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Comparative Effectiveness of Proton Irradiation Treatment

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PREFACE

Quality Enhancement Research Initiative's (QUERI) Evidence-based Synthesis Program (ESP) was established to provide timely and accurate syntheses of targeted healthcare topics of particular importance to Veterans Affairs (VA) clinicians, managers and policymakers as they work to improve the health and healthcare of Veterans. The ESP disseminates these reports throughout the VA, and some evidence syntheses inform the clinical guidelines of large professional organizations.

QUERI provides funding for four ESP Centers and each Center has an active university affiliation. The ESP Centers generate evidence syntheses on important clinical practice topics, and these reports help:

- develop clinical policies informed by evidence;
- guide the implementation of effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures; and
- set the direction for future research to address gaps in clinical knowledge.

In 2009, the ESP Coordinating Center was created to expand the capacity of HSR&D Central Office and the four ESP sites by developing and maintaining program processes. In addition, the Center established a Steering Committee comprised of QUERI field-based investigators, VA Patient Care Services, Office of Quality and Performance, and Veterans Integrated Service Networks (VISN) Clinical Management Officers. The Steering Committee provides program oversight, guides strategic planning, coordinates dissemination activities, and develops collaborations with VA leadership to identify new ESP topics of importance to Veterans and the VA healthcare system.

Comments on this evidence report are welcome and can be sent to Nicole Floyd, ESP Coordinating Center Program Manager, at Nicole.Floyd@va.gov.

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EXECUTIVE SUMMARY

BACKGROUND

Maximizing target tumor dose while minimizing healthy tissue damage continues to be a challenge in radiation therapy. Because of its appealing dosimetric characteristics, proton beam therapy (PBT) has held the clinical promise of allowing for higher doses of radiation to be delivered more safely, especially for ocular, skull base, and spinal tumors that require exceptional precision. But the role of protons is less clear for more common tumors, like prostate, where their dosimetric advantages may be diminished and for which intensity-modulated radiation therapy (IMRT) can now safely deliver optimally high radiation doses.

To help consider the increased number of offers from University Affiliates to provide contracted off-site proton irradiation therapy, the VA Radiation Oncology Program requested that the Evidence-based Synthesis Program Coordinating Center (ESP CC) synthesize the most recent literature on the comparative effectiveness of PBT in various cancers. This report of that synthesis focuses on the following questions:

How does PBT compare with conventional X-ray-based external beam treatments and state-of-the-art therapies with regard to benefits and harms for both new patients and those who have locally recurrent tumors after irradiation?

How do the comparative effects of proton and photon beam therapies differ according to variation in tumor motion?

METHODS

Our research librarian searched MEDLINE® (via PubMed®), the Cochrane Clinical Register of Controlled Trials, and ClinicalTrials.gov using the terms “proton beam” and “cancer” to identify articles relevant to the key questions. We also hand-searched reference lists, consulted experts, requested information from proton therapy system manufacturers and centers, and searched ClinicalTrials.gov.

We selected studies that compared benefits (survival, quality of life, functional capacity, local tumor control, delivery of planned chemotherapy and radiation regimens) and harms (toxicity and secondary malignancies) for PBT versus other modalities in adults with any cancer type (except ocular). We used standardized methods to assess internal validity and the overall strength of evidence for each outcome.

RESULTS

We reviewed a total of 2,774 citations. From these, we included 25 relevant primary comparative studies and 6 systematic reviews. Requests to manufacturers and proton beam facilities did not identify any additional published or unpublished comparative studies, but only 6 manufacturers affirmed they weren’t aware of any additional studies.

Most existing systematic reviews are outdated, as their literature searches were conducted prior to the publication of most of the comparative studies. The 2014 review produced by the Institute

for Clinical and Economic Review (ICER)[1] for the Washington State Health Care Authority Health Technology Assessment Program (HTA) included 22 of the 25 comparative studies. The ICER review was useful for its accurate data abstraction, but we couldn't rely on its conclusions.

COMPARATIVE EFFECTIVENESS OF PBT (KEY QUESTIONS 1, 2, & 4)

Breast

There is low-strength evidence of comparable 7-year cumulative local recurrence for single field PBT versus photon-based 3D conformal accelerated partial-breast irradiation for patients with stage I breast cancer, but various 7-year skin toxicities were more common in the proton therapy group (range, increased from 15-28% to 54-90%). However, there was no difference in patients' ratings of good or excellent for 7-year overall cosmetic outcomes or in local failure rates. This evidence came from one fair-quality prospective trial of 98 patients with stage I breast cancer treated between October 2003 and April 2006 at Massachusetts General Hospital.[2]

Esophageal

There is low-strength evidence that, when used in trimodal therapy (neoadjuvant chemoradiation followed by surgical resection), IMRT and proton beam have comparable risk of postoperative pulmonary complications (OR: 2.23; 95% CI: 0.86-5.75) and GI complications (OR: 1.02; 95% CI: 0.47-2.25), 3-dimensional conformal radiation therapy (3D-CRT) and proton beam have comparable risk of GI complications (OR: 2.31; 95% CI: 0.69-7.74; 28.4% vs 18.1), but that 3D-CRT has a higher risk than proton beam of pulmonary complications (OR: 9.13; 95% CI: 1.83-45.42; 30.3% vs 13.9%). When given alone, there is low-strength evidence that proton therapy is associated with a higher risk of acute pneumonitis compared with IMRT/3D-CRT (33% vs 15%; P=.04).

Medulloblastoma

There is low-strength evidence that PBT 54.6 GyE and photon therapy 52.9 Gy have comparable 2-year overall and progression-free survival, proportion of patients with treatment breaks, and locoregional failure, but some 1-month toxicities were less common in the proton beam therapy group, including medical management of esophagitis (5% vs 57%; P<.001), > 5% weight loss (16% vs 64%; P=.004), and Grade ≥ 2 nausea/vomiting (26% vs 71%; P=.004). This evidence came from a fair-quality retrospective cohort study of 40 adults with medulloblastoma treated at the MD Anderson Cancer Center from 2003 to 2011.[3]

Non-small cell lung cancer

In patients with locally-advanced NSCLC, there is low-strength evidence that, even at a higher dose (74 Gy), acute risk of severe esophagitis (grade ≥ 3) at 6 months for PBT is similar to 3D-CRT 63 Gy, but lower than with IMRT 63 Gy (6% vs 28%; P<.0001).[4] This evidence came from one cohort study of 652 patients with NSCLC, mostly clinical stage IIIA-B and mean age of 66 years, who were treated at MD Anderson Cancer Center between 2000 and 2008. Evidence on survival and 15-17 month toxicity in a subgroup of those patients given concurrent chemotherapy was insufficient to draw conclusions. There is also insufficient evidence to draw conclusions about proton-based stereotactic ablative therapy for early-stage lung cancer compared with photon-based stereotactic ablative therapy.

Prostate

Table 1 summarizes the numbers and types of comparative studies and our conclusions for each different comparison of PBT to IMRT, 3D-CRT, brachytherapy, and conventional photon therapy, respectively.

Table 1. Conclusions for Comparative Studies in Prostate Cancer

Comparator	Benefits (Strength of Evidence Grade)	Harms (Strength of Evidence Grade)
PBT vs IMRT	Similar Quality of Life (QOL) (low SOE): 2 historically-controlled cohorts (N=1695):[5,6]	Transiently lower GU toxicity at 0-6 months for PBT (low SOE),[7] but similar GI and GU toxicity at 12-24 months (low to moderate),[7,8] and increased GI toxicity with PBT at 4-5 years (low SOE): 4 retrospective cohorts [8-10] N=34,185
PBT vs 3D-CRT	Similar QOL (insufficient SOE), but survival vs 3D-CRT remains unknown: 1 historically-controlled cohort[5]; N=218	Increased acute GI toxicity with PBT (low SOE): 1 retrospective cohort[9]; N=NR
PBT vs brachytherapy	Similar 8-yr survival and distant metastasis (low SOE): 1 historically-controlled cohort[11]; N=282	No evidence
PBT+photon vs photon alone	Similar overall 5-8 year survival and QOL (low SOE): (1 RCT, 2 cohort studies; N=567) [12-14]	Increased 8-year rectal bleeding and urethral stricture (low SOE): 1 RCT[14]; N=202

Spinal cord glioma

There is low-strength evidence that use of PBT may be disadvantageous for highly infiltrative tumors such as intermedullary spinal cord gliomas, as demonstrated by a reduced chance of 5-year overall survival (photon vs proton, aHR: 55.82; 95% CI: 1.34-2316.8).[15] This conclusion is based on one retrospective cohort study of 32 patients treated for intramedullary gliomas at Massachusetts General Hospital with either PBT (N=10) or IMRT (N=22) at an average dose of 51 Gy in 1.8 median daily fractions over 29 treatments.

Mixed cancer types – secondary malignancies

There is insufficient evidence to draw conclusions about how PBT compares to other radiation modalities in the risk of secondary malignancy. While secondary cancer risk for PBT patients was half that of photon patients in a retrospective cohort of patients with a variety of non-metastatic cancers, this study had numerous methodological limitations.[16]

Other cancer types

Although we found comparative studies in giant cell tumors of the bone, head and neck cancer, uveal hemangiomas, and meningiomas, they provided insufficient evidence for drawing conclusions.

KEY QUESTION 3: PATIENTS WITH LOCAL RECURRENCES

There is insufficient evidence to draw conclusions about the comparative effects of PBT versus other radiation modalities among patients with recurrent tumors. We identified 2 comparative studies on recurrent tumors, one among patients with recurrent malignant brain tumors[17] and one among patients with recurrent liver cancer,[18] but both studies were rated poor quality due to their failure to account for potentially important confounding.

KEY QUESTION 4A: EFFECTS OF TUMOR MOTION VARIABILITY

There is insufficient evidence to determine how the comparative effects of proton and photon beam therapies differ according to variation in tumor motion. Although dosimetric studies comparing methods of accounting for respiratory motion in treatment planning report that 4-dimensional computed tomography (4DCT) imaging decreases doses to normal structures compared with other multiphase,[19] free-breathing,[20] or 3-dimensional computed tomography (3DCT) imaging,[21] how this translates to clinical outcomes is not clear. We did not identify any studies that evaluated clinical outcomes of interest based on variability in tumor motion, imaging and planning methods used to account for respiratory motion, or quality assurance standards.

DISCUSSION

For the cancer sites and types reviewed here, there are no reliable data from long-term randomized trials on survival, quality of life, or functional capacity of patients who underwent PBT compared with any other modality. We could not fully assess the overall net health benefit of proton beam therapy versus its comparators because comparative observational studies did not consistently report many outcomes of greatest interest. Comparative risk of secondary malignancies was only evaluated by one poor-quality retrospective cohort study of non-metastatic cancer patients treated with PBT or photon modalities for a variety of cancers.[16] Ability to deliver planned treatments was only reported by one small retrospective cohort study.[3] No studies reported functional capacity outcomes or overall severe late toxicity. Table 2 summarizes the key findings on comparative benefits and harms that are supported by low-strength evidence. Although we found comparative studies in giant cell tumors, head and neck cancer, uveal hemangiomas, and meningiomas, they provided insufficient evidence for drawing conclusions. There is insufficient evidence to draw conclusions about the comparative effects of PBT versus other radiation modalities among patients with recurrent tumors or how the comparative effects of proton and photon beam therapies differ according to variation in tumor motion.

Table 2. Key Findings Supported by Low-strength Evidence

Cancer Type		Results (Low Strength of Evidence)	Studies*
Breast	↑	N/A	one fair prospective study (N=98)
	=	Long-term self-reported cosmetic outcomes and local failure rate	
	↓	Increased skin toxicity for accelerated partial breast irradiation when delivered in single-field: 54-90% (PBT) vs 15-28% (3D-CRT)	
Esophageal	↑	Lower 30-day post-op pulmonary complications when given as trimodal therapy (OR: 9.13 (3D-CRT vs PBT))	2 fair studies (N=519)
	=	When given as trimodal therapy, IMRT and proton beam have similar risk of postoperative pulmonary complications (OR: 2.23; 95% CI: 0.86-5.75) and GI complications (OR: 1.02; 95% CI: 0.47-2.25) and 3D-CRT and proton beam have comparable risk of GI complications (OR: 2.31; 95% CI: 0.69-7.74),	
	↓	Acute Pneumonitis: 33% (PBT) vs 15% (IMRT/3D-CRT), P=.04	
Medullo-blastoma	↑	1-month medical management of esophagitis: 5% (PBT) vs 57% (photon), P<.001; > 5% weight loss: 16% (PBT) vs 64% (photon), P=.004; Grade ≥ 2 nausea/vomiting: 26% (PBT) vs 71% (photon), P=.004	one fair study (N=40)
	=	2-year overall and progression-free survival, proportion of patients with treatment breaks, and locoregional failure	
	↓	N/A	
NSCLC	↑	6-month severe esophagitis (grade ≥ 3) in locally advanced NSCLC: 6% (PBT) vs 28% (IMRT), P<.0001	one fair study (N=652)
	=	6-month severe esophagitis (grade ≥ 3) in locally advanced NSCLC: 6% (PBT) vs 8% (3D-CRT), P=.42	
	↓	N/A	
Prostate	↑	GU toxicity at 0-6 months: PBT=5.9% vs IMRT=9.5%; OR (PBT vs IMRT): 0.60; 95% CI: 0.38-0.96	vs IMRT: 5 fair-poor (N=8987) vs 3D-CRT: 2 fair-poor (N=19281) vs brachytherapy: 1 fair (N=282) PBT+photon vs photon alone: 3 fair-poor, 2 prospective (N=567)
	=	Urinary incontinence: 3.3 per 100 person-years (PBT) vs 3.7 per 100 person-years (3D-CRT) Erectile dysfunction: 7.4 per 100 person-years (PBT) vs 5.3 per 100 person-years (3D-CRT) Similar 2-year QOL vs IMRT/3D-CRT Similar 8-year overall survival and freedom from distant metastasis vs brachytherapy Similar 8-year survival, QOL, urethral stricture, gross hematuria (PBT+photon vs photon alone) Similar 6-month GI toxicity and 12-24 month GI/GU toxicity vs IMRT	

Cancer Type		Results (Low Strength of Evidence)	Studies*
Prostate (continued)	↓	Any GI toxicity after 5 years: 20.1 per 1,000 patient-years (PBT) vs 8.3 per 1,000 patient-years (IMRT); HR (PBT vs IMRT): 3.32 (95% CI: 2.12-5.20); GI toxicity at 46-50 months: procedures: 18% (IMRT) vs 21% (PBT); RR (IMRT vs PBT): 0.82 (0.70-0.97); diagnoses: 12% (IMRT) vs 18% (PBT); RR (IMRT vs PBT): 0.66 (95% CI: 0.55-0.79) Increased 1-year GI toxicity: aHR (PBT vs 3D-CRT): 2.13 (95% CI: 1.45-3.13) 8-year rectal bleeding: 32% (PBT+photon) vs 12% (photon alone); P=.002	
Spinal cord glioma	↑	N/A	one cohort study (N=32)
	=	N/A	
	↓	5-year survival: aHR (photon vs proton): 55.82; 95% CI: 1.34-2316.8	

↑ = PBT advantage; = = comparable outcome; ↓ = PBT increased harm; *retrospective unless otherwise noted.

The main limitations of the comparative studies were that they (1) were retrospective and some used historical control groups for the photon-based comparator groups, (2) potentially gave proton beam groups an unfair advantage by comparing them to photon-based groups with poorer prognostic profiles without accounting for the important differences, (3) lacked data on radiation dose and field size, (4) could not reliably differentiate toxicity grade, (5) did not measure many outcomes of greatest interest, including recurrence, ability to deliver planned chemotherapy and radiation regimens, functional capacity, overall severe late toxicity, and secondary malignancies, and (6) may have limited applicability to current practices and across all 14 available facilities, since they mainly came from only 3 proton facilities and involved patients treated between 1991 and 2003. The biggest gaps in evidence include the lack of assessment of many important outcomes including recurrence, ability to deliver planned chemotherapy and radiation regimens, functional capacity, overall severe late toxicity, and secondary malignancies. Also, although there are many studies that have compared the dosimetric impact between different methods of accounting for tumor motion in treatment planning, including 4DCT imaging, multiphase, free-breathing, or 3DCT imaging, we found no studies of how they compare in clinical outcomes.

CONCLUSION

Despite the common claim that the advantage of proton beam therapy is self-evident, comparative studies have not demonstrated any common clinical situations in which proton beam therapy has an important clinical advantage over photon radiotherapy modalities on meaningful *long-term* health outcomes, but have uncovered low-strength evidence of the potential for increased late toxicity compared with IMRT and 3D-CRT for breast, esophageal, prostate, and spinal cord glioma cancers. Existing comparative studies have numerous methodological deficiencies that limited our confidence in their findings, and their findings may have limited applicability across all US proton beam facilities. Although numerous randomized controlled trials are underway that carry the promise of improved toxicity measurement, it is unclear

whether they will fully address gaps in evidence on other important outcomes including recurrence, ability to deliver planned chemotherapy and radiation regimens, functional capacity, overall severe late toxicity, and secondary malignancies. Because this is still a rapidly evolving field, with ongoing efforts to improve techniques and reduce costs, this review may need frequent updating to keep up-to-date with emerging research.

ABBREVIATIONS LIST

3D-CRT	3-dimensional conformal radiation therapy
3DCT	3-dimensional computed tomography
4DCT	4-dimensional computed tomography
ACR	American College of Radiology
ADT	Androgen deprivation therapy
aHR	Adjusted hazard ratio
AHRQ	Agency for Health Research and Quality
APBI	Accelerated partial breast irradiation
aOR	Adjusted odds ratio
AMSTAR	A Measurement Tool to Assess Systematic Reviews
ASTRO	The American Society for Radiation Oncology
BCBS	Blue Cross Blue Shield
CER	Comparative effectiveness research
CI	Confidence interval
CGE	Cobalt gray equivalent
CNS	Central nervous system
CRT	Conventional radiotherapy
CSI	Craniospinal irradiation
CT	Computed tomography
CTAF	California Technology Assessment Forum
ECRI	Emergency Care Research Institute
EPIC	Expanded Prostate Cancer Index Composite
ESP CC	Evidence-based Synthesis Program Coordinating Center
FDA	Food and Drug Administration
FDG	Fluorodeoxyglucose
GI	Gastrointestinal
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GU	Genitourinary
Gy	Gray
GyE	Gray equivalent
HR	Hazard ratio
HTA	Health Technology Assessment Program
ICER	Institute for Clinical and Economic Review
IMRT	Intensity-modulated radiation therapy
NICE	National Institute for Health and Care Excellence
NSD	No significant difference
NR	Not reported
NRC	Nuclear Regulatory Commission
NSCLC	Non-small cell lung cancer
OR	Odds ratio
PBT	Proton Beam Therapy
PCSI	Prostate Cancer Symptom Indices

PET	Positron emission tomography
PROST-QA	Prostate Cancer Outcomes and Satisfaction with Treatment Quality Assessment
PSA	Prostate-specific antigen
QOL	Quality of life
QUERI	Quality Enhancement Research Initiative
RBE	Relative biological effectiveness
RCT	Randomized control trial
RR	Relative risk
SBRT	Stereotactic body radiotherapy
SEER	Surveillance Epidemiology and End Results
SOE	Strength of evidence
TEC	Technology Evaluation Center
UA	University Affiliates
VA TAP	Veterans Affairs Technology Assessment Program
VHA	Veterans Health Administration

EVIDENCE REPORT

INTRODUCTION

The Veterans Health Administration's (VHA) current policy on proton therapy is that it "will not be deemed appropriate as routine therapy for organ-confined adenocarcinoma of the prostate." According to a May 2012 Department of Veterans Affairs (VA) Memorandum on the appropriate use of proton beam therapy for radiation therapy treatment, the reason for this is that although "it has become clear that proton therapy improves the safety of radiation delivery to tumors requiring exceptionally precise treatment," such as ocular melanomas, sacral and base of skull chordomas, and para-spinal primitive neuroectodermal tumors, "less certain are the advantages of proton therapy for tumors which can be treated successfully with photon therapy or other treatment modalities, such as by resection." However, the VHA continues to evaluate the possibility of contracting with University Affiliates (UA) to provide proton irradiation as part of off-site radiation therapy care. To help inform their decision to support or not support a proton therapy center for Veterans, the VHA is interested in whether any evidence has emerged that identifies any additional tumor sites and presentations as candidates for improved outcomes following proton irradiation. Therefore, the VHA National Radiation Oncology Program Office (10P4H) requested that the VA Evidence-based Synthesis Program Coordinating Center (ESP CC) conduct an evidence review to examine the benefits and harms of proton irradiation treatment compared to other available conventional and state-of-the-art radiation treatment modalities for a variety of cancer types.

BACKGROUND

Radiation therapy harms both malignant and healthy tissues and higher absorbed radiation dose increases cellular damage. Administering sufficient radiation to the target tumor while sparing adjacent healthy tissue continues to be a challenge in radiation therapy. For external beam radiotherapy, maximizing the dose to the target tumor and minimizing healthy tissue damage is achieved by (1) delivering beams of radiation via paths that spare critical and vulnerable tissues, (2) using multiple beams that intersect at the tumor site, avoiding undue exposure in other tissue, and (3) delivering radiation in smaller doses over successive sessions allowing healthy tissue to recover between treatments.[22] The most common radiotherapy options use these methods to varying degrees.

Several forms of radiotherapy modalities are available, which vary in the type of beams used and their delivery methods. Brachytherapy is a form of internal radiation that involves implanting encapsulated radioactive sources within or adjacent to tumors. These sources deposit beta radiation or alpha particles in immediately neighboring tissue and so deliver very little radiation to healthy tissues. However, brachytherapy has very specific indications and is not used for many cancers.[23]Among the many types of external radiotherapy modalities available, photon beams are still the most widely used, including 3-dimensional conformal radiation therapy (3D-CRT), intensity-modulated radiation therapy (IMRT), and tomotherapy. Since the peak dose of radiation from a photon beam is deposited near the entrance to tissue, different methods of delivering photon beams have been developed to maximize the dose to the target tumor and minimize the dose to healthy tissues. IMRT is one of the most advanced methods of delivering

high-dose radiation with photons. IMRT reduces radiation to normal tissue by splitting the overall dose across multiple fields of small volumes coming from different directions that are custom tailored to each unique tumor shape. Other advances in IMRT include image-guided radiation therapy, which may improve the precision of dose delivery, and volumetric modulated arc therapy, which reduces the time needed to deliver each treatment.

Less widely used are heavier particle beams, such as protons and carbon ions. Currently only proton beam therapy (PBT) has been cleared by the US Food and Drug Administration (FDA) for use in the US. Compared to photons, protons have inherently different energy distribution patterns that can potentially spare more healthy tissue in front of and behind the tumor target. Tissue in the proton beam's path to the target tumor receives a small radiation dose, tissue surrounding the target receives even less radiation, and the maximum dose of radiation can be directed to the tumor target.[24,25] Because of its theoretical dosimetric advantages, proton therapy has held the clinical promise of allowing for higher doses of radiation to be delivered more safely. However, protons' exit dose advantage has been shown to deteriorate with increased beam path distances.[26] Therefore, there may be less opportunity for proton beam therapy to improve clinical outcomes for deep-seated tumors, like prostate, for which IMRT can now safely deliver optimally high radiation doses. Further, compared to photon radiation, dose delivery in PBT is more sensitive to tissue density and heterogeneity.[25,26] Because of this sensitivity, organ motion can have a greater impact on PBT dose delivery compared with photon radiation.[26]

Published coverage policies consider PBT medically necessary only for cancers requiring exceptional precision in dose delivery (see Appendix A). The American Society for Radiation Oncology (ASTRO) supports the use of PBT for ocular tumors, tumors that approach or are located at the base of the skull, certain tumors of the spine, primary hepatocellular cancer treated in a hypofractionated regimen, solid tumors in children treated with curative intent, and in patients with genetic syndromes for whom minimizing the total volume of radiation is crucial.[27] For prostate cancer, ASTRO recommends "Proton beam therapy for primary treatment… should only be performed within the context of a prospective clinical trial or registry."[27] With the exception of hepatocellular cancer, which is not explicitly covered by other organizations, other coverage policies generally agree with ASTRO's conclusions. PBT for ocular, skull-base, and pediatric tumors is usually considered medically necessary, while PBT for more common cancers, such as lung cancer and prostate cancer, is usually considered not medically necessary and therefore is not covered. Even so, treatment of common cancers with PBT is widespread. In a study of Medicare patients receiving proton beam therapy between 2006 and 2009, the most common diagnosis on Medicare claims was prostate cancer (69.9%), followed by lung (7.1%), eye (6.6%), and other or unknown conditions including leukemia, lymphoma, skin, and unspecified sites (6.5%).[28]

In 1988, the FDA granted 510(k) marketing clearance to the PBT center and system at the Loma Linda University Proton Beam Therapy System (K872369). Currently, 6 manufacturers produce proton therapy systems that have received marketing clearance under the 510(k) process: Hitachi, Ltd., Mitsubishi Electric Inc., IBA Inc., Varian Medical Systems Inc., Sumitomo Inc., and Mevion Medical Systems, Inc. Proton therapy accelerators that are designed and built on-site are not subject to FDA premarket approval processes.[24]

According to the National Association of Proton Therapy, there are 14 PBT centers in operation in the United States with 10 additional centers under construction (http://proton-therapy.org/map.htm). Facility components vary, but are typically customized, multi-room buildings that must include an accelerator and required shielding, treatment rooms (gantry- or fixed-beam), patient alignment and digital imaging equipment, and treatment-planning rooms with computerized control units.[24] Multi-room proton beam facilities can cost between 100 and 225 million dollars to construct and equip and between 15 and 25 million dollars annually to maintain.[24] Similarly, the treatment itself remains costly compared with other radiation therapy modalities. Among Medicare patients treated for prostate cancer in 2008 and 2009, the median amount reimbursed by Medicare for PBT was $32,428 while the median amount reimbursed for matched IMRT patients was $18,575.[7]

As with other external beam radiation therapies, treatment typically occurs once daily for 5 days, up to 8 weeks, and patients attend pretreatment planning sessions to confirm tumor location and plan for patient immobilization, including designing body casts, bite-molds, and masks.[24] Additional expenses associated with PBT is the creation of individual brass apertures for each beam, requiring special facilities and personnel. Two types of rooms are used in treatment: gantry-beam rooms rotate the beam around the patients, and fixed-beam rooms direct the beam horizontally. The patient is first positioned in the treatment room and then the proton beam is delivered to the target tumor. Each treatment session lasts a half-hour to a hour, with most of this time devoted to patient positioning.[24] Because of the limited number of proton beam centers and therefore reduced availability of PBT compared with other modalities, travel and treatment delay may be a burden for patients.

Recently, manufacturers have started developing smaller proton beam radiation therapy systems in the hopes of reducing some of the initial costs of implementing PBT.[24,26] Some argue that more affordable PBT systems will deescalate the debate on the use of PBT for more common cancers and lead to more individualized treatment using a combination of treatment modalities.[26] The development and utilization of more precise proton beam delivery methods, such as pencil-beam scanning technology, may also lead to better clinical outcomes compared to photon modalities.

METHODS

TOPIC DEVELOPMENT

The following key questions guiding this systematic review were developed after a topic refinement process that included a review of published peer-reveiwed literature and consultation with the technical expert panel, operational partners, and experts in the field:

KQ1: What is the effectiveness of proton beam irradiation compared to conventional X-ray-based external beam modalities?

KQ2: What is the effectiveness of proton beam irradiation compared to state-of-the-art therapies?

KQ3: In patients with local recurrences after irradiation, what is the effectiveness of proton beam irradiation compared to conventional X-ray-based external beam modalities and state-of-the-art therapies?

KQ4: What are the short- and long-term harms of proton beam irradiation compared to conventional X-ray-based external beam modalities and state-of-the-art therapies?

KQ4A: What are the harms of proton beam irradiation compared to photon-based therapies in treating mobile targets that may move during treatment?

We selected studies that compared benefits (survival, quality of life, functional capacity, local tumor control, delivery of planned chemotherapy and radiation regimens) and harms (toxicity and secondary malignancies) for PBT versus other radiation modalities in adults with any cancer type, with the exception of ocular cancer.

