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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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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

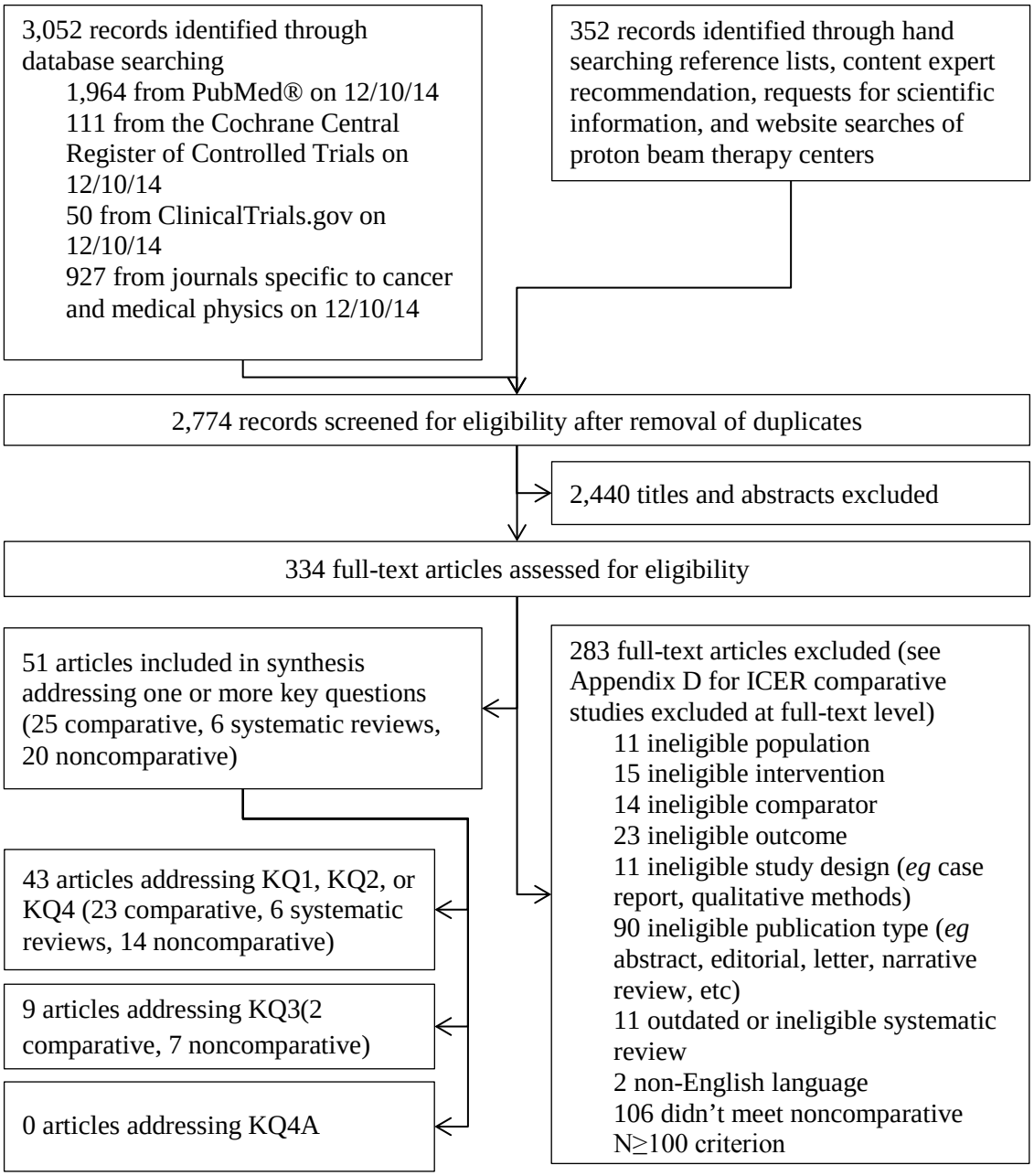
RESULTS OF SEARCH AND STUDY SELECTION

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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