Evidence Brief: Proton Beam Therapy for Treatment of Localized Prostate Cancer

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This report was prepared by the Evidence Synthesis Program Coordinating Center located at the **VA Portland Health Care System**, directed by Mark Helfand, MD, MPH, MS and funded by the Department of Veterans Affairs, Veterans Health Administration, Health Services Research and Development.

PREFACE

The VA Evidence Synthesis Program (ESP) was established in 2007 to provide timely and accurate syntheses of targeted health care topics of importance to clinicians, managers, and policymakers as they work to improve the health and health care of Veterans. These reports help:

- Develop clinical policies informed by evidence;
- Implement 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.

The program comprises four ESP Centers across the US and a Coordinating Center located in Portland, Oregon. Center Directors are VA clinicians and recognized leaders in the field of evidence synthesis with close ties to the AHRQ Evidence-based Practice Center Program. The Coordinating Center was created to manage program operations, ensure methodological consistency and quality of products, interface with stakeholders, and address urgent evidence needs. To ensure responsiveness to the needs of decision-makers, the program is governed by a Steering Committee composed of health system leadership and researchers. The program solicits nominations for review topics several times a year via the program website.

The present report was developed in response to a request from the VHA National Radiation Oncology Program (NROP). The scope was further developed with input from Operational Partners (below) and the ESP Coordinating Center review team.

ACKNOWLEDGMENTS

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Operational Partners

Operational partners are system-level stakeholders who help ensure relevance of the review topic to the VA, contribute to the development of and approve final project scope and timeframe for completion, provide feedback on the draft report, and provide consultation on strategies for dissemination of the report to the field and relevant groups.

Maria Kelly, MD, FACR, FASTRO, FAAWR
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Peer Reviewers

The Coordinating Center sought input from external peer reviewers to review the draft report and provide feedback on the objectives, scope, methods used, perception of bias, and omitted evidence (see Appendix E in Supplemental Materials for disposition of comments). Peer reviewers must disclose any relevant financial or non-financial conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained.

The Coordinating Center works to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

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EXECUTIVE SUMMARY

Key Findings

- Comparative evidence on gastrointestinal (GI) and genitourinary (GU) toxicity after treatment of localized prostate cancer with proton beam therapy (PBT) or intensity-modulated radiation therapy (IMRT) is low strength.
- Risk of early GI and GU toxicity is possibly lower after treatment with PBT compared with IMRT (RR_{GI} = 0.76, 95% CI [0.39, 1.50]; RR_{GU} = 0.65, 95% CI [0.28, 1.34]).
- In the first year after PBT or IMRT, GI toxicity risk may not differ between modalities, while risk of GU toxicity is possibly lower after treatment with PBT compared with IMRT (RR_{GI} = 1.08, 95% CI [0.68, 1.95]; RR_{GU} = 0.82, 95% CI [0.57, 1.29]).
- Low-strength evidence suggests that PBT and brachytherapy confer similar overall survival rates, and that GI and GU toxicity rates are similar for hypofractionation and conventional dosing.
- Evidence is insufficient to determine whether second cancers are less likely after PBT compared with IMRT, or whether PBT has advantages over IMRT for the treatment of relapsed prostate cancer initially treated with radical prostatectomy.
- Underway RCTs could provide important additions to the evidence base on the comparative effectiveness of PBT.

Background

The VA Evidence Synthesis Program (ESP) Coordinating Center is responding to a request from the VHA National Radiation Oncology Program (NROP) for an Evidence Brief updating a 2015 ESP evidence review on the benefits and harms of proton beam therapy (PBT) for localized prostate cancer. Findings from this report will be used to inform NROP policies on the provision of PBT for the treatment of prostate cancer.

Methods

To identify studies, we searched MEDLINE, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, and other sources up to February 2022. We used prespecified criteria for study selection, data abstraction, and rating internal validity and strength of the evidence. See the Methods section and our PROSPERO protocol for full details of our methodology.

Prostate cancer accounts for more than 25% of new cancer cases diagnosed in men. The most commonly used strategies for managing prostate cancer are surveillance without initial active treatment, treatment with surgical resection (radical prostatectomy), or radiation therapy. Because active treatments destroy cancer cells but can damage surrounding nerves, the bladder, the urethra, or the rectum, it is important that patients and providers understand the benefits and potential harms of available treatment and management options.