SEARCH STRATEGY

To identify articles relevant to the key questions, our research librarian searched MEDLINE® (via PubMed®), the Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov using the terms “proton beam” and “cancer” (see Appendix C for complete search strategies). Additional citations were identified from hand searching reference lists and consultation with content experts. We limited the search to published and indexed articles involving human subjects and available in the English language.

To identify additional published, unpublished and ongoing studies, we searched ClinicalTrials.gov, and requested information from and searched the websites of manufacturers and proton therapy centers. Formal Requests for Scientific Information were sent to manufacturers of proton therapy systems (Hitachi, IBA, Mevion Medical Systems, Mitsubishi Electric, Sumitomo Heavy Industries, and Varian Medical Systems) and proton beam therapy centers located at Loma Linda University Medical Center, University of California San Francisco Radiation Oncology, Massachusetts General Hospital, Indiana University Health Center, University of Florida, ProCure Proton Therapy Centers (Oklahoma City, New Jersey, and Seattle), University of Pennsylvania, CDH Proton Center, Hampton University, Washington University School of Medicine, Scripps Proton Therapy Center, and ProTom International. All ciations were imported into an electornic database (EndNote X).

STUDY SELECTION

We selected studies that compared benefits (survival, quality of life, functional capacity, local tumor control, delivery of planned chemotherapy and radiation regimens) and harms (toxicity and secondary malignancies) for PBT versus other radiation modalities in adults with any cancer type (except ocular). In studies with a comparison to brachytherapy, soreness, bruising and surgical complications were also considered. Titles, abstracts, and full-text articles were reviewed by one investigator then checked by another. All disagreements were resolved by consensus. We first reviewed titles and abstracts for potential inclusion, then reviewed relevant full-text articles. Articles meeting eligibility criteria were included for data abstraction.

DATA ABSTRACTION

We evaluated the following information from each study: study site, years of recruitment, sample size, patient demographic information, proton and photon treatment protocols, follow-up time, and outcomes assessed including benefits and harms. We checked the accuracy of data abstraction for these elements from the 2014 review produced by ICER for the Washington State Health Care Authority Health Technology Assessment Program (HTA).[1] We found their abstraction to be reliable for these elements, so we only abstracted data from studies that were not already included in the ICER review. All data abstraction was first completed by one reviewer and then checked by another.

QUALITY ASSESSMENT

We used the Cochrane Collaboration's Risk of Bias Tool[29] to rate the internal validity of included RCTs based on adequate sequence generation, allocation concealment, blinding, assessment of incomplete data, outcome reporting bias, and other sources of bias. We used the methods from the Drug Effectiveness Review Project to assess the quality of observational studies.[30] Additionally, we used AMSTAR to assess the quality of included systematic reviews.[31] All internal validity ratings were first completed by one reviewer and then checked by another. All disagreements were resolved by consensus.

RATING THE BODY OF EVIDENCE

We rated the overall strength of evidence about each outcome based on the guidance established for the Evidence-based Practice Center Program of the Agency for Healthcare Research and Quality (AHRQ).[32] This method considers the internal validity, directness of comparison, consistency of effect, precision of estimate, and reporting bias across the studies relevant to that outcome. We assigned the following evidence grades:

> High: We are very confident that the estimate of effect lies close to the true effect for this outcomes.
>
> Moderate: We are moderately confident that the estimate of effect lies close to the true effects for this outcome.
>
> Low: We have limited confidence that the estimate of effect lies close to the true effects for this outcome.

Insufficient: We have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome.

DATA SYNTHESIS

We qualitatively synthesized the body of literature for each key question after abstracting relevant data and producing strength of evidence tables. We did not conduct meta-analyses because few studies reported on outcomes of interest and the studies were methodologically heterogeneous.

PEER REVIEW

Eight invited peer reviewers provided comments on the draft version of this systematic review. See Appendix I for the peer review disposition table.

RESULTS

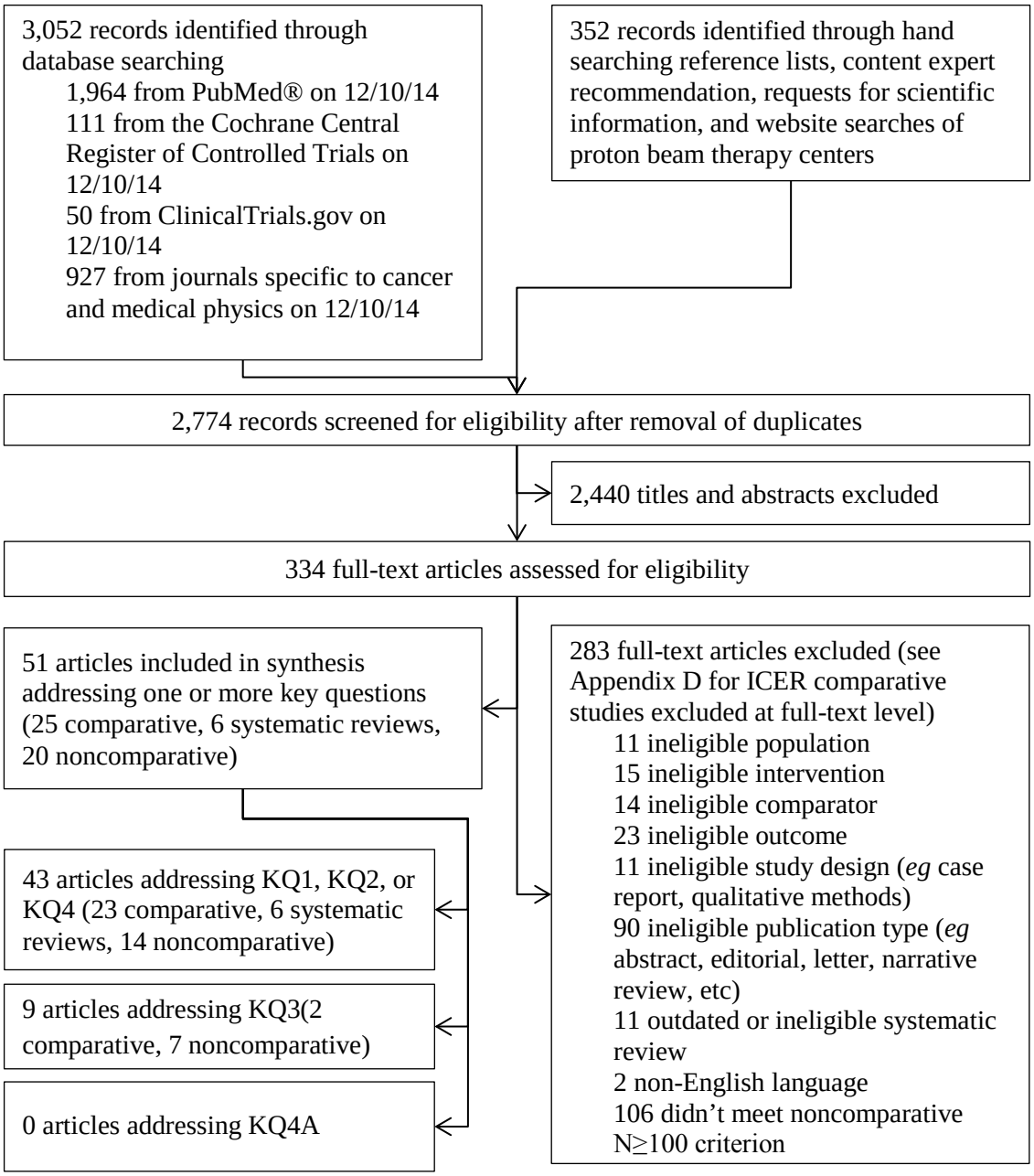
RESULTS OF SEARCH AND STUDY SELECTION

Figure 1 provides the results of the study selection process. We identified 3,052 titles and abstracts from the database search and 352 additional references through manual searching, suggestions from content experts, or from requests for scientific information. We reviewed 334 full-text articles and included 51 articles in our synthesis.

Scientific information requests to proton therapy system manufacturers and representatives of proton beam therapy centers resulted in submissions from IBA, Sumitomo, Varian, University of Pennsylvania, the Proton Therapy Consortium, and the Proton Collaborative Group. None identified any primary comparative studies that we did not also identify through our own searching, but they did provide extensive information on ongoing studies and identified a recent systematic review completed by ICER on proton beam therapy for various cancers.[1] Our searching of ClinicalTrials.gov did not identify any additional published or unpublished completed comparative studies, but our review of abstracts from the 2014 PTCOG-NA conference identified one unpublished comparative study of 25 patients with head and neck cancer treated at Memorial Sloan Kettering Cancer Center that we briefly discuss in the head and neck cancer section.

Nine ongoing RCTs were identified via requests for scientific information and ClinicalTrials.gov (see Appendix F). Comparators to PBT include conventional photon beam therapy (N=3), IMRT (N=5), SBRT (N=1), and 3D-CRT (N=1). Populations include non-small cell lung cancer (NSCLC), prostate cancer, meningioma, glioblastoma, esophageal cancer, and oropharyngeal cancer patients. These ongoing studies are being conducted at the University of Texas MD Anderson Cancer Center, Massachusetts General Hospital, and the University of Pennsylvania, as well as other centers in the US and abroad.

Figure 1. Literature Flow Chart



OVERVIEW OF PRIMARY STUDIES AND SYSTEMATIC REVIEWS

We identified a total of 25 primary comparative studies. Table 1 shows which comparators were evaluated for different cancer sites. IMRT was the comparator in 12 studies[4-10,15,33-36], including 6 observational studies in prostate cancer patients.[5-10] Other comparators were 3D-CRT (6 studies),[2,4,9,33,34,36] conventional photon therapy (5 studies),[3,17,18,37,38] and combination of proton plus photon radiation compared to either photon alone (5 studies)[12-14,39,40] or to brachytherapy (1 studies).[11] Table 1 provides a detailed listing of all 25 comparative studies.

Most comparative studies were either retrospective cohorts (17 studies)[3,7-10,12,15-18,33,35-40] or cohort studies including a historical control (3 studies).[4,11,34] Additionally, we identified one randomized controlled trial,[14] 2 controlled before/after studies,[5,6] one prospective cohort study,[13] and one prospective phase 1 nonrandomized trial.[2] We rated the majority of studies as poor quality (14 studies)[3,5,6,12,15-18,34,35,37-40] and the remainder as fair quality (11 studies).[2,4,7-11,13,14,33,36] The main quality concerns were failing to adequately adjust for potential confounders and potentially biasing selection by comparing outcomes from PBT patients with historical results (see Appendix E for complete quality assessments of included comparative studies).

Table 1. Relevant Comparative Studies

Cancer type	Comparison	No. and design of comparative studies
Breast	APBI: Single-field PBT vs 3D CRT	1 fair-quality prospective phase 1 nonrandomized trial (N=98): Galland-Girodet et al 2014[2]
CNS: Medulloblastoma	PBT vs conventional photon	1 poor-quality retrospective cohort (N=40): Brown et al 2013[3]
CNS: Spinal cord glioma	PBT vs IMRT	1 poor-quality retrospective cohort (N=32): Kahn et al 2011[15]
CNS: Recurrent malignant brain tumor	PBT vs conventional photon	1 poor-quality retrospective cohort (N=26): Mizumoto et al 2013[17]
Esophageal	PBT vs IMRT or 3D-CRT	2 fair-quality retrospective cohorts (N=519): McCurdy et al 2013,[33] Wang et al 2013[36]
Giant cell tumors of bone	PBT+photon vs conventional photon	1 poor-quality retrospective cohort (N=20): Chakravarti et al 1999[39]
Head/neck: Malignant clival tumors	PBT vs IMRT	1 poor-quality retrospective cohort (N=6): Solares et al 2006[35]
Liver: Recurrent hepatocellular carcinoma	PBT vs conventional photon	1 poor-quality retrospective cohort (N=8): Otsuka et al 2003[18]
Lung	PBT vs IMRT or 3D-CRT	1 fair-quality and 1 poor-quality cohort study with historical controls(N=1,104): Gomez et al 2012,[4] Sejpal et al 2011[34]
Meningiomas	PBT vs conventional photon	1 poor-quality retrospective cohort (N=25): Arvold et al 2009[37]
	PBT+photon vs various photon modalities	1 poor-quality retrospective cohort (N=31): Hug et al 2000[40]
Prostate	PBT vs IMRT	Benefits: 2 poor-quality controlled before/after studies (N=1,695): Gray et al 2013,[5] Hoppe et al 2014[6] Harms: 4 fair-quality retrospective cohorts (N=34,185): Kim et al 2011,[9] Sheets et al 2012,[10] Yu et al 2013,[7] Fang et al 2014[8]
	PBT vs 3D-CRT	Benefits: 1 poor-quality controlled before/after study (N=218): Gray et al 2013[5] Harms: 1 fair-quality retrospective cohort (N=12,107): Kim et al 2011[9]
Prostate	PBT+photon vs brachytherapy	1 fair-quality cohort study with a historical control (N=282): Coen 2012[11]
	PBT+photon vs photon alone	1 fair-quality RCT, 1 poor-quality prospective cohort, and 1 poor-quality retrospective cohort (N=567): Shipley et al 1995,[14] Galbraith et al 2001,[13] Duttenhaver et al 1983[12]
Uveal hemangioma	PBT vs conventional photon	1 poor-quality retrospective cohort (N=44): Hocht et al 2006[38]
Various cancers	PBT vs various photon modalities	1 poor-quality retrospective cohort (N=1,116): Chung et al 2013[16]

Overview of previous systematic reviews

The ESP generally prioritizes existing good-quality systematic reviews as the best source of evidence to guide our reports. We identified numerous reviews conducted on proton beam therapy in the past 5 years.[1,24,41-54] Table 2 briefly summarizes their scope and relevant conclusions. However, many existing reviews had limited usefulness because they (1) were outdated as their literature searches were conducted prior to the publication of most of the comparative studies,[45,46,48,52] (2) were noncomparative,[41,42,47] or (3) did not review full-text articles of primary studies.[24,43,44] The 2014 review by the Institute for Clinical and Economic Review (ICER)[1] is the most comprehensive, including 22 of the 25 comparative studies we identified. Although we had hoped to rely on the ICER review findings, we undertook our own analysis of the primary data because our conclusions differed from ICER's as discussed below. For the other systematic reviews identified, we assessed their internal validity (Appendix G) and included findings from those that included a majority of comparative studies[1,53,54] or conducted indirect meta-analyses.[49-51]

Table 2. Previous Systematic Reviews on the Effectiveness of Proton Beam Therapy for Cancer

Review	Funding source	Cancer types	Search end date	Scope	Relevant Conclusions
Included in synthesis					
Agency for Healthcare Research and Quality (AHRQ) 2014[53]	U.S. Department of Health and Human Services	Prostate	March 7, 2014	Includes 2 of 10 comparative studies: Sheets et al 2012 and Kim et al 2011	Evidence is inadequate.
Institute for Clinical and Economic Review (ICER) 2014[1] Produced for Washington State Health Care Authority Health Technology Assessment Program (HTA)	Various (government grants, non-profit organizations, health plans/ provider contributions, manufacturer grants, contracts, contributions), funding is not accepted from manufacturers or private insurers to perform review of specific technologies.	Various	February 2014	Includes 22 of 25 comparative studies; excludes: Galland-Girodet et al 201 (breast cancer) and Fang et al 2014 (prostate cancer) that were published after search date and Duttenhaver et al 1983 in prostate cancer.	Net health benefit is incremental for brain/spinal (reduced harms, low strength), comparable for uveal hemangiomas (low strength), liver (low strength), lung (moderate strength), prostate (moderate strength), and insufficient for all other cancers.
California Technology Assessment Forum (CTAF) 2012[54]	NR	Prostate	August 2012	Covers comparisons to conventional photon and brachytherapy, but but only includes 1 of 6 studies of IMRT (Sheets et al 2012) because most were published after its search date	Proton beam therapy was not found to be as beneficial as any established alternatives.

Review	Funding source	Cancer types	Search end date	Scope	Relevant Conclusions
Grimm et al 2012[49]	NR	Prostate	2010	Indirect comparison of PSA-free progression of uncontrolled studies of various treatments	For low risk prostate cancer, higher average progression-free survival was reported for brachytherapy compared with all other treatment modalities
Grutters et al 2010[50]	Siemens Medical Solutions	Lung	August 2008	Indirect comparison of summary event rates from uncontrolled studies of proton vs uncontrolled studies of photon. Did not include two comparative studies published after its search date (Sejpal et al 2011, Gomez et al 2012)	5-yr overall survival rate for proton beam was higher than for conventional radiation therapy, but similar to SBRT
Patel et al 2014[51]	Mayo Foundation for Medical Education and Research	Head & Neck: Paranasal sinus and nasal cavity	April 2014	Indirect comparison of between pooled event rates from uncontrolled studies of PBT (including 1-8 cohorts) and uncontrolled studies of IMRT (including 2-8 cohorts)	Disease-free survival at 5 years and locoregional control at longest follow-up were significantly higher with PBT compared with IMRT
Not included in synthesis – outdated					
American Society for Therapeutic Radiology and Oncology (ASTRO) 2012[45]	National Cancer Institute	Various	November 2009	Only includes 2 comparative studies on prostate (Shipley et al 1995, Duttenhaver et al 1983) as most comparative studies were published after its search date.	CNS, GI, head/neck: Insufficient evidence Lung, prostate: No clear benefit over existing therapies
Amichetti et al 2010[46]	NR	Head & Neck: Skull base chondrosarcoma	June 2008	4 uncontrolled studies	PBT has a high probability of "medium- and long-term cure" with few complications.
De Ruysscher et al 2012[48]	European Investment Bank	Various	December 2010	Only includes one comparative study on uveal hemangioma (Hocht et al 2006) as most comparative studies were published after its search date.	Except for rare indications such as childhood cancer, the gain from proton therapy is controversial.

Review	Funding source	Cancer types	Search end date	Scope	Relevant Conclusions
Ramaekers et al 2011[52]	None	Head & Neck	February 2010	Indirect comparison of summary event rates from uncontrolled studies of proton vs uncontrolled studies of photon	Except for paranasal and sinonasal cancer, survival and tumor control for proton therapy were generally similar to the best available photon radiotherapy.
Not included in synthesis – noncomparative					
Blue Cross Blue Shield (BCBS) 2011 – in press[42]	AHRQ	Lung	June 2010	8 uncontrolled studies	Evidence is insufficient to make any conclusions about PBT for NSCLC
Cianchetti et al 2012[47]	NR	Head & Neck: Sinonasal malignancies	October 2011	5 uncontrolled studies	Promising results must be confirmed in further studies.
Not included in synthesis for various reasons					
ECRI 2014[44]	Various (memberships, clients, contracts – often governmental)	Prostate	February 2014	Hotline response – review of abstracts, not full texts	N/A
ECRI 2013[43]	Various (memberships, clients, contracts – often governmental)	Brain, head, neck, skull base	April 2013	Hotline response – review of abstracts, not full texts	N/A
ECRI 2013[24]	Various (memberships, clients, contracts – often governmental)	Various	July 2012	Overview, RCTs only	No analysis possible because no appropriately designed trials were identified.
Blue Cross Blue Shield (BCBS) 2011 – in press[41]	AHRQ	Prostate	October 2010	Unclear, citations not available	Evidence from comparative studies is insufficient to make conclusions on PBT for prostate cancer

ICER review

The ICER review used a comprehensive search and broad prespecified study selection criteria to minimize study selection bias.[1] They used appropriate methods for rating study quality and the strength of the evidence but provided insufficient detail to assess the validity of their ratings.

The ICER review proved useful for its accurate data abstraction, but we couldn't rely on it for quality assessment or conclusions. Our conclusions often differed from ICER's (Table 3) and ICER provided insufficient details to verify how they reached their conclusions. There is no clear pattern to the discrepancies between our conclusions and ICER's. For CNS, lung, and prostate cancers, we drew separate conclusions for each comparison of PBT to IMRT, 3D-CRT, conventional photon, etcetera, respectively, whereas ICER's conclusions merged data from various comparisons despite dissimilar findings. Our strength of evidence ratings were higher than ICER's for esophageal cancer and lower for both liver cancer and uveal hemangiomas.

Table 3. Comparison of ICER and ESP Findings by Cancer Type

Cancer type	Comparison	Comparative studies	Findings of comparative studies	ICER conclusions	ESP comments on ICER's Conclusions
Breast	APBI: Single-field PBT vs 3D CRT	1 fair-quality prospective phase 1 nonrandomized trial (N=98): Galland-Girodet et al 2014	Benefits: Similar local recurrence Harms: Higher 7-yr mod-severe dyspigmentation and patchy/marked atrophy, but similar fat necrosis, fibrosis, breast pain, rib fracture	N/A – not included because published after ICER's search end date	N/A
CNS: Medulloblastoma	PBT vs conventional photon	1 poor-quality retrospective cohort (N=40): Brown et al 2013	Benefits: NSD in 2-yr overall and progress-free survival and locoregional failure Harms: Lower medical management of esophagitis	Overall incremental net benefit with PBT: equal benefits (low SOE), lower harms (low SOE)	Overgeneralization, conclusion applies to medulloblastoma, but not spinal cord glioma
CNS: Spinal cord glioma	PBT vs IMRT	1 poor-quality retrospective cohort (N=32): Kahn et al 2011	Benefits: Increased mortality within 5 years (adjusted HR: 55.82; (95% CI: 1.34-2316.8)) Harms: No long-term toxicity		
Esophageal	PBT vs IMRT or 3D-CRT	2 fair-quality retrospective cohorts (N=519): McCurdy et al 2013, Wang et al 2013	Benefits: Not analyzed Harms: Pneumonitis: Worse for PB GI toxicity: NSD Post-op pulmonary complications: PBT less than 3D-CRT and similar to IMRT	Evidence is inadequate to draw conclusions	Disagree that evidence is inadequate
Liver	PBT vs conventional photon	1 poor-quality retrospective cohort (N=8): Otsuka et al 2003	Benefits: similar survival Harms: Not reported	Equal benefits (low SOE), equal harms (low SOE)	Disagree: evidence is insufficient because serious imprecision (N=8), poor quality, unknown consistency

Cancer type	Comparison	Comparative studies	Findings of comparative studies	ICER conclusions	ESP comments on ICER's Conclusions
Lung	PBT vs IMRT or 3D-CRT	1 fair-quality and 1 poor-quality cohorts with historical control groups (N=854); Gomez et al 2012, Sejpal et al 2011	Benefits: similar months of survival in Sejpal et al 2011 Harms: severe esophagitis similar to 3D-CRT and lower than IMRT at 6 months	Equal benefits (low SOE), equal harms (low SOE)	Overgeneralization; harms do not appear similar compared with IMRT
Prostate	PBT vs IMRT	Benefits: 2 poor-quality controlled before/after studies (N=1695): Gray et al 2013, Hoppe et al 2014 Harms: 3 fair-quality retrospective cohorts (N=7,292): Kim et al 2011, Sheets et al 2012, Yu et al 2013	Benefits: NSD in QOL Harms: GI toxicity: similar early 'treatment-related' (Yu et al 2013), worse late in 2 studies (Sheets et al 2012, Kim et al 2011)	Equal benefits (moderate SOE), comparable major harms (moderate SOE)	Overgeneralizations, findings vary by comparison
	PBT vs 3D-CRT	Benefits: 1 poor-quality controlled before/after study (N=218): Gray et al 2013 Harms: 1 fair-quality retrospective cohort (N=19,063): Kim et al 2011	Harms: risk of GI toxicity higher among patients that underwent PBT		
	PBT vs brachytherapy	1 fair-quality cohort with historical control (N=282): Coen et al 2012	Benefits: similar 8-yr survival Harms: NR		

Cancer type	Comparison	Comparative studies	Findings of comparative studies	ICER conclusions	ESP comments on ICER's Conclusions
Prostate	PBT+photon vs photon alone	1 poor quality RCT, 1 poor quality prospective cohort, and 1 fair quality prospective cohort(N=567); Shipley et al 1995, Duttenhaver et al 1983, Galbraith et al 2001	Benefits: similar 5-yr overall survival, 8-year overall survival, quality of life, and health status Harms: similar rectal, urinary symptoms in two studies, higher rectal bleeding in one study		
Head and neck cancers	PBT vs IMRT	1 poor-quality retrospective cohort (N=6): Solares et al 2006	Benefits: similar 8-month overall survival Harms: NR	Insufficient	Agree
Uveal hemangioma	PBT vs conventional photon	1 poor-quality retrospective cohort (N=44): Hocht et al 2006	Benefits: NSD in vision stabilization Harms: Grade ≥ 3 harms: Comparable lacrimation	Equal benefits (low SOE), equal harms (low SOE)	Disagree that evidence is sufficient for drawing conclusions
Giant cell tumors of the bone	PBT+photon vs conventional photon	1 poor-quality retrospective cohort (N=20): Chakravati et al 1999	Benefits: disease progression lower in radiation-only subgroup and higher in partial resection+radiation subgroup Harms: NR	Insufficient	Agree
Meningiomas	PBT vs conventional photon	1 poor-quality retrospective cohort (N=25): Arvold et al 2009	Benefits: similar improved vision, but lower stable and more worsened Harms: NSD in late asymptomatic retinopathy	Insufficient	Agree

KEY QUESTIONS 1, 2, AND 4:

What is the effectiveness of proton beam irradiation compared to conventional x-ray-based external beam modalities?

What is the effectiveness of proton beam irradiation compared to state-of-the-art therapies?

What are the short- and long-term harms of proton beam irradiation compared to conventional x-ray-based external beam modalities and state-of-the-art therapies?

OVERALL

We could not fully assess the overall net health benefit of proton beam therapy versus its comparators because comparative observational studies did not consistently report many outcomes of greatest interest. No studies reported functional capacity outcomes or overall severe late toxicity. No *prospective* comparative studies reported secondary malignancies. Ability to deliver planned treatments was only reported by one small retrospective cohort study.[3]

BREAST CANCER

One small, nonrandomized trial of PBT versus photon-based 3-dimensional conformal accelerated partial-breast irradiation provided low-strength evidence of comparable 7-year cumulative local recurrence rates, and higher rates of some 7-year skin toxicities, including moderate/severe dyspigmentation and patchy/marked atrophy.[2] This trial was published after the ICER review. Fat necrosis, moderate/severe fibrosis, 7-year moderate/severe breast pain, 5-year rib fracture. and 7-year self-reported cosmetic outcomes did not differ (Table 4). Treatment was administered twice daily over 4 consecutive days at a dose of 32 Gy in 8 fractions. In the proton beam group, only one field was treated per fraction using the passive double scattering system. Patients' median age was 61 years. The type of breast cancer was invasive ductal carcinoma (92%), tubular (5%), or mucinous (3%), and median tumor size was 0.9 cm. The tumor grade was 1 in 47% of patients, 2 in 42%, and 3 in 10%. Breast cancer cells tested negative for estrogen receptors in 11% of patients, progesterone receptors in 20%, and were triple-negative in 10%. Authors suggested that their inferior cosmetic results of PBT may have been due to their use of only a single field per fraction, which may have resulted in a greater entry/skin dose. They recommend that use of multiple beam scattering or a scanning-beam technique may better minimize skin toxicity. In fact, there were no cases of grade 3 or higher skin toxicity at 5 years in a series of 100 patients at Loma Linda when proton beam therapy at was delivered at 40 Gy in 10 fractions, once daily over 2 weeks, using multiple fields.[55]

With the advent of intensity-modulated proton therapy (IMPT), it may now be more feasible to expand the role of PBT beyond partial breast irradiation. However, we found no studies of IMPT for whole breast or nodal irradiation. It will be important to consider whether IMPT can improve on the 7.4%-per-gray rate for major coronary events within the first 5 years observed in a population-based case-control study of 2168 women who underwent external radiotherapy for breast cancer between 1958 and 2001 in Sweden and Denmark.[56]

Table 4. Strength of Evidence (SOE) for Comparative Benefits and Harms of PBT or Photons or Mixed Photons/Electrons in Partial Breast Treatment for Early-stage Breast Cancer

Strength of evidence: Low for all outcomes	Findings
No. studies (N): 1 prospective nonrandomized trial (98) Study limitations: Medium Directness: Direct Consistency: Unknown Precision: Imprecise Reporting bias: Undetected Other issues: None	*Benefits* 7-year cumulative local recurrence: 11% (PBT) vs 4% (3D-CRT); P=.22 *Toxicity* Moderate/severe dyspigmentation: 90% (PBT) vs 27% (3D-CRT); P<.0001; telangiectasia: 70% (PBT) vs 28% (3D-CRT); P<.0001; patchy/marked atrophy: 54% (PBT) vs 15% (3D-CRT); P<.0001; fat necrosis: 10% (PBT) vs 12% (3D-CRT); P=.7329; moderate/severe fibrosis: 51% (PBT) vs 32% (3D-CRT); P=.1490; moderate/severe breast pain: 21% (PBT) vs 17% (3D-CRT); P=.4597; rib fracture at 5 years: 1 (PBT) vs 3 (3D-CRT); P=.072

CNS CANCERS

Summary

We identified 2 comparative studies in patients with CNS cancers. One is a retrospective cohort study that compared PBT to conventional photon therapy in 40 adults with medulloblastoma from the MD Anderson Cancer Center in Texas.[3] The other is a retrospective cohort study that compared PBT to intensity-modulated radiation therapy (IMRT) in 32 patients treated for intramedullary gliomas at Massachusetts General Hospital.[15] Based on these 2 studies, the ICER review concluded that there is low-strength evidence that proton beam therapy has an incremental net benefit in the form of decreased harms. We agree with ICER's conclusion as specifically related to medulloblastoma and only for acute toxicity, but not for intramedullary gliomas.

