreported) with diffuse or circumscribed choroidal hemangiomas who were treated with either PBT (20-23 GyE) or photon therapy (16-20 Gy) and followed for an average of 2.5 years (Höcht, 2006). Unadjusted outcomes were reported for the entire cohort only; reduction in tumor thickness, resolution of retinal detachment, and stabilization of visual acuity were observed in >90% of the overall sample. In Kaplan-Meier analysis of outcomes adjusting for differential follow-up between treatment groups, therapeutic modality had no statistically-significant effects on stabilization of visual acuity (p=0.43).

Two hemangioma series reported on clinical effectiveness of PBT in 84 patients (Levy-Gabriel, 2009; Hannouche, 1997). Overall survival was 100% in both studies.

Other Benign Tumors

We identified two comparative studies of PBT's clinical effectiveness in other benign tumors, both of poor quality. One was a retrospective cohort of consisting of 20 patients with giant-cell bone tumors (mean age: 40 years; 35% male) who were treated with PBT+photon therapy (mean: 59 GyE) or photons alone (mean: 52 Gy) and followed for median of 9 years (Chakravati, 1999). Patients could also have received partial tumor resection. Of note, however, the PBT population consisted entirely of young adults (mean age: 23 years), while the photon-only population was much older (mean: 46 years); no attempt was made to control for differences between treatment groups. Rates of disease progression, progression-free survival, and distant metastases were numerically similar between groups, although these rates were not statistically tested.

The other study was a small cohort study comparing PBT alone, photon therapy alone, or PBT + photons in 25 patients with optic nerve sheath meningioma (ONSM) (Arvold, 2009). On an overall basis, visual acuity improved in most patients. Rates did not numerically differ between treatment groups, although these were not tested statistically.

We identified seven case series with information on the clinical effectiveness of PBT in other benign tumors (primarily meningiomas) (see Appendix F, Table 15 for specific citations). Overall survival ranged from 72-100% in these studies.

Impact of Proton Beam Therapy on Outcomes in Patients with Recurrent Cancer or Noncancerous Conditions (KQ2)

The evidence base comparing PBT to alternative treatment approaches in patients with recurrent disease and/or failure of initial treatment is extremely limited. Across all conditions, a total of seven comparative studies were identified that included patients with recurrent disease or prior failed treatment. In addition, some of these studies included a mix of primary and recurrent disease without formal subgroup or stratified analyses to differentiate outcomes between them. Both comparative studies and case series are described in detail in the sections that follow.

Cancers

Bone Tumors

In a previously-described study of 27 patients with sacral chordomas who were treated with PBT/photon radiation alone or in combination with surgery (Park, 2006), seven radiation/surgery patients and four radiation-only patients had recurrent disease. Among patients in the radiation/surgery group, four patients died of disease 4-10 years after treatment; the remainder was alive with disease at last follow-up. In the radiation-only group, two of four patients died of disease at 4-5 years of follow-up; the other two were alive with disease at last follow-up.

No case series were identified that were comprised of all or a majority of recurrent cancers.

Brain, Spinal, and Paraspinal Tumors

We identified no comparative studies or case series of the clinical effectiveness of PBT for recurrent disease in patients with brain, spinal, and paraspinal tumors.

Breast Cancer

We identified no comparative studies or case series focusing on the clinical effectiveness of PBT for recurrent disease in patients with breast cancer.

Esophageal Cancer

We identified no comparative studies or case series focusing on the clinical effectiveness of PBT for recurrent disease in patients with esophageal cancer.

Gastrointestinal Cancers

We identified no comparative studies or case series focusing on the clinical effectiveness of PBT for recurrent disease in patients with gastrointestinal cancers.

Gynecologic Cancers

We identified no comparative studies or case series focusing on the clinical effectiveness of PBT for recurrent disease in patients with gynecologic cancers.

Head and Neck Cancers

In a previously-described study comparing PBT with or without photon radiation in 33 patients with a variety of head and neck cancers (Tokuuye, 2004), four patients were identified as having recurrent disease, three of whom received PBT alone. Two of the three PBT-only patients were alive with local tumor control at last follow-up (5 and 17 years respectively); one patient had their cancer recur three months after PBT and died in month 7 of follow-up. The one PBT+photon patient died at 2.5 years of follow-up, but was described as having local tumor control.

Two case series were identified with information on recurrent or persistent disease in 32 patients (McDonald, 2013; Lin, 1999). Overall survival was reported to be 50-80% at two years.

Liver Cancer

Two studies were identified with information on recurrent disease. One was a poor-quality comparison of PBT to conventional photon radiation in eight patients with recurrent HCC after hepatectomy (Otsuka, 2003). Five patients were treated with PBT (68.8-84.5 GyE), and three with photons (60-70 Gy). Seven of eight patients died of liver failure or lung metastasis a median of 1.5 years after radiation; the one patient alive at the end of follow-up was a photon patient. The rate of local tumor control was 78%, and did not differ between treatment groups.

The other study was a previously-described prospective comparison of PBT to carbon-ion therapy in 350 patients with primary or recurrent HCC (Komatsu, 2011). No subgroup analyses were performed, but prior treatment history for HCC was found not to have a statistically-significant impact on local tumor control (p=0.73). Prior treatment was not examined as a risk factor for overall survival, however.

Two case series were identified with information on PBT in populations that were comprised mostly or all with liver cancer (Abei, 2013; Fukumitsu, 2009). Five-year overall survival estimates ranged from 33-39% in these studies.

Lung Cancer

In a previously-described study of patients with locally-advanced, unresectable NSCLC who were treated with PBT, IMRT, or 3D-CRT (Sejpal, 2011), 22% of the study sample was identified as having a prior malignancy of any type. The effects of prior malignancy on overall survival were not reported, however.

One case series was identified with data on 33 PBT patients with recurrent disease (McAvoy, 2013). Overall survival was estimated to be 47% and 33% at one and two years respectively.

Lymphomas

We identified no comparative studies or case series focusing on the clinical effectiveness of PBT for recurrent disease in patients with lymphomas.

Ocular Tumors

We identified a single comparative study of PBT in recurrent ocular cancer. In this fair-quality, comparative cohort study, a total of 73 patients with uveal melanoma had recurrence of disease following an initial course of PBT at Massachusetts General Hospital (Marucci, 2011). Patients (mean age: 58 years) were treated with either a second course of PBT (70 GyE) in five fractions or surgical enucleation and followed for 5-7 years. The likelihood of overall survival at five years was significantly ($p=0.04$) longer in the PBT group (63% vs. 36% for enucleation), as was the probability of being free of metastasis at this timepoint (66% vs. 31% respectively, $p=0.028$). Findings were similar after Cox proportional hazards regression adjusting for tumor volume and year of retreatment as well as patient age. The likelihood of local tumor recurrence at five years was 31% in the PBT group. No local recurrences were found in the enucleation group, which is not surprising given the nature of the treatment.

Three case series were identified in which most or all patients had recurrent ocular cancers (Lumbroso-LeRouic, 2006; Marucci, 2006; Wuestmeyer, 2006). Overall survival ranged from 74-100% in these studies.

Pediatric Cancers

We identified no comparative studies of the clinical effectiveness of PBT for recurrent disease in patients with pediatric cancers. Two case series were identified in which most or all patients had recurrent disease (Chang, 2011; Hug, 2002b). Overall survival ranged from 85-100% in these studies.

Prostate Cancer

We identified no comparative studies of the clinical effectiveness of PBT for recurrent disease in patients with prostate cancer. We identified no case series that focused on patients with recurrent prostate cancer.

Soft Tissue Sarcomas

We identified no comparative studies or case series focusing on the clinical effectiveness of PBT for recurrent disease in patients with sarcomas.

Seminomas

We identified no comparative studies or case series focusing on the clinical effectiveness of PBT for recurrent disease in patients with seminomas.

Thymomas

We identified no comparative studies or case series focusing on the clinical effectiveness of PBT for recurrent disease in patients with thymomas.

Noncancerous Conditions

Arteriovenous Malformations

We identified no comparative studies or case series of the clinical effectiveness of PBT for recurrent disease in patients with arteriovenous malformations.

Hemangiomas

We identified no comparative studies or case series focusing on the clinical effectiveness of PBT for recurrent disease in patients with hemangiomas.

Other Benign Tumors

In a previously-described retrospective cohort of consisting of 20 patients with giant-cell bone tumors who were treated with PBT+photon therapy or photons alone (Chakravati, 1999), five of 20 were identified as having recurrent disease. Two of the five were treated with PBT+photon therapy, one of whom had progression of disease at eight months but no further progression after retreatment at five years of follow-up. The other patient was free of local progression and metastases as of 9 years of follow-up. In the three photon patients, one had local progression at 12 months but no further progression as of year 19 of follow-up, one patient was free of progression and metastases as of five years of follow-up, and one patient had unknown status.

We identified a single case series with information on PBT's effects in patients with recurrent meningioma (29 of 46 total patients) (Wenkel, 2000). Overall survival was 93% at 5 years and 77% at 10 years.

Comparative Harms of Proton Beam Therapy in Patients with Multiple Cancers or Noncancerous Conditions (KQ3)

As with information on clinical effectiveness, data on potential harms of PBT come from RCTs, comparative cohort studies, and case series, although comparative harms data are still lacking for many condition types. Across all condition types, a total of 25 studies reported comparative information on treatment-related harms; differences in the types of harms relevant to each condition, as well as variability in harms classification even within conditions, precludes any attempt to summarily present harms data across all 19 condition categories. However, summary statements regarding our overall impression of the effects of PBT on patient harms are provided within each condition type in the sections that follow. In addition, summary statistics from case series data on harms requiring medical attention are provided for each cancer type, with a focus on severe (grade 3) or life-threatening (grade 4) events only.

Secondary Malignancy

Of note, observational data on secondary malignancy with PBT are generally lacking. Two studies were identified with comparative information. One was a fair-quality matched retrospective cohort study comparing 1,116 patients in a linked Medicare-SEER database who received either PBT or photon radiation for a variety of cancers and were followed for a median of 6.4 years (Chung, 2013). On an unadjusted basis, the incidence rates of any secondary malignancy and malignancies occurring in the prior radiation field were numerically lower for PBT, but not statistically-significantly so. After adjustment for age, sex, primary tumor site, duration of follow-up, and year of diagnosis, PBT was associated with a risk of secondary malignancy approximately one-half that of photon therapy (HR=0.52; 95% CI: 0.32, 0.85; p=0.009). There are challenges with these findings, however. First and foremost, the lower rate of secondary malignancy with PBT appeared to be manifested almost entirely in the first five years after radiotherapy, a time period in which a second cancer event is not typically attributed to prior radiation (Bekelman, 2013). In addition, patients were accrued over a very long time period (1973-2001), only the very end of which included highly conformal photon techniques like IMRT.

The second study was a poor-quality retrospective cohort study comparing PBT to photon radiotherapy in 86 infants who were treated for retinoblastoma and followed for a median of 7 years (PBT) or 13 years (photon radiotherapy) (Sethi, 2013). Therapy was received at two different centers (PBT at MGH and photon radiotherapy at Children's Hospital Boston). Kaplan-Meier analyses were conducted to control for differential follow-up but no adjustments were made for other differences between groups. Ten-year estimates of the cumulative incidence of secondary malignancy were numerically lower for PBT, but not statistically-significantly so (5% vs. 14% for photon, p=0.12). However, when malignancies were restricted to those occurring in-field or thought to be radiation-induced, a significant difference in favor of PBT was observed (0% vs. 14%, p=0.015). In addition, significant differences in favor of PBT in

both cumulative incidence and radiotherapy-related malignancy were observed for the subgroup of patients with hereditary disease.

Other harms are presented in detail for each condition type in the sections that follow.

Cancers

Bone Tumors

Evidence is limited and inadequate to compare the potential harms of PBT relative to other radiation modalities in patients with bone cancer.

In a previously-described study of 27 patients with sacral chordomas who were treated with PBT/photon radiation alone or in combination with surgery (Park, 2006), multiple descriptive harms were reported. Patients receiving radiation alone reported numerically lower rates of abnormal bowel or bladder function as well as difficulty ambulating in comparison to those receiving combination therapy, but rates were not statistically tested. PBT patients also reported higher rates of return to work, although this was also not tested statistically.

Of the four bone cancer case series, three reported data on harms. Toxicities were minimal in all but one study, which reported late grade 3 and 4 effects in 15% and 16% of patients respectively (Ciernik, 2011).

Brain, Spinal, and Paraspinal Tumors

Limited, low-quality evidence suggests that PBT is associated with reductions in acute radiation-related toxicity relative to photon radiation in patients with brain and spinal tumors.

In a previously-described study comparing PBT to photon therapy in 40 adult patients treated for medulloblastoma (Brown, 2013), PBT was associated with statistically-significantly lower rates of weight loss (median % of baseline: -1.2% vs. 5.8% for photon, $p=0.004$) as well as requirements for medical management of esophagitis (5% vs. 57% respectively, $p<0.001$). PBT patients also experienced less RTOG grade 2 or greater nausea and vomiting (26% vs. 71%, $p=0.004$).

In a second poor-quality study comparing primarily 10 pediatric patients (mean age: 14 years) receiving PBT for spinal cord gliomas to 22 adults receiving IMRT for the same condition (mean age: 44 years) (Kahn, 2011), no cases of long-term toxicity or myelopathy were reported in either group. Minor side-effect rates were reported for the overall cohort only.

In two case series grading severity of adverse effects in 39 patients with glioma or glioblastoma (Hauswald, 2012; Mizumoto, 2010), grade 3 and 4 hematologic effects occurred in 65% and 30% of patients respectively. In one study, 10% of patients also developed grade 3 leukoencephalopathy (Mizumoto, 2010).

Breast Cancer

Evidence is insufficient to determine the comparative harms of PBT in patients with breast cancer.

We identified no comparative studies of the potential harms of PBT in patients with breast cancer. Two case series graded the severity of treatment-related harms in breast cancer (MacDonald, 2013; Bush, 2011). Acute effects grade 3 or higher were recorded in 0% and 8% of patients in these studies respectively. No late effects were observed.

Esophageal Cancer

Evidence is limited and inadequate to compare the potential harms of PBT relative to other radiation modalities in patients with esophageal cancer, particularly in comparison to IMRT.

Two studies were identified that examined comparative harms in patients treated with PBT for esophageal cancer. One was a relatively large, fair-quality, retrospective comparative cohort study of 444 patients (median age: 61 years; 91% male) who were treated with chemotherapy and radiation (PBT, IMRT, or 3D-CRT) followed by surgical resection (Wang, 2013). Patients were followed for up to 60 days after hospital discharge. After adjustment for patient characteristics and clinical variables, 3D-CRT was associated with a significantly greater risk of postoperative pulmonary complications vs. PBT (Odds Ratio [OR]: 9.13, 95% CI: 1.83, 45.42). No significant differences were observed between PBT and IMRT, however. No differences in the rate of gastrointestinal complications were observed for any treatment comparison.

In addition, a fair-quality comparative study was identified that examined early impact on lung inflammation and irritation in 75 patients receiving PBT, IMRT, or 3D-CRT for esophageal cancer (McCurdy, 2013); patients were followed for up to 75 days following radiation. Nearly all outcome and toxicity measures were reported for the entire cohort only. However, the rate of pneumonitis was found to be significantly higher among PBT patients (33% vs. 15% for IMRT/3D-CRT, p=0.04).

Of the six case series evaluating esophageal cancer, five reported data on harms in 278 patients. Commonly reported acute effects were grade 3 pneumonitis (2-7%) and esophagitis (5-12%). Three studies identified late grade 5 effects in 2-5% of patients (Lin, 2012; Mizumoto, 2010; Sugahara, 2005).

Gastrointestinal Cancers

Evidence is insufficient to determine the comparative harms of PBT in patients with gastrointestinal cancers.

We identified no comparative studies of the potential harms of PBT in patients with gastrointestinal cancers. A total of seven case series identified acute and late effects in 255 patients. Grade 3 and 4 acute effects consisted primarily of hematologic and gastrointestinal harms, ranging from 0-100%. Reported late effects also varied (0-20%) with two studies reporting late grade 5 events in 2-3% of patients (Takatori, 2013; Terashima, 2012).

Gynecologic Cancers

Evidence is insufficient to determine the comparative harms of PBT in patients with gynecologic cancers.

We identified no comparative studies of the potential harms of PBT in patients with gynecologic cancers. One of two identified case series reported on late effects in 25 patients with uterine cervical carcinoma (Kagei, 2003). Grade 4 gastrointestinal and genitourinary harms were each identified in 4% of patients.

Head and Neck Cancers

Evidence is limited and inadequate to compare the potential harms of PBT relative to other radiation modalities in patients with head and neck cancer.

In a previously-described study comparing PBT with versus without photon radiation in 33 patients with a variety of head and neck cancers (Tokuuye, 2004), rates of tongue ulceration, osteonecrosis, and esophageal stenosis differed somewhat between treatment groups, but were not statistically tested. Overall toxicity rates were estimated to be 22.8% at both three and five years, but were not stratified by treatment modality.

In a separate, fair-quality study comparing rates of vision loss from radiation-induced optic neuropathy in 75 patients treated with PBT or carbon-ion therapy for head and neck or skull base tumors (Demizu, 2009), unadjusted rates of vision loss were similar between modalities (8% and 6% for PBT and carbon-ion respectively, not statistically tested). In multivariate analyses controlling for demographic and clinical characteristics, treatment modality had no effect on rates of vision loss (p=0.42). Another comparison of PBT and carbon-ion therapy in 59 patients with head and neck or skull base tumors (Miyawaki, 2009) was of poor quality (due to no control for differences between patient groups) and focused on the incidence of radiation-induced brain changes. The incidence of CTCAE brain injury of any grade was significantly (p=0.002) lower in the PBT group. MRI-based assessment of brain changes showed a lower rate in the PBT group (17% vs. 64% for carbon-ion), although this was not tested statistically.

Harms were reported in 18 case series of PBT in head and neck cancers. Rates of severe toxicities ranged widely depending on cancer type. For example, rates of grade 3 or worse mucositis ranged from 6-30%. Rates of severe complications such as temporal lobe damage and cerebrospinal fluid leakage were <5% in most studies.

Liver Cancer

Limited, low-quality evidence suggests that PBT is associated with comparable rates of toxicity to other radiation modalities in patients with liver cancer.

Two comparative studies were identified with comparative information on radiation-related harms. In a previously-described study of eight patients with recurrent HCC after hepatectomy (Otsuka, 2003), there were no instances of bone marrow depression or gastrointestinal complications in either group. Serum aspartate aminotransferase (AST) level s increased in the three photon patients and 4/5 PBT patients, although this was not tested statistically.

In the other study, a previously-described comparison of PBT to carbon-ion therapy in 350 patients with primary or recurrent HCC (Komatsu, 2011), rates of toxicities as graded by the Common Terminology Criteria for Adverse Events (CTCAE) framework were comparable between groups, including dermatitis, GI ulcer, pneumonitis, and rib fracture. The rate of grade 3 or higher toxicities was similar between groups (3% vs. 4% for PBT and carbon-ion respectively), although this was not statistically tested.

Potential harms were reported in 23 case series. Rates of grade 3 toxicities ranged from 0-23% (higher rates observed with hematologic events). Rates of late grade 3 effects were ≤2%. Grade 4 events were reported in one series (rib fracture in 4%, bile duct stenosis and hepatic failure in 7%).

Lung Cancer

Moderate evidence suggests that rates of treatment-related toxicities with PBT are comparable to those seen with other radiation modalities in patients with lung cancer.

A total of three comparative studies assessed harms in patients with lung cancer. One was a study of severe radiation-induced esophagitis (within six months of treatment) among 652 patients treated for NSCLC with PBT, IMRT, or 3D-CRT at MD Anderson Cancer Center (Gomez, 2012). Rates of grade 3 or higher esophagitis were 6%, 8%, and 28% for PBT, 3D-CRT, and IMRT respectively ($p<.05$ for PBT and 3D-CRT vs. IMRT).

In a previously-described noncontemporaneous case series comparison of patients with locally-advanced, unresectable NSCLC who were treated with PBT, IMRT, or 3D-CRT (Sejpal, 2011), hematologic toxicity rates did not differ by radiation modality. Significant differences in favor of PBT were seen in rates of grade 3 or higher esophagitis (5%, 39%, and 18% for PBT, IMRT, and 3D-CRT respectively, $p<0.001$) as well as pneumonitis (2%, 6%, and 30%, $p<0.001$), while rates of grade 3 or higher dermatitis were significantly greater in the PBT group (24% vs. 17% and 7% for IMRT and 3D-CRT, $p<0.001$).

Finally, in a previously-described comparison of PBT to carbon-ion therapy in 111 patients in Japan (Fujii, 2013), rates of pneumonitis, dermatitis, and rib fracture did not differ statistically between radiation modalities across all toxicity grades.

Harms were reported in 14 lung cancer case series. Rates of grade 3 or worse effects ranged from 0-21% (higher rates were observed for pulmonary effects).

Lymphomas

Evidence is insufficient to determine the comparative harms of PBT in patients with lymphomas.

We identified no comparative studies of the potential harms of PBT in patients with lymphomas. One case series identified no grade 3 or worse acute effects in 10 patients (Li, 2011).

Ocular Tumors

Limited, low-quality evidence suggests comparable rates of harm for PBT relative to treatment alternatives in patients with ocular tumors.

We identified three comparative studies assessing the harms of PBT for ocular cancers. In the previously-described Desjardins RCT comparing PBT with thermotherapy to PBT alone in 151 patients with uveal melanoma (Desjardins, 2006), no statistically-significant differences were observed between groups in rates of cataracts, maculopathy, pappilopathy, glaucoma, or intraocular pressure. The combination therapy group had a significantly lower rate of secondary enucleation (p=0.02), although actual figures were not reported.

In a previously-described comparison of PBT to enucleation in 132 patients treated for unilateral choroidal tumors (Mosci, 2012), rates of eye loss in the PBT arm were assessed and estimated to be 26% at five years of follow-up.

Harms data were collected in 25 case series of ocular cancers (see Appendix F, Table 11 for specific citations). The most common harm reported was secondary enucleation, which occurred in 4-35% of patients in these studies.

Pediatric Cancers

PBT's theoretical potential to lower radiation-induced toxicity in children serves as the comparative evidence base. Comparative studies are lacking, most likely due to a lack of clinical equipoise.

Other than the study of secondary malignancy described above, we identified no comparative studies of the potential harms of PBT in patients with pediatric cancers.

A total of 18 case series were identified with information on patient harms (see Appendix F, Table 12 for specific citations). Grade 3 or worse effects were rare in most studies, occurring in less than 4% of patients.

Prostate Cancer

Moderate evidence suggests that rates of major harms are comparable between PBT and photon radiation treatments, particularly IMRT.

We identified four comparative studies of the harms associated with PBT and alternative treatments in patients with prostate cancer. The previously-described RCT of PBT+photon therapy vs. photons alone (Shipley, 1995) examined rates of rectal bleeding, urethral stricture, hematuria, incontinence, and loss of full potency; no patients in either arm had grade 3 or higher toxicity during radiation therapy. Actuarial estimates of rectal bleeding at eight years were significantly higher in the PBT+photon arm (32% vs. 12% for photons alone, p=0.002), although this was primarily grade 2 or lower toxicity. Rates of urethral stricture, hematuria, incontinence, and loss of potency did not differ between groups.

Three additional studies involved retrospective comparisons using available databases. The most recent was a matched comparison of 314 PBT and 628 IMRT patients treated for early-stage prostate cancer

using the linked Chronic Condition Warehouse-Medicare database with a focus on complications occurring within 12 months of treatment (Yu, 2013). At six months, rates of genitourinary toxicity were significantly lower in the PBT arm (5.9% vs. 9.5%, p=0.03). This difference was not apparent after 12 months of follow-up, however (18.8% vs. 17.5%, p=0.66). Rates of gastrointestinal and other (e.g., infection, nerve damage) complications did not statistically differ at either timepoint.

Another recent study compared matched cohorts of men with prostate cancer in the linked Medicare-SEER database who were treated with PBT or IMRT (684 patients in each arm) and followed for a median of four years (Sheets, 2012). IMRT patients had a statistically-significantly lower rate of gastrointestinal morbidity (12.2 vs. 17.8 per 100 person-years, p<0.05). No other statistical differences were noted in genitourinary morbidity, erectile dysfunction, hip fracture, or use of additional cancer therapy.

Finally, Kim and colleagues conducted an analysis of nearly 30,000 men in the Medicare-SEER database who were treated with PBT, IMRT, 3D-CRT, brachytherapy, or conservative management (observation alone) and evaluated for gastrointestinal toxicity (Kim, 2011). All forms of radiation had higher rates of GI morbidity than conservative management. In pairwise comparisons using Cox proportional hazards regression, PBT was associated with higher rates of GI morbidity than conservative management (HR: 13.7; 95% CI: 9.1, 20.8), 3D-CRT (HR: 2.1; 95% CI: 1.5, 3.1), and IMRT (HR: 3.3; 95% CI: 2.1, 5.2).

Harms were assessed in 13 prostate cancer case series (see Appendix F, Table 13 for specific citations). Urinary toxicity of grade 3 or 4 ranged from <1-4% for acute toxicities and 1-8% for late toxicities. Gastrointestinal toxicities were less frequently reported, and ranged from 0.2-1% at both acute and late timepoints.

Soft Tissue Sarcomas

Evidence is insufficient to determine the comparative harms of PBT in patients with sarcomas.

We identified no comparative studies of the potential harms of PBT in patients with sarcomas. Late effects were identified in one case series evaluating 10 patients, with 8% reporting Grade 3 brain necrosis.

Seminomas

Evidence is insufficient to determine the comparative harms of PBT in patients with seminomas.

We identified no comparative studies or case series of the potential harms of PBT in patients with seminomas.

Thymomas

Evidence is insufficient to determine the comparative harms of PBT in patients with thymomas.

We identified no comparative studies or case series of the potential harms of PBT in patients with thymomas.

Noncancerous Conditions

Arteriovenous Malformations

Evidence is insufficient to determine the comparative harms of PBT in patients with arteriovenous malformations.

We identified no comparative studies of the potential harms of PBT in patients with arteriovenous malformations. A single case series reported on severe adverse effects of PBT in AVMs (Vernimmen, 2005). Acute grade 4 epilepsy occurred in 3% of 64 patients, while late grade 3-4 effects occurred in 6%.

Hemangiomas

Limited evidence suggests comparable rates of harm for PBT relative to treatment alternatives in patients with hemangiomas.

A single, previously-described retrospective comparative cohort study assessed outcomes in patients with circumscribed or diffuse hemangiomas treated with PBT or photon radiation (Höcht, 2006). Small differences in unadjusted rates of optic nerve/disc atrophy, lacrimation (formation of tears) and ocular pressure as well as effects on the retina, lens, and iris were observed between groups, but most side effects were grade 1 or 2. The rate of retinopathy was substantially higher in PBT patients (40% vs. 16% for photons). However, in Cox proportional hazards regression adjusting for between-group differences, no effects of radiation modality on outcomes was observed, including retinopathy (p=0.12).

One case series of hemangiomas reported no acute or late effects in 13 patients (Hannouche, 1997).

Other Benign Tumors

Evidence is limited and inadequate to compare the potential harms of PBT relative to other radiation modalities in patients with other benign tumors.

The previously-described Arvold study comparing PBT, PBT+photon, and photon therapy alone in 25 patients treated for optic nerve sheath meningiomas (Arvold, 2009) showed numerically lower rates of acute orbital pain and headache for both PBT groups compared to photon therapy, and numerically higher rates of late asymptomatic retinopathy. None of these comparisons were tested statistically, however.

Three case series were identified with the severity of harms recorded (Nöel, 2005; Weber, 2003; Wenkel, 2000). Grade 3 or 4 toxicities occurred in 4-17% of patients in two meningioma studies. In a study of vestibular schwannoma in 88 patients, 6% of patients had severe facial nerve dysfunction (Weber, 2003).

Differential Effectiveness and Safety of Proton Beam Therapy in Key Patient Subgroups (KQ4)

The sections below summarize available information on how the effectiveness and safety of PBT differs relative to treatment alternatives in specific patient subgroups as delineated in Key Question 4. Because the focus of this question is on differential effects of PBT in key subgroups, the focus of this section is on comparative studies only. Case series with subgroup data available are noted as such in evidence tables, however.

Patient Demographics

Limited comparative subgroup data are available on the differential impact of PBT according to patient demographics. In a retrospective comparison of PBT and surgical enucleation in uveal melanoma, the rate of death due to metastatic disease through two years of follow-up increased with older age in the surgical group but not in the PBT group (Seddon, 1990). In a retrospective analysis of secondary malignancy with PBT vs. photon radiation in multiple cancer types (Chung, 2013), reductions in malignancy rates with PBT of 5% were seen with each year of increasing age (mean age was 59 years in both groups). In other comparative studies, patient demographics had no impact on the effect of treatment (Tokuuye, 2004; Marucci, 2011).

Clinical Characteristics

In a comparison of secondary malignancy rates in 86 infants with retinoblastoma treated with PBT or photon radiation (Sethi, 2013), statistically-significant reductions in the estimated incidence of secondary malignancy at 10 years were observed in favor of PBT for the subset of patients with hereditary disease (0% vs. 22% for photons, p=0.005). No significant differences were observed in the overall cohort, however. In other comparative studies, clinical characteristics, including prior therapy received, had no effect on treatment outcomes (Brown, 2013; Tokuuye, 2004).

Tumor Characteristics

The impact of tumor characteristics on estimates of treatment effect was measured in six comparative studies. In one study comparing PBT to carbon-ion therapy in liver cancer (Komatsu, 2011), larger tumor sizes were associated with a greater risk of cancer recurrence in PBT patients but not in those receiving carbon-ion therapy. In the Shipley RCT comparing PBT+photon therapy to photons alone in men with prostate cancer (Shipley, 1995), the 8-year estimate of local control was significantly higher in patients receiving PBT among those with poorly-differentiated tumors (85% vs. 40% for photons, p=0.0014). No

differences were observed among those with well- or moderately-differentiated tumors. In the other studies, tumor characteristics (e.g., volume, thickness, level of prostate cancer risk) had no differential impact on outcomes (Tokuuye, 2004; Sejpal, 2011; Mosci, 2012; Coen, 2012).

Treatment Protocol

Four RCTs were identified that involved comparisons of different dosing regimens for PBT. Two of these were in men with prostate cancer (Kim, 2013; Zietman, 2010). In the more recent study, five different fractionation schemes were compared in 82 men with stage T1-T3 prostate cancer, with total doses ranging from 35-60 GyE (Kim, 2013); patients were followed for a median of approximately 3.5 years. Rates of biochemical failure using two different definitions did not differ statistically between treatment groups. Similarly, no significant differences were observed in rates of acute and late skin, gastrointestinal, or genitourinary toxicity between arms.

In another RCT conducted at MGH and Loma Linda University, 395 men with stage T1b-T2b prostate cancer were randomized to receive a conventional dose of combination PBT+photon therapy (70.2 GyE total dose) or a "high dose" of combination therapy (79.2 GyE) (Zietman, 2010). Patients were followed for a median of 9 years. Significant differences in favor of the high-dose group were seen for disease control as measured by a PSA nadir value <0.5 ng/mL (59.8% vs. 44.7% for high and conventional dose respectively, p=0.003) and 10-year estimates of biochemical failure (16.7% vs. 32.3%, p=0.0001). Survival and mortality rates did not differ. Acute GI toxicity was significantly more frequent in the high-dose group (63% vs. 44% for conventional, p=0.0006); no differences were observed in other measures of toxicity. A quality-of-life subset analysis of this RCT found no differences between groups in patient-reported measures of urinary obstruction and irritation, urinary incontinence, bowel problems, or sexual dysfunction (Talcott, 2010).

Gragoudas and colleagues examined the impact of two different total doses of PBT (50 vs. 70 GyE) on clinical outcomes and potential harms in 188 patients with melanoma of the choroid or ciliary body (Gragoudas, 2006). Patients were followed for up to five years. No statistical differences were observed in any measure of effectiveness (visual acuity, vision preservation, local recurrence, death from metastases) or harm (hemorrhage, subretinal exudation, glaucoma, uveitis, secondary enucleation).

The fourth RCT involved 96 patients with chordomas and skull base tumors who received combination PBT and photon therapy at total doses of either 66.6 or 72 GyE (Santoni, 1998). Patients were followed for a median of 3.5 years. This RCT focused on harms alone. No significant differences were observed in the rate of temporal lobe damage between groups or in grade 1, 2, or 3 clinical symptoms such as headache and motor function.

Finally, in a previously-described comparative cohort study assessing outcomes for both PBT and carbon-ion therapy (Fujii, 2013), no differences were observed in estimates of local control, progression-free survival, or overall survival when stratified by number of fractions received or total radiation dose.

Costs and Cost-Effectiveness of Proton Beam Therapy in Patients with Multiple Cancers and Noncancerous Conditions (KQ5)

A total of 16 studies were identified that examined the costs and cost-effectiveness of PBT in a variety of settings and perspectives (see Appendix E for study details). Studies are organized by cancer type in the sections that follow. Five of the 16 studies focused attention on the operating costs, reimbursement, and/or viability of proton treatment centers for multiple types of cancer, and are summarized at the end of this section.

Breast Cancer

Three studies modeled the costs and cost-effectiveness of PBT in breast cancer. One U.S.-based study examined reimbursement for treatment with 3D-conformal partial breast irradiation using protons or photons vs. traditional whole breast irradiation (Taghian, 2004). Payments included those of treatment planning and delivery as well as patient time and transport. Total per-patient costs were substantially higher for PBT vs. photon partial irradiation ($13,200 vs. $5,300) but only modestly increased relative to traditional whole breast irradiation ($10,600), as the latter incurred higher professional service fees and involved a greater amount of patient time.

Two additional studies from the same group assessed the cost-effectiveness of PBT vs. photon radiation among women with left-sided breast cancer in Sweden (Lundkvist, 2005a and 2005c). In the first of these, photon radiation was assumed to increase the risk of ischemic and other cardiovascular disease as well as pneumonitis relative to PBT (Lundkvist, 2005a); clinical effectiveness was assumed to be identical. Reductions in adverse events led to a gain in quality-adjusted life years (QALYs) equivalent to approximately one month (12.35 vs. 12.25 for photon). Costs of PBT were nearly triple those of photon therapy, however ($11,124 vs. $4,950), leading to an incremental cost-effectiveness ratio (ICER) of $65,875 per QALY gained. The other study used essentially the same model but focused attention only on women at high risk of cardiac disease (43% higher than general population) (Lundkvist, 2005c). In this instance, a much lower ICER was observed ($33,913 per QALY gained).

Head and Neck Cancer

Two studies modeled the cost-effectiveness of PBT in head and neck cancers. In one study, Ramaekers and colleagues used a Markov model to assess the cost-effectiveness of intensity-modulated PBT (IMPT) or IMRT therapy among patients with locally-advanced, Stage III-IV head and neck cancers in the Netherlands (Ramaekers, 2013). IMPT and IMRT were assumed to result in equivalent rates of disease progression and survival, but IMPT was assumed to result in lower rates of significant dysphagia (difficulty swallowing) and xerostomia (dry mouth syndrome). IMPT was found to result in one additional month of quality-adjusted survival (6.62 vs. 6.52 QALYs for IMRT), but treatment costs were

estimated to be 24% higher. The resulting ICER was estimated to be $159,421 per QALY gained vs. IMRT. Use of IMPT only in patients at high risk of radiation toxicity (and IMRT in all others) resulted in an ICER that was approximately half of the base case ($75,106 per QALY gained).

Head and neck cancer was also evaluated in the above-mentioned Swedish model (Lundkvist, 2005c). The base case involved a 65 year-old cohort with head and neck cancers of all stages. PBT was assumed not only to reduce the risk of xerostomia and acute mucositis (ulceration of mucous membranes), but also to reduce overall mortality at 8 years by 25% based on modeled delivery of a higher curative dose. As a result, PBT generated an additional 1.02 QALYs over photon radiation at an additional cost of approximately $4,000, resulting in an ICER of $3,769 per QALY gained.

Lung Cancer

Two studies from the same center evaluated the economic impact of PBT in lung cancers among patients in the Netherlands (Grutters, 2011; Grutters, 2010). One was a Markov model comparing PBT to carbon-ion therapy, stereotactic radiation therapy, and conventional radiation in patients with stage 1 non-small-cell lung cancer (NSCLC) over a 5-year time horizon (Grutters, 2010). Effects of therapy included both overall and disease-related mortality as well as adverse events such as pneumonitis and esophagitis. For inoperable NSCLC, PBT was found to be both more expensive and less effective than either carbon-ion or stereotactic radiation and was therefore not included in subsequent analyses focusing on inoperable disease. While not reported in the paper, PBT's derived cost-effectiveness relative to conventional radiation (based on approximately $5,000 in additional costs and 0.35 additional QALYs) was approximately $18,800 per QALY gained.

The second study was a "value of information" analysis that examined the implications of adopting PBT for Stage I NSCLC in three scenarios: (a) without further research; (b) along with the conduct of a clinical trial; and (c) delay of adoption while a clinical trial is conducted (Grutters, 2011). Costs included those of treatment (currently abroad as the Netherlands has no proton facilities), the clinical trial vs. conventional radiation, and adverse events due to suboptimal care. These were calculated and compared to the expected value of sampling information (reduced uncertainty), obtained through simulation modeling of uncertainty in estimates both before and after the trial. The analysis found that adoption of PBT along with conduct of a clinical trial produced a net gain of approximately $1.9 million for any trial with a sample size <950, while the "delay and trial" strategy produced a net loss of ~$900,000. Results were sensitive to a number of parameters, including treatment costs abroad and costs of suboptimal treatment.

Pediatric Cancers

Three decision analyses were available that focused on pediatric cancers, all of which focused on a lifetime time horizon in children with medulloblastoma who were treated at 5 years of age (Mailhot Vega, 2013; Lundkvist, 2005b; Lundkvist, 2005c). In a US-based model that incorporated costs and patient preference (utility) values of treatment and management of adverse events such as growth hormone deficiency, cardiovascular disease, hypothyroidism, and secondary malignancy (Maillhot Vega,

2013), PBT was found to generate lower lifetime costs ($80,000 vs. $112,000 per patient for conventional radiation) and a greater number of QALYs (17.37 vs. 13.91). Reduced risks for PBT were estimated based on data from dosimetric and modeling studies. Sensitivity analyses on the risk of certain adverse events changed the magnitude of PBT's cost-effectiveness, but it remained less costly and more effective in all scenarios.

The same Swedish group that examined breast and head/neck cancer also assessed medulloblastoma in two modeling studies (Lundkvist, 2005b; Lundkvist, 2005c). As with the analysis above, PBT was assumed to reduce both mortality and nonfatal adverse events relative to conventional photon therapy. On a per-patient basis, PBT was assumed to reduce lifetime costs by approximately $24,000 per patient and increase quality-adjusted life expectancy by nearly nine months (12.8 vs. 12.1 QALYs) (Lundkvist, 2005b). On a population basis, 25 medulloblastoma patients treated by PBT would have lifetime costs reduced by $600,000 and generate an additional 17.1 QALYs relative to conventional photon radiation (Lundkvist, 2005c).

Prostate Cancer

We identified four studies examining the costs and cost-effectiveness of PBT for prostate cancer. The analysis of the 2008-2009 Chronic Condition Warehouse previously reported under KQ 3 (harms) also examined treatment costs for matched Medicare beneficiaries with prostate cancer who received PBT or IMRT (Yu, 2013). Median Medicare reimbursements were $32,428 and $18,575 for PBT and IMRT respectively (not statistically tested).

A relatively recent Markov decision analysis estimated the lifetime costs and effectiveness of PBT, IMRT, and stereotactic body radiation therapy (SBRT) for localized prostate cancer (Parthan, 2012). Clinical effectiveness and impact on mortality were assumed to be equivalent across all three groups. SBRT was found to have the lowest treatment costs and shortest time in treatment of the three modalities, and produced slightly more QALYs (8.11 vs. 8.05 and 8.06 for IMRT and PBT respectively) based on an expected rate of sexual dysfunction approximately half that of IMRT or PBT. SBRT was cost-saving or cost-effective vs. PBT in 94% of probabilistic simulations.

An earlier decision analysis estimated the potential cost-effectiveness of a hypothetically-escalated PBT dose (91.8 GyE) vs. 81 Gy delivered with IMRT over a 15-year time horizon (Konski, 2007). The model focused on mortality and disease progression alone (i.e., toxicities were assumed to be similar between groups), and assumed a 10% reduction in disease progression from PBT's higher dose. This translated into QALY increases of 0.42 and 0.46 years in 70- and 60-year-old men with intermediate-risk disease respectively. Costs of PBT were $25,000-$27,000 higher in these men. ICERs for PBT vs. IMRT were $63,578 and $55,726 per QALY for 70- and 60-year-old men respectively.

Finally, the Lundkvist model also evaluated costs and outcomes for a hypothetical cohort of 300 65 year-old men with prostate cancer (Lundkvist, 2005, e30). PBT was assumed to result in a 20% reduction in cancer recurrence relative to conventional radiation as well as lower rates of urinary and gastrointestinal toxicities. PBT was estimated to be approximately $8,000 more expensive than

conventional radiation over a lifetime but result in a QALY gain of nearly 4 months (0.297). The resulting cost-effectiveness ratio was $26,481 per QALY gained.

Facility-based Analyses

Two recent U.S.-based studies modeled the case distribution necessary to service the debt incurred from the construction of new proton facilities (Elnahal, 2013; Johnstone, 2012). The more recent of these examined the impact of accountable care organization (ACO) Medicare reimbursement scenarios on debt servicing, by assessing the potential mix of complex or pediatric cases along with noncomplex and prostate cases that could be delivered with session times <30 minutes (Elnahal, 2013). Overall, replacing fee-for-service reimbursement with ACO payments would be expected to reduce daily revenue by 32%. Approximately one-quarter of complex cases would need to be replaced by noncomplex cases simply to cover debt, and PBT facilities would need to operate 18 hours per day.

The earlier study assessed the fee-for-service case distribution required to service debt in PBT facilities of various sizes (Johnstone, 2012). A single-room facility would be able to cover debt while treating only complex and pediatric cases if 85% of treatment slots were filled, but could also achieve this by treating four hours of noncomplex (30 minutes per session) and prostate (24 minutes) cases. Three- and four-room facilities could not service debt by treating complex and pediatric cases alone; an estimated 33-50% of volume would need to be represented by simple/prostate cases to service debt in larger facilities.

An additional U.S. study examined the potential impact on reimbursement of replacing 2007 radiation therapy volume at Rhode Island Hospital (i.e., IMRT, stereotactic radiation, GammaKnife®) with PBT in all instances, based on Medicare reimbursement rates (Dvorak, 2010). No impact on capital expenditures was assumed. A total of 1,042 patients were treated with other radiation modalities, receiving nearly 20,000 treatment fractions. Estimated Medicare reimbursement was approximately $6 million at baseline. Replacing all of these fractions with PBT would increase reimbursement to approximately $7.3 million, representing a 22% increase. It was further estimated that 1.4 PBT gantries would be necessary to treat this patient volume.

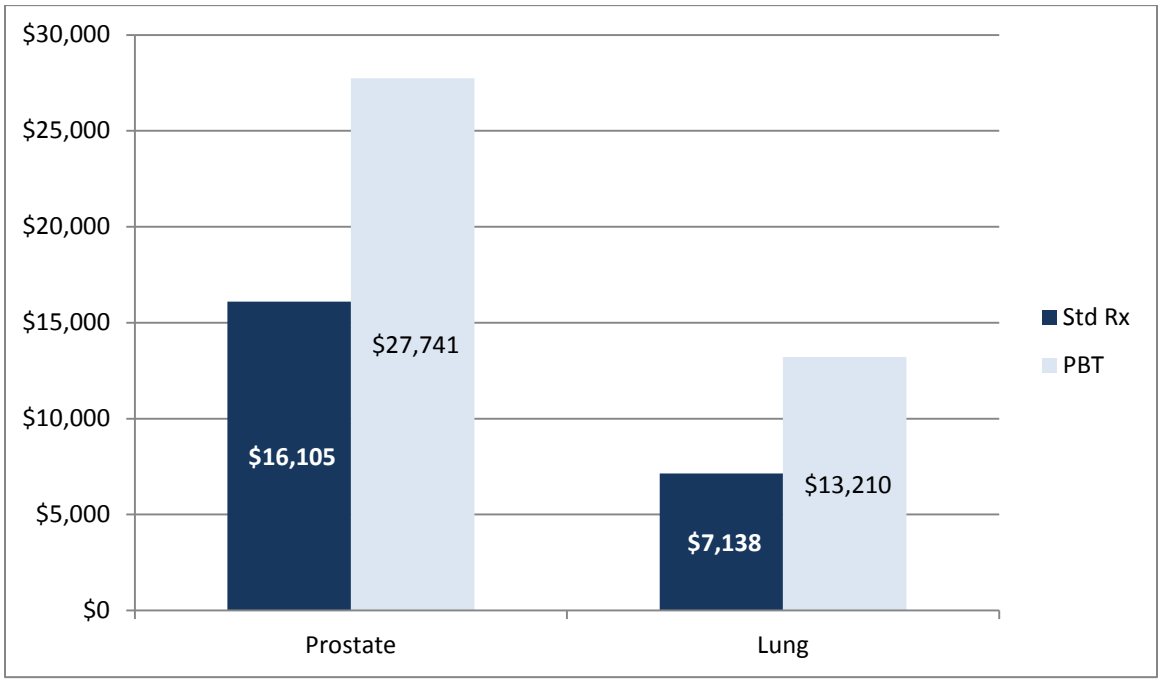
Two additional studies modeled the costs of new construction of proton facilities in Europe (Peeters, 2010; Goitien, 2003). Both assumed a 30-year facility lifetime and 13-14 hours of daily operation. Taking into account both construction and daily operating costs, the total institutional costs to deliver PBT was estimated to be 2.4-3.2 times higher than that of conventional photon radiation in these studies. The Peeters study also estimated the costs to operate a combined proton-carbon ion facility, and estimated these costs at approximately 5 times higher than that of a photon-only facility (Peeters, 2010).

Budget Impact Analysis: Prostate and Lung Cancer

To provide additional context for an understanding of the economics of PBT, we performed a simple budget impact analysis based on 2012 radiation therapy volume within the Public Employees Benefits Board (PEBB) at the HCA. We focused on prostate and lung cancer as two common cancers for which treatment with PBT would be considered.

In 2012, 110 prostate cancer patients received treatment with IMRT or brachytherapy. Considering only the costs of treatment delivery (i.e., not of planning or follow-up), allowed payments averaged $19,143 and $10,704 for IMRT and brachytherapy respectively, and totaled approximately $1.8 million for the population. A single PEBB prostate cancer patient was referred for PBT; in this patient, allowed payments totaled $27,741 for 21 treatment encounters ($1,321 per encounter). Applying this payment level to all 110 patients would result in a total of approximately $3.1 million, or a 73% increase. Comparisons of weighted average payments per patient can be found in Figure 5 on the following page.

Figure 5. Comparisons of average per-patient payments in PEBB plan based on current radiation therapy volume and expected payments for proton beam therapy.



NOTE: "Std Rx" refers to the current mix of radiation treatments used in each population (IMRT and brachytherapy for prostate cancer, IMRT and radiosurgery for lung cancer)

In 2012, 33 PEBB patients received radiation treatment for lung cancer. Allowed payments for treatment delivery averaged $15,963 and $4,792 for IMRT and radiosurgery respectively, and totaled approximately $240,000 for the population. Because PEBB had no lung cancer referrals for PBT, we assumed that treatment with 10 fractions would cost the same per fraction as for prostate cancer

($1,321), summing to a total cost of $13,210. Based on these assumptions, converting all 33 patients to PBT would raise total payment to approximately $440,000 annually, or an 84% increase.
Because volume of radiation treatments in the PEBB plan for these cancers was relatively low, and a single case was referred out of state for PBT, these payment estimates might be considered too variable for comparison. We conducted an additional analysis for prostate cancer patients using national Medicare payment estimates from a publicly-available analysis of changes in Hospital Outpatient Prospective Payment System (HOPPS) rates conducted by Revenue Cycle, Inc. for Varian Medical Systems (Varian, Inc., 2014). We used 2013 payment estimates for HDR brachytherapy, IMRT, and PBT. We assumed 40 fractions were delivered each for IMRT and PBT. Payment estimates, including simulation, planning, and treatment, were $8,548, $21,884, and $30,270 for brachytherapy, IMRT, and PBT respectively. Based on the 2012 mix of treatments in the PEBB plan (70 IMRT, 40 brachytherapy), expected Medicare HOPPS payments would total approximately $1.9 million. If all 110 patients were treated instead with PBT, expected payments would be approximately $3.3 million. This represents a 78% increase, which is similar in magnitude to that estimated using actual PEBB payments.

There are clear limitations to this analysis in that we do not know whether patients treated by PBT would have the same severity mix as the existing population, or whether some of these patients would not even be candidates for PBT. We also did not estimate total costs of care for these patients, so any potential cost-offsets are not represented here. Nevertheless, this analysis represents a reasonable estimate of the treatment expenditures the PEBB plan could expect to incur if all prostate and lung cancer patients currently receiving other radiation modalities were switched to PBT.