Radiation therapy for prostate cancer can be categorized into external beam therapy using high-intensity photons, brachytherapy, and charged particle therapy (usually using proton beams). In the last 2 decades, the use of brachytherapy has declined in the US, while the use of proton beam therapy (PBT) has increased. Evidence from direct comparisons of alternative modalities has high potential value for guiding treatment choice. A 2015 review conducted by the VA Evidence Synthesis Program (ESP) on PBT concluded that there was not enough evidence on its effectiveness to determine whether it was better, worse, or equivalent to conventional therapies for prostate cancer. There continues to be considerable demand for PBT, however, and this

review provides an up-to-date synthesis of evidence on benefits and harms of PBT compared with other radiation modalities.

Forty-seven studies (in 52 publications) reported outcomes of treatment with PBT and were included in this updated review. A summary of available evidence is provided in the ES Table.

Ten included studies compared PBT to contemporary forms of photon-based radiation therapy (*eg*, intensity-modulated radiation therapy [IMRT]) and were rated as having a low risk of bias. Evidence from 3 studies comparing PBT and IMRT for initial treatment of newly diagnosed prostate cancer suggests that risk of early gastrointestinal (GI) and genitourinary (GU) toxicity is possibly lower after PBT compared with IMRT. Results of 4 studies suggest that in the first year after PBT or IMRT, GI toxicity risk may not differ between modalities, while GU toxicity risk is possibly lower after treatment with PBT compared with IMRT. No pooled findings on GI or GU toxicity risk were statistically significant, and evidence on both outcomes was rated as low strength. Single studies reported on quality of life, second malignancy, and overall survival, and it is unclear whether PBT and IMRT differ in these outcomes. Two studies observed similar overall survival after PBT or brachytherapy.

ES Table. Summary of Evidence

Outcome	Evidence	Findings
PBT vs IMRT for Initial Therapy of Prostate Cancer		
3-month GI Toxicity	3 cohort studies[1-3]	*Low SOE:* Risk of early GI toxicity is possibly lower after PBT compared with IMRT (RR_{Mean} = 0.76, 95% CI [0.39, 1.50]).
3-month GU Toxicity	3 cohort studies[1-3]	*Low SOE:* Risk of early GU toxicity is possibly lower after PBT compared with IMRT (RR_{Mean} = 0.65, 95% CI [0.28, 1.34]).
1-year GI Toxicity	4 cohort studies[1,2,4,5]	*Low SOE:* Risk of GI toxicity may not differ 1 year after PBT or IMRT (RR_{Mean} = 1.08, 95% CI [0.68, 1.95]).
1-year GU Toxicity	4 cohort studies[1,2,4,5]	*Low SOE:* Risk of GU toxicity is possibly lower 1 year after PBT compared with IMRT (RR_{Mean} = 0.82, 95% CI [0.57, 1.29]).
Second Malignancy	1 cohort study[6]	*Insufficient SOE:* It is unclear whether PBT and IMRT differ in risk of second malignancy after treatment.
Quality of Life	1 cohort study[1]	*Insufficient SOE:* It is unclear whether PBT and IMRT differ in quality-of-life scores following treatment.
Overall Survival	1 cohort study[7]	*Insufficient SOE:* It is unclear whether PBT and IMRT differ in survival following treatment.
PBT vs Brachytherapy for Initial Therapy of Prostate Cancer		
Overall Survival	2 cohort studies[7,8]	*Low SOE:* PBT and brachytherapy confer similar impacts on overall survival.
Rates of Toxicity	0 studies	*Insufficient SOE:* It is unclear whether PBT and brachytherapy differ in toxicity rates (including GI and GU toxicities and second cancer incidence) after treatment.

Outcome	Evidence	Findings
Effect of Patient Factors on the Results of Treatment with PBT		
Effect of Patient Race	2 cohort studies[9,10]	*Low SOE:* Black and white patients had similar GU and GI toxicity rates.
Anticoagulant Use	3 cohort studies[11-13]	*Low SOE:* Patients who used anticoagulant medications had a higher rate of rectal bleeding.
Prior Prostate Surgery	2 cohort studies[14,15]	*Low SOE:* Patients who had prior prostate surgery had higher rates of GU toxicity.
Baseline Cancer Risk Score	13 cohort studies[9,10,12,15-26]	*Low SOE:* Patients with worse baseline risk assessments experienced higher rates of cancer recurrence over time.
Impact of Technical Aspects of PBT Delivery		
Hypofractionation Effect on Toxicity Rates	2 RCTs and 2 cohort studies[27-31]	*Low SOE:* Patients treated with hypofractionation had similar rates of GU and GI toxicity as patients who were treated with conventional dosing schedules.
Hypofractionation Effect on Cancer Relapse	1 RCT[27]	*Insufficient SOE:* It is unclear whether patients treated with hypofractionation have different rates of cancer recurrence than patients treated with conventional dosing schedules.
PBT vs IMRT for Therapy of Relapsed Prostate Cancer		
Disease Progression Following Treatment	1 cohort study[32]	*Insufficient SOE:* It is unclear whether PBT has advantages over IMRT for the treatment of relapsed prostate cancer following original initial therapy with radical prostatectomy.