Medulloblastoma: Proton versus conventional photon

One poor-quality retrospective cohort study of 40 adults with medulloblastoma provided low-strength evidence that PBT 54.6 GyE and photon therapy 52.9 Gy have comparable benefits, but proton beam therapy was associated with reduced acute toxicity (Table 5).[3] Long-term toxicity was not reported.

Table 5. SOE for Proton Craniospinal Irradiation (CSI) versus Conventional Photon CSI for Medulloblastoma

Strength of evidence: Low for all outcomes	Findings
No. Studies (N): 1 retrospective cohort (40) Study limitations: High Directness: Direct Consistency: Unknown Precision: Imprecise Reporting bias: Undetected Other issues: None	*Benefits* 2-year overall survival: 94% (PBT) vs 90% (photon); P=.67 2-year progression-free survival: 94% (PBT) vs 85% (photon); P=.27 Proportion of patients with treatment breaks: 0% (PBT) vs 10% (photon); P=.27 Locoregional failure: 5% (PBT) vs 14% (photon); P=.41 *Acute toxicity (one month)* Patients with > 5% weight loss: 16% (PBT) vs 64% (photon); P=.004 Medical management of esophagitis: 5% (PBT) vs 57% (photon); P<.001 Grade ≥ 2 nausea/vomiting: 26% (PBT) vs 71% (photon); P=.004

Spinal cord glioma: Proton versus IMRT

There is low-strength evidence that use of PBT may be disadvantageous for highly infiltrative tumors such as intermedullary spinal cord gliomas.[15] This conclusion is based on one retrospective cohort study of 32 patients treated for intramedullary gliomas at Massachusetts General Hospital with either PBT (N=10) or IMRT (N=22) at an average dose of 51 Gy in 1.8 median daily fractions over 29 treatments. The main limitation of this study is that patients in the proton beam group had more favorable prognostic factors, such as lower age (14 years compared with 44 years) and a higher rate of partial resection (70% compared with 55%). However, after adjustment for age and pathology, proton beam-treated patients were more likely to die within 5 years (adjusted hazard ratio, 55.82; 95% CI: 1.34-2316.8). Local recurrence occurred in 20% of proton beam-treated patients and 23% in those treated with IMRT, but interpretation of this result is limited by the lack of multivariate analysis.

Table 6. SOE for PBT versus IMRT for Spinal Cord Gliomas

Strength of evidence: Low for survival, insufficient for others	Findings
No. Studies (N): 1 retrospective cohort (32) Study limitations: High Directness: Direct Consistency: Unknown Precision: Imprecise Reporting bias: Undetected Other issues: None	*Benefits* 5-year overall survival: 20% (PBT) vs 32% (IMRT); aHR (PBT vs IMRT): 55.82 (95% CI: 1.34-2,316.8) Local recurrence: 20% (PBT) vs 23% (IMRT); P=.89 *Acute toxicity (one month)* Not reported *Long-term toxicity* "No patients experienced significant long-term toxicity."

ESOPHAGEAL CANCER

Summary

Comparative evidence in esophageal cancer is limited to 2 fair-quality retrospective cohort studies that compare acute toxicity, but not benefits, between PBT, IMRT, or 3-dimensional conformal radiation therapy (3D-CRT) in patients treated at the MD Anderson Cancer Center in Texas from 1998 to 2011 (N=75)[33] and from 2003 to 2011 (N=444).[36] Based on these 2 studies, the ICER review concluded that "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." We disagree with ICER's conclusion and conclude that these studies provide low-strength evidence of some differences in acute toxicity. But evidence on benefits and long-term toxicity is still needed to adequately assess net health benefit of proton beam.

Detailed analysis

Radiation modality (50.4 Gy of PBT, IMRT, or 3D-CRT) was associated with variation in 30-day post-operative complications when it was a component of trimodal therapy comprised of neoadjuvant chemoradiation followed by surgical resection. There is low-strength evidence that IMRT and proton beam have comparable risk of postoperative pulmonary complications (OR 2.23; 95% CI: 0.86-5.75) and GI complications (OR 1.02; 95% CI: 0.47-2.25), 3D-CRT and proton beam have comparable risk of GI complications (OR 2.31; 95% CI: 0.69-7.74; 28.4% vs 18.1), but that 3D-CRT has a higher risk than proton beam of pulmonary complications (OR: 9.13; 95% CI: 1.83-45.42; 30.3% vs 13.9%).[36] The second study evaluated the role of lung lobes in radiation pneumonitis in 75 patients who received restaging [^{18}F]-fluorodeoxyglucose (FDG) positron emission tomography (PET) imaging 1 to 3 months after chemoradiation involving 50.4 Gy of either PBT, IMRT or 3D-CRT.[33] This study provides low-strength evidence that proton therapy is associated with a higher risk of acute pneumonitis compared with IMRT/3D-CRT (33% vs 15%; P=.04).

Table 7. SOE for PBT versus IMRT and 3D-CRT in Esophageal Cancer

Strength of evidence: Low for all outcomes	Findings
Postoperative complications No. Studies (N): 1 retrospective cohort (N=444) Study limitations: Medium Directness: Direct Consistency: Unknown Precision: Imprecise Reporting bias: Undetected Other issues: None	Postoperative pulmonary complications: OR (IMRT vs PBT): 2.23 (95% CI: 0.86-5.75); OR (3D-CRT vs PBT): 1.83 (95% CI: 1.83-45.42); 30.3% (3D-CRT) vs 13.9% (PBT) GI complications: OR (IMRT vs PBT): 1.02 (95% CI: 0.47-2.25); OR (3D-CRT vs PBT): 2.31 (95% CI: 0.69-7.74); 28.4% (3D-CRT) vs 18.1% (PBT)

Strength of evidence: Low for all outcomes	Findings
Acute Pneumonitis No. Studies (N): 1 retrospective cohort (N=75) Study limitations: Medium Directness: Direct Consistency: Unknown Precision: Imprecise Reporting bias: Undetected Other issues: None	Acute Pneumonitis: 33% (PBT) vs 15% (IMRT/3D-CRT); P=.04

GIANT CELL TUMOR OF THE BONE

Combined PBT+photons versus photons alone

We identified one poor-quality retrospective comparative cohort that evaluated the clinical effectiveness of combination proton and photon treatment versus photon-only treatment in giant cell tumor of bone. ICER was the only systematic review to include this study and they determined that there was insufficient evidence to make a conclusion regarding PBT for giant cell tumor of bone. We agree with their conclusion. In this study, patients were treated with PBT+photons (N=6; mean: 59 GyE) or photons alone (N=14; mean: 52 Gy) with a median duration of follow up of 9.3 years.[39] Thirteen patients also received partial tumor resection. In this study, the 10-year lack of progression rate was 17% for the PBT+photons patients and 14% among the photons only patients (P=.88). No harms were reported in this study. This study did not control for differences between groups including age (median: 23.5 years for PBT+photons patients; 52.5 years for photons only patients). Further, it is unclear how patients were selected for the PBT+photons group or the photons alone group (see Appendix E for complete quality assessment).

Table 8. SOE for Combined PBT+Photons versus Photons Alone for Giant Cell Tumor of Bone

Strength of evidence: Insufficient for all outcomes	Findings
No. Studies (N): 1 retrospective cohort (20) Study limitations: High Directness: Direct Consistency: Unknown Precision: Imprecise Reporting bias: Undetected Other issues: None	*Benefits* 10-year lack of progression rate: 17% (PBT+photons) vs 14% (photons); P=.88

HEAD AND NECK CANCERS

Summary

Comparative evidence for proton beam versus IMRT in head and neck cancers is limited to one small (N=6) poor-quality retrospective cohort[35] and 2 indirect meta-analyses of non-comparative studies.[51,52] We agree with ICER's conclusion that the cohort study provided insufficient evidence to draw conclusions about PBT in head and neck cancers. The indirect meta-analyses of non-comparative studies also provide insufficient evidence to draw conclusions about proton beam in head and neck cancers due to unacceptably high methodological limitations.

Detailed analysis

PBT versus IMRT

Direct evidence

One small (N=6) poor-quality retrospective cohort[35] provided insufficient evidence to draw conclusions about PBT and IMRT for cancers of the head and neck. In the cohort study, when radiation therapy was given following endoscopic resection of malignant clival tumors, overall survival was 100% in the proton group after 8 months and 67% in the IMRT group after 16-24 months.[35] However, we have no confidence in these findings because the study was extremely small with many limitations (such as no baseline demographic information on patients by treatment group), and while the comparison was direct, consistency was unknown and the survival estimates were imprecise.

We also identified a PTCOG-NA 2014 conference proceeding of a new comparative study including 25 patients with major salivary gland cancer or cutaneous squamous cell carcinoma metastases. These patients were treated at the Memorial Sloan Kettering Cancer Center and the results suggest the potential for reduced acute toxicity with PBT versus IMRT, but we could not assess the strength of the evidence beacause the abstract did not provide sufficient detail to adequately address internal validity.[57]

Indirect evidence

The meta-analyses of non-comparative studies also provide insufficient evidence to draw conclusions about proton beam in head and neck cancers due to unacceptably high methodological limitations. Both meta-analyses used similar statistical methods, but the more recent one is more comprehensive since it includes more studies.[51] Patel et al made indirect comparisons between pooled event rates from uncontrolled studies of PBT (including 1-8 cohorts) and uncontrolled studies of IMRT (including 2-8 cohorts) for patients with paranasal sinus and nasal cavity malignancies.[51] They found no difference in overall survival at longest follow-up, 5-year overall survival, disease-free survival at longest follow-up, and 5-year locoregional control, but found improved disease-free survival at 5 years (RR: 1.44; 95% CI: 1.01-2.05) and locoregional control at longest follow-up (RR: 1.26; 95% CI: 1.05-1.51) in the proton therapy group. Harms were pooled across all charged particle therapy cohorts, so PBT-specific harms could not be compared with those after photon modalities. However, we have serious concerns about the methods that Patel et al used for indirect comparison. Because there are no common control groups in the uncontrolled studies, it is impossible to verify the

underlying prognostic comparability between the PBT and IMRT populations. But, at minimum, there does appear to be the potential for temporal and location confounding. For example, the analysis of 5-year disease-free survival included one study of 36 patients from Massachusetts General Hospital treated between 1991 and 2001 for proton therapy and 3 studies of 187 total patients, mostly from Belgium treated between 1998 and 2009 for IMRT.

Table 9. SOE for Comparative Benefits of PBT or IMRT for Paranasal Sinus and Nasal Cavity Malignancies

Strength of evidence: Insufficient for all outcomes	Findings
No. Studies (N): 4-16 cohort studies (202-539) Study limitations: High Directness: Indirect Consistency: Inconsistent Precision: Imprecise Reporting bias: Undetected Other issues: None	*Benefits* Overall survival at longest duration of follow-up: RR (PBT vs IMRT): 1.02 (95% CI: 0.77-1.35) 5-year overall survival: RR(PBT vs IMRT): 1.39 (95% CI: 0.99-1.94) Disease-free survival at longest duration of follw-up:RR(PBT vs IMRT): 0.98 (95% CI: 0.40-2.42) 5-year disease-free survival: RR(PBT vs IMRT): 1.44 (95% CI: 1.01-2.05) Locoregional control at longest duration of follow-up: RR: 1.26 (95% CI: 1.05-1.51) 5-year locoregional control: RR(PBT vs IMRT): 0.73 (95% CI: 0.15-3.58)

UVEAL HEMANGIOMA

One poor-quality retrospective cohort provides comparative evidence on the benefits and harms of radiation treatment with protons or photons in uveal hemangiomas. Based on this study, the ICER review concluded that there was low-strength evidence suggesting that PBT has comparable benefits and harms compared with other treatment modalities for uveal hemangiomas. We disagree, and conclude that this study provides insufficient evidence to draw conclusions about PBT compared with photons for the treatment of uveal hemangioma. In this study, patients were treated with protons (N=25; 20-22.5 CGE) or photons (N=19; 16-30 Gy) between 1993 and 2002 at the Charite Campus Benjamin Franklin center in Berlin and followed up for a median of 27.7 months. There was no statistically significant difference between radiation modality on stabilization of visual acuity (P=.43), optic disc/optic nerve atrophy (P=.27), or retinopathy (P=.098).[38] There were no significant differences in treatment side effects between treatment groups. Grade 3 side effects occurred in 2 patients in each treatment group (P=.7718) and Grade 4 side effects occurred in one patient in the PBT group (P=.3789). While baseline uveal hemangioma thickness was different between the 2 groups, it is not clear that this would affect prognosis.

Table 10. SOE for PBT versus Photons for Uveal Hemangiomas

Strength of evidence: Insufficient for all outcomes	Findings
No. Studies (N): 1 retrospective cohort (44) Study limitations: Medium Directness: Direct Consistency: Unknown Precision: Imprecise Reporting bias: Undetected Other issues: None	*Benefits* Stabilization of visual acuity: no difference; P=.43 *Late toxicity* Grade 3: no difference; P=.7718 Grade 4: no difference; P=.3789

LIVER CANCER

We identified one retrospective cohort examining PBT among patients with recurrent liver cancer.[18] This study is discussed under Key Question 3.

LUNG CANCER

Summary

Comparative evidence on the use of PBT versus IMRT,[4,34] 3D-CRT,[4,34] SBRT,[50] or conventional radiotherapy[50] in non-small cell lung cancer (NSCLC) patients comes from 2 historically-controlled cohort studies[4,34] and one meta-analysis that compared pooled event rates from case series of CRT, SBRT and PBT.[50] Based on the historically controlled cohort studies,[4,34] the ICER review concluded that "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." We disagree, and conclude that for locally advanced NSCLC these studies provide low-strength evidence that, even at a higher dose, PBT's risk of 6-month severe esophagitis is lower than IMRT and similar to 3D-CRT. However, there is insufficient evidence on survival and 15- to 17-month toxicity when given with concurrent chemotherapy. Comparability of late toxicity is unknown. For early stage NSCLC, due to unacceptable methodological limitations, the indirect meta-analysis provides insufficient evidence to draw conclusions about the comparison of PBT with SBRT or conventional radiotherapy.[50]

Detailed analysis

Proton-based ablative RT versus photon-based ablative RT for early stage NSCLC

The indirect meta-analysis by Grutters et al provides insufficient evidence to draw conclusions about the comparison of proton beam versus stereotactic body radiotherapy (SBRT) or conventional radiotherapy (CRT) for NSCLC due to methodological limitations which are described below.[50] Grutters et al made indirect comparisons between adjusted pooled event rates for 2- and 5-year disease-specific and overall survival outcomes from 11 uncontrolled cohorts of CRT, 11 of SBRT, and 5 of PBT, and found that 5-year overall survival was significantly higher among PBT patients compared with CRT patients (P=.014) and similar to SBRT patients (Table 11).[50] A strength of this analysis is that it included adjustment for some sources of potential confounding. The percentage of medically inoperable patients significantly influenced model

coefficients, so it was used to correct the pooled outcome estimates. Age, percentage of small tumors (<3 cm), percentage of medically inoperable patients, and median follow-up time were ruled out as effect modifiers. However, there is a remaining risk of potential confounding by variation in study setting and temporal trends. For example, in the outcome of 5-year disease-specific survival, most CRT cohorts were from the Netherlands or the US and were followed as early as 1976 to usually the mid-1990s. In contrast, most SBRT cohorts were from Japan and followed as early as 1994 to usually the mid-2000s. Finally, only 2 PBT cohorts, from the US and Japan, were included in this outcome and recruitment dates were unknown for one cohort.

Table 11. Findings and SOE for PBT versus SBRT and CRT in Early-stage NSCLC

Strength of evidence: Insufficient for all outcomes	**Findings**
No. Studies (N):Indirect meta-analysis of 27 uncontrolled cohorts (N=2,401) Study limitations: High Directness: Indirect Consistency: Inconsistent Precision: Imprecise Reporting bias: Undetected Other issues: None	*Benefits* 2-year overall survival:53% (CRT) (95% CI: 46-60%); 70% (SBRT) (95% CI: 63-77%); 61% (PBT) (95% CI: 47-75%) 2-year disease-specific survival:67% (CRT) (95% CI: 59-76%); 83% (SBRT) (95% CI: 75-92%); 74% (PBT) (95% CI: 61-87%) 5-year overall survival:19% (CRT) (95% CI: 15-24%); 42% (SBRT) (95% CI: 34-50%); 40% (PBT) (95% CI: 24-55%) 5-year disease-specific survival:43% (CRT) (95% CI: 31-56%); 63% (SBRT) (95% CI: 50-75%); 52% (PBT) (95% CI: 32-72%)

PBT versus IMRT or 3D-CRT for locally advanced NSCLC

Benefits

There is insufficient evidence to draw a conclusion about survival after higher-dose proton beam (74 Gy) versus 3D-CRT (63 Gy) or IMRT (63 Gy) with concurrent chemotherapy in patients with primarily stage IIIA-B unresectable NSCLC.[34] One poor-quality historically controlled cohort study included 202 patients who were treated at MD Anderson Cancer Center in Texas with either proton beam between 2006 and 2008, IMRT between 2003 and 2005, or with 3D-CRT between 2001 and 2003. Follow-up time was 17.9 months (range: 2.3-76.1) for 3D-CRT patients, 17.4 months (range: 1.8-65.5) for IMRT patients, and 15.2 months (range: 3.3-27.4) for PBT patients (P<.001). Median survival times were 17.7, 17.6, and 24.4 months for 3D-CRT, IMRT, and PBT, respectively, but not statistically significantly different between groups (P=.1061). This study is limited by lack of adjustment for important baseline characteristics such as: older mean age, higher proportion of nonwhite, lower proportion of clinical disease stage 3B and above, lower tumor volume, lower proportion with adjuvant chemotherapy, and more recent treatment in the proton beam group. This lack of adjustment confounded the effect of PBT on survival. Also, differences between radiation modalities in methods used to account for tumor motion may have confounded their effects on survival. The authors indicated that 4-dimensional CT scanning had been used to account for tumor motion since 2004, but that would only apply to the proton group and the last year of the IMRT group, but not the 3D-CRT group. Finally, the study is potentially limited by differences in lung cancer care in the time periods studied.

Harms

There is low-strength evidence that, even at a higher dose (74 Gy), acute risk of severe esophagitis (grade ≥ 3) at 6 months for proton beam therapy (6%) is similar to 3D-CRT 63 Gy (8%; P=.42) and lower than IMRT 63 Gy (28%, P<.0001).[4] One cohort study involving 652 patients with NSCLC, mostly clinical stage IIIA-B and mean age of 66 years, followed patients who were treated at MD Anderson Cancer Center between 2000 and 2008 and evaluated harms among those treated with PBT versus 3D-CRT or IMRT.[4] Across the whole cohort, predictors of severe esophagitis were concurrent chemotherapy and treatment with over 30 fractions, but not age, gender, smoking status, stage, or histology. Risk of Grade 3 esophagitis at 15-17 months was lower with proton beam therapy 74 Gy (5%) than with 3D-CRT 63 Gy (18%; P=.02) and IMRT 63 Gy (39%; P<.0001) in a subgroup of 202 patients with primarily stage IIIA-B NSCLC treated with concurrent chemotherapy during that same time period.[34] In the subgroup with concurrent chemotherapy, risk of Grade 3 pneumonitis for PBT (2%) was similar to IMRT (6%, P=.23) but lower than 3D-CRT (30%, P<.0001). However, higher dose PBT was associated with a higher risk of Grade 3 dermatitis (24%) than 3D-CRT (5%, P=.005) and similar to IMRT (17%, P=.30). There were no statistically significant differences in Grade 3 fatigue, with rates of 19% for proton beam, compared with 15% for IMRT (P=.54) and 29% for 3D-CRT (P=.09). Limitations of these toxicity findings are the same as described above for benefits. Although in the study of the subgroup undergoing concurrent chemotherapy the authors found tumor size to be independent of Grade 2 or greater toxicities and disease stage to be independent of pneumonitis overall, we don't know how applicable these findings are to Grade 3 toxicity and still cannot rule out potential confounding by the other unbalanced factors. Also, we cannot account for the discrepancy in magnitude of the rates of Grade 3 esophagitis (5-6%) and pneumonitis (2%) for proton therapy between the historically-controlled cohort studies[4,34] and those from a case series from the same facility (MD Anderson Cancer Center, 2006-2009)[58,59] and other proton facilities between 2001 and 2010 for esophagitis (11%) and pneumonitis (2-6%).[60-64]

Table 12. Findings and SOE for PBT versus IMRT and 3D-CRT in Locally Advanced NSCLC

Strength of evidence: Insufficient for survival time and 15-17 month toxicity, low for 6-month esophagitis	Findings
Median survival time and 15-17 month toxicity No. Studies (N): 1 cohort with historical control (N=202) Study limitations: High Directness: Direct Consistency: Unknown Precision: Imprecise Reporting bias: Undetected Other issues: None	*Benefits* Median survival time: 17.7 months (3D-CRT), 17.6 months (IMRT), 24.4 months (PBT); P=.1061 *Toxicity* Esophagitis: 5% (PBT), 39% (IMRT) (P<.0001), 18% (3D-CRT) (P=.02) Pneumonitis: 2% (PBT), 6% (IMRT) (P=.23), 30% (3D-CRT) (P<.0001) Dermatitis: 24% (PBT), 17% (IMRT), (P=.30), 5% (3D-CRT) (P=.005). Fatigue: 19% (PBT), 15% (IMRT) (P=.54), 29% (3D-CRT) (P=.09)
6-month severe esophagitis No. Studies (N): 1 cohort with historical control (N=652) Study limitations: Medium Directness: Direct Consistency: Unknown Precision: Imprecise Reporting bias: Undetected Other issues: None	*Toxicity* Severe esophagitis at 6 months: 6% (PBT), 8% (3D-CRT) (P=.42), 28% (IMRT) (P<.0001)

MENINGIOMA

Summary

Comparative evidence for PBT versus conventional photon therapy is limited to one small (N=22) poor-quality retrospective cohort[37] and evidence for combined PBT and photon therapy versus photon therapy alone is limited to another small (N=31) poor-quality retrospective cohort.[40] The ICER review only included the study of PBT versus conventional photon therapy[37] and concluded that the evidence was insufficient to draw conclusions about PBT for meningiomas. We agree with their conclusion since this small study did not provide any data or statistical tests on benefits or harms by treatment group. Based on the additional retrospective cohort we identified, we concluded that there is insufficient evidence to make a conclusion about the benefits and harms of combined PBT and photon therapy for meningioma.[40]

Detailed analysis

PBT versus conventional photon

One poor-quality retrospective cohort provides insufficient evidence on the use of PBT for meningioma.[37] All patients with optic nerve sheath meningioma treated at Massachusetts General Hospital between 1999 and 2006 were included in the study (N=25), with 13 patients receiving photon irradiation, 9 receiving proton irradiation, and 3 patients receiving combination PBT and photon treatment (average dose: 51.4, 51.1, and 57 GyE, respectively). The authors state, "There was no significant difference at most recent follow-up between proton and photon irradiation with regard to tumor control, visual outcome, or treatment side effects." Unfortunately, no data or statistical tests were reported by treatment group. Another limitation of this study is that they did not account for the potential confounding effects of the larger average tumor size in the proton group (4.15 mL vs 2.25 and 3.63 mL), which could have a worse prognosis, or its shorter duration of follow-up (12.5 months vs 42 and 78 months).

Table 13. SOE for Comparative Benefits of PBT or Conventional Photon Therapy for Optic Nerve Sheath Meningioma

Strength of evidence: Insufficient for all outcomes	**Findings**
No. Studies (N): 1 (25) Study limitations: High Directness: Direct Consistency: Unknown Precision: Imprecise Reporting bias: Undetected Other issues: None	*Benefits and toxicity* "There was no significant difference at most recent follow-up between proton and photon irradiation with regard to tumor control, visual outcome, or treatment side effects."

PBT+photon versus photon alone

Evidence on the benefits and harms of combined PBT and photon therapy (59.5-72.0 CGE) compared with photon therapy alone (40.5-76 Gy) is limited to one small, poor-quality retrospective cohort study and is insufficient to draw conclusions about combined PBT and photon therapy for meningioma.[40] In this study, 5-year local control was significantly higher in the combined therapy group (80% vs 17%; P=.008), but was not different at 8 years (40% vs 17%, estimated from figure 2). Among patients with malignant meningioma (N=13), 5- and 8-year overall survival was again significantly higher in the combined therapy group (100% vs 44%; P=.025). Late toxicity outcomes were reported in 3 patients (2 cases of symptomatic necrosis and one case of extensive visual deficits), but the study did not state which treatment these patients received. Because baseline characteristics were not reported by treatment group, it is unclear whether the 2 groups were balanced at baseline on prognostic factors.

Table 14. SOE for Comparative Benefits of Combined PBT and Photon Therapy or Photon Therapy Alone for Meningioma

Strength of evidence: Insufficient for all outcomes	Findings
No. Studies (N): 1 (31) Study limitations: High Directness: Direct Consistency: Unknown Precision: Imprecise Reporting bias: Undetected Other issues: None	*Benefits* 5-year local control:80% (PBT+photon) vs 17% (photon); P=.008 8-year local control:40% (PBT+photon) vs 17% (photon) 5- and 8-year overall survival among malignant meningioma patients:100% (PBT+photon) vs 44% (photon); P=.025

PROSTATE CANCER

Summary

Previous reviews have reached divergent conclusions about the comparative effectiveness of proton beam in prostate cancer.[1,53,54] The ICER review concluded that there is low-strength evidence of comparable benefits and moderate-strength evidence of comparable major harms for proton beam without distinguishing between the various comparators (*eg*, IMRT, 3D-CRT, conventional photon, *etc*). For the comparison of proton beam to IMRT or 3D-CRT, the December 2014 AHRQ Comparative Effectiveness Review[53] on therapies for clinically localized prostate cancer concluded that evidence is inadequate to make a conclusion on the effectiveness of PBT versus IMRT[9,10] or 3D-CRT.[9] For the comparisons of proton beam to brachytherapy and conventional photon therapy, the 2012 California Technology Assessment Forum (CTAF) review concluded that PBT has not been shown to be as beneficial as any established alternatives and, "Thus the role of proton beam therapy for localized prostate cancer within the current list of treatment options remains unclear." Table 15 summarizes the numbers and types of comparative studies and our conclusions for each different comparison of PBT to IMRT, 3D-CRT, brachytherapy, and conventional photon therapy, respectively.