9. Summary and Recommendations for Future Research

Proton beam therapy (PBT) has been used for clinical purposes for over 50 years and has been delivered to tens of thousands of patients with a variety of cancers and noncancerous conditions. Despite this, evidence of PBT's comparative clinical effectiveness and comparative value is lacking for nearly all conditions under study in this review. As mentioned previously, it is unlikely that significant comparative study will be forthcoming for childhood cancers despite uncertainty over long-term outcomes, as the potential benefits of PBT over alternative forms of radiation appear to be generally accepted in the clinical and payer communities. In addition, patient recruitment for potential studies may be untenable in very rare conditions (e.g., thymoma, arteriovenous malformations). In other areas, however, including common cancers such as breast and prostate, the poor evidence base and residual uncertainty around the effects of PBT is highly problematic.

We rated the net health benefit of PBT relative to alternative treatments to be "Superior" (moderate-large net health benefit) in ocular tumors and "Incremental" (small net health benefit) in adult brain/spinal and pediatric cancers. We judged the net health benefit to be "Comparable" (equivalent net health benefit) in several other cancers, including liver, lung, and prostate cancer, as well as hemangiomas. It should be noted, however, that we made judgments of comparability based on a limited evidence base that provides relatively low certainty that PBT is roughly equivalent to alternative therapies. While further study may reduce uncertainty and clarify differences between treatments, it is currently the case that PBT is far more expensive than its major alternatives, and evidence of its short or long-term relative cost-effectiveness is lacking for many of these conditions. It should also be noted that we examined evidence for 11 cancers and noncancerous conditions not listed above, and determined that there was insufficient evidence to obtain even a basic understanding of PBT's comparative clinical effectiveness and comparative value.

For relatively common cancers, the ideal evidence of PBT's clinical impact would come from randomized clinical trials such as those currently ongoing in liver, lung, and prostate cancer (see Section 6 for further details). To allay concerns regarding the expense and duration of trials designed to detect survival differences, new RCTs can focus on validated intermediate endpoints such as tumor progression or recurrence, biochemical evidence of disease, development of metastases, and near-term side effects or toxicities. In any event, overall and disease-free survival should be included as secondary measures of interest.

In addition, the availability of large, retrospective databases that integrate clinical and economic information should allow for the development of robust observational studies even as RCTs are being conceived of and designed. Advanced statistical techniques and sampling methods have been used to create observational datasets of patients treated with PBT and alternative therapies using national databases like the Medicare-SEER database and Chronic Conditions Warehouse used in some of the studies summarized in this review. These studies will never produce evidence as persuasive as

randomized comparisons because of concerns regarding selection and other biases, and administrative databases lack the clinical detail necessary to create rigorously-designed observational datasets. The continued growth of electronic health records from integrated health systems may allow for the creation of more detailed clinical and economic comparisons in large, well-matched patient groups receiving alternative radiation modalities. Use of clinical records-based registries and other observational datasets may therefore yield substantial information on PBT's benefits and harms under typical-practice conditions, as well as an indication of whether RCTs should be considered in the first place. Use of available clinical and administrative datasets also represents an opportunity for the payer and clinical communities to collaborate in setting standards for study design, identifying the outcomes of most interest, and sharing resources so that evidence can be generated in the most efficient manner possible.

References

1. Abei M, Okumura T, Fukuda K, et al. A phase I study on combined therapy with proton-beam radiotherapy and in situ tumor vaccination for locally advanced recurrent hepatocellular carcinoma. *Radiat Oncol.* 2013;8:239.
2. Agency for Healthcare Research & Quality (AHRQ). Methods guide for effectiveness and comparative effectiveness reviews (2014). AHRQ publication No. 10(14)-EHC063-EF. http://www.effectivehealthcare.ahrq.gov/ehc/products/60/318/CER-Methods-Guide-140109.pdf. Accessed January, 2014.
3. Agency for Healthcare Research & Quality (AHRQ). U.S. Preventive Services Task Force Procedure Manual: Criteria for Assessing Internal Validity of Individual Studies (2008). http://www.uspreventiveservicestaskforce.org/uspstf08/methods/procmanualap7.htm. Accessed January, 2014.
4. Ahmadi T, Itai Y,Onaya H, Yoshioka H, Okumura T, Akine Y. CT evaluation of hepatic injury following proton beam irradiation: appearance, enhancement, and 3D size reduction pattern. *J Comput Assist Tomogr.* 1999;23(5):655-663.
5. Ahmadi T, Okumura T, Onaya H, Akine Y, Itai Y. Preservation of hypervascularity in hepatocellular carcinoma after effective proton-beam radiotherapy – CT observation. *Clin Radiol*. 1999;54(4):253-256.
6. American Cancer Society. Cancer facts & figures 2013. http://www.cancer.org/acs/groups/content/@epidemiologysurveilance/documents/document/acspc-036845.pdf. Accessed January, 2014.
7. American Cancer Society. Prostate cancer. How is prostate cancer staged? http://www.cancer.org/cancer/prostatecancer/detailedguide/prostate-cancer-staging. Accessed March, 2014.
8. American Joint Committee on Cancer. Cancer staging references. http://cancerstaging.org/references-tools/Pages/What-is-Cancer-Staging.aspx. Accessed March, 2014.
9. Amsbaugh MJ, Grosshans DR, McAleer MF, et al. Proton therapy for spinal ependymomas: planning, acute toxicities, and preliminary outcomes. *Int J Radiat Oncol Biol Phys.* 2012;83(5):1419-1424.
10. Ares C, Hug EB, Lomax AJ, et al. Effectiveness and safety of spot scanning proton radiation therapy for chordomas and chondrosarcomas of the skull base: first long-term report. *Int J Radiat Oncol Biol Phys*. 2009;75(4):1111-1118.
11. Arimoto T, Kitagawa T, Tsujii H, Ohhara K. High-energy proton beam radiation therapy for gynecologic malignancies. Potential of proton beam as an alternative to brachytherapy. *Cancer*. 1991;68(1):79-83.
12. Arvold ND, Lessell S, Bussiere M, et al. Visual outcome and tumor control after conformal radiotherapy for patients with optic nerve sheath meningioma. *Int J Radiat Oncol Biol Phys*. 2009;75(4):1166-1172.

13. Aziz S, Taylor A, McConnachie A, Kacperek A, Kemp E. Proton beam radiotherapy in the management of uveal melanoma: clinical experience in Scotland. *Clin Ophthalmol*. 2009;3(1):49-55.

14. Barker FG II, Butler WE, Lyons S, et al. Dose-volume prediction of radiation-related complications after proton beam radiosurgery for cerebral arteriovenous malformations. *J Neurosurg*. 2003;99(2):254-263.

15. Barney CL, Brown AP, Grosshans DR, et al. Technique, outcomes, and acute toxicities in adults treated with proton beam craniospinal irradiation. *Neuro Oncol*. 2014;16(2):303-309.

16. Bekelman JE, Hahn SM. The body of evidence for advanced technology in radiation oncology. *J Natl Cancer Inst*. 2013;105(1):6-7.

17. Bekelman JE, Schultheiss T, Berrington De Gonzalez A. Subsequent malignancies after photon versus proton therapy. *Int J Radiat Oncol Biol Phys*. 2013;87(1):10-12.

18. Bellmann C, Lumbroso-Le Rouic L, Levy C, et al. Uveal melanoma: management and outcome of patients with extraocular spread. *Br J Ophthalmol*. 2010;94(5):569-574.

19. Benk VA, Adams JA, Shipley WU, et al. Late rectal bleeding following combined x-ray and proton high dose irradiation for patients with stages T3-T4 prostate cancer. *Int J Radiat Oncol Biol Phys*. 1993;26(3):551-557.

20. Benk V, Liebsch NJ, Munzenrider JE, Efird J, McManus P, Suit H. Base of skull and cervical spine chordomas in children treated by high-dose irradiation. *Int J Radiat Oncol Biol Phys.* 1995;31(3):577-581.

21. Bhattacharyya N, Thornton AF, Joseph MP, Goodman ML, Amrein PC. Successful treatment of esthesioneuroblastoma and neuroendocrine carcinoma with combined chemotherapy and proton radiation. Results in 9 cases. *Arch Otolaryngol Head Neck Surg.* 1997;123(1):34-40.

22. Bian SX, McAleer MF, Vats TS, Mahajan A, Grosshans DR. Pilocytic astrocytoma with leptomeningeal dissemination. *Childs Nerv Syst*. 2013;29(3):441-450.

23. Bonnet RB, Bush D, Cheek GA, et al. Effects of proton and combined proton/photon beam radiation on pulmonary function in patients with resectable but medically inoperable non-small cell lung cancer. *Chest*. 2001;120(6):1803-1810.

24. Boskos C, Feuvret L, Noël J, et al. Combined proton and photon conformal radiotherapy for intracranial atypical and malignant meningioma. *Int J Radiat Oncol Biol Phys*. 2009;75(2):399-406.

25. Bostrom PJ, Soloway MS. Secondary cancer after radiotherapy for prostate cancer: should we be more aware of the risk? *Eur Urol.* 2007;52(4):973-982.

26. Bowyer J, Natha S, Marsh I, Foy P. Visual complications of proton beam therapy for clival chordoma. *Eye*. 2003;17(3):318-323.

27. Brown AP, Barney CL, Grosshans DR, et al. Proton beam craniospinal irradiation reduces acute toxicity for adults with medulloblastoma. *Int J Radiat Oncol Biol Phys*. 2013;86(2):277-284.

28. Bruce JY, Lang JM, McNeel DG, Liu G. Current controversies in the management of biochemical failure in prostate cancer. *Clin Adv Hematol Oncol*. 2012;10(11):716-722.

29. Bush DA, Cheek G, Zaheer S, et al. High-dose hypofractionated proton beam radiation therapy is safe and effective for central and peripheral early-stage non-small cell lung cancer: results of a 12-

year experience at Loma Linda University Medical Center. *Int J Radiat Oncol Biol Phys*. 2013;86(5):964-968.

30. Bush DA, Dunbar RD, Bonnet R, Slater JD, Cheek GA, Slater JM. Pulmonary injury from proton and conventional radiotherapy as revealed by CT. *AJR Am J Roentgenol*. 1999;172(3):735-739.
31. Bush DA, Hillebrand DJ, Slater JM, Slater JD. High-dose proton beam radiotherapy of hepatocellular carcinoma: preliminary results of a phase II trial. *Gastroenterology*. 2004;127(5 Suppl 1):S189-S193.
32. Bush DA, Kayali Z, Grove R, Slater JD. The safety and efficacy of high-dose proton beam radiotherapy for hepatocellular carcinoma: a phase 2 prospective trial. *Cancer*. 2011;117(13):3053-3059.
33. Bush DA, Slater JD, Bonnet R, et al. Proton-beam radiotherapy for early-stage lung cancer. *Chest*. 1999;116(5):1313-1319.
34. Bush DA, Slater JD, Garberoglio C, Do S, Lum S, Slater JM. Partial breast irradiation delivered with proton beam: results of a phase II trial. *Clin Breast Cancer*. 2011;11(4):241-245.
35. Bush DA, Slater JD, Garberoglio C, Yuh G, Hocko JM, Slater JM. A technique of partial breast irradiation utilizing proton beam radiotherapy: comparison with conformal x-ray therapy. *Cancer J*. 2007;13(2):114-118.
36. Bush DA, Slater JD, Shin BB, Cheek G, Miller DW, Slater JM. Hypofractionated proton beam radiotherapy for stage I lung cancer. *Chest*. 2004;126(4):1198-1203.
37. Brown AP, Barney CL, Grosshans DR, et al. Proton beam craniospinal irradiation reduces acute toxicity for adults with medulloblastoma. *Int J Radiat Oncol Biol Phys*. 2013;86(2):277-284.
38. Cassoux N, Cayette S, Plancher C, et al. Choroidal melanoma: does endoresection prevent neovascular glaucoma in patient treated with proton beam irradiation? *Retina*. 2013;33(7):1441-1447.
39. Caujolle J-P, Mammar H, Chamorey E, Pinon F, Herault J, Gastaud P. Proton beam radiotherapy for uveal melanomas at Nice teaching hospital: 16 years' experience. *Int J Radiat Oncol Biol Phys*. 2010;78(1):98-103.
40. Caujolle J-P, Paoli V, Chamorey E, et al. Local recurrence after uveal melanoma proton beam therapy: recurrence types and prognostic consequences. *Int J Radiat Oncol Biol Phys*. 2013;85(5):1218-1224.
41. Chakravarti A, Spiro IJ, Hug EB, et al. Megavoltage radiation therapy for axial and inoperable giant-cell tumor of bone. *J Bone Joint Surg Am*. 1999;81(11):1566-1573.
42. Chang JH, Lee NK, Kim JY, et al. Phase II trial of proton beam accelerated partial breast irradiation in breast cancer. *Radiother Oncol*. 2013;108(2):209-214.
43. Chang JW, Yu YS, Kim JY, et al. The clinical outcomes of proton beam radiation therapy for retinoblastomas that were resistant to chemotherapy and focal treatment. *Korean J Ophthalmol*. 2011;25(6):387-393.
44. Chang JY, Komaki R, Lu C, et al. Phase 2 study of high-dose proton therapy with concurrent chemotherapy for unresectable stage III nonsmall cell lung cancer. *Cancer*. 2011;117(20):4707-4713.

45. Chang JY, Komaki R, Wen HY, et al. Toxicity and patterns of failure of adaptive/ablative proton therapy for early-stage, medically inoperable non-small cell lung cancer. *Int J Radiat Oncol Biol Phys*. 2011;80(5):1350-1357.

46. Chappell MC, Char DH, Cole TB, et al. Uveal melanoma: molecular pattern, clinical features, and radiation response. *Am J Ophthalmol*. 2012;154(2):227-232.

47. Char DH, Bove R, Phillips TL. Laser and proton radiation to reduce uveal melanoma-associated exudative retinal detachments. *Trans Am Ophthalmol Soc*. 2003;101:53-56.

48. Chen Y-L, Liebsch N, Kobayashi W, et al. Definitive high-dose photon/proton radiotherapy for unresected mobile spine and sacral chordomas. *Spine*. 2013;38(15):E930-E936.

49. Chiba T, Tokuuye K, Matsuzaki Y, et al. Proton beam therapy for hepatocellular carcinoma: a retrospective review of 162 patients. *Clin Cancer Res.* 2005;11(10):3799-3805.

50. Childs SK, Kozak KR, Friedmann AM, et al. Proton radiotherapy for parameningeal rhabdomyosarcoma: clinical outcomes and late effects. *Int J Radiat Oncol Biol Phys*. 2012;82(2):635-642.

51. Chung CS, Yock TI, Nelson K, Xu Y, Keating NL, Tarbell NJ. Incidence of second malignancies among patients treated with proton versus photon radiation. *Int J Radiat Oncol Biol Phys*. 2013;87(1):46-52.

52. Ciernik IF, Niemierko A, Harmon DC, et al. Proton-based radiotherapy for unresectable or incompletely resected osteosarcoma. *Cancer*. 2011;117(19):4522-4530.

53. Coen JJ, Bae K, Zietman AL, et al. Acute and late toxicity after dose escalation to 82 GyE using conformal proton radiation for localized prostate cancer: initial report of American College of Radiology phase II study 03-12. *Int J Radiat Oncol Biol Phys*. 2011;81(4):1005-1009.

54. Coen JJ, Paly JJ, Niemierko A, et al. Long-term quality of life outcome after proton beam monotherapy for localized prostate cancer. *Int J Radiat Oncol Biol Phys*. 2012;82(2):e201-e209.

55. Coen JJ, Zietman AL, Rossi CJ, et al. Comparison of high-dose proton radiotherapy and brachytherapy in localized prostate cancer: a case-matched analysis. *Int J Radiat Oncol Biol Phys*. 2012;82(1):e25-e31.

56. Colaco RJ, Huh S, Nichols RC, et al. Dosimetric rationale and early experience at UFPTI of thoracic proton therapy and chemotherapy in limited-stage small cell lung cancer. *Acta Oncol.* 2013;52(3):506-513.

57. Combs SE, Kessel K, Habermehl, Haberer T, Jäkel O, Debus J. Proton and carbon ion radiotherapy for primary brain tumors and tumors of the skull base. *Acta Oncol.* 2013;52(7):1504-1509.

58. Combs SE, Laperriere N, Brada M. Clinical controversies: proton radiation therapy for brain and skull base tumors. *Semin Radiat Oncol.* 2013;23(2):120-126.

59. Combs SE, Welzel T, Habermehl D, et al. Prospective evaluation of early treatment outcome in patients with meningiomas treated with particle therapy based on target volume definition with MRI and 68Ga-DOTATOC-PET. *Acta Oncol.* 2013;52(3):514-520.

60. Conway RM, Poothullil AM, Daftari IK, Weinberg V, Chung JE, O'Brien JM. Estimates of ocular and visual retention following treatment of extra-large uveal melanomas by proton beam ratiotherapy. *Arch Ophthalmol*. 2006;124(6):838-843.

61. Cotter SE, Herrup DA, Friedmann A, et al. Proton radiotherapy for pediatric bladder/prostate rhabdomyosarcoma: clinical outcomes and dosimetry compared to intensity-modulated radiation therapy. *Int J Radiat Oncol Biol Phys*. 2011;81(5):1367-1373.

62. Counsell C. Formulating questions and locating primary studies for inclusion in systematic reviews. *Ann Intern Med.* 1997;127(5):380-387.

63. Courdi A, Caujolle J-P, Grange J-D, et al. Results of proton therapy of uveal melanomas treated in Nice. *Int J Radiat Oncol Biol Phys*. 1999;45(1):5-11.

64. Damato B, Kacperek A, Chopra M, Campbell IR, Errington RD. Proton beam radiotherapy of choroidal melanoma: the Liverpool-Clatterbridge experience. *Int J Radiat Oncol Biol Phys*. 2005;62(5):1405-1411.

65. Damato B, Kacperek A, Chopra M, Sheen MA, Campbell IR, Errington RD. Proton beam radiotherapy of iris melanoma. *Int J Radiat Oncol Biol Phys*. 2005;63(1):109-115.

66. De Amorim Bernstein K, Sethi R, Trofimov, et al. Early clinical outcomes using proton radiation for children with central nervous system atypical teratoid rhabdoid tumors. *Int J Radiat Oncol Biol Phys*. 2013;86(1):114-120.

67. Debus J, Hug EB, Liebsch NJ, et al. Brainstem tolerance to conformal radiotherapy of skull base tumors. *Int J Radiat Oncol Biol Phys*. 1997;39(5):967-975.

68. Delaney G, Jacob S, Featherstone C, Barton M. The role of radiotherapy in cancer treatment. Estimating optimal utilization from a review of evidence-based clinical guidelines. *Cancer*. 2005;104(6):1129-1137.

69. DeLaney TF, Liebsch NJ, Pedlow FX, et al. Phase II study of high-dose photon/proton radiotherapy in the management of spine sarcomas. *Int J Radiat Oncol Biol Phys.* 2009;74(3):732-739.

70. Demizu Y, Murakami M, Miyawaki D, et al. Analysis of vision loss caused by radiation-induced optic neuropathy after particle therapy for head-and-neck and skull-base tumors adjacent to optic nerves. *Int J Radiat Oncol Biol Phys*. 2009;75(5):1487-1492.

71. De Ruysscher D, Lodge MM, Jones B, et al. Charged particles in radiotherapy: a 5-year update of a systematic review. *Radiotherapy and Oncology* 2012;103:5-7.

72. Desjardins L, Lumbroso-Le Rouic L, Levy-Gabriel C, et al. Combined proton beam radiotherapy and transpupillary thermotherapy for large uveal melanomas: a randomized study of 151 patients. *Ophthalmic Res*. 2006;38(5):255-260.

73. Do SY, Bush DA, Slater JD. Comorbidity-adjusted survival in early stage lung cancer patients treated with hypofractionated proton therapy. *J Oncol*. 2010;251208.

74. Dvorak T, Wazer DE. Evaluation of potential proton therapy utilization in a market-based environment. *J Am Coll Radiol*. 2010;7(7):522-528.

75. Echeverria AE, McCurdy M, Castillo R, et al. Proton therapy radiation pneumonitis local dose-response in esophagus cancer patients. *Radiother Oncol*. 2013;106(1):124-129.

76. Efstathiou JA, Gray PJ, Zietman AL. Proton beam therapy and localized prostate cancer: current status and controversies. *Br J Cancer*. 2013;108(6):1225-1230.

77. Elnahal SM, Kerstiens J, Helsper RS, Zietman AL, Johnstone PAS. Proton beam therapy and accountable care: the challenges ahead. *Int J Radiat Oncol Biol Phys*. 2013;85(4):e165-e172.

78. Esiashvili N, Koshy M, Landry J. Intensity-modulated radiation therapy. *Curr Probl Cancer.* 2004;28(2):47-84.

79. Fagundes MA, Hug EB, Liebsch NJ, Daly W, Efird J, Munzenrider JE. Radiation therapy for chordomas of the base of skull and cervical spine: patterns of failure and outcome after relapse. *Int J Radiat Oncol Biol Phys*. 1995;33(3):579-584.

80. Feuvret L, Noël G, Calugaru V, Terrier P, Habrand J-L. Chondromyxoid fibroma of the skull base: differential diagnosis and radiotherapy: two case reports and a review of the literature. *Acta Oncol*. 2005;44(6):545-553.

81. Fitzek MM, Linggood RM, Adams J, Munzenrider JE. Combined proton and photon irradiation for craniopharyngioma: long-term results of the early cohort of patients treated at Harvard Cyclotron Laboratory and Massachusetts General Hospital. *Int J Radiat Oncol Biol Phys*. 2006;64(5):1348-1354.

82. Fitzek MM, Thornton AF, Harsh G, et al. Dose-escalation with proton/photon irradiation for Daumas-Duport lower-grade glioma: results of an institutional phase I/II trial. *Int J Radiat Oncol Biol Phys*. 2001;51(1):131-137.

83. Fitzek MM, Thornton AF, Rabinov JD, et al. Accelerated fractionated proton/photon irradiation to 90 cobalt gray equivalent for glioblastoma multiforme: results of a phase II prospective trial. *J Neurosurg*. 1999;91(2):251-260.

84. Fitzek MM, Thornton AF, Varvares M, et al. Neuroendocrine tumors of the sinonasal tract. Results of a prospective study incorporating chemotherapy, surgery, and combined proton-photon radiotherapy. *Cancer*. 2002;94(10):2623-2634.

85. Fujii O, Demizu Y, Hashimoto N, et al. A retrospective comparison of proton therapy and carbon ion therapy for stage I non-small cell lung cancer. *Radiother Oncol.* 2013;109(1):32-37.

86. Fukumitsu N, Okumura T, Mizumoto M, et al. Outcome of T4 (International Union Against Cancer Staging System, 7th edition) or recurrent nasal cavity and paranasal sinus carcinoma treated with proton beam. *Int J Radiat Oncol Biol Phys*. 2012;83(2):704-711.

87. Fukumitsu N, Sugahara S, Nakayama H, et al. A prospective study of hypofractionated proton beam therapy for patients with hepatocellular carcinoma. *Int J Radiat Oncol Biol Phys*. 2009;74(3):831-836.

88. Fukumoto T, Komatsu S, Hori Y, Murakami M, Hishikawa Y, Ku Y. Particle beam radiotherapy with a surgical spacer placement for advanced abdominal leiomyosarcoma results in a significant clinical benefit. *J Surg Oncol.* 2010;101(1):97-99.

89. Galbraith ME, Ramirez JM, Pedro LW. Quality of life, health outcomes, and identity for patients with prostate cancer in five different treatment groups. *Oncol Nurs Forum*. 2001;28(3):551-560.

90. Gardner BG, Zietman AL, Shipley WU, Skowronski UE, McManus P. Late normal tissue sequelae in the second decade after high dose radiation therapy with combined photons and conformal protons for locally advanced prostate cancer. *J Urol*. 2002;167(1):123-126.

91. Glatstein E, Glick J, Kaiser L, Hahn SM. Should randomized clinical trials be required for proton radiotherapy? An alternative view. *J Clin Oncol.* 2008;26(15):2438-2439.

92. Glimelius B, Montelius A. Proton beam therapy – do we need the randomised trials and can we do them? *Radiother Oncol*. 2007;83(2):105-109.

93. Goitein M. Magical protons? *Int J Radiat Oncol Biol Phys*. 2008;70(3):654-656.

94. Goitein M, Jermann M. The relative costs of proton and x-ray radiation therapy. *Clin Oncol (R Coll Radiol)*. 2003;15(1):S37-S50.

95. Gomez DR, Gillin M, Liao Z, et al. Phase 1 study of dose escalation in hypofractionated proton beam therapy for non-small cell lung cancer. *Int J Radiat Oncol Biol Phys*. 2013;86(4):665-670.

96. Gomez DR, Tucker SL, Martel MK, et al. Predictors of high-grade esophagitis after definitive three-dimensional conformal therapy, intensity-modulated radiation therapy, or proton beam therapy for non-small cell lung cancer. *Int J Radiat Oncol Biol Phys*. 2012;84(4):1010-1016.

97. Gragoudas ES, Lane AM, Munzenrider J, Egan KM, Li W. Long-term risk of local failure after proton therapy for choroidal/ciliary body melanoma. *Trans Am Ophthalmol Soc*. 2002a;100:43-50.

98. Gragoudas ES, Lane AM, Regan S, et al. A randomized controlled trial of varying radiation doses in the treatment of choroidal melanoma. *Arch Ophthalmol*. 2000;118(6):773-778.

99. Gragoudas E, Li W, Goitein M, Lane AM, Munzenrider JE, Egan KM. Evidence-based estimates of outcome in patients irradiated for intraocular melanoma. *Arch Ophthalmol*. 2002b;120(12):1665-1671.

100. Gragoudas ES, Li W, Lane AM, Munzenrider J, Egan KM. Risk factors for radiation maculopathy and papillopathy after intraocular irradiation. Ophthalmology. 1999;106(8):1571-1578.

101. Gray PJ, Paly JJ, Yeap BY, et al. Patient-reported outcomes after 3-dimensional conformal, intensity-modulated, or proton beam radiotherapy for localized prostate cancer. *Cancer*. 2013;119(9):1729-1735.

102. Gray ST, Chen Y-L, Lin DT. Efficacy of proton beam therapy in the treatment of Ewing's sarcoma of the paranasal sinuses and anterior skull base. *Skull Base*. 2009;19(6):409-416.

103. Gridley DS, Bonnet RB, Bush DA, et al. Time course of serum cytokines in patients receiving proton or combined photon/proton beam radiation for resectable but medically inoperable non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys.* 2004;60(3):759-766.

104. Grutters JPC, Abrams KR, de Ruysscher D, et al. When to wait for more evidence? Real options analysis in proton therapy. *Oncologist*. 2011;16(12):1752-1761.

105. Grutters JPC, Pijls-Johannesma M, De Ruysscher, et al. The cost-effectiveness of particle therapy in non-small cell lung cancer: exploring decision uncertainty and areas for future research. *Cancer Treat Rev*. 2010;36(6):468-476.

106. Gudjonsson O, Blomquist E, Nyberg G, et al. Stereotactic irradiation of skull base meningiomas with high energy protons. *Acta Neurochir (Wien).* 1999;141(9):933-940.

107. Habrand J-L, Mammar H, Ferrand R, et al. Proton beam therapy (PT) in the management of CNS tumors in childhood. *Strahlenther Onkol*. 1999;175(Suppl 2):91-94.

108. Habrand J-L, Schneider R, Alapetite C, et al. Proton therapy in pediatric skull base and cervical canal low-grade bone malignancies. *Int J Radiat Oncol Biol Phys*. 2008;71(3):672-675.

109. Hadden PW, Damato BE, McKay IC. Bilateral uveal melanoma: a series of four cases. *Eye*. 2003;17(5):613-616.

110. Halasz LM, Bussière MR, Dennis ER, et al. Proton stereotactic radiosurgery for the treatment of benign meningiomas. *Int J Radiat Oncol Biol Phys*. 2011;81(5):1428-1435.

111. Hannouche D, Frau E, Desjardins L, Cassoux N, Habrand J-L, Offret H. Efficacy of proton therapy in circumscribed choroidal hemangiomas associated with serous retinal detachment. *Ophthalmology*. 1997;104(11):1780-1784.

112. Harsh GR, Thornton AF, Chapman PH, Bussiere MR, Rabinov JD, Loeffler JS. Proton beam stereotactic radiosurgery of vestibular schwannomas. *Int J Radiat Oncol Biol Phys*. 2002;54(1):35-44.

113. Hashimoto T, Isobe T, Hashii H, et al. Influence of secondary neutrons induced by proton radiotherapy for cancer patients with implantable cardioverter defibrillators. *Radiat Oncol.* 2012;7:10.

114. Hashimoto T, Tokuuye K, Fukumitsu N, et al. Repeated proton beam therapy for hepatocellular carcinoma. *Int J Radiat Oncol Biol Phys*. 2006;65(1):196-202.

115. Hata M, Miyanaga N, Tokuuye K, et al. Proton beam therapy for invasive bladder cancer: a prospective study of bladder-preserving therapy with combined radiotherapy and intra-arterial chemotherapy. *Int J Radiat Oncol Biol Phys*. 2006;64(5):1371-1379.

116. Hata M, Tokuuye K, Kagei K, et al. Hypofractionated high-dose proton beam therapy for stage I non-small-cell lung cancer: preliminary results of a phase I/II clinical study. *Int J Radiat Oncol Biol Phys*. 2007;68(3):786-793.

117. Hata M, Tokuuye K, Sugahara S, et al. Proton beam therapy for hepatocellular carcinoma with limited treatment options. *Cancer*. 2006a;107(3):591-598.

118. Hata M, Tokuuye K, Sugahara S, et al. Proton beam therapy for hepatocellular carcinoma patients with severe cirrhosis. *Strahlenther Onkol*. 2006b;182(12):713-720.

119. Hata M, Tokuuye K, Sugahara S, et al. Proton beam therapy for hepatocellular carcinoma with portal vein tumor thrombus. *Cancer*. 2005;104(4):794-801.

120. Hata M, Tokuuye K, Sugahara S, et al. Proton irradiation in a single fraction for hepatocellular carcinoma patients with uncontrollable ascites. *Strahlenther Onkol.* 2007;183(8):411-416.

121. Hata M, Tokuuye K, Sugahara S, et al. Proton beam therapy for aged patients with hepatocellular carcinoma. *Int J Radiat Oncol Biol Phys*. 2007;69(3):805-812.

122. Hattangadi JA, Chapman PH, Bussière MR, et al. Planned two-fraction proton beam stereotactic radiosurgery for high-risk inoperable cerebral arteriovenous malformations. *Int J Radiat Oncol Biol Phys*. 2012;83(2):533-541.

123. Hattangadi J, Esty B, Winey B, Duigenan S, Huang M, Tock T. Radiation recall myositis in pediatric Ewing sarcoma. *Pediatr Blood Cancer*. 2012;59(3):570-572.

124. Hattangadi JA, Rombi B, Yock TI, et al. Proton radiotherapy for high-risk pediatric neuroblastoma: early outcomes and dose comparison. *Int J Radiat Oncol Biol Phys.* 2012;83(3):1015-1022.

125. Hauswald H, Rieken S, Ecker S, et al. First experiences in treatment of low-grade glioma grade I and II with proton therapy. *Radiat Oncol.* 2012;7:189.

126. Henderson RH, Hoppe BS, Marcus RB Jr, et al. Urinary functional outcomes and toxicity five years after proton therapy for low- and intermediate-risk prostate cancer: results of two prospective trials. *Acta Oncol*. 2013;52(3):463-469.

127. Hill-Kayser C, Tochner Z, Both S, et al. Proton versus photon radiation therapy for patients with high-risk neuroblastoma: the need for a customized approach. *Pediatr Blood Cancer.* 2013;60(10):1606-1611.

128. Hoch BL, Nielsen GP, Liebsch NJ, Rosenberg AE. Base of skull chordomas in children and adolescents. A clinicopathologic study of 73 cases. *Am J Surg Pathol.* 2006;30(7):811-818.

129. Höcht S, Bechrakis NE, Nausner M, et al. Proton therapy of uveal melanomas in Berlin. 5 years of experience at the Hahn-Meitner Institute. *Strahlenther Onkol*. 2004;180(7):419-424.

130. Hofmann B. Fallacies in the arguments for new technology: the case of proton therapy. *J Med Ethics.* 2009;35(11):684-687.

131. Höcht S, Wachtlin J, Bechrakis NE, et al. Proton or photon irradiation for hemangiomas of the choroid? A retrospective comparison. *Int J Radiat Oncol Biol Phys*. 2006;66(2):345-351.

132. Hojo H, Zenda S, Akimoto T, et al. Impact of early radiological response evaluation on radiotherapeutic outcomes in the patients with nasal cavity and paranasal sinus malignancies. *J Radiat Res (Tokyo).* 2012;53(5):704-709.

133. Hong TS, Ryan DP, Blaszkowsky LS, et al. Phase I study of preoperative short-course chemoradiation with proton beam therapy and capecitabine for resectable pancreatic ductal adenocarcinoma of the head. *Int J Radiat Oncol Biol Phys.* 2011;79(1):151-157.

134. Hoppe BS, Flampouri S, Henderson RH, et al. Proton therapy with concurrent chemotherapy for non-small-cell lung cancer: technique and early results. *Clin Lung Cancer.* 2012;13(5):352-358.

135. Hoppe BS, Michalski JM, Mendenhall NP, et al. Comparative effectiveness study of patient-reported outcomes after proton therapy or intensity-modulated radiotherapy for prostate cancer. *Cancer*. 2013. [Epub ahead of print].

136. Hoppe BS, Nichols RC, Henderson RH, et al. Erectile function, incontinence, and other quality of life outcomes following proton therapy for prostate cancer in men 60 years old and younger. *Cancer*. 2012;118(18):4619-4626.

137. Hug EB, Adams J, Fitzek M, De Vries A, Munzenrider JE. Fractionated, three-dimensional, planning-assisted proton-radiation therapy for orbital rhabdomyosarcoma: a novel technique. *Int J Radiat Oncol Biol Phys*. 2000;47(4):979-984.

138. Hug EB, DeVries A, Thornton AF, et al. Management of atypical and malignant meningiomas: role of high-dose, 3D-conformal radiation therapy. *J Neurooncol*. 2000;48(2):151-160.

139. Hug EB, Fitzek MM, Liebsch NJ, Munzenrider JE. Locally challenging osteo- and chondrogenic tumors of the axial skeleton: results of combined proton and photon radiation therapy using three-dimensional treatment planning. *Int J Radiat Oncol Biol Phys*. 1995;31(3):467-476.

140. Hug EB, Loredo LN, Slater JD, et al. Proton radiation therapy for chordomas and chondrosarcomas of the skull base. *J Neurosurg*. 1999;91(3):432-439.

141. Hug EB, Muenter MW, Adams JA, De Vries A, Rosenberg AE, Munzenrider JE. 3-D-conformal radiation therapy for pediatric giant cell tumors of the skull base. *Strahlenther Onkol.* 2002;178(5):239-244.

142. Hug EB, Muenter MW, Archambeau JO, et al. Conformal proton radiation therapy for pediatric low-grade astrocytomas. *Strahlenther Onkol.* 2002;178(1):10-17.

143. Hug EB, Sweeney RA, Nurre PM, Holloway KC, Slater JD, Munzenrider JE. Proton radiotherapy in management of pediatric base of skull tumors. *Int J Radiat Oncol Biol Phys.* 2002;52(4):1017-1024.

144. Ito Y, Okumura T, Suzuki K, Matsumura A, Tokuuye K, Tsuboi. Long-term outcome of proton beam radiosurgery for arteriovenous malformations larger than 30 mm in diameter. *Neurol Med Chir (Tokyo)*. 2011;51(9):624-629.

145. Iwata H, Murakami M, Demizu Y, et al. High-dose proton therapy and carbon-ion therapy for stage I nonsmall cell lung cancer. *Cancer*. 2010;116(10):2476-2485.

146. Jabbari S, Weinberg VK, Shinohara K, et al. Equivalent biochemical control and improved prostate-specific antigen nadir after permanent prostate seed implant brachytherapy versus high-dose three-dimensional conformal radiotherapy and high-dose conformal proton beam radiotherapy boost. *Int J Radiat Oncol Biol Phys*. 2010;76(1):36-42.

147. Jarlskog CZ, Paganetti H. Sensitivity of different dose scoring methods on organ-specific neutron dose calculations in proton therapy. *Phys Med Biol.* 2008;53(17):4523-4532.

148. Jarosek S, Elliott S, Virnig BA. Proton beam radiotherapy in the U.S. Medicare population: growth in use between 2006 and 2009 (2012). AHRQ publication No. 12-EHC005. http://www.effectivehealthcare.ahrq.gov/ehc/products/439/1062/Data-Points-10_20120529.pdf. Accessed December, 2013.

149. Jimenez RB, Sethi R, Depauw N, et al. Proton radiation therapy for pediatric medulloblastoma and supratentorial primitive neuroectodermal tumors: outcomes for very young children treated with upfront chemotherapy. *Int J Radiat Oncol Biol Phys*. 2013;87(1):120-126.

150. Johansson S, Åström L, Sandin F, Isacsson U, Montelius A, Turesson I. Hypofractionated proton boost combined with external beam radiotherapy for treatment of localized prostate cancer. *Prostate Cancer*. 2012;654861.

151. Johnstone PAS, Kerstiens J, Helsper R. Proton facilities economics: the importance of “simple” treatments. *J Am Coll Radiol*. 2012;9(8):560-563.

152. Kagei K, Tokuuye K, Okumura T, et al. Long-tem results of proton beam therapy for carcinoma of the uterine cervix. *Int J Radiat Oncol Biol Phys*. 2003;55(5):1265-1271.

153. Kahn J, Loeffler JS, Niemierko A, Chiocca EA, Batchelor T, Chakravarti A. Long-term outcomes of patients with spinal cord gliomas treated by modern conformal radiation techniques. *Int J Radiat Oncol Biol Phys*. 2011;81(1):232-238.

154. Kanemoto A, Ishikawa H, Mizumoto M, et al. Proton beam therapy for liver metastasis from breast cancer: five case reports and a review of the literature. *Int Canc Conf J.* 2012;1(4):210-214.

155. Kanemoto A, Mizumoto M, Okumura T, et al. Dose-volume histogram analysis for risk factors of radiation-induced rib fracture after hypofractionated proton beam therapy for hepatocellular carcinoma. *Acta Oncol*. 2013;52(3):538-544.

156. Kanemoto A, Okumura T, Ishikawa H, et al. Outcomes and prognostic factors for recurrence after high-dose proton beam therapy for centrally and peripherally located stage I non-small-cell lung cancer. *Clin Lung Cancer*. 2014;15(2):e7-e12.

157. Kawashima M, Furuse J, Nishio T, et al. Phase II study of radiotherapy employing proton beam for hepatocellular carcinoma. *J Clin Oncol*. 2005;23(9):1839-1846.

158. Kawashima M, Kohno R, Nakachi K, et al. Dose-volume histogram analysis of the safety of proton beam therapy for unresectable hepatocellular carcinoma. *Int J Radiat Oncol Biol Phys.* 2011;79(5):1479-1486.

159. Kent D, Noonan CP, Damato BE. Management of Irish patients with intraocular melanoma referred to Liverpool, England. *Acta Ophthalmol Scand*. 1998;76(5):584-588.

160. Kil WJ, Nichols RC Jr., Hoppe BS, et al. Hypofractionated passively scattered proton radiotherapy for low- and intermediate-risk prostate cancer is not associated with post-treatment testosterone suppression. *Acta Oncol*. 2013;52(3):492-497.

161. Kim IK, Lane AM, Egan KM, Munzenrider J, Gragoudas ES. Natural history of radiation papillopathy after proton beam irradiation of parapapillary melanoma. *Ophthalmology*. 2010a;117(8):1617-1622.

162. Kim S, Shen S, Moore DF, et al. Late gastrointestinal toxicities following radiation therapy for prostate cancer. *Eur Urol*. 2011;60(5):908-916.

163. Kim Y-J, Cho KH, Pyo HR, et al. A phase II study of hypofractionated proton therapy for prostate cancer. *Acta Oncol.* 2013;52(3):477-485.

164. Kjellberg RN, Sweet WH, Preston WM, Koehler AM. The Bragg peak of a proton beam in intracranial therapy of tumors. *Trans Am Neurol Assoc*. 1962;87:216-218.

165. Koay EJ, Lege D, Mohan R, Komaki R, Cox JD, Chang JY. Adaptive/nonadaptive proton radiation planning and outcomes in a phase II trial for locally advanced non-small cell lung cancer. *Int J Radiat Oncol Biol Phys.* 2012;84(5):1093-1100.

166. Kodjikian L, Roy P, Rouberol F, et al. Survival after proton-beam irradiation of uveal melanomas. *Am J Ophthalmol*. 2004;137(6):1002-1010.

167. Komatsu S, Fukumoto T, Demizu Y, et al. The effectiveness of particle radiotherapy for hepatocellular carcinoma associated with inferior vena cava tumor thrombus. *J Gastroenterol*. 2011;46(7):913-920.

168. Komatsu S, Fukumoto T, Demizu Y, et al. Clinical results and risk factors of proton and carbon ion therapy for hepatocellular carcinoma. *Cancer*. 2011;117(21):4890-4904.

169. Konski A, Speier W, Hanlon A, Beck JR, Pollack A. Is proton beam therapy cost effective in the treatment of adenocarcinoma of the prostate? *J Clin Oncol.* 2007;25(24):3603-3608.

170. Konstantinidis L, Roberts D, Errington RD, Kacperek A, Damato B. Whole anterior segment proton beam radiotherapy for diffuse iris melanoma. *Br J Ophthalmol*. 2013;97(4):471-474.

171. Koyama S, Tsujii H. Proton beam therapy with high-dose irradiation for superficial and advanced esophageal carcinomas. *Clin Cancer Res*. 2003;9(10 Pt 1):3571-3577.

172. Koyama S, Tsujii H, Yokota H, et al. Proton beam therapy for patients with esophageal carcinoma. *Jpn J Clin Oncol*. 1994;24(3):144-153.

173. Kozak KR, Smith BL, Adams J, et al. Accelerated partial-breast irradiation using proton beams: initial clinical experience. *Int J Radiat Oncol Biol Phys*. 2006;66(3):691-698.

174. Kuhlthau KA, Pulsifer MB, Yeap BY, et al. Prospective study of health-related quality of life for children with brain tumors treated with proton radiotherapy. *J Clin Oncol*. 2012;30(17):2079-2086.

175. Laffond C, Dellatolas G, Alapetite C, et al. Quality-of-life, mood and executive functioning after shildhood craniopharyngioma treated with surgery and proton beam therapy. *Brain Inj.* 2012;26(3):270-281.

176. Lane AM, Kim IK, Gragoudas ES. Proton irradiation for peripapillary and parapapillary melanomas. *Arch Ophthalmol*. 2011;129(9):1127-1130.

177. Larsson B, Leksell L, Rexed B, Sourander P, Mair W, Andersson B. The high-energy proton beam as a neurosurgical tool. *Nature*.1958;182(4644):1222-1223.

178. Levin WP, Kooy H, Loeffler, DeLaney TF. Proton beam therapy. *Br J Cancer*. 2005;93(8):849-854.

179. Levy-Gabriel C, Lumbroso-Le Rouic L, Plancher C, et al. Long-term results of low-dose proton beam therapy for circumscribed choroidal hemangiomas. *Retina*. 2009;29(2):170-175.

180. Li J, Dabaja B, Reed V, et al. Rationale for and preliminary results of proton beam therapy for mediastinal lymphoma. *Int J Radiat Oncol Biol Phys*. 2011;81(1):167-174.

181. Li W, Gragoudas ES, Egan KM. Tumor basal area and metastatic death after proton beam irradiation for choroidal melanoma. *Arch Ophthalmol*. 2003;121(1):68-72.

182. Li W, Gragoudas ES, Egan KM. Metastatic melanoma death rates by anatomic site after proton beam irradiation for uveal melanoma. *Arch Ophthalmol*. 2000;118(8):1066-1070.

183. Lin R, Slater JD, Yonemoto LT, et al. Nasopharyngeal carcinoma: repeat treatment with conformal proton therapy – dose-volume histogram analysis. *Radiology*. 1999;213(2):489-494.

184. Lin SH, Komaki R, Liao Z, et al. Proton beam therapy and concurrent chemotherapy for esophageal cancer. *Int J Radiat Oncol Biol Phys*. 2012;83(3):e345-e351.

185. Llovet JM, Fuster J, Bruix J of the Barcelona-Clinic Liver Cancer Group. The Barcelona approach: diagnosis, staging, and treatment of hepatocellular carcinoma. *Liver Transpl*. 2004;10(2 suppl 1):S115-S120.

186. Lopez Guerra JL, Gomez DR, Zhuang Y, et al. Changes in pulmonary function after three-dimensional conformal radiotherapy, intensity-modulated radiotherapy, or proton beam therapy for non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys*. 2012;83(4):e537-e543.

187. Lumbroso L, Desjardins L, Levy C, et al. Intraocular inflammation after proton beam irradiation for uveal melanoma. *Br J Ophthalmol*. 2001;85(11):1305-1308.

188. Lumbroso-Le Rouic L, Delacroix S, Dendale R, et al. Proton beam therapy for iris melanomas. *Eye*. 2006;20(11):1300-1305.

189. Lundkvist J, Ekman M, Ericsson SR, Isacsson U, Jönsson B, Glimelius B. Economic evaluation of proton radiation therapy in the treatment of breast cancer. *Radiother Oncol*. 2005a;75(2):179-185.

190. Lundkvist J, Ekman M, Ericsson SR, Jönsson B, Glimelius B. Cost-effectiveness of proton radiation in the treatment of childhood medulloblastoma. *Cancer*. 2005b;103(4):793-801.

191. Lundkvist J, Ekman M, Ericsson SR, Jönsson B, Glimelius B. Proton therapy of cancer: potential clinical advantages and cost-effectiveness. *Acta Oncol*. 2005c;44(8):850-861.

192. Luu QT, Loredo LN, Archambeau JO, Yonemoto LT, Slater JM, Slater JD. Fractionated proton radiation treatment for pediatric craniopharyngioma: preliminary report. *Cancer J.* 2006;12(2):155-159.

193. Macbeth FR, Williams MV. Proton therapy should be tested in randomized trials. *J Clin Oncol*. 2008;26(15):2590-2591.

194. Macdonald ECA, Cauchi P, Kemp EG. Proton beam therapy for the treatment of uveal melanoma in Scotland. *Br J Ophthalmol*. 2011;95(12):1691-1695.

195. MacDonald SM, Patel SA, Hickey S, et al. Proton therapy for breast cancer after mastectomy: early outcomes of a prospective clinical trial. *Int J Radiat Oncol Biol Phys*. 2013;86(3):484-490.

196. MacDonald SM, Safai S, Trofimov A, et al. Proton radiotherapy for childhood ependymoma: initial clinical outcomes and dose comparisons. *Int J Radiat Oncol Biol Phys.* 2008;71(4):979-986.

197. MacDonald SM, Sethi R, Lavally B, et al. Proton radiotherapy for pediatric central nervous system ependymoma: clinical outcomes for 70 patients. *Neuro Oncol*. 2013;15(11):1552-1559.

198. MacDonald SM, Trofimov A, Safai S, et al. Proton radiotherapy for pediatric central nervous system germ cell tumors: early clinical outcomes. *Int J Radiat Oncol Biol Phys*. 2011;79(1):121-129.

199. MacDonald T. Pediatric medulloblastoma (2012). http://reference.medscape.com/article/987886-overview. Accessed March, 2014.

200. Mailhot Vega RB, Kim J, Bussière M, et al. Cost effectiveness of proton therapy compared with photon therapy in the management of pediatric medulloblastoma. *Cancer*. 2013;119(24):4299-4307.

201. Makita C, Nakamura T, Takada A, et al. Clinical outcomes and toxicity of proton beam therapy for advanced cholangiocarcinoma. *Radiat Oncol*. 2014;9:26.

202. Maor Y, Malnick S. Liver injury induced by anticancer chemotherapy and radiation therapy. *Int J Hepatol.* 2013:815105.

203. Marucci L, Ancukiewicz M, Lane AM, Collier JM, Gragoudas ES, Munzenrider JE. Uveal melanoma recurrence after fractionated proton beam therapy: comparison of survival in patients treated with reirradiation or with enucleation. *Int J Radiat Oncol Biol Phys*. 2011;79(3):842-846.

204. Marucci L, Lane AM, Li W, et al. Conservation treatment of the eye:conformal proton reirradiation for recurrent uveal melanoma. *Int J Radiat Oncol Biol Phys*. 2006;64(4):1018-1022.

205. Marucci L, Niemierko A, Liebsch NJ, Aboubaker, Liu MCC, Munzenrider JE. Spinal cord tolerance to high-dose fractionated 3D conformal proton-photon irradiation as evaluated by equivalent uniform dose and dose volume histogram analysis. *Int J Radiat Oncol Biol Phys*. 2004;59(2):551-555.

206. Matsuzaki Y, Osuga T, Chiba T, et al. New, effective treatment using proton irradiation for unresectable hepatocellular carcinoma. *Intern Med*. 1995;34(4):302-304.

207. Mayahara H, Murakami M, Kagawa K, et al. Acute morbidity of proton therapy for prostate cancer: the Hyogo Ion Beam Medical Center experience. *Int J Radiat Oncol Biol Phys*. 2007;69(2):434-443.

208. McAllister B, Archambeau JO, Nguyen MC, et al. Proton therapy for pediatric cranial tumors: preliminary report on treatment and disease-related morbidities. *Int J Radiat Oncol Phys*. 1997;39(2):455-460.