Table 15. Conclusions of Comparative Studies of PBT versus IMRT, 3D-CRT, Brachytherapy, and Conventional Photon Therapy in Prostate Cancer

Comparator	Benefits (Strength of Evidence Grade)	Harms (Strength of Evidence Grade)
PBT vs IMRT	Similar Quality of Life (QOL) (low SOE): 2 historically-controlled cohorts (N=1695):[5,6]	Transiently lower GU toxicity at 0-6 months for PBT (low SOE),[7] but similar GI and GU toxicity at 12-24 months (low to moderate),[7,8] and increased GI toxicity with PBT at 4-5 years (low SOE): 4 retrospective cohorts [8-10] N=34,185
PBT vs 3D-CRT	Similar QOL (insufficient SOE), but survival vs 3D-CRT remains unknown: 1 historically-controlled cohort[5]; N=218	Increased acute GI toxicity with PBT (low SOE): 1 retrospective cohort[9]; N=NR

Comparator	Benefits (Strength of Evidence Grade)	Harms (Strength of Evidence Grade)
PBT vs brachytherapy	Similar 8-yr survival and distant metastasis (low SOE): 1 historically-controlled cohort[11]; N=282	No evidence
PBT+photon vs photon alone	Similar overall 5-8 year survival and QOL (low SOE): (1 RCT, 2 cohort studies; N=567) [12-14]	Increased 8-year rectal bleeding and urethral stricture (low SOE): 1 RCT[14]; N=202

Detailed analysis

PBT versus IMRT

Benefits

No study has directly compared the survival of patients with prostate cancer who were treated with either PBT or IMRT.[5-7,9,10] But based on consistent findings from 2 historically-controlled cohort studies, there is low-strength evidence of no significant differences between PBT and IMRT in bowel, urinary, and sexual quality of life at 2 years (Table 16).[5,6] The main limitation of both studies is their use of a historical IMRT control group from a different site; therefore, it is impossible to rule out confounding by temporal trends or site-specific variables. In both studies, the IMRT groups were drawn from the same population of patients from the Prostate Cancer Outcomes and Satisfaction with Treatment Quality Assessment (PROST-QA) Consortium who were treated between March 2003 and March 2006 at dose ranges of 75.6-79.2 Gy. The PBT groups were 95 patients treated with 74-82 Gy(RBE) at Massachusetts General Hospital between August 2004 and December 2008 and 1,243 patients who had been treated with 78-82 Gy(RBE) at the University of Florida between 2006 and 2010. Patients were in their mid-60s and most had clinical T1 disease. Both studies had between-group differences at baseline, including that PBT patients were more likely to be older, white, have smaller prostate volumes, and to be less likely to receive androgen deprivation therapy (ADT). Results from the Hoppe 2014 study (Table 16) are likely more valid, though, as they used statistical techniques to control for the clinical diversity, whereas the Gray 2013 study did not. An additional major limitation of the Gray 2013 study is that they used different instruments to assess quality of life in each group: the Prostate Cancer Symptom Indices (PCSI) scale for the PBT group and the Expanded Prostate Cancer Index Composite (EPIC) for the IMRT group.

Harms

Some dose-escalation studies have found increased GI complication risks with increased dose of photons,[65] but not with protons.[66] But when compared head-to-head in prostate cancer, proton beam has only transiently reduced risk of 6-month acute GU toxicity versus IMRT, but may increase risk of late GI toxicity after 4-5 years.

GI and GU toxicity at 6 months. One fair-quality retrospective cohort study provides low-strength evidence of transiently lower GU toxicity for PBT versus IMRT at 0-6 months, but no significant difference in GI toxicity (Table 16).[7] This study by Yu and colleagues was a population-based study of Medicare claims data from the Chronic Condition Warehouse database that matched 314 patients with early-stage prostate cancer treated with proton beam

database that matched 314 patients with early-stage prostate cancer treated with proton beam during 2008-2009 at an unknown dose with 628 treated with IMRT.[7] Moderate to severe GI and GU toxicity at 12 months was assessed based on diagnosis or procedure codes.

GI and GU toxicity at 12 to 24 months. Two fair-quality retrospective cohort studies provide moderate-strength consistent evidence of no significant difference between proton beam therapy and IMRT in early GI or GU toxicity (Table 16).[7,8] The first was the study by Yu and colleagues described above.[7] The second study was a matched comparison of prospectively-collected clinician-reported grade 2 or greater GI and GU toxicity for 94 pairs of patients with localized low-intermediate risk prostate cancer who received 79.2 Gy delivered with either proton beam therapy or IMRT between 2010 to 2012 at University of Pennsylvania's proton center.[8] Despite methodological differences (*ie*, claims vs primary source data), the 2 studies were consistent in finding no significant differences in GI or GU toxicity at 12 months. The 2014 retrospective cohort study from the University of Pennsylvania proton center also provides low-strength evidence of no significant differences in GI or GU toxicity at 24 months .[8]

GI toxicity at 4-5 years. Two fair-quality, population-based retrospective cohort studies of Medicare claims data linked to the Surveillance Epidemiology and End Results (SEER) database provide low-strength evidence of an increased risk of late GI toxicity at 4-5 years (Table 16).[9,10] The first of the SEER-database studies, by Kim et al, included patients diagnosed with early-stage localized prostate cancer between 1992 and 2005 and used ICD-9 or CPT procedure codes to assess grade 3 to 4 bleeding, ulceration, fistula, stricture, and colostomy that developed at least 6 months after diagnosis and required intervention.[9] The second of the SEER-database studies, by Sheets et al, assessed risk of unspecified GI morbidity-related procedures (including colonoscopy) and diagnoses that occurred at least 12 months after diagnosis in patients diagnosed with early-stage prostate cancer between 2000 and 2007.[10] The main limitations of both studies include their high potential for exposure and outcome misclassification biases.[67-69] Regarding exposure ascertainment, risk of bias was high because dose and field size specifics were unknown; therefore, the increased risk of late GI toxicity with PBT may have been entirely due to higher doses. Regarding outcome ascertainment, risk of bias was high because of the questionable reliability of using surrogate procedure (including colonoscopy) and diagnosis code-based measures to detect the actual clinical events of interest. Also, both studies may suffer from potential confounding by study site since likely a high majority of proton patients were treated at the single Loma Linda study site, whereas IMRT patients were likely treated at a variety of sites.

Table 16. SOE for Comparative Benefits and Harms of PBT versus IMRT in Prostate Cancer

Strength of evidence	Findings
2-year quality of life: Low No. Studies (N): 2 historically-controlled cohort studies (N=1,695) Study limitations: High Directness: Direct Consistency: Consistent Precision: Imprecise Reporting bias: Undetected Other issues: None	Patients with differences in EPIC summary scores > 50% SD from Hoppe 2014: Bowel: 37% (PBT) vs 38% (IMRT); P=.99 Urinary incontinence: 32% (PBT) vs 34% (IMRT); P=.99 Urinary irritative/obstructive: 17% (PBT) vs 19% (IMRT); P=.99 Sexual: 40% (PBT) vs 41% (IMRT); P=.99
6-month GI and GU toxicity: Low No. Studies (N): 1 retrospective cohort studies (N=1263) Study limitations: Medium Directness: Direct Consistency: Unknown Precision: Imprecise Reporting bias: Undetected	6-month GI diagnosis or procedure codes: PBT=2.9% vs IMRT=3.6%; OR, PBT vs IMRT: 0.84 (0.42 to 1.66) 6-month GU diagnosis or procedure codes: PBT=5.9% vs IMRT=9.5%; OR, PBT vs IMRT: 0.60 (0.38 to 0.96)
12-month GI and GU toxicity: Moderate No. Studies (N): 2 retrospective cohort studies (N=1130) Study limitations: Medium Directness: Direct Consistency: Consistent Precision: Imprecise Reporting bias: Undetected	**Early GI toxicity (12 months)** Claims database analysis: 9.9% (PBT) vs 10.2% (IMRT); OR (PBT vs IMRT): 0.97 (95% CI: 0.61-1.53) Clinician-reported grade ≥ 2 GI toxicity: 4.3% (PBT) vs 13.8% (IMRT); OR (PBT vs IMRT): 0.27 (95% CI: 0.06-1.24) **Early GU toxicity (12 months)** Claims database analysis: 18.8% (PBT) vs 17.5% (IMRT); OR (PBT vs IMRT): 1.08 (95% CI: 0.76-1.54) Clinician-reported grade ≥ 2 GU toxicity:21.3% (PBT) vs 28.7% (IMRT); OR (PBT vs IMRT): 0.69 (95% CI: 0.32-1.51)
24-month GI and GU toxicity: Low No. Studies (N): 1 retrospective cohort study (N=188) Study limitations: Medium Directness: Direct Consistency: Unknown Precision: Imprecise Reporting bias: Undetected	**Late GI toxicity (24 months):** Clinician-reported grade ≥ 2 GI toxicity:12.8% (PBT) vs 10.8% (IMRT); HR (PBT vs IMRT): 1.24 (95% CI: 0.53-2.94) **Late GU toxicity (24 months):** Clinician-reported grade ≥ 2 GU toxicity: 12.8% (PBT) vs 18.3% (IMRT); HR (PBT vs IMRT): 0.56 (95% CI: 0.22-1.41)

4-5 year GI toxicity: Low No. Studies (N): 2 retrospective cohort studies (N=6,350) Directness: Indirect Consistency: Consistent Precision: Imprecise Reporting bias: Undetected	Any GI toxicity after 5 years: 20.1 (PBT) vs 8.3 (IMRT) per 1,000 patient-years; HR (PBT vs IMRT): 3.32 (95% CI: 2.12-5.20) Procedures (including colonoscopy) at 46-50 months: 18 (IMRT) vs 21 (PBT) per 100 person-years; RR (IMRT vs PBT): 0.82 (95% CI: 0.70-0.97) Diagnoses at 46-50 months: 12(IMRT) vs 18(PBT) per 100 person-years; RR (IMRT vs PBT): 0.66 (95% CI: 0.55-0.79)

PBT versus 3D-CRT

Benefits

One poor-quality controlled before/after study provides insufficient evidence on the QOL of prostate cancer patients after PBT or 3D-CRT.[5] This study compares a historical cohort of 123 men who underwent 3D-CRT (66.4-79.2 Gy) between 1994 and 2000 at Harvard-affiliated hospitals with 95 men who underwent PBT (74-82 Gy(RBE)) between 2004 and 2008 at Massachusetts General Hospital. QOL was assessed in both cohorts using the PCSI. After 24 months, both the 3D-CRT (P<.001) and PBT (P=.004) treatment groups reported significantly improved mean bowel/rectal QOL scores compared with baseline. Neither group reported significantly different urinary irritation/obstruction or urinary incontinence QOL scores compared with baseline. Differences were not assessed between treatment groups. This study has a number of limitations, including using a historical cohort from a different site and not controlling for temporal or site differences and uncontrolled baseline differences between the treatment groups. The PBT group was younger, had lower baseline prostate-specific antigen (PSA) values, and included more patients with clinical T1 disease than the 3D-CRT group, potentially improving overall outcomes relative to the 3D-CRT group.

Harms

One fair-quality retrospective cohort provides low-strength evidence that PBT results in more frequent acute GI toxicities compared with 3D-CRT for prostate cancer.[9] Patients included in this study were residents of SEER regions that were diagnosed with T1-T2 clinically localized prostate cancer between 1992 and 2005. A total of 19,063 patients between 66 and 85 years of age that underwent 3D-CRT, IMRT, or PBT were included, but the study did not report how many patients were treated with each modality, or the average dose of each treatment. The overall rate of any GI toxicity was 20.1 events per 1,000 patients treated with PBT followed for one year and 9.2 events per 1,000 patients treated with 3D-CRT followed for one year. After controlling for year of cancer diagnosis, comorbidity, age group, clinical stage at diagnosis, SEER region, race, marital status, poverty status, and cancer grade, the risk of GI toxicity was higher among patients that underwent PBT compared with patients that underwent 3D-CRT (HR:2.13; 95% CI: 1.45-3.13).

Table 17. SOE for PBT versus 3D-CRT in Prostate Cancer

Strength of evidence: Insufficient for bowel/rectal, urinary irritation/obstruction, and urinary incontinence, low for risk of GI toxicity	Findings
Bowel/rectal, urinary irritation/obstruction, and urinary incontinence No. Studies (N): 1 cohort with historical control (N=218) Study limitations: High Directness: Direct Consistency: Unknown Precision: Imprecise Reporting bias: Undetected Other issues: None	24-month mean bowel/rectal QOL scores compared with baseline: significantly improved (P<.001 (3D-CRT), P=.004 (PBT)) 24-month mean urinary irritation/obstruction QOL scores compared with baseline: no difference (P>.05 (3D-CRT and PBT)) 24-month mean urinary incontinence QOL scores compared with baseline: no difference (P>.05 (3D-CRT and PBT))
Risk of acute GI toxicity No. Studies (N): 1 cohort (N=19,063) Study limitations: Medium Directness: Direct Consistency: Unknown Precision: Imprecise Reporting bias: Undetected Other issues: None	Adjusted hazard ratio (PBT vs 3D-CRT): 2.13 (95% CI: 1.45-3.13)

PBT versus brachytherapy

A 2012 study by Coen et al provided low-strength evidence of similar 8-year overall survival and freedom from distant metastasis after combined proton and photon radiation (79.2 GyE) or brachytherapy (^{125}I or ^{103}Pd to doses of 145 Gy or 115 Gy, respectively), but no comparative evidence on toxicity. Coen et al included 141 patients that were treated with a combination of conformal photon radiation and PBT (79.2 GyE) at either the Loma Linda University Medical Center or at Massachusetts General Hospital between 1996 and 1999.[11,70] These patients were matched on T stage, Gleason score, PSA level, and age to 141 patients treated with permanent prostate brachytherapy at Massachusetts General Hospital between 1997 and 2002. Eight-year overall survival was 93% among combination therapy patients and 96% among brachytherapy patients (P=.45). Eight-year freedom from distant metastasis was 99% among combination therapy patients and 96% among brachytherapy patients (P=.42). Subgroup analyses by risk group, T stage, initial PSA level, and Gleason score did not reveal any significant differences between the two treatment groups.

Alternatively, a 2012 meta-analysis by Grimm et el that was based on single-arm brachytherapy studies and two PBT studies[71,72] utilizing data from the PROG/ACR 95-09 RCT[70] concluded that brachytherapy had *higher* average progression-free survival. However, because the Grimm et al

meta-analysis suffered from numerous methodological limitations, we used the higher strength evidence from Coen 2012 to form the basis of our conclusion about how PBT compares to brachytherapy. The Grimm 2012 meta-analysis indirectly compared the proportion of patients with PSA progression-free survival in uncontrolled studies of radical prostatectomy, brachytherapy, EBRT, androgen deprivation therapy, high intensity focused ultrasound, and high dose radiotherapy for low and intermediate risk prostate cancer.[49] The authors of this study concluded that for low risk prostate cancer, higher average progression-free survival was reported for brachytherapy compared with all other treatment modalities. But since there were no common control groups among the included studies, comparability of the study populations cannot be verified. The authors also did not control for potential confounders such as the date or location of treatment in each study. For example, patients receiving PBT were treated at Loma Linda University and Massachusetts General Hospital between 1996 and 1999,[70] while one brachytherapy study included patients treated at a hospital in Michigan and a hospital in Germany from 1991-2002 and 1986-1999, respectively.[73]

Table 18. SOE for Comparative Benefits of Conformal Photon Radiation and PBT or Brachytherapy for Prostate Cancer

Strength of evidence: Low for all outcomes	Findings
No. Studies (N): 1 (282) Study limitations: Medium Directness: Direct Consistency: Unknown Precision: Imprecise Reporting bias: Undetected Other issues: None	*Benefits* 8-year overall survival:93% (PBT+photon) vs 96% (brachytherapy); P=.45 8-year freedom from distant metastasis:99% (PBT+photon) vs 96% (brachytherapy) P=.21

PBT+photon versus photon alone

Benefits

For overall survival, there was low-strength evidence that photon therapy with a proton "boost" and conventional photon therapy had comparative benefits at 8 and 5 years. The 8-year data comes from the fair-quality RCT of 202 patients with advanced stage T3 and T4 treated between 1982 and 1992, which found survival rates of 55% for photon therapy with a proton "boost" and 51% for photon therapy alone.[14] At 5 years, survival rates reported in the RCT were 75% and 80% for photon therapy with a proton "boost" and only photon therapy, respectively[14] and 62% (estimated from figure 3E in Duttenhaver et al) in both groups in a poor-quality retrospective cohort with a broader population of patients with stage T1-T4 who were treated in the decade earlier (1973-1979).[12] The retrospective cohort study was rated poor quality for this outcome since the potentially confounding effects of tumor differentiation were not controlled for and could lead to better survival outcomes.

For other 8-year outcomes, there was no difference in Kaplan-Meier estimates of disease-free survival (72% vs 62%), or local control (77% vs 60%) overall, but local control was significantly improved in the subgroup of patients with poorly differentiated (Gleason score: 4-5) tumors (85% vs 40%; P=.0014).[14]

Neither health-related QOL nor health status differed overall between treatment groups at 18 months in the fair-quality prospective cohort study that followed patients in 5 different treatment groups (surgery, conventional radiation, PBT, a combination of conventional external-beam radiation and PBT, and watchful waiting).[13]

It is important to note that in all 3 studies, the total dose was greater in the combined treatment group compared with the group that just received conventional photon therapy: 75.6 Gy versus 67.2 Gy in the RCT;[14] 70-76.5 CGE versus 60-68.4 Gy in the retrospective cohort study;[12] and 74-75 Gy versus 65-70 Gy in the prospective cohort study.[13] Further, the radiotherapy techniques used in the RCT[14] and the retrospective cohort[12] are outdated and so these outcomes may not be applicable to current radiotherapy methods.

Harms

For 8-year harms, there was low-strength evidence that rectal bleeding was higher among the combined therapy group (32% vs 12%; P=.002) while urethral stricture and gross hematuria were not significantly different between the 2 groups.[14] For earlier time points, there was no difference in toxicity.[12,13] As reported in the retrospective cohort study, urinary and rectal symptom incidence up to 5 years were not significantly different between the 2 treatment groups, but the median follow-up time was not reported.[12] Finally, there was low-strength evidence of no difference in sexual, GI, and urinary treatment symptoms between combined PBT and photon therapy groups after 18 months.[13] As discussed above, in all 3 studies, the total dose was greater in the combined PBT and photon therapy compared with the photon-only group.

Table 19. SOE for Benefits and Harms of Higher Dose PBT+Photon versus Lower Dose Conventional Photon in Prostate Cancer

Strength of Evidence Grade	Study Design: No. Studies (N)	Study Limitations	Direct-ness	Consistency	Precision	Reporting Bias	Other Issues	Findings
Outcome: 8-year overall survival								
Low	RCT: 1 (202)	Medium	Direct	Unknown	Imprecise	Undetected	None	No difference: 55% (PBT+photon) vs 51% (photon)
Outcome: 5-year overall survival								
Low	RCT: 1 (202) Retrospective cohort: 1 (180)	Medium High	Direct	Inconsistent	Imprecise	Undetected	None	No difference: 75% (PBT+photon) vs 80% (photon)
Outcome: quality of life and health status								
Low	Prospective cohort: 1 (185)	Medium	Direct	Unknown	Imprecise	Undetected	None	No difference
Outcome: 8-year rectal bleeding								
Low	RCT: 1 (202)	Medium	Direct	Unknown	Precise	Undetected	None	32% (PBT+photon) vs 12% (photon); P=.002
Outcome: 8-year urethral stricture								
Low	RCT: 1 (202)	Medium	Direct	Unknown	Imprecise	Undetected	None	19% (PBT+photon) vs 8% (photon); P=.07
Outcome: 8-year gross hematuria								
Low	RCT: 1 (202)	Medium	Direct	Unknown	Imprecise	Undetected	None	14% (PBT+photon) vs 8% (photon); P=.25
Outcome: 18-month PTSS measure: sexual, gastrointestinal, and urinary								
Low	Prospective cohort: 1 (185)	Medium	Direct	Unknown	Imprecise	Undetected	None	No difference

SECONDARY MALIGNANCIES IN VARIOUS CANCERS

There is insufficient evidence to draw conclusions about how proton beam therapy compared to other radiation modalities in risk of secondary malignancy. We identified one retrospective cohort study that provided comparative evidence on secondary malignancies in non-metastatic cancer patients treated with PBT or photon modalities for a variety of cancers, but it has numerous methodological limitations which are described below.[16] A total of 558 patients treated with PBT at Massachusetts General Hospital/Harvard Cyclotron between 1973 and 2001 were matched to 558 patients treated with external beam photon radiation included in the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program cancer registry based on cancer site, histology, age at treatment (±10 years), year of treatment (±5 years), and sex. Most patients in the PBT group received 20% of their total dose from photon radiation and the SEER cohort likely contained very few patients that received IMRT. The most common tumor sites in both groups were CNS (32%), head and neck (24%), genitourinary (33%), and musculoskeletal (7.7%). Fewer patients had GI (2.7%), lung (0.4%), and lymphoma (0.2%) cancers. After a median follow-up time of 6.7 years for PBT patients and 6.0 years for photon radiation patients, secondary malignancies developed in 5.2% and 7.5% of the PBT and photon patients, respectively. Among PBT patients, secondary malignancies included 26 solid tumors, 2 lymphomas, and one leukemia. Among photon patients, secondary malignancies included 38 solid tumors and 4 lymphomas. The incidence rate of secondary malignancies was 6.9 and 10.3 cancers per 1,000 person-years among PBT and photon patients, respectively (P=.085) while 10-year cumulative incidence rates were 5.4% and 8.6%, respectively (P=.085). After controlling for age at treatment, sex, tumor site, and year of diagnosis, the risk for developing secondary cancer among PBT patients was half that of photon patients (HR=0.52; 95% CI: 0.32-0.85; P<.01).

The main limitations of this study are its potential for unmeasured confounding due to (1) missing data, (2) unknown radiation field size or dose, and (3) variation in ascertainment methods across groups. First, no information on secondary malignancies was obtained in 27% of patients in the proton therapy group who had no follow-up appointments or could not be reached by mail or phone. As it is plausible that the loss to follow-up is associated with secondary malignancy events, exclusion of those patients could have either over- or under- estimated the effects of proton therapy. Second, although patients were matched by treatment site and histology in an attempt to control for irradiation volume, we still cannot rule out the potential for unmeasured confounding based on this factor because the comparability of the radiation dose and field size are unknown. Thirdly, we cannot rule out the risk of differential misclassification due to variation of ascertainment methods across groups. Data for the proton group are likely more reliable because they were "…abstracted from pathology reports, radiology reports, operative notes and clinic visit notes in accordance with a standardized protocol. Patients were also contacted by mail and scripted telephone calls to obtain data. The second cancer incidence was verified by review of pathology reports." Ascertainment of second cancers in the photon group was based on diagnosis codes from the SEER database, which are known to be prone to misclassification.

Also, these findings may not be widely generalizable. PBT patients that were not matched with SEER patients were significantly different than matched PBT patients, potentially limiting the generalizability of the findings to all PBT patients. Unmatched PBT patients were younger, more likely to be female, followed for a shorter amount of time, and were more likely to have rare

malignancies. Further, it is not clear that the majority of secondary malignancies are a result of treatment because they mostly occurred within the first 5 years of treatment when solid cancers are not plausibly attributed to radiation therapy.[74] Bekelman and colleagues estimated that in the first 5 years after treatment, the incidence rate of secondary malignancies was 11.4 and 25.1 cancers per 1,000 person-years among PBT and photon patients, respectively, while after 5 years, the incidence rate of secondary malignancies was 5.7 and 5.8 cancers per 1,000 person-years among PBT and photon patients, respectively.

Table 20. Findings and SOE for PBT versus Photon and Secondary Malignancy in Various Cancers

Strength of evidence: Insufficient for all outcomes	Findings
No. Studies (N):1 retrospective cohort (N=1,116) Study limitations: High Directness: Direct Consistency: Unknown Precision: Imprecise Reporting bias: Undetected Other issues: None	Secondary malignancy incidence rate:6.9 (PBT) vs 10.3 (photon) per 1,000 person-years; P=.085 10-year cumulative secondary malignancy incidence rates:5.4% (PBT) vs 8.6% (photon); P=.085; Adjusted hazard ratio (PBT vs photon): 0.52 (95% CI: 0.32-0.85)

KEY QUESTION 3: In patients with local recurrences after irradiation, what is the effectiveness of proton beam irradiation compared to conventional x-ray-based external beam modalities and state-of-the-art therapies?

There is insufficient evidence to draw conclusions about the comparative effects of PBT versus other radiation modalities among patients with recurrent tumors. We identified 2 comparative studies on recurrent tumors, one among patients with recurrent malignant brain tumors[17] and one among patients with recurrent liver cancer,[18] but both studies were rated poor quality due to their failure to account for potentially important confounding.

Proton versus SRT or conventional photon in recurrent malignant brain tumors

One retrospective cohort[17] provides insufficient evidence to draw conclusions about PBT compared with SRT or conventional photon therapy for recurrent malignant brain tumor. Patients with recurrent malignant brain tumor after radiotherapy were reirradiated with conventional photons (N=8), stereotactic radiotherapy (N=10), or PBT (N=8) between 2005 and 2010. Patients received an average reirradiation dose of 43.7 (conventional photon), 41.7 (SRT), or 39.5 Gy (PBT). The median follow-up period for survivors was 19.4 months. After a median of 11.6 months, 5 patients (62.5%) in the conventional photon group had died, 5 patients (50%) in the SRT group had died, and 5 patients (62.5%) in the PBT group had died (P>.99). Local recurrence occurred in 2 patients (25%) in the conventional photon group, 3 patients (30%) in the SRT group, and 2 patients (25%) in the PBT group (P>.99). Two patients, both in the SRT treatment group, experienced radiation necrosis. This study was rated poor quality because it did not

account for the potentially confounding effects of younger age (51 vs 64.5 years (SRT)), lower reirradiation dose and larger average tumor size (70.4 vs 11.5 cc (SRT)).

Table 21. SOE for Comparative Benefits of PBT, SRT, or Conventional Photon Therapy for Recurrent Malignant Brain Tumors[17]

Strength of evidence: Insufficient for all outcomes	Findings
No. Studies (N): 1 retrospective cohort (26) Study limitations: High Directness: Direct Consistency: Unknown Precision: Imprecise Reporting bias: Undetected Other issues: None	*Benefits* Mortality after a median of 11.6 months:62.5% (conventional photon), 50% (SRT), 62.5% (PBT); P>.99 Local recurrence:25% (conventional photon), 30% (SRT), 25% (PBT); P>.99

Proton versus photon in recurrent liver cancer

One poor-quality retrospective cohort[18] provides insufficient evidence to draw conclusions about PBT compared with conventional photon therapy for recurrent liver cancer. This study included 8 patients with recurrent hepatocellular carcinoma, 5 treated with protons (68.8-84.5 Gy) and 3 treated with x-rays (60 or 70 Gy). Similar numbers of patients died in the proton and x-ray treatment groups after a median of 18 and 15.5 months, respectively (80% vs 100%; P=.62). This study was rated poor quality mainly because it did not account for the potentially better prognosis in the proton group due the lower median age (56 vs 60 years) and smaller average tumor size (2.7 vs 3.6 cm).

Table 22. SOE for Comparative Benefits of PBT or X-rays for Recurrent Hepatocellular Carcinoma[18]

Strength of evidence: Insufficient for all outcomes	Findings
No. Studies (N): 1 retrospective cohort (8) Study limitations: High Directness: Direct Consistency: Unknown Precision: Imprecise Reporting bias: Undetected Other issues: None	*Benefits* Median survival time:18 months (PBT) vs 15.5 months (X-ray)

Noncomparative studies of proton treatment for various recurrent tumors

Any treatment form is less effective in the setting of disease recurrence, including proton therapy. Compared with results from single-arm studies of proton beam in patients with primary tumors, there is lower survival and higher recurrences in single-arm studies of proton beam in patients with recurrent tumors. In a cohort of chordoma patients with primary (N=36) or locally recurrent (N=14) malignancies, 8-year local recurrence after treatment with a combination of

photons and protons (median dose: 76.6 CGE) was greater among patients with recurrent compared with primary tumors (53% vs 15%; P=.002).[75] Similarly, single-arm studies of recurrent nasopharyngeal carcinoma,[76] hepatocellular carcinoma,[77] and non-small cell lung cancer[78] report lower rates of overall survival compared with single-arm studies of patients with primary tumors of the same type.[58,79,80] However, we have limited confidence that the reduced benefits of proton therapy were primarily due to recurrent tumors, as the difference may have been confounded by clinical and methodological variability between the groups of single-arm studies, including that some of the recurrent tumor studies used a lower dose of radiation,[76,78] were published earlier,[76] and included younger patients[76,77] compared with primary tumor studies.