209. McAvoy SA, Ciura KT, Rineer JM, et al. Feasibility of proton beam therapy for reirradiation of locoregionally recurrent non-small cell lung cancer. *Radiother Oncol.* 2013;109(1):38-44.

210. McCurdy M, Bergsma DP, Hyun E, et al. The role of lung lobes in radiation pneumonitis and radiation-induced inflammation in the lung: a retrospective study. *J Radiat Oncol*. 2013;2(2):203-208.

211. McDonald MW, Linton OR, Shah MV. Proton therapy for reirradiation of progressive or recurrent chordoma. *Int J Radiat Oncol Biol Phys*. 2013;87(5):1107-1114.

212. McGee L, Mendenhall NP, Henderson RH, et al. Outcomes in men with large prostates (≥60 cm^3) treated with definitive proton therapy for prostate cancer. *Acta Oncol.* 2013;52(3):470-476.

213. Mendenhall NP, Li Z, Hoppe BS, et al. Early outcomes from three prospective trials of image-guided proton therapy for prostate cancer. *Int J Radiat Oncol Biol Phys.* 2012;82(1):213-221.

214. Mishra KK, Daftari IK, Weinberg V, et al. Risk factors for neovascular glaucoma after proton beam therapy of uveal melanoma: a detailed analysis of tumor and dose-volume parameters. *Int J Radiat Oncol Biol Phys*. 2013;87(2):330-336.

215. Miyawaki D, Murakami M, Demizu Y, et al. Brain injury after proton therapy or carbon ion therapy for head-and-neck cancer and skull base tumors. *Int J Radiat Oncol Biol Phys.* 2009;75(2):378-384.

216. Mizumoto M, Nakayama H, Tokita M, et al. Technical considerations for noncoplanar proton-beam therapy of patients with tumors proximal to the optic nerve. *Strahlenther Onkol*. 2010;186(1):36-39.

217. Mizumoto M, Okumura T, Hashimoto T, et al. Evaluation of liver function after proton beam therapy for hepatocellular carcinoma. *Int J Radiat Oncol Biol Phys*. 2012;82(3):e529-e535.

218. Mizumoto M, Okumura T, Hashimoto T, et al. Proton beam therapy for hepatocellular carcinoma: a comparison of three treatment protocols. *Int J Radiat Oncol Biol Phys*. 2011;81(4):1039-1045.

219. Mizumoto M, Sugahara S, Nakayama H, et al. Clinical results of proton-beam therapy for locoregionally advanced esophageal cancer. *Strahlenther Onkol*. 2010;186(9):482-488.

220. Mizumoto M, Sugahara S, Okumura T, et al. Hyperfractionated concomitant boost proton beam therapy for esophageal carcinoma. *Int J Radiat Oncol Biol Phys*. 2011;81(4):e601-e606.

221. Mizumoto M, Tokuuye K, Sugahara S, et al. Proton beam therapy for hepatocellular carcinoma with inferior vena cava tumor thrombus: report of three cases. *Jpn J Clin Oncol.* 2007;37(6):459-462.

222. Mizumoto M, Tokuuye K, Sugahara S, et al. Proton beam therapy for hepatocellular carcinoma adjacent to the porta hepatis. *Int J Radiat Oncol Biol Phys*. 2008;71(2):462-467.

223. Mizumoto M, Tsuboi K, Igaki H, et al. Phase I/II trial of hyperfractionated concomitant boost proton radiotherapy for supratentorial glioblastoma multiforme. *Int J Radiat Oncol Biol Phys*. 2010;77(1):98-105.

224. Moeller BJ, Chintagumpala M, Philip JJ, et al. Low early ototoxicity rates for pediatric medulloblastoma patients treated with proton radiotherapy. *Radiat Oncol.* 2011;6:58.

225. Moore MG, Lin DT, Deschler DG, Wang JJ, Chan AW. Risk of incisional recurrence after midface and anterior skull base surgery in sinonasal malignancies. *Skull Base*. 2011;21(2):87-92.

226. Mosci C, Lanza FB, Barla A, et al. Comparison of clinical outcomes for patients with large choroidal melanoma after primary treatment with enucleation or proton beam radiotherapy. *Ophthalmologica*. 2012;227(4):190-196.

227. Naeser P, Blomquist E, Montelius A, Thuomas K-A. Proton irradiation of malignant uveal melanoma. *Ups J Med Sci*. 1998;103(3):203-211.

228. Nakai Y, Ito Y, Sato M, et al. Multimodality treatment for cerebral arteriovenous malformations. Complementary role of proton beam radiotherapy. *Neurol Med Chir (Tokyo)*. 2012;52(12):859-864.

229. Nakayama H, Satoh H, Sugahara S, et al. Proton beam therapy of stage II and III non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys*. 2011;81(4):979-984.

230. Nakayama H, Sugahara S, Fukuda K, et al. Proton beam therapy for hepatocellular carcinoma located adjacent to the alimentary tract. *Int J Radiat Oncol Biol Phys*. 2011;80(4):992-995.

231. Nakayama H, Sugahara S, Tokita M, et al. Proton beam therapy for hepatocellular carcinoma. The University of Tsukuba experience. *Cancer*. 2009;115(23):5499-5506.

232. Nakayama H, Sugahara S, Tokita M, et al. Proton beam therapy for patients with medically inoperable stage I non-small-cell lung cancer at the University of Tsukuba. *Int J Radiat Oncol Biol Phys*. 2010;78(2):467-471.

233. National Cancer Institute. Cancer Therapy Evaluation Program (CTEP). http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. Accessed March, 2014.

234. National Cancer Institute. NCI dictionary of cancer terms. http://www.cancer.gov/dictionary. Accessed March, 2014.

235. Nguyen PL, Zietman AL. High-dose external beam radiation for localized prostate cancer: current status and future challenges. *Cancer J*. 2007;13(5):295-301.

236. Nichols AC, Chan AW, Curry WT, Barker FG II, Deschler DG, Lin DT. Esthesioneuroblastoma: the Massachusetts Eye and Ear Infirmary and Massachusetts General Hospital experience with craniofacial resection, proton beam radiation, and chemotherapy. *Skull Base*. 2008. 18;(5):327-336.

237. Nichols RC Jr, George TJ, Zaiden RA Jr, et al. Proton therapy with concomitant capecitabine for pancreatic and ampullary cancers is associated with a low incidence of gastrointestinal toxicity. *Acta Oncol.* 2013;52(3):498-505.

238. Nichols RC Jr, Morris CG, Hoppe BS, et al. Proton radiotherapy for prostate cancer is not associated with post-treatment testosterone suppression. *Int J Radiat Oncol Biol Phys*. 2012;82(3):1222-1226.

239. Nihei K, Ogino T, Ishikura S, et al. Phase II feasibility study of high-dose radiotherapy for prostate cancer using proton boost therapy: first clinical trial of proton beam therapy for prostate cancer in Japan. *Jpn J Clin Oncol*. 2005;35(12):745-752.

240. Nihei K, Ogino T, Ishikura S, Nishimura H. High-dose proton beam therapy for stage I non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys*. 2006;65(1):107-111.

241. Nihei K, Ogino T, Onozawa M, et al. Multi-institutional phase II study of proton beam therapy for organ-confined prostate cancer focusing on the incidence of late rectal toxicities. *Int J Radiat Oncol Biol Phys*. 2011;81(2):390-396.

242. Niizawa G, Ikegami T, Matsuzaki Y, et al. Monitoring of hepatocellular carcinoma, following proton radiotherapy, with contrast-enhanced color Doppler ultrasonography. *J Gastroenterol.* 2005;40(3):283-290.

243. Nishimura H, Ogino T, Kawashima M, et al. Proton-beam therapy for olfactory neuroblastoma. *Int J Radiat Oncol Biol Phys*. 2007;68(3):758-762.

244. Noël G, Bollet MA, Calugaru V, et al. Functional outcome of patients with benign meningioma treated by 3D conformal irradiation with a combination of photons and protons. *Int J Radiat Oncol Biol Phys*. 2005;62(5):1412-1422.

245. Noël G, Feuvret L, Calugaru V, et al. Chordomas of the base of the skull and upper cervical spine. One hundred patients irradiated by a 3D conformal technique combining photon and proton beams. *Acta Oncol*. 2005;44(7):700-708.

246. Noël G, Feuvret L, Ferrand R, Boisserie G, Mazeron J-J, Habrand J-L. Radiotherapeutic factors in the management of cervical-basal chordomas and chondrosarcomas. *Neurosurgery*. 2004;55(6):1252-1260.

247. Noël G, Habrand J-L, Jauffret E, et al. Radiation therapy for chordoma and chondrosarcoma of the skull base and the cervical spine. Prognostic factors and patterns of failure. *Strahlenther Onkol*. 2003;179(4):241-248.

248. Noël G, Habrand J-L, Helfre S, et al. Proton beam therapy in the management of central nervous system tumors in childhood: the preliminary experience of the Centre de Protonthérapie d'Orsay. *Med Pediatr Oncol*. 2003;40(5):309-315.

249. Noël G, Habrand J-L, Mammar H, et al. Highly conformal therapy using proton component in the management of meningiomas. *Strahlenther Onkol.* 2002;178(9):480-485.

250. Noël G, Habrand J-L, Mammar H, et al. Combination of photon and proton radiation therapy for chordomas and chondrosarcomas of the skull base: the Centre de Protonthérapie d'Orsay experience. *Int J Radiat Oncol Biol Phys*. 2001;51(2):392-398.

251. O'Connell JX, Renard LG, Liebsch NJ, Efird JT, Munzenrider JE, Rosenberg AE. Base of skull chordoma. A correlative study of histologic and clinical features of 62 cases. *Cancer*. 1994;74(8):2261-2267.

252. Ohara K, Okumura T, Tsuji H, et al. Radiation tolerance of cirrhotic livers in relation to the preserved functional capacity: analysis of patients with hepatocellular carcinoma treated by focused proton beam radiotherapy. *Int J Radiat Oncol Biol Phys*. 1997;38(2):367-372.

253. Ohara K, Okumura T, Tsuji H, et al. Clearance of parenchymal tumors following radiotherapy: analysis of hepatocellular carcinomas treated by proton beams. *Radiother Oncol.* 1996;41(3):233-236.

254. Okano S, Tahara M, Zenda S, et al. Induction chemotherapy with docetaxel, cisplatin and S-1 followed by proton beam therapy concurrent with cisplatin in patients with T4b nasal and sinonasal malignancies. *Jpn J Clin Oncol*. 2012;42(8):691-696.

255. Ollendorf DA, Pearson SD. An integrated evidence rating to frame comparative effectiveness assessments for decision makers. *Med Care.* 2010;48(6 Suppl):S145-S152.

256. Oshiro Y, Mizumoto M, Okumura T, et al. Clinical results of proton beam therapy for advanced neuroblastoma. *Radiat Oncol.* 2013;8(1):142.

257. Oshiro Y, Sugahara S, Fukushima T, et al. Pediatric nasopharyngeal carcinoma treated with proton beam therapy. Two case reports. *Acta Oncol.* 2011;50(3):470-473.

258. Otsuka M, Ohara K, Takada Y, et al. Radiation therapy for intrahepatic recurrence after hepatectomy for hepatocellular carcinoma. *Int J Clin Oncol*. 2003;8(3):151-155.

259. Oya S, Kawai K, Nakatomi H, Saito N. Significance of Simpson grading system in modern meningioma surgery: integration of the grade with the MIB-1 labeling index as a key to predict the recurrence of WHO grade 1 meningiomas. *J Neurosurg*. 2012;117(1):121-128.

260. Paganetti H, Niemierko A, Ancukiewicz M, et al. Relative biological effectiveness (RBE) values for proton beam therapy. *Int J Radiat Oncol Biol Phys*. 2002;53(2):407-421.

261. Pai HH, Thornton A, Katznelson L, et al. Hypothalamic/pituitary function following high-dose conformal radiotherapy to the base of skull: demonstration of a dose-effect relationship using dose-volume histogram analysis. *Int J Radiat Oncol Biol Phys.* 2001;49(4):1079-1092.

262. Park L, DeLaney TF, Liebsch NJ, et al. Sacral chordomas: impact of high-dose proton/photon-beam radiation therapy combined with or without surgery for primary versus recurrent tumor. *Int J Radiat Oncol Biol Phys*. 2006;65(5):1514-1521.

263. Park SS, Walsh SM, Gragoudas ES. Visual-field deficits associated with proton beam irradiation for parapapillary choroidal melanoma. Ophthalmology. 1996;103(1):110-116.

264. Parthan A, Pruttivarasin N, Davies D, et al. Comparative cost-effectiveness of stereotactic body radiation therapy versus intensity-modulated and proton radiation therapy for localized prostate cancer. *Front Oncol*. 2012;2:81.

265. Particle Therapy Co-Operative Group. http://www.ptcog.ch/. Accessed March, 2014.

266. Pavy JJ, Denekamp J, Letschert J, et al. EORTC Late Effects Working Group. Late effects toxicity scoring: the SOMA scale. *Radiother Oncol*. 1995;35(1):11-15.

267. Peeters A, Grutters JPC, Pijls-Johannesma M, et al. How costly is particle therapy? Cost analysis of external beam radiotherapy with carbon ions, proton and photons. *Radiother Oncol*. 95(1):45-53.

268. Pehlivan B, Ares C, Lomax AJ, et al. Temporal lobe toxicity analysis after proton radiation therapy for skull base tumors. *Int J Radiat Oncol Biol Phys*. 2012;83(5):1432-1440.

269. Petit JH, Biller BMK, Yock TI, et al. Proton stereotactic radiotherapy for persistent adrenocorticotropin-producing adenomas. *J Clin Endocrinol Metab*. 2008;93(2):393-399.

270. Petrovic A, Bergin C, Schalenbourg A, Goitein G, Zografos L. Proton therapy for uveal melanoma in 43 juvenile patients. *Ophthalmology*. 2014. [Epub ahead of print].

271. Péus D, Newcomb N, Hofer S. Appraisal of the Karnofsky Performance Status and proposal of a simple algorithmic system for its evaluation. *BMC Med Inform Decis Mak*. 2013;13(1):72.

272. Pieters RS, Niemierko A, Fullerton BC, Munzenrider JE. Cauda equine tolerance to high-dose fractionated irradiation. *Int J Radiat Oncol Biol Phys*. 2006;64(1):251-257.

273. Pommier P, Liebsch NJ, Deschler DG, et al. Proton beam radiation therapy for skull base adenoid cystic carcinoma. *Arch Otolaryngol Head Neck Surg*. 2006;132(11):1242-1249.

274. Pugh TJ, Munsell MF, Choi S, et al. Quality of life and toxicity from passively scattered and spot-scanning proton beam therapy for localized prostate cancer. *Int J Radiat Oncol Biol Phys*. 2013;87(5):946-953.

275. Radiation Therapy Oncology Group (RTOG). Acute radiation morbidity scoring criteria. http://www.rtog.org/researchassociates/adverseeventreporting/acuteradiationmorbidityscoringcriteria.aspx. Accessed March, 2014.

276. Radiation Therpay Oncology Group (RTOG). RTOG/EORTC late radiation morbidity scoring schema. http://www.rtog.org/ResearchAssociates/AdverseEventReporting/RTOGEORTCLateRadiationMorbidityScoringSchema.aspx. Accessed. March, 2014.

277. Ramaekers BLT, Grutters JPC, Pijls-Johannesma M, Lambin P, Joore MA, Langendijk. *Int J Radiat Oncol Biol Phys*. 2013;85(5):1282-1288.

278. Rana S, Zeidan O, Ramirez E, Rains M, Gao J, Zheng Y. Measurements of lateral penumbra for uniform scanning proton beams under various beam delivery conditions and comparison to the XiO treatment planning system. *Med Phys*. 2013;40(9):091708.

279. Ray GL, Buchsbaum JC, McMullen KP, et al. Definitive treatment of leptomeningeal spinal metastases in children. *Pediatr Blood Cancer*. 2013;60(11):1839-1841.

280. Resto VA, Chan AW, Deschler DG, Lin DT. Extent of surgery in the management of locally advanced sinonasal malignancies. *Head Neck*. 2008;30(2):222-229.

281. Roda RH, Gallia GL, Eberhart CG, Weingart JD, Laterra J. Epilepsy and temporal lobe injury after skull base proton beam therapy. *J Clin Neurosci*. 2009;16(9):1220-1221.

282. Rombi B, Ares C, Hug EB, et al. Spot-scanning proton radiation therapy for pediatric chordoma and chondrosarcoma: clinical outcome of 26 patients treated at Paul Scherrer Institute. *Int J Radiat Oncol Biol Phys*. 2013;86(3):578-584.

283. Rombi B, DeLaney TF, MacDonald SM, et al. Proton radiotherapy for pediatric Ewing's sarcoma: initial clinical outcomes. *Int J Radiat Oncol Biol Phys*. 2012;82(3):1142-1148.

284. Ronson BB, Schulte RW, Han KP, Loredo LN, Slater JM, Slater JD. Fractionated proton beam irradiation of pituitary adenomas. *Int J Radiat Oncol Biol Phys*. 2006;64(2):425-434.

285. Rosenberg AE, Nielsen GP, Keel SB, et al. Chondrosarcoma of the base of the skull: a clinicopathologic study of 200 cases with emphasis on its distinction from chordoma. *Am J Surg Pathol*. 1999;23(11):1370-1378.

286. Rossi CJ Jr, Slater JD, Yonemoto LT, et al. Influence of patient age on biochemical freedom from disease in patients undergoing conformal proton radiotherapy of organ-confined prostate cancer. *Urology*. 2004;64(4):729-732.

287. Rubin P, Constine LS 3rd, Fajardo LF, Phillips TL, Wasserman TH. EORTC Late Effects Working Group. Overview of late effects normal tissues (LENT) scoring system. *Radiother Oncol*. 1995;35(1):9-10.

288. Rundle P, Singh AD, Rennie I. Proton beam therapy for iris melanoma: a review of 15 cases. *Eye*. 2007;21(1):79-82.

289. Rutz HP, Weber DC, Goitein G, et al. Postoperative spot-scanning proton radiation therapy for chordoma and chondrosarcoma in children and adolescents: initial experience at Paul Scherrer Institute. *Int J Radiat Oncol Biol Phys.* 2008;71(1):220-225.

290. Rutz HP, Weber DC, Sugahara S, et al. Extracranial chordoma: outcome in patients treated with function-preserving surgery followed by spot-scanning proton beam irradiation. *Int J Radiat Oncol Biol Phys.* 2007;67(2):512-520.

291. Sabin ND, Merchant TE, Harreld JH, et al. Imaging changes in very young children with brain tumors treated with proton therapy and chemotherapy. *AJNR Am J Neuroradiol.* 2013;34(2):446-450.

292. Sandinha MT, Kacperek A, Errington RD, Coupland SE, Damato B. Recurrence of iris melanoma after proton beam therapy. *Br J Ophthalmol*. 2014. [Epub ahead of print].

293. Sandler HM, Liu PY, Dunn RL, et al. Reduction in patient-reported acute morbidity in prostate cancer patients treated with 81-Gy intensity-modulated radiotherapy using reduced planning target volume margins and electromagnetic tracking: assessing the impact of margin reduction study. *Urology*. 2010;75(5):1004-1008.

294. Santoni R, Liebsch N, Finkelstein DM, et al. Temporal lobe (TL) damage following surgery and high-dose photon and proton irradiation in 96 patients affected by chordomas and chondrosarcomas of the base of the skull. *Int J Radiat Oncol Biol Phys*. 1998;41(1):59-68.

295. Schauer DA, Linton OW. National Council on Radiation Protection and Measurements report shows substantial medical exposure increase. *Radiology*.2009;253(2):293-296.

296. Schneider RA, Vitolo V, Albertini F, et al. Small bowel toxicity after high dose spot scanning-based proton beam therapy for paraspinal/retroperitoneal neoplasms. *Strahlenther Onkol*. 2013;189(12):1020-1025.

297. Schulte RW, Slater JD, Rossi CJ Jr, Slater JM. Value and perspectives of proton radiation therapy for limited stage prostate cancer. *Strahlenther Onkol*. 2000;176(1):3-8.

298. Sejpal S, Komaki R, Tsao A, et al. Early findings on toxicity of proton beam therapy with concurrent chemotherapy for nonsmall cell lung cancer. *Cancer*. 2011;117(13):3004-3013.

299. Sethi RV, Shih HA, Yeap BY, et al. Second nonocular tumors among survivors of retinoblastoma treated with contemporary photon and proton radiotherapy. *Cancer*. 2014;120(1):126-133.

300. Shah SK, Lui PD, Baldwin DD, Ruckle HC. Urothelial carcinoma after external beam radiation therapy for prostate cancer. *J Urol*. 2006;175(6):2063-2066.

301. Sheets NC, Goldin GH, Meyer A-M, et al. Intensity-modulated radiation therapy, proton therapy, or conformal radiation therapy and morbidity and disease control in localized prostate cancer. *JAMA*. 2012;307(15):1611-1620.

302. Shioyama Y, Tokuuye K, Okumura T, et al. Clinical evaluation of proton radiotherapy for non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys.* 2003;56(1):7-13.

303. Shipley WU, Verhey LJ, Munzenrider JE, et al. Advanced prostate cancer: the results of a randomized comparative trial of high dose irradiation boosting with conformal protons compared with conventional dose irradiation using photons alone. *Int J Radiol Oncol Biol Phys*. 1995;32(1):3-12.

304. Silander H, Pellettieri L, Enblad P, et al. Fractionated, stereotactic proton beam treatment of cerebral arteriovenous malformations. *Acta Neurol Scand*. 2004;109(2):85-90.

305. Slater JD, Loredo LN, Chung A, et al. Fractionated proton radiotherapy for benign cavernous sinus meningiomas. *Int J Radiat Oncol Biol Phys*. 2012;83(5):e633-e637.

306. Slater JD, Rossi CJ Jr, Yonemoto LT, et al. Proton therapy for prostate cancer: the initial Loma Linda University experience. *Int J Radiat Oncol Biol Phys*. 2004;59(2):348-352.

307. Slater JD, Rossi CJ Jr, Yonemoto LT, et al. Conformal proton therapy for early-stage prostate cancer. *Urology*. 1999;53(5):978-84.

308. Slater JD, Yonemoto LT, Mantik DW, et al. Proton radiation for treatment of cancer of the oropharynx: early experience at Loma Linda University Medical Center using a concomitant boost technique. *Int J Radiat Oncol Biol Phys.* 2005;62(2):494-500.

309. Slater JD, Yonemoto LT, Rossi CJ Jr, et al. Conformal proton therapy for prostate carcinoma. *Int J Radiat Oncol Biol Phys.* 1998;42(2):299-304.

310. Smith AR. Vision 20/20: proton therapy. *Med Phys*. 2009;36(2):556-568.

311. Sobin LH. The international histological classification of tumours. *Bull World Health Organ*. 1981;59(6):813-819.

312. Solares CA, Fakhri S, Batra PS, Lee J, Lanza DC. Transnasal endoscopic resection of lesions of the clivus: a preliminary report. *Laryngoscope*. 2005;115(11):1917-1922.

313. Srivastava A, Vischioni B, Fiore MR, et al. Quality of life in patients with chordomas/chondrosarcomas during treatment with proton beam therapy. *J Radiat Res*. 2013;54 suppl 1:i43-i48.

314. Staab A, Rutz HP, Area C, et al. Spot-scanning-based proton therapy for extracranial chordoma. *Int J Radiat Oncol Biol Phys*. 2011;81(4):e489-e496.

315. Sugahara S, Nakayama H, Fukuda K, et al. Proton-beam therapy for hepatocellular carcinoma associated with portal vein tumor thrombosis. *Strahlenther Onkol.* 2009;185(12):782-788.

316. Sugahara S, Oshiro Y, Nakayama H, et al. Proton beam therapy for large hepatocellular carcinoma. *Int J Radiat Oncol Biol Phys*. 2010;76(2):460-466.

317. Sugahara S, Tokuuye K, Okumura T, et al. Clinical results of proton beam therapy for cancer of the esophagus. *Int J Radiat Oncol Biol Phys*. 2005;61(1):76-84.

318. Suneja G, Poorvu PD, Hill-Kayser C, Lustig RA. Acute toxicity of proton beam radiation for pediatric central nervous system malignancies. *Pediatr Blood Cancer*. 2013;60(9):1431-1436.

319. Taghian AG, Kozak KR, Katz A, et al. Accelerated partial breast irradiation using proton beams: initial dosimetric experience. *Int J Radiat Oncol Biol Phys*. 2006;65(5):1404-1410.

320. Takatori K, Terashima K, Yoshida R, et al. Upper gastrointestinal complications associated with gemcitabine-concurrent proton radiotherapy for inoperable pancreatic cancer. *J Gastroenterol*. 2013. [Epub ahead of print].

321. Talcott JA, Rossi C, Shipley WU, et al. Patient-reported long-term outcomes after conventional and high-dose combined proton and photon radiation for early prostate cancer. *JAMA*. 2010;303(11):1046-1053.

322. Terahara A, Niemierko A, Goitein M, et al. Analysis of the relationship between tumor dose inhomogeneity and local control in patients with skull base chordoma. *Int J Radiat Oncol Biol Phys*. 1999;45(2):351-358.

323. Terashima K, Demizu Y, Hashimoto N, et al. A phase I/II study of gemcitabine-concurrent proton radiotherapy for locally advanced pancreatic cancer without distant metastasis. *Radiother Oncol.* 2012;103(1):25-31.

324. Thorp N. Proton therapy for children. *RAD Magazine*. 2010;36(418):17-18.

325. Thuomas K-A, Naeser P. Long-term follow-up of proton irradiated malignant melanoma by glucose-fructose enhanced magnetic resonance imaging. *Acta Ophthalmol Scand*. 1997;75(1):17-21.

326. Timmermann B, Schuck A, Niggli F, et al. Spot-scanning proton therapy for malignant soft tissue tumors in childhood: first experiences at the Paul Scherrer Institute. *Int J Radiat Oncol Biol Phys*. 2007;67(2):497-504.

327. Tokuuye K, Akine Y, Kagei K, et al. Proton therapy for head and neck malignancies at Tsukuba. *Strahlenther Onkol*. 2004;180(2):96-101.

328. Tran E, Ma R, Paton K, Blackmore E, Pickles T. Outcomes of proton radiation therapy for peripapillary choroidal melanoma at the BC Cancer Agency. *Int J Radiat Oncol Biol Phys.* 2012;83(5):1425-1431.

329. Truong MT, Kamat UR, Liebsch NJ, et al. Proton radiation therapy for primary sphenoid sinus malignancies: treatment outcome and prognostic factors. *Head Neck.* 2009;31(10):1297-308.

330. Tseng YD, Wo JY, Ancukiewicz M, et al. Dosimetric predictors of nausea and vomiting: an exploratory analysis of a prospective phase I/II trial with neoadjuvant accelerated short-course radiotherapy and capecitabine for resectable cancer. *J Radiat Oncol*. 2013;2(4):427-434.

331. Tsina EK, Lane AM, Zacks DN, Munzenrider JE, Collier JM, Gragoudas ES. Treatment of metastatic tumors of the choroid with proton beam irradiation. *Ophthalmology*. 2005;112(2):337-343.

332. Tuan J, Vischioni B, Fossati P, et al. Initial clinical experience with scanned proton beams at the Italian National Center for Hadrontherapy (CNAO). *J Radiat Res*. 2013;54 suppl 1:i31-i42.

333. Umebayashi Y, Uyeno K, Tsujii H, Otsuka F. Proton radiotherapy of skin carcinomas. *Br J Dermatol.* 1994;130(1):88-91.

334. University of Michigan Health System. Department of Urology. Expanded Prostate Cancer Index Composite (EPIC). http://www.med.umich.edu/urology/research/epic.html. Accessed March, 2014.

335. University of Washington Medical Center. Criteria for Child-Pugh classification. http://depts.washington.edu/uwhep/calculations/childspugh.htm. Accessed March, 2014.

336. Unkelbach J, Chan TC, Bortfeld T. Accounting for range uncertainties in the optimization of intensity modulated proton therapy. *Phys Med Biol*. 2007;52(10):2755-2773.

337. Valery R, Mendenhall NP, Nichols RC Jr, et al. Hip fractures and pain following proton therapy for management of prostate cancer. *Acta Oncol*. 2013;52(3):486-491.

338. Varian Medical Systems. Summary of Proposed 2014 Rules for the Hospital Outpatient Prospective Payment System & Medicare Fee Schedule. Accessed at: http://www.varian.com/media/oncology/resources/pdf/Summary2013ProposedRules_HOPPSMPFS.pdf, March 11, 2014.

339. Vavvas D, Kim I, Lane AM, Chaglassian A, Mukai S, Gragoudas E. Posterior uveal melanoma in young patients treated with proton beam therapy. *Retina*. 2010;30(8):1267-1271.

340. Vernimmen FJ, Harris JK, Wilson JA, Melvill R, Smit BJ, Slabbert JP. Stereotactic proton beam therapy of skull base meningiomas. *Int J Radiat Oncol Biol Phys*. 2011;49(1):99-105.

341. Vernimmen FJAI, Slabbert JP, Wilson JA, Fredericks S, Melvill R. Stereotactic proton beam therapy for intracranial arteriovenous malformations. *Int J Radiat Oncol Biol Phys*. 2005;62(1):44-52.

342. Voelter V, Schalenbourg A, Pampallona S, et al. Adjuvant intra-arterial hepatic fotemustine for high-risk uveal melanoma patients. *Melanoma Res.* 2008;18(3):220-224.

343. Walcott BP, Hattangadi-Gluth JA, Stapleton CJ, Ogilvy CS, Chapman PH, Loeffler JS. Proton beam stereotactic radiosurgery for pediatric cerebral arteriovenous malformations. *Neurosurgery*. 2014;74(4):367-374.

344. Wang J, Wei C, Tucker SL, et al. Predictors of postoperative complications after trimodality therapy for esophageal cancer. *Int J Radiat Oncol Biol Phys*. 2013;86(5):885-891.

345. Weber DC, Chan AW, Bussiere MR, et al. Proton beam radiosurgery for vestibular schwannoma: tumor control and cranial nerve toxicity. *Neurosurgery*. 2003;53(3):577-586.

346. Weber DC, Chan AW, Lessell S, et al. Visual outcome of accelerated fractionated radiation for advanced sinonasal malignancies employing photons/protons. *Radiother Oncol*. 2006;81(3):243-249.

347. Weber DC, Lomax AJ, Rutz HP, et al. Spot-scanning proton radiation therapy for recurrent, residual or untreated intracranial meningiomas. *Radiother Oncol.* 2004;71(3):251-258.

348. Weber DC, Rutz HP, Bolsi A, et al. Spot scanning proton therapy in the curative treatment of adult patients with sarcoma: the Paul Scherrer Institute experience. *Int J Radiat Oncol Biol Phys*. 2007;69(3):865-871.

349. Weber DC, Rutz HP, Pedroni ES, et al. Results of spot-scanning proton radiation therapy for chordoma and chondrosarcoma of the skull base: the Paul Scherrer Institut experience. *Int J Radiat Oncol Biol Phys*. 2005;63(2):401-409.

350. Weber DC, Schneider R, Goitein G, et al. Spot scanning-based proton therapy for intracranial meningioma: long-term results from the Paul Scherrer Institute. *Int J Radiat Oncol Biol Phys.* 2012;83(3):865-871.

351. Wenkel E, Thornton AF, Finkelstein D, et al. Benign meningioma: partially resected, biopsied, and recurrent intracranial tumors treated with combined proton and photon radiotherapy. *Int J Radiat Oncol Biol Phys*. 2000;48(5):1363-1370.

352. Westover KD, Seco J, Adams JA, et al. Proton SBRT for medically inoperable stage I NSCLC. *J Thorac Oncol.* 2012;7(6):1021-1025.

353. Wilson MW, Hungerford JL. Comparison of episcleral plaque and proton beam radiation therapy for the treatment of choroidal melanoma. *Ophthalmology*. 1999;106(8):1579-1587.

354. Winkfield KM, Linsenmeier C, Yock TI, et al. Surveillance of craniopharyngioma cyst growth in children treated with proton radiotherapy. *Int J Radiat Oncol Biol Phys.* 2009;73(3):716-721.

355. Wuestmeyer H, Sauerwein W, Meller D, et al. Proton radiotherapy as an alternative to extenteration in the management of extended conjunctival melanoma. *Graefes Arch Clin Exp Ophthalmol*. 2006;244(4):438-446.

356. Xiang Z-L, Erasmus J, Komaki R, Cox JD, Chang JY. FDG uptake correlates with recurrence and survival after treatment of unresectable stage III non-small cell lung cancer with high-dose proton therapy and chemotherapy. *Radiat Oncol.* 2012;7:144.

357. Yock TI, Tarbell NJ. Technology insight: proton beam radiotherapy for treatment in pediatric brain tumors. *Nat Clin Pract Oncol.* 2004;1(2):97-103.

358. Yonekawa Y, MacDonald SM, Shildkrot Y, Mukai S. Standard fractionation low-dose proton radiotherapy for diffuse choroidal hemangiomas in pediatric Sturge-Weber syndrome. *J AAPOS*. 2013;17(3):318-322.

359. Yonemoto LT, Slater JD, Rossi CJ Jr, et al. Combined proton and photon conformal radiation therapy for locally advanced carcinoma of the prostate: preliminary results of a phase I/II study. *Int J Radiat Oncol Biol Phys*. 1997;37(1):21-29.

360. Yoon SS, Chen Y-L, Kirsch DG, et al. Proton-beam, intensity-modulated, and/or intraoperative electron radiation therapy combined with aggressive anterior surgical resection for retroperitoneal sarcomas. *Ann Surg Oncol*. 2010;17(6):1515-1529.

361. Yu JB, Soulos PR, Herrin J, et al. Proton versus intensity-modulated radiotherapy for prostate cancer: patterns of care and early toxicity. *J Natl Cancer Inst*. 2013;105(1):25-32.

362. Zenda S, Kawashima M, Nishio T, et al. Proton beam therapy as a nonsurgical approach to mucosal melanoma of the head and neck: a pilot study. *Int J Radiat Oncol Biol Phys*. 2011a;81(1):135-139.

363. Zenda S, Kohno R, Kawashima M, et al. Proton beam therapy for unresectable malignancies of the nasal cavity and paranasal sinuses. *Int J Radiat Oncol Biol Phys*. 2011b;81(5):1473-1478.

364. Zietman AL. J Clin Oncol. The Titanic and Iceberg: prostate proton therapy and health care economics. *J Clin Oncol.* 2007;25(24):3565-3566.

365. Zietman AL, Bae K, Slater JD, et al. Randomized trial comparing conventional-dose with high-dose conformal radiation therapy in early-stage adenocarcinoma of the prostate: long-term results from Proton Radiation Oncology Group/American College of Radiology 95-09. *J Clin Oncol.* 2010;28(7):1106-1111.

366. Zietman AL, DeSilvio ML, Slater JD, et al. Comparison of conventional-dose vs high-dose conformal radiation therapy in clinically localized adenocarcinoma of the prostate: a randomized controlled trial. *JAMA*. 2005;294(10):1233-1239.

367. Zografos L, Ducrey N, Beati D, et al. Metastatic melanoma in the eye and orbit. *Ophthalmology*. 2003;110(11):2245-2256.

368. Zografos L, Egger E, Bercher L, Chamot L, Munkel G. Proton beam irradiation of choroidal hemangiomas. *Am J Ophthalmol*. 1998;126(2):261-268.

Appendix A

Definitions

General Evaluation Tools

American Joint Committee on Cancer (AJCC) criteria
Based on the extent of a tumor, the spread of the cancer to the lymph nodes, and presence of metastasis, the AJCC developed the TNM staging system which allows clinicians to evaluate different cancers in a standardized manner. The basic parameters are described below.

T: description of the primary tumor	
TX	Tumor cannot be evaluated
T0	No evidence of tumor
Tis	Early cancer without spread to nearby tissue
T1-T4	Size and/or extent of tumor
N: impact of tumor on nearby lymph nodes	
NX	Lymph nodes cannot be evaluated
N0	No lymph node involvement
N1-N3	Number and/or size of spread
M: presence of metastasis	
M0	No distant metastasis
M1	Distant metastasis

Source: American Joint Committee on Cancer. Cancer staging references. *http://cancerstaging.org/references-tools/Pages/What-is-Cancer-Staging.aspx*.

World Health Organization (WHO) classification for histological typing of tumors
In an effort to help provide a uniform histological definition for various cancer types, the WHO has established a classification system based on the microscopic characteristics of tumors. Rooted in the collaborative work of centers worldwide, the definition and grading of tumors continually evolves to reflect current findings and knowledge including incorporation of genetic profiles.

Karnofsky Performance Status (KPS)
The KPS is a standardized assessment of how well cancer patients conduct daily activities. The scale ranges in 10-point increments from 100 (normal activity without any special care) to 0 (dead). Intermediate points balance a patient's care needs with his/her ability to carry out normal activities.

Eastern Cooperative Oncology Group (ECOG) Performance Status
The ECOG Performance Status (also referred to as the WHO Performance Status or the Zubrod performance status) is derived from the KPS and offers an alternate assessment of a patient's functional status. The scale ranges from 0 (fully active) to 5 (dead) with the intermediate grades as described below.

Grade 0	Fully active without restriction
Grade 1	Restricted in physically strenuous activity, but ambulatory and able to carry out light housework or office work
Grade 2	Ambulatory and capable of self-care, but unable to work; active for >50% of waking hours
Grade 3	Limited self-care; confined to bed or chair >50% of waking hours
Grade 4	Completely disabled; confined to bed or chair; incapable of self-care
Grade 5	Dead

Source: Péus D, Newcomb N, Hofer S. Appraisal of the Karnofsky Performance Status and proposal of a simple algorithmic system for its evaluation. BMC Med Inform Decis Mak. 2013;13(1):72.

National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE)
The CTCAE is a widely disseminated and utilized catalog of adverse events encountered in oncology medicine. Adverse events are organized by System Organ Class (SOC) (e.g., cardiac disorders, renal and urinary disorders) with guiding clinical descriptions for evaluation of severity. The general principles for grading adverse event severity are listed below.

Grade1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate activities of daily living (ADL)
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
Grade 4	Life-threatening consequences; urgent intervention needed; urgent intervention indicated
Grade 5	Death related to adverse event

Source: National Cancer Institute. Cancer Therapy Evaluation Program (CTEP). *http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm*.

Radiation Therapy Oncology Group (RTOG)/ European Organisation for Research and Treatment of Cancer (EORTC) morbidity scoring system

Widely utilized along with CTCAE, the RTOG/EORTC scoring system establishes parameters for separate evaluation of acute and late radiation effects in tissues and organs. Events are evaluated on a scale ranging from 0 (no change from baseline) to 5 (death) for organs or body areas impacted by therapy. The range of acute effects in the lungs is described below.

Lung – acute effects

0	1	2	3	4	5
No change over baseline	Mild symptoms of dry cough or dyspnea on exertion	Persistent cough requiring narcotic, antitussive agents; dyspnea with minimal effort but not at rest	Severe cough unresponsive to narcotic antitussive agent or dyspnea at rest; clinical or radiologic evidence of acute pneumonitis; intermittent oxygen or steroids may be required	Severe respiratory insufficiency; continuous oxygen or assisted ventilation	Death related to effects

Source: Radiation Therapy Oncology Group (RTOG). Acute radiation morbidity scoring criteria. http://www.rtog.org/researchassociates/adverseeventreporting/acuteradiationmorbidityscoringcriteria.aspx.

Late radiation effects are similarly evaluated on a scale ranging from 0 (no effects) to 5 (death) for organs or body areas impacted by therapy. The range of late events in the lungs is described below.

Lung – late effects

0	1	2	3	4	5
None	Asymptomatic or mild symptoms (dry cough); slight radiographic appearances	Moderate symptomatic fibrosis or penumonitis (severe cough); low grade fever; patchy radiographic appearances	Severe symptomatic fibrosis or pneumonitis; dense radiographic changes	Severe respiratory insufficiency; continuous oxygen or assisted ventilation	Death related to effects

Source: Radiation Therpay Oncology Group (RTOG). RTOG/EORTC late radiation morbidity scoring schema.
http://www.rtog.org/ResearchAssociates/AdverseEventReporting/RTOGEORTCLateRadiationMorbidityScoringSchema.aspx.

Late Effects Normal Tissues (LENT) scoring system and the SOMA scale (subjective, objective, management and analytic)

The LENT/SOMA grading system represents early efforts by the RTOG and the European Organisation for Research and Treatment of Cancer (EORTC) to establish a universal system for evaluation of late radiation effects in normal tissue. Use of SOMA allows for incorporation of different data including clinical assessment and patient experience. The parameters for the grading system are described below.

Grade 1	Minor symptoms that require no treatment
Grade 2	Moderate symptoms requiring conservative treatment
Grade 3	Severe symptoms, requiring more aggressive treatment, with significant negative impact on daily activities
Grade 4	Irreversible functional damage, with major therapeutic intervention required
Grade 5	Death or loss of organ

Source: Pavy JJ, Denekamp J, Letschert J, et al. EORTC Late Effects Working Group. Late effects toxicity scoring: the SOMA scale. Radiother Oncol. 1995;35(1):11-15.

Cancer-specific Evaluation Tools

Pediatric Cancers

Chang staging system
Originally based on the size and extent of the tumor and any evidence of metastasis, the Chang staging system provides information for describing pediatric medulloblastoma. Modified to reflect diagnostic findings based on imaging and cerebrospinal fluid (CSF) analysis, the M-stage delineates the extent of metastasis as described below.

M0	No gross subarachnoid or hematogenous metastasis
M1	Microscopic tumors cells found in the CSF
M2	Gross nodular seeding in the cerebellum, cerebral subarachnoid space, or in the third or fourth ventricles
M3	Gross nodular seeding in spinal subarachnoid space
M4	Extraneural metastasis

Source: MacDonald T. Pediatric medulloblastoma (2012). *http://reference.medscape.com/article/987886-overview*.

Prostate Cancer

Expanded Prostate Cancer Index Composite (EPIC)
EPIC is a health-related quality-of-life assessment tool that evaluates patient function in men with prostate cancer. Included domains are urinary, bowel, sexual and hormonal health. Men are asked to evaluate their experiences and symptoms over the previous 4-week period.

Gleason score
Following a biopsy of the prostate, cancerous tissue will be graded based on microscopic findings. The Gleason score typically ranges from 2 to 10, with higher scores indicating a greater likelihood of the cancer spreading.

Gleason score	Related description of findings
≤ 6	Well-differentiated, less likely to spread
7	Moderately differentiated
8 - 10	Poorly differentiated, more likely to spread

Source: American Cancer Society. Prostate cancer. How is prostate cancer staged? *http://www.cancer.org/cancer/prostatecancer/detailedguide/prostate-cancer-staging*.

American Society for Therapeutic Radiology and Oncology (ASTRO): Biochemical failure
In consensus with RTOG, ASTRO has established the following definition for biochemical failure in patients who have received radiation therapy for prostate cancer: a rise in the prostate-specific antigen (PSA) of 2 ng/ml or more above the lowest measured PSA level.

Liver Cancer

Child-Pugh Classification
Designed to assess the severity of liver cirrhosis on a 15-point scale, the Child-Pugh assessment is based on clinical and biochemical measurements associated with liver function. For each item, up to 3 points are assigned for increasing abnormality. The parameters and summary grades are listed below.

Measurements

- Grade of hepatic encephalopathy
- Ascites
- Total bilirubin
- Serum albumin
- Prothrombin time (sec. prolonged or INR)

Child-Pugh classification: Grade A = 5-6 points; Grade B = 7-9 points; Grade C = 10-15 points

Barcelona Clinic Liver Cancer (BCLC) staging system
Combining information regarding tumor burden, liver function and patient status, the BCLC is an evidence-based algorithm designed to stage liver cancer and propose various treatment strategies. Specific treatment pathways may be found at the following link:
http://www.medscape.com/viewarticle/720694_3

Appendix B
Search Strategy

Search Strategy for Medline

Databases searched:
- Medline 1946 to present with weekly update
- EBM Reviews - Cochrane Central Register of Controlled Trials, September, 2013
- EBM Reviews – Database of Abstracts of Reviews of Effects, 3rd Quarter 2013

1. exp Protons/
2. proton.mp
3. proton beam.mp
4. proton beam therapy.mp
5. exp Proton Therapy/
6. proton*.mp
7. proton$ therap$.mp
8. protontherap$.mp
9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10. (neoplasm* or cancer* or carcinoma*).mp
11. 9 and 10
12. Limit 11 to (English language and humans and yr=”1990 – Current”)
13. Proton Pump Inhibitors/
14. 12 not 13
15. Limit 14 to (comment or letter or “review”)
16. 14 not 15

Search Strategy for EMBASE

1. 'proton'/exp
2. proton:de,lnk,ab,ti
3. 'proton therapy'/exp
4. 'proton therapy':de,lnk,ab,ti
5. 'proton radiation':de,lnk,ab,ti
6. proton*:de,lnk,ab,ti
7. 1 or 2 or 3 or 4 or 5 or 6
8. neoplasm*:de,lnk,ab,ti
9. cancer*:de,lnk,ab,ti
10. carcinoma*:de,lnk,ab,ti
11. 8 or 9 or 10
12. 7 and 11
13. 'proton pump inhibitor'/exp
14. 12 not 13

Search limits included:
- Publication year (2000-2014)
- Humans
- English language
- Publication type (inclusion of article, article in press or editorial)

Appendix C
Comparative Studies

Table 1. Bone Tumors: Study Characteristics.

Author (Year) Study Design Study Site	Sample Size Patient Characteristics	Inclusion/Exclusion Criteria	Treatment Protocol	Outcomes Assessed Main Findings*	Harms*	Quality	Notes
Park (2006) Retrospective Comparative Cohort Massachusetts General Hospital, MA, USA Study Objective Evaluation of PBT with surgery in the treatment of sacral chordoma Intervention Comparator Follow-up PBT ± photon F/U: 61.3 months (mean), (range, 35-91) PBT ± photon w/surgery F/U: 99.6 months (mean), (range, 26-261)	PBT ± photon N=6 • Male: 67% • Age: 68 • Tumor type Primary: 33% Recurrent: 67% • Prior surgery: 67% • Mean tumor size (cm): 5.6 PBT ± photon w/surgery N=21 • Male: 62% • Age: 54 • Tumor type Primary: 67% Recurrent: 33% • Prior surgery (recurrent group only): 100% • Mean tumor size (cm): 7.6 • Positive surgical margins: 76%	Inclusion • Patients treated with PBT ± photon w/or without surgery for primary and recurrent sacral chordomas	PBT ± photon • Mean total dose: 70.6 GyE • 2 patients received only photon therapy, mean dose = 61 Gy PBT ± photon w/surgery • Mean total dose:72.8 GyE • 3 patients received only photon therapy, mean dose = 63.7 Gy	Local failure PBT ± photon: 50% PBT ± photon w/surgery:38% Metastases PBT ± photon: 83% PBT ± photon w/surgery: 24% • Status at last f/u No evidence of disease PBT ± photon: 17% PBT ± photon w/surgery: 48% Alive w/disease PBT ± photon: 33% PBT ± photon w/surgery: 29% Mortality PBT ± photon: 50% PBT ± photon w/surgery: 24%	• Reported for patients achieving local control following treatment PBT ± photon, n=3 PBT ± photon w/surgery, n=13 Abnormal bowel function PBT ± photon: 33% PBT ± photon w/surgery: 69% Abnormal bladder function PBT ± photon: 0% PBT ± photon w/surgery: 38% Sexual dysfunction (reported in 9 patients receiving PBT ± photon w/surgery): 67% Difficulty ambulating PBT ± photon: 0% PBT ± photon w/surgery: 23% Return to work PBT ± photon: 100% PBT ± photon w/surgery: 57% (2 patients w/unknown status)	Poor	• Baseline data available for primary and recurrent disease treated with both modalities • Outcome analyses by primary and recurrent disease available

* No p-values reported.
F/U: follow-up; N: number; PBT: proton beam therapy

Table 2. Brain, Spinal, and Paraspinal Tumors: Study Characteristics.

Author (Year) Study Design Study Site	Sample Size Patient Characteristics	Inclusion/Exclusion Criteria	Treatment Protocol	Outcomes Assessed Main Findings	Harms	Quality	Notes
Brown (2013) Retrospective Comparative Cohort MD Anderson Cancer Center, TX, USA Study Objective Evaluation of different radiation therapy for medulloblastoma Intervention Comparator Follow-up PBT F/U: 26.3 months (median), (range, 11-63) Photon F/U: 57.1 months (median), (range, 4-103)	PBT N=19 • Male: 74% • Age: 29.9 (median) • Chang stage M0: 95% M1:0% M2: 5% M3: 0% M4: 0% • Gross residual tumor at RT <1.5 cm^2: 74% ≥1.5 cm^2: 26% • Any chemotherapy: 84% Photon N=21 • Male: 57% • Age: 32.7 (median) • Chang stage M0: 71% M1: 5% M2: 0% M3: 19% M4: 5% • Gross residual tumor at RT <1.5 cm^2: 81% ≥1.5 cm^2: 19% • Any chemotherapy: 81% • Significant differences between groups including f/u, Chang stage	Inclusion • Patients w/histologically confirmed medulloblastoma • Patients ≥16 years at radiation therapy	• All patients underwent surgical resection • All patients received prescribed radiation dose + boost dose PBT • Mean total dose (GyE): 54.6 ± 1.1 Photon • Mean total dose (Gy): 52.9 ± 6.3	Locoregional failure* PBT: 5% Photon: 14% 2-year overall survival PBT: 94% Photon: 90% p=NS 2-year progression-free survival PBT: 94% Photon: 85% p=NS	Suppression of WBC (median % baseline) PBT: 55% Photon: 46% p=0.04 Decreased hemoglobin (median % baseline) PBT: 97% Photon: 88% p=0.009 Medical management of esophagitis PBT: 5% Photon: 57% p<0.001 Median weight loss PBT: -1.2% Photon: -5.8% p=0.004	Poor	• Data on grades of acute toxicities available • Subgroup analyses of harms, excluding patients receiving chemotherapy available

* P-value not reported.