KEY QUESTION 4A: What are the harms of proton beam irradiation compared to photon-based therapies in treating mobile targets that may move during treatment?

Tumors of the lungs, esophagus, liver, pancreas, breast, prostate, and kidneys are subject to respiratory motion and the magnitude and trajectory of this motion can vary across patients. Respiratory motion can cause problems during imaging, planning, and delivery of radiation therapy, potentially leading to reduced dose calculation accuracy, difficulty quantifying the magnitude of margins, and differences between planned and delivered doses. Methods used to account for respiration motion include respiratory gating (radiation is delivered during a specific point in the breathing cycle), breath-hold, forced shallow-breathing involving a stereotactic body frame, and real-time tumor tracking. To determine the harms of proton beam irradiation compared to photon-based therapies in treating mobile targets that may move during treatment, we looked for studies that reported on (1) comparability of tumor motion between treatment groups and whether tumor motion affected clinical outcomes of interest, (2) existence or comparability of imaging and planning methods used to account for respiratory motion, and (3) existence or comparability of quality assurance standards used to monitor respiratory motion control methods.

Although dosimetric studies comparing methods of accounting for respiratory motion in treatment planning report that 4DCT imaging decreases doses to normal structures compared with other multiphase,[19] free-breathing,[20] or 3DCT imaging,[21] how this translates to clinical outcomes is not clear. We did not identify any studies that evaluated clinical outcomes of interest based on variability in tumor motion, imaging and planning methods used to account for respiratory motion, or quality assurance standards. Only 4 comparative studies explicitly describe imaging and planning methods used to account for respiratory motion, but none evaluated the effects of variability in methods.[11,18,33,34] One retrospective cohort study of lung cancer patients[34] treated with 3D-CRT (2001-2003), IMRT (2003-2005), and PBT (2006-2008) noted that methods of managing tumor motion were used with IMRT and PBT, but not 3D-CRT. Respiration-induced 3D motion of lung tumors was assessed using 4DCT imaging,[81] but the authors did not discuss management of this movement. Survival times did not differ by treatment group. In one retrospective cohort study of esophageal cancer patients,[33] radiation dose was calculated with a free-breathing treatment planning CT or with an average CT calculated from a 4DCT image set, and around 66% of images were attenuation corrected with mid-inspiratory breath-hold from the PET/CT scanner. Clinical outcomes were not discussed by method of radiation dose calculation. In one retrospective cohort study of recurrent hepatocellular

carcinoma,[18] a respiration-gated irradiation system was used on all patients. Finally, in one cohort study of PBT prostate cancer patients case-matched with brachytherapy patients,[11] PBT patients were immobilized for daily treatment using body casts.[70]

SUMMARY OF EVIDENCE BY KEY QUESTION

The table below summarizes the evidence for each key question.

Table 23. Summary of Evidence by Key Question

Key Questions 1, 2, and 4		
Population	**Comparator**	**Findings**
Breast	Single field PBT vs photon-based 3D conformal accelerated partial-breast irradiation	We found low-strength evidence of comparable 7-year cumulative local recurrence, but higher rates of some 7-year skin toxicities with PBT, including moderate/severe dyspigmentation, patchy/marked atrophy, but not for fat necrosis or moderate/severe fibrosis.
CNS: Medulloblastoma	Proton CSI vs photon CSI	We found low-strength evidence that PBT 54.6 GyE and photon therapy 52.9 Gy have comparable benefits, but proton beam therapy was associated with reduced acute toxicity.
CNS: Spinal cord glioma	PBT vs IMRT	We found low-strength evidence that use of PBT may be disadvantageous for highly infiltrative tumors such as intermedullary spinal cord gliomas.
Esophageal	IMRT vs PBT and 3D-CRT vs PBT	There is low-strength evidence that trimodal therapy with neoadjuvant chemoradiation, surgical resection and either proton beam, IMRT or 3D-CRT have comparable risk of 30-day postoperative GI complications, but that 30-day postoperative pulmonary complications for trimodal therapy with proton beam are lower than with 3D-CRT and similar to IMRT. There is also low-strength evidence that proton therapy is associated with a higher risk of 3-month pneumonitis compared with IMRT/3D-CRT. Evidence on benefits and long-term toxicity is still needed to adequately assess net health benefit of proton beam.
Giant cell tumor of the bone	Combined PBT+ photons vs photons alone	We identified insufficient evidence to draw conclusions regarding PBT for giant cell tumor of bone.
Head and neck	PBT vs IMRT	We identified insufficient evidence to draw conclusions about PBT in head and neck cancers.
Uveal hemangioma	PBT vs photons	We identified insufficient evidence to draw conclusions about PBT compared with photons for the treatment of uveal hemangioma.
NSCLC	PBT vs SBRT or CRT	Evidence in early-stage NSCLC was insufficient to draw conclusions.
NSCLC (continued)	PBT vs IMRT or 3D-CRT	In patients with locally advanced NSCLC, there is low-strength evidence that, even at a higher dose (74 Gy), acute risk of severe esophagitis (grade ≥ 3) at 6 months for PBT is similar to 3D-CRT 63 Gy and lower than IMRT 63 Gy. Evidence on survival and 15-17 month toxicity in a subgroup of patients given concurrent chemotherapy was insufficient.

Key Questions 1, 2, and 4		
Population	**Comparator**	**Findings**
Meningioma	PBT vs conventional photon PBT+ photon vs photon alone	We identified insufficient evidence on the use of PBT or combined PBT and photon therapy for meningioma.
Prostate	PBT vs IMRT	We identified low-strength evidence of no significant differences between PBT and IMRT in bowel, urinary, and sexual quality of life at 2 years. Transiently lower GU toxicity at 0-6 months for PBT (low SOE), but similar GI and GU toxicity at 12-24 months (low to moderate), and increased GI toxicity with PBT at 4-5 years (low SOE).
	PBT vs 3D-CRT	We identified insufficient evidence on the QOL of prostate cancer patients after PBT or 3D-CRT. There is low-strength evidence that PBT results in more frequent acute GI toxicities compared with 3D-CRT for prostate cancer.
	PBT vs brachytherapy	There is low-strength evidence of similar 8-year overall survival and freedom from distant metastasis after combined proton and photon radiation (79.2 GyE) and brachytherapy (^{125}I or ^{103}Pd to doses of 145 Gy or 115 Gy, respectively), but no comparative evidence on toxicity.
	PBT+ photon vs photon alone	There is low strength evidence that combined PBT and photon therapy and conventional photon therapy have similar overall survival at 8 years and 5 years. For 8-year harms, there was low-strength evidence that rectal bleeding was higher among the combined therapy group while urethral stricture and gross hematuria were not significantly different between the 2 groups.
Secondary malignancies – various cancers	PBT vs photon	There is insufficient evidence to draw conclusions about how proton beam therapy compares to other radiation modalities in risk of secondary malignancy.

Key Question 3
There is insufficient evidence to make conclusions about the use of PBT among patients with recurrent cancers.

Key Question 4A
We did not identify any studies that evaluated clinical outcomes of interest based on variability in tumor motion, imaging and planning methods used to account for respiratory motion, or quality assurance standards.

DISCUSSION

For all cancer sites and types, except for ocular and pediatric cancers which were not reviewed here, there are no reliable data from long-term randomized trials on survival, quality of life, or functional capacity of patients who underwent PBT compared with any other modality. We could not fully assess the overall net health benefit of proton beam therapy versus its comparators because comparative observational studies did not consistently report many outcomes of greatest interest. No studies reported functional capacity outcomes or overall severe late toxicity. No prospective comparative studies reported secondary malignancies. Ability to deliver planned treatments was reported by only one small retrospective cohort study.

Despite the common claim that the advantage of proton beam therapy is self-evident in all circumstances, comparative studies have not demonstrated any common clinical situations in which proton beam therapy has a measurable advantage over photon radiotherapy modalities on meaningful long-term health outcomes, but have uncovered the potential for increased harm. The only advantages we found were for early toxicities: (1) for medulloblastoma, proton beam may reduce risk of 1-month medical management of esophagitis (5% vs 57%; P<.001), > 5% weight loss (16% vs 64%; P=.004), and Grade ≥ 2 nausea/vomiting (26% vs 71%; P=.004); (2) for esophageal cancer, compared to 3D-CRT, proton beam may lead to a substantial risk reduction in post-operative pulmonary complications (aOR 9.13 for 3D-CRT vs PBT; 30.3% vs 18.1%) when used in trimodal therapy (neoadjuvant chemoradiation followed by surgical resection; 28.4% vs 18.1%); (3) for NSCLC, proton beam may reduce risk of 6-month severe esophagitis compared to IMRT (6% vs 28%; P<.0001); and (4) for prostate cancer, compared with IMRT, proton beam may transiently reduce risk of 6-month GU diagnosis or procedure codes (OR 0.60; 95% CI, 0.38-0.96; 5.9% vs 9.5%). Increased harms include (1) for partial breast irradiation, various skin toxicities are more common with PBT than with 3D-CRT when PBT is delivered in single-fields (range, 54-90% vs 15-28%), (2) for esophageal cancer, acute pneumonitis was more common with PBT than IMRT and 3D-CRT (33% versus 15%; P=.04), (3) for prostate cancer, there is variable increased risk for GI toxicity compared with IMRT and 3D-CRT and for late rectal bleeding for a high-dose combination of protons plus photons compared with photons alone, and (4) for spinal cord gliomas, there is an 18% increased risk of 5-year mortality. We only found one clinical scenario in which there was at least low-strength evidence that proton beam is comparable to other treatment modalities across outcomes and that was for prostate cancer, in which combined proton and photon radiation had similar 8-year overall survival and freedom from distant metastasis compared with brachytherapy. Although we found comparative studies in giant cell tumors of the bone, head and neck cancer, uveal hemangiomas, and meningiomas, they provided insufficient evidence for drawing conclusions. There is insufficient evidence to draw conclusions about the comparative effects of PBT versus other radiation modalities among patients with recurrent tumors or how the comparative effects of proton and photon beam therapies differ according to variation in tumor motion.

Strength of evidence

Overall, however, we have low confidence that these findings reflect the true overall effects of proton beam therapy because the body of comparative studies for proton beam therapy has numerous deficiencies. Typical circumstances that can increase our confidence in the certainty of the findings are when multiple individual studies within an evidence base have a high degree of similarity in the direction or magnitude of effect (consistency) and when the potential for random

error is reduced through the use of sufficient sample sizes (precision). But in most cases among the comparative studies for proton beam therapy, consistency was unknown because there was typically only a single study for each outcome within each cancer type and the effect estimates were imprecise because of small sample sizes. The main limitations in study design and conduct include that most studies (1) were retrospective and some used historical control groups for the photon-based comparator groups, (2) potentially gave proton beam groups an unfair advantage by comparing them to photon-based groups with poorer prognostic profiles without accounting for the important differences, (3) lacked data on radiation dose and field size, (4) could not reliably differentiate toxicity grade, and (4) did not measure many outcomes of greatest interest, including recurrence, ability to deliver planned chemotherapy and radiation regimens, functional capacity, overall severe late toxicity, and secondary malignancies.

Applicability

There are 2 characteristics of the studies worth mentioning that may restrict the applicability of their findings. First, the majority of the proton beam treatment groups came from one of 3 proton facilities that are among the oldest in operation (Loma Linda, MD Anderson, or Massachusetts General). It is unclear whether the patient outcomes of these centers would generalize to other facilities with less experience treating patients and that may have difference standards of care. Second, the majority of the studies include patients that were treated as far back as 1991 to 2003, and it is unclear whether their findings would generalize to current standards of care, which may reflect improvements in proton beam administration skill levels and other advances.

Comparison to previous systematic reviews

It is difficult to directly compare our conclusions to those of many previous reviews as most included many fewer of the more recently published comparative studies. The 2014 review produced by ICER for the Washington State Health Care Authority Health Technology Assessment Program (HTA) had the largest overlap with our scope, but our conclusions differed greatly from theirs. There is no clear pattern to the discrepancies between our conclusions. We did not detect a clear conflict of interest for ICER as their funding statement indicated support from various sources, including government grants, non-profit organizations, health plans/ provider contributions, manufacturer grants, contracts, contributions, but that it was “not accepted from manufacturers or private insurers to perform reviews of specific technologies.” The differences in conclusions could also not clearly be attributed to differences in eligibility criteria, study inclusion, or methods of assessing internal validity or rating strength of evidence.

General limitations of our systematic review

As with other types of research, the limitations of this systematic review are important to recognize. The generalizability of the results are limited by the scope of the key questions and inclusion criteria and by the generalizability of the studies included. The main methodological limitation of this review within the defined scope is the exclusion of studies published in languages other than English. But it is likely that findings from studies published in non-English language journals may have limited applicability to the VA populations.

Gaps in evidence and future research recommendations

Gaps in evidence include the lack of studies on the newer PBT delivery systems and methods (*ie*, pencil beam scanning), assessment of many important outcomes including recurrence, ability to deliver planned chemotherapy and radiation regimens, functional capacity, overall severe late toxicity, and secondary malignancies. Also, although there are many studies that have compared the dosimetric impact between different methods of accounting for tumor motion in treatment planning, including 4DCT imaging, multiphase, free-breathing, or 3DCT imaging, we found no studies of how they compare in clinical outcomes. It is clear that further comparative studies are needed to address the these gaps in evidence. We will discuss the ideal characteristics of future studies using the PICOS framework.

For population and intervention, to further minimize the risk of confounding, we recommend use of greater standardization in measurement of and greater reporting of important patient characteristics by treatment group and proton beam dose and delivery parameters and better accounting for baseline differences. For outcomes, at minimum, future studies should start with using reliable and standardized methods for measuring overall early and late toxicity that account for severity grade, rather than focusing an entire study on just one specific toxicity reflecting a wide range of severity. Ideally, future studies should measure many outcomes of greatest interest, including recurrence, ability to deliver planned chemotherapy and radiation regimens, functional capacity, overall severe late toxicity, and secondary malignancies. For setting, to improve the generalizability and precision, we recommend using a multi-site design. The Proton Therapy Consortium offers an opportunity for its 14 participating proton beam facilities to collectively conduct a cooperative study that would combine data across multiple study sites, which would increase the overall generalizability of their findings. For study design, it is not clear that RCTs are necessary or possible, and well-designed prospective cohort studies may be acceptable. Some practitioners of and advocates for PBT have argued that conducting studies that randomize patients to PBT or photon-based treatment is unethical.[82] Due to the superior dose distribution achieved by PBT, they argue, protons can provide therapy superior to photons in almost every circumstance and so randomizing patients to receive proton or non-proton therapy would preclude the requirement of equipoise needed to ethically conduct a RCT.[82] Other clinicians and experts in radiation oncology question whether PBT's dosimetric characteristics translate into measurable clinical benefits or increased survival for patients.[83] The lack of obvious clinical benefit in some observational studies[84] lead some to question whether conducting RCTs would in fact be unethical.[83] We identified 9 ongoing RCTs that are comparing proton beam therapy to conventional photon beam therapy (N=3), IMRT (N=5), SBRT (N=1), and 3D-CRT (N=1) and include the cancer types of non-small cell lung cancer (NSCLC), prostate cancer, meningioma, glioblastoma, esophageal cancer, and oropharyngeal cancer patients (see Appendix F). Four of these ongoing studies are multi-site and are being conducted at MD Anderson Cancer Center, Massachusetts General Hospital, and the University of Pennsylvania as well as other centers in the US and abroad. Many have estimated completion dates in the next 2 years. A review of their protocols suggests the potential for some improvement in toxicity measurement. For example, NCT01512589, a Phase III randomized trial of proton beam therapy versus IMRT for esophageal cancer, has a planned outcome of total toxicity burden. However, it is not clear they will fully address all missing outcomes.

CONCLUSION

Despite the common claim that the advantage of proton beam therapy is self-evident, comparative studies have not demonstrated any common clinical situations in which proton beam therapy has a measurable advantage over photon radiotherapy modalities on meaningful *long-term* health outcomes, but have uncovered low-strength evidence of the potential for increased late toxicity compared with IMRT and 3D-CRT for breast, esophageal, prostate, and spinal cord glioma cancers. Existing comparative studies have numerous methodological deficiencies that limited our confidence in their findings and their findings may have limited applicability across all US proton beam facilities. Although numerous randomized controlled trials are underway that carry the promise of improved toxicity measurement, it is unclear whether they will fully address gaps in evidence on other important outcomes including recurrence, ability to deliver planned chemotherapy and radiation regimens, functional capacity, overall severe late toxicity, and secondary malignancies. Because this is still a rapidly evolving field, with ongoing efforts to improve techniques and reduce costs, this review may need more frequent updating to keep up-to-date with emerging research.

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APPENDIX A. PROTON BEAM THERAPY COVERAGE POLICIES

Organization	Title	Last Review	Policy
Aetna	Clinical Policy Bulletin: Proton Beam and Neutron Beam Radiotherapy	8/8/2014	Aetna considers proton beam radiotherapy medically necessary in any of the following radiosensitive tumors: A. Chordomas or chondrosarcomas arising at the base of the skull or cervical spine without distant metastases; or B. Malignancies in children (21 years of age and younger); or C. Uveal melanomas confined to the globe (*ie*, not distant metastases) (the uvea is comprised of the iris, ciliary body, and choroid [the vascular middle coat of the eye]). Aetna considers proton beam radiotherapy for treatment of prostate cancer not medically necessary for individuals with localized prostate cancer because it has not been proven to be more effective than other radiotherapy modalities for this indication. Proton beam therapy for metastatic prostate cancer is considered experimental and investigational. Aetna considers proton beam radiotherapy experimental and investigational for all other indications.
American Society for Radiation Oncology (ASTRO)	Model Policy: Proton Beam Therapy	5/20/2014	The Model Policy lists the following disease sites that support the use of PBT: (1) Ocular tumors, including intraocular melanomas; (2) Tumors that approach or are located at the base of skull, including but not limited to chordoma and chondrosarcomas; (3) Primary or metastatic tumors of the spine where the spinal cord tolerance may be exceeded with conventional treatment or where the spinal cord has previously been irradiated; (4) Primary hepatocellular cancer treated in a hypofracitonated regimen; (5) Primary or benign solid tumors in children treated with curative intent and occasional palliative treatment of childhood tumors when at least one of the four criteria noted above apply; (6) Patients with genitive syndromes making total volume of radiation minimization crucial such as but not limited to NF-1 patients and retinoblastoma patients. All other indications…are suitable for Coverage with Evidence Development (CED). Radiation therapy for patients treated under the CED paradigm should be covered by the insurance carrier as long as the patient is enrolled in either an IRB-approved clinical trial or in a multi-institutional patient registry adhering to Medicare requirements for CED. At this time, no indications are deemed inappropriate for CED and therefore…includes various systems such as, but not limited to, the following: head and neck malignancies, thoracic malignancies, abdominal malignancies, pelvic malignancies including genitourinary, gynecologic, and gastrointestinal carcinomas.

Organization	Title	Last Review	Policy
Anthem	Proton Beam Radiation Therapy Medical Policy	5/15/2014	All Conditions other than Localized Prostate Cancer Proton beam radiation therapy, with or without stereotactic techniques, is considered medically necessary for the following conditions: (1) As primary therapy for melanoma of the uveal tract (iris, choroid, or ciliary body) involving tumors of up to 24 mm in largest diameter and 14 mm in height, and with no evidence of metastasis or extrascleral extension; (2) As postoperative therapy for individuals who have undergone biopsy or partial resection of a chordoma or low-grade (I or II) chondrosarcoma of the basisphenoid region (for example, skull-base chordoma or chondrosarcoma) or cervical spine and have residual, localized tumor without evidence of metastasis; (3) Pituitary adenoma when conventional stereotactic radiation is not an available option; (4) Intracranial arteriovenous malformation (AVM) not amenable to surgical excision or other conventional forms of treatment; (5) Central nervous system (CNS) lesions including but not limited to, primary or metastatic CNS malignancies or arteriovenous malformations, adjacent to critical structures such as the optic nerve, brain stem or spinal cord. Proton beam radiation therapy is considered not medically necessary for the treatment of choroidal neovascularization secondary to age-related macular degeneration (AMD). Proton beam radiation therapy is considered investigational and not medically necessary for all other indications not meeting the criteria above. Localized Prostate Cancer Proton beam radiation therapy is considered medically necessary for the initial monotherapy radiation treatment of localized prostate cancer. The use of proton beam radiation as dose escalation therapy, in conjunction with stereotactic radiosurgery, IMRT, three-dimensional conformal radiation therapy (3D CRT), or brachytherapy for the treatment of localized prostate cancer is considered investigational and not medically necessary. Proton beam radiation therapy is considered investigational and not medically necessary for the treatment of prostate cancer for all other indications not meeting the criteria above.

Organization	Title	Last Review	Policy
BlueCross BlueShield of North Carolina	Corporate Medical Policy Charged Particle Radiotherapy (Proton or Helium Ion)	6/2014	Charged particle irradiation with proton or helium ion beams may be considered medically necessary for the following clinical indications: (1) primary therapy for melanoma of the uveal tract (iris, choroid or ciliary body), with no evidence of metastasis or extrascleral extension, and with tumors up to 24 millimeters in largest diameter and 14 millimeters in height; (2) post-operative therapy (with or without conventional high energy X-rays) in patients who have undergone biopsy or a partial resection of chordoma or low grade (I or II) chondrosarcoma of the basisphenoid region (skull-base chordoma or chondrosarcoma) or cervical spine. Patients eligible for this treatment have residual localized tumor without evidence of metastasis; (3) In the treatment of pediatric central nervous system (CNS) tumors. Charged particle irradiation with proton beams using standard treatment doses is considered not medically necessary and therefore non -covered in patients with clinically localized prostate cancer, because the clinical outcomes with this treatment have not been shown to be superior to other approaches including intensity modulated radiation therapy (IMRT) or conformal radiation therapy. Charged particle irradiation is considered investigational for all other indications not addressed above under, When Charged Particle Radiotherapy is covered
BlueCross BlueShield of California	Charged-Particles (Proton or Helium) Radiation Therapy Medical Policy	10/28/2013	Charged-particle irradiation with proton or helium ion beams may be considered medically necessary and a covered benefit in any of the following clinical situations: (1) Primary therapy for melanoma of the uveal tract (iris, choroid, or ciliary body) and both of the following: a. No evidence of metastasis or extrascleral extension, b. Tumor size up to 24 millimeters in largest diameter and 14 millimeters in height; (2) Postoperative therapy (with or without conventional high-energy x-rays) for residual localized tumor without metastasis in patients who have undergone biopsy or partial resection of one of the following: a. Chordoma, b. Low-grade (I or II) chondrosarcoma of the basisphenoid region (*eg*, skull-base chordoma or chondrosarcoma) or cervical spine; (3) Treatment of pediatric central nervous system tumors. Charged-particle irradiation with proton or helium beams is generally not a covered service for prostate cancer (clinically localized prostate cancer) because it is not cost-effective. Other applications of charged-particle irradiation with proton beams are considered investigational.

Organization	Title	Last Review	Policy
CIGNA	Proton Beam Therapy for Intracranial and Skull Base Tumors	Unknown	CIGNA HealthCare covers proton beam therapy as medically necessary for the treatment of intracranial and skull base tumors when radiation therapy is indicated and recommended by the treating physician.
CIGNA	Proton Beam Therapy for Ocular Melanoma, Ocular Hemangiomas and Macular Degeneration	Unknown	CIGNA HealthCare covers proton beam therapy as medically necessary for the treatment of melanoma of the uveal tract (*ie*, iris, ciliary body and choroid). CIGNA HealthCare does not cover proton beam therapy for choroidal hemangiomas or macular degeneration, because it is considered experimental, investigational or unproven.
CIGNA	Proton Beam Therapy for Prostate Cancer	Unknown	CIGNA HealthCare considers proton beam therapy to be clinically equivalent to conventional external beam radiation therapy for the treatment of localized prostate cancer (*ie*, cancer that is confined to the prostate), but does not consider it to be clinically superior to conventional external beam radiation therapy. Coverage for proton beam therapy for the treatment of localized prostate cancer may depend upon the applicable health benefit plan definition of medical necessity. Many health benefit plans administered by CIGNA HealthCare contain definitions of medical necessity which include a cost comparison component. Because proton beam therapy for the treatment of prostate cancer is significantly more expensive than conventional external beam radiation therapy but is not clinically superior, it is considered not medically necessary under those plans. For health benefit plans which contain definitions of medical necessity that do not include a cost comparison component, proton beam therapy may be covered as medically necessary for the treatment of localized prostate cancer (*ie*, cancer that is confined to the prostate).
CIGNA	Proton Beam Therapy for Lung Cancer	Unknown	Cigna does not cover proton beam therapy for the treatment of lung cancer because it is considered experimental, investigational or unproven.

Organization	Title	Last Review	Policy
HealthPartners	Proton Beam Radiation Therapy	7/2014	Indications that are covered: (1) Melanoma of the uveal tract that is not amenable to surgical excision or other conventional forms of treatment; (2) Chordomas or chondrosarcomas arising at the base of the skull or along the axial skeleton without distant metastases; (3) Pituitary neoplasms; (4) Other central nervous system tumors located near vital structures; (5) Salivary gland tumors. Indications not covered: (1) Prostate cancer; (2) Hepatocellular cancer; (3) Lung cancer; (4) Bladder cancer; (5) Breast cancer; (6) Esophageal cancer; (7) Cervical cancer; (8) Age-related maculardegeneration (AMD); (9) Chorical hemangiomas; (10) Non-uveal melanoma; (11) Parotid gland tumor; (12) Colon cancer; (13) Kidney cancer; (14) Pancreatic cancer; (15) Rectal cancer; (16) Soft tissue sarcomas.
Medica	Proton Beam Radiation Therapy	6/2013	Proton beam radiation therapy is indicated for individuals with conditions not amenable to surgical excision or other conventional forms of treatment AND have one of the following diagnoses: A. Chordomas or chondrosarcomas arising at the base of the skull or along the axial skeleton without distant metastasis; B. Pediatric central nervous system tumors adjacent to vital structures (*eg* optic nerve, spinal cord); C. Melanoma of the uveal tract (iris, choroid, ciliary body) without extrascleral extension and with no evidence of metastasis. Proton beam radiation therapy for hepatocellular cancer, prostate cancer or non-small cell lung cancer (NSCLC) is investigative and therefore not covered.

Organization	Title	Last Review	Policy
Regence	Charged-Particle (Proton or Helium Ion) Radiation Therapy	6/2014	Charged-particle irradiation with proton or helium ion beams may be considered medically necessary in the following clinical situations: A. Primary therapy for melanoma of the uveal tract (iris, choroid, or ciliary body), with no evidence of metastasis or extrascleral extension, and with tumors up to 24 mm in largest diameter and 14 mm in height; B. Postoperative therapy (with or without conventional high-energy x-rays) in patients who have undergone biopsy or partial resection of the chordoma or low-grade (I or II) chondrosarcoma of the basisphenoid region (skull-base chordoma or chondrosarcoma) or cervical spine. Patients eligible for this treatment have residual localized tumor without evidence of metastasis.; C. In the treatment of pediatric (less than 21 years of age) central nervous system tumors and retinoblastoma. Charged-particle irradiation with proton beams is considered not medically necessary in patients with clinically localized prostate cancer. Other applications of charged-particle irradiation are considered investigational.
United Healthcare	Medical Policy: Proton Beam Radiation Therapy	9/2014	Proton beam radiation therapy is proven and medically necessary for the following indications: (1) Intracranial arteriovenous malformations (AVMs); (2) Ocular tumors, including intraocular/uveal melanoma (includes the iris, ciliary body and choroid); (3) Skull-based tumors (*eg*, chordomas or chondrosarcomas). Proton beam radiation therapy is unproven and not medically necessary for treating ALL other indications.

Organization	Title	Last Review	Policy
Wellmark	Proton Beam Radiation Therapy	1/2014	Proton beam therapy may be considered medically necessary for the following conditions: (1) Primary therapy for melanoma of the uveal tract (*ie* iris, choroid, or ciliary body), with no evidence of metastasis or extrascleral extension and with tumors up to 24mm in largest diameter and 14mm in height; (2) Post operative therapy (with or without conventional high energy x-ray) in patients who have under gone biopsy or partial resection of the chordoma or low grade (I or II) chondrosarcoma of the basisphenoid region (skull-base chordoma or chondrosarcoma) or cervical spine. Patients eligible for this treatment have residual localized tumor without evidence of metastasis. (3) Osteosarcoma for patients with unresectable or incompletely resected osteosarcoma; (4) Central nervous system tumors (*ie* tumors within the skull, skull based tumors and spinal cord tumors); (5) Intracranial arteriovenous malformations, small lesions when surgery may be associated with increased risk based on anatomic location or feeding vessel anatomy; (6) Soft tissue sarcoma. Postoperative use in retroperitoneal soft tissue sarcoma not amenable to other radiotherapy (*eg*, IMRT, stereotactic body radiotherapy) in persons who have not received preoperative radiotherapy. Proton beam therapy as a treatment for prostate cancer is considered not medically necessary because the clinical outcomes with this treatment have not been shown to be superior or more effective than the other radiotherapy modalities for this indication. Proton beam radiation therapy is considered investigational for all other indications not meeting the criteria above.

APPENDIX B. CLINICAL PRACTICE GUIDELINES IN OTHER ORGANIZATIONS

Organization	Population	Title	Year	Statement
Alberta Health Services, Cancer Care	All diagnoses	Proton beam radiation therapy	2013	"Adult tumour sites that may be considered for referral for out-of-country proton beam radiotherapy include: a. The following CNS tumours or lesions: arteriovenous malformations, benign meningioma, neuromas, craniopharyngioma, CNS germ cell tumours, and low grade gliomas b. The following non-CNS tumours: sarcoma including chordoma and chondrosarcoma, lymphoma in patients under the age of 30 years, and paranasal sinus and nasal cavity tumours. Adult, pediatric, and adolescent patients with ocular melanomas requiring proton beam radiotherapy should be sent to the TRIUMF Proton Treatment Facility in Vancouver, British Columbia (BC) for treatment. Members of the working group do not currently recommend that patients with prostate cancer, non-small cell lung cancer, or most lymphomas be referred for proton beam radiotherapy, due to an insufficient evidence base. However, individual patient cases should be discussed by the multidisciplinary team during a Tumour Board meeting."
American College of Radiology	Stage T1 and T2 prostate cancer	ACR Appropriateness Criteria® definitive external-beam irradiation in stage T1 and T2 prostate cancer.	2013	"There are only limited data comparing proton beam therapy to other methods of irradiation or to radical prostatectomy for treating stage T1 and T2 prostate cancer. Further studies are needed to clearly define its role for such treatment."
American College of Radiology	N2 non-small cell lung cancer	ACR Appropriateness Criteria® induction and adjuvant therapy for N2 non–small-cell lung cancer.	2013	"The utility of intensity-modulated radiation therapy (IMRT) or protons to potentially further reduce normal tissue toxicity remains to be explored."

Organization	Population	Title	Year	Statement
American College of Radiology	Lymphoma	ACR Appropriateness Criteria® localized nodal indolent lymphoma.	2013	"Advanced radiation techniques, such as IMRT and proton therapy, may be considered depending on the clinical scenario and whether an improvement in the therapeutic ratio is expected."
American College of Radiology	Cervical cancer	ACR Appropriateness Criteria® advanced cervical cancer.	2012	"The combined use of imaging, advanced radiotherapeutic modalities, and chemotherapy has led to better treatment for cancer of the cervix." Particle therapy is included as one of the external beam radiotherapies.
American College of Radiology	Prostate cancer	ACR Appropriateness Criteria® external beam radiation therapy treatment planning for clinically localized prostate cancer.	2011	Proton beam therapy is "usually appropriate" (rating of 7) for treating prostate cancer.
American College of Radiology	Breast cancer	ACR Appropriateness Criteria® locally advanced breast cancer.	2011	"Maximal cardiac sparing achieved through proton therapy has the potential to decrease [common treatment-related toxicities]."
American College of Radiology	Brain cancer	ACR Appropriateness Criteria® pre-irradiation evaluation and management of brain metastases.	2011	Not mentioned

Organization	Population	Title	Year	Statement
American College of Radiology	Head/neck cancer	ACR Appropriateness Criteria® retreatment of recurrent head and neck cancer after prior definitive radiation.	2010	"Experience with nasopharyngeal retreatment has included combinations of nasopharyngectomy, chemotherapy, external beam radiation therapy (EBRT), brachytherapy, intraoperative radiotherapy, hyperthermia, radiosurgery, and proton therapy."
BlueCross BlueShield	Prostate cancer	Proton Beam Therapy for Prostate Cancer	2014	"Based on the above, proton beam therapy as a boost to photon external-beam radiotherapy or proton beam therapy without photon external-beam radiotherapy in the treatment of prostate cancer does not meet the TEC criteria."
BlueCross BlueShield	Non-small cell lung cancer	Proton Beam Therapy for Prostate Cancer	2014	"Proton beam radiotherapy for treatment of non-small cell lung cancer at any stage or for recurrent non-small cell lung cancer does not meet the TEC criteria."
National Comprehensive Cancer Network	Prostate Cancer	NCCN Guidelines Version 1.2015 Prostate Cancer	2014	"An ongoing prospective randomized trial is accruing patients and comparing prostate proton therapy to prostate IMRT. The NCCN panel believes there is no clear evidence supporting a benefit or decrement to proton therapy over IMRT for either treatment efficacy or long-term toxicity. Conventionally fractionated prostate proton therapy can be considered a reasonable alternative to X-ray based regimens at clinics with appropriate technology, physics, and clinical expertise."

APPENDIX C. SEARCH STRATEGIES

MEDLINE® via PubMed® searched on December 10, 2014

Concept	Search Terms	Comments
All Cancers	neoplasm* OR cancer* OR carcinom*	Key words in title/abstract
Proton Beam Therapy	proton OR "proton beam" OR "proton beam therapy" OR proton* OR proton* therap* OR protontherap*	Key words in title/abstract
	"Protons"[Mesh] OR "Proton Therapy"[Mesh]	MeSH terms
Limits	AND Humans[Mesh] AND English[lang]	Removes non-English language articles and animal studies
	NOT (Comment[ptyp] OR Letter[ptyp] OR Review[ptyp])	Removes publication types that are not studies. (this is more sensitive than restricting the search to RCTs)
	NOT ("Proton Pump Inhibitors"[Mesh] OR "Proton Pump Inhibitors" [Pharmacological Action])	Removes Proton Pump Inhibitor Studies
	NOT AND (infant[MeSH] OR child[MeSH] OR adolescent[MeSH])	Removes Children from search (safer than limiting to adults only)
Total Results = 1,964		

Cochrane Central Register of Controlled Trials via OVID searched on December 10, 2014

Step	Term	Results
1	exp Protons/	106
2	proton.mp.	2,172
3	proton beam.mp.	37
4	proton beam therapy.mp.	7
5	exp Proton Therapy/	3
6	proton*.mp.	2,239
7	proton$ therap$.mp.	19
8	protontherap$.mp.	0
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8	2,239
10	(neoplasm* or cancer* or carcinoma*).mp.	68,072
11	9 and 10	169
12	limit 11 to english language	146
13	Proton Pump Inhibitors/	811
14	12 not 13	111
15	limit 14 to (editorial or letter or "review")	0
16	14 not 15	111

ClinicalTrials.gov searched on December 10, 2014

Term	Results
neoplasm* or cancer* or carcinoma* | proton therapy | Adult, Senior	50

MEDLINE® via PubMed® searched on December 10, 2014 with special emphasis on selected journals without any limitations for cancer type for proton beam therapy

Concept	Search Terms	Comments
Proton Beam Therapy	proton[tiab] AND irradiation OR radiation OR radiotherap* OR therap* OR beam[tiab]	Keywords in title or abstract
	OR "Proton Therapy"[Mesh] OR "Protons/therapeutic use"[Mesh]	Medical Subject terms
Selected Journals	"Acta oncologica (Stockholm, Sweden)"[Journal] OR "American journal of clinical oncology"[Journal] OR "BMC cancer"[Journal]) OR "Cancer"[Journal] OR "Cancer journal (Sudbury, Mass.)"[Journal] OR "International journal of radiation oncology, biology, physics"[Journal] OR "J Clin Oncol"[Journal] OR "J Surg Oncol"[Journal] OR "JAMA : the journal of the American Medical Association"[Journal] OR "J Thorac Oncol"[Journal] OR "Jpn J Clin Oncol"[Journal] OR "Radiat Oncol"[Journal] OR “Radiother Oncol” [Journal] OR "Strahlenther Onkol"[Journal] OR "Urology"[Journal]	Top journals from previous search
Total Results = 927		

APPENDIX D. ICER COMPARATIVE STUDIES EXCLUDED AT FULL-TEXT LEVEL

Citation	Reason for Exclusion
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.* Dec 1 2009;75(5):1487-1492.	Ineligible comparator: carbon ion therapy
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.	Ineligible population: uveal melanoma patients
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.* Oct 2013;109(1):32-37.	Ineligible comparator: carbon ion therapy
Gragoudas ES, Lane AM, Regan S, et al. A randomized controlled trial of varying radiation doses in the treatment of choroidal melanoma. *Arch Ophthalmol.* Jun 2000;118(6):773-778.	Ineligible population: uveal melanoma patients
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.* Jan 1 2010;76(1):36-42.	Ineligible outcomes: interval to reach PSA nadir, PSA level, biological no evidence of disease
Komatsu S, Fukumoto T, Demizu Y, et al. Clinical results and risk factors of proton and carbon ion therapy for hepatocellular carcinoma. *Cancer.* Nov 1 2011;117(21):4890-4904.	Ineligible comparator: carbon ion therapy
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.* Jul 15 2012;83(4):e537-543.	Ineligible outcome: decline in lung diffusing capacity for carbon monoxide
Matsuzaki Y, Osuga T, Chiba T, et al. New, effective treatment using proton irradiation for unresectable hepatocellular carcinoma. *Intern Med.* Apr 1995;34(4):302-304.	Ineligible comparator: proton beam therapy plus chemotherapy
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.* Oct 1 2009;75(2):378-384.	Ineligible comparator: carbon ion therapy
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.* Aug 1 2006;65(5):1514-1521.	Ineligible comparator: proton beam therapy plus photon therapy and surgery
Sethi RV, Shih HA, Yeap BY, et al. Second nonocular tumors among survivors of retinoblastoma treated with contemporary photon and proton radiotherapy. *Cancer.* Jan 1 2014;120(1):126-133.	Ineligible population: pediatric and retinoblastoma
Tokuuye K, Akine Y, Kagei K, et al. Proton therapy for head and neck malignancies at Tsukuba. *Strahlenther Onkol.* Feb 2004;180(2):96-101.	Ineligible comparator: proton beam therapy plus photon therapy

APPENDIX E. QUALITY ASSESSMENT OF PRIMARY STUDIES

Observational Studies

Author Year Country	Non-biased selection?	High overall loss to follow-up or differential loss to follow-up?	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality rating
Arvold 2009 US	"The decision to treat patients with photons versus protons versus a combination of both was made by the treating radiation oncologist and was based primarily on treatment machine availability."	No. 12% (3/25) loss to follow-up.	Yes.	Yes.	Yes.	No. Differences in tumor size at baseline (2.25 mL, 3.63 mL, and 4.15 mL).	No. 42 months for photon therapy, 78 months for combination therapy, and 12.5 months for proton therapy.	Poor.

Author Year Country	Non-biased selection?	High overall loss to follow-up or differential loss to follow-up?	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality rating
Brown 2013 US	Unclear how patients were selected for each group.	Unclear.	Yes.	Yes.	Yes. Unknown whether outcome ascertainers were blinded, outcomes are not subjective.	Not adequate. Only performed for hematologic toxicity endpoints.	No. 26.3 months (PBT) vs 57.1 months (photon)	Poor.
Chakravarti 1999 US	Unclear how patients were selected for each group.	N/A	Yes.	Yes.	Yes.	No. Differences in age at baseline (23.5 yrs vs 52.5 yrs for combined and photon only groups, respectively).	Yes.	Poor.

Author Year Country	Non-biased selection?	High overall loss to follow-up or differential loss to follow-up?	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality rating
Chung 2013 US	Yes. Patients compared with historical results, but matched.	Yes. 27% excluded from proton cohort because they were lost to follow-up and it is plausible that their loss is associated with second cancer events.	Yes.	Yes.	No. Method of data collection differed between groups. PBT: "data abstracted from pathology reports, operative notes and clinic visit notes ... Patients were also contacted by mail and scripted telephone calls to obtain data." Photon group: based on diagnosis codes from SEER database.	Age at treatment, sex, primary tumor site, and year of treatment. No information on dose of RT or chemotherapy in either group.	No.	Poor.

Author Year Country	Non-biased selection?	High overall loss to follow-up or differential loss to follow-up?	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality rating
Coen 2012 US	Yes. Patients compared with historical results, but matched.	N/A	Yes.	Yes.	Unclear.	No, but matched on T stage, Gleason score, PSA level, and age.	Yes.	Fair.
Duttenhaver 1983 US	Unclear how patients were selected for each group.	No.	Yes.	Yes.	Yes. While outcome ascertainers were apparently not blinded, outcomes are not subjective.	No. Did not control for potentially confounding effects of differentiation which could lead to better survival, but had an unknown effect on local control. XRT: 55% had poorly differentiated tumors XRT+PBT: 35% had poorly differentiated tumors	Yes.	Local control: Fair. Other outcomes: Poor.

Author Year Country	Non-biased selection?	High overall loss to follow-up or differential loss to follow-up?	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality rating
Fang 2014 US	Allocation to PBT or IMRT was based on suitability for PBT as determined by triage committee, patient desire, machine availability, and insurance coverage.	N/A	Yes.	Yes.	Unknown whether outcome assessors were blinded	Yes. Matched on prostate cancer risk group, age at diagnosis, prior GI or GU disorders. Potential confounders included ADT, hypertension, hemorrhoids, diabetes, Eastern Cooperative Oncology Group performance status, IPSS score and Bowel Symptom Score.	No. Shorted F/U time for the PBT group compared with IMRT group (29 months vs 47 months)	Fair.

Author Year Country	Non-biased selection?	High overall loss to follow-up or differential loss to follow-up?	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality rating
Galbraith 2001 US	Yes.	No. 17% attrition at 18 months.	Yes.	Yes.	Yes.	No. Age and stage assessed as covariates, but were not significant.	Yes.	Fair.
Galland-Girodet 2014 US	Unclear how patients were selected for each group.	No. 2% loss to follow-up	Yes.	Yes.	Yes. While outcome ascertainers were apparently not blinded, outcomes are not subjective.	No. No significant differences in patient or tumor characteristics between the two groups.	Yes.	Fair.
Gomez 2012 US	No. PBT patients compared with historical results.	No.	Yes.	Yes.	Yes.	Yes. Age, gender, smoking status, stage, and histology did not predict severe esophagitis.	Yes.	Fair.

Author Year Country	Non-biased selection?	High overall loss to follow-up or differential loss to follow-up?	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality rating
Gray 2013 US	No. PBT patients compared with historical results.	No.	Yes.	Yes.	Unclear.	No. Did not control for time or site-specific variables.	Yes.	Poor.
Hocht 2006 Germany	Patients received protons once they were made available in Germany in 1998.	N/A	Yes.	No.	Unclear.	Controlled for differential follow-up time, tumor characteristics differed at baseline.	Yes.	Fair.
Hoppe 2014 US	No. PBT patients compared with historical results.	No.	Yes.	Yes.	Unclear.	Yes. Controlled for age, prostate size, ADT use, baseline QOL, but not for time or site-specific variables.	Yes.	Poor.

Author Year Country	Non-biased selection?	High overall loss to follow-up or differential loss to follow-up?	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality rating
Hug 2000 US	"Patients were selected for protons or photons based on the specific dose conformity advantages of protons for certain anatomic locations and for high degrees of target irregularity."	No.	Yes.	Yes.	Yes.	Unknown. No baseline patient characteristics were given by treatment group.	Yes.	Poor.
Kahn 2011 US	Unclear how patients were selected for each group.	No.	Yes.	Yes.	Yes. Unknown whether outcome ascertainers were blinded, outcomes are not subjective.	Performed for survival but not local control outcome.	Yes.	Poor.

Author Year Country	Non-biased selection?	High overall loss to follow-up or differential loss to follow-up?	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality rating
Kim 2011 US	Yes.	N/A	Yes.	Yes.	Yes.	Yes. Controlled for diagnosis year, comorbidity, age group, clinical stage, SEER region, race, marital status, poverty, cancer grade.	Yes.	Fair.
McCurdy 2013 US	Unclear how patients were selected for each group.	No.	Yes.	Yes.	Yes.	No.	Yes.	Fair.
Mizumoto 2013 Japan	Treatment modality was chosen based on the location, distribution, and size of recurrent tumor.	No.	Yes.	Yes.	Yes.	No. Initial radiation dose, age, tumor volume differed between the reirradiation treatment groups.	Yes.	Poor.

Author Year Country	Non-biased selection?	High overall loss to follow-up or differential loss to follow-up?	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality rating
Otsuka 2003 Japan	Patients were selected for each group based on availability of PBT system.	No.	No.	No.	Unclear.	No. X-ray group older (60 vs 56 years) and had larger tumors (3.6 vs 2.7 cm) at baseline.	Yes.	Poor.
Sejpal 2011 US	No. PBT patients compared with historical results.	No.	Yes.	Yes.	Yes.	Performed stratification of harms, but not multivariate regression. Didn't control for temporal trends or differences at baseline (age, race, disease stage, tumor volume, adjuvant chemotherapy, time since treatment)	Yes.	Poor.

Author Year Country	Non-biased selection?	High overall loss to follow-up or differential loss to follow-up?	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality rating
Sheets 2012 US	Yes.	N/A	Yes.	Yes.	Yes.	Yes. Propensity score weighting.	Yes.	Fair.
Solares 2005 US	Unclear how patients were selected for each group.	No.	Yes.	No.	Unclear.	No. No baseline demographic information given by patient group.	Yes.	Poor.
Wang 2013 US	Unclear how patients were selected for each group.	No.	Yes.	Yes.	Yes.	Yes.	Yes.	Fair.
Yu 2013 US	Yes.	N/A	Yes.	Yes.	Yes.	No, but matched on age, race, residence, comorbidity, receipt of ADT, prior influenza vaccination, or prior visit to a primary care physician.	Yes.	Fair.

Randomized Controlled Trial

Author Year	Adequate sequence generation?	Adequate allocation concealment?	Blinding of participants, personnel and outcome assessors?	Incomplete outcome data adequately addressed?	Study reports free of suggestion of outcome reporting bias?	Study free of other sources of bias?	Risk of bias?
Shipley 1995 US	Unknown.	Unknown.	Unknown. Outcomes are not subjective.	No. 6.4% (13/202) did not complete planned protocol, excluded from analysis.	Yes.	Yes.	Medium.

APPENDIX F. ONGOING CLINICAL TRIALS

Title Trial Sponsor Location(s) Identifier	Design	Treatment/ Comparators	Patient Population	Primary Outcomes	Estimated Completion Date
A Bayesian Randomized Trial of Image-Guided Adaptive Conformal Photon vs Proton Therapy, With Concurrent Chemotherapy, for Locally Advanced Non-Small Cell Lung Carcinoma: Treatment Related Pneumonitis and Locoregional Recurrence MD Anderson Cancer Center MD Anderson Cancer Center, Massachusetts General Hospital USA 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	Time to treatment failure	June 2015

Title Trial Sponsor Location(s) Identifier	Design	Treatment/ Comparators	Patient Population	Primary Outcomes	Estimated Completion Date
Prostate Advanced Radiation Technologies Investigating Quality of Life (PARTIQoL): A Phase III Randomized Clinical Trial of Proton Therapy vs IMRT for Low or Intermediate Risk Prostate Cancer Massachusetts General Hospital Massachusetts General Hospital, University of Pennsylvania USA NCT01617161	RCT	PBT IMRT	N=400 ≥18 years Histologically confirmed adenocarcinoma of the prostate Clinical stages T1c-T2b	Efficacy of PBT vs IMRT QOL Long-term survival	January 2016
Randomized Comparison of Proton and Carbon Ion Radiotherapy With Advanced Photon Radiotherapy in Skull Base Meningiomas: The PINOCCHIO Trial University Hospital Heidelberg University Hospital of Heidelberg Germany 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 after one year) Overall survival Progression-free survival QOL	February 2016

Title Trial Sponsor Location(s) Identifier	Design	Treatment/ Comparators	Patient Population	Primary Outcomes	Estimated Completion Date
Randomized Phase II Study Comparing Stereotactic Body Radiotherapy (SBRT) With Stereotactic Body Proton Therapy (SBPT) for Centrally Located Stage I, Selected Stage II and Recurrent Non-Small Cell Lung Cancer MD Anderson Cancer Center MD Anderson Cancer Center USA 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	SBRT and SBPT related toxicity Treatment response	August 2016
A Prospective Phase II Randomized Trial to Compare Intensity Modulated Proton Radiotherapy (IMPT) vs Intensity Modulated Radiotherapy (IMRT) for Newly Diagnosed Glioblastoma (WHO Grade IV) MD Anderson Cancer Center MD Anderson Cancer Center USA 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	May 2017

Title Trial Sponsor Location(s) Identifier	Design	Treatment/ Comparators	Patient Population	Primary Outcomes	Estimated Completion Date
Phase III Randomized Trial of Proton Beam Therapy Versus Intensity-Modulated Radiation Therapy for the Treatment of Esophageal Cancer MD Anderson Cancer Center MD Anderson Cancer Center USA 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 Total toxicity burden (TTB)	April 2018
Phase III Randomized Trial Comparing Overall Survival After Photon Versus Proton Chemoradiotherapy for Inoperable Stage II-IIIB NSCLC Radiation Therapy Oncology Group University of Florida, MD Anderson Cancer Center USA 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 Progression-free survival Adverse events QOL Changes in pulmonary function	December 2020

Title Trial Sponsor Location(s) Identifier	Design	Treatment/ Comparators	Patient Population	Primary Outcomes	Estimated Completion Date
Phase II/III Randomized Trial of Intensity-Modulated Proton Beam Therapy (IMPT) Versus Intensity-Modulated Photon Therapy (IMRT) for the Treatment of Oropharyngeal Cancer of the Head and Neck Cancer MD Anderson Cancer Center MD Anderson Cancer Center USA 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 IMRT and IMPT	August 2023
Randomized Phase II Trial of Hypofractionated Dose-Escalated Photon IMRT or Proton Beam Therapy Versus Conventional Photon Irradiation With Concomitant and Adjuvant Temozolomide in Patients With Newly Diagnosed Glioblastoma NRG Oncology NRG Oncology, Cadence Cancer Center USA NCT02179086	RCT	3-D conformal radiation therapy IMRT Photon beam radiation therapy Proton beam radiation therapy Temozolomide	N=576 ≥18 years MRI of the brain performed postoperatively within 72 hours of resection; enhancing tumor must have a maximal diameter of 5 cm GBM tumor located in the supratentorial compartment only Histologically proven diagnosis of glioblastoma (WHO grade IV) Karnofsky performance status ≥70	Overall survival Progression-free survival Incidence of treatment-related toxicity Change in cognitive and neurocognitive function	May 2019

APPENDIX G. QUALITY ASSESSMENT OF SYSTEMATIC REVIEWS

Author Year	Was an 'a priori' design provided?	Was there duplicate study selection and data extraction?	Was a comprehensive literature search performed?	Was the status of publication (*ie* grey literature) used as an inclusion criterion?	Was a list of studies (included and excluded) provided?	Were the characteristics of the included studies provided?	Was the scientific quality of the included studies assessed and documented?	Was the scientific quality of the included studies used appropriately in formulating conclusions?	Were the methods used to combine the findings of studies appropriate?	Was the likelihood of publication bias assessed?	Was the conflict of interest stated?
Amichetti 2010	Can't answer. *No protocol number noted.*	Can't answer. *Duplicate study selection, but unknown data abstraction.*	No. *Only PubMed® was searched.*	Yes. *Restricted to English language.*	No.	Yes.	No.	No.	Not applicable.	No.	No.
De Ruysscher 2012	Can't answer.	Can't answer.	Yes.	No.	No.	Yes.	Assessed but not documented.	No.	Not applicable.	No.	Yes.
Cianchetti 2012	Can't answer.	Can't answer.	Yes.	Yes. *Restricted to English language.*	No. *Did not provide a list of excluded studies.*	Yes.	No.	No.	Not applicable.	No.	No.
Grimm 2012	Can't answer.	Can't answer.	Yes.	Can't answer.	A list of included, but not excluded, studies was provided.	Yes.	No.	No.	No. Did not control for confounding between non-comparative studies.	No.	Yes.

Author Year	Was an 'a priori' design provided?	Was there duplicate study selection and data extraction?	Was a comprehensive literature search performed?	Was the status of publication (*ie* grey literature) used as an inclusion criterion?	Was a list of studies (included and excluded) provided?	Were the characteristics of the included studies provided?	Was the scientific quality of the included studies assessed and documented?	Was the scientific quality of the included studies used appropriately in formulating conclusions?	Were the methods used to combine the findings of studies appropriate?	Was the likelihood of publication bias assessed?	Was the conflict of interest stated?
Grutters 2010	Can't answer. *Duplicate data abstraction, but unknown study selection.*	Can't answer.	Yes.	Yes. *Restricted to English language.*	No. *Did not provide a list of excluded studies.*	Yes.	No.	No.	Yes.	No.	No.
Ollendorf 2014 (ICER)	Can't answer. *No protocol number noted.*	No.	Yes. *"The electronic databases we searched… included MEDLINE, EMBASE, and The Cochrane Library… for health technology assessments, systematic reviews, and primary studies."*	Yes. *Restricted to English language, but didn't tell us whether they included grey lit.*	Yes. *Did not provide a list of excluded studies, gave PRISMA flow chart*	Yes.	Assessed but not documented.	Yes.	Not applicable.	Yes.	Yes. No statement on author conflict of interest.

Author Year	Was an 'a priori' design provided?	Was there duplicate study selection and data extraction?	Was a comprehensive literature search performed?	Was the status of publication (*ie* grey literature) used as an inclusion criterion?	Was a list of studies (included and excluded) provided?	Were the characteristics of the included studies provided?	Was the scientific quality of the included studies assessed and documented?	Was the scientific quality of the included studies used appropriately in formulating conclusions?	Were the methods used to combine the findings of studies appropriate?	Was the likelihood of publication bias assessed?	Was the conflict of interest stated?
Patel 2014	Yes.	Yes.	Yes.	Can't answer.	Yes. *Did not provide a list of excluded studies, gave PRISMA flow chart*	Yes.	Yes.	No.	Yes.	No.	Yes.
Ramaekers 2011	Can't answer.	Can't answer. *Duplicate data abstraction, but unknown study selection.*	No. *Only PubMed® was searched.*	Yes. *Restricted to English language.*	Yes.	Yes.	No.	No.	Yes.	No.	Yes.
Walsh 2012 (CTAF)	Can't answer.	Can't answer.	Yes.	Yes. *Restricted to English language, no grey literature search.*	No. *Did not provide a list of excluded studies.*	Yes.	No.	No.	Not applicable.	No.	No.