F/U: follow-up; HR: hazard ratio; IMRT: intensity-modulated radiation therapy; N; number; NS: not significant; PBT: proton beam therapy; WBC: white blood cell

Table 2. Brain, Spinal, and Paraspinal Tumors: Study Characteristics.

Author (Year) Study Design Study Site	Sample Size Patient Characteristics	Inclusion/Exclusion Criteria	Treatment Protocol	Outcomes Assessed Main Findings	Harms	Quality	Notes
Kahn (2011) Retrospective Comparative Cohort Massachusetts General Hospital, MA, USA Study Objective Evaluation of long-term outcomes of spinal cord glioma patients treated w/radiation therapy Intervention Comparator Follow-up PBT IMRT F/U: 24 months (median)	<u>PBT</u> N=10 • Male: 50% • Age: 14 • Tumor pathology Astrocytoma: 60% Ependymoma: 40% • WHO grade Low: 60% High: 40% • Surgery Biopsy: 30% Partial resection: 70% <u>IMRT</u> N=22 • Male: 50% • Age: 44 • Tumor pathology Astrocytoma: 55% Ependymoma: 45% • WHO grade Low: 91% High: 0% • Surgery Biopsy: 45% Partial resection: 55% • Overall, 91% of patients were Caucasian; 3% were each African American, Hispanic and Asian • Significant differences between groups including age	<u>Inclusion</u> • Patients w/primary intramedullary gliomas • Tumor types included astrocytoma, ependymoma, and oligodendroglioma	<u>PBT</u> • Total dose (Gy) <50: 30% 50-52: 50% >52: 20% <u>IMRT</u> • Total dose (Gy) <50: 14% 50-52: 50% >52: 36% • Fraction sizes ranged from 1.0 – 2.0 Gy • For entire patient cohort, 31% of patients received adjuvant chemotherapy	<u>Local recurrence*</u> PBT: 20% IMRT: 23% <u>Brain metastasis*</u> PBT: 10% IMRT: 5% <u>Mortality*</u> PBT: 20% IMRT: 32% <u>Multivariate analysis</u> • PBT significantly associated with worse overall survival HR 40 (p=0.02)	• No patients experienced significant long-term toxicity • No cases of myelopathy reported	Poor	

* P-value not reported.

F/U: follow-up; HR: hazard ratio; IMRT: intensity-modulated radiation therapy; N; number; NS: not significant; PBT: proton beam therapy; WBC: white blood cell; WHO: World Health Organization

Table 3. Breast Cancer: Study Characteristics.

Author (Year) Study Design Study Site	Sample Size Patient Characteristics	Inclusion/Exclusion Criteria	Treatment Protocol	Outcomes Assessed Main Findings	Harms	Quality	Notes
No comparative studies identified							

Table 4. Esophageal Cancer: Study Characteristics.

Author (Year) Study Design Study Site	Sample Size Patient Characteristics	Inclusion/Exclusion Criteria	Treatment Protocol	Outcomes Assessed Main Findings	Harms	Quality	Notes
McCurdy (2013) Retrospective Comparative Cohort MD Anderson Cancer Center, TX, USA Study Objective Evaluation of treatment effects to the lungs following radiation therapy for esophageal cancer Intervention Comparator Follow-up PBT IMRT 3D-CRT F/U: up to 75 days following completion of radiation therapy	<u>Presented for entire cohort only (N=75)</u> • Male: 76% • Age: 64 (median), (range, 42-82) •Smoking status Never: 27% Former: 69% Current: 4% • Clinical stage I: 0% IIA: 15% IIB: 5% III: 60% IV: 17% • Radiation therapy PBT: 32% IMRT: 57% 3D-CRT: 11% • Chemotherapy: 100%	<u>Inclusion</u> • Patients treated for esophageal cancer w/CT treatment planning and follow-up PET/CT imaging 25-75 days after radiation therapy • Volume receiving radiation ≥5 Gy must be ≥30%, and volume receiving ≥40 Gy must be ≥2%	• Total radiation dose for all patients was 50.4 Gy or CGE	NR	<u>Pneumonitis (grade ≥2)</u> • PBT:33% • Photon: 15% p=0.04	Fair	

3D-CRT: 3D conformal radiation therapy; CT: computed tomography; F/U: follow-up; GI: gastrointestinal; IMRT: intensity-modulated radiation therapy; N: number; PBT: proton beam therapy; PET: positron emission tomography

Table 4. Esophageal Cancer: Study Characteristics.

Author (Year) Study Design Study Site	Sample Size Patient Characteristics	Inclusion/Exclusion Criteria	Treatment Protocol	Outcomes Assessed Main Findings	Harms	Quality	Notes
Wang (2013) Retrospective Comparative Cohort MD Anderson Cancer Center, TX, USA Study Objective Evaluation of clinical predictors of postoperative complications in patients treated for esophageal cancer Intervention Comparator Follow-up PBT IMRT 3D-CRT F/U: up to 60 days following hospital discharge	<u>PBT</u> N=72 • Male: 93% • Age: 63 (median), (range, 29-76) • Clinical stage I: 4%; II: 35%; III: 56%; IVa: 6% • Receipt of induction chemotherapy: 38% • Surgery intent Planned: 97% Salvage: 3% <u>IMRT</u> N=164 • Male: 90% • Age: 60 (median), (range, 27-78) • Clinical stage I: 2%; II: 34%; III: 60%; IVa: 4% • Receipt of induction chemotherapy: 41% • Surgery intent Planned: 89% Salvage: 11% <u>3D-CRT</u> N=208 • Male: 89% • Age: 60 (median), (range, 22-79) • Clinical stage I: 1%; II: 40%; III: 54%; IVa: 5% • Receipt of induction chemotherapy: 61% • Surgery intent Planned: 94% Salvage: 6%	<u>Inclusion</u> • Patients treated with preoperative concurrent chemoradiation with or without chemotherapy followed by surgical resection	• All patients treated with neoadjuvant chemoradiation, with or without chemotherapy • 5-6 weeks after completion of neoadjuvant therapy, patients were evaluated for surgery <u>PBT</u> • Median dose: 50.4 CGE (range, 45-50.4) <u>IMRT</u> • Median dose: 50.4 Gy (range, 45-50.4) <u>3D-CRT</u> • Median dose: 50.4 Gy (range, 41-59.4)	NR	<u>Univariate analyses</u> • Incidence of postoperative pulmonary complications associated w/radiation modality (p=0.019) • Incidence of postoperative GI complications associated w/radiation modality (p=0.04) <u>Multivariate adjusted analyses</u> • Significant increase in risk of postoperative pulmonary complications for 3D-CRT vs. PBT (OR 9.127, 95% CI, 1.834-45.424), but not for IMRT vs. PBT (OR 2.228, 95% CI, 0.863-5.755) after adjustment for pre-RT diffusing capacity for carbon monoxide (DLCO) level • After adjustment, no significant association in risk of GI complications for 3D-CRT vs. PBT (OR 2.311, 95% CI, 0.69-7.74) or IMRT vs. PBT (OR 1.025, 95% CI, 0.467-2.249)	Fair	• Potential patient overlap w/ McCurdy (2013) • Rates of perioperative complications reported by radiation modality

3D-CRT: 3D conformal radiation therapy; CT: computed tomography; F/U: follow-up; GI: gastrointestinal; IMRT: intensity-modulated radiation therapy; N: number; PBT: proton beam therapy; PET: positron emission tomography

Table 5. Gastrointestinal Cancers: Study Characteristics.

Author (Year) Study Design Study Site	Sample Size Patient Characteristics	Inclusion/Exclusion Criteria	Treatment Protocol	Outcomes Assessed Main Findings	Harms	Quality	Notes
No comparative studies identified							

Table 6. Gynecologic Cancers: Study Characteristics.

Author (Year) Study Design Study Site	Sample Size Patient Characteristics	Inclusion/Exclusion Criteria	Treatment Protocol	Outcomes Assessed Main Findings	Harms	Quality	Notes
No comparative studies identified							

Table 7. Head and Neck Cancers (including skull-base tumors): Study Characteristics.

Author (Year) Study Design Study Site	Sample Size Patient Characteristics	Inclusion/Exclusion Criteria	Treatment Protocol	Outcomes Assessed Main Findings*	Harms	Quality	Notes
Solares (2005) Retrospective Comparative Cohort Cleveland Clinic Foundation, OH, USA Study Objective Evaluation of treatment of clival tumors utilizing endoscopy and radiation therapy Intervention Comparator Follow-up PBT IMRT Endoscopy alone F/U: 13 months (mean), (range, 8-24)	PBT N=2 IMRT N=3 Endoscopy alone N=1 Patient characteristics reported for entire cohort • Male: 67% • Age: 50 • Prior therapy: 67%	Inclusion • Patients undergoing transnasal endoscopic resection for malignant clival lesions	NR	No evidence of disease PBT: 0% IMRT: 67% Endoscopy: 100% Residual disease PBT: 100% IMRT: 0% Endoscopy: 0% Disease recurrence PBT: 0% IMRT: 33% Endoscopy: 0% Mortality PBT: 0% IMRT: 33% Endoscopy: 0%	NR	Poor	• Data on surgical complications provided

* P-values not reported.

F/U: follow-up; IMRT: intensity-modulated radiation therapy; N: number; NR: not reported; PBT: proton beam therapy

Table 7. Head and Neck Cancers (including skull-base tumors): Study Characteristics.

Author (Year) Study Design Study Site	Sample Size Patient Characteristics	Inclusion/Exclusion Criteria	Treatment Protocol	Outcomes Assessed Main Findings*	Harms*	Quality	Notes
Tokuuye (2004) Retrospective Comparative Cohort University of Tsukuba Proton Medical Research Center, Japan Study Objective Evaluation of PBT in patients w/head and neck cancers Intervention Comparator Follow-up PBT F/U: 71.3 months (mean), (range, 9-208) PBT + photon F/U: 36.6 months (mean), (range, 6-125)	PBT N=17 • Male: 82% • Age: 67 • Prior therapy Chemotherapy: 35% Resection of previous tumor: 18% Radiation therapy: 6% Cryotherapy: 24% None: 35% • Clinical stage T1: 12% T2: 6% T3: 29% T4: 24% Recurrence: 18% N/A: 12% PBT + photon N=16 • Male: 44% • Age: 54 • Prior therapy Chemotherapy: 44% Resection of previous tumor: 6% Radiation therapy: 0% Cryotherapy: 0% None: 44% • Clinical stage T1: 0% T2: 31% T3: 0% T4: 50% Recurrence: 6% N/A: 13%	Inclusion • Patients w/malignant tumors of the head and neck • Refusal of surgery before or after PBT or tumors inoperable Exclusion • Prior PBT • Prior surgical resection of tumor of study focus	PBT • Median dose: 75 Gy (range, 42-99) • Median dose per fraction: 3.0 Gy (range, 2.5 – 6) PBT + photon • PBT Median dose: 32.5 Gy (range, 16-60) Median dose per fraction: 2.5 Gy (range, 1.5-3) • Photon Median dose: 40 Gy (range, 16-75) Median dose per fraction: 1.8 Gy (range, 1.7-2.1)	Local control PBT: 76% PBT + photon: 88% Mean control period (months) PBT: 69 PBT + photon: 34 Recurrence PBT: 24% PBT + photon: 13% Mean time of recurrence (months) PBT: 12 PBT + photon: 18 Mortality PBT: 76% PBT + photon: 50%	Treatment-related Toxicities • Ulceration PBT: 24% PBT + photon: 6% • Osteonecrosis PBT: 18% PBT + photon: 0% • Esophageal stenosis PBT: 0% PBT + photon: 6% • No reported toxicities PBT: PBT + photon: • Mean time to toxicities (months) PBT: 33 PBT + photon: 24	Poor	• Analyses for overall outcomes and harms available

* P-values not reported.

F/U: follow-up; IMRT: intensity-modulated radiation therapy; N: number; N/A: not available; NR: not reported; PBT: proton beam therapy

Table 8. Liver Cancer: Study Characteristics.

Author (Year) Study Design Study Site	Sample Size Patient Characteristics	Inclusion/Exclusion Criteria	Treatment Protocol	Outcomes Assessed Main Findings	Harms*	Quality	Notes
Komatsu (2011b) Prospective Comparative Cohort Hyogo Ion Beam Medical Center, Japan Study Objective Evaluation of efficacy and safety of proton and carbon ion therapy for HCC Intervention Comparator Follow-up PBT Carbon ion therapy F/U: 31.0 months (median) or until death	PBT N=242 • Male: 75% • Age ≥70: 52% • Tumor size (mm) <50: 71% 50-100: 23% >100: 6% • BCLC-based category Inoperable: 80% • Child-Pugh A: 76% B: 23% C: 1% • Previous treatment of target tumor Yes: 47% Carbon N=108 • Male: 72% • Age ≥70: 46% • Tumor size (mm) <50: 75% 50-100: 20% >100: 5% • BCLC-based category Inoperable: 71% • Child-Pugh A: 77% B: 20% C: 3% • Previous treatment of target tumor Yes: 45%	Inclusion • Patients w/HCC Exclusion • Uncontrolled ascites • Tumor size >15cm	PBT • 8 dosing protocols utilized • 52.8-84 GyE given in 4-38 fractions • 150, 190, 210 or 230 MeV beam Carbon • 4 dosing protocols utilized • 52.8-76 GyE given in 4-20 fractions • 250 or 320 MeV beam	5-year local control rate PBT: 90.2% Carbon: 93% 5-year local control rate based on BED_{10} <100 PBT:93.3% Carbon: 87.4% ≥100 PBT: 80.7% Carbon: 95.7% 5-year overall survival rate PBT: 38% Carbon: 36.3% 5-year overall survival rate <100 PBT: 31.7% Carbon: 32.3% ≥100 PBT: 43.9% Carbon: 48.4% • No significant differences found between PBT and carbon ion therapy	Dermatitis Grade 2 PBT: 5% Carbon: 5% Increased transaminase Grade 2 PBT: 2% Carbon: 3% Rib fracture Grade 2 PBT: 3% Carbon: 3% Pneumonitis Grade 2 PBT: 2% Carbon 2% Nausea/ anorexia/ pain/ ascites Grade 2 PBT: 2% Carbon: 2% Grade ≥3 late toxicities PBT: 3% Carbon: 4% • No deaths due to treatment-related toxicities	Fair	Univariate analysis for PBT • Prior treatment history not associated w/local control (p=0.73) Multivariate analyses for PBT • Tumor size significantly associated with local control rate (p=0.003) • Baseline characteristics including Child-Pugh classification and vascular invasion significantly correlated with overall survival rate Subgroup analysis • Patients w/HCC and inferior vena cava tumor thrombus receiving PBT (81%) and carbon ion therapy, curative vs. palliative intent: median survival time greater for curative treatment (25.4 vs. 7.7 months, p=0.0183)†

* P-values not reported.

† Findings reported in Komatsu (2011a).

AST: (serum) aspartate aminotransferase; BCLC: Barcelona Clinic Liver Cancer; BED_{10}: radio-biologic equivalent dose for acute-reacting tissues; F/U: follow-up; HCC: hepatocellular carcinoma; N: number; PBT: proton beam therapy; SD: standard deviation

Table 8. Liver Cancer: Study Characteristics.

Author (Year) Study Design Study Site	Sample Size Patient Characteristics	Inclusion/Exclusion Criteria	Treatment Protocol	Outcomes Assessed Main Findings*	Harms*	Quality	Notes
Otsuka (2003) Retrospective Comparative Cohort University of Tsukuba, Japan Study Objective Evaluation of patients undergoing radiation therapy for recurrent HCC after hepatectomy Intervention Comparator Follow-up PBT Photon F/U: variable	PBT N=5 • Male: 100% • Mean age: 57 • Mean initial recurrence interval: 10 months (range, 4-28) • Mean tumor size: 2.5 cm • TFactor† T1: 40% T2: 20% T3: 40% • Child-Pugh A: 60% B: 40% Photon N=3 • 1 patient with 2 recurrences • Male: 100% • Mean age: 58 • Mean initial recurrence interval: 45 months (range, 24-80) • Mean tumor size: 3.9 cm • TFactor† T1: 0% T2: 0% T3: 100% • Child-Pugh A: 66% B: 33%	Inclusion • Patients w/HCC who underwent hepatectomy Selection criteria for radiotherapy following tumor recurrence: • Ineligible/ patient refusal of re-hepatectomy • Difficult/ incomplete primary surgery • Target tumor with single-treatment volume • Multiple tumors in 2 treatment volumes	PBT Mean interval from hepatectomy: 21.8 months • 250 MeV beam • 3.0-4.5 Gy/fraction • Mean dose: 75.9 Gy Photon Mean interval from hepatectomy: 71.8 months • 6 MV beam • 2.0 Gy/fraction • Mean dose: 62.5 Gy	Death from liver failure PBT: 40% Photon: 33% Death from lung metastasis PBT: 60% Photon: 33% Alive PBT: 0% Photon: 33% Mean survival time (months) PBT: 23.8 Photon: 15.5 Tumor recurrence PBT: 40% Photon: 0%	• No bone marrow depression or GI complications in either group AST increase (up to 2x baseline) • PBT: 80% • Photon: 100% Hypoalbuminemia (<3g/dl) w/ascites • PBT: 40% • Photon: 33% Bilirubin increase (1.1 to 2.2 mg/dl) • PBT: 20% • Photon: 0%	Poor	

*** P-values not reported.**

† Tfactor based on 3 conditions: 1) solitary tumor; 2) tumor size ≤2cm; 3) no involvement of portal, hepatic veins or bile duct; T1 = all 3 conditions fulfilled; T2 = 2/3 conditions met; T3 = 1/3 conditions met.

AST: (serum) aspartate aminotransferase; BCLC: Barcelona Clinic Liver Cancer; BED_{10}: radio-biologic equivalent dose for acute-reacting tissues; F/U: follow-up; HCC: hepatocellular carcinoma; N: number; PBT: proton beam therapy; SD: standard deviation

Table 8. Liver Cancer: Study Characteristics.

Author (Year) Study Design Study Site	Sample Size Patient Characteristics	Inclusion/Exclusion Criteria	Treatment Protocol	Outcomes Assessed Main Findings*	Harms	Quality	Notes
Matsuzaki (1995) Prospective Comparative Cohort University of Tsukuba, Japan Study Objective Evaluation of PBT in the treatment of HCC Intervention Comparator Follow-up PBT PBT + chemotherapy F/U: up to 4 years	<u>PBT</u> N=21 (with 26 tumors) • Tumor size: 3.6 ± 2.2 (mean, SD) <u>PBT + chemotherapy</u> N=14 (with 18 tumors) • Tumor size: 4.6 ± 2.1 (mean, SD)	<u>Inclusion</u> • Patients w/unresectable HCC	<u>PBT</u> • 250 MeV beam • 3-4 Gy/treatment • Duration of therapy: 17-69 days • Dose: 76.5 ± 9.5 (mean, SD) <u>Chemotherapy</u> • No details provided	• Number of tumors w/reduction in size <u>3 weeks</u> PBT: 26/26 (100%) PBT + chemotherapy: 18 /18 (100%) <u>1 year</u> PBT: 24/25 (96%) PBT + chemotherapy: 13/13 (100%) <u>2 years</u> PBT: 7/8 (88%) PBT + chemotherapy: 5/5 (100%) • Local tumor control (no sign of growth or development of new lesion on CT/ultrasound) <u>2 years</u> PBT: 25/26 (96%) PBT + chemotherapy: 18/18 (100%)	• Reported for entire cohort only	Fair	

*** P-values not reported**.

AST: (serum) aspartate aminotransferase; BCLC: Barcelona Clinic Liver Cancer; BED_{10}: radio-biologic equivalent dose for acute-reacting tissues; F/U: follow-up; HCC: hepatocellular carcinoma; N: number; PBT: proton beam therapy; SD: standard deviation

Table 9. Lung Cancer: Study Characteristics.

Author (Year) Study Design Study Site	Sample Size Patient Characteristics	Inclusion/Exclusion Criteria	Treatment Protocol	Outcomes Assessed Main Findings	Harms	Quality	Notes
Fujii (2013) Prospective Comparative Cohort Hyogo Ion Beam Medical Center, Japan Study Objective Evaluation of PBT and carbon ion therapy for the treatment of Stage I NSCLC Intervention Comparator Follow-up PBT F/U: 45 months (median), (range, 5-103) Carbon ion therapy F/U: 39 months (median), (range, 5-72)	PBT N=70 • Male: 71% • Age: 76 (median), (range, 48-88) • Smoking (yes): 73% • Median tumor diameter (mm) (range): 30 (11-48) •Tumor stage T1a: 11% T1b: 40% T2a: 49% • Operability (yes): 49% •Median BED_{10} (GyE_{10}) (range): 96 (89-122) Carbon N=41 • Male: 63% • Age: 76 (median), (range, 39-89) • Smoking (yes): 71% • Median tumor diameter (mm) (range): 28 (12-48) •Tumor stage T1a: 22% T1b: 41% T2a: 37% • Operability (yes): 46% •Median BED_{10} (GyE_{10}) (range): 122 (89-122) • Significant differences between groups including median BED_{10}	Inclusion • Patients w/histologically confirmed primary NSCLC staged as 1A or 1B • Medical inoperability or refusal of surgery • WHO performance status ≤2 • No history of previous lung cancer • No prior chest radiation therapy or chemotherapy	• Treatment protocols varied according to treatment period PBT • Total dose ranged from 52.8 – 80 GyE, given in 4 – 20 fractions Carbon • Total dose ranged from 52.8 – 70.2 GyE, given in 4 – 26 fractions	Local recurrence PBT: 17% Carbon: 24% p=NR Regional lymph node and/or distant metastases without local progression PBT: 34% Carbon: 20% p=NR 3-year overall survival PBT: 72% Carbon: 76% 3-year progression-free survival PBT: 44% Carbon: 53% 3-year local control PBT: 81% Carbon: 78% • Differences between groups for 3-year outcomes were not statistically significant	Pneumonitis (p=0.443) • Grade 0-1 PBT: 84% Carbon: 90% • Grade 2 PBT: 16% Carbon: 5% • Grade 3 PBT: 0% Carbon: 5% Dermatitis (p=0.424) • Grade 0-1 PBT: 82% Carbon: 89% • Grade 2 PBT: 14% Carbon: 7% • Grade 3 PBT: 4% Carbon: 2% • Grade 4 PBT: 0% Carbon: 2% Rib fracture (p=0.532) • Grade 0-1 PBT: 75% Carbon: 78% • Grade 2 PBT: 24% Carbon: 22% • Grade 3 PBT: 1% Carbon: 0%	Fair	• 3-year overall survival and local control rates available for different dosing protocols

3D-CRT: 3D conformal radiation therapy; BED_{10}: biological effective dose; DLCO: diffusing capacity of the lung for carbon monoxide; F/U: follow-up; IMRT: intensity-modulated radiotherapy; N: number; NR: not reported; NSCLC: non-small-cell lung cancer; PBT: proton beam therapy; PFT: pulmonary function test; WHO: World Health Organization

Table 9. Lung Cancer: Study Characteristics.

Author (Year) Study Design Study Site	Sample Size Patient Characteristics	Inclusion/Exclusion Criteria	Treatment Protocol	Outcomes Assessed Main Findings	Harms	Quality	Notes
Gomez (2012) Retrospective Comparative Cohort MD Anderson Cancer Center, TX, USA Study Objective Evaluation of radiation-induced esophagitis in patients treated for NSCLC Intervention Comparator Follow-up PBT IMRT 3D-CRT F/U: up to 6 months following the start of radiation therapy	PBT N=108 • Male: 55% • Age: 67 (median) • Former and current smokers: 89% • Clinical stage IA: 3%; IB: 11%; IIA: 0%; IIB: 12%; IIIA: 25%; IIIB: 28%; IV: 4%; Recurrent/post-op: 6% IMRT N=139 • Male: 55% • Age: 64 (median) • Former and current smokers: 94% • Clinical stage IA: 2%; IB: 5%; IIA: 1%; IIB: 4%; IIIA: 33%; IIIB: 41%; IV: 9%; Recurrent/post-op: 3% 3D-CRT N=405 • Male: 50% • Age: 65 (median) • Former and current smokers: 92% • Clinical stage IA: 8%; IB: 9%; IIA: 1%; IIB: 5%; IIIA: 34%; IIIB: 36%; IV: 6%; Recurrent/post-op: 0% • Significant differences among groups including clinical stage, tumor histology, concurrent therapy	Inclusion • Patients treated for NSCLC with a total radiation dose of ≥50 Gy • Radiation therapy delivered in 1.8-2.5 Gy fractions Exclusion • Previous irradiation of the lung • History of esophageal cancer • Boost field used during treatment	PBT • Median total dose: 74 Gy (RBE) (range 50-87.5) IMRT • Median total dose: 63 Gy (range, 50-74.25) 3D-CRT • Median total dose: 63 Gy (range, 54-84) • Total doses were significantly different (p<0.001)	NR	Rates of severe radiation esophagitis (grade ≥3) PBT: 6% IMRT: 28% 3D-CRT: 8% p<0.05 • No grade 5 toxicities seen	Fair	• Overlapping patient populations w/Lopez Guerra (2012) and Sejpal (2011)

3D-CRT: 3D conformal radiation therapy; BED_{10}: biological effective dose; DLCO: diffusing capacity of the lung for carbon monoxide; F/U: follow-up; IMRT: intensity-modulated radiotherapy; N: number; NR: not reported; NSCLC: non-small-cell lung cancer; PBT: proton beam therapy; PFT: pulmonary function test; WHO: World Health Organization

Table 9. Lung Cancer: Study Characteristics.

Author (Year) Study Design Study Site	Sample Size Patient Characteristics	Inclusion/Exclusion Criteria	Treatment Protocol	Outcomes Assessed Main Findings	Harms	Quality	Notes
Lopez Guerra (2012) Retrospective Comparative Cohort MD Anderson Cancer Center, TX, USA Study Objective Evaluation in pulmonary function following radiation therapy for NSCLC Intervention Comparator Follow-up PBT IMRT 3D-CRT F/U: up to 1 year following radiation therapy	PBT N=60 • Male: 58% • Age: 71 (median) • Race White: 93% Other: 7% • Clinical stage I,II: 40% III,IV: 60% • Former and current smokers: 95% IMRT N=97 • Male: 61% • Age: 69 (median) • Race White: 90% Other: 10% • Clinical stage I,II: 9% III,IV: 91% • Former and current smokers: 95% 3D-CRT N=93 • Male: 52% • Age: 74 (median) • Race White: 89% Other: 11% • Clinical stage I,II: 18% III,IV: 82% • Former and current smokers: 95%	Inclusion • Patients w/a primary diagnosis of NSCLC • Patients w/DLCO analyses before and after radiation therapy Exclusion • Patients undergoing postradiation PFT analysis following locoregional or distant relapse • No PFT analyses done 1 month prior and 2 months after diagnosis of radiation pneumonitis	PBT • Median total dose: 74 GyE (range, 60-87.5) IMRT • Median total dose: 66 Gy (range, 60-74) 3D-CRT • Median total dose: 66 Gy (range, 60-84) • All radiation given in fractions of 1.2-2.5 Gy	• Use of 3D-CRT associated w/larger post-treatment declines in lung diffusing capacity for carbon monoxide (DLCO) during 5-8 months following treatments, as compared to PBT (p=0.009)	NR	Fair	• Overlapping patient populations w/Gomez (2012) and Sejpal (2011)

3D-CRT: 3D conformal radiation therapy; BED_{10}: biological effective dose; DLCO: diffusing capacity of the lung for carbon monoxide; F/U: follow-up; IMRT: intensity-modulated radiotherapy; N: number; NR: not reported; NSCLC: non-small-cell lung cancer; PBT: proton beam therapy; PFT: pulmonary function test; WHO: World Health Organization

Table 9. Lung Cancer: Study Characteristics.

Author (Year) Study Design Study Site	Sample Size Patient Characteristics	Inclusion/Exclusion Criteria	Treatment Protocol	Outcomes Assessed Main Findings	Harms	Quality	Notes
Sejpal (2011) Non-contemporaneous Case Series MD Anderson Cancer Center, TX, USA Study Objective Evaluation of acute toxicities associated with treatment of locally advanced NSCLC Intervention Comparator Follow-up PBT F/U: 15.2 months (median), (range, 3.3-27.4) IMRT F/U: 17.4 months (median), (range, 1.8-65.5) 3D-CRT F/U: 17.9 months (median), (range, 2.3-76.1)	PBT N=62 • Male: 55% • Age: 67 (median) • Ethnicity: White: 60%; Non-white: 40% • Prior malignancy: 27% • Clinical stage 1B: 3%; 2A: 0%; 2B: 8%; 3A: 40%; 3B: 27%; 4: 8%; Recurrent: 13% IMRT N=66 • Male: 61% • Age: 62 (median) • Ethnicity: White: 70%; Non-white: 30% • Prior malignancy: 27% • Clinical stage 1B: 0%; 2A: 0%; 2B: 5%; 3A: 23%; 3B: 58%; 4: 11%; Recurrent: 4% 3D-CRT N=74 • Male: 50% • Age: 61 (median) • Ethnicity: White: 88%; Non-white: 12% • Prior malignancy: 14% • Clinical stage 1B: 0%; 2A: 3%; 2B: 3%; 3A: 41%; 3B: 46%; 4: 8%; Recurrent: 0% • Significant differences among groups including age, ethnicity, clinical stage, induction chemotherapy	Inclusion • Patients w/locally advanced, unresectable NSCLC Exclusion • Prior thoracic irradiation • Malignant pleural effusion • Karnofsky performance score <60 • Weight loss >10% in 6 months prior to diagnosis	• All patients received concurrent chemotherapy PBT • Median total dose: 74 Gy (RBE) (range, 63-80.95) IMRT • Median total dose: 63 Gy (range, 60-76) 3D-CRT • Median total dose: 63 Gy (range, 60-69.9) • Total doses were significantly different (p<0.001)	Median overall survival (months) PBT: 24.4 IMRT: 17.6 3D-CRT: 17.7 p=0.1061	• No differences in hematological toxicities found among groups (e.g., anemia, thrombocytopenia, neutropenia) Esophagitis • Grade 3 PBT: 5% IMRT: 39% 3D-CRT: 18% • Grade 4 seen w/IMRT: 4.5% Pneumonitis • Grade 3 PBT: 2% IMRT: 6% 3D-CRT: 30% • No cases of Grade 4 seen; Grade 5 seen w/IMRT: 3% Dermatitis • Grade 3 PBT: 24% IMRT: 17% 3D-CRT: 7% • No cases of Grade 4 or 5 seen • Significant differences among groups across all grades of toxicities	Fair	• Overlapping patient populations w/Gomez (2012) and Lopez Guerra (2012) • Data available for all grades of harms, including fatigue • Analyses of harms based on treatment modality and gross tumor volume available

3D-CRT: three-dimensional conformal radiotherapy; BED_{10}: biological effective dose; DLCO: diffusing capacity of the lung for carbon monoxide; F/U: follow-up; IMRT: intensity-modulated radiotherapy; N: number; NSCLC: non-small-cell lung cancer; PBT: proton beam therapy; PFT: pulmonary function test

Table 10. Lymphomas: Study Characteristics.

Author (Year) Study Design Study Site	Sample Size Patient Characteristics	Inclusion/Exclusion Criteria	Treatment Protocol	Outcomes Assessed Main Findings	Harms	Quality	Notes
No comparative studies identified							

Table 11. Ocular Tumors: Study Characteristics.

Author (Year) Study Design Study Site	Sample Size Patient Characteristics	Inclusion/Exclusion Criteria	Treatment Protocol	Outcomes Assessed Main Findings	Harms	Quality	Notes
Cassoux (2013) Non-contemporaneous Case Series Institut Curie, France	PBT N=57 • Male: 60% • Age: 56 • Median tumor diameter (mm) (range): 18 (10-23) • Median tumor thickness (mm) (range): 8 (5-11) • Tumor location – posterior: 21% •Tumor stage ≥T3: 98% PBT + TTT N=51 • Male: 45% • Age: 59 • Median tumor diameter (mm) (range): 17 (13-23) • Median tumor thickness (mm) (range): 8 (5-12) • Tumor location – posterior: 30% •Tumor stage ≥T3: 100% PBT + endoresection N=63 • Male: 67% • Age: 57 • Median tumor diameter (mm) (range): 14 (8-19) • Median tumor thickness (mm) (range): 9 (6-12) • Tumor location – posterior: 26% •Tumor stage ≥T3: 81% • Significant differences between groups including tumor diameter & thickness, clinical stage and presence of retinal detachment	Inclusion • Patients w/choroidal melanoma >10mm diameter and >5mm thickness	PBT • Total dose: 60 Gy RBE given in 4 fractions PBT + TTT • Total dose: 60 Gy RBE given in 4 fractions • 3 sessions of TTT provided PBT + endoresection • Total dose: 60 Gy RBE given in 4 fractions • Endoresection performed following PBT	• No significant differences among groups in initial visual acuity (p=.67), or in final visual acuity at 2 years (p=.54) 2-year survival without neovascular glaucoma • PBT: 55% • PBT + TTT: 62% • PBT + endoresection: 93% P=.0001 2-year survival without secondary enucleation • PBT: 89% • PBT + TTT: 98% • PBT + endoresection: 96% P=.203 2-year survival without metastasis • PBT: 86% • PBT + TTT: 86% • PBT + endoresection: 90% P=NS	NR	Poor	• Potential patient population overlap w/Desjardins (2006)

Author (Year) Study Design Study Site	Sample Size Patient Characteristics	Inclusion/Exclusion Criteria	Treatment Protocol	Outcomes Assessed Main Findings	Harms	Quality	Notes
Study Objective Evaluation of PBT ± adjunct therapy in patients with choroidal melanoma Intervention Comparator Follow-up <u>PBT</u> F/U: 112 months (median), (range, (107-126) <u>PBT + TTT</u> F/U: 99 months (median), (range, 89-124) <u>PBT + endoresection</u> F/U: 23 months (median), (range 20-26)							

BCVA: best-corrected visual acuity; CI: confidence interval; F/U: follow-up; HR: hazard ratio; N: number; N/A: not available; NR: not reported; NS: not significant; PBT: proton beam therapy; RCT: randomized controlled trial; RR: rate ratio; SD: standard deviation; TTT: transpupillary thermotherapy; VA: visual acuity

Table 11. Ocular Tumors: Study Characteristics.

Author (Year) Study Design Study Site	Sample Size Patient Characteristics	Inclusion/Exclusion Criteria	Treatment Protocol	Outcomes Assessed Main Findings*	Harms	Quality	Notes
Mosci (2012) Retrospective Comparative Cohort Ocular Oncology Service, Italy Study Objective Evaluation of survival following treatment of large uveal tumors Intervention Comparator Follow-up PBT F/U: 53.4 ± 29.3 months Enucleation F/U: 45.5 ± 21.6 months	PBT N=70 • Male: 55% • Age: 62.7 ± 14.1 • Mean (SD) tumor thickness (mm): 9.8 ± 1.6 • Mean (SD) largest basal diameter (mm): 15.2 ± 2.7 • Clinical stage T3: 84% T4: 16% Enucleation N=62 • Male: 61% • Age: 66.7 ± 14.5 • Mean (SD) tumor thickness (mm): 12.0 ± 2.8 • Mean (SD) largest basal diameter (mm): 14.4 ± 4.5 • Clinical stage T3: 58% T4: 42% • Significant difference between groups in tumor thickness	Inclusion • Patients w/unilateral choroidal tumors classified as T3 and T4 tumors Exclusion • Previously treated tumors • Diffuse, ring or multifocal tumors • Tumors judged to be predominantly ciliary body melanoma • Patients w/metastatic disease or other primary tumors • Patients w/history of cancer	PBT • Total dose: 60 GyE given in 4 fractions	5-year all-cause mortality • PBT: 34% • Enucleation: 43% 5-year melanoma-related mortality • PBT: 38% • Enucleation: 39% 5-year metastasis-free survival • PBT: 72% • Enucleation: 55% Local recurrence PBT: 14% • Secondary enucleation: 9/10 (90%) • Second course of PBT: 1/10 (10%) Visual acuity (PBT) BCVA ≥ 0.1 Baseline: 73% 12 months: 47.5% 24 months: 39% 60 months: 32%	PBT Eye retention: 74%, over 5 years	Fair	• After correcting for age, tumor thickness and sex, no significant effect seen on metastasis-free survival associated w/type of treatment • Analysis of outcomes based on tumor type revealed no significant differences between treatment type for both T3 and T4 tumors

* P-values not reported.

BCVA: best-corrected visual acuity; CI: confidence interval; F/U: follow-up; HR: hazard ratio; N: number; N/A: not available; NR: not reported; NS: not significant; PBT: proton beam therapy; RCT: randomized controlled trial; RR: rate ratio; SD: standard deviation; TTT: transpupillary thermotherapy; VA: visual acuity

Table 11. Ocular Tumors: Study Characteristics.

Author (Year) Study Design Study Site	Sample Size Patient Characteristics	Inclusion/Exclusion Criteria	Treatment Protocol	Outcomes Assessed Main Findings	Harms	Quality	Notes
Marucci (2011) Retrospective Comparative Cohort Massachusetts General Hospital, MA, USA Study Objective Evaluation of survival following treatment with PBT or enucleation for recurrent uveal melanoma Intervention Comparator Follow-up PBT F/U: 74 months (mean), (5-189, range) Enucleation F/U: 88 months (mean), (10-225, range)	PBT N=31 •Male: 33% • Age: 66 • Mean largest tumor diameter (mm): 14.6 • Tumor location – posterior: 36% • Visual acuity ≥ 20/200: 71% Enucleation N=42 •Male: 46% • Age: 60 • Mean largest tumor diameter (mm): 15.7 • Tumor location – posterior: 29% • Visual acuity ≥ 20/200: N/A • Significant differences between groups in tumor volume	Inclusion • Patients w/ recurrent uveal melanoma, originally treated with PBT	PBT • 70 CGE in 5 fractions (1 patient received 48 CGE)	PBT • 5-year cumulative rate of local recurrence: 31% • Enucleation: 29% • Visual acuity ≥20/200 maintained: 5/15 (33%) Survival without metastasis* PBT: 54% Enucleation: 36% Alive w/metastasis* PBT: 3% Enucleation: 2% Death due to metastasis* PBT: 32% Enucleation: 59% Death from other causes* PBT: 10% Enucleation: 5% Median survival duration PBT: 90 months Enucleation: 42 months p=0.04 Median time free from metastasis PBT: 97 months Enucleation: 38 months p=0.028	NR	Fair	Adjusted analyses • Adjustment for tumor volume and year of re-treatment, outcomes more favorable for PBT compared to enucleation: Mortality: HR 0.14 (p=0.002) Distant metastasis: HR 0.15 (p=0.005); similar findings with the addition of age to the model • Patients evaluated were a subgroup of patients from Gragoudas (2000)

* P-values not reported.

BCVA: best-corrected visual acuity; CI: confidence interval; F/U: follow-up; HR: hazard ratio; N: number; N/A: not available; NR: not reported; NS: not significant; PBT: proton beam therapy; RCT: randomized controlled trial; RR: rate ratio; SD: standard deviation; TTT: transpupillary thermotherapy; VA: visual acuity

Table 11. Ocular Tumors: Study Characteristics.

Author (Year) Study Design Study Site	Sample Size Patient Characteristics	Inclusion/Exclusion Criteria	Treatment Protocol	Outcomes Assessed Main Findings	Harms	Quality	Notes
Bellman (2010) Retrospective Comparative Cohort Institut Curie, France Study Objective Evaluation of tumor recurrence and survival in uveal melanoma with extraocular spread Intervention Comparator Follow-up Conservative treatment (PBT, plaque radiotherapy) Enucleation F/U: 38 months (7-79) (median, range)	<u>Conservative</u> N=38 • Male: 34% • Age ≥63: 50% • Largest tumor basal diameter, mean ≤15mm: 55% • Tumor location – posterior: 5% • Extraocular spread mean ≤1000mm^3: 100% <u>Enucleation</u> N=29 • Male: 72% • Age ≥63: 55% • Largest tumor basal diameter, mean ≤15mm: 38% • Tumor location – posterior: 34% • Extraocular spread mean ≤1000mm^3: 93% • Significant differences between groups including gender, tumor site and height, and retinal detachment	<u>Inclusion</u> • Patients w/choroidal melanoma and cilio-choroidal melanoma presenting w/ extraocular spread <u>Exclusion</u> • Patients w/disseminated melanoma	<u>Conservative</u> PBT • 60 GyE given in 4 fractions Plaque radiotherapy • Iodine-125 plaque, 2-4 mm larger than tumor base; 90 Gy <u>Enucleation</u> • Postoperative orbital radiotherapy, avg. dose 50 Gy over 40 days	• No intraocular or orbital tumor recurrence observed <u>5-year overall survival rate</u> Conservative: 79.3% Enucleation: 40.4% p<0.01 • Subgroup analysis PBT: 57.6% Plaque therapy: 100% p=0.01 <u>5-year metastasis-free survival rate</u> Conservative: 59.0% Enucleation: 39.4% p=0.02	NR	Fair	<u>Size of extraocular spread (mm^3)</u> (played a role in treatment choice) p=NR • Conservative PBT: 14.8 ± 19.9 Plaque: 4.6 ± 4.8 •Enucleation 136.7 ± 346.4

BCVA: best-corrected visual acuity; CI: confidence interval; F/U: follow-up; HR: hazard ratio; N: number; N/A: not available; NR: not reported; NS: not significant; PBT: proton beam therapy; RCT: randomized controlled trial; RR: rate ratio; SD: standard deviation; TTT: transpupillary thermotherapy; VA: visual acuity

Table 11. Ocular Tumors: Study Characteristics.

Author (Year) Study Design Study Site	Sample Size Patient Characteristics	Inclusion/Exclusion Criteria	Treatment Protocol	Outcomes Assessed Main Findings	Harms	Quality	Notes
Voelter (2008) Retrospective Comparative Cohort Paul Scherrer Institut, Switzerland Study Objective Evaluation of adjuvant chemotherapy following PBT in the treatment of uveal melanoma Intervention Comparator Follow-up <u>PBT</u> F/U: 8.5 years (median) <u>PBT + chemotherapy</u> F/U: 4.6 years (median)	<u>PBT</u> N=66 • Male: 59% • Age 20-55: 59% >55: 41% • Largest tumor diameter >20mm: 91% <u>PBT + chemotherapy</u> N=22 • Male: 73% • Age 20-55: 77% >55: 23% • Largest tumor diameter >20mm: 91%	<u>Inclusion</u> • Patients w/nonmetastatic uveal melanoma • Patients meeting at least 1 of following criteria: 1) choroidal involvement; 2) largest tumor diameter >20mm; 3) extrascleral extension; 4) tumor height >15mm	• All patients received PBT <u>Chemotherapy</u> • Initiated 4-6 weeks following PBT • Fotemustine (100 mg/m^2) infused as an intra-arterial hepatic infusion over 4 hours • Once-weekly administration for 4 weeks, followed by a 5-week break, then 1 infusion every 3 weeks • Total treatment duration: 6 months	<u>Median overall survival</u> PBT: 7.4 years PBT + chemotherapy: 9 years p=0.5 <u>5-year survival rate</u> PBT: 56% PBT + chemotherapy: 75% p=0.539 • Cox regression model (covariates including largest tumor diameter, age, sex, tumor thickness): death at 5 years, HR 0.98 (95% CI, 0.38-2.61)	NR	Fair	• Data on side effects of fotemustine provided

BCVA: best-corrected visual acuity; CI: confidence interval; F/U: follow-up; HR: hazard ratio; N: number; N/A: not available; NR: not reported; NS: not significant; PBT: proton beam therapy; RCT: randomized controlled trial; RR: rate ratio; SD: standard deviation; TTT: transpupillary thermotherapy; VA: visual acuity

Table 11. Ocular Tumors: Study Characteristics.

Author (Year) Study Design Study Site	Sample Size Patient Characteristics	Inclusion/Exclusion Criteria	Treatment Protocol	Outcomes Assessed Main Findings	Harms	Quality	Notes
Desjardins (2006) RCT Institut Curie, France Study Objective Evaluation of transpupillary thermotherapy (TTT) combined w/PBT in the treatment of uveal melanoma Intervention Comparator Follow-up PBT PBT + TTT F/U: 38 months (median)	<u>PBT</u> N=75 • Male: 60% • Age: 56 • Mean tumor diameter (mm): 17.6 • Mean tumor thickness (mm): 7 • Tumor location – posterior: 24% <u>PBT + TTT</u> N=76 • Male: 43% • Age: 59 • Mean tumor diameter (mm): 17.6 • Mean tumor thickness (mm): 7.6 • Tumor location – posterior: 26% • Median initial visual acuity across the cohort: 20/60 (range, 20/400-20/20)	<u>Inclusion</u> • Patients w/uveal melanomas • Tumor diameter ≥15 mm and/or tumor thickness ≥7 mm <u>Exclusion</u> • Presence of metastases • Pre-existing glaucoma • Opaque media preventing TTT (e.g., cataract, vitreous hemorrhage)	<u>PBT</u> • Total dose: 60 GyE given in 4 fractions of 15 GyE <u>PBT + TTT</u> • Total dose: 60 GyE given in 4 fractions of 15 GyE • Spot laser treatment utilizing 810 nm wavelength	• Outcomes assessed according to original randomization • Mortality reported for entire study cohort only	• No statistically significant difference between groups in terms of cataracts, maculopathy, and papillopathy (data not shown) <u>Incidence of glaucoma</u> PBT: 55% PBT + TTT: 46% p=NS <u>Mean peak intraocular pressure (mmHg)</u> PBT: 34.5 PBT + TTT: 31 p=NS • Reduction of tumor thickness greater for PBT + TTT vs. PBT (p=0.06) • Significantly lower secondary enucleation rate in PBT + TTT vs. PBT (p=0.02)	Fair	• In PBT-only group, 7 patients received TTT following development of complications (e.g., massive exudates from tumor scar) • In PBT + TTT group, 9 patients did not receive TTT due to retinal detachment or vitreous hemorrhage

BCVA: best-corrected visual acuity; CI: confidence interval; F/U: follow-up; HR: hazard ratio; N: number; N/A: not available; NR: not reported; NS: not significant; PBT: proton beam therapy; RCT: randomized controlled trial; RR: rate ratio; SD: standard deviation; TTT: transpupillary thermotherapy; VA: visual acuity

Table 11. Ocular Tumors: Study Characteristics.

Author (Year) Study Design Study Site	Sample Size Patient Characteristics	Inclusion/Exclusion Criteria	Treatment Protocol	Outcomes Assessed Main Findings	Harms	Quality	Notes
Char (2003) Non-contemporaneous Case Series Site: NR Study Objective Evaluation of laser treatment plus PBT in decreasing exudative detachments in choroidal melanoma Intervention Comparator Follow-up PBT + laser F/U: 13.6 months (2-35) (mean, range) PBT F/U: 30.8 months (3-89) (mean, range)	PBT + laser N=11 • Male: 55% • Age: 45.4 • Mean largest diameter (mm): 12.3 • Largest diameter ≤10mm: 18% • Tumor location – posterior: 73% PBT N=45 • Male: 48% • Age: 60.5 • Mean largest diameter (mm): 12.6 • Largest diameter ≤10mm: 20% • Tumor location – posterior: 60%	Inclusion • Patients w/choroidal melanomas w/exudative retinal detachments ≥15% of fundus Exclusion • No prior tumor therapy • Tumors overhanging optic nerve • Tumors contiguous to fovea • ≥40% ciliary body involvement	PBT + laser • Confluent 810 nm laser spots • PBT, total dose: 56 GyE PBT • Total dose: 56 GyE	Mean time to fluid resorption (days) PBT + laser: 192 PBT: 263 p<0.04 Change in VA at 1 year (log VA) PBT + laser (n=8): 0.599 PBT (n=42): 0.584 p=NR • No significant difference in visual field scotoma in 2 groups	NR	Poor	

BCVA: best-corrected visual acuity; CI: confidence interval; F/U: follow-up; HR: hazard ratio; N: number; N/A: not available; NR: not reported; NS: not significant; PBT: proton beam therapy; RCT: randomized controlled trial; RR: rate ratio; SD: standard deviation; TTT: transpupillary thermotherapy; VA: visual acuity

Table 11. Ocular Tumors: Study Characteristics.