APPENDIX H. DATA ABSTRACTION OF COMPARATIVE STUDIES NOT INCLUDED IN THE ICER REVIEW

Author Year Study Design Study Site	Intervention Comparator Follow-up	Sample Size Patient characteristics	Treatment protocol	Outcomes assessed Main findings	Harms	Quality
Duttenhaver 1983 Prospective cohort Massachusetts General Hospital	XRT plus PBT XRT only 5 years	<u>XRT plus PBT</u> N=64 Age: 67.7 (mean) Race: unknown Clinical stage: T1: 3%, T2: 25%, T3: 59%, T4: 13% <u>XRT only</u> N=116 Age: 67.7 (mean) Race: unknown Clinical stage: T1: 4%, T2: 30%, T3: 56%, T4: 10%	<u>XRT plus PBT</u> Initial 50 Gy given using standard external beam Total dose: 70-76.5 CGE (mean: 74 CGE) <u>XRT only</u> Pelvis treated to 50 Gy in 5 ½ weeks, 5 fractions per week, 1.8 Gy fractions, initial dose followed by a boost to prostatic tumor volume Total dose: 60-68.4 Gy (mean: 67 Gy)	<u>Survival</u> Did not differ between XRT plus PBT and XRT groups <u>Disease-free survival</u> Did not differ between XRT plus PBT and XRT groups <u>Clinical local recurrence-free survival</u> "As yet there is no observed improvement in local control in the XRT plus PRT group despite an 8-10% increase in radiation dose, when compared to the XRT group."	<u>Mild dysuria/increased frequency</u> XRT plus PBT: 11% XRT: 10% <u>Hematuria</u> XRT plus PBT: 8% XRT: 10% <u>Benign structure</u> XRT plus PBT: 5% XRT: 4% <u>Mild proctitis</u> XRT plus PBT: 8% XRT: 11% <u>Moderate proctitis</u> XRT plus PBT: 13% XRT: 5% <u>Severe proctitis</u> XRT plus PBT: 0% XRT: 1%	Poor

Author Year Study Design Study Site	Intervention Comparator Follow-up	Sample Size Patient characteristics	Treatment protocol	Outcomes assessed Main findings	Harms	Quality
Fang 2014 Retrospective cohort University of Pennsylvania (PBT: 01/10-12/12; IMRT: 07/09-12/12)	PBT IMRT PBT median: 47 months (5-65) IMRT median: 29 months (5-50)	PBT N=94 IMRT N=94	PBT and IMRT: 79.2 Gy delivered in 44 fractions		Clinician-reported grade ≥ 2 GI toxicity: 4.3% (PBT) vs 13.8% (IMRT); OR (PBT vs IMRT): 0.27 (95% CI, 0.06-1.24) Clinician-reported grade ≥ 2 GU toxicity:21.3% (PBT) vs 28.7% (IMRT); OR (PBT vs IMRT): 0.69 (95% CI, 0.32-1.51)	Fair
Galland-Grirodet 2014 Prospective phase 1 nonrandomized trial Massachusetts General Hospital (10/03—04/06)	PBT Photon-based 3D-APBI Median: 82.5 months Range: 1.6—103.8 months	PBT N=19 Age: 63 (median) Race: unknown Grade: 1: 53%, 2: 32%, 3: 15% Photon-based 3D-APBI N=79 Age: 60 (median) Race: unknown Grade: 1: 46%, 2: 46%, 3: 8%	PBT Dose: 32 Gy in 8 fractions Photon-based 3D-APBI Dose: 32 Gy in 8 fractions	7-year cumulative incidence of local failure rate PBT: 11% Photon: 4% (P=.22)	5-year skin color change PBT: 44% Photon: 2% ($P \leq 0.0001$) Patchy atrophy PBT: 50% Photon: 5% ($P \leq 0.0001$) "At 7 years, physician assessments of skin color change (P=.02) and late skin toxicity (P=.029) were significantly worse in the PBT group. Telangiectasia >4 cm^2 was observed for 38.5% of the PBT group as compared with 4% of the photon-based group (P=.0013)." "There was no difference between the treatment groups in noncutaneous toxicities, including breast pain, breast edema, and rib tenderness, at either 5 or 7 years."	Fair

Author Year Study Design Study Site	Intervention Comparator Follow-up	Sample Size Patient characteristics	Treatment protocol	Outcomes assessed Main findings	Harms	Quality
Mizumoto 2013 Retrospective cohort University of Tsukuba (01/05-09/10)	PBT Traditional radiotherapy and stereotactic radiotherapy Median follow-up for survivors: 19.4 months	PBT N=8 Age: 51 (median) Initial dose: 64.1 Gy Tumor volume: 70.4 cc RT N=8 Age: 41 (median) Initial dose: 57.1 Gy Tumor volume: 70.9 cc SRT N=10 Age: 64.5 (median) Initial dose: 58.9 Gy Tumor volume: 11.5 cc	PBT Mean reirradiation dose: 39.5 Gy RT Mean reirradiation dose: 43.7 Gy SRT Mean reirradaition dose: 41.7 Gy	Overall survival PBT: 19.4 months RT: 5.15 months SRT:11.6 months Mortality after a median of 11.6 months:62.5% (conventional photon), 50% (SRT), 62.5% (PBT); P>.99 Local recurrence:25% (conventional photon), 30% (SRT), 25% (PBT); P>.99		Poor

APPENDIX I. PEER REVIEW COMMENT DISPOSITION TABLE

Comment #	Reviewer #	REVIEWER COMMENT	RESPONSE
1.	**Are the objectives, scope, and methods for this review clearly described?**		
1	1	Yes (*no comments*)	
2	2	Yes (*no comments*)	
3	3	Yes (*no comments*)	
4	4	Yes (*no comments*)	
5	5	Yes (*no comments*)	
6	6	Yes (*no comments*)	
7	7	Yes (*no comments*)	
8	8	Yes (no comments)	
2.	**Is there any indication of bias in our synthesis of the evidence?**		
1	1	No (*no comments*)	
2	2	No (*no comments*)	
3	3	No (*no comments*)	
4	4	No (*no comments*)	
5	5	No (*no comments*)	
6	6	No (*no comments*)	
7	7	No (*no comments*)	
8	8	Yes: The actual title, "Effectiveness and Harms of proton irradiation treatment" seems to imply there is something bad with proton beam RT vs other forms of radiation therapy. While there have been studies reported with possibly worse than expected toxicities, these are entirely related to technique vs proton beam itself. For example, the partial breast proton beam series toxicity was related to the use of a single-beam, not protons itself. The more contemporary series from Loma Linda	We changed the title of our review to “Comparative Effectiveness of Proton Irradiation Treatment”

Comment #	Reviewer #	REVIEWER COMMENT	RESPONSE
		published earlier this year (D. Bush, IJROBP 2014) showed this quite nicely and was supported by the accompanying editorial from E. Strom. This theme continues with prostate, where the series from Shipley, published in the 1990's, used single perineal fields, an outdated technique. I think re-titling this, "Proton Beam Therapy: An Updated Review" would be more appropriate and less inflammatory.	
3.	**Are there any published or unpublished studies that we may have overlooked?**		
1	1	No (*no comments*)	
2	2	No (*no comments*)	
3	3	Yes: Systematic reviews of the past 5 years were included. Although it will not add value to the data and will not influence the overall conclusion, below three more reviews to add: • van de Water TA, Bijl HP, Schilstra C, Pijls-Johannesma M, Langendijk JA. The potential benefit of radiotherapy with protons in head and neck cancer with respect to normal tissue sparing: a systematic review of literature. Oncologist. 2011;16(3):366-77.Review. • Pijls-Johannesma M, Grutters JP, Verhaegen F, Lambin P, De Ruysscher D. Do we have enough evidence to implement particle therapy as standard treatment in lung cancer? A systematic literature review. Oncologist. 2010;15(1). Review. • Combs SE, Laperriere N, Brada M. Clinical controversies: proton radiation therapy for brain and skull base tumors. Semin Radiat Oncol 2013r;23(2):120-6. Review.	Thank you for suggesting these additional systematic reviews. We excluded the 2011 van de Water et al. publication because, as a review of in silico planning studies, it did not include any outcomes of interest for our review. We excluded the 2010 Pijls-Johannesma et al. publication because none of the included PBT studies included comparison groups. We excluded the 2013 Combs et al. publication because this systematic review included non-comparative studies and did not perform any pooling of studies or meta-analysis.
4	4	Yes - Grimm et al., 2012, mentioned in my review	Thank you for bringing this study to our attention. We added a discussion of Grimm et al. 2012 in the Prostate Cancer section.
5	5	Yes: Talcott JA et al, JAMA 303(11):1046-53, 2010. Fang P, et al. Cancer 2014 Epub, PMID: 25423899	Thank you for these suggestions. We excluded the 2010 Talcott et al publication because we could not isolate the effect of PBT since it compared two different doses of combined proton beam and photon

Comment #	Reviewer #	REVIEWER COMMENT	RESPONSE
			therapies. Fang: Added
6	6	No (*no comments*)	N/A
7	7	Yes: Please see my written report	N/A
8	8	Yes: Receny partial breast RT series (Bush et al, PMID: 25084608)(Strom et al, PMID: 25304946)	Bush 2014 is already included. Strom 2014 is an editorial that provides interpretation of the differences between Galland-Girodet 2014 and Bush 2014; which are consistent with ours.
4.	**Additional suggestions or comments can be provided below. If applicable, please indicate the page and line numbers from the draft report.**		
1	4	Pg. 1 line 10 “Dosimetric advantages are not theoretical. I would rephrase: "because of the physical properties of the proton beam, which can translate into dosimetric advantages for certain clinical situation..."	Changed to “appealing dosimetric characteristics”
2	4	Pg. 2 line 14 “It is critical to note that this trial was only for the partial-breast irradiation, which means only patients with Stage I cancer were eligible, and the partial breast concept is to eliminate the dose to lungs and heart. Therefore there is not much advantage for protons in the partial breast RT. HOWEVER, proton beam is a very interesting concept for patients with LEFT breast locally advanced cancer (Stages II and III), where the entire left chest wall needs to be irradiates. A regular 3D photon treatment exposes too much heart, with a 7.5% risk of coronary events for each Gray of RT to the heart. Protons can significantly spare the dose to the heart in these clinical scenarios. For patients with Left locally advanced breast cancer, proton beam therapy should be considered, if a regular 3D plan cannot achieve a heart mean dose of less than 5 Gy.”	We clarified that the patients in this trial were being treated for stage I breast cancer.
3	4	Pg. 2 line 38 “This dose (54.6 vs 52.9) is to the primary disease in the brain. Yes, protons allow for a very modest dose escalation to the primary disease, and it is not yet clear whether 1.7 Gy of difference leads to improved survival. However,	We thank the reviewer for these insights. No change needed.

Comment #	Reviewer #	REVIEWER COMMENT	RESPONSE
		protons allow for much less dose to the healthy brain parenchyma, and to Right and Left cochleas. This could lead to improved hearing and cognitive function with a long follow-up. In terms of esophagitis and nausea/vomiting - this comes from the toxicity of the spinal cord irradiation for medulloblastoma. The dose is the same with photons and with protons, but there is much less exit dose into the body cavity with all internal organs, which leads to better acute tolerance of treatment, and theoretically decreased risk of secondary malignancies in these organs, when patients are followed for longer than 15 years."	
4	4	Pg. 3 line 4 "Rephrase this: There is also insufficient evidence to draw conclusions of proton beam -based stereotactic ablative therapy for early stage lung cancer, in comparison to photon-based stereotactic ablative therapy."	We rephrased this sentence: "There is also insufficient evidence to draw conclusions about proton-based stereotactic ablative therapy for early-stage lung cancer compared with photon-based stereotactic ablative therapy."
5	4	Pg. 3 line 23 "Survival difference is known - there is NO survival difference. In prostate cancer, one cannot find a difference in survival between two treatment modalities - it takes over decades for prostate cancer failure to translate into survival difference. All studies of IMRT vs protons have used the same radiation dose, therefore the only question that was ever asked in these studies - is the quality of life and toxicity."	Deleted "but unknown survival" for IMRT and 3D-CRT comparisons. We take your point that calling out the lack of evidence on survival may lack relevance here given that finding a difference in survival at 5 years may not be plausible given the natural history of the disease.
6	4	Pg. 3 line 58 "It is critical to mention that the main disadvantage of this study was a very low number of patients analyzed, therefore any outcome is likely to be influenced by chance alone. Moreover, proton beam was not associated on a univariate analysis (table 4), therefore it is more likely that selection of patients for proton beam was influenced more by worse pathology and size of the tumor, inability to resect the tumor, etc, rather than the choice of therapy itself."	We agree with the reviewer that the strength of the evidence is low due to the mentioned methodological limitations and have described these in the full results section. No change needed to the Executive Summary.
7	4	Pg. 4 line 7 "Why you have not included a special section on chordoma and chondrosarcoma of the spine and base of skull? These are pathologies that SHOULD only be treated with	We did not identify any comparative studies in chordoma or chondrosarcoma patients so did not include a separate section for these conditions. In our

Comment #	Reviewer #	REVIEWER COMMENT	RESPONSE
		protons at this moment, as there is no data that photon-based therapy is equivalent to results achieved with protons."	introduction we cite a VA Memorandum that acknowledges the improved safety of radiation delivery to sacral and base of skull chordomas.
8	4	Pg. 4 line 13 "Evaluation of recurrent tumors is very patient-specific. If patient has a locally recurrent tumor with no evidence of metastatic disease, and re-irradiation offers a second chance of cure, then attention should be drawn to the cumulative dose to the organs, when previous and present treatment plans are combined. If dosimetrically, the physician cannot achieve a dose high enough for tumor control, without damaging normal structures, based on their radiation tolerance, and a physician can show that a proton beam therapy can improve this, then there is an indication for proton beam therapy."	We appreciate the reviewer's rationale for the role of proton beam therapy in recurrent tumors. We do not think that Mizumoto 2013 and Otsuka 2003 are the last word on proton beam for recurrent tumors and would strongly encourage this as an area for future research efforts.
9	4	Pg. 4 line 39 "This is not true. A SEER-based publication showed fewer secondary malignancies for kids treated with proton vs photons (Chung et al., 2013). Therefore when one applies the same criterias for young adults (young men with seminoma, young women with breast cancer or lymphoma), the same principle applies to this population - less normal tissue exposed to overall radiation translates into fewer secondary malignancies. This cannot be applied to elderly population, as it takes at least 15 to 20 years to develop secondary malignancy after RT, but for young adults this is very applicable."	Yes, Chung 2013 is included in our review. But it is retrospective, not prospective, so this statement is correct and relevant. But, we have added a section about its findings to the Executive Summary.
10	4	Pg. 9 line 32 "you mean genetic?"	We rephrased this sentence to more clearly reflect ASTRO's model policy: "The American Society for Radiation Oncology supports the use of PBT for ocular tumors, tumors that approach or are located at the base of the skull, certain tumors of the spine, primary hepatocellular cancer treated in a hypofractionated regimen, solid tumors in children treated with curative intent, and in patients with genetic syndromes for whom minimizing the total volume of radiation is
11	4	Pg. 9 line 33 "Hepatocellular carcinoma has nothing to do with the genetic syndromes. It is all about how much of normal liver receives radiation therapy. At least 700 cc of normal liver should be completely spared of any radiation dose in order for treatment to be safe and for patients not to develop radiation-induced liver disease (RILD). This means that with proton beams, larger tumors can be safely irradiated, in comparison to	

Comment #	Reviewer #	REVIEWER COMMENT	RESPONSE
		photon-based treatment."	crucial."
12	4	Pg. 10 line 19 "An additional expense that comes with proton beam therapy is the need to create brass apertures for each beam used on an individual patient. This requires special facilities, specially trained personnel. The cost of brass material is very high."	Thank you for this information. We added the following sentence: "Additional expenses associated with PBT is the creation of individual brass apertures for each beam, requiring special facilities and personnel."
13	4	Pg. 15 line 53 "Massachusetts General Hospital and MD Anderson. The prostate randomized trial was started at Mass General Hospital, the second institution that joined the trial is UPenn. Lung Cancer was a collaborative work between MGH and MDACC."	We altered Appendix G and updated this sentence: "These ongoing studies are being conducted at the University of Texas MD Anderson Cancer Center, Massachusetts General Hospital and the University of Pennsylvania as well as other centers in the US and abroad."
14	4	Pg. 26 line 4 "partial breast treatment for early stage breast cancer. It is very crucial to distinguish whole breast treatment or chest wall treatment with radiation therapy for advanced breast cancer vs partial breast treatment for patients with Stage I breast cancer."	We altered the title of table 4: "Strength of evidence (SOE) for comparative benefits and harms of PBT or photons or mixed photons/electrons in partial breast treatment for early-stage breast cancer"
15	4	Pg. 27 line 16 "Exactly! The effectiveness of both treatments was the same. When patients die from the spinal cord glioma, they die from the local disease progression. The fact that the local recurrence rates were the same puts the multi-variable analysis under suspicion, that it inappropriately adjusted for large difference in age and made proton beam therapy look horrible, whereas on univariate analysis there was no difference. I am worried that this inappropriate analysis will make proton beam look so much worse for the spinal cord gliomas, where in reality the effectiveness dose per dose is the same."	Yes, we also have low confidence in the stability of this estimate for the reasons you've mentioned, including the insufficient sample size and the inconsistency between the univariate and multivariate analyses. For these reasons, we have rated the strength of this evidence as low.
16	4	Pg. 28 line 48 "Poorly worded. Effectiveness of combination of protons with photons vs photons alone?"	We rephrased this sentence: "We identified one poor-quality retrospective comparative cohort that evaluated the clinical effectiveness of combination proton and photon treatment versus photon-only treatment in giant cell tumor of bone."

Comment #	Reviewer #	REVIEWER COMMENT	RESPONSE
17	4	Pg. 31 line 41 “Proton-based Ablative RT vs photon-based ablative RT for early stage NSCLC.”	We rephrased this heading: “Proton-based Ablative RT versus photon-based ablative RT for early stage NSCLC”
18	4	Pg. 32 line 30 “for locally advanced NSCLC”	Added to this heading: “PBT versus IMRT or 3D-CRT for locally advanced NSCLC”
19	4	Pg. 39 line 38 “I am not sure this is relevant now. Almost everyone agrees that IMRT is superior to 3D-CRT for high-dose RT to prostate (over 70 Gy), therefore no one is treating patients with localized disease without IMRT.”	Thank you for this comment. As the scope of our review includes both conventional and state-of-the art therapies, we included this evidence for the sake of completeness
20	4	Pg. 41 line 18 “There is a meta-analysis of various treatment modalities for prostate cancer which indicates that brachytherapy is superior to all forms of external beam RT, including proton beam therapy. Grimm et al., BJUI 2012. If you look at the names of co-authors, you will see that these are all leaders of the prostate cancer treatment in radiation oncology. I think it is important to incorporate this study.”	Thank you for bringing this study to our attention. We added a discussion of Grimm et al. 2012 in the Prostate Cancer section.
21	4	Pg. 41 line 38 “The "boost" was only a few fractions at the very end of the treatment. The main question of this randomized trial at MGH was to determine whether increasing the dose beyond 70 Gy, what was considered standard back then with 3D-CRT would improve the outcomes, not the protons. But since the trail was done at MGH where protons are available, the study used protons for the last five fractions. So this study is really about 79.2 Gy vs 70 Gy of radiation therapy, not about photons alone vs photons + protons.”	We altered our discussion of both Shipley et al. 1995 and Duttenhaver et al 1983 to emphasize that these studies used a “boost” of protons in addition to photon therapy and that this combined group received a larger overall dose compared with the group that received photon treatment only.
22	4	Pg. 44 line 32 “$p<0.01$”	Added.
23	4	Pg. 44 line 41 “These patients were treated for non-metastatic disease, using standard treatments doses, therefore we can be sure that the doses were comparable, if not exactly the same, diagnosis for diagnosis.”	We disagree. Although patients were matched by treatment site and histology in an attempt to control for irradiation volume, we still cannot be completely sure radiation dose and field size were comparable.
24	4	Pg. 44 line 60 “Yes!!! This is the MAIN criticism and argument against this article. We do not anticipate to see 2nd malignancy	Agreed.

Comment #	Reviewer #	REVIEWER COMMENT	RESPONSE
		during the RT within the first 5 years, more likely to develop these malignancies in 15 years or longer."	
25	4	Pg. 45 line 37 "This is a situation where there will be no data. It is similar to taking very difficult surgical cases and trying to determine which technique led to improved outcomes. Based on the amount of disease, prior radiation therapy plan, patient's anatomy, physician should be able to decide how best to approach the treatment - and if proton beam allows for less dose to previously irradiated organs, then protons will be superior. Similar to open vs laparoscopic surgery - surgeon decides at the time of surgery which technique is necessary for best visualization/access, etc, and that in theory should be left to the physician to decide and will never be analyzed in literature."	It is precisely because this is a particularly difficult to treat population that this is a worthwhile question to ask. Knowing whether patients with recurrences are more or less likely to benefit from proton therapy compared with other alternatives could be particularly useful when, in general, recurrent tumors may be less sensitive to all treatments. And, in fact, there are already studies that have evaluated the comparative effectiveness of proton therapy in recurrent tumors.
26	4	Pg. 46 line 53 "It is incorrect to say that proton therapy is less beneficial in patients with recurrent tumors. The correct statement is: 'Any treatment form is less effective in the setting of disease recurrence.' This is primarily driven by two factors: often patients have metastatic disease at the time of recurrence, and if the tumor comes back, it is more likely to be less sensitive to treatment effect. Therefore physicians always tell patients that the effectiveness of treatment is lower in the setting of disease recurrence. Don't state that this is specific to proton beam therapy."	Thank you for this information. We replaced this sentence with: "Any treatment form is less effective in the setting of disease recurrence, including proton therapy."
27	4	Pg. 47 line 7 "Have all the confidence in the world with this statement! It has absolutely nothing to do with protons! The same can be shown for brachytherapy, surgery, external beam RT, chemotherapy, you name it! Cancer at the time of recurrence is always worse than at the time of the new diagnosis."	Agreed, our point is not about protons. It is that the reduced benefit of protons for recurrent vs primary tumors seen in these studies is likely not entirely due to the inherently worse prognosis for recurrences, given the potential for confounding due to differences in radiation dosage, years of treatment and patient age.
28	4	Pg. 47 line 20 "What this means is that experience with proton beam is more important than the experience with photon therapy. A fresh proton beam facility with minimal experience	We thank the reviewer for this insight. No change needed.

Comment #	Reviewer #	REVIEWER COMMENT	RESPONSE
		is likely to have initially worse outcomes than a proton beam facility with 20 years of experience. It is similar to neurosurgeons who are fresh out of residency programs, vs experienced surgeons."	
29	4	Pg. 51 line 13 "again, chordoma and chondrosarcoma have only successfully been treated with protons, so it is up to IMRT-based treatment studies to prove IMRT is just as good. Uveal melanoma is also can be treated with brachytherapy or proton beam therapy, IMRT-based therapy is not used for uveal melanoma."	We did not identify any comparative studies in chordoma or chondrosarcoma patients so did not include a separate section for these conditions. In our introduction we cite a VA Memorandum that acknowledges the improved safety of radiation delivery to sacral and base of skull chordomas. We altered this sentence: "For all cancer sites and types, except for ocular and pediatric cancers which were not reviewed here…"
30	4	Pg. 51 line 40 "again, only in the setting of PARTIAL BREAST IRRADIATION. This should be stated very clearly, that this does not apply to whole breast RT situations."	We rephrased the beginning of this sentence: "Increased harms include that (1) for partial breast irradiation, various skin toxicities are more common with PBT than with 3D-CRT when PBT is delivered in single-fields…"
31	4	Pg. 51 line 46 "again, would not use this study to claim that proton beam causes more death."	Agree that Kahn 2011 has major deficiencies and provides only low-strength evidence. We added the low-strength evidence qualifier to our statement about Kahn's 2011 findings.
32	4	Pg. 53 line 53 "Not true."	We altered Appendix G and updated this sentence: "Many of these ongoing studies are multi-site and are being conducted at MD Anderson Cancer Center, Massachusetts General Hospital, and the University of Pennsylvania as well as other centers in the US and abroad."
33	4	Pg. 54 line 19 "I think the conclusion is pretty nihilistic. A current randomized study of protons vs IMRT for prostate cancer as done at MGH and UPenn is actually a very good study, well designed, with all biases controlled, that will show	Changed to: "Although numerous randomized controlled trials are underway that carry the promise of improved toxicity measurement, it is unclear whether they will fully address gaps in evidence on other

Comment #	Reviewer #	REVIEWER COMMENT	RESPONSE
		whether there is any difference in rectal toxicity."	important outcomes including recurrence, ability to deliver planned chemotherapy and radiation regimens, functional capacity, overall severe late toxicity, and secondary malignancies"
34	1	Table 1, page 3, Harms column. For each entry, make explicit which is the reference arm. For IMRT on lines 23-27, it appears proton beam is compared to IMRT (in that order, so PB is the reference) and proton beam has higher GI toxicity with HR = 3.32. However, in lines 29-35, the order appears to be reversed (IMRT vs PB) with IMRT now the reference and with RR of less than 1, so proton beam is again more toxicity. This change in reference is prone to confusion. This is repeated in Table 2, page 5.	Thank you for this suggestion. We clarified the reference group for every measure of association listed in a table.
35	2	Conclusions stated within the tables, such as Table 15, are occasionally unclear. Though the accompanying text clearly attributes relative benefits or harms to the appropriate radiation modality, table entries are less clear.	We labeled all outcomes by treatment group in tables throughout the report.
36	3	This report represents a review on the clinical evidence of proton therapy as compared to conventional/state of the art photon therapy. This systematic review was very well performed, including a risk of bias analysis. Methodological I have nothing to add. Systematic reviews of the past 5 years were included. Although it will not add value to the data and will not influence the overall conclusion, below three more reviews to add: • van de Water TA, Bijl HP, Schilstra C, Pijls-Johannesma M, Langendijk JA. The potential benefit of radiotherapy with protons in head and neck cancer with respect to normal tissue sparing: a systematic review of literature. Oncologist. 2011;16(3):366-77.Review. • Pijls-Johannesma M, Grutters JP, Verhaegen F, Lambin P, De Ruysscher D. Do we have enough evidence to implement particle therapy as standard treatment in lung cancer? A	Thank you for suggesting these additional systematic reviews. We excluded the 2011 van de Water et al. publication because, as a review of in silico planning studies, it did not include any outcomes of interest for our review. We excluded the 2010 Pijls-Johannesma et al. publication because none of the included PBT studies included comparison groups. We excluded the 2013 Combs et al. publication because this systematic review included non-comparative studies and did not perform any pooling of studies or meta-analyses.

Comment #	Reviewer #	REVIEWER COMMENT	RESPONSE
		systematic literature review. Oncologist. 2010;15(1). Review. • Combs SE, Laperriere N, Brada M. Clinical controversies: proton radiation therapy for brain and skull base tumors. Semin Radiat Oncol 2013r;23(2):120-6. Review. Although disappointedly, mainly due to lack of evidence, I fully agree with the overall conclusions that was drawn by the authors. I have no additional comments.	
37	5	Overall, this is an outstanding article and demonstrates that the authors have an impressive insight into radiation treatment and outcomes.	Thank you.
38	5	Please see two suggested articles (Talcott, Fang), which add to the literature (and perhaps level of overall evidence) on comparative patient-reported outcomes of proton vs photon for prostate cancer.	We excluded the 2010 Talcott et al publication because we could not isolate the effect of PBT since it compared two different doses of combined proton beam and photon therapies. Added Fang 2014
39	5	In the lung sections, it may be worthwhile for the authors to examine whether IMRT is deemed "standard of care" for this disease. I think many insurers do not cover IMRT routinely for lung cancer radiation treatment. This consideration provides important practical insight to the reader of this review, in terms of the proton vs 3DCRT (standard) and proton vs IMRT (not standard) comparisons.	Defining the standard of care is outside of the scope of this review as it may vary across health systems and over time and may incorporate other information (*eg*, clinical expert input, cost, adherence)
40	5	For prostate cancer, it is important to note that the randomized trial of PBT+photon vs photon alone used different doses in the 2 arms. This is an important detail that was left out of the review. Some would interpret the data from this trial to suggest that proton can be used to safely increase dose of prostate cancer radiation without increasing toxicity. It is also important to note that the photon used in this trial was not IMRT. So this trial does not directly provide evidence on the toxicity outcomes of PBT vs IMRT for prostate cancer.	We amended the discussion of PBT+photon versus photon alone in the prostate cancer section to include information on the delivered dose in each treatment group of the three included studies.
41	5	Table 4 and other tables: it would be helpful to label the outcomes. For example "7-year cumulative local recurrence:	Thank you for the suggestion. We labeled all outcomes by treatment group in tables throughout the report.