Author (Year) Study Design Study Site	Sample Size Patient Characteristics	Inclusion/Exclusion Criteria	Treatment Protocol	Outcomes Assessed Main Findings	Harms	Quality	Notes
Seddon (1990) Retrospective Comparative Cohort Massachusetts General Hospital, MA, USA Study Objective Evaluation of mortality following enucleation or PBT for treatment of uveal melanoma Intervention Comparator Follow-up PBT F/U: 5.0 years (median), (range, <1-12.9) Enculeation (1965-June 1975) F/U: 8.8 years (median), (range, <1-23.8) Enucleation (July 1975-1984) F/U: 6.7 years (median), (range, <1-13.6)	PBT N=556 • Male: 48% • Age >60: 42% • Largest tumor diameter >15mm: 36% • Tumor height ≤5mm: 47% • Tumor location – posterior: 45% Enucleation (1965-75) N=238 • Male: 43% • Age >60: 43% • Largest tumor diameter >15mm: 41% • Tumor height ≤5mm: 43% • Tumor location – posterior: 58% Enucleation (1975-84) N=257 • Male: 47% • Age >60: 59% • Largest tumor diameter >15mm: 47% • Tumor height ≤5mm: 33% • Tumor location – posterior: 50% • Significant differences among groups including age, tumor location, height and diameter	Inclusion • Patients w/unilateral melanoma involving the choroid and/or ciliary body • Primary treatment w/enucleation or PBT Exclusion • Patients w/clinical evidence of metastatic disease • Prior treatment of the intraocular tumor • From enucleation group, patients w/tumors larger in area than the largest tumor in the PBT series	NR	Overall mortality* PBT: 22% Enucleation (65-75): 65% Enucleation (75-84): 44% >9-10-year survival rate* PBT: 0.63 Enucleation (65-75): 0.50 Enucleation (75-84): 0.53 Adjusted overall death rates (PBT is referent) (RR, 95% CI) • Metastatic death Enucleation (65-75): 1.7 (1.2-2.4) Enucleation (75-84): 1.1 (0.8-1.5) • Cancer death Enucleation (65-75): 1.6 (1.2-2.1) Enucleation (75-84): 1.0 (0.7-1.4) • All cause mortality Enucleation (65-75): 1.6 (1.2-2.1) Enucleation (75-84): 1.2 (0.9-1.6)	NR	Fair	• Survival rates calculated for yearly intervals after treatment up to 10 years • Adjusted hazards model (adjustments including tumor height, anterior margin, age) for interval specific death by treatment group available • Significant increase in rate of death up to 2 years after treatment for patients w/enucleation compared to PBT (95% CI available); differences are essentially non-significant after 2 year

* P-values not reported.

BCVA: best-corrected visual acuity; CI: confidence interval; F/U: follow-up; HR: hazard ratio; N: number; N/A: not available; NR: not reported; NS: not significant; PBT: proton beam therapy; RCT: randomized controlled trial; RR: rate ratio; SD: standard deviation; TTT: transpupillary thermotherapy; VA: visual acuity

Table 12. Pediatric Cancers: Study Characteristics.

Author (Year) Study Design Study Site	Sample Size Patient Characteristics	Inclusion/Exclusion Criteria	Treatment Protocol	Outcomes Assessed Main Findings	Harms	Quality	Notes
Sethi (2013) Retrospective Comparative Cohort Massachusetts General Hospital, MA, USA Study Objective Evaluation of secondary malignancy in patients treated for retinoblastoma Intervention Comparator Follow-up PBT F/U: 6.9 years (median), (range 2-24 years) Photon F/U: 13.1 years (median), (range 1-24 years)	PBT N=55 • Male: 44% • Median age at diagnosis: 7.5 months • Median age at treatment: 14.8 months • Receipt of chemotherapy: 56% Photon N=31 • Male: 55% • Median age at diagnosis: 7.2 months • Median age at treatment: 10.0 months • Receipt of chemotherapy: 16% • Significant differences between groups including year of treatment, hereditary status, receipt of chemotherapy, median follow-up	Inclusion • Patients with retinoblastoma Exclusion • Patients receiving PBT after prior photon therapy • Patients w/ <6 months follow-up	PBT • Median RBE dose (Gy): 44 (range, 40-50) Photon • Median RBE dose (Gy): 45 (range, 34-83)	NR	Secondary malignancy PBT: 2% Photon: 13% p=NR 10-year cumulative incidence of secondary malignancy PBT: 5% Photon: 14% p=0.12 10-year cumulative incidence of RT-induced or in-field malignancies PBT: 0% Photon: 14% p=0.015	Poor	• Subgroup analysis of patients w/hereditary disease 10-year cumulative incidence of secondary malignancy PBT: 5% Photon: 22% p=0.021 10-year cumulative incidence of RT-induced or in-field malignancies PBT: 0% Photon: 22% p=0.005

F/U: follow-up; N: number; NR: not reported; PBT: proton beam therapy; RBE: relative biological effectiveness; RT: radiation therapy

Table 13. Prostate Cancer: Study Characteristics.

Author (Year) Study Design Study Site	Sample Size Patient Characteristics	Inclusion/Exclusion Criteria	Treatment Protocol	Outcomes Assessed Main Findings	Harms	Quality	Notes
Gray (2013) Non-contemporaneous Case Series Multiple clinical sites Study Objective Evaluation of patient-reported QoL after different treatments for prostate cancer Intervention Comparator Follow-up PBT IMRT 3D-CRT F/U: 24 months	<u>PBT</u> N=95 • Age: 64 (median) • Race White: 93%; Black: 6%; Other: 1% • Clinical stage T1: 80%; T2:20%; T3: 0% • Gleason score 4-6: 67%; 7: 32%; 8-10: 1% <u>IMRT</u> N=153 • Age: 69 (median) • Race White: 79%; Black: 18%; Other: 1% • Clinical stage T1: 80%; T2: 20%; T3: 0% • Gleason score 4-6: 63%; 7: 37%; 8-10: 0% <u>3D-CRT</u> N=123 • Age: 70 (median) • Race White: 94%; Black: 2%; Other: 1% • Clinical stage T1: 40%; T2: 51%; T3: 6% • Gleason score 4-6: 54%; 7: 31%; 8-10: 12% • Significant differences among groups including age, race, PSA and clinical stage of tumor	<u>Inclusion</u> • Patients w/localized prostate cancer • No receipt of androgen-suppression therapy	<u>PBT</u> •Dose: 74-82 Gy (RBE) <u>IMRT</u> • Dose: 75.6-79.2 Gy <u>3D-CRT</u> • Dose: 66.4-79.2 Gy • All therapy given in 1.8-2.0 Gy fractions	• No between-group comparisons provided • Mean score change from baseline, 24 months post-treatment <u>Bowel/rectal QoL*</u> PBT: -3.7 IMRT: -7.4 3D-CRT: -4.3 • All changes significant • All changes clinically meaningful (>0.5 SD of baseline) <u>Urinary irritation/ obstruction QoL*</u> PBT: -2.3 IMRT: 1.7 3D-CRT: -2.0 • No significant changes <u>Urinary incontinence QoL*</u> PBT: -4.1 IMRT: -5.1 3D-CRT: -1.9 • Only IMRT w/significant change from baseline	NR	Poor	• Data available for 3 domains at time points: 2-3 months and 12 months post-treatment

* QoL evaluated for PBT and 3D-CRT using the Prostate Cancer Symptom Indices (PCSI) scale, and for IMRT w/the Expanded Prostate Cancer Index Composite (EPIC) instrument.
3D-CRT: 3D conformal radiation therapy; ADT: androgen deprivation therapy; BF: biological freedom; bNED: biological no evidence of disease; CI: confidence interval; EBRT: external beam radiation therapy; F/U: follow-up; IMRT: intensity-modulated radiation therapy; N stage: describes spread of tumor to nearby lymph nodes; nADT: neoadjuvant androgen deprivation therapy; NR: not reported; PBT: proton beam therapy; PSA: prostate specific antigen; QoL: quality-of-life; RBE: relative biological effectiveness ; RCT: randomized controlled trial

Table 13. Prostate Cancer: Study Characteristics.

Author (Year) Study Design Study Site	Sample Size Patient Characteristics	Inclusion/Exclusion Criteria	Treatment Protocol	Outcomes Assessed Main Findings	Harms	Quality	Notes
Hoppe (2013) Non-contemporaneous Case Series University of Florida Proton Therapy Institute, FL, USA Study Objective Evaluation of patient-reported QoL after different treatments for prostate cancer Intervention Comparator Follow-up PBT IMRT F/U: up to 2 years	PBT N=1,243 • Age: 66 • Race White: 91% Black: 6% Other: 3% • PSA >10 ng/ml: 14% • Clinical stage T1: 74% T2: 26% T3: <1% • Gleason score <7: 53% • Receipt of ADT: 15% IMRT N=204 • Age: 69 • Race White: 81% Black: 17% Other: 0% • PSA >10 ng/ml: 19% • Clinical stage T1: 73% T2: 27% T3: 0% • Gleason score <7: 51% • Receipt of ADT: 24% • Significant differences between groups including age, race, size of prostate and receipt of ADT	• Patients w/localized prostate cancer PBT Exclusion • Failure to complete treatment • Hypofractionated PBT • Weekly docetaxel • Pelvic lymph node irradiation IMRT Exclusion • Pelvic radiation therapy	PBT • Dose: 78-82 Gy (RBE) IMRT • Dose: 75.6-79.2 Gy	• QoL evaluated using the EPIC-26 questionnaire • Median score change from baseline, 2 years post-treatment Bowel summary score PBT: -4 IMRT: 0 P=.99 Urinary incontinence summary score PBT: 0 IMRT: 0 P=.99 Urinary irritative/ obstructive summary score PBT: 0 IMRT: 0 P=.99 Sexual summary score* PBT: 0 IMRT: 0 P=.99 • In adjusted analyses for baseline differences, patients receiving IMRT reported more “moderate” problems w/ rectal urgency (p=.02) and bowel frequency (p=.05) compared to PBT	NR	Poor	• Patient overlap w/Mendenhall (2012)

* Evaluated only in patients not receiving ADT.

3D-CRT: 3D conformal radiation therapy; ADT: androgen deprivation therapy; BF: biological freedom; bNED: biological no evidence of disease; CI: confidence interval; EBRT: external beam radiation therapy; F/U: follow-up; IMRT: intensity-modulated radiation therapy; N stage: describes spread of tumor to nearby lymph nodes; nADT: neoadjuvant androgen deprivation therapy; NR: not reported; PBT: proton beam therapy; PSA: prostate specific antigen; QoL: quality-of-life; RBE: relative biological effectiveness ; RCT: randomized controlled trial

Table 13. Prostate Cancer: Study Characteristics.

Author (Year) Study Design Study Site	Sample Size Patient Characteristics	Inclusion/Exclusion Criteria	Treatment Protocol	Outcomes Assessed Main Findings	Harms	Quality	Notes
Yu (2013) Retrospective Comparative Cohort Data Source: Chronic Condition Warehouse – Medicare linked database Study Objective Evaluation of early toxicity associated with PBT and IMRT Intervention Comparator Follow-up PBT IMRT F/U: up to 12 months following treatment	<u>PBT</u> N=314 •Age ≥70: 63.7% •Race White: 93% Black: <3.5% Other: >3.5% • Comorbidities 0:73.6% 1-2: >22.9% ≥3: <3.5% • Receipt of ADT: 20.7% <u>IMRT</u> N=628 •Age ≥70: 63.7% •Race White: 93% Black: 2.9% Other: 4.1% • Comorbidities 0: 73.4% 1-2: 23.2% ≥3: 3.3% • Receipt of ADT: 21%	<u>Inclusion</u> • Patients w/early-stage, treated prostate cancer • PBT or IMRT as primary treatment <u>Exclusion</u> • Patients without Medicare A & B, 9 months prior to treatment through 3 months after	NR	NR	• For OR calculation, likelihood of complication w/PBT and IMRT as referent <u>6-month toxicities</u> • Genitourinary PBT: 5.9% IMRT: 9.5% OR 0.60 (95% CI, 0.38,0.96) • GI PBT: 2.9% IMRT: 3.6% OR 0.84 (95% CI, 0.42, 1.66) • Other PBT: <2.6% IMRT: 2.5% OR 0.69 (95% CI 0.29, 1.66) <u>12-month toxicities</u> • Genitourinary PBT: 18.8% IMRT: 17.5% OR 1.08 (95% CI, 0.76, 1.54) • GI PBT: 9.9% IMRT: 10.2% OR 0.97 (95% CI, 0.61, 1.53) • Other PBT: 4.5% IMRT: 5.6% OR 0.78 (95% CI, 0.41, 1.50)	Fair	• Mahalanobis-matched data utilized <u>Patterns of care analysis</u> • Age Patients 66-69 years 3X more likely to receive PBT than patients 85-94 (3.3% vs. 1.0%, p<0.001) • Race White patients more likely to receive PBT than black patients (2.2% vs. 0.5%, p<0.001) • Comorbidities Patients w/no comorbidities more likely to receive PBt than patients w/ ≥3 comorbidities (2.6% vs. 0.8%, p<0.001) • Distance Patients living closer (<75 miles) and farther (>500 miles) more likely to receive PBT than patients 75-500 miles from center (4.9%, 4.2% vs. 1.5%, p<0.001)

3D-CRT: 3D conformal radiation therapy; ADT: androgen deprivation therapy; BF: biological freedom; bNED: biological no evidence of disease; CI: confidence interval; EBRT: external beam radiation therapy; F/U: follow-up; IMRT: intensity-modulated radiation therapy; N stage: describes spread of tumor to nearby lymph nodes; nADT: neoadjuvant androgen deprivation therapy; NR: not reported; PBT: proton beam therapy; PSA: prostate specific antigen; QoL: quality-of-life; RBE: relative biological effectiveness ; RCT: randomized controlled trial

Table 13. Prostate Cancer: Study Characteristics.

Author (Year) Study Design Study Site	Sample Size Patient Characteristics	Inclusion/Exclusion Criteria	Treatment Protocol	Outcomes Assessed Main Findings	Harms	Quality	Notes
Coen (2012) Non-contemporaneous Case Series Massachusetts General Hospital, MA, USA Study Objective Evaluation of high-dose PBT and brachytherapy for the treatment of prostate cancer Intervention Comparator Follow-up PBT + photon (data from Zietman, 2010) F/U: 8.6 years (median), (range, 1.2-12.3) Brachytherapy F/U: 7.4 years (median), (range, 3.1-11.3)	PBT + photon (Subset of Zietman, 2010 – high dose arm) N=141 • Age: 67 (median) • Median PSA (ng/mL): 6.1 • T stage 1c: 74% 2a: 25% 2b: 1% • Gleason score 6: 89% 7: 11% • No patients received hormonal therapy Brachytherapy N=141 • Age: 65 (median) • Median PSA (ng/mL): 5.6 • T stage 1c: 74% 2a: 25% 2b: 1% • Gleason score 6: 89% 7: 11% • ^{125}I implant: 91% • ^{103}Pd implant: 9% • No patients received EBRT or ADT	PBT + photon Inclusion • Patients w/clinically localized prostate adenocarcinoma • Tumors stage T1b – T2b • Serum PSA <15 ng/ml • No evidence of metastatic disease Exclusion • Gleason score >7 Brachytherapy Inclusion • Patients w/ T1-T2 prostate cancer • Implant performed 1997-2002 • Gleason score ≤7 • PSA ≤15 ng/mL • At least 3 years of f/u available	PBT + photon • PBT: 28.8 GyE • Photon: 50.4 Gy • Fraction size: 1.8 Gy Brachytherapy • ^{125}I implant Dose: 145 Gy • ^{103}Pd implant Dose: 115 Gy	8-year overall survival PBT + photon: 93% Brachytherapy: 96% p=0.45 8-year freedom from metastasis PBT + photon: 99% Brachytherapy: 96% p=0.21 8-year BF rates PBT + photon: 7.7% Brachytherapy: 16.1% p=0.42 Median nadir PSA (ng/mL) PBT + photon: 0.3 Brachytherapy: 0.1 p=NR Mean nadir ≤0.5 ng/mL PBT + photon: 74% Brachytherapy: 92% p=0.0003	NR	Fair	• Subgroup analysis of 8-year BF: no significant differences between treatment groups in low risk and intermediate risk patients • Additional data on PSA levels available (e.g., PSA bounce, last PSA level)

3D-CRT: 3D conformal radiation therapy; ADT: androgen deprivation therapy; BF: biological freedom; bNED: biological no evidence of disease; CI: confidence interval; EBRT: external beam radiation therapy; F/U: follow-up; IMRT: intensity-modulated radiation therapy; N stage: describes spread of tumor to nearby lymph nodes; nADT: neoadjuvant androgen deprivation therapy; NR: not reported; PBT: proton beam therapy; PSA: prostate specific antigen; QoL: quality-of-life; RBE: relative biological effectiveness ; RCT: randomized controlled trial

Table 13. Prostate Cancer: Study Characteristics.

Author (Year) Study Design Study Site	Sample Size Patient Characteristics	Inclusion/Exclusion Criteria	Treatment Protocol	Outcomes Assessed Main Findings	Harms	Quality	Notes
Sheets (2012) Retrospective Comparative Cohort Data source: Surveillance Epidemiology and End Results (SEER) – Medicare linked database Study Objective Evaluation of morbidity and disease control after different treatments for prostate cancer Intervention Comparator Follow-up PBT • F/U: 50 months (median), (range, 0.3-90.2) IMRT • F/U: 46 months (median), (range, 0.4-88.3)	PBT N=684 • Age ≥70: 63.9% • Race White: 92.5% Black: 2.9% Other: 4.5% • Concurrent ADT: 31% • Clinical stage T1: 50.7% T2: 45.9% T3/T4: 3.4% • Tumor grade Well/mod diff.: 60.2% Poorly diff.: 39.2% IMRT N=684 • Age ≥70: 64.3% • Race White: 92.8% Black: 2.3% Other: 4.8% • Concurrent ADT: 29.2% • Clinical stage T1: 50.6% T2: 46.6% T3/T4: 2.8% • Tumor grade Well/mod diff.: 62.3% Poorly diff.: 37.1%	Inclusion • Patients w/a diagnosis of prostate cancer • No additional cancers, meta-static disease, or disease diagnosis at autopsy • Patients w/at least 1 year of claims data prior to diagnosis Exclusion • Patients enrolled in HMOs, or not enrolled in Medicare A & B • Patients w/radiation and brachytherapy or prostatectomy	NR	NR	• Event rate per 100 person-years • P-values not reported GI • Procedures PBT: 16.2 IMRT: 17.7 • Diagnoses PBT: 17.8 IMRT: 12.2 Urinary Incontinence • Procedures PBT: 7.8 IMRT: 7.6 • Diagnoses PBT: 3.3 IMRT: 3.1 ED Dysfunction • Procedures PBT: 1.4 IMRT: 0.8 • Diagnoses PBT: 7.4 IMRT:6.6 Hip Fracture PBT: 0.7 IMRT: 0.8 Additional Cancer Therapy PBT: 1.9 IMRT: 2.2	Fair	• Propensity- score adjusted data utilized • Rate ratios available for IMRT vs. PBT for all harms

3D-CRT: 3D conformal radiation therapy; ADT: androgen deprivation therapy; BF: biological freedom; bNED: biological no evidence of disease; CI: confidence interval; EBRT: external beam radiation therapy; F/U: follow-up; IMRT: intensity-modulated radiation therapy; N stage: describes spread of tumor to nearby lymph nodes; nADT: neoadjuvant androgen deprivation therapy; NR: not reported; PBT: proton beam therapy; PSA: prostate specific antigen; QoL: quality-of-life; RBE: relative biological effectiveness ; RCT: randomized controlled trial

Table 13. Prostate Cancer: Study Characteristics.

Author (Year) Study Design Study Site	Sample Size Patient Characteristics	Inclusion/Exclusion Criteria	Treatment Protocol	Outcomes Assessed Main Findings	Harms	Quality	Notes
Kim (2011) Retrospective Comparative Cohort Data source: Surveillance Epidemiology and End Results (SEER) – Medicare linked database Study Objective Evaluation of long-term risk of GI toxicities requiring intervention following radiation therapy Intervention Comparator Follow-up <u>Radiation therapy</u> • Including EBRT, brachytherapy and EBRT + brachytherapy; • EBRT included PBT, IMRT and 3D-CRT • PBT included PBT ± 3D-CRT or IMRT Conservative management F/U: at least 6 months after cancer diagnosis	<u>Radiation</u> (for entire cohort only) N=28,088 • Age ≥70: 76% • Race White: 81%; Black: 11%; Other: 8% • Hormone therapy within 1 year: 44% • Clinical stage T1: 52% T2: 48% • Gleason score 2-4: 5% 5-7: 64% 8-10: 29% <u>Conservative</u> N=13,649 • Age ≥70: 85% • Race White: 77%; Black: 13%; Other: 10% • Hormone therapy within 1 year: 0% • Clinical stage T1: 65% T2: 35% • Gleason score 2-4: 20% 5-7: 59% 8-10: 15% • Significant differences between groups including age, race, Gleason score, clinical stage	<u>Inclusion</u> • Patients aged 66-85 years w/T1-T2 clinically localized prostate cancer • Patients enrolled in Medicare A & B for 12 months prior to diagnosis <u>Exclusion</u> • Having another cancer prior to prostate cancer • Metastasis w/in 6 months of diagnosis • Palliative radiation treatment w/in 12 months of diagnosis • Cryotherapy or radioisotope therapy • Repeated brachytherapy • Primary ADT not combined w/radiotherapy • Radical prostatectomy in the first 12 months after diagnosis • Existing GI toxicity in year before diagnosis • Enrollment in an HMO, private insurance or VA coverage	NR	NR	• Event rate per 1000 person-years <u>Any GI toxicity</u> PBT: 20.1 IMRT: 8.9 3D-CRT: 9.3 Brachytherapy only: 5.3 Conservative: 2.1 p=NR <u>GI Bleeding</u> PBT: 20.1 IMRT: 8.3 3D-CRT: 7.8 Brachytherapy only: 4.4 Conservative: 0.9 p=NR <u>Pairwise comparisons for any GI toxicity</u> • PBT vs. Conservative: HR 13.7 (9.09-20.8) • PBT vs. 3D-CRT: HR 2.13 (1.45-3.13) • PBT vs. IMRT: HR 3.32 (2.12-5.20)	Fair	

3D-CRT: 3D conformal radiation therapy; ADT: androgen deprivation therapy; BF: biological freedom; bNED: biological no evidence of disease; CI: confidence interval; EBRT: external beam radiation therapy; F/U: follow-up; IMRT: intensity-modulated radiation therapy; N stage: describes spread of tumor to nearby lymph nodes; nADT: neoadjuvant androgen deprivation therapy; NR: not reported; PBT: proton beam therapy; PSA: prostate specific antigen; QoL: quality-of-life; RBE: relative biological effectiveness ; RCT: randomized controlled trial

Table 13. Prostate Cancer: Study Characteristics.

Author (Year) Study Design Study Site	Sample Size Patient Characteristics	Inclusion/Exclusion Criteria	Treatment Protocol	Outcomes Assessed Main Findings*	Harms	Quality	Notes
Jabbari (2010) Non-contemporaneous Case Series University of CA, San Francisco and Massachusetts General Hospital, MA, USA Study Objective Evaluation of efficacy of brachytherapy vs. PBT + photon for prostate cancer Intervention Comparator Follow-up PBT + Photon • F/U (reported for entire study population, Zietman, 2005): 5.5 years (median), (range, 1.2-8.2) Brachytherapy • F/U: 5.3 years (median), (range, 0.3-8.3)	<u>PBT + photon</u> (data from Zietman, 2005) N=195 • Age: 66 (median) • Additional treatment nADT: 0% • Clinical stage T1: 61.5% T2a: 25.6% T2b: 12.8% • Gleason score ≤6: 75.4% 7: 15.3% 8-10: 7.7% • PSA (ng/mL): 6.2 (median) <u>Brachytherapy</u> N=206 • Age: 63 (median) • Additional treatment nADT: 28% EBRT ± nADT: 25% • Clinical stage T1: 47% T2a: 36% T2b: 17% • Gleason score ≤6: 83.5% 7: 16% 8-10: 0.5% • PSA (ng/mL): 6.3 (median) • Significant differences between groups including tumor stage	<u>PBT + photon</u> Inclusion • Patients w/clinically localized adenocarcinoma of the prostate • Tumor stage T1b – T2b • PSA <15 ng/mL • No evidence of metastatic disease <u>Brachytherapy</u> Inclusion • Patients treated w/permanent prostate implant brachytherapy Exclusion • Radiotherapy from alternate institution • Receipt of adjuvant ADT	<u>PBT + photon</u> • Phase 1-PBT Dose: 28.8 GyE, given in 1.8 GyE fractions (160 or 250 mV beam) • Phase 2-photon Dose: 50.4 Gy, given in 1.8 Gy fractions (10-23 mV beam) <u>Brachytherapy</u> • Monotherapy ^{125}I: 144 Gy ^{103}Pd: 125 Gy • Multimodal ^{125}I: 110 Gy + 45 Gy EBRT ^{103}Pd: 90 Gy + 45 Gy EBRT	<u>Interval to reach PSA nadir (median)</u> PBT + photon: 39.6 months Brachytherapy: 43.2 months <u>Number of patients to achieve PSA ≤0.5 ng/mL</u> PBT + photon: 59% Brachytherapy: 91% <u>Number of patients to achieve PSA ≤0.1 ng/mL</u> PBT + photon: 87% Brachytherapy: 96% <u>5-year estimate of bNED</u> PBT + photon:91% (95% CI, 87-95%) Brachytherapy: 93% (95% CI, 88-95%)	NR	Poor	• Analyses by risk and therapy: bNED in low-risk and high-risk patients

* P-values not reported.

3D-CRT: 3D conformal radiation therapy; ADT: androgen deprivation therapy; BF: biological freedom; bNED: biological no evidence of disease; CI: confidence interval; EBRT: external beam radiation therapy; F/U: follow-up; IMRT: intensity-modulated radiation therapy; N stage: describes spread of tumor to nearby lymph nodes; nADT: neoadjuvant androgen deprivation therapy; NR: not reported; PBT: proton beam therapy; PSA: prostate specific antigen; QoL: quality-of-life; RBE: relative biological effectiveness ; RCT: randomized controlled trial

Table 13. Prostate Cancer: Study Characteristics.

Author (Year) Study Design Study Site	Sample Size Patient Characteristics	Inclusion/Exclusion Criteria	Treatment Protocol	Outcomes Assessed Main Findings	Harms	Quality	Notes
Shah (2006) Retrospective Comparative Cohort Loma Linda University Medical Center, CA, USA Study Objective Evaluation of patients developing urothelial carcinoma following EBRT for prostate cancer Intervention Comparator Follow-up PBT + EBRT EBRT F/U: 4.04 years (mean), (range, 0.5-8)	PBT + EBRT N=7 EBRT N=4 • Mean age at diagnosis of urothelial carcinoma: 72 • Other baseline data not reported	Inclusion • Patients w/new onset urothelial carcinoma after receiving curative doses of radiation therapy for prostate cancer	PBT + EBRT • Dose: 75 Gy (mean), (range, 68-80) EBRT (reported for 1/4 patients) • Dose: 75 Gy	NR	• Gross hematuria present in all patients • All patients presented w/coexisting radiation cystitis Latency period to development of urothelial carcinoma • PBT + EBRT: 3.07 years (mean) • EBRT: 5.75 years (mean) p=0.09 Tumor Grade • PBT + EBRT Grade 1: 57% Grade 2:14% Grade 3: 29% • EBRT: Grade 1: 25% Grade 2: 0% Grade 3: 75% •No significant differences in mean grade, p=0.23 • No significant difference in patients requiring eventual cystectomy, p=0.6	Poor	•No significant difference in percent tobacco users, p=0.2

3D-CRT: 3D conformal radiation therapy; ADT: androgen deprivation therapy; BF: biological freedom; bNED: biological no evidence of disease; CI: confidence interval; EBRT: external beam radiation therapy; F/U: follow-up; IMRT: intensity-modulated radiation therapy; N stage: describes spread of tumor to nearby lymph nodes; nADT: neoadjuvant androgen deprivation therapy; NR: not reported; PBT: proton beam therapy; PSA: prostate specific antigen; QoL: quality-of-life; RBE: relative biological effectiveness ; RCT: randomized controlled trial

Table 13. Prostate Cancer: Study Characteristics.

Author (Year) Study Design Study Site	Sample Size Patient Characteristics	Inclusion/Exclusion Criteria	Treatment Protocol	Outcomes Assessed Main Findings	Harms	Quality	Notes
Galbraith (2001) Prospective Comparative Cohort San Bernardino County, CA, USA Study Objective Evaluation of QoL following different treatments for prostate cancer Intervention Comparator Follow-up PBT PBT + EBRT EBRT Surgery Watchful Waiting F/U: up to 18 months following treatment	<u>PBT</u> N=24 • Age: 68 • Race White:100% Black or Hispanic: 0% • PSA: 17.6 <u>PBT + EBRT</u> N=47 • Age: 69 • Race White: 81% Black or Hispanic: 9% • PSA: 14.1 <u>EBRT</u> N=25 • Age: 71 • Race White: 63% Black or Hispanic: 22% • PSA: 22.8 <u>Surgery</u> N=59 • Age: 65 • Race White: 83% Black or Hispanic: 14% • PSA: 9.8 <u>WW</u> N=30 • Age: 73 • Race White: 79% Black or Hispanic: 14% • PSA: 11.6 • Significant differences among groups including age, PSA	• No age or race limitations <u>Inclusion</u> • Patients able to speak, write, understand English • No known cognitive disabilities • Able to meet basic needs independently <u>Exclusion</u> •Patients w/other primary comorbidities	<u>PBT</u> • Dose: 74-75 Gy <u>PBT + EBRT</u> • Dose: 74-75 Gy <u>EBRT</u> • Dose: 65-70 Gy <u>Surgery</u> NR <u>WW</u> NR	• Multiple QoL scales utilized including Quality of Life Index, Southwest Oncology Group Prostate Treatment-Specific Symptoms Measure, and Importance of Sex-Role Identity <u>18 month - QoL</u> No significant differences among groups <u>18 month - Health Status</u> • PBT better physical function than surgery (p=0.01) or EBRT (p=0.02) • PBT better emotional functioning than WW (p=0.02) or EBRT (p=0.004) <u>18 month - Treatment-specific Symptoms</u> • WW more urinary symptoms than PBT, p=0.04 • No differences in masculinity noted among groups over 18 months (p=0.49)	NR	Fair	<u>Withdrawals</u> 6 months: 22 (12%) 12 months: 31 (17%) 18 months: 32 (17%) • Multiple analyses available for 6, 12 and 18 months

3D-CRT: 3D conformal radiation therapy; ADT: androgen deprivation therapy; BF: biological freedom; bNED: biological no evidence of disease; CI: confidence interval; EBRT: external beam radiation therapy; F/U: follow-up; IMRT: intensity-modulated radiation therapy; N stage: describes spread of tumor to nearby lymph nodes; nADT: neoadjuvant androgen deprivation therapy; NR: not reported; PBT: proton beam therapy; PSA: prostate specific antigen; QoL: quality-of-life; RBE: relative biological effectiveness ; RCT: randomized controlled trial

Table 13. Prostate Cancer: Study Characteristics.

Author (Year) Study Design Study Site	Sample Size Patient Characteristics	Inclusion/Exclusion Criteria	Treatment Protocol	Outcomes Assessed Main Findings*	Harms*	Quality	Notes
Shipley (1995) RCT Massachusetts General Hospital, MA, USA Study Objective Evaluation of efficacy of a higher radiation dose for locally advanced prostate cancer Intervention Comparator Follow-up PBT + photon Photon F/U: 61 months (median), (range, 3-139)	<u>PBT + photon</u> N=103 • Age: 70 (median) • T stage T3: 94% T4: 6% • N Stage N0: 7.8% N+:3.9% Nx: 88% • Gleason score 1-2: 5.8% 3: 62% 4-5: 32% <u>Photon</u> N=99 • Age: 68.6 (median) • T stage T3: 96% T4: 4% • N Stage N0: 4% N+: 5% Nx: 91% • Gleason score 1-2: 11.1% 3: 56.6% 4-5: 32.3%	<u>Inclusion</u> • Patients w/T3-T4, Nx, 0-2, M0 prostate cancer • Performance status ≥2 • Normal enzymatic serum acid phosphatase level • No evidence of metastases to bone, to retroperitoneal lymph nodes, or to bifurcation of common iliac vessels <u>Exclusion</u> • Patients w/medical contraindications to pelvic radiation therapy • Patients w/prior abdominal perineal resection	• No concomitant/ adjuvant endocrine therapy given <u>PBT + Photon</u> • Photon dose: 50.4 Gy given in 1.8 Gy fractions • PBT dose: 25.2 CGE, given in 2.1 Gy fractions (160 MeV beam) <u>Photon</u> • Initial dose: 50.4 Gy given in 1.8 Gy fractions • Total tumor dosing to 67.2 Gy, given in 2.1 Gy fractions (10-25 Mv beam)	<u>Overall Survival</u> •5-year PBT + photon: 75% Photon: 80% • 8-year PBT + Photon: 55% Photon: 51% <u>Disease-specific Survival</u> •5-year PBT + photon: 86% Photon: 83% • 8-year PBT + Photon: 67% Photon: 62% <u>Local Control</u> •5-year PBT + photon: 86% Photon: 81% • 8-year PBT + Photon: 73% Photon: 59% <u>Total Tumor-free Survival</u> •5-year PBT + photon: 39% Photon: 41% • 8-year PBT + Photon: 20% Photon: 16%	PBT + photon N=93 Photon N=96 <u>Rectal bleeding (incidence)</u> PBT + photon: 27% Photon: 9% • 91% of total events were ≤grade 2 toxicity <u>Urethral stricture (incidence)</u> PBT + photon: 13% Photon: 5% <u>Hematuria (incidence)</u> PBT + photon: 14% Photon: 6% <u>Urinary incontinence</u> PBT + photon: 1% Photon: 1% <u>Loss of full potency</u> PBT + photon: 24/40 (60%) Photon: 24/38 (63%)	Fair	<u>Withdrawals</u> PBT + photon: 10 (9.7%) Photon: 3 (3.0%) • Subgroup analyses based on Gleason score available for outcomes (well – and moderately-differentiated vs. poorly) • Actuarial 8-year rates calculated for harms w/statistical differences • Benk (1993), preliminary reporting on patient population (n=191); subgroup analysis of dose volume w/incidence of rectal bleeding

* P-values not reported.

3D-CRT: 3D conformal radiation therapy; ADT: androgen deprivation therapy; BF: biological freedom; bNED: biological no evidence of disease; CI: confidence interval; EBRT: external beam radiation therapy; F/U: follow-up; IMRT: intensity-modulated radiation therapy; N stage: describes spread of tumor to nearby lymph nodes; nADT: neoadjuvant androgen deprivation therapy; NR: not reported; PBT: proton beam therapy; PSA: prostate specific antigen; QoL: quality-of-life; RBE: relative biological effectiveness ; RCT: randomized controlled trial

Table 14. Soft Tissue Sarcomas: Study Characteristics.

Author (Year) Study Design Study Site	Sample Size Patient Characteristics	Inclusion/Exclusion Criteria	Treatment Protocol	Outcomes Assessed Main Findings	Harms	Quality	Notes
No comparative studies identified							

Table 15. Seminomas: Study Characteristics.

Author (Year) Study Design Study Site	Sample Size Patient Characteristics	Inclusion/Exclusion Criteria	Treatment Protocol	Outcomes Assessed Main Findings	Harms	Quality	Notes
No comparative studies identified							

Table 16. Thymomas: Study Characteristics.

Author (Year) Study Design Study Site	Sample Size Patient Characteristics	Inclusion/Exclusion Criteria	Treatment Protocol	Outcomes Assessed Main Findings	Harms	Quality	Notes
No comparative studies identified							

Table 17. Noncancerous Conditions: Study Characteristics.

Author (Year) Study Design Study Site	Sample Size Patient Characteristics	Inclusion/Exclusion Criteria	Treatment Protocol	Outcomes Assessed Main Findings	Harms	Quality	Notes
Arteriovenous malformations: no comparative studies identified							

Table 17. Noncancerous Conditions: Study Characteristics.

Author (Year) Study Design Study Site	Sample Size Patient Characteristics	Inclusion/Exclusion Criteria	Treatment Protocol	Outcomes Assessed Main Findings*	Harms	Quality	Notes
Giant cell tumors of bone							
Chakravarti (1999) Retrospective Comparative Cohort Massachusetts General Hospital, MA, USA Study Objective Evaluation of PBT in the management of giant-cell tumors of bone Intervention Comparator Follow-up PBT + photon Photon F/U: 9.3 years (median), (range, 3-19)	<u>PBT + photon</u> N=6 • Male: 17% • Age: 23 • Tumor site Cervical spine: 33% Sacrum: 50% Temporal bone: 17% • Tumor size (cm): range, 2x2 – 6x7 •Tumor grade 1: 50%; 2: 0%; 3: 0%; Unknown: 50% • Tumor stage Primary: 67% Recurrent: 33% Metastases: 0% <u>Photon</u> N=14 (15 tumors) • Male: 43% • Age: 46 • Tumor site Sacrum: 13% Femur: 20% Thoracic spine: 20% Lumbar spine: 13% Sphenoid, Pubis, Lung, Wrist, Tibia: each 7% • Tumor size (cm): range, 2x2 – 12x12 •Tumor grade 1: 47%; 2: 33%; 3: 7%; Unknown: 13% • Tumor stage Primary: 67% Recurrent: 20% Metastases: 13%	<u>Inclusion</u> • Patients w/giant-cell tumors of bone treated w/megavoltage radiation • Contraindication to operative management • Use of operative management would lead to major morbidity or functional impairment <u>Exclusion</u> • Patients w/Paget disease • Patients w/brown tumors of hyperparathyroidism	<u>PBT + photon</u> • Photon Cobalt 60 or 2-25 MeV beams • Proton 160 MeV beam Mean total dose: 58.8 Gy given in fractions of 1.8-2.0 Gy <u>Photon</u> Cobalt 60 or 2-25 MeV beams Mean total dose: 51.6 Gy given in fractions of 1.8-2.0 Gy <u>Patients receiving radiation only (n=7)</u> PBT + photon: 43% Photon: 57% <u>Patients w/partial resection + radiation (n=13)</u> PBT + photon: 23% Photon: 77%	• Total study population (partial resection ± RT) <u>Progression of disease</u> PBT + photon: 17% Photon: 14% <u>Distant metastases</u> PBT + photon: 17% Photon: 14% <u>Mean duration w/lack of progression (months)</u> PBT + photon: 87.7 Photon: 132.3 • Radiation only population <u>Progression of disease</u> PBT + photon: 0% Photon: 25% <u>Distant metastases</u> PBT + photon: 0% Photon: 0% <u>Mean duration w/lack of progression (months)</u> PBT + photon: 114.7 Photon: 135 • Partial resection + radiation population <u>Progression of disease</u> PBT + photon: 33% Photon: 10% <u>Distant metastases</u> PBT + photon: 33% Photon: 20% <u>Mean duration w/lack of progression (months)</u> PBT + photon: 60.7 Photon: 131.3	NR	Poor	• Specific detail provided on all patient cases

* P-values not reported.

CCH: circumscribed choroidal hemangioma; DCH: diffuse choroidal hemangioma; EBRT: external beam radiation therapy; F/U: follow-up; NR: not reported; PBT: proton beam therapy

Table 17. Noncancerous Conditions: Study Characteristics.

Author (Year) Study Design Study Site	Sample Size Patient Characteristics	Inclusion/Exclusion Criteria	Treatment Protocol	Outcomes Assessed Main Findings	Harms	Quality	Notes
Hemangiomas							
Höcht (2006) Retrospective Comparative Cohort Charité Campus Benjamin Franklin, Germany Study Objective Evaluation of EBRT in the treatment of choroidal hemangiomas Intervention Comparator Follow-up PBT F/U: 26.3 months (mean), (median, 23.7) Photon F/U: 38.9 months (mean), (median, 29)	PBT N=25 • Male: NR • Age: 46.8 Photon N=19 • Male: NR • Age: 43.7 Overall cohort • Circumscribed hemangiomas: 82% • Diffuse hemangiomas: 18% Hemangioma size (optic disc diameters) • Mean: 6.67 • Median: 4 Mean hemangioma thickness (mm) • Circumscribed PBT-treated: 3.3 Photon-treated: 4.2 • Diffuse: 3.9 • Mean visual acuity of affected eye: 0.1-0.125	Inclusion • Patients w/symptomatic diffuse or circumscribed hemangiomas	PBT • 68 MeV beam •Dose: 20 CGE, given in 4 fractions (1 patient received 22.5 CGE) Photon • 6 MV beam • Dose: 16-30 Gy, given in 5 fractions (2.0 Gy per fraction)	Visual acuity and resolution of retinal detachment reported for entire cohort only • Cox regression model: no significant impact of PBT vs. photon seen on stabilization of vision (p=0.43)	• Late side effects (graded using LENT/SOMA system)* Optic nerve/optic disc • PBT Grade I: 48% • Photon CCH, Grade I: 25% DCH, Grade I: 43% Retina • PBT Grade I: 28% Grade II: 8% Grade IV: 4% • Photon CCH, Grade II: 17% DCH, Grade II: 14% Ocular pressure • PBT Grade I: 4% • Photon CCH: 0% DCH, Grade II: 14% Lacrimation • PBT Grade III: 8% • Photon CCH, Grade I: 8% Grade II: 8% Grade III: 8% DCH: 0% Radiation retinopathy • PBT: 40% • Photon: 16%	Poor	• Data available for harms related to lens and iris also available • Cox regression model: no significant impact based on therapeutic modality seen on optic disc/optic nerve atrophy (p=0.27), or retinopathy (p=0.098)

* P-values not reported.

CCH: circumscribed choroidal hemangioma; DCH: diffuse choroidal hemangioma; EBRT: external beam radiation therapy; F/U: follow-up; NR: not reported; PBT: proton beam therapy

Table 17. Noncancerous Conditions: Study Characteristics.

Author (Year) Study Design Study Site	Sample Size Patient Characteristics	Inclusion/Exclusion Criteria	Treatment Protocol	Outcomes Assessed Main Findings*	Harms*	Quality	Notes
Meningiomas							
Arvold (2009) Retrospective Comparative Cohort Massachusetts General Hospital, MA, USA Study Objective Evaluation of patients w/ONSM treated w/PBT and/or photon therapy Intervention Comparator Follow-up PBT Photon PBT + photon F/U: 30 months (3-168) (median, range)	<u>PBT</u> N=9 • Male: 33% • Age: 38.9 • Tumor size (mL): 3.7 • Symptoms: Vision†: 89% Pain: 22% None: 11% <u>Photon</u> N=13 • Male: 23% • Age: 47.7 • Tumor size (mL): 2.2 • Symptoms: Vision†: 77% Pain: 7.7% None: 15% <u>PBT + Photon</u> N=3 • Male: 100% • Age: 43 • Tumor size (mL): 3.6 • Symptoms: Vision†: 100% Pain: 0% Proptosis: 33% None: 0%	<u>Inclusion</u> • Patients w/ONSM <u>Exclusion</u> • Patients w/meningiomas w/only secondary involvement of the optic nerve sheath	<u>PBT</u> • Mean dose (GyE): 51 (range, 50.4-54) <u>Photon</u> • Mean dose (GyE): 50.8 (range, 45-54) <u>PBT + photon</u> • Mean dose (GyE): 57 (range, 55.8-59.4)	<u>Visual outcome</u> • PBT (n=8) Improved:62.5% Stable: 25% Worsened: 12.5% • Photon (n=11) Improved: 63.6% Stable: 36.3% Worsened: 0% • PBT + photon (n=3) Improved: 66% Stable: 33% Worsened: 0% • No tumor growth seen at latest follow-up in all patient except 1, treated w/PBT + photon; regrowth 11 years after therapy	<u>Acute effects</u> • PBT (n=8): 0% • Photon (n=11): Orbital pain: 9% Headache: 9% (same patient) • PBT + photon: 0% <u>Late effects</u> • PBT (n=8) Asymptomatic retinopathy: 12.5% • Photon (n=11) Asymptomatic retinopathy: 9% • PBT + photon (n=3) Asymptomatic retinopathy: 33%	Poor	

* P-values not reported.

† Vision symptoms included decline in visual acuity, color vision change, or visual field deficit.

BCVA: best-corrected visual acuity; CI: confidence interval; F/U: follow-up; HR: hazard ratio; N: number; N/A: not available; NR: not reported; ONSM: optic nerve sheath meningioma; PBT: proton beam therapy; RCT: randomized controlled trial; RR: rate ratio; SD: standard deviation; TTT: transpupillary thermotherapy; VA: visual acuity

Table 18. Mixed Cancers: Study Characteristics.

Author (Year) Study Design Study Site	Sample Size Patient Characteristics	Inclusion/Exclusion Criteria	Treatment Protocol	Outcomes Assessed Main Findings	Harms	Quality	Notes
Chung (2013) Non-contemporaneous Case Series Massachusetts General Hospital, MA, USA Data source: Surveillance Epidemiology and End Results (SEER) – Medicare linked database Study Objective Evaluation of secondary malignancies in patients treated w/PBT and photon therapy Intervention Comparator Follow-up PBT F/U: 6.7 years (median), (IQR 7.4) Photon F/U: 6.0 years (median), (IQR 9.3)	PBT N=558 (Pediatric, n=44) • Male: 70% • Age: 59 (median) • Primary tumor sites CNS: 32% Head and neck: 24% GU: 33% Musculoskeletal: 7.7% Others: 3.3% Photon N=558 (Pediatric, n=44) • Male: 70% • Age: 59 (median) • Primary tumor sites CNS: 32% Head and neck: 24% GU: 33% Musculoskeletal: 7.7% Others: 3.3%	Inclusion • Patients treated w/PBT or photon therapy for nonmetastatic cancer Exclusion • Patients receiving therapy to the eye • Patients treated for acromegaly or AVMs •Patients w/history of malignancy	NR	NR	Incidence of secondary malignancies PBT: 5.2% Photon: 7.5% p=NR Median time to development of secondary malignancies PBT: 6.0 years Photon: 4.75 years p=0.085 Incidence rate of secondary malignancies (per 1000 person-years) PBT: 6.9 Photon: 10.3 p=NR 10-year cumulative incidence rate for secondary malignancies PBT: 5.4% Photon: 8.6% p=NR Adjusted HR of secondary malignancy • PBT vs. photon: 0.52 (95% CI, 0.32-0.85) Secondary malignancy occurring in prior field of radiation PBT: 10% Photon: 16.7% p=0.20	Good	Pediatric patient analyses • Second malignancies PBT: 0% Photon: 0% p=NR •Median duration of f/u: 4.1 years

AVM: arteriovenous malformation; CNS: central nervous system; ECOG: Eastern Cooperative Oncology Group; F/U: follow-up; GU: genitourinary; IQR: interquartile range; N: number; NR: not reported; PBT: proton beam therapy; PF: pterygopalatine fossa; PNS: paranasal sinus; PPS: parapharyngeal space; RIBC: radiation-induced brain change

Table 18. Mixed Cancers: Study Characteristics.

Author (Year) Study Design Study Site	Sample Size Patient Characteristics	Inclusion/Exclusion Criteria	Treatment Protocol	Outcomes Assessed Main Findings	Harms	Quality	Notes
Demizu (2009) Prospective Comparative Cohort Hyogo Ion Beam Medical Center, Japan Study Objective Evaluation of vision loss following radiation therapy for tumors adjacent to optic nerves Intervention Comparator Follow-up PBT F/U: 25 months (median) Carbon ion therapy F/U: 28 months (median)	PBT N=62 • Male: 45% • Age: 63 (median) • Tumor site Nasal/PNS: 68% Skull base: 16% PF: 5% Nasopharynx/PPS: 8% Orbita: 3% • Treatment history None: 74% Chemotherapy: 19% Surgery: 7% • Diabetes: 3% • Hypertension: 13% Carbon N=13 • Male: 38% • Age: 57 (median) • Tumor site Nasal/PNS: 77% Skull base: 0% PF: 15% Nasopharynx/PPS: 0% Orbita: 8% • Treatment history None: 69% Chemotherapy: 31% Surgery: 0% • Diabetes: 8% • Hypertension: 23%	Inclusion • Patients w/head and neck or skull-base tumors adjacent to optic nerves	PBT • Total dose: 65 GyE, given in 26 fractions Carbon • Total dose: 57.6 GyE, given in 16 fractions	NR	Vision loss caused by radiation-induced optic neuropathy PBT: 9.7% Carbon: 15% p=NR Incidence rate of vision loss for all eligible optic nerves PBT: 8% Carbon: 6% p=NR • No significant difference in the incident rates of vision loss observed between PBT and carbon-treated patients (p=0.4225)	Fair	• Patient overlap w/ Miyawaki (2009)

AVM: arteriovenous malformation; CNS: central nervous system; ECOG: Eastern Cooperative Oncology Group; F/U: follow-up; GU: genitourinary; IQR: interquartile range; N: number; NR: not reported; PBT: proton beam therapy; PF: pterygopalatine fossa; PNS: paranasal sinus; PPS: parapharyngeal space; RIBC: radiation-induced brain change

Table 18. Mixed Cancers: Study Characteristics.