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		11% vs 4%" – which is PBT and which is photon? I can give a good guess based on the data, but labeling this in the Tables would be even better.	
42	5	Page 38, the significant space used for criticisms of the Sheets et al study seems way out of proportion with the rest of the document, and suggests bias by the authors. As the authors note, all of the literature comparing PBT to photons have significant flaws – but the criticisms of this one study took up almost an entire page of space and seems unusual. The language of "widely criticized" to describe this study seems especially harsh, especially given the context that the 3 cited letters-to-the editor all came from physicians from proton centers, who may have inherent bias and financial conflicts of interest. To provide full disclosure, I am one of the authors of that study and am able to provide further insight on the limitations of the study. The reason that critiques were not all fully answered was because of the significant JAMA word count limitations for author responses. The criticism of using surrogate measures and data from few proton institutions – apply to all SEER-Medicare studies (include Kim et al, and Yu et al), not just the Sheets study. Frankly, until 2006, there were only 2-3 proton centers treating prostate cancer in total. I believe it is inappropriate to directly translate results from the Sheets study to institutional series. The institutional series reported % of patients with toxicity attributed to radiation treatment. The Sheets (and Yu and Kim) studies examined % of patients who had a diagnosed GI or GU morbidity, or had GI or GU procedures after radiation treatment. These are very different outcomes, and one cannot be calculated to compare to the other. Patients can have GI or GU diagnosed morbidity or procedures not related to radiation treatment, which are counted	We streamlined our discussion of the Kim 2011 and Sheets 2012 weaknesses to focus on the similar and well-accepted problems in both with exposure and outcome assessment methods: "*GI toxicity at 4-5 years.* Two fair-quality, population-based retrospective cohort studies of Medicare claims data linked to the Surveillance Epidemiology and End Results (SEER) database provide low-strength evidence of an increased risk of late GI toxicity at 4-5 years (Table 16).[9,10] The first of the SEER-database studies, by Kim et al, included patients diagnosed with early-stage localized prostate cancer between 1992 and 2005 and used ICD-9 or CPT procedure codes to assess grade 3 to 4 bleeding, ulceration, fistula, stricture, and colostomy that developed at least 6 months after diagnosis and required intervention.[9] The second of the SEER-database studies, by Sheets et al, assessed risk of unspecified GI morbidity-related procedures (including colonoscopy) and diagnoses that occurred at least 12 months after diagnosis in patients diagnosed with early-stage prostate cancer between 2000 and 2007.[10] The main limitations of both studies include their high potential for exposure and outcome misclassification biases.[67-69] Regarding exposure ascertainment, risk of bias was high because dose and field size specifics were unknown; therefore, the increased risk of late GI toxicity with PBT may have been entirely due to higher doses. Regarding outcome ascertainment, risk of bias was high because of the questionable reliability of using surrogate procedure (including colonoscopy) and

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		as events in the SEER/Medicare studies – with unclear attribution to radiation treatment, but with the assumption that underlying events unrelated to treatment should be similar between PBT and IMRT patients. There is an underlying "baseline" event rate in these elderly patients (many elderly patients have GI or GU problems anyway). But differences found in event rates between PBT and IMRT patients are possibly due to treatment outcome differences. If there is bias, the bias should favor PBT patients who are usually younger, healthier, and can travel longer distances to receive treatment – and therefore may have lower baseline event rates than photon patients. The criticism about photon with lower dose than PBT: this applies to all 3 SEER/Medicare studies. Further, the Sheets study directly addresses the common claim by proton center physicians that proton treatment can deliver a higher dose to the prostate safely, therefore increase cure rate compared to IMRT. In fact, if indeed PBT patients received a modestly higher dose than IMRT in the Sheets study, the results do not support these claims – there was no higher cure rate, and morbidity was higher.	diagnosis code-based measures to detect the actual clinical events of interest. Also, both studies may suffer from potential confounding by study site since likely a high majority of proton patients were treated at the single Loma Linda study site, whereas IMRT patients were likely treated at a variety of sites."
43	5	Applicability section, page 52: "more or less experience." It is unlikely that newer proton facilities would have "more" experience compared to the facilities that have been treating patients for many years/decades.	We changed this sentence to read: "First, the majority of the proton beam treatment groups came from one of 3 proton facilities that are among the oldest in operation (Loma Linda, MD Anderson, or Massachusetts General). It is unclear whether the patient outcomes of these centers would generalize to other facilities with less experience treating patients and that may have difference standards of care."
44	5	Page 53: It is worth noting that some dosimetric comparison studies show that PBT can have worse dose distribution compared to IMRT. For example, in prostate cancer, PBT vs IMRT delivers higher doses to the femoral heads, and more	Changed to: "Other clinicians and experts in radiation oncology question whether PBT's dosimetric characteristics translate into measurable clinical benefits or increased survival for patients."

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		high dose to the bladder. The statement of "obvious superior dose distribution" is not always true.	
45	6	This was a well written review of the evidence for the treatment of adult cancers with proton radiotherapy. The authors have done an outstanding job collecting all the comparative studies.	Thank you.
46	6	Page 3, Table 1. "IMRT" Comparator: "Harms" column: The Yu et al. (ref 11) did not find increased late GI toxicity. Also, in the "Benefits" column for the "IMRT" Comparator: the Yu et al. (ref 11) paper found transiently lower GU toxicity for 0-6 months after treatment.	Moved Yu 2013 citation to statement about similar acute toxicity at beginning of sentence; added evidence on transient GU advantage at 6 months.
47	6	Page 4: Rather than simply saying "hemangiomas", which can occur anywhere, I would specify "uveal hemangiomas", which given their location in the eye there is much more impetus to use proton beam radiotherapy. I would replace "hemangiomas" throughout the whole review with "uveal hemangiomas."	We made this change throughout the report.
48	6	Page 5: Table 2: Prostate row "-vs IMRT": the Yu et al. study found a transiently lower GU toxicity for 0-6 months after treatment but no long term differences. This is a potential advantage. For the disadvantage row "-PBT + photon vs photon alone:" the comparison is a little difficult to make as the "PBT+photon" was a higher dose than the photon alone. The study cited (Shipley et al) was testing PBT as a boost therapy. This would be clearer if the row reads "-PBT Boost + Photon vs photon alone". Furthermore, the Shipley et al study used much older radiotherapy techniques, and so should not be indicative of current outcomes and is of limited relevance. The same can be said for Duttenhaver et al.	Added evidence on transient GU advantage at 6 months We altered our discussion of both Shipley et al. 1995 and Duttenhaver et al 1983 to emphasize that these studies used a "boost" of protons in addition to photon therapy and that this combined group received a larger overall dose compared with the group that received photon treatment only.
49	6	Page 9 – line 60: "with 9 additional centers under construction." I believe 10 centers are under construction (Mayo is constructing 2 centers in different locations).	We changed the number of centers under construction to 10.
50	6	Page 22: Row "Esophageal". The Wang paper seems to indicate	It is difficult to compare these two studies because they

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		that pulmonary complications are improved with PBT, but the McCurdy reports the opposite – that PBT is associated with greater complications – specifically pneumonitis. Given this conflicting data – should not the evidence considered inadequate?	report very different outcomes: Wang reports a 30-day broad composite outcome of any pulmonary complication and McCurdy reports a 3-month specific outcome of pneumonitis. We evaluated them separately for this reason.
51	6	Page 23: Line 28: GI toxicity was not worse in the Yu 2013 study, but in the Kim 2011 study. Also, the Yu 2013 study showed transient genitourinary benefits for proton beam (as noted above in comments 1 and 3)	Moved Yu 2013 citation to statement about similar acute toxicity at beginning of sentence; added evidence on transient GU advantage at 6 months.
52	6	Page 24: Line 11: again, the "PBT + Photon" would be clearer if it was "PBT boost + photon". Though there were higher rectal bleeding with PBT boost, it was a higher dose of radiation (75.6 CGE vs 67.2 Gy). Duttenhaver et al also used a higher dose for the proton arm. This is also noted above in comment 3.	We altered our discussion of both Shipley et al. 1995 and Duttenhaver et al 1983 to emphasize that these studies used a "boost" of protons in addition to photon therapy and that this combined group received a larger overall dose compared with the group that received photon treatment only.
53	6	Page 26: General comment re: CNS cancers. There is some evidence / consensus in the medulloblastoma literature that for pediatric cancers there is long term benefit in terms of IQ, etc. I'm not sure whether this is important for the VA ESP.	Thank you for this information, but reviewer is right that pediatric outcomes are not relevant to this review.
54	6	Page 28: "Giant cell tumor" – would be better to entitle this section "Giant cell tumor of the bone."	We made this change throughout the report.
55	6	Page 30: "Hemangioma" – would be better to entitle this section "uveal hemangioma."	We made this change throughout the report.
56	6	Page 41: Line 34: Again, it should be emphasized that PBT and photon therapy was to a greater dose than photon therapy alone in the Shipley study. It also used older technique and is so dated that the findings are not helpful to the technology assessment of PBT in current practice.	We amended the discussion of PBT+photon versus photon alone in the prostate cancer section to include information on the delivered dose in each treatment group as well as noting that the radiotherapy techniques used in Duttenhaver 1983 and Shipley 1995 are outdated.
57	6	Page 49: Line 31: "Giant cell tumor" again would be better to write as "Giant cell tumor of the bone"	We made this change throughout the report.
58	6	Page 49: Line 37: "Hemangioma" again would be better as	We made this change throughout the report.

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		"Uveal Hemangioma"	
59	7	Overall this is a very well-researched and written summary report and reasonably current. As the report outlines, 4 key strategies were utilized, a literature review, a summary of clinical trials, review of coverage policies by various insurance companies, and review of prior summary reports, and this report clearly highlights one major limitation of any such exercise, that this field is extremely dynamic and fluid, and therefore, obsolence is a very rapid phenomenon, rendering most prior reports significantly out-of-date.	Thank you.
60	7	As key examples of this rapid obsolence, while the report was being commissioned, several new pieces of data were presented at the PTCOG-NA meeting in October 2014, and most of these have not made it into the current report.	We thank the reviewer for this information. We reviewed the abstract book from the October 2014 PTCOG-NA meeting and identified one comparative study on head and neck cancer which we now include in that section of the report (Abstract #33, P.B. Romesser, O. Cahlon, E. Scher, Y. Zhou, T. Leven, R. Wong, N. Riaz, S. McBride, N.Y. Lee).
61	7	A second important example of the rapidly shifting field, is the update to the NCCN guidelines; for example, the 2015 Prostate Cancer NCCN guidelines now include the following phrase: "conventionally fractionated prostate proton therapy can be considered a reasonable alternative to x-ray based regimens at clinics with appropriate technology, physics, and clinical expertise." (The 2014 version provided as follows: "proton therapy is not recommended for routine use at this time. Research hasn't shown proton beams to be the same or better for treating prostate cancer than conventional external beams.") This is a very clear example of how within 1 year, there is a dramatic change even in NCCN coverage language relative to protons. Further examples of this significant and rapid change in recommendations will be highlighted in disease-specific categories.	Thank you for this information. We added the most recent guidelines issues by the NCCN regarding PBT for prostate cancer: "An ongoing prospective randomized trial is accruing patients and comparing prostate proton therapy to prostate IMRT. The NCCN panel believes there is no clear evidence supporting a benefit or decrement to proton therapy over IMRT for either treatment efficacy or long-term toxicity. Conventionally fractionated prostate proton therapy can be considered a reasonable alternative to X-ray based regimens at clinics with appropriate technology, physics, and clinical expertise."
62	7	Pencil Beam Scanning (PBS) Intensity Modulated Proton	We discuss PBS in the Introduction, but added a

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		Therapy (IMPT): In the last 3+ years, a dramatic technological change has occurred in this field, *ie* the rapid and almost immediate adaptation of PBS IMPT over the historic spread-out Bragg peak (SOBP) approach; this is widely, and almost universally recognized as having multiple advantages such as superior dosimetry, and more importantly the robust ability to expand the reach of proton therapy into various organ sites and disease categories, not historically treated with SOBP because of technical limitations; this major technological advance potentially has huge clinical implications and the development and consequences of this aspect have largely been ignored in this report; going forward, significant data are expected to emerge for PBS, and therefore, a focus on this technology is crucial for any such report.	mention of the lack of studies on the newer PBT delivery systems and methods (*ie*, pencil beam scanning) to the 'Gaps in Evidence' section of the Discussion
63	7	Breast Cancer: This disease has historically not been the focus of proton therapy, primarily because prior to approximately 3+ years ago, the technology did not permit easy delivery of whole breast and regional nodal irradiation, a scenario that has changed dramatically with the advent of PBS IMPT. Therefore, it is now technically feasible to expand the role of proton therapy to much beyond partial breast irradiation, which is what was primarily discussed in the VA report. Two key clinical facts have also created a "perfect storm". There are now 2 randomized clinical trials that underscore the fact that in several subcategories, regional nodal irradiation, especially internal mammary (IM) irradiation improves overall survival, making this an integral component of future therapeutic approaches (Budach, 2013). An unfortunate consequence of this is the guaranteed increase in cardiac dose, relative to treatment planning that avoids the internal mammary nodal chain. A seminal long-term cohort study published in the NEJM in 2013 by Darby et al, very convincingly established that the adverse cardiac outcome risk level is directly proportional to the mean heart radiation dose, and therefore, although IM irradiation is	Added: "With the advent of intensity-modulated proton therapy (IMPT), it may now be more feasible to expand the role of PBT beyond partial breast irradiation. However, we found no IMPT for whole breast or nodal irradiation. It will be important to consider whether IMPT can improve on the 7.4%-per-gray rate for major coronary events within the first 5 years observed in a population-based case-control study of 2168 women who underwent external radiotherapy for breast cancer between 1958 and 2001 in Sweden and Denmark. [56]"

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		now the new standard, women receiving this will be expected to have a categorical increase in late adverse cardiac events, some delayed by 10+ years, as a consequence of increased mean heart dose. Numerous dosimetric studies in the literature have demonstrated the categorical, and unquestioned superiority of proton beam therapy over photon therapy (something that is analogous to an in-silico randomized trial) in terms of decreasing cardiac dose. Further, as more and more cardiotoxic systemic therapies, such as Adriamycin, and anti-her2 agents are combined in the management of non-metastatic breast cancer, the risk to these women of developing late cardiac toxicities should not be underestimated; in this context, relying on the low level evidence regarding the MGH partial breast irradiation papers is not an appropriate approach to making a determination regarding the development of VA recommendations for whole breast and nodal irradiation, especially because a short-sighted approach could result in subjecting a large number of women with breast cancer to late cardiotoxicity which may not become apparent for a decade or more, and in addition to the negative clinical consequences of this approach, the global cost of managing these cardiac toxicities would most likely exceed the up-front investment in treating such women with proton therapy. The VA should therefore seriously consider either launching its own trial, or whole-heartedly supporting the randomized and non-randomized efforts currently in development to test proton vs photon therapy for breast cancer, at least for women who need whole breast and/or chest wall irradiation, especially in the event that they also need IM irradiation, and also for those women who have other underlying cardiac risk factors. This is an absolutely key healthcare consideration, and a major focus of the future VA effort, in cognizance of the dramatic increase of women as a proportion of our veterans.	
64	7	Prostate Cancer: The biochemical progression free survival	Yes, we agree that dose considerations are key and we

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		improves as function of dose, and modern conventionally fractionated approaches requires doses in the order of 78+ Gy.	are hopeful they are being better addressed in ongoing studies. The dose in the new Fang 2014 study, for example, was 79.2 Gy.
	7	Prostate Cancer: Retrospective comparisons of databases, most notably the SEER database suggests that the disease-related clinical outcomes are comparable for photon versus proton treated patients, and some toxicities might in fact be higher in frequency in the proton cohort. These retrospective comparisons, in fact, are seriously flawed; radiation toxicities are a function, among other things, of total dose. In the comparative studies that have been referenced, no dose-correction was applied; in fact most proton patients were treated to higher doses. Further, most of the proton patients received a combination of photons and protons, and the reported toxicities are largely artefactual because of the fact that the photon treated patients were not on any trials, whereas several of the proton treated patients were, with the trial requiring a more intense level of scrutiny, including the use of endoscopies, one of the endpoints reported on by the Shelby study.	Yes we fully agree with this reviewer's criticism and have discussed in detail their high potential for exposure and outcome misclassification biases
65	7	Prostate Cancer: The very large University of Florida experience with protons which reports (in a non-randomized context, and therefore subject to bias) some of the best clinical outcomes for prostate cancer following radiotherapy, ever reported (Hoppe et al, IJROBP, 2014).	We clarified with the reviewer that he is referencing: Mendenhall NP, Hoppe BS, Romaine NC, et al. Five-year outcomes from 3 prospective trials of image-guided proton therapy for prostate cancer. *Int J Radiat Oncol Biol Phys*. 2014;88(3):596-602. This is a noncomparative study in which all patients received proton beam therapy. We had already been aware of this study, but did not discuss its findings because it did not compare outcomes with any other radiation modality. Although its results are promising, as the study authors themselves admit, it does not address remaining concerns about comparative effectiveness.
66	7	Prostate Cancer: The elegant very recently reported case-matched study of protons versus photons for prostate cancer	Thank you for this information. We added Fang 2014 to our analysis.

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		from the University of Pennsylvania, which does not show the increase in rectal/GI toxicities and colonoscopies attributed to the SEER study (Fang 2014).	
67	7	Prostate Cancer: The very significant comparative effectiveness study of patient-reported outcomes after proton therapy or intensity-modulated radiotherapy for prostate cancer (Hoppe et al, cancer 2014) which compared patient-reported quality-of-life (QOL) outcomes after proton therapy (PT) and intensity-modulated radiation therapy (IMRT) for prostate cancer, performed on prospectively collected QOL data using the Expanded Prostate Cancer Index Composite (EPIC) questionnaire. PT was delivered to 1243 men at doses from 76 to 82 Gy. IMRT was delivered to 204 men who were included in the Prostate Cancer Outcomes and Satisfaction with Treatment Quality Assessment (PROSTQA) study in doses from 75.6 Gy to 79.4 Gy. No differences were observed in summary score changes for bowel, urinary incontinence, urinary irritative/obstructive, and sexual domains between the 2 cohorts. However, more men who received IMRT reported moderate/big problems with rectal urgency (P = 0.02) and frequent bowel movements (P = 0.05) than men who received PT. These outcomes highlight the need for further comparative studies of PT and IMRT.	We agree that the Hoppe et al study published in Cancer in 2014 provides important information on QOL outcomes for prostate cancer patients treated with IMRT or PBT. This study has already been included in our discussion of IMRT vs PBT for prostate cancer.
68	7	Prostate Cancer: Proton therapy has become widely accepted as a key standard of care by thousands of men with prostate cancer, especially when it comes to assessing patient satisfaction, and reporting patient-based outcomes; in fact the quality of data for proton therapy far exceeds anything that is available for photon therapy in this context, especially when one recognizes the “power of numbers”. As an example, at the National proton Conference in April 2014, the National Association of Proton Therapy (NAPT) released a patient-centered report on the outcomes following proton therapy for	Thank you for this information. Since we did not include patient satisfaction as an outcome and the report that you reference did not compare prostate cancer patients that received photon modalities, this study does not meet our inclusion criteria.

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		prostate cancer in almost 4000 men treated at 12 different proton centers, with the following key observations: 1. 96% have recommended proton therapy to others 2. 98% rated their proton therapy experience as “excellent” or “good” 3. 98% believed they made the best treatment decision for themselves 4. 96% were “satisfied” or “extremely satisfied” with their proton therapy treatment 5. 85% reported that their quality of life was “better than” or “the same as” before their treatment. Collectively, these data very strongly suggest that modern proton therapy, especially PBS, deserves to be seriously incorporated and evaluated as an option for men with prostate cancer, either in the context of a prospective longitudinal multi-institutional cohort study, or a randomized trial, with the VA being a key player in either or both efforts, given the extremely high patient satisfaction ratings for this therapy.	
69	7	Lung Cancer: For NSCLC, the factual elements in play are a categorical dose-response relationship favoring higher dose radiotherapy in terms of improved loco-regional control, but the review also categorically demonstrates that the major US trial seeking a survival benefit from this dose-escalation strategy failed; however, there are several important observations that are missed in this top-line conclusion: a. There is already a previous, randomized phase III trial from China that shows a categorical survival improvement with higher doses (Chen et al., 2013). b. More detailed analysis of the RTOG trial demonstrates that the likely cause of “endpoint failure” was excess toxicities associated with higher doses, especially higher cardiac and pulmonary doses (Cox et al., 2012). c. An analysis of technique in the RTOG trial shows that when “tissue-sparing” IMRT techniques were employed (in	We agree that these studies do not provide conclusive evidence on the comparative effectiveness of PBT and look forward to evidence from additional ongoing RCTs

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		comparison to 3-D techniques), patient reported QOL (using the FACT-L TOI tool) was superior, and translated to a survival benefit, underscoring the enormous significance of decreasing cardiac and lung dose, something that PBS has been shown in several dosimetric studies to achieve readily. At this point, several randomized trials are evaluating the photon versus proton question in various stages and clinical presentation of NSCLC, and the VA would be ideally positioned to contribute to this in a major way.	
70	7	Esophageal Cancer: The review appropriately summarizes the data, in particular highlighting the key observation of decreased mortality in the context of trimodality therapy, in favor of proton therapy, underscoring the need and value in supporting such an approach, ideally in a prospective multi-institutional registry trial, or perhaps even through a prospective randomized trial.	Thank you for confirming our findings.
71	7	Medulloblastoma: This is an uncommon disease in the adult context; however, the data that exist show a very dramatic reduction in several toxicities, and given the very dramatic toxicities from photon therapy for large field irradiation, especially craniospinal, this should be considered as a default indication in favor of proton therapy.	Thank you for confirming our findings.
72	7	Head and Neck Cancer: Emerging data from the ongoing randomized MDACC trial very strongly favor consideration of PBS IMPT in several forms of H/N cancer. The extent of reduction in radiation dose to several H/N substructures is very dramatic, and emerging data regarding acute toxicities and cost effectiveness lean toward IMPT. Given the relatively high incidence of this diagnosis in the VA patient population, a major opportunity exists to support the ongoing trials and categorically establish the value in this disease.	We look forward to the final results of the MDACC trial.
73	7	Ocular Tumors: Although not reviewed, PBT is an obvious choice for these tumors.	Agreed. It was not reviewed because the VA already covers PBT for ocular melanomas.

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74	7	Skull base and Brain Tumors: For several tumors in this category, such as chordoma, chondrosarcoma, and possibly craniopharyngioma, low grade glioma, meningioma, etc., PBS IMPT is the logical therapy; for example, the high radiation doses necessary to control chordoma simply cannot be delivered with photon therapy; meningiomas represented a logical target for PBS IMPT, given that radiation the the meningeal surface is one of the few known causes of this condition, and photons would irradiate a dramatically larger volume of meninges, etc.	Agreed. At least some of these tumors are already covered by the VA.
75	7	Combination therapy approaches: Increasingly, in several malignancies, combination chemoradiotherapy is becoming the defacto standard. This combination is frequently associated with profound myelotoxicity and two pieces of data have recently become very clear: a. Proton therapy decrease myelotoxicity in comparison to photon therapy. b. Treatment-induced lymphopenia is associated with inferior survival in several disease types, and inadvertent irradiation of the circulating lymphocyte compartment is a major causative factor in this. PBT would very likely diminish this. The additional recognition in the last 2+ years that up-regulation of effector T cells can dramatically improve cancer outcomes in several malignancies underscores the major need to use therapies with the lowest likelihood of treatment-associated lymphopenia, and PBS would be much better suited for this purpose, compared to IMRT.	We confirmed with the reviewer that the data sources supporting his statement (a) about decreased myelotoxicity with proton vs photon are: Komaki R. Reduction of bone marrow suppression for patients with stage III NSCLC treated by protons and chemotherapy compared with IMRT and chemotherapy. The Particle Therapy Cooperative Group (PTCOG) 47 Conference; May 19-24 2008; Jacksonville, FL and Krause M, Baumann M. [Reduced acute toxicity for adults with medulloblastoma treated with proton beam craniospinal irradiation]. *Strahlenther Onkol.* 2014;190(1):111-112. As a conference abstract, Komaki 2008 lacks adequate detail about methodology to fully assess its internal validity (*eg*, patient selection and outcome ascertainment methods, baseline characteristics, statistical methods, N analyzed). Krause 2014 is in German and our methods do not include translation of non-English articles.
76	7	Conclusion: The purpose of this report is to synthesize the evidence supporting the role/value of proton therapy, specifically in terms of assisting the VA in making further recommendations as to how to approach this modality. My summary comments should provide strong rationale for	Thank you.

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		pursuing this in a logical, organized, and structured manner, and if done smartly, without a dramatic escalation in cost-of-care.	
77	8	Overall, I think there is confusion in what is toxicity due to proton beam itself vs proton beam techniques. Proton beam is a relatively young technology. Although centers have been using this technology for 2+ decades, the overall number is low (just 2 - Loma Linda and MGH). Of the 14 currently operating proton centers, 12 have been treating for less than 10 years. As a result, techiques are still evolving. In contrast, there are probably ~3000 RT centers in operation today. If you look at the metric of "proton years" vs "IMRT years", it's probably 150 years vs 30,000 years. This is not meant to be a soapbox defense of proton beam, but rather an explanation of what should be considered by the reviewers.	Added to conclusion: "Because this is still a rapidly evolving field, with ongoing efforts to improve techniques and reduce costs, this review may need more frequent updating to keep up-to-date with emerging research"
78	8	I think in lung cancer, the Sejpal MDA manuscript, along with other manuscripts from MDA, indicate that much higher doses of RT can be delivered with proton beam vs either 3D conformal RT or IMRT and result in much lower complication rates.	Yes, we agree that Sejpal found lower Grade 3 esophagitis for PBT vs 3D-CRT and IMRT in a subgroup of 202 patients treated with concurrent chemotherapy.
79	8	For prostate cancer, there are now 6 dose escalation studies. All 6 showed that higher doses lead to higher biochemical control rates. But 5 of 6 studies showed increased GI complication risks with dose escalation. The 6th study used proton beam for the final RT boost (PROG 9509, Zietman JCO 2010) and showed the same complication rates in the low and high dose arms. In looking at these 6 studies together, it is very reasonable to conclude that the only method in which dose escalation in prostate cancer has been shown to feasible WITHOUT an increase in GI toxicity is with the use of proton beam.	Yes, this is a reasonable inference to make based on comparing findings from high vs low dose comparisons of proton beam to high vs low dose comparisons of non-proton beam modalities; yet, that didn't translate into an actual GI toxicity advantage based on direct evidence from a head-to-head comparison of proton beam vs IMRT in the newest Fang 2014 study. Added dose escalation studies to the report.
80	8	If the Sheets article is to be used, then the comparison of the 6 dose-escalation studies should also be used. The Sheets article has multiple flaws, not the least of which was the use of a	Yes, we agree that the Sheets article has multiple flaws which we have described in detail and have cited the JAMA letters to the editor.

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		surrogate marker (colonoscopcies) to quantify GI morbidity. No one knows the indications for ordering the colonoscopies. The letter to the editor from Mendenhall, Shields, and Slater in JAMA outlined the flaws in the Sheets article.	Also added comparison of dose escalation studies: "Some dose-escalation studies have found increased GI complication risks with increased dose of photons,[65] but not with protons.[66] But when compared head-to-head in prostate cancer, proton beam has only transiently reduced risk of 6-month acute GU toxicity versus IMRT, but may increase risk of late GI toxicity after 4-5 years."
81	8	Finally, secondary malignancies may well be lower with the use of proton beam RT. The article from Chung et al only examined one side, if protons had a higher rate of radiation induced malignanices than X-rays. They found a lower rate of second cancers in the matched populations.	Yes, Chung's finding can seem promising, but it provided insufficient evidence to draw any conclusions at this time due to its high potential for unmeasured confounding due to higher missing data but superior outcome ascertainment methods in the proton group and unknown radiation dose.