Author (Year) Study Design Study Site	Sample Size Patient Characteristics	Inclusion/Exclusion Criteria	Treatment Protocol	Outcomes Assessed Main Findings	Harms	Quality	Notes
Miyawaki (2009) Prospective Comparative Cohort Hyogo Ion Beam Medical Center, Japan Study Objective Evaluation of radiation-induced brain injury following radiation therapy in head and neck and skull-base tumors Intervention Comparator Follow-up <u>PBT</u> F/U: 32 months (median) <u>Carbon ion therapy</u> F/U: 39 months (median)	<u>PBT</u> N=48 • Male: 42% • Age: 59 (median) • Tumor site Skull base: 25% Maxillary sinus: 17% Nasal cavity: 15% Sphenoid sinus: 13% Ethmoid sinus: 4% Others: 26% <u>Carbon</u> N=11 • Male: 45% • Age: 58 (median) • Tumor site Skull base: 27% Maxillary sinus: 9% Nasal cavity: 9% Sphenoid sinus: 9% Ethmoid sinus: 18% Others: 27%	<u>Inclusion</u> • Patients w/head and neck or skull-base tumors • Patients w/partial radiation therapy to the brain • No evidence of metastases to distant sites • ECOG performance status of 0, 1,or 2	<u>PBT</u> • Total dose: 65 GyE, given in 26 fractions • 150 or 190 MeV beam <u>Carbon</u> • Total dose: 57.6 GyE, given in 16 fractions • 250 or 320 MeV beam		<u>Incidence of brain injury (CTCAE grade)</u> • Grade 0 PBT: 83% Carbon: 36% • Grade 1 PBT: 13% Carbon: 45% • Grade 2 PBT: 4% Carbon: 0% • Grade 3 PBT: 0% Carbon: 18% • Grade 4-5 PBT: 0% Carbon: 0% p=NR • Incidence rate of RIBC significantly different between carbon and PBT (data not provided) (p=0.002) <u>MRI findings of RIBC</u> PBT: 17% Carbon: 64% p=NR <u>Median time to development of RIBC (range)</u> PBT: 17 months (6-49) Carbon: 21 months (11-41) p=NR	Poor	• Patient overlap w/ Demizu (2009) • Data provided on patients diagnosed w/RIBC • Data provided on dose relationship with RIBC

CTCAE grade: 0; 1: radiographic findings only; 2: symptomatic, not interfering w/activities of daily living; 3: symptomatic, interfering w/activities of daily living; 4-5: life-threatening or death

AVM: arteriovenous malformation; CNS: central nervous system; ECOG: Eastern Cooperative Oncology Group; F/U: follow-up; GU: genitourinary; IQR: interquartile range; N: number; NR: not reported; PBT: proton beam therapy; PF: pterygopalatine fossa; PNS: paranasal sinus; PPS: parapharyngeal space; RIBC: radiation-induced brain change

Appendix D
Dose Comparison Studies

Table 1. Dose Comparisons: Study Characteristics.

Author (Year) Study Design Study Site	Sample Size Patient Characteristics	Inclusion/Exclusion Criteria	Treatment Protocol	Outcomes Assessed Main Findings	Harms	Quality	Notes
Kim (2013) RCT Proton Therapy Center, National Cancer Center, Korea Study Objective Evaluation of hypofractionated PBT for prostate cancer Intervention Comparator Follow-up PBT (Arm 1) 60 CGE, 20 fractions (4x/wk) PBT (Arm 2) 54 CGE, 15 fractions (3x/wk) PBT (Arm 3) 47 CGE, 10 fractions (2x/wk) PBT (Arm 4) 35 CGE, 5 fractions (2x/wk) PBT (Arm 5)	Arm 1 N=19 • Age: 66 (median) • Gleason score ≤6: 79%; 7: 21%; 8-10: 0% • Tumor stage T1: 42%; T2: 53%; T3: 5% Arm 2 N=16 • Age: 69 (median) • Gleason score ≤6: 38%; 7: 50%; 8-10: 13% • Tumor stage T1: 56%; T2: 25%; T3: 19% Arm 3 N=17 • Age: 71 (median) • Gleason score ≤6: 82%; 7: 12%; 8-10: 9% • Tumor stage T1: 18%; T2: 65%; T3: 18% Arm 4 N=18 • Age: 67 (median) • Gleason score	Inclusion • Patients w/biopsy-proven, androgen-deprivation therapy-naïve prostate adenocarcinoma, stage T1-3N0M0 Exclusion • Previous curative surgery or radiation therapy • Evidence of distant metastasis • Previous ADT Arm 5 N=12 • Age: 70 (median) • Gleason score ≤6: 42%; 7: 42%;	PBT (Arm 1) 60 CGE, 20 fractions (4x/wk) for 5 weeks PBT (Arm 2) 54 CGE, 15 fractions (3x/wk) for 5 weeks PBT (Arm 3) 47 CGE, 10 fractions (2x/wk) for 5 weeks PBT (Arm 4) 35 CGE, 5 fractions (2x/wk) for 2 weeks PBT (Arm 5) 35 CGE, 5 fractions (1x/wk) for 2 weeks	Biochemical failure (ASTRO) Arm 1: 5.3% Arm 2: 18.8% Arm 3: 11.8% Arm 4: 11.1% Arm 5: 25% p=NS Biochemical failure (Nadir +2 ng/ml) Arm 1: 5.3% Arm 2: 12.5% Arm 3: 11.8% Arm 4: 5.6% Arm 5: 16.7% p=NS	• No significant differences among groups in acute and late toxicities Acute toxicity • Skin and GI: Grade 0 & 1 across all arms • GU: Grade 2 toxicity in 1 patient from Arms 1,2, 4 & 5 (5-8%) Late toxicity • Skin: Grade 0 & 1 across all arms • GI: Grade 2 toxicities in Arms 1, 3, 4 & 5 (8-21%); Grade 3 toxicity in Arm 1 (11%) • GU: Grade 2 toxicity in Arms 3 & 4 (11-24%)	Fair	• Data on patient-reported harms available (urinary QoL, sexual function, GU and GI toxicities)

Author (Year) Study Design Study Site	Sample Size Patient Characteristics	Inclusion/Exclusion Criteria	Treatment Protocol	Outcomes Assessed Main Findings	Harms	Quality	Notes
35 CGE, 5 fractions (1x/wk) F/U: 42 months (median), (range, 11-52)	≤6: 67%; 7: 28%; 8-10: 6% • Tumor stage T1: 28%; T2: 67%; T3: 6%	8-10: 17% • Tumor stage T1: 33%; T2: 58%; T3: 8%					

ADT: androgen deprivation therapy; F/U: follow-up; GI: gastrointestinal; GU: genitourinary; N: number; PBT: proton beam therapy; PCSI: prostate cancer symptom indices; Q1-Q3: 25^{th} – 75^{th} percentile interquartile range; QoL: quality-of-life; RCT: randomized controlled trial; RTOG: Radiation Therapy Oncology Group

Table 1. Dose Comparisons: Study Characteristics.

Author (Year) Study Design Study Site	Sample Size Patient Characteristics	Inclusion/Exclusion Criteria	Treatment Protocol	Outcomes Assessed Main Findings	Harms	Quality	Notes
Talcott (2010) Cross-sectional survey of patients enrolled in PROG #95-09 Loma Linda University Medical Center, CA, USA Massachusetts General Hospital, MA, USA Study Objective Evaluation of long-term, patient-reported dose-related toxicities Intervention Comparator Follow-up PBT + photon 70.2 GyE Standard dose PBT + photon 79.2 GyE High dose F/U: 9.4 years (median), (range, 7.4-12.1)	PBT + photon Standard dose N=139 • Age at time of survey: 67 (median) • Race White: 91% African American: 7% Asian: 1% Hispanic: 1% • PSA increase following treatment: 38% • Other local treatment RP: 2% Cryotherapy: 8% • Receipt of hormonal therapy: 13% PBT + photon High dose N=141 • Age at time of survey: 67 (median) • Race White: 95% African American: 1% Asian: 1% Hispanic: 3% • PSA increase following treatment: 14% • Other local treatment RP: 0% Cryotherapy: 1% • Receipt of hormonal therapy: 6% •Significant differences between groups including PSA increase, local treatments	• Surviving patients enrolled in original study Inclusion • Patients w/clinically localized prostate adenocarcinoma • Tumors stage T1b – T2b • Serum PSA <15 ng/ml • No evidence of metastatic disease	• All radiation delivered in 1.8 Gy(E) fractions PBT + photon Standard • PBT: 19.8 GyE • Photon: 50.4 Gy PBT + photon High • PBT: 28.8 GyE • Photon: 50.4 Gy	NR	• PCSI scales (mean scores) Urinary obstruction and irritation Standard: 23.3 High: 24.6 p=0.36 Urinary incontinence Standard: 10.6 High: 9.7 p=0.99 Bowel problems Standard: 7.7 High: 7.9 p=0.70 Sexual dysfunction Standard: 68.2 High: 65.9 p=0.65 • Utilizing numerical functional scales, no significant differences were found in the 4 domains w/results based on normal, intermediate and poor function between the standard and high dose groups • Perceived health and attitudes toward treatment decisions: Standard group less confident regarding cancer control (p<0.001), and more regret about treatment choice (p=0.02)	Fair	• Original study findings reported in Zietman (2005) and Zietman (2010) • Multivariate analysis: controlling for cancer progression, no significant association between treatment dose and any outcome variable (data not shown) • Analysis of level of function vs. patient-perceived level of function provided

ADT: androgen deprivation therapy; F/U: follow-up; GI: gastrointestinal; GU: genitourinary; N: number; PBT: proton beam therapy; PCSI: prostate cancer symptom indices; Q1-Q3: 25th – 75th percentile interquartile range; QoL: quality-of-life; RCT: randomized controlled trial; RTOG: Radiation Therapy Oncology Group

Table 1. Dose Comparisons: Study Characteristics.

Author (Year) Study Design Study Site	Sample Size Patient Characteristics	Inclusion/Exclusion Criteria	Treatment Protocol	Outcomes Assessed Main Findings	Harms	Quality	Notes
Zietman (2010)* RCT (RTOG #95-09) Loma Linda University Medical Center, CA, USA Massachusetts General Hospital, MA, USA Study Objective Evaluation of high-dose conformal radiation therapy for prostate cancer Intervention Comparator Follow-up <u>PBT + photon</u> 70.2 GyE Conventional dose <u>PBT + photon</u> 79.2 GyE High dose F/U: 8.9 years (median), (range, 0.8-12.5)	<u>PBT + photon</u> Conventional dose N=196 • Age ≥70: 32% • Race White: 89% Hispanic: 2% Black: 6% • Combined Gleason score 2-6: 75% 7: 15% 8-10: 9% • Tumor stage T1b: 1% T1c: 61% T2a: 22% T2b: 16% <u>PBT + photon</u> High dose N=195 • Age ≥70: 28% • Race White: 91% Hispanic: 3% Black: 3% • Combined Gleason score 2-6: 75% 7: 15% 8-10: 8% • Tumor stage T1b: 0% T1c: 61% T2a: 26% T2b: 13%	<u>Inclusion</u> • Patients w/clinically localized prostate adenocarcinoma • Tumors stage T1b – T2b • Serum PSA <15 ng/ml • No evidence of metastatic disease	• All radiation delivered in 1.8 Gy(E) fractions <u>PBT + photon</u> Conventional • PBT: 19.8 GyE • Photon: 50.4 Gy <u>PBT + photon</u> High • PBT: 28.8 GyE • Photon: 50.4 Gy	<u>PSA nadir <1.0 ng/mL</u> • Conventional: 81% • High: 86.6% p=NS <u>PSA nadir <0.5 ng/mL</u> • Conventional: 44.7% • High: 59.8% p=0.003 <u>10-year ASTRO BF rate</u> • Conventional: 32.3% • High: 16.7% p=0.0001 <u>Local failure rate</u> • Men treated w/ high dose less likely to have local failure than those w/conventional dose: HR 0.57 (95% CI, 0.43-0.74), p<0.0001 <u>Overall survival rate</u> • Conventional: 78.4% • High: 83.4% p=0.41 <u>Mortality</u> • Conventional: 17%% • High: 14%%	<u>Acute GU</u> • Grade 2 Conventional: 51% High: 60% p=NS •Grade 3: 3% in conv. dose; 2% in high dose • Grade 4: 0% in conv. dose; 1% in high dose <u>Acute GI (rectal)</u> • Grade 2 Conventional: 44% High: 63% p=0.0006 • Grade 3: 1% in each arm • No grade 4 events <u>Late GU</u> • Grade 2 Conventional: 22% High: 27% p=NS • Grade 3: 2% in each arm • No grade 4 events <u>Late GI</u> • Grade 2 Conventional: 13% High: 24% p=NS •Grade 3: 0% in conv. dose; 1% in high dose • No grade 4 events	Good	• Conventional: 7 patients (3.6%) received a lower dose; 8 patients (4.1%) received higher doses; 1 patient underwent radical prostatectomy • High: 5 patients (2.6%) received a higher dose; 18 patients (9.2%) received lower doses • Analyses of factors associated w/ASTRO BF rate (e.g., disease risk, tumor stage, Gleason score)

* Zietman (2005) reported on original findings with median follow-up of 5.5 years (range, 1.2-8.2).

ADT: androgen deprivation therapy; F/U: follow-up; GI: gastrointestinal; GU: genitourinary; N: number; PBT: proton beam therapy; PCSI: prostate cancer symptom indices; Q1-Q3: 25^{th} – 75^{th} percentile interquartile range; QoL: quality-of-life; RCT: randomized controlled trial; RTOG: Radiation Therapy Oncology Group

Table 1. Dose Comparisons: Study Characteristics.

Author (Year) Study Design Study Site	Sample Size Patient Characteristics	Inclusion/Exclusion Criteria	Treatment Protocol	Outcomes Assessed Main Findings	Harms	Quality	Notes
Gragoudas (2000) RCT Massachusetts General Hospital, MA, USA Study Objective Evaluation of reduced dose of PBT and impact on radiation-induced complications in patients w/uveal melanoma Intervention Comparator Follow-up PBT • 50 CGE PBT • 70 CGE F/U: up to 5 years after radiation	PBT, 50 CGE N=94 •Male: 47% • Age: 62 (median) • Largest tumor diameter (mm) (median, range): 11.0 (7.0-16.0) • Tumor height (mm) (median, range): 3.0 (1.2-6.3) • Macular detachment: 14% • Visual acuity (median, range): 20/32 (16-800) PBT, 70 CGE N=94 •Male: 59% • Age: 57 (median) • Largest tumor diameter (mm) (median, range): 10.0 (7.0-17.0) • Tumor height (mm) (median, range): 3.0 (1.0-5.5) • Macular detachment: 16% • Visual acuity (median, range): 20/32 (16-hand motions) • Significant differences between groups including gender, largest tumor diameter, tumor location	Inclusion • Patients w/melanoma of the choroid and/or ciliary body located w/in 4 disc diameters of the optic disc Exclusion • Presence of metastatic disease • Prior treatment for the intraocular tumor • Tumors ≥15mm in diameter or ≥5 mm in height	• Total dose delivered in 5 fractions	• Visual outcome was similar throughout study regardless of PBT dose 5-year visual acuity (median, Q1-Q3) • 50 CGE: 20/160 (20/25 – 20/900) • 70 CGE: 20/100 (20/25 – 20/900) p=0.91 5-year letters read (median, Q1-Q3) • 50 CGE: 60 (25-98) • 70 CGE: 62 (25-95) p=0.86 At 5-years, number of patients w/vision ≥20/200 • 50 CGE: 56% • 70 CGE: 54% p=0.82 Local recurrence w/in 5 years of radiation • 50 CGE: 2% • 70 CGE: 3% p>0.99 Metastatic death w/in 5 years of radiation • 50 CGE: 7% • 70 CGE: 8% p=0.79	• No statistically significant differences in other radiation complications between groups Vitreous hemorrhage • 50 CGE: 15% • 70 CGE: 13% Subretinal exudation in macula • 50 CGE: 11% • 70 CGE: 8% Rubeosis/ neovascular glaucoma • 50 CGE: 10% • 70 CGE: 7% Uveitis • 50 CGE: 0% • 70 CGE: 1% Enucleation • 50 CGE: 4% • 70 CGE: 5%	Fair	• Withdrawals 50 CGE:15% 70 CGE: 14% •Visual outcome data available for 12, 24, 36, and 48 months

ADT: androgen deprivation therapy; F/U: follow-up; GI: gastrointestinal; GU: genitourinary; N: number; PBT: proton beam therapy; PCSI: prostate cancer symptom indices; Q1-Q3: 25^{th} – 75^{th} percentile interquartile range; QoL: quality-of-life; RCT: randomized controlled trial; RTOG: Radiation Therapy Oncology Group

Table 1. Dose Comparisons: Study Characteristics.

Author (Year) Study Design Study Site	Sample Size Patient Characteristics	Inclusion/Exclusion Criteria	Treatment Protocol	Outcomes Assessed Main Findings	Harms	Quality	Notes
Santoni (1998) RCT (RTOG #85-26) Massachusetts General Hospital, MA, USA Study Objective Evaluation of temporal lobe damage in patients receiving high-dose PBT for treatment of skull-base tumors Intervention Comparator Follow-up PBT + photon • 66.6 CGE PBT + photon • 72 CGE F/U: 43.8 months (mean), (median, range: 41, 18-126)	• Data provided for entire patient cohort PBT + photon 66.6 CGE N=44 PBT + photon 72 CGE N=52 • Male: 53% • Age ≤50: 67% >50: 33& • Tumor site Occipital bone: 43% Sphenoid bone: 27% Temporal bone: 29% Nasopharynx: 1% • Tumor type Chordoma: 51% Chondrosarcoma: 49% • Presentation Primary: 78% Persistent/recurrent: 22% • Number of surgical procedures 1: 67% >1: 33%	Inclusion • Patients w/chordomas and chondrosarcomas at the base of the skull	• Total dose delivered in 4 proton fractions and 1 photon fraction per week • Treatment delivered as 1.8 CGE/fraction PBT • Proton contribution to dose ranged from 30.6 – 66.2 CGE • Mean dose: 55.3 • Median dose: 55.8 Photon • Photon contribution to dose ranged from 5.4 – 36 Gy • Mean dose: 13.9 • Median dose: 12.6	NR	Patients w/ temporal lobe damage* 66.6 CGE: 4/10 (40%) 72 CGE: 6/10 (60%) Clinical symptoms (n=9)* • Grade 1 66.6 CGE: 0% 72 CGE: 1/6 (17%) • Grade 2 66.6 CGE: 0% 72 CGE: 1/6 (17%) • Grade 3 66.6 CGE: 3/3 (100%) 72 CGE: 4/6 (67%) • Prescribed radiation dose not found to be significantly associated with rate of temporal lobe damage, p=0.304	Poor	•Data on status of patients w/temporal lobe damage provided

* P-value not reported.

ADT: androgen deprivation therapy; F/U: follow-up; GI: gastrointestinal; GU: genitourinary; PBT: proton beam therapy; PCSI: prostate cancer symptom indices; Q1-Q3: 25^{th} – 75^{th} percentile interquartile range; RCT: randomized controlled trial; RTOG: Radiation Therapy Oncology Group

Appendix E
Economic Studies

Table 1. Economic Evaluations: Study Characteristics.

Author (Year) Study Design Study Setting Study Objective	Intervention Comparator Follow-up	Sample Size Patient and/or Study Characteristics Study Perspective	Inclusion/ Exclusion Criteria	Outcomes	Notes
Elnahal (2013) Modeling study PBT facility in the US Evaluation of debt management under different reimbursement scenarios	N/A <u>Patient case assumptions</u> • Complex case or pediatric case w/anesthesia: 1 hour/treatment • Simple case: 30 min./treatment • Prostate cancer case: 24 min./ treatment • Short prostate cancer case: 15 min./ treatment	<u>Key model assumptions</u> • 14 hours of daily operation in treatment rooms • Private payer reimbursement $1.75 times that of Medicare/ACO • Reimbursement for simple case ACO: $510/treatment Medicare - FFS: $753/treatment • FFS & ACO reimbursement for complex cases identical • Facility cost 1-room: $30 million 4-room: $150 million	N/A	• Facilities treating only simple cases would generate 32% less daily revenue w/ACO reimbursement • Incremental revenue gained w/replacing 1 complex case w/1 noncomplex case lowest for simple cases, highest for short prostate cases • ACO reimbursement reduced incremental revenue by 53.2% (simple cases) and 41.7% (short prostate cases) • Single-room facilities able to cover debt w/any case mix <u>4-room facilities, debt coverage</u> • 52% lower w/all simple cases • 50% lower w/all prostate cases • 41% lower w/all short prostate cases	• Costs (2012 levels): Medicare and private payer reimbursement rates for treatment <u>Sensitivity analyses</u> • Incremental revenue values sensitive to FFS reimbursement rates for noncomplex cases, modeled ACO rates and private rates • Debt coverage for 4-room facilities sensitive to interest rates and total capital costs
Mailhot Vega (2013) Decision analysis Outpatient treatment in the US Evaluation of cost effectiveness of treatment w/PBT vs. photon therapy in pediatric medulloblastoma	PBT Photon therapy Time horizon: lifetime WTP threshold: $50,000	<u>Base case</u>: patients at age 5 years treated for medulloblastoma Societal perspective	N/A	<u>Total QALYs</u> • PBT: 17.37 • Photon: 13.91 • Difference: 3.46 <u>Total costs</u> • PBT: $80,210.79 • Photon: $112,789.87 • Difference: -$32,579.08 <u>ICER</u>: PBT dominates	• Health benefits and costs tracked beginning at age 18 • Costs (2012 levels): RT (including salaries & overhead) and management of adverse events • Sensitivity analyses: risk of hearing loss, risk of secondary malignant neoplasm, and risk of heart failure were most influential on incremental effectiveness of PBT; PBT still dominant

Table 1. Economic Evaluations: Study Characteristics, continued.

Author (Year) Study Design Study Setting Study Objective	Intervention Comparator Follow-up	Sample Size Patient and/or Study Characteristics Study Perspective	Inclusion/ Exclusion Criteria	Outcomes	Notes
Ramaekers (2013) Decision analysis Outpatient treatment in The Netherlands Evaluation of swallow-sparing treatment following radiation therapy	IMPT IMRT IMPT/IMRT* Time horizon: lifetime WTP threshold: €80,000 ($99,680)	Base case: patients w/locally advanced (stage III-IV) head and neck cancers (e.g., oral cavity, laryngeal, and pharyngeal cancer), age 61 years w/pretreatment RTOG grade <2 dysphagia and xerostomia Health care perspective	N/A	ICER for IMPT vs. IMRT: €127,946/QALY ($159,421) ICER for IMPT/IMRT vs. IMRT: €60,278/QALY ($75,106) ICER for IMPT vs. IMRT: €7,936/DTFLY ($9,888) ICER for IMPT/IMRT vs. IMRT: €3,854/DTFLY ($4,802) (DTFLY: disease and toxicity free life year)	• Costs (2010 levels): treatment-related costs of dysphagia and xerostomia • Sensitivity analyses: equal disease progression for patients treated w/IMRT and IMPT relaxed, and IMRT dominated for all patients compared to IMPT for all patients
Yu (2013) CC (database study) Outpatient treatment in the US Evaluation of treatment costs of radiation therapy	PBT IMRT F/U: 3 months following initiation of RT	PBT N=314 •Age ≥70: 63.7% •Race White: 93% Black: <3.5% Other: >3.5% • Comorbidities 0:73.6% 1-2: >22.9% ≥3: <3.5% • Receipt of ADT: 20.7% IMRT N=628 •Age ≥70: 63.7% •Race White: 93% Black: 2.9% Other: 4.1% • Comorbidities 0: 73.4% 1-2: 23.2% ≥3: 3.3% • Receipt of ADT: 21%	Inclusion • Patients w/early-stage, treated prostate cancer • PBT or IMRT as primary treatment Exclusion • Patients without Medicare A & B, 9 months prior to treatment through 3 months after	Treatment reimbursement (median, IQR) • PBT: $32,428 ($31,265-$34,189) • IMRT: $18,575 ($14,911-$23,022)	• Costs (2008-2009 levels): Medicare reimbursement for treatment planning, management, and delivery based on 6-month costs

Table 1. Economic Evaluations: Study Characteristics, continued.

Author (Year) Study Design Study Setting Study Objective	Intervention Comparator Follow-up	Sample Size Patient and/or Study Characteristics Study Perspective	Inclusion/ Exclusion Criteria	Outcomes	Notes
Johnstone (2012) Modeling study PBT facility in the US Evaluation of practical case distribution necessary to facilitate debt management	N/A <u>Patient case assumptions</u> • Complex case or pediatric case w/anesthesia: 1 hour/treatment • Simple case: 30 min./treatment • Prostate cancer: 24 min./treatment	<u>Key model assumptions</u> • Unit of analysis: per room w/14 hours of daily operation • Private payer reimbursement $1.75 times that of Medicare • Facility cost 1-room: $25 million 4-room: $150 million	N/A	• Number of patients treated per day per room is maximized w/greater percentages of simple and prostate cancer cases • 1-room facility: 12 hours of complex/pediatric cases to service debt • 1-room facility: 4 hours of prostate cancer/simple cases to service debt • 3- and 4-room facilities: cannot service debt without inclusion of simple cases	• Costs (year of levels not reported): Medicare and private payer reimbursement rates per treatment

Table 1. Economic Evaluations: Study Characteristics, continued.

Author (Year) Study Design Study Setting Study Objective	Intervention Comparator Follow-up	Sample Size Patient and/or Study Characteristics Study Perspective	Inclusion/ Exclusion Criteria	Outcomes	Notes
Parthan (2012) Decision analysis Outpatient treatment in the U.S. Evaluation of the cost effectiveness of different external beam radiation therapies in the treatment of prostate cancer	PBT IMRT SBRT Time horizon: lifetime WTP threshold: $50,000/QALY	Base case: 65-year old men with localized prostate cancer who are unwilling or ineligible for surgery Payer and societal perspectives	N/A	• Localized prostate cancer **PAYER PERSPECTIVE** Lifetime healthcare costs • PBT: $69,412 • IMRT: $33,068 • SBRT: $24,873 QALYs • PBT: 8.06 • IMRT: 8.05 • SBRT: 8.11 ICER costs/QALY gained • IMRT, PBT dominated by SBRT **SOCIETAL PERSPECTIVE** Lifetime healthcare costs • PBT: $71,657 • IMRT: $35,088 • SBRT: $25,097 QALYs • PBT: 8.06 • IMRT: 8.05 • SBRT: 8.11 ICER costs/QALY gained • IMRT, PBT dominated by SBRT	• Costs (2011 levels): Medicare payments for treatment, follow-up and management of gastrointestinal, genitourinary and sexual dysfunction toxicities; societal perspective includes work-time lost (cost/hour) • Sensitivity analyses with varying toxicities (using confidence intervals) and costs (±25%) resulted in SBRT as the dominant strategy • Sensitivity analyses equating toxicity of PBT to that of SBRT (in place of IMRT) resulted in SBRT weakly dominating IMRT and no longer dominating PBT

Table 1. Economic Evaluations: Study Characteristics, continued.

Author (Year) Study Design Study Setting Study Objective	Intervention Comparator Follow-up	Sample Size Patient and/or Study Characteristics Study Perspective	Inclusion/ Exclusion Criteria	Outcomes	Notes
Grutters (2011) Real Options Analysis (ROA) Outpatient treatment in The Netherlands Evaluation of adoption of PBT in the treatment of stage I NSCLC	ROA: • "Adopt and trial" vs. "delay and trial" in the adoption of PBT as preferred therapy over SBRT WTP threshold: €80,000 ($99,680)†	Base case • Time horizon: 5 years • Study design: single-arm cohort of PBT • Costs include fixed & variable trial costs, extra costs of treatment abroad, cost of health benefits forgone due to suboptimal treatment • Benefits: value of reduced uncertainty after trial	N/A	For a trial of 200 patients, expected net gain • Adopt & trial: €1,592,586 ($1,984,362)† • Delay & trial: -€744,306 (-$927,405)† • Expected net gain of adopt & trial higher than that of delay & trial for study sample size <950 patients	• Sensitivity analyses demonstrated that the model was sensitive to increased treatment costs abroad and costs of reversal
Dvorak (2010) Cost utilization model Hospital- or clinic-based PBT in the US Evaluation of the costs associated w/cancer treatment utilizing PBT in place of other EBRTs	PBT EBRT (including IMRT, SBRT, and Gamma Knife radiosurgery) Timeline: 1 year	Key model assumptions • EBRT techniques used as a proxy for PBT • Average PBT time slot: 30 minutes • 9 hours of daily operation • Identical fractionation schedules used	N/A	Highly conformal EBRT utilization • Number of courses: 431 (38% of total courses) • Number of fractions: 6,151 (31% of total fractions) • Baseline annual cost: approximately $6 million • Use of PBT in place of EBRT would increase annual cost to $7.3 million (22% above baseline)	• Costs (2008 levels): Medicare reimbursement rates per fraction of radiation therapy delivered (other technical and professional charges excluded)

Table 1. Economic Evaluations: Study Characteristics, continued.

Author (Year) Study Design Study Setting Study Objective	Intervention Comparator Follow-up	Sample Size Patient and/or Study Characteristics Study Perspective	Inclusion/ Exclusion Criteria	Outcomes	Notes
Grutters (2010) Decision analysis Outpatient treatment in The Netherlands Evaluation of the cost effectiveness of particle therapies in the treatment of NSCLC	PBT Carbon ion therapy SBRT CRT Time horizon: 5 years WTP threshold: €80,000 ($108,160)	Base case: Patients w/inoperable and operable stage I NSCLC Health care perspective	N/A	• Inoperable stage I NSCLC Total healthcare costs over 5 years • PBT: €27,567 • Carbon: €19,215 • SBRT: €13,871 • CRT: €22,696 QALYs • PBT: 2.33 • Carbon: 2.67 • SBRT: 2.59 • CRT: 1.98 ICER for carbon vs. SBRT: €67,257/QALY ($90,931) • PBT, CRT dominated by carbon and SBRT	• Costs (2007 levels): treatment, follow-up and management of pneumonitis and esophagitis • For operable stage I NSCLC, SBRT and carbon evaluated • Sensitivity analysis for inoperable stage I NSCLC utilizing data published after 2004 (as CRT data were generally older): ICER for PBT vs. carbon: €81,479 ($110,160) ICER for carbon vs. SBRT: €36,017 ($48,695) CRT dominated by carbon
Peeters (2010) Cost analysis Facilities in The Netherlands Comparative evaluation of capital and operational costs associated with radiation therapy facilities	PBT-only PBT + carbon ion Photon	Key model assumptions • Lifetime of facility = 30 years • 3-room facility for PBT+carbon and PBT; 2 rooms for photon • 14 hours of daily operation • Average time per radiation fraction PBT: 18 minutes PBT+carbon: 18 minutes Photon: 10 minutes • Number of fractions per year PBT: 33,614 PBT+carbon: 32,585 Photon: 41,160 Hospital perspective	N/A	Total costs/year (million) • PBT: €24,964,716 ($33,752,296) • PBT+carbon: €36,758,027 ($49,696,852) • Photon: €9,581,850 ($12,954,661) Cost/fraction • PBT: €743 ($1,004) • PBT+carbon: €1,128 ($1,525) • Photon: €233 ($315) Cost/fraction ratio to photon • PBT: 3.2 • PBT+carbon: 4.8	• Total costs (2007 levels): Capital and operational costs • Sensitivity analyses indicate that the cost/fraction of PBT and PBT+carbon compared to photon is most sensitive to a shorter lifecycle of the facility, increased average time per fraction and increased number of special (e.g., stereotactic radiotherapy or IMRT) cases • For specific kinds of tumors, the cost difference among the different therapies was small for lung and prostate tumors, and larger for skull-base chordomas and head & neck tumors

Table 1. Economic Evaluations: Study Characteristics, continued.

Author (Year) Study Design Study Setting Study Objective	Intervention Comparator Follow-up	Sample Size Patient and/or Study Characteristics Study Perspective	Inclusion/ Exclusion Criteria	Outcomes	Notes
Konski (2007) Decision analysis Outpatient treatment in the US Evaluation of the cost effectiveness of PBT vs. IMRT for prostate cancer	PBT IMRT Time horizon: 15 years WTP threshold: $50,000	Base case: a 70-year-old man diagnosed w/intermediate-risk prostate adenocarcinoma Payer's (Medicare) perspective	N/A	Mean cost of treatment • PBT: $63,511 • IMRT: $36,808 QALYs • PBT: 9.91 • IMRT: 9.45 ICER: $63,578/QALY	• Costs (2005 levels): Hospital and physician reimbursement rates, treatment costs (including hormone therapy and chemotherapy) • Sensitivity analyses evaluated effect on the net monetary benefit where PBT would be favored if cost of IMRT >$45,000, cost of PBT <$39,000 or utility associated w/IMRT <0.85 • Secondary analysis w/base case of a 60-year-old man resulted in marginal cost effectiveness of PBT (ICER=$55,726/QALY)
Taghian (2006) Cost analysis Hospital-based outpatient treatment in the US Comparative evaluation of treatment utilizing alternative radiation modalities	3D-CPBI proton 3D-CPBI photon WBI-B	Base case: 60-year old woman w/stage I breast cancer Societal perspective	N/A	Overall cost of a treatment regimen • 3D-CPBI proton: $13,200 • 3D-CPBI photon: $5,300 • WBI-B: $10,600	• Costs (2006 levels): Professional and technical direct costs of treatment, including patient time and transport based on Medicare reimbursement

Table 1. Economic Evaluations: Study Characteristics, continued.

Author (Year) Study Design Study Setting Study Objective	Intervention Comparator Follow-up	Sample Size Patient and/or Study Characteristics Study Perspective	Inclusion/ Exclusion Criteria	Outcomes	Notes
Lundkvist (2005c) Decision analysis Outpatient treatment in Sweden Evaluation of the cost effectiveness of PBT vs. photon therapy in the treatment of 4 different cancers	PBT Conventional radiation (photon) Time horizon: lifetime WTP threshold: NR	Breast cancer, base case: 55-year-old women w/left-sided breast cancer, at high risk of cardiac disease Prostate cancer, base case: 65-year-old-men Head and neck cancer, base case: 65-year-old patients Pediatric, base case: patients at age 5 years treated for medulloblastoma Societal perspective	N/A	Number of patients treated per year: 300 each for breast, prostate and head and neck cancers, 25 for medulloblastoma ICER • Breast: €34,290/QALY ($33,913) • Prostate: €26,776/QALY ($26,481) • Head and neck: €3,811/QALY ($3,769) • Pediatric: cost saving Total cost difference, for all treated patients in 1 year (M€) • Breast: 1.8 ($1.78) • Prostate: 2.4 ($2.37) • Head and neck: 1.2 ($1.19) • Pediatric: -0.6 (-$0.59) Total difference in QALYs, for all treated patients in 1 year • Breast: 51.8 • Prostate: 89.1 • Head and neck: 306.0 • Pediatric: 17.1	• Model results from Lundkvist (2005a) and Lundkvist (2005b) utilized • Costs (2002 levels): RT (including operation & capital costs, and travel/hotel costs) and management of adverse events • Average ICER for all 4 cancers: €10,130 ($10,019) • For a WTP of €55,000 ($54,395), total yearly net benefit of treating 925 patients (w/specific cancer types and patient profiles): approximately €20.8 million ($20.6 million)
Lundkvist (2005a) Decision analysis Outpatient treatment in Sweden Evaluation of cost effectiveness of PBT vs. conventional radiation in the treatment of breast cancer	PBT Conventional radiation (photon) Time horizon: lifetime WTP threshold: NR	Base case: 55-year-old women w/left-sided breast cancer Societal perspective	N/A	Total costs • PBT: €11,248 ($11,124) • Photon: €5,005 ($4,950) • Difference: €6,243 ($6,174) QALYs • PBT: 12.3460 • Photon: 12.2523 • Difference: 0.0937 ICER: €66,608/QALY ($65,875)	• Costs (2002 levels): treatment, follow-up and management of adverse events (cardiac and pulmonary) • Sensitivity analyses demonstrated substantial decreases in ICER when treating a high-risk population w/doubled risk of cardiac disease: base case = €34,290/QALY ($33,913)

Table 1. Economic Evaluations: Study Characteristics, continued.

Author (Year) Study Design Study Setting Study Objective	Intervention Comparator Follow-up	Sample Size Patient and/or Study Characteristics Study Perspective	Inclusion/ Exclusion Criteria	Outcomes	Notes
Lundkvist (2005b) Decision analysis Outpatient treatment in Sweden Evaluation of cost effectiveness of treatment w/PBT vs. photon therapy in pediatric medulloblastoma	PBT Conventional radiation (photon) Time horizon: lifetime WTP threshold: NR	Base case: patients at age 5 years treated for medulloblastoma Societal perspective	N/A	Total costs • PBT: €14,450 ($14,291) • Photon: €38,096 ($37,677) • Difference: -€23,647 (-23,387) QALYs • PBT: 12.778 • Photon: 12.095 • Difference: 0.683 ICER: PBT dominates	• Costs (2002) levels: treatment, follow-up and management of adverse events • Sensitivity analyses: PBT remained dominant with reductions in IQ loss and growth hormone deficiency being key factors in cost effectiveness evaluation
Goitein (2003) Cost analysis Hospital-integrated facility (US & Switzerland data) Comparative evaluation of capital and operational costs associated with radiation therapy facilities	PBT Photon therapy	Key model assumptions • Lifetime of facility = 30 years • 2-room facilities • Daily hours of operation PBT: 13 Photon: 8 • Average time per radiation fraction PBT: 22 minutes Photon: 14 minutes • Mean number of fractions per patient: 25 • Number of fractions delivered per year: 15,000	N/A	Construction costs (k€) • PBT: 62,500 ($61,813) • Photon: 16,800 ($16,615) Operation costs (k€) • PBT: 15,300 ($15,132) • Photon: 6,400 ($6,330) Cost per fraction (k€) • PBT: 1.025 ($1.014) • Photon: 0.425 ($0.420) Cost per treatment (k€) • PBT: 25.6 ($25.3) • Photon: 10.6 ($10.5) Ratio of costs • PBT: 2.4 • Photon: 1	• Total costs (2002 levels): Capital and operational costs • Alternate scenarios Facilities in 5-10 years: decrease in equipment costs for PBT, increase in number of fractions delivered/year for both types of facilities (18,900) • Cost per fraction (k€) PBT: 0.65 ($0.64) Photon: 0.31 ($0.31) • Ratio of costs: 2.1 Initial capital investment forgiven: • Cost per fraction (k€) PBT: 0.37 ($0.37) Photon: 0.23 ($0.23) • Ratio of costs: 1.6

* IMPT given to patients when expected to be cost-effective; all other patients receive IMRT.
† Converted to US$ utilizing 2010 exchange rate.
3D-CPBI: 3D conformal, external-beam accelerated partial breast irradiation; ACO: accountable care organization; ADT: androgen deprivation therapy; FFS: fee-for-service; ICER: incremental cost effectiveness ratio; IMPT: intensity-modulated proton therapy; IMRT: intensity-modulated radiation (photon) therapy; k€: thousand euro; M€: million euro; NR: not reported; N/A: not applicable; NR: not reported; NSCLC: non-small cell lung cancer; PBT: proton beam therapy; QALY: quality-adjusted life-year; RT: radiation therapy; RTOG: Radiation Therapy Oncology Group; SBRT: stereotactic body radiotherapy; WBI-B: whole-breast irradiation w/a boost; WTP: willingness-to-pay

Appendix F
Single-arm Case Series

Table 1. Single-arm Case Series: Bone Cancers.

Author (Year) Study Site	Condition Type	Sample Size	Total PBT Dose	Follow-up	Survival Outcomes	Harms*	Notes
Chen (2013) Massachusetts General Hospital, MA, USA	Chordoma of the mobile or saccrococcygeal spine	N=24	• Dose: 75 or 77.4 Gy RBE (range, 71.6-79.2)	• Median: 56 months (range, 18-172)	3-year • Overall survival: 92% • Local progression-free survival: 90% 5-year • Overall survival: 78% • Local progression-free survival: 80%	• CTCAE & RTOG/EORTC scoring • Acute effects ≥ Grade 3: 0% • Late effects ≥ Grade 3: 0%	• All patients w/primary disease • Subgroup data reported
Ciernik (2011) Massachusetts General Hospital, MA, USA	Unresectable or incompletely resected osteosarcoma	N=55	• PBT ± photon, mean: 68.4 Gy	• Median: 27 months (range, 0-196)	2-year • Overall survival: 84% • Disease-free survival: 68% 5-year • Overall survival: 67% • Disease-free survival: 65%	• Scoring methodology: NR • Acute effects: NR • Late effects Grade 3: 15% Grade 4: 16%	• 17/55 (31%) w/recurrent disease • Subgroup data reported
Staab (2011) Paul Scherrer Institute, Switzerland	Extracranial chordoma	N=40	• PBT ± photon, mean: 72.5 Gy(RBE) (range, 59.4-75.2)	• Median: 43 months (range, 24-91)	5-year • Overall survival: 80% • Disease-free survival: 57%	• CTCAE scoring • Acute effects ≥ Grade 3: 0% • Late effects Grade 3 (osteonecrosis, fistula): 5%	• 8/40 (20%) w/recurrent disease • Subgroup data reported
Hug (1995) Massachusetts General Hospital, MA, USA	Osteo- and chondrogenic tumors of the axial skeleton	N=47	• PBT + photon, mean CGE • Chordoma: 74.6 • Chondrosarcoma: 72.2 • Osteogenic sarcoma: 69.8 • Mixed: 61.8	• Mean: 38 months (range, 6-136)	5-year overall survival • Chordoma: 50% • Chondrosarcoma: 100% • Osteogenic sarcoma: 44% • Mixed: NR	• Severity of acute/late effects: NR	• Patients w/primary and recurrent disease, number NR • No skull-base tumors included in analysis • Subgroup data reported

* Different versions of the CTCAE/Common Toxicity Criteria are utilized in the listed studies.

CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organization for Research and the Treatment of Cancer; N: number; NR: not reported; PBT: proton beam therapy; RTOG: Radiation Therapy Oncology Group

Table 2. Single-arm Case Series: Brain, Spinal, and Paraspinal Tumors.

Author (Year) Study Site	Condition Type	Sample Size	Total PBT Dose	Follow-up	Survival Outcomes	Harms	Notes
Hauswald (2012) University of Heidelberg, Germany	Low-grade glioma (WHO I/II)	N=19	• Median: 54 GyE (range, 48.6-54)	• Median: 5 months (range, 0-22)	• Overall survival: 100%	• CTCAE scoring • Acute effects ≥ Grade 3: 0% • Late effects: NR	
Mizumoto (2010) University of Tsukuba, Japan	Supratentorial glioblastoma multiforme	N=20	• PBT + photon Photon dose: 50.4 Gy PBT dose: 46.2 GyE	NR	<u>Overall survival</u> • 1-year: 71% • 2-year: 45%	• CTCAE & RTOG/EORTC scoring • Acute effects Grade 3 hematologic: 65% Grade 4 hematologic: 30% • Late effects Grade 3 leukoencephalopathy: 10%	
Fitzek (2006)* Massachusetts General Hospital, MA, USA	Craniopharyngioma (median age: 15.9 years)	N=5	• PBT ± photon, median: 55.6 CGE	• Median: 186 months (range, 122-212)	<u>Overall survival</u> • 5-year: 93% • 10-year: 72%	• Severity of acute/late effects: NR	• 6/15 (40%) w/recurrent disease
Fitzek (2006)* Massachusetts General Hospital, MA, USA	Craniopharyngioma (median age: 36.2 years)	N=10	• PBT ± photon, median: 62.7 CGE				
Fitzek (2001)† Massachusetts General Hospital, MA, USA	Grade 2/4 malignant glioma	N=7	• PBT + photon, dose: 68.2 CGE	• Median: 61 months	• 5-year survival: 71%	• Severity of harms: NR	• Subgroup data reported
Fitzek (2001)† Massachusetts General Hospital, MA, USA	Grade 3/4 malignant glioma	N=13	• PBT + photon, dose: 79.7 CGE	• Median: 55 months	• 5-year survival: 23%		

Table 2. Single-arm Case Series: Brain, Spinal, and Paraspinal Tumors.

Author (Year) Study Site	Condition Type	Sample Size	Total PBT Dose	Follow-up	Survival Outcomes	Harms	Notes
Hug (2000) Massachusetts General Hospital, MA, USA	Atypical/malignant meningioma	N=31	• PBT + photon (52%) or photon alone (48%), dose: ranging from 40-72 CGE (PBT)	• Mean: 59 months (range, 7-155)	5- and 8-year overall survival • Atypical: 89% • Malignant: 51%	• Severity of acute/late effects: NR	• 15/31 (48%) w/recurrent disease • Subgroup data reported
Fitzek (1999) Massachusetts General Hospital, MA, USA	Glioblastoma multiforme	N=23	• PBT + photon, median: 93.5 CGE (range, 81.6-94.2)	NR	Overall survival • 1-year: 78% • 2-year: 34% • 3-year: 18%	• Severity of harms: NR	• Subgroup data reported

* Fitzek (2006) reported on 2 patient populations. Separate results are reported where available.
† Fitzek (2001) reported on 2 dosing protocols, based on tumor grade. Separate results are reported where available.

CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organization for Research and the Treatment of Cancer; N: number; NR: not reported; PBT: proton beam therapy; RTOG: Radiation Therapy Oncology Group; WHO: World Health Organization

Table 3. Single-arm Case Series: Breast Cancers.

Author (Year) Study Site	Condition Type	Sample Size	Total PBT Dose	Follow-up	Survival Outcomes	Harms	Notes
Chang (2013) Proton Therapy Center, Korea	Early stage breast cancer w/primary tumors ≤3cm	N=30	• Dose: 30 CGE	• Median: 59 months (range, 43-70)	• Overall survival: 100%	• Severity of harms: NR*	
MacDonald (2013) Massachusetts General Hospital, MA, USA	Invasive breast cancer	N=12	• Dose Chest wall: 50.4 Gy(RBE) Regional lymphatics at risk: 45-50.4 Gy(RBE)	• Up to 2 months	• Overall survival: 100%	• CTCAE scoring† • Acute effects Grade 3 fatigue: 8%	
Bush (2011) Loma Linda University Medical Center, CA, USA	Invasive nonlobular breast carcinoma ≤3cm	N=50	• Dose: 40 Gy	• Median: 48 months	5-year • Overall survival: 96% • Disease-free survival: 92%	• CTCAE scoring† • Acute effects ≥ Grade 3: 0% • Late effects ≥ Grade 3: 0%	
Kozak (2006) Massachusetts General Hospital, MA, USA	Stage I breast cancer w/tumor-free margin ≥2mm	N=20	• Dose: 32 CGE	• Median: 12 months (range, 8-22)	• Overall survival: 100%	• Severity of harms: NR*	

* Proposed grading scale does not follow standardized scales.
† Different versions of the CTCAE are utilized in the listed studies.

CTCAE: Common Terminology Criteria for Adverse Events; N: number; NR: not reported; PBT: proton beam therapy;

Table 4. Single-arm Case Series: Esophageal Cancer.

Author (Year) Study Site	Condition Type	Sample Size	Total PBT Dose	Follow-up	Survival Outcomes	Harms	Notes
Echeverria (2013) MD Anderson Cancer Center, TX, USA	Esophageal cancer	N=100	• Median: 50.4 CGE (range, 45-60.6)	• Median: 1 month (0.7-3)	NR	• CTCAE scoring • Acute effects Grade 3 pneumonitis: 7% Other acute effects: NR	• Potential patient overlap w/Lin (2012)
Lin (2012) MD Anderson Cancer Center, TX, USA	Esophageal cancer	N=62	• Dose: 50.4 Gy(RBE)	• Median (among survivors): 20 months	• 3-year overall survival: 52%	• Scoring: NR • Acute/late effects Grade 3 esophagitis: 10% Grade 3 dysphagia: 10% Grade 3 nausea/vomiting: 8% Grade 3 dermatitis: 3% Grade 3 fatigue: 8% Grade 3 anorexia: 5% Grade 3 pneumonitis: 2% Grade 5: 5%	• Potential patient overlap w/Echeverria (2013) • Subgroup data reported
Mizumoto (2011)* University of Tsukuba, Japan	Esophageal cancer	N=19	• PBT + photon, median: 78 GyE (range, 70-83)	• Median (among survivors): 111 months (range, 11-121)	<u>Overall survival</u> • 1-year: 79% • 5-year: 43%	• RTOG/EORTC scoring • Acute effects Grade 3 esophagitis: 5% • Late effects Grade 3 esophagitis: 5%	• Subgroup data reported
Mizumoto (2010)* University of Tsukuba, Japan	Esophageal cancer, stage T1N1M0 or T2-4N0/1	N=51	• PBT + photon (n=33), median: 80 GyE (range, 70-90) • PBT (n=18), median: 79 GyE (range, 62-98)	• Median (among survivors): 23 months	• 5-year overall survival: 21%	• RTOG/EORTC scoring • Acute effects Grade 3 esophagitis: 12% • Late effects Grade 5: 2%	• All patients w/primary disease • Subgroup data reported
Sugahara (2005)* University of Tsukuba, Japan	Esophageal cancer	N=46	• PBT + photon (n=40), median: 76 GyE (range, 69.1-87.4) • PBT (n=6), median: 82 GyE (range, 75-89.5)	• Median: 35 months	• 5-year overall survival: 34%	• RTOG/EORTC scoring • Acute effects Grade 3 esophagitis: 11% • Late effects Grade 3: 7% Grade 5: 4%	• All patients w/primary disease • Subgroup data reported

Table 4. Single-arm Case Series: Esophageal Cancer.

Author (Year) Study Site	Condition Type	Sample Size	Total PBT Dose	Follow-up	Survival Outcomes	Harms	Notes
Koyama (2003)*† University of Tsukuba, Japan	Superficial esophageal cancer	N=13	• PBT + photon, mean: 77.7 Gy (2 patients w/PBT alone)	• Median: 48 months (range, 5-132)	Overall survival • 5-year: 100% • 10-year: 88%	• Severity of harms: NR	• Subgroup data reported
Koyama (2003)*† University of Tsukuba, Japan	Advanced esophageal cancer	N=17	• PBT + photon, mean: 80.7 Gy (4 patients w/PBT alone)		Overall survival • 5-year: 49% • 10-year: 38%		

* Potential patient overlap among patients in these studies.
† Koyama (2003) reported on 2 patient populations, based on level of disease. Separate results are reported where available.

CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organization for Research and the Treatment of Cancer; LENT/SOMA: Late Effects of Normal Tissue – subjective, objective, management, analytic; N: number; NR: not reported; PBT: proton beam therapy; RTOG: Radiation Therapy Oncology Group

Table 5. Single-arm Case Series: Gastrointestinal Cancers.

Author (Year) Study Site	Condition Type	Sample Size	Total PBT Dose	Follow-up	Survival Outcomes	Harms*	Notes
Makita (2014) Hyogo Ion Beam Medical Center, Japan	Advanced cholangiocarcinoma	N=28	• Median dose: 68.2 Gy (RBE) (range, 50.6-80)	• 12 months (range, 3-29)	1-year • Overall survival: 49% • Progression-free survival: 30%	• CTCAE scoring • Acute effects Grade 3 cholangitis: 4% • Late effects Grade 3 cholangitis: 7% Grade 3 bile duct stenosis: 4% Grade 3 duodenal ulcer: 4% Grade 3 duodenal hemorrhage: 7% Grade 3 duodenal stenosis:4%	• 10/28 (36%) w/recurrent disease • Subgroup data reported
Nichols (2013) University of Florida Proton Therapy Institute, FL, USA	Pancreatic or ampullary adenocarcinoma	N=22	• Dose: ranging from 50.4 – 59.4 CGE	• Median: 11 months (range, 5-36)	• Overall survival: 36%	• CTCAE scoring • Acute/late effects ≥ Grade 3: 0%	
Takatori (2013)† Hyogo Ion Beam Medical Center, Japan	Locally advanced pancreatic cancer	N=91	• Dose: 67.5 GyE	• Up to 10 months	NR	• CTCAE scoring • Acute effects ≥ Grade 3: 0% • Late effects Grade 4 GI: 1% Grade 5 GI: 2%	• Subgroup data reported
Tseng (2013) Massachusetts General Hospital, MA, USA	Resectable adenocarcinoma of the pancreatic head or neck	N=47	• Dose: 25 GyE (3 patients received 30 GyE)	• 1 week	NR	• CTCAE scoring • Acute effects ≥ Grade 3: 0%	• Patient overlap w/Hong (2011) • Subgroup data reported

Table 5. Single-arm Case Series: Gastrointestinal Cancers.

Author (Year) Study Site	Condition Type	Sample Size	Total PBT Dose	Follow-up	Survival Outcomes	Harms*	Notes
Terashima (2012)†‡ Hyogo Ion Beam Medical Center, Japan	Locally advanced pancreatic cancer, adjacent to the GI	N=5	• P-1 Dose: 50 GyE	• Median: 12 months (range, 8-19)	<u>1-year</u> • Overall survival: 77% • Progression-free survival: 64% <u>P-3 protocol</u> • 1-year Overall survival: 79% Progression-free survival: 61%	• CTCAE scoring • Acute effects Grade 3 hematologic: 40% Grade 3 GI: 40% Grade 3 fatigue: 20% • Late effects ≥ Grade 3: 0%	• All patients w/primary disease
Terashima (2012)†‡ Hyogo Ion Beam Medical Center, Japan	Locally advanced pancreatic cancer, non-adjacent to the GI	N=5	• P-2 Dose: 70.2 GyE	• Median: 20 months (range, 18-22)		• CTCAE scoring • Acute effects Grade 3 hematologic: 100% Grade 3 GI: 20% • Late effects Grade 3 GI: 20%	
Terashima (2012)†‡ Hyogo Ion Beam Medical Center, Japan	Locally advanced pancreatic cancer	N=40	• P-3 Dose: 67.5 GyE	• Median: 12 months (range, 3-22)		• CTCAE scoring • Acute effects Grade 3 hematologic: 65% Grade 4 hematologic: 8% Grade 3 GI: 20% Grade 3 weight loss: 8% Grade 3 fatigue: 3% • Late effects Grade 3 GI: 10% Grade 3 fatigue: 3% Grade 5 GI:3%	
Hong (2011)§ Massachusetts General Hospital, MA, USA	Resectable adenocarcinoma of the pancreatic head or neck	N=3	• Dose: 30 GyE	• Median: 12 months	• 1-year overall survival: 75%	• Scoring protocol: NR • Acute effects Grade 3 GI: 67% • Late effects: NR	
Hong (2011)§ Massachusetts General Hospital, MA, USA	Resectable adenocarcinoma of the pancreatic head or neck	N=12	• Dose: 25 GyE			• Scoring protocol: NR • Acute effects Grade 3 GI: 8% Grade 3 pain: 8% • Late effects: NR	

Table 5. Single-arm Case Series: Gastrointestinal Cancers.

Author (Year) Study Site	Condition Type	Sample Size	Total PBT Dose	Follow-up	Survival Outcomes	Harms*	Notes
Fukumoto (2010) Hyogo Ion Beam Medical Center, Japan	Advanced abdominal leiomyosarcoma	N=2	• Mean: 75.2 (GyE)	• Up to 14 months	NR	• RTOG/EORTC scoring • Acute/late effects ≥ Grade 3: 0%	

* Different versions of the CTCAE are utilized in the listed studies.
† Potential patient overlap among patients in these studies.
‡ Terashima (2012) reported on 3 dosing protocols based on disease. Separate results are reported where available.
§ Hong (2011) reported on 2 dosing levels. Separate results are reported where available.

Table 6. Single-arm Case Series: Gynecologic Cancers.

Author (Year) Study Site	Condition Type	Sample Size	Total PBT Dose	Follow-up	Survival Outcomes	Harms	Notes
Kagei (2003) University of Tsukuba, Japan	Stage IIB-IVA carcinoma of the uterine cervix	N=25	• PBT + photon, median: 86 Gy (range, 71-101)	• Median: 139 months (range, 11-184)	• 10-year overall survival: 59%	• RTOG/EORTC scoring • Severity of acute effects: NR • Late effects Grade 3 GI/GU: 0% Grade 4 GI: 4% Grade 4 GU: 4%	• Subgroup data reported
Arimoto (1991) University of Tsukuba, Japan	Uterine cervical or vaginal carcinoma, ≤stage IIIB disease	N=15	• PBT ± photon PBT: ranging from 74.5 – 86 cGy Photon: ranging from 14.4-37.8 cGy	• Ranging from 15-57 months	• 2-year overall survival: 93%	• Severity of harms: NR	• Subgroup data reported

EORTC: European Organization for Research and the Treatment of Cancer; GI: gastrointestinal; GU: genitourinary; N: number; NR: not reported; PBT: proton beam therapy; RTOG: Radiation Therapy Oncology Group

Table 7. Single-arm Case Series: Head and Neck Cancers (including skull-base tumors).

Author (Year) Study Site	Condition Type	Sample Size	Total PBT Dose	Follow-up	Survival Outcomes	Harms*	Notes
McDonald (2013) Indiana University Health Proton Therapy Center, IN, USA	Progressive or recurrent chordoma	N=16	• Median: 75.2 Gy (range, 40-79.2)	• Median: 24 months (range, 6-63)	• 2-year overall survival: 80%	• CTCAE scoring • Acute effects Grade 3 laryngeal edema: 6% Grade 4 ventricular obstruction: 6% • Late effects Grade 3 radiation necrosis: 6% Grade 4 stroke: 6% Grade 4 CSF leak: 6%	• All patients with recurrent disease • Subgroup data reported
Fukumitsu (2012) University of Tsukuba, Japan	Unresectable stage IV and local recurrent carcinoma of the nasal cavity and paranasal sinuses	N=17	• Median: 78 GyE (range, 72.4-89.6) (3 patients w/additional photon therapy)	• Median: 23 months	<u>Overall survival</u> • 2-year: 47% • 5-year: 16%	• RTOG scoring •Acute effects Grade 3 mucositis: 6% Grade 3 dermatitis: 6% • Late effects Grade 3 brain necrosis: 6% Grade 4 fracture: 6% Grade 4 visual: 6%	• 2/17 (12%) w/recurrent disease • Subgroup data reported
Hojo (2012) National Cancer Center Hospital East, Japan	Nasal cavity or paranasal malignancies	N=65	• Median: 65 GyE (range, 60-70)	• Median: 52 months (range, 25-125)	<u>3-year</u> • Overall survival: 72% • Progression-free survival: 44%	NR	• 52/65 (80%) of patients received PBT
Okano (2012) National Cancer Center Hospital East, Japan	T4b nasal and sinonasal malignancies	N=13	• Dose: 65 CGE	• Median: 57 months (range, 1-64)	<u>5-year</u> • Overall survival: 76% • Progression-free survival: 34%	• CTCAE scoring • Acute effects Grade 3 mucositis: 15% • No reported late effects	

Table 7. Single-arm Case Series: Head and Neck Cancers (including skull-base tumors).

Author (Year) Study Site	Condition Type	Sample Size	Total PBT Dose	Follow-up	Survival Outcomes	Harms*	Notes
Pehlivan (2012) Paul Scherrer Institute, Switzerland	Chordoma and chondrosarcoma of the skull base	N=62	• Chordoma, mean: 73.5 Gy (RBE) (range, 67-74) • Chondrosarcoma, mean: 68.4 Gy (RBE) (range, 63-74)	• Median: 38 months (range, 14-92)	<u>Chordoma</u> • 5-year overall survival: 62% • 5-year disease-free survival: 81% <u>Chondrosarcoma</u> • 5-year overall survival: 91% • 5-year disease-free survival: 100%	• CTCAE scoring • Acute effects: NR • Late effects Grade 3 temporal lobe damage: 3%	• 17/62 (27%) w/recurrent disease • Subgroup of patients in Ares (2009)
Moore (2011) Massachusetts General Hospital, MA, US	Stage II-IV sinonasal malignancies	N=70	• PBT ± photon, median: 69 Gy (range, 59.4-77.8)	• Median: 65 months	<u>5-year</u> • Overall survival: 59% • Disease-free survival: 55%	NR	• All patients w/primary disease
Zenda (2011a) National Cancer Center Hospital East, Japan	Mucosal melanoma of the head and neck	N=14	• Dose: 60 GyE	• Median: 37 months	• 3-year overall survival: 58% • 2-year progression-free survival: 44%	• CTCAE scoring • Acute effects Grade 3 mucositis: 21% • Late effects Grade 3 neuropathy: 14%	
Zenda (2011b) National Cancer Center Hospital East, Japan	Unresectable malignancies of the nasal cavity and paranasal sinuses	N=39	• Dose: ranging from 60-70 GyE	• Median: 45 months (range, 1-91)	<u>3-year</u> • Overall survival: 59% • Progress-free survival: 49% <u>5-year</u> • Overall survival: 55%	• CTCAE scoring • Acute effects ≥ Grade 3: 0% • Late effects Grade 3 cataract: 3% Grade 3 neuropathy: 3% Grade 3 bone necrosis: 3% Grade 4 neuropathy: 3% Grade 5 CSF leakage: 3%	• Subgroup data reported

Table 7. Single-arm Case Series: Head and Neck Cancers (including skull-base tumors).

Author (Year) Study Site	Condition Type	Sample Size	Total PBT Dose	Follow-up	Survival Outcomes	Harms*	Notes
Ares (2009) Paul Scherrer Institute, Switzerland	Chordoma and chondrosarcoma of the skull base	N=64	• Chordoma, mean: 73.5 Gy (RBE) (range, 67-74) • Chondrosarcoma, mean: 68.4 Gy (RBE) (range, 63-74)	• Median: 34 months (range, 14-92)	5-year overall survival • Chordoma: 62% • Chondrosarcoma: 91%	• CTCAE scoring • Acute effects: NR • Late effects Grade 3 neuropathy: 2% Grade 4 neuropathy: 2% Grade 3 temporal lobe damage: 3%	• 17/64 (27%) w/recurrent disease • Subgroup data reported
Roda (2009) NR	Skull-base neoplasm	N=3	• Dose: ranging from 6,600 - 7,200 cGy, 15 CGE	• Mean: 24 months (range, 6-48)	•Overall survival: 100%	• Acute effects: NR • Severity of late effects: NR	
Truong (2009) Massachusetts General Hospital, MA, US	Primary sphenoid sinus malignancy	N=20	• PBT + photon, median: 76 Gy (range, 66-78)	• Median: 21 months	2-year • Overall survival: 53% • Disease-free survival: 31%	• CTCAE scoring • Acute effects Grade 3 mucositis: 30% Grade 3 skin: 10% • Late effects Grade 3 nasal: 5% Grade 5 CSF leak: 5% Grade 4 pituitary dysfunction: 5%	• All patients w/primary disease • Subgroup data reported
Nichols (2008) Massachusetts General Hospital, MA, US	Esthesio-neuroblastoma	N=10	• PBT + photon, median: 62.7 CGE (range, 54-70) (3 patients with PBT alone)	• Median: 53 months	5-year • Overall survival: 86% • Disease-free survival: 90%	• CTCAE scoring • Acute/late effects ≥ Grade 3: 0%	• All patients w/primary disease • Subgroup data reported
Resto (2008) Massachusetts General Hospital, MA, US	Locally advanced sinonasal malignancies	N=102	• PBT + photon, median: 71.6 Gy (range, 55.4-79.4)	• Median: 43 months (range, 1-157)	• Overall survival, disease-free survival reported based on surgical procedure	NR	• Subgroup data reported
Nishimura (2007) National Cancer Center Hospital East, Japan	Olfactory neuroblastoma	N=14	• Dose: 65 GyE	• Median: 40 months (range, 11-74)	5-year • Overall survival: 93% • Local progression-free survival: 84%	• RTOG/EORTC scoring • Acute/late effects ≥ Grade 3: 0%	• 1/14 (7%) w/recurrent disease

Table 7. Single-arm Case Series: Head and Neck Cancers (including skull-base tumors).

Author (Year) Study Site	Condition Type	Sample Size	Total PBT Dose	Follow-up	Survival Outcomes	Harms*	Notes
Pommier (2006) Massachusetts General Hospital, MA, US	Adenoid cystic carcinoma of the skull base	N=23	• PBT + photon, median: 76.4 CGE (range, 70-79.1)	• Median: 62 months	5-year • Overall survival: 77% • Disease-free survival: 56% 8-year • Overall survival: 59% • Disease-free survival: 31%	• CTCAE scoring • Acute effects ≥ Grade 3: 0% • Late effects Grade 4 retinopathy: 4% Grade 3 (cataract, ectropion, dacryocystorrhinostomy): 13% Grade 3 neurologic: 43% Grade 5 CSF leak: 4%	• All patients w/primary disease • Subgroup data reported
Weber (2006) Massachusetts General Hospital, MA, US	Advanced nasal cavity and paranasal sinus cancer	N=36	• PBT + photon, median: 69.6 CGE (range, 60.8-77)	• Median: 52 months (range, 17-123)	3-year • Overall survival: 90% • Disease-free survival: 77% 5-year • Overall survival: 81% • Disease-free survival: 73%	• LENT/SOMA and CTCAE scoring • Severity of acute effects: NR • Late effects Grade 3 cataract: 3% Grade 3 nasolacrimal duct blockage: 3%	• 3/36 (8%) w/recurrent disease • Subgroup data reported
Feuvret (2005) Centre de Protonthérapie d'Orsay, France	Chondromyxoid fibroma of the skull base	N=2	• PBT + photon: 59 CGE	• Ranging from 1 - 4 years	• Overall survival: 100%	• Severity of harms: NR	
Noël (2005) Centre de Protonthérapie d'Orsay, France	Chordoma of the skull base or upper cervical spine	N=100	• PBT + photon, median: 67 CGE (range, 60-71)	• Median: 31 months (range, 0-87)	Overall survival • 2-year: 94% • 4-year: 90%% • 5-year: 81%	• Severity of acute/late effects: NR	• 30/100 (30%) w/recurrent disease • Subgroup data reported
Slater (2005) Loma Linda University Medical Center	Localized stage II-IV oropharyngeal cancer	N=29	• PBT + photon, dose: 75.9 GyE	• Median: 28 months (range, 2-96)	Disease-free survival • 2-year: 81% • 5-year: 65%	• RTOG scoring • Severity of acute effects: NR • Late effects Grade 3 (fibrosis, trismus, vocal cord paralysis): 11%	• All patients w/primary disease

Table 7. Single-arm Case Series: Head and Neck Cancers (including skull-base tumors).

Author (Year) Study Site	Condition Type	Sample Size	Total PBT Dose	Follow-up	Survival Outcomes	Harms*	Notes
Marucci (2004) Massachusetts General Hospital, MA, USA	Chordoma or chondrosarcoma of the cervical spine and cervico-occipital junction	N=85	• PBT + photon, mean: 76.3 CGE (range, 68.6-83.5)	• Median: 41 months (range, 2-117)	NR	• RTOG/EORTC scoring • Acute effects: NR • Late effects ≥ Grade 3: 5%	• Subgroup data reported
Noël (2004) Centre de Protonthérapie d'Orsay, France	Chordoma or chondrosarcoma of the cranial base and cervical spine	N=90	• PBT + photon, median: 67 CGE (range, 22-70)	• Median: 34 months (range, 3-74)	<u>Overall survival</u> • 2-year: 93% • 3-year: 92% • 4-year: 86%	• LENT/SOMA & RTOG scoring • Severity of acute effects: NR • Late effects Grade 3 oculomotor: 2% Grade 3 hearing loss: 1% Grade 4 visual: 1%	• 30/90 (33%) w/recurrent disease • Subgroup data reported
Bowyer (2003) Walton Hospital, Liverpool , UK	Clival chordoma	N=4	• PBT + photon, mean: 76.7 CGE (range, 72-83.5)	• Mean: 34 months (range, 17-60)	• Overall survival: 100%	• Severity of acute/late effects: NR	
Fitzek (2002) Massachusetts General Hospital, MA, USA	Olfactory neuroblastoma or neuroendocrine carcinoma	N=19	• PBT + photon, median: 69.2 CGE (range, 67.2-72.6)	• Median: 45 months (range, 20-92)	• 5-year overall survival: 74%	• CTCAE & LENT/SOMA scoring • Severity of acute effects: NR • Late effects Grade 3 temporal lobe damage: 5% Grade 3 xerostomia: 11%	• All patients w/primary disease • Subgroup data reported
Hug (1999) Loma Linda University Medical Center, CA, USA	Chordoma and chondrosarcoma of the skull base	N=58	• Mean: 70.7 CGE (range, 64.8-79.2) (6 patients received additional photon therapy)	• Mean: 33 months (7-75)	<u>3-year overall survival</u> • Chordoma: 87% • Chondrosarcoma: 100% <u>5-year overall survival</u> • Chordoma: 79% • Chondrosarcoma: 100%	• LENT/SOMA scoring •Severity of acute effects: NR • Late effects Grade 3-4: 7%	• 14/58 (24%) w/recurrent disease • Subgroup data reported
Lin (1999) Loma Linda University Medical Center, CA, USA	Recurrent or persistent nasopharyngeal carcinoma	N=16	• Mean: 62.8 CGE (range, 59.4-70.2)	• Mean: 24 months (range, 4-47)	<u>2-year</u> • Overall survival: 50% • Disease-free survival: 50%	• Severity of harms: NR	• All patients w/recurrent or persistent disease • Subgroup data reported

Table 7. Single-arm Case Series: Head and Neck Cancers (including skull-base tumors).

Author (Year) Study Site	Condition Type	Sample Size	Total PBT Dose	Follow-up	Survival Outcomes	Harms*	Notes
Rosenberg (1999) Massachusetts General Hospital, MA, USA	Chondrosarcoma of the skull base	N=200	• Median: 72.1 CGE (range, 64.2-79.6)	• Mean: 65 months (range, 2-222)	NR	NR	
Terahara (1999) Massachusetts General Hospital, MA, USA	Skull-base chordoma	N=115	• PBT + photon, median: 68.9 CGE (range, 66.6-79.2) (2 patients received PBT alone)	• Median: 41 months (range, 5-174)	NR	NR	• Subgroup data reported
Debus (1997) Massachusetts General Hospital, MA, USA	Chordoma and low-grade chondrosarcoma of the skull base	N=367	• PBT + photon, mean: 67.8 CGE (range, 63-79.2)	• Mean: 43 months (range, 6-257)	<u>Overall survival</u> • 5-year: 94% • 10-year: 86%	• Scoring consistent w/LENT/SOMA • Acute effects: NR • Late effects (brainstem toxicity only) Grade 3: 1% Grade 4: 1% Grade 5: 0.8%	• Subgroup data reported
Fagundes (1995) Massachusetts General Hospital, MA, USA	Relapsed chordoma of the skull base or cervical spine	N=63	• PBT + photon, median: 70.1 CGE (range, 66.6-77.4)	• Median: 54 months (range, 8-158)	<u>Overall survival</u> • 3-year: 43% • 5-year: 7%	NR	• Subgroup data reported
O'Connell (1994) Massachusetts General Hospital, MA, USA	Skull-base chordoma	N=62	• PBT + photon dose: ranging from 64.9-73.5 CGE	• Median: 69 months (range, 20-158)	• Overall survival: 66%	NR	• Patient overlap w/Terahara (1999) • Subgroup data reported

* Different versions of the CTCAE/Common Toxicity Criteria are utilized in the listed studies.
CSF: cerebrospinal fluid; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organization for Research and the Treatment of Cancer; LENT/SOMA: Late Effects of Normal Tissue – subjective, objective, management, analytic; N: number; NR: not reported; PBT: proton beam therapy; RBE: relative biological effectiveness; RTOG: Radiation Therapy Oncology Group

Table 8. Single-arm Case Series: Liver Cancer.

Author (Year) Study Site	Condition Type	Sample Size	Total PBT Dose	Follow-up	Survival Outcomes	Harms*	Notes
Abei (2013) University of Tsukuba, Japan	Locally advanced recurrent HCC	N=9	• Mean: 72.2 GyE (range, 52.8-87.6)	NR	• Overall survival: 33%	• CTCAE scoring • Acute effects ≥ Grade 3: 0% • Late effects: NR	• All patients w/recurrent disease
Kanemoto (2013) University of Tsukuba, Japan	HCC	N=67	• Dose: 66 Gy (RBE)	• Median: 28 months (range, 7-81)	NR	• Severity of harms: NR	• Subgroup data reported
Kanemoto (2012) University of Tsukuba, Japan	Liver metastases from breast cancer	N=5	• Dose: 66 or 72.6 GyE	• Median: 33 months (range, 20-102)	• Overall survival: 100%	• CTCAE scoring • No acute/late effects ≥ Grade 3	
Mizumoto (2012) University of Tsukuba, Japan	HCC	N=259	• Dose: ranging from 66 – 77 GyE based on tumor location as described in Mizumoto (2011)	• Up to 24 months following PBT	NR	NR	• Patients evaluated in Mizumoto (2011) • Subgroup data reported
Bush (2011) Loma Linda University Medical Center, CA, USA	HCC	N=76	• Dose: 63 CGE	NR	• Overall survival, progression-free survival in figures only	• Common Toxicity Criteria • No acute/late effects ≥ Grade 3	• Subgroup data reported

Table 8. Single-arm Case Series: Liver Cancer.

Author (Year) Study Site	Condition Type	Sample Size	Total PBT Dose	Follow-up	Survival Outcomes	Harms*	Notes
Kawashima (2011) National Cancer Center Hospital East, Japan	HCC ≤10 cm	N=60	• Dose: ranging from 60-76 CGE	NR	3-year • Overall survival: 56% • Disease-free survival: 18% 5-year • Overall survival: 25% • Disease-free survival: 4%	• CTCAE scoring • Proton-induced hepatic insufficiency: 18% •Acute effects Grade 3 elevation of bilirubin: 2% Grade 3 elevation of transaminases: 13% Grade 3 hematologic: 23% ≥Grade 3 GI: 2% • Late effects Grade 3 GI: 2%	• 10/60 (17%) w/recurrent disease • Subgroup data reported
Mizumoto (2011)† University of Tsukuba, Japan	HCC >2cm from the GI tract or porta hepatis	N=104	• Protocol A: 66 GyE	NR	1-year • Overall survival: 87% • Progression-free survival: 56% 3-year • Overall survival: 61% • Progression-free survival: 21% 5-year • Overall survival: 48% • Progression-free survival: 12%	• CTCAE & RTOG/EORTC scoring • Acute effects Grade 3 dermatitis: 0.8% • Late effects Grade 3 dermatitis: 0.8% Grade 3 GI: 1%	• Patients from Mizumoto (2008) included in analysis • Subgroup data reported
Mizumoto (2011)† University of Tsukuba, Japan	HCC ≤2cm from the porta hepatis	N=95	• Protocol B: 72.6 GyE				
Mizumoto (2011)† University of Tsukuba, Japan	HCC ≤2cm from the GI tract	N=60	•Protocol C: 77 GyE				

Table 8. Single-arm Case Series: Liver Cancer.

Author (Year) Study Site	Condition Type	Sample Size	Total PBT Dose	Follow-up	Survival Outcomes	Harms*	Notes
Nakayama (2011) University of Tsukuba, Japan	HCC located ≤2cm to the alimentary tract	N=47	• Dose: ranging from 72.6 – 77 GyE	• Median: 23 months (range, 3-52)	<u>1-year</u> • Overall survival: 70% • Local progression-free survival: 92% <u>3-year</u> • Overall survival: 50% • Local progression-free survival: 88% <u>4-year</u> • Overall survival: 34% • Local progression-free survival: 88%	• CTCAE scoring • Acute effects ≥ Grade 3: 0% • Late effects Grade 3 hemorrhage: 2%	• Subgroup data reported
Sugahara (2010) University of Tsukuba, Japan	HCC >10cm	N=22	• Median: 72.6 CGE (range, 47.3-89.1)	• Median: 13 months (range, 2-85)	<u>1-year</u> • Overall survival: 64% • Progression-free survival: 62% <u>2-year</u> • Overall survival: 36% • Progression-free survival: 24%	• CTCAE & RTOG/EORTC scoring • Acute effects ≥ Grade 3: 0% • No reported late effects	
Fukumitsu (2009) University of Tsukuba, Japan	HCC located ≥2cm from porta hepatis or digestive tract	N=51	• Dose: 66 GyE	• Ranged from 19-60 months	<u>Overall survival</u> • 3-year: 49% • 5-year: 39%	• RTOG/EORTC scoring • Acute effects ≥ Grade 3: 0% • Late effects Grade 3 radiation pneumonitis: 2%	• 33/51 (65%) w/recurrent disease • Subgroup data reported
Nakayama (2009) University of Tsukuba, Japan	HCC	N=318	• Median: 72.6 GyE (range, 55-79.2)	• Median: 19 months (range, 1-64)	<u>Overall survival</u> • 1-year: 90% • 3-year: 65% • 5-year: 45%	• CTCAE scoring • Overall effects Grade 3 skin: 1% Grade 3 GI: 0.3%	

Table 8. Single-arm Case Series: Liver Cancer.

Author (Year) Study Site	Condition Type	Sample Size	Total PBT Dose	Follow-up	Survival Outcomes	Harms*	Notes
Sugahara (2009) University of Tsukuba, Japan	Advanced HCC w/portal vein tumor thrombosis (PVTT)	N=35	• Median: 72.6 GyE (range, 55-77)	• Median: 21 months (range, 2-88)	2-year • Overall survival: 48% • Local progression-free survival: 46% 5-year • Overall survival: 21% • Local progression-free survival: 20%	• RTOG/EORTC scoring • Acute effects Grade 3 hematologic: 6% Grade 4 hematologic: 3% • Late effects ≥ Grade 3: 0%	• 14/35 (40%) of patients w/recurrent PVTT • Subgroup data reported
Mizumoto (2008) University of Tsukuba, Japan	HCC located ≤2cm of the main portal vein	N=53	• Dose: 72.6 GyE	NR	2-year • Overall survival: 57% • Progression-free survival: 38% 3-year • Overall survival: 45% • Progression-free survival: 25%	• NCI Common Toxicity Criteria & RTOG/EORTC scoring • Acute effects ≥ Grade 3: 0% • Late effects ≥ Grade 3: 0%	• Patients included in Mizumoto (2011) • Subgroup data reported
Hata (2007a) University of Tsukuba, Japan	HCC w/uncontrollable ascites	N=3	• Dose: 24 Gy	• Up to 30 months	• Overall survival: 67%	• CTCAE scoring • No reported acute effects • Late effects ≥ Grade 3: 0%	
Hata (2007b) University of Tsukuba, Japan	Patients ≥80 years w/HCC	N=21	• Dose: ranging from 60 – 70 Gy	• Median: 16 months (range, 6-49)	1-year • Overall survival: 84% • Disease-free survival: 70% 3-year • Overall survival: 62% • Disease-free survival: 51%	• RTOG/EORTC scoring • Acute effects Grade 3 hematologic: 10% • No reported late effects	• 10/21 (48%) of patients w/recurrent disease
Mizumoto (2007) University of Tsukuba, Japan	HCC w/inferior vena cava tumor thrombus	N=3	• Dose: ranging from 50 – 70 Gy	• Up until death	• All patients died, 13-55 months following PBT	• No toxicities ≥ Grade 3 observed	

Table 8. Single-arm Case Series: Liver Cancer.

Author (Year) Study Site	Condition Type	Sample Size	Total PBT Dose	Follow-up	Survival Outcomes	Harms*	Notes
Hashimoto (2006) University of Tsukuba, Japan	Patients w/HCC w/ ≥2 courses of PBT	N=27	• Dose: ranging from 40-83	• Median: 62 months (range, 9-149)	5-year survival • From the first course: 56% • From the second course: 26%	• CTCAE & RTOG/EORTC scoring • Acute effects Grade 4 hepatic failure: 7% • Late effects Grade 4 rib fracture: 4% Grade 4 bile duct stenosis: 7%	
Hata (2006a) University of Tsukuba, Japan	HCC in patients w/limited treatment options (contraindications)	N=21	• Median: 73 Gy (range, 63-84)	• Median: 40 months (range, 4-128)	Overall Survival • 2-year: 62% • 5-year: 33% Disease-free rate • 1-year: 72% • 2-year: 33%	• RTOG/EORTC scoring • Acute effects ≥ Grade 3: 0% • Late effects ≥ Grade 3: 0%	
Hata (2006b) University of Tsukuba, Japan	HCC w/Child-Pugh class C cirrhosis	N=19	• Median: 72 Gy (range, 50-84)	• Median: 17 months (range,3-63)	1-year • Overall survival: 53% • Progression-free survival: 47% 2-year • Overall survival: 42% • Progression-free survival: 42%	• RTOG/EORTC scoring • Acute effects ≥ Grade 3: 0% • No reported late effects	• Subgroup data reported
Chiba (2005) University of Tsukuba, Japan	HCC in patients unsuitable for surgery	N=162	• Median: 72 Gy (range, 50-88)	• Ranged from 32 – 133 months	• 5-year overall survival: 24%	• RTOG/EORTC scoring • Acute effects ≥ Grade 3: 0% • Late effects: reported for ≥ Grade 2	• Subgroup data reported
Hata (2005) University of Tsukuba, Japan	HCC w/tumor thrombus in main trunk branches of the portal vein	N=12	• Median: 55 Gy (range, 50-72)	• Median: 28 months (range, 4-88)	2-year • Overall survival: 88% • Progression-free survival: 67% 5-year • Overall survival: 58% • Progression-free survival: 24%	• RTOG/EORTC scoring • Acute effects ≥ Grade 3: 0% • Late effects ≥ Grade 3: 0%	• 3/12 (25%) w/recurrent disease

Table 8. Single-arm Case Series: Liver Cancer.

Author (Year) Study Site	Condition Type	Sample Size	Total PBT Dose	Follow-up	Survival Outcomes	Harms*	Notes
Niizawa (2005) University of Tsukuba, Japan	HCC	N=22	• Mean: 65.8 Gy (TACE in 6 patients, 27%)	• Mean: 12 months (range, 6-15)	NR	NR	
Ahmadi (1999a) University of Tsukuba, Japan	HCC	N=46	• Mean: 70.4 Gy (range, 50-84)	• Ranging from 12-76 months	Overall survival • 3-year: 76% • 5-year: 49%	• Severity of harms: NR	• Subgroup data reported
Ahmadi (1999b) University of Tsukuba, Japan	Unresectable hypervascular HCC	N=4	• Mean: 70 Gy (range, 55-82)	• Mean: 14 months (range, 9-22)	• Overall survival: 100%	NR	
Ohara (1997) University of Tsukuba, Japan	HCC	N=26	• Dose: ranging from 55 – 84 Gy	• Ranging from 12-27 months	NR	• Severity of harms: NR	
Ohara (1996) University of Tsukuba, Japan	HCC	N=18	• Dose: ranging from 50.5 – 82 Gy	• Ranging from 7-33 months	NR	NR	• All patients w/primary disease

* Different versions of the CTCAE/Common Toxicity Criteria are utilized in the listed studies.
† Mizumoto (2011) reported on different dosing protocols for PBT, determined by tumor location, delivered to patients w/HCC tumors. Results for each arm are listed separately.

CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organization for Research and the Treatment of Cancer; GI: gastrointestinal; HCC: hepatocellular carcinoma; LENT/SOMA: Late Effects of Normal Tissue – subjective, objective, management, analytic; N: number; NCI: National Cancer Institute; NR: not reported; PBT: proton beam therapy; PVTT: portal vein tumor thrombosis; RBE: relative biological effectiveness; RTOG: Radiation Therapy Oncology Group

Table 9. Single-arm Case Series: Lung Cancer.

Author (Year) Study Site	Condition Type	Sample Size	Total PBT Dose	Follow-up	Survival Outcomes	Harms*	Notes
Kanemoto (2014) University of Tsukuba, Japan	Stage I NSCLC (central & peripheral sites)	N=74	• Dose: 66 or 72.6 GyE	• Median: 31 months (range, 7-104)	<u>3-year</u> • Overall survival: 77% • Progression-free survival: 59% <u>5-year</u> • Overall survival: 66% • Progression-free survival: 53%	• CTCAE & RTOG/EORTC scoring • Acute effects Grade 3 pneumonitis: 1% • Late effects Grade 3 pneumonitis: 1% Grade 3 skin ulcer: 1% Grade 4 rib fracture: 15%	• Patient overlap w/Nakayama (2010) • Subgroup data reported
Bush (2013) Loma Linda University Medical Center, CA, USA	Stage I NSCLC	N=111	• Dose: 51, 60 or 70 Gy	• Median: 48 months	<u>4-year overall survival</u> • Dose, 51 Gy: 18% • Dose, 60 Gy: 32% • Dose, 70 Gy: 51% (p=0.006)	• CTCAE scoring • No acute/late effects ≥ Grade 3	• Subgroup data reported
Colaco (2013) University of Florida Proton Therapy Institute, FL, USA	Limited stage-SCLC	N=6	• Dose: ranging from 45 CGE in 1 patient to 60-66 CGE	• Median: 12 months (range, 8-41)	<u>1-year</u> • Overall survival: 83% • Progression-free survival: 66%	• CTCAE scoring • No acute/late effects ≥ Grade 3	
Gomez (2013) MD Anderson Cancer Center, TX, USA	NSCLC	N=25	• Dose: 45, 52.5, or 60 Gy(RBE)	• Median (in patients alive at analysis): 13 months (range, 8-28)	NR	• CTCAE scoring •Acute effects ≥ Grade 3: 0% • Late effects Grade 3 (pneumonitis, esophagitis): 8%	
McAvoy (2013) MD Anderson Cancer Center, TX, USA	Locoregionally recurrent NSCLC	N=33	• Median: 66 Gy(RBE)	• Median: 11 months (range, 1-32)	<u>1-year</u> • Overall survival: 47% • Progression-free survival: 28% <u>2-year</u> • Overall survival: 33% • Progression-free survival: 14%	• CTCAE scoring • Acute/late effects ≥ Grade 3 esophageal: 9% ≥ Grade 3 pulmonary: 21% ≥ Grade 3 cardiac: 3%	• All patients w/recurrent disease • Subgroup data reported

Table 9. Single-arm Case Series: Lung Cancer.

Author (Year) Study Site	Condition Type	Sample Size	Total PBT Dose	Follow-up	Survival Outcomes	Harms*	Notes
Hoppe (2012) University of Florida Proton Therapy Institute, FL, USA	Regionally advanced NSCLC	N=19	• Median: 74 CGE (range, 62-80) (12 patients also received adjacent nodal PBT, median 40 CGE)	• Median: 15 months (range, 7-26)	• Overall survival: 42%	• CTCAE scoring • Acute effects Grade 3 hematologic: 37% Grade 3 hypoxia/dyspnea: 11% Grade 3 weight loss: 5% Grade 4/5 (PS, fatigue, esophagitis): 16% • Late effects Grade 3 PS: 6% Grade 3 fatigue: 6% Grade 3 pulmonary: 18% Grade 4/5 pulmonary: 13% Grade 4/5 hematologic: 13%	
Westover (2012) Massachusetts General Hospital, MA, USA	Medically inoperable stage I NSCLC	N=15	• Median: 45 Gy(RBE) (range, 42-50)	• Median: 24 months	• 2-year overall survival: 64%	• CTCAE scoring • Acute/late effects Grade 3 pneumonitis: 7%	• All patients w/primary disease
Xiang (2012) MD Anderson Cancer Center, TX, USA	Unresectable stage III NSCLC	N=84	• Dose: 74 Gy(RBE)	• Median: 19 months (range, 6-52)	3-year • Overall survival: 37% • Progression-free survival: 31%	NR	• Patients from 2 prospective trials • Subgroup data reported
Chang (2011a) MD Anderson Cancer Center, TX, USA	Unresectable stage III NSCLC	N=44	• Dose: 74 Gy(RBE)	• Median: 20 months (range, 6-44)	1-year • Overall survival: 86% • Progression-free survival: 63%	• CTCAE scoring • Acute effects Grade 3 dermatitis: 11% Grade 3 esophagitis: 11% Grade 3 dehydration: 7% Grade 3 fatigue: 2% • Late effects Grade 3 pulmonary: 5%	

Table 9. Single-arm Case Series: Lung Cancer.

Author (Year) Study Site	Condition Type	Sample Size	Total PBT Dose	Follow-up	Survival Outcomes	Harms*	Notes
Chang (2011b) MD Anderson Cancer Center, TX, USA	Inoperable stage IA, IB or II NSCLC	N=18	• Dose: 87.5 Gy(RBE)	• Median: 16 months (range, 5-36)	1-year • Overall survival: 93% • Disease-free survival: 53% 2-year • Overall survival: 55% • Disease-free survival: 46%	• CTCAE scoring • Acute effects Grade 3 dermatitis: 17% • Late effects ≥ Grade 3: 0%	
Nakayama (2011) University of Tsukuba, Japan	Stage II & III NSCLC	N=35	• Median: 78.3 Gy(RBE) (range, 67.1-91.3)	• Median: 17 months	1-year • Overall survival: 82% • Progression-free survival: 60% 2-year • Overall survival: 59% • Progression-free survival: 29%	• CTCAE scoring • No acute/late effects ≥ Grade 3	
Nakayama (2010) University of Tsukuba, Japan	Stage I NSCLC	N=55	• Dose: 66 or 72.6 GyE	• Median: 18 months (range, 1-53)	2-year • Overall survival: 98% • Progression-free survival: 89% 3-year • Progression-free survival: 79%	• CTCAE scoring • Acute/late effects Grade 3 pneumonitis: 4% • Severity of other effects: NR	• Subgroup data reported
Hata (2007) University of Tsukuba, Japan	Stage I NSCLC	N=21	• Dose: 50 or 60 Gy	• Median: 25 months	2-year • Overall survival: 74% • Disease-free survival: 79%	• RTOG/EORTC scoring • No acute/late effects ≥ Grade 3	• Subgroup data reported
Nihei (2006) National Cancer Center East, Chiba, Japan	Stage I NSCLC, tumor ≤5cm	N=37	• Dose: ranging from 70-94 GyE	• Median: 24 months (range, 3-62)	1-year • Disease progression-free survival: 73% 2-year • Overall survival: 84% • Disease progression-free survival: 58%	• CTCAE & RTOG/EORTC scoring • Acute effects ≥ Grade 3: 0% •Late effects Grade 3 pulmonary: 8%	• Subgroup data reported

Table 9. Single-arm Case Series: Lung Cancer.

Author (Year) Study Site	Condition Type	Sample Size	Total PBT Dose	Follow-up	Survival Outcomes	Harms*	Notes
Shioyama (2003) University of Tsukuba, Japan	NSCLC	N=51	• Median: 76 Gy (range, 49-93)	• Median: 30 months (range, 18-153)	5-year • Overall survival: 29% • Disease-free survival: 37%	• Common Toxicity Criteria • Acute effects Grade 3 pulmonary: 2% • Late effects ≥ Grade 3: 0%	• 5/51 (10%) w/recurrent disease • Subgroup data reported
Bonnet (2001)† Loma Linda University Medical Center, CA, USA	Stage I-II NSCLC w/FEV_1≤ 1L	N=10	• Dose: 51 CGE	• Up to 12 months	NR	• Severity of acute/late effects: NR	• Overlapping patient population w/Bush (1999a & 1999b)
Bonnet (2001)† Loma Linda University Medical Center, CA, USA	Stage I-IIIA NSCLC w/FEV_1> 1L	N=15	• PBT + photon, dose: 73.8 Gy				
Bush (1999b)‡ Loma Linda University Medical Center, CA, USA	Stage I-IIIa NSCLC in patients w/poor cardiopulmonary function	N=19	• Dose: 51 CGE	• Median: 14 months (range, 3-45)	• 2-year overall survival: 31%	• Pulmonary injury reported in Bush (1999a) • Severity of acute/late effects: NR	• Overlapping patient population w/Bonnet (2001)
Bush (1999b)‡ Loma Linda University Medical Center, CA, USA	Stage I-IIIa NSCLC in patients w/adequate cardiopulmonary function (FEV_1> 1L)	N=18	• PBT + photon, dose: 73.8 Gy				

* Different versions of the CTCAE/Common Toxicity Criteria are utilized in the listed studies.
† Bonnet (2001) reported on different dosing protocols for PBT, determined by disease stage, delivered to patients w/NSCLC. Results for each arm are listed separately.
‡ Bush (1999) reported on patients treated w/different dosing protocols. Overall findings are listed.
CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organization for Research and the Treatment of Cancer; FEV_1: forced expiratory volume in 1 second; N: number; NR: not reported; NSCLC: non-small-cell lung cancer; PBT: proton beam therapy; RBE: relative biological effectiveness; RTOG: Radiation Therapy Oncology Group; SCLC: small-cell lung cancer

Table 10. Single-arm Case Series: Lymphomas.

Author (Year) Study Site	Condition Type	Sample Size	Total PBT Dose	Follow-up	Survival Outcomes	Harms	Notes
Li (2011) MD Anderson Cancer Center, TX, USA	Mediastinal masses from lymphoma	N=10	• Mean: 39.1 CGE (range, 28-50.4)	NR	NR	• Scoring protocol: NR • Acute effects ≥ Grade 3: 0% • Late effects: NR	• 2/10 (20%) w/recurrent disease

N: number; NR: not reported

Table 11. Single-arm Case Series: Ocular Tumors.

Author (Year) Study Site	Condition Type	Sample Size	Total PBT Dose	Follow-up	Survival Outcomes	Harms*	Notes
Petrovic (2014) Paul Scherrer Institute, Switzerland	Uveal melanoma	N=129	• Dose: 60 Gy (RBE)	• Mean: 79 months (range, 4-281)	NR	• Severity of harms: NR • Secondary enucleation: 16%	• Subgroup data reported
Sandinha (2014) Clatterbridge Cancer Centre, UK	Iris melanoma	N=150	• Dose: 53.1 Gy	• Median: 66 months (range, 12-108)	NR	NR	• Patient overlap w/ Konstantinidis (2013)
Konstantinidis (2013) Clatterbridge Cancer Centre, UK	Diffuse or multifocal primary iris melanoma	N=12	• Dose: 53.1 Gy	• Median: 3.5 years (range, 1-12)	• Overall survival: 92%	• Acute effects: NR • Severity of late effects: NR	• All patients w/ primary disease
Mishra (2013) University of San Francisco, CA, USA	Uveal melanoma	N=704	• Dose: 56 GyE	• Median: 58.3 months (range, 6-194)	NR	• Acute effects: NR <u>Late effects</u> • Secondary enucleation: 4% • Other late effects: NR	• Subgroup data reported
Caujolle (2012) Centre Antoine Lacassagne, Nice, France	Uveal melanoma	N=1102	• Dose: 60 CGE	<u>Median</u> • Patients w/recurrence: 5 years • Patients w/out recurrence: 4 years	<u>10-year overall survival</u> • Patients w/local recurrence: 43% • Patients free of recurrence: 69%	NR	• Subgroup data reported
Chappell (2012) University of San Francisco, CA, USA	Uveal melanoma	N=197	NR	• Median: 22 months (range, 2-112)	NR	NR	• Subgroup data reported
Tran (2012) Vancouver Hospital Eye Care Centre, Canada	Peripapillary choroidal melanoma (≤2mm from optic disc)	N=59	• Mean: 57 CGE (32% w/54 CGE, 68% w/60 CGE)	• Median: 63 months (range, 4-131)	• 5-year overall survival: 85%	• Acute effects: NR <u>Late effects</u> • Secondary enucleation:14% • Severity of other late effects not reported	• Subgroup data reported

Table 11. Single-arm Case Series: Ocular Tumors.

Author (Year) Study Site	Condition Type	Sample Size	Total PBT Dose	Follow-up	Survival Outcomes	Harms*	Notes
Lane (2011)† Massachusetts General Hospital, MA, USA	Peripapillary and parapapillary melanomas located within 1 disc diameter of the optic nerve	N=573	NR	• Median: 96 months (range, 10-173)	• Overall survival: 69%	• Severity of harms: NR • Secondary enucleation: 10%	
Macdonald (2011) NR	Ciliary body and choroidal melanomas	N=147	NR	• Median: 3.1 years (3 months-15 years)	• Overall survival: 75%	• Acute effects: NR <u>Late effects</u> • Secondary enucleation: 12% • Other late effects: NR	• All patients w/ primary disease
Caujolle (2010) Centre Antoine Lacassagne, Nice, France	Uveal melanoma	N=886	• Dose: 60 CGE	• Median: 63.7 months (range, 6-185)	• 15-year overall survival: 54%	• Severity of harms: NR • Secondary enucleation: 4%	• Subgroup data reported
Kim (2010)† Massachusetts General Hospital, MA, USA	Parapapillary choroidal melanoma within 1 disc diameter of the optic nerve	N=93	• Dose: 70 CGE	• Mean: 5.5 years (range, 6 months-13 years)	NR	• Severity of harms: NR	• Subgroup data reported
Mizumoto (2010) NR	Tumors proximal to the optic nerve	N=3	• Patient 1: 55.4 GyE • Patient 2 Photon: 50.4 Gy PBT: 46.2 GyE • Patient 3: 67.3 GyE	• Median: 10 months (range, 7-12)	• Overall survival: 100%	• CTCAE scores • Acute effects ≥ Grade 3: 0% • No reported late effects	
Vavvas (2010)† Massachusetts General Hospital, MA, USA	Posterior unilateral choroidal or ciliary melanoma	N=50	NR	• Median: 16.7 years (range, 2.7-24.5)	• Overall survival: 84%	NR	
Aziz (2009) Clatterbridge Centre for Oncology, UK	Uveal melanoma	N=76	• Dose: 58 CGE	• Mean: 39 months (range, 3-122)	NR	• Severity of harms: NR • Secondary enucleation: 17%	• 9/76 (12%) w/recurrent disease • Subgroup data reported

Table 11. Single-arm Case Series: Ocular Tumors.

Author (Year) Study Site	Condition Type	Sample Size	Total PBT Dose	Follow-up	Survival Outcomes	Harms*	Notes
Mosci (2009) Centre Lacassagne Cyclotron Biomedical of Nice, France	Intraocular melanoma	N=368	• Dose: 60 GyE	• Median: 3.9 years	• 6-year overall survival rate: 90%	• Acute effects: NR • Late effects Secondary enucleation: 4%	• All patients w/ primary disease • Subgroup data reported
Rundle (2007) Royal Hallamshire Hospital, Sheffield, UK	Unresectable iris melanoma	N=15	• Dose: 5,310 cGy	• Median: 40 months (range, 6-65)	• Overall survival: 100%	• Severity of harms: NR • Secondary enucleation: 13%	• 2/15 (13%) w/recurrent disease
Conway (2006) University of San Francisco, CA, USA	Extra-large uveal melanoma (≥10mm max thickness, 20mm in max basal diameter, or ≤3mm of optic nerve and w/≥8mm max thickness or 16mm in max basal diameter	N=21	• Dose: 5600 cGy	• Median: 28 months (range, 13-85)	• Overall survival: 86%	• Severity of harms: NR • Secondary enucleation: 29%	• Severity described for subset of adverse effects only • Subgroup data reported
Dendale (2006) Institut Curie, France	Uveal melanoma	N=1406	• Dose: 60 CGE	• Median (of surviving patients): 73 months (range, 24-142)	• Overall survival: 79%	• Severity of harms: NR • Secondary enucleation: 7%	• All patients w/ primary disease • No patients w/iris melanoma • Subgroup data reported
Lumbroso-Le Rouic (2006) Institut Curie, France	Iris melanoma	N=21	• Dose: 60 CGE	• Median: 33 months (range, 8-72)	• Overall survival: 100%	• Severity of harms: NR • Secondary enucleation: 0%	• 15/21 (71%) w/recurrent disease • Subgroup data reported
Marucci (2006) Massachusetts General Hospital, MA, USA	Locally recurrent uveal melanoma	N=31	• Dose: 70 CGE (1 patient received 48 CGE)	• Median: 36 months (range, 6-164)	• Overall survival: 74%	• Severity of harms: NR • Secondary enucleation: 13%	• All patients w/recurrent disease

Table 11. Single-arm Case Series: Ocular Tumors.

Author (Year) Study Site	Condition Type	Sample Size	Total PBT Dose	Follow-up	Survival Outcomes	Harms*	Notes
Wuestmeyer (2006) Cyclotron Biomedical of the Centre Antoine-Lacassagne, France	Conjunctival melanoma	N=20	• Primary target dose: 45 Gy • Secondary target dose: 31 Gy	• Median: 34 months (range, 13-117)	• Overall survival: 95%	• Severity of harms: NR	• 16/20 (80%) w/recurrent disease
Damato (2005a) Clatterbridge Centre for Oncology, UK	Choroidal melanoma	N=349	• Dose: 53.1 Gy (RBE)	• Median: 3.1 years (range, 0.01-11.5)	NR	• Severity of harms: NR • Secondary enucleation: 4%	• All patients w/ primary disease • Subgroup data reported
Damato (2005b) Clatterbridge Centre for Oncology, UK	Iris melanoma	N=88	• Dose: 58.4 CGE	• Median: 2.7 years	• Overall survival: 97%	• Severity of harms: NR • Secondary enucleation: 0%	• All patients w/ primary disease • Subgroup data reported
Tsina (2005) Massachusetts General Hospital, MA, USA	Choroidal metastatic disease	N=63	• Dose: 28 CGE	• Median (among survivors): 8 months (range, 1-34)	• Overall survival: 22%	• Severity of harms: NR • Secondary enucleation: 0%	• Unknown if patients w/recurrent disease
Höcht (2004) Hahn-Meitner Institute, Germany	Primary uveal melanoma	N=245	• Dose: 60 CGE	• Median: 18.4 months	NR	• Severity of harms: NR	• Subgroup data reported
Kodjikian (2004) Lacassagne Cyclotron Biomedical Centre, France	Posterior uveal melanoma	N=224	• Dose: 60 CGE	• Median (among survivors): 41 months	• 5-year overall survival: 78%	• Severity of harms: NR • Secondary enucleation: 8%	• Subgroup data reported
Egger (2003) Paul Scherrer Institute, Switzerland	Uveal melanoma	N=2645	• Dose: 60 CGE	• Median: 44 months (range, 0-187)	• Overall survival: 84%	• Acute effects: NR <u>Late effects</u> • Secondary enucleation: unable to determine • Other late effects: NR	• Subgroup data reported

Table 11. Single-arm Case Series: Ocular Tumors.

Author (Year) Study Site	Condition Type	Sample Size	Total PBT Dose	Follow-up	Survival Outcomes	Harms*	Notes
Hadden (2003) Ocular Oncology Centre, Liverpool, UK	Bilateral uveal melanoma	N=2	NR	• Variable: 4 – 22 months	• Overall survival: 100%	• Acute effects: NR <u>Late effects</u> • Secondary enucleation: 50% • Severity of other late effects: NR	
Li (2003)† Massachusetts General Hospital, MA, USA	Primary choroidal melanoma	N=1204	• Dose: 70 CGE	• Median: 95 months	• Overall survival: 70%	NR	• All patients w/ primary disease
Zografos (2003) Paul Scherrer Institute, Switzerland	Intraocular metastatic melanoma	N=6	• Mean: 48 Gy (range, 25-60)	• Mean: 11 months (range, 1-42)	• Overall survival: 0%	• Severity of harms: NR	
Gragoudas (2002a)† Massachusetts General Hospital, MA, USA	Choroidal/ciliary body melanoma	N=1922	• Dose: 70 CGE (95% of patients) (5% received 50 CGE)	• Median: 62 years	NR	NR	• All patients w/ primary disease • Subgroup data reported
Gragoudas (2002b)† Massachusetts General Hospital, MA, USA	Unilateral choroidal or ciliary melanoma	N=2069	• Dose: 70 CGE	• Median (among survivors) : 9.4 years (range, 10 months – 24 years)	NR	• Acute effects: NR • Late effects Secondary enucleation: 7%	
Fuss (2001) Loma Linda University Medical Center, CA, USA	Medium and large choroidal melanomas	N=78	• Dose: 70.2 CGE	• Median: 34 months (range, 6-102)	• 5-year overall survival: 70%	• Acute effects: NR <u>Late effects</u> • Secondary enucleation: 9% • Severity of other late effects: NR	
Lumbroso (2001) Institut Curie, France	Uveal melanoma	N=480	• Dose: 60 CGE	• Median: up to 62 months	NR	• Severity of harms: NR	• Subgroup data reported

Table 11. Single-arm Case Series: Ocular Tumors.

Author (Year) Study Site	Condition Type	Sample Size	Total PBT Dose	Follow-up	Survival Outcomes	Harms*	Notes
Li (2000)† Massachusetts General Hospital, MA, USA	Uveal melanoma	N=1848	• Dose: 70 CGE (range, 54-100)	• Median (among survivors): 9.5 years	NR	NR	• Subgroup data reported
Courdi (1999) Centre A. Lacassagne, France	Uveal melanoma	N=538	• Dose: 57.2 CGE	• Up to 78 months	• Overall survival: 73.8%	• Acute effects: NR • Late effects Secondary enucleation: 3%	• 5 patients w/secondary enucleation w/out attributable cause • Subgroup data reported
Egan (1999)† Massachusetts General Hospital, MA, USA	Choroidal melanoma	N=1818	• Dose: 70 CGE	• Median f/u among survivors: 8.5 years	• 10-year overall survival Men: 61% Nulliparous women: 59% Parous women: 66%	NR	• All patients w/ primary disease • Subgroup data reported
Gragoudas (1999)† Massachusetts General Hospital, MA, USA	Choroidal tumors, <5mm in height and <15mm in diameter, located within 4 disc diameters of macula or optic nerve	N=558	• Dose: 70 CGE	• Median: 4 years	NR	• Severity of harms: NR	• Subgroup data reported
Wilson (1999) St. Bartholomew's Hospital and Moorfields Eye Hospital, London, England	Choroidal melanoma	N=267	• Dose: 60 GyE	• Mean: 43 months (range, 4-85)	NR	NR	
Egan (1998)† Massachusetts General Hospital, MA, USA	Unilateral choroidal or ciliary body melanoma	N=1541	• Dose: 70 CGE	• Median (among survivors): 8 years (range, 6 months-18.3 years)	• 10-year overall survival: 63%	• Acute effects: NR • Late effects Secondary enucleation: 7%	• All patients w/ primary disease • Subgroup data reported

Table 11. Single-arm Case Series: Ocular Tumors.

Author (Year) Study Site	Condition Type	Sample Size	Total PBT Dose	Follow-up	Survival Outcomes	Harms*	Notes
Kent (1998) Ocular Oncology Service, UK	Uveal melanoma	N=17	• Dose: 53 Gy	(Reported for entire study population) • Median: 268 days (range, 0-892)	• Overall survival: 94%	• Severity of harms: NR	
Naeser (1998) Uppsala University, Sweden	Uveal melanoma	N=20	• Dose: 54.6 Gy	• Up to 5 years	• Overall survival: 85%	• Severity of harms: NR • Late effects Secondary enucleation: 35%	
Foss (1997) St. Bartholomew's Hospital and Moorfields Eye Hospital, London, England	Primary uveal melanoma	N=127	• Dose: 52 CGE	• Median: 36 months	NR	• Acute effects: NR <u>Late effects</u> • Secondary nucleation: 13% • Other late effects: NR	• Subgroup data reported
Thuomas (1997) Uppsala University, Sweden	Choroidal melanoma	N=18	NR	• Up to 6 years	NR	NR	
Park (1996) Massachusetts General Hospital, MA, USA	Parapapillary choroidal melanoma	N=59	NR	• Mean: 53 months (range, 29-94)	NR	• Severity of harms: NR	• Subgroup data reported

* Secondary enucleation rates reported for adverse effects not related to tumor recurrence.

† Potential patient overlap among studies.

CTCAE: Common Terminology Criteria for Adverse Events; N: number; NR: not reported; PBT: proton beam therapy

Table 12. Single-arm Case Series: Pediatric Conditions.

Author (Year) Study Site	Condition Type	Sample Size	Total PBT Dose	Follow-up	Survival Outcomes	Harms*	Notes
Petrovic (2014) Paul Scherrer Institute, Switzerland	Uveal melanoma	N=43	• Dose: 60 Gy (RBE)	• Mean: 155 months (range, 6-336)	NR	• Severity of harms: NR • Secondary enucleation†: 9%	• Subgroup data reported
Walcott (2014) Massachusetts General Hospital, MA, USA	Cerebral arteriovenous malformations	N=44	• Median: 15.5 Gy (RBE) (range, 14-17)	• Median: 52 months (range, 9-111)	• Overall survival: 100%	• Severity of harms: NR	• Subgroup data reported
Bian (2013) MD Anderson Cancer Center, TX, USA	Pliocytic astrocytoma	N=6	• Mean initial dose: 37.8 CGE (range, 30.6-48.6) • 4 patients received boost doses, ranging from 45-104.4 CGE	• Median: 24 months (range, 5-95)	• Overall survival: 83%	• Severity of harms: NR	
De Amorim Bernstein (2013) Massachusetts General Hospital, MA, USA	Atypical teratoid rhabdoid tumors	N=10	• Median: 50.4 Gy (RBE) (range, 50.4-55.8)	• Median: 27.3 months (11.3-99.4)	• Overall survival: 90%	• Severity of harms: NR	
Hill-Kayser (2013) Children's Hospital of Philadelphia, PA, USA	High-risk neuroblastoma	N=13	• Mean: 2,271 cGy (RBE) (range, 2,160-3,600) (2 patients w/photon therapy)	• Median: 16 months (5-27)	• Overall survival: 85%	• Severity of harms: NR	

Table 12. Single-arm Case Series: Pediatric Conditions.

Author (Year) Study Site	Condition Type	Sample Size	Total PBT Dose	Follow-up	Survival Outcomes	Harms*	Notes
Jimenez (2013) Massachusetts General Hospital, MA, USA	Medulloblastoma or supratentorial primitive neuroectodermal tumor	N=15	• Median: 54.0 Gy (RBE) (range, 39.6-54.0)	• Median: 39 months (range, 3-102)	• 3-year overall survival: 86%	• CTCAE scoring • Ototoxicity Grade 3: 2/13 (15%) (patients received concurrent chemotherapy) • No significant changes from baseline in neuropsychological testing • Excluding patients w/endocrine dysfunction, no significant changes from baseline in vertical height impairment	• Subgroup data reported
MacDonald (2013) Massachusetts General Hospital, MA, USA	Intracranial ependymoma	N=70	• Median: 55.8 Gy (range, 50.4-60)	• Median: 46 months (range, 12-140)	3-year • Overall survival: 95% • Progression-free survival: 76%	• Median height loss was not significant (p=.142) • Changes in Mental Development Index and IQ were not significant across comparisons • Severity of other harms: NR	• Subgroup data reported
Oshiro (2013) University of Tsukuba, Japan	Neuroblastoma	N=14	• Median: 30.6 GyE (range, 19.8-45.5)	• Median: 40 months (range, 17 months-30 years)	• Overall survival: 57% • Overall progression-free survival: 50%	• CTCAE scoring • No toxicities ≥ Grade 3	• 6/14 (43%) w/recurrent disease
Ray (2013) Indiana University Health Proton Therapy Center, IN, USA	Leptomeningeal spinal metastases	N=22	• Median: 37.8 Gy (range, 21.6-54)	• Median: 14 months (range, 4-33)	• 12-month overall survival: 68%	NR	• 5/22 (23%) w/recurrent disease • Subgroup data reported

Table 12. Single-arm Case Series: Pediatric Conditions.

Author (Year) Study Site	Condition Type	Sample Size	Total PBT Dose	Follow-up	Survival Outcomes	Harms*	Notes
Rombi (2013) Paul Scherrer Institute, Switzerland	Chordoma and chondrosarcoma	N=26	• Chordoma, mean dose: 74 Gy (RBE) (range, 73.8-75.6) • Chondrosarcoma, mean dose: 66 Gy(RBE) (range, 54-72)	• Mean: 46 months (range, 4.5-126.5)	5-year overall survival • Chordoma: 89% • Chondrosarcoma: 75%	• CTCAE scoring • Acute effects ≥ Grade 3: 0% • Late effects ≥ Grade 3: 0%	• Subgroup data reported
Sabin (2013) NR	CNS embryonal tumors	N=8	• Total dose: 54 Gy	• Median: 3.9 months (mean, 4.2)	• Overall survival: 75%	• Severity of harms: NR	
Suneja (2013) Roberts Proton Center, University of Pennsylvania	CNS malignancies involving the brain	N=48	• Median dose: 5,400 cGy (RBE) (range, 4,500-6,300)	NR	NR	• CTCAE scoring • Fatigue ≥ Grade 3: 0% • Headache Grade 3: 2% • Insomnia ≥ Grade 3: 0% • Anorexia Grade 3: 4% • Nausea ≥ Grade 3: 0% • Vomiting ≥ Grade 3: 0% • Alopecia ≥ Grade 3: 0%	• Subgroup data reported
Yonekawa (2013) Massachusetts General Hospital, MA, USA	Diffuse choroidal hemangioma in Sturge-Weber syndrome	N=2	• Dose: 20 Gy (RBE)	• Mean: 18.5 months (range, 16-19)	• Overall survival: 100%	• No severe harms reported	
Childs (2012) Massachusetts General Hospital, MA, USA	Parameningeal rhabdomyosarcoma	N=17	• Median: 50.4 CGE (range, 50.4-56)	• Median: 5.0 years (range, 2-10.8)	• 5-year overall survival: 64%	• Severity of harms: NR	• Subgroup data reported

Table 12. Single-arm Case Series: Pediatric Conditions.

Author (Year) Study Site	Condition Type	Sample Size	Total PBT Dose	Follow-up	Survival Outcomes	Harms*	Notes
Hattangadi (2012a) Massachusetts General Hospital, MA, USA	Ewing sarcoma	N=2	• Mean: 56.7 CGE (range, 55.8-57.6)	• Mean: 4.8 years (range, 2-7.5)	• Overall survival: 50%	• Severity of harms: NR	
Hattangadi (2012b) Massachusetts General Hospital, MA, USA	High-risk neuroblastoma	N=9	• Mean: 26.9 Gy(RBE) (range, 18-36)	• Median: 38 months (11-70)	• Overall survival: 78%	• CTCAE scoring • Acute effects ≥ Grade 3: 0% • Severity of late effects: NR	
Kuhlthau (2012) Massachusetts General Hospital, MA, USA	Brain tumors (including medulloblastoma, ependymoma and glioma)	N=142	• PBT Dose <45 Gy_{RBE}: 4.2% ≥45 Gy_{RBE}: 95.8%	• Up to 5 years	NR	NR	• Subgroup data reported
Laffond (2012) Institut Curie, France	Benign craniopharyngioma	N=29	• Postoperative PBT: range, 54-55.2 Gy	• Mean: 6.2 months (range, 1.7 months – 19 years)	NR	NR	• 13/29 (45%) w/recurrent disease • Subgroup data reported
Rombi (2012) Massachusetts General Hospital, MA, USA	Ewing sarcoma	N=30	• Median total dose: 54 Gy (RBE) (range, 45-59.4) • Fraction: 1.8 Gy (RBE) daily	• Median: 38.4 months (range, 17.4 months-7.4 years)	• 3-year event-free survival: 60% • 3-year overall survival: 89%	• Scoring methodology: NR • Grade 3 skin reactions: 17% • Grade 3 fatigue: 3% • Severity of other effects: NR	• Subgroup data reported
Amsbaugh (2011) MD Anderson Cancer Center, TX, USA	Ependymoma of the spine	N=8	• Mean: 51.1 CGE (range, 45-54)	• Mean: 26 months (7-51)	• Overall survival: 100%	• CTCAE scores • Acute effects ≥ Grade 3: 0% • No late effects identified	• 3/8 (38%) w/recurrent disease

Table 12. Single-arm Case Series: Pediatric Conditions.

Author (Year) Study Site	Condition Type	Sample Size	Total PBT Dose	Follow-up	Survival Outcomes	Harms*	Notes
Chang (2011) National Cancer Center, Korea	Retinoblastoma	N=3	• Mean: 47 CGE (range, 46-50.4)	• Median: 24 weeks (range, 3-32)	• Overall survival: 100%	• Secondary enucleation: 66%	• 2/3 (67%) w/recurrent disease
Cotter (2011) Massachusetts General Hospital, MA, USA	Bladder/prostate rhabdomyosarcoma	N=7	• Mean: 42.9 CGE (range, 36-50.4)	• Median: 27 months (range 10-90)	• Overall survival: 100%	• Severity of harms: NR	
MacDonald (2011) Massachusetts General Hospital, MA, USA	CNS germinoma or nongerminomatous germ cell tumor	N=22	• Mean total dose (3D-CPT + other modalities): 44.0 Gy(RBE) (range, 30.6-57.6)	• Median: 28 months (range, 13-97)	• Overall survival: 100% • Overall progression-free survival: 95%	• Acute effects: NR • No severe late effects	
Moeller (2011) MD Anderson Cancer Center, TX, USA	Medulloblastoma	N=19	• Adjuvant PBT, total dose: 54.0 CGE	• Mean: 11 months (range, 8-16)	NR	• Brock ototoxicity scale • High grade (grade 3-4) ototoxicity: 5%	• Subgroup data reported
Oshiro (2011) University of Tsukuba, Japan	Nasopharyngeal carcinoma	N=2	• Mean: 65.3 GyE (range, 59.4-71.3)	• Mean: 5.3 years (4.5-6)	• Overall survival: 100%	• Scoring methodology: NR • Acute effects Grade 3, mucositis: 1 patient (50%) • Late effects ≥ Grade 3: 0%	
Vavvas (2010) Massachusetts General Hospital, MA, USA	Posterior unilateral choroidal or ciliary melanoma	N=17	NR	• Median: 16 years (5-25)	• Overall survival: 100%	• Acute effects: NR • Late effects Secondary enucleation: 0%	• Subgroup data reported
Gray (2009) Massachusetts General Hospital, MA, USA	Sinonasal Ewing sarcoma	N=2	• Mean: 57.6 GyE (range, 55.8-59.4)	NR	• Overall survival: 100%	• Severity of harms: NR	• All patients w/primary disease

Table 12. Single-arm Case Series: Pediatric Conditions.

Author (Year) Study Site	Condition Type	Sample Size	Total PBT Dose	Follow-up	Survival Outcomes	Harms*	Notes
Winkfield (2009) Massachusetts General Hospital, MA, USA	Benign craniopharyngioma	N=24	• Total dose: range, 52.2 – 54 GyE	• Median: 40.5 months (range, 6-78)	NR	NR	• 8/24 (33%) w/recurrent disease
Habrand (2008) Institut Curie, France	Skull base and cervical canal primary bony malignancies	N=30	• Postoperative PBT + photon (3% w/PBT only) • Mean total dose: 68.3 CGE (range, 54.6 – 71)	• Mean: 26.5 months (range, 5-102)	5-year overall survival: • Chondrosarcoma: 100% • Chordoma: 100% 5-year progression-free survival: • Chondrosarcoma: 81% • Chordoma: 77%	• CTCAE scores • Auditory (unilateral hypoacousia) Grade 3: 9% • Visual (unilateral blindness) Grade 3-4: 17%	• 1/30 (3%) w/recurrent disease • Subgroup data reported
MacDonald (2008) Massachusetts General Hospital, MA, USA	Intracranial ependymoma	N=17	• Median: 55.8 CGE (range, 52.2-59.4)	• Median: 26 months (range, 43 days-78 months)	• Overall survival: 89% • Progression-free survival: 80%	• No acute effects reported • Too early to report late effects	• 1/17 (6%) w/recurrent disease • Subgroup data reported
Rutz (2008) Paul Scherrer Institute, Switzerland	Chordoma and chondrosarcoma	N=10	• Chordoma, dose: 74.0 CGE • Chondrosarcoma, mean dose: 66 CGE (range, 63.2-68)	• Median: 36 months (range, 8-77)	• All patients alive at last follow-up	• CTCAE scores • Acute effects ≥ Grade 3: 0% • Late effects ≥ Grade 3: 0%	• 2/10 (20%) w/recurrent disease
Timmermann (2007) Paul Scherrer Institute, Switzerland	Sarcomas of the head, neck, parameningeal, paraspinal or pelvic region	N=16	• Median: 50 CGE (range, 46-61.2) (2 patients received additional photon therapy)	• Median: 18.6 months (4.3-70.8)	• 2-year overall survival: 69% • Progression-free survival: 72%	• RTOG/EORTC criteria • Acute effects Bone marrow (seen in patients w/parallel chemotherapy) Grade 3: 4/13 (31%) Grade 4: 3/13 (23%) • Severity of late effects: NR	• 2/16 (13%) w/recurrent disease

Table 12. Single-arm Case Series: Pediatric Conditions.

Author (Year) Study Site	Condition Type	Sample Size	Total PBT Dose	Follow-up	Survival Outcomes	Harms*	Notes
Hoch (2006) Massachusetts General Hospital, MA, USA	Skull-base chordoma	N=73	NR	• Mean: 7.25 years (range, 1-21)	• Overall survival: 81%	NR	
Luu (2006) Loma Linda University Medical Center, CA, USA	Benign craniopharyngioma	N=16	• Dose: range, 50.4-59.4 CGE	• Mean: 60.2 months (range, 12-121)	• Overall survival: 80%	• Severity of harms: NR	• 7/16 (44%) w/recurrent disease • Subgroup data reported
Noël (2003) Centre de Protonthérapie d'Orsay, France	Intracranial tumors (benign & malignant)	N=17	• PBT + photon Median PBT dose: 20 CGE (range, 9-31) Median photon dose: 40 Gy (24-54)	• Mean: 27 months (3-81)	• 36-month overall survival: 83%	• LENT/SOMA scoring • Severity of harms: NR	• 7/17 (41%) w/recurrent disease
Hug (2002a) Massachusetts General Hospital, MA, USA	Giant cell tumors of the skull base	N=4	• PBT + photon Mean dose: 59.0 CGE (range, 57.6-61.2)	• Mean: 52 months (37-69)	• Overall survival: 100%	• Severity of harms: NR	• 2/4 (50%) w/recurrent disease
Hug (2002c) Massachusetts General Hospital, MA, USA Loma Linda University Medical Center, CA, USA	Skull-base mesenchymal neoplasms	N=29	• Patients received PBT alone (45%) or PBT+photon (55%) • Total dose: range, 45-78.6 CGE	• Mean: 40 months (range, 13-92)	• 5-year overall survival: 56%	• Severity of harms: NR	• 14/29 (48%) w/recurrent disease • Subgroup data reported
Hug (2002b) Loma Linda University Medical Center, CA, USA	Low-grade astrocytoma	N=27	• Mean: 55.2 CGE (range, 50.4-63) (1 patient received PBT+photon)	• Mean: 39 months (range, 7-81)	• Overall survival: 85% • Progression-free survival: 78%	• LENT/SOMA scoring <u>Acute effects</u> • All were Grade 1-2 • Severity of late effects: NR	• 15/27 (56%) w/recurrent disease • Subgroup data reported
Hug (2000) Massachusetts General Hospital, MA, USA	Orbital rhabdomyosarcoma	N=2	• Mean: 53 CGE (range, 50-55)	• Mean: 36 months (range, 30-41)	• Overall survival: 100%	• Severity of harms: NR	

Table 12. Single-arm Case Series: Pediatric Conditions.

Author (Year) Study Site	Condition Type	Sample Size	Total PBT Dose	Follow-up	Survival Outcomes	Harms*	Notes
McAllister (1997) Loma Linda University Medical Center, CA, USA	Tumors in the cranium, skull base or in the orbit	N=28	• Patients received PBT alone (71%) or PBT+photon (29%) • PBT only, median: 54 CGE (range, 40-70.2) • PBT + photon Median photon: 36 Gy (range, 18-45) Median PBT: 18 CGE (range, 12.6-31.6)	• Median: 25 months (range, 7-49)	• Overall survival: 100% • Progression-free survival: 61%	• Severity of harms: NR	
Benk (1995) Massachusetts General Hospital, MA, USA	Skull-base or cervical spine chordomas	N=18	• Median: 69 CGE (range, 55.8-75.6)	• Median: 72 months (range, 19-120)	• 5-year overall survival: 68% • 5-year disease-free survival: 63%	• Severity of harms: NR	• Subgroup data reported

* Different versions of the CTCAE/Common Toxicity Criteria are utilized in the listed studies.
† Secondary enucleation rates reported for adverse effects not related to tumor recurrence.
CNS: central nervous system; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organization for Research and the Treatment of Cancer; LENT/SOMA: Late Effects of Normal Tissue – subjective, objective, management, analytic; N: number; NR: not reported; PBT: proton beam therapy; RTOG: Radiation Therapy Oncology Group

Table 13. Single-arm Case Series: Prostate Cancer.

Author (Year) Study Site	Condition Type	Sample Size	Total PBT Dose	Follow-up	Survival Outcomes	Harms*	Notes
Henderson (2013) University of Florida Proton Therapy Institute, FL, USA	Low- and intermediate-risk disease	N=171	PR-01 • Dose: 78 CGE PR-02 • Dose: 78-82 CGE	• Median: 60 months (range, 0-71)	• Overall survival: 91%	• CTCAE scoring • Acute/late effects Grade 3 GU: 3%	• Patients enrolled in PR-01 and PR-02
Kil (2013) University of Florida Proton Therapy Institute, FL, USA	Low- and intermediate-risk disease	N=228	• Low-risk dose: 70 CGE • Intermediate-risk dose: 70-72.5 CGE	• Median: 24 months	NR	NR	• Patient overlap w/Hoppe (2012) • Subgroup data reported
McGee (2013) University of Florida Proton Therapy Institute, FL, USA	Disease in patients w/large prostates (≥60 cm^3)	N=186	• Median: 78 CGE (range, 58-82)	• Median: 24 months	NR	• CTCAE scoring • Acute effects Grade 3 GU: 2% • Late effects Grade 3 GU: 6% Grade 3 GI: 0.5%	• Patient overlap w/Mendenhall (2012) • Subgroup data reported
Pugh (2013) MD Anderson Cancer Center, TX, USA	Localized, non-metastatic disease	N=291	• Dose: 76 Gy (RBE)	• At least 24 months	NR	• modified RTOG scoring • Acute/late effects ≥ Grade 3 GU: 0% Grade 3 GI: 0.3%	• All patients w/primary disease • Subgroup data reported
Valery (2013) University of Florida Proton Therapy Institute, FL, USA	Low-, intermediate- and high-risk disease	N=382	• Dose: ranging from 70-82 CGE	• Median: 48 months (range, 8-66)	• Overall survival: 94%	• Severity of harms: NR	• Patients enrolled in PR-01, PR-02, and PR-03
Coen (2012) Massachusetts General Hospital, MA, USA	Clinical stage T1c-T2b disease	N=95	• Dose: ranging from 74-79 GyE to 82 GyE	• Median: 37 months (range, 12-64)	NR	NR	• Patient overlap w/Coen (2011)
Hoppe (2012) University of Florida Proton Therapy Institute, FL, USA	Patients ≤60 years	N=262	• Dose: ranging from 70-80 CGE	• Median: 24 months (range, 6-53)	NR	NR	• Patient overlap w/Mendenhall (2012) • Subgroup data reported

Table 13. Single-arm Case Series: Prostate Cancer.

Author (Year) Study Site	Condition Type	Sample Size	Total PBT Dose	Follow-up	Survival Outcomes	Harms*	Notes
Johansson (2012) The Svedberg Laboratory, Uppsala, Sweden	Clinical stage T1b-T4N0M0 disease	N=265	• PBT + EBRT EBRT dose: 50 Gy PBT dose: 20 Gy	• Median: 57 months (range, 6-109)	<u>Overall survival</u> • 5-year: 89% • 8-year: 71%	• RTOG scoring • Acute effects: NR • Late effects Grade 3 GU: 7% Grade 4 GU: 2% Grade 3-4 GI: NR	• Subgroup data reported
Mendenhall (2012)† University of Florida Proton Therapy Institute, FL, USA	Low-risk disease	N=89	PR-01 • Dose: 78 CGE	• ≥ 24 months	<u>2-year</u> • Overall survival: 96% • Progression-free survival: 99% <u>2-year progression-free survival by protocol</u> • PR-01: 100% • PR-02: 99% • PR-03: 94%	• CTCAE scoring • Acute/late effects Grade 3 GU: 2% Grade 3 GI: 0.4%	• All patients w/primary disease • Subgroup data reported
Mendenhall (2012)† University of Florida Proton Therapy Institute, FL, USA	Intermediate-risk disease	N=82	PR-02 • Dose: 78-82 CGE				
Mendenhall (2012)† University of Florida Proton Therapy Institute, FL, USA	High-risk disease	N=40	PR-03 • Dose: 78 CGE (w/concomitant therapy)				
Nichols (2012) University of Florida Proton Therapy Institute, FL, USA	Low- and intermediate-risk disease	N=171	PR-01 • Dose: 78 CGE PR-02 • Dose: 78-82 CGE	• Up to 24 months	NR	NR	• Patients enrolled in PR-01 and PR-02 • Subgroup data reported
Coen (2011) Loma Linda University Medical Center, CA, USA Massachusetts General Hospital, MA, USA	Clinical stage T1c-T2b disease	N=85	• Dose: 82 GyE	• Median: 32 months (range, 2-51)	NR	• CTCAE & RTOG/EORTC scoring • Acute effects Grade 3 (GU, pain): 4% • Late effects Grade 3 GU: 8% Grade 3 GI: 1% Grade 4 GI: 1%	• All patients w/primary disease

Table 13. Single-arm Case Series: Prostate Cancer.

Author (Year) Study Site	Condition Type	Sample Size	Total PBT Dose	Follow-up	Survival Outcomes	Harms*	Notes
Nihei (2011) Multi-institutional (n=3), Japan	Stage II disease (clinical stage T1-T2N0M0)	N=151	• Dose: 74 GyE	• Median: 43 months (range, 3-62)	• Overall survival: 99%	• CTCAE scoring • Acute effects ≥ Grade 3: 0% • Late effects Grade 3 bladder: 1%	
Mayahara (2007) Hyogo Ion Beam Medical Center, Japan	Any clinical stage of disease	N=287	• Dose: 74 GyE	• At least 3 months	NR	• Common Toxicity Criteria • Acute effects Grade 3 GU: 1%	• Subgroup data reported
Nihei (2005) National Cancer Center East, Chiba, Japan	Clinical stage T1-3N0M0 disease	N=30	• PBT + photon Photon dose: 50 Gy PBT dose: 26 GyE	• Median: 30 months (range, 20-45)	• Overall survival: 100%	• Common Toxicity Criteria & RTOG/EORTC • No acute/late effects ≥ Grade 3	• Subgroup data reported
Rossi (2004) Loma Linda University Medical Center, CA, USA	Clinical stage T1-T2c disease	N=1038	• PBT + photon, dose: 75 CGE (38% of patients received PBT alone) Photon dose:45 Gy PBT dose: 30 CGE	• Median: 62 months (range, 1-128)	NR	NR	• Patient overlap w/Slater (2004), Slater (1999), Yonemoto (1997) • Subgroup data reported
Slater (2004) Loma Linda University Medical Center, CA, USA	Stage Ia-III disease (clinical stage T1-T3)	N=1255	• PBT + photon, dose: 75 CGE (42% of patients received PBT alone) Photon dose:45 Gy PBT dose: 30 CGE	• Median: 62 months (range, 1-132)	NR	• RTOG scoring • Acute effects Grade 3 GI/GU: <1% • Late effects Grade 3 GU: 1% Grade 3 GI: 0.2%	• Patient overlap w/ Rossi (2004), Slater (1999), Yonemoto (1997) • Subgroup data reported
Gardner (2002) Massachusetts General Hospital, MA, USA	Clinical stage T3-T4 disease	N=39	• PBT + photon, dose: 77.4 Gy Photon dose: 50.4 Gy PBT dose: 27 Gy	• Median: 157 months (range, 84-276)	NR	• RTOG/EORTC scoring w/incorporated measure for urinary incontinence (SOMA) • Acute effects: NR • Late effects Grade 3-4 GU: 21%	

Table 13. Single-arm Case Series: Prostate Cancer.

Author (Year) Study Site	Condition Type	Sample Size	Total PBT Dose	Follow-up	Survival Outcomes	Harms*	Notes
Slater (1999) Loma Linda University Medical Center, CA, USA	Stage T1-T2B disease	N=319	• PBT + photon, dose: 75 CGE (71% of patients received PBT alone) Photon dose:45 Gy PBT dose: 30 CGE	• Median: 43 months (range, 12-74)	5-year • Overall survival: 100% • Disease-free survival: 95%	• RTOG scoring • No acute/late effects ≥ Grade 3	• Patient overlap w/Rossi (2004), Slater (2004), Yonemoto (1997)
Yonemoto (1997) Loma Linda University Medical Center, CA, USA	Locally advanced disease, clinical stage T2b-T4	N=106	• PBT + photon, dose: 75 CGE Photon dose:45 Gy PBT dose: 30 CGE	• Median: 20 months (range, 10-30)	• Overall survival: 96%	• RTOG scoring • Acute effects: NR • Late effects ≥ Grade 3: 0%	• Patient overlap w/Rossi (2004), Slater (2004), Slater (1999)

* Different versions of the CTCAE/Common Toxicity Criteria are utilized in the listed studies.
† Mendenhall (2012) reported on 3 dosing protocols, based on level of disease risk. Separate results are reported where available.
CTCAE: Common Terminology Criteria for Adverse Events; EBRT: external-beam radiation therapy; EORTC: European Organization for Research and the Treatment of Cancer; GI: gastrointestinal; GU: genitourinary; LENT/SOMA: Late Effects of Normal Tissue – subjective, objective, management, analytic; N: number; NCI: National Cancer Institute; NR: not reported; PBT: proton beam therapy; RBE: relative biological effectiveness; RTOG: Radiation Therapy Oncology Group

Table 14. Single-arm Case Series: Soft Tissue Sarcomas.

Author (Year) Study Site	Condition Type	Sample Size	Total PBT Dose	Follow-up	Survival Outcomes	Harms	Notes
Yoon (2010) Massachusetts General Hospital, MA, USA	Retroperitoneal or pelvic soft-tissue sarcoma	N=28	• PBT ± IMRT, median: 50 Gy (range, 37.5-66.6) (12 patients received IOERT)	• Median: 33 months	• 3-year overall survival: 87%	• Severity of harms: NR	• 8/28 (29%) w/recurrent disease • Subgroup data reported
Weber (2007) Paul Scherrer Institute, Switzerland	Nonmetastatic soft-tissue sarcoma	N=13	• PBT ± photon, median: 69.4 CGE (range, 50.4-76)	• Median: 48 months (range, 19-101)	• 4-year overall survival: 83%	• CTCAE scoring • Acute effects: NR • Late effects Grade 3 brain necrosis: 8%	• 4/13 (31%) w/recurrent disease

CTCAE: Common Terminology Criteria for Adverse Events; IMRT: intensity-modulated radiation therapy; IOERT: intraoperative electron radiation therapy; N: number; NR: not reported; PBT: proton beam therapy

Table 15. Single-arm Case Series: Noncancerous Conditions.

Author (Year) Study Site	Condition Type	Sample Size	Total PBT Dose	Follow-up	Survival Outcomes	Harms	Notes
Nakai (2012) University of Tsukuba, Japan	Cerebral arteriovenous malformations	N=8	• Mean: 37.5 GyE (range, 24-46.2)	• Mean: 39 months (range, 18-84)	• Overall survival: 88%	• No reported acute effects • Severity of late effects: NR	
Slater (2012) Loma Linda University Medical Center, CA, USA	Benign cavernous sinus malignancies	N=72	• Median: 57 or 59 Gy	• Median: 74 months (range, 3-183)	• 5-year overall survival: 72%	• Severity of acute/late effects: NR	• Subgroup data reported
Halasz (2011) Massachusetts General Hospital, MA, USA	Benign meningiomas	N=50	• Median: 13 Gy (RBE) (range, 10-15.5)	• Median: 32 months (range, 6-133)	NR	• Severity of acute/late effects: NR	• Subgroup data reported
Hattangadi (2011) Massachusetts General Hospital, MA, USA	High-risk inoperable cerebral arteriovenous malformations	N=59	• Median: 16 Gy(RBE) (range, 12-28)	• Median: 56 months (range, 7-173)	• Overall survival: 81%	• CTCAE scoring • Acute effects ≥ Grade 3: 0% • Late effects ≥ Grade 3: 0%	
Ito (2011) University of Tsukuba, Japan	Arteriovenous malformation ≥30mm in diameter	N=11	• Mean: 25.3 GyE (range, 22-27.5)	• Median: 138 months (range, 81-198)	• Overall survival: 91%	• Severity of acute/late effects: NR	
Levy-Gabriel (2009) Institut Curie, France	Circumscribed choroidal hemangioma	N=71	• Dose: 20 CGE	• Median: 52 months (8-133)	• Overall survival: 100%	• Severity of acute/late effects: NR	• 9/71 (13%) w/failed previous laser therapy
Petit (2008) Massachusetts General Hospital, MA, USA	Refractory ACTH-producing pituitary adenoma	N=38	• Median: 20 CGE (range, 15-20)	• Median: 62 months (range, 20-136)	• Overall survival: 100%	• Severity of acute/late effects: NR	

Table 15. Single-arm Case Series: Noncancerous Conditions.

Author (Year) Study Site	Condition Type	Sample Size	Total PBT Dose	Follow-up	Survival Outcomes	Harms	Notes
Ronson (2006) Loma Linda University Medical Center, CA, USA	Pituitary adenoma	N=47	• Median: 54 CGE (range, 50.4-55.9)	• Median: 47 months (range, 6-139)	• Overall survival: 87%	• Severity of acute/late effects: NR	• 10/47 (21%) w/recurrent disease • Subgroup data reported
Noël (2005) Institut Curie, France	Intracranial meningioma	N=51	• PBT + photon, median: 60.6 CGE (range, 54-64)	• Median: 21 months (range, 1-90)	• 4-year overall survival: 100%	• LENT/SOMA scoring • Acute effects: NR • Late effects Grade 3 (hypophysis insufficiency, hearing loss): 4%	• 16/51 (31%) w/recurrent disease
Vernimmen (2005) iThemba LABS, South Africa	Intracranial arteriovenous malformations	N=64	• Mean: 27.5 Gy (range, 16.1-38.4)	• Median: 62 months	NR	• RTOG/EORTC scoring • Acute effects Grade 4 epilepsy: 3% • Late effects Grade 3-4 (epilepsy, neurologic deficits): 6%	
Silander (2004) University Hospital, Uppsala, Sweden	Cerebral arteriovenous malformations	N=26	• Dose: ranging from 16-25 Gy	• Median: 40 months (range, 33-62)	NR	• Severity of acute/late effects: NR	
Barker (2003) Massachusetts General Hospital, MA, USA	Cerebral arteriovenous malformations	N=1250	• Median: 10.5 Gy (range, 4-65)	• Median: 78 months (range, 1-302)	NR	• Severity of acute/late effects: NR	• Subgroup data reported

Table 15. Single-arm Case Series: Noncancerous Conditions.

Author (Year) Study Site	Condition Type	Sample Size	Total PBT Dose	Follow-up	Survival Outcomes	Harms	Notes
Weber (2003) Massachusetts General Hospital, MA, USA	Vestibular schwannoma	N=88	• Median: 12 CGE (range, 10-18)	• Median: 39 months (range, 12-103)	NR	• Hearing function, Gardner-Robertson scale • Facial nerve function, House-Brackmann scale • 7/21 (33%) retained functional hearing • Grade 4-5 facial nerve dysfunction: 6% • Severity of other late effects: NR	• Subgroup data reported
Vernimmen (2001)* National Accelerator Center, South Africa	Intracranial meningioma	N=18	• Mean: 20.3 CGE	• Mean: 40 months (range, 13-69)	• Overall survival: 100%	• Severity of acute/late effects: NR	
Vernimmen (2001)* National Accelerator Center, South Africa	Intracranial meningioma	N=5	• Dose: ranging from 54-61.6 CGE		• Overall survival: 100%	• No reported acute effects • Severity of late effects: NR	
Wenkel (2000) Massachusetts General Hospital, MA, USA	Recurrent, biopsied, or subtotally resected meningioma	N=46	• PBT + photon, median: 59 CGE (range, 53.1-74.1)	• Median: 53 months (range, 12-207)	<u>Overall survival</u> • 5-year: 93% • 10-year: 77%	• RTOG scoring • Acute effects Severe: 11% • Late effects Grade 3-4: 17%	• 29/46 (63%) w/recurrent disease
Gudjonsson (1999) University Hospital, Uppsala, Sweden	Skull-base meningioma	N=19	• Dose: 24 Gy	• ≥ 36 months	• Overall survival: 100% • Progression-free survival: 100%	• Severity of acute/late effects: NR	

Table 15. Single-arm Case Series: Noncancerous Conditions.

Author (Year) Study Site	Condition Type	Sample Size	Total PBT Dose	Follow-up	Survival Outcomes	Harms	Notes
Zografos (1998) Paul Scherrer Institute, Switzerland	Choroidal hemangioma	N=53	• Dose: ranging from 16.4 – 27.3 Gy	• Up to 108 months	NR	• Severity of acute/late effects: NR	
Hannouche (1997) Institut Curie, France	Circumscribed choroidal hemangioma	N=13	• Dose: 30 CGE	• Mean: 26 months (range, 9-48)	• Overall survival: 100%	• No reported acute/late effects	• 4/13 (31%) w/failed previous laser therapy

* Vernimmen (2001) reported on patients receiving different dosing protocols depending on meningioma location. Separate results reported where available.

ACTH: adrenocorticotropic hormone; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organization for Research and the Treatment of Cancer; LENT/SOMA: Late Effects of Normal Tissue – subjective, objective, management, analytic; N: number; NCI: National Cancer Institute; NR: not reported; PBT: proton beam therapy; RTOG: Radiation Therapy Oncology Group

Table 16. Single-arm Case Series: Mixed Conditions.

Author (Year) Study Site	Condition Type	Sample Size	Total PBT Dose	Follow-up	Survival Outcomes	Harms*	Notes
Barney (2014) MD Anderson Cancer Center, TX, USA	Medulloblastoma (38%); germ cell tumor (30%); pineoblastoma (14%)	N=50	• Median: 54 Gy (RBE) (range, 24-58.6)	• Median: 20.1 months (range, 0.3-59)	2-year • Overall survival: 96% • Progression-free survival: 82% 5-year • Overall survival: 84% • Progression-free survival: 68%	• RTOG scoring • Acute effects Grade 3 ototoxicity: 4% Grade 3 leukopenia: 9% Grade 3 thrombocytopenia: 2% Grade 4 thrombocytopenia: 2%	
Combs (2013a) Heidelberg Ion Therapy Center, Germany	Low-grade meningioma (27%); atypical/anaplastic meningioma (14%); low-grade glioma (12%); glioblastoma (11%)	N=260	NR • Patients received PBT (67%) or carbon ± photon therapy (33%)	• Median: 12 months (range, 2-39)	NR	• CTCAE scoring • No acute/late effects ≥ Grade 3	
Combs (2013b) Heidelberg Ion Therapy Center, Germany	Benign, atypical, and anaplastic meningiomas	N=70	• PBT (54%) or carbon ± photon (46%) • PBT dose: ranging from 52.2-57.6 GyE	• Median: 6 months (range, 2-22)	• Overall survival: 100%	• Severity of harms: NR	• Some patients w/recurrent disease, % not reported
Schneider (2013) Paul Scherrer Institute, Switzerland	Mixed paraspinal and retroperitoneal neoplasms	N=31	• Mean: 72.3 Gy (RBE) (range, 64-76)	• Mean: 59 months (range, 19-125)	• 3-year overall survival: 84% • 5-year overall survival: 72%	• CTCAE scoring • Acute effects Grade 3 skin: 13% • Late effects Grade 3 non-GI: 6% Grade 3 skin: 3% Grade 3 bone necrosis: 3%	
Tuan (2013) Italian National Hadrontherapy Center for Cancer, Italy	Chordoma and chondrosarcoma of the skull base and sacral/ paraspinal sites	N=21	• Median: 74 GyE (range, 70-74)	• Mean: 5 months (range, 1-12)	NR	• CTCAE scoring • Acute effects ≥ Grade 3: 0% MMSE scoring • No significant changes occurred from start to finish of PBT	• Preliminary data, including quality-of-life outcomes, reported in Srivastava (2013) • 5/21 (24%) w/recurrent disease

Table 16. Single-arm Case Series: Mixed Conditions.

Author (Year) Study Site	Condition Type	Sample Size	Total PBT Dose	Follow-up	Survival Outcomes	Harms	Notes
Weber (2012) Paul Scherrer Institute, Switzerland	Benign, atypical, and anaplastic meningiomas	N=39	• Median: 56 Gy(RBE) (range, 52.2-66.6)	• Median: 55 months (range, 6-147)	• 5-year overall survival: 82%	• CTCAE & RTOG scoring • Acute effects ≥ Grade 3: 0% • Late effects Grade 3 brain necrosis: 8% Grade 4 optic neuropathy: 5%	• Subgroup data reported
Boskos (2009) Centre de Protonthérapie d'Orsay, France	Atypical and malignant meningiomas	N=24	• PBT + photon, median: 68 CGE	• Median: 32 months (range, 1-72)	Overall survival • 1-year: 100% • 2-year: 96% • 4-year: 65% • 8-year: 43%	• No reported acute effects • Severity of late effects: NR	• Potential patient overlap w/Noël (2002) • Subgroup data reported
DeLaney (2009) Massachusetts General Hospital, MA, USA	Skull-base and paraspinal tumors (chordoma, 58%; chondrosarcoma, 28%)	N=50	• Median: 76.6 (range, 59.4-77.4)	• Median: 48 months (range, 37-124)	Overall survival • 1-year: 98% • 3-year: 87% • 5-year: 87%	• CTCAE scoring • Acute effects Grade 3 fracture: 2% • Late effects Grade 3 neuropathy: 4% Grade 3 fracture: 2% Grade 3 GU: 2% Grade 3 GI: 2%	• Subgroup data reported
Pieters (2006) Massachusetts General Hospital, MA, USA	Tumors of the retroperitoneum, paravertebral areas, lumbar and sacral vertebral bodies	N=62	• Median: 65.8 CGE (range, 31.9-85.1)	• Median: 87 months (range,14-217)	Disease-free survival • 5-year: 66% • 10-year: 53%	• LENT scoring •Acute effects: NR • Late effects Grade 3 neurologic toxicity: 3% Grade 4 neurologic toxicity: 6%	• Subgroup data reported
Noël (2002) Centre de Protonthérapie d'Orsay, France	Atypical/malignant and benign meningiomas	N=17	• PBT + photon, median: 61 CGE (range, 25-69) (1 patient w/PBT alone)	• Median: 37 months (range, 17-60)	• 4-year overall survival: 89%	• Severity of harms: NR	

Table 16. Single-arm Case Series: Mixed Conditions.

Author (Year) Study Site	Condition Type	Sample Size	Total PBT Dose	Follow-up	Survival Outcomes	Harms	Notes
Pai (2001) Massachusetts General Hospital, MA, USA	Neoplasms of the skull base, not associated w/the pituitary gland or hypothalamus (chondrosarcoma, 50%, chordoma, 43%, benign meningioma, 4%)	N=107	• Median: 68.4 CGE (range, 55.8-79)	• Median: 66 months	Overall survival • 5-year: 96% • 10-year 87%	• Severity of harms: NR	• Subgroup data reported

* Different versions of the CTCAE/Common Toxicity Criteria are utilized in the listed studies.
CTCAE: Common Terminology Criteria for Adverse Events; GI: gastrointestinal; GU: genitourinary; LENT/SOMA: Late Effects of Normal Tissue – subjective, objective, management, analytic; MMSE: Mini Mental Status Exam; N: number; NCI: National Cancer Institute; NR: not reported; PBT: proton beam therapy; RBE: relative biological effectiveness; RTOG: Radiation Therapy Oncology Group

Table 17. Single-arm Case Series: Bladder Cancers.

Author (Year) Study Site	Condition Type	Sample Size	Total PBT Dose	Follow-up	Survival Outcomes	Harms	Notes
Hata (2006) University of Tsukuba, Japan	Invasive bladder cancer, T2-T3N0M0	N=23	• Dose: 33 Gy	NR	5-year • Overall survival: 61% • Disease-free survival: 50%	• CTCAE & LENT/SOMA scoring • Harms reported for entire patient population, including those without PBT	• Subgroup data reported

CTCAE: Common Terminology Criteria for Adverse Events; LENT/SOMA: Late Effects of Normal Tissue – subjective, objective, management, analytic; N: number; NR: not reported; PBT: proton beam therapy

Table 18. Single-arm Case Series: Skin Cancers.

Author (Year) Study Site	Condition Type	Sample Size	Total PBT Dose	Follow-up	Survival Outcomes	Harms	Notes
Umebayashi (1994) University of Tsukuba, Japan	Skin carcinomas	n=12	• Mean: 71.1 Gy (range, 51-99.2)	• Up to 84 months	• Overall survival: 75%	• Severity of harms: NR	

N: number; NR: not reported