Abbreviations. CI=confidence interval; Freq.=Frequentist; GI=gastrointestinal; GU=genitourinary; IMRT=intensity-modulated radiation therapy; PBT=proton beam therapy; RCT=randomized control trial; RR=risk ratio; SOE=strength of evidence.

The remaining studies on the effectiveness of PBT provided low- or insufficient-strength evidence on the role of patient and technical factors in PBT benefits and harms. Several patient factors were associated with a higher incidence of GI or GU toxicity (older age, history of prior prostate surgery, use of anticoagulation medications) or disease progression (baseline cancer risk score). Black and white patients appear to experience similar GI and GU toxicity risk. Studies on hypofractionation (which reduces the total number of PBT treatment sessions and overall duration of treatment) report similar GI and GU toxicity rates for hypofractionation and conventional dosing schedules. Available evidence is insufficient to reach conclusions about 2 other aspects of PBT delivery: total radiation dose and use of pencil beam scanning.

Although additional studies have been published on PBT in the last 7 years, evidence on its comparative benefits and harms remains low or insufficient strength. More studies are needed to address evidence gaps, including cancer recurrence rates following PBT and IMRT, toxicity among comparable patients receiving PBT or brachytherapy, and use of PBT in cases of prostate cancer relapse after initial treatment with another therapy. Several controlled clinical trials are currently underway and could address some open questions, but their results are likely years away. Currently available evidence may be useful in patient-provider decisions about the treatment of localized prostate cancer, yet it also reveals important uncertainties that are necessary to consider in the complex and nuanced choice of treatment modality.

EVIDENCE BRIEF

INTRODUCTION

PURPOSE

The Evidence Synthesis Program (ESP) Coordinating Center is responding to a request from the VHA National Radiation Oncology Program (NROP) for an Evidence Brief updating a 2015 ESP evidence review on the benefits and harms of proton beam therapy (PBT) for localized prostate cancer. Findings from this report will be used to inform NROP policies on the provision of PBT for the treatment of prostate cancer.

BACKGROUND

About 1 in every 8 American men will be diagnosed with prostate cancer.[33] Based on data from the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) Program, an estimated 248,530 new cases of prostate cancer were diagnosed in 2021, comprising about 13% of all newly diagnosed cancers in the US. Among men, prostate cancer accounts for more than 25% of new cancer diagnoses, and non-Hispanic Black men and older men are at highest risk.[33]

Prostate cancer screening is widespread in the US and most cases are discovered while the cancer is still localized.[34] Some men have relatively small and nonaggressive tumors for which surveillance without initial active treatment is appropriate. For men who elect initial treatment, the most commonly used modalities are surgical resection (*ie*, radical prostatectomy) or radiation therapy. Radiation therapies for prostate cancer can be grouped into 3 general categories. The most frequently used radiation therapy delivers high-energy photons via external beams. Brachytherapy is an alternative approach that imbeds radiation sources directly into the prostate that deliver photon radiation over several months. Finally, PBT targets the prostate with a beam of protons generated by a cyclotron. Over the last 2 decades, use of PBT has increased in the US, while use of brachytherapy has declined.[35]

Active treatment approaches for localized prostate cancer destroy cancer cells but can damage surrounding nerves, the bladder, the urethra, or the rectum, leading to undesirable symptoms of varying duration. As treatment strategies for localized prostate cancer have evolved over recent decades, limiting damage to healthy tissues surrounding the prostate has become a major focus. For instance, technological advances have led to widespread adoption of intensity-modulated radiation therapy (IMRT), a type of external beam photon therapy. IMRT is intended to reduce clinical complications of conventional external beam photon therapy by altering the direction of the external beam and regulating the intensity of the radiation delivered to the prostate and nearby tissues. As of 2011, IMRT was used in 70% of patients receiving radiation therapy for prostate cancer, while PBT was used in only 3%.[35]

Research has also explored whether the overall duration of external beam radiation therapy using photons or protons could be shortened through dosage schedules known as hypofractionation. Conventional external beam radiation therapy for prostate cancer typically has been performed with a few dozen treatment sessions spread over a period of 1-2 months. Hypofractionation shortens the period of treatment by delivering larger doses of radiation in each session over fewer total sessions. Additionally, newer approaches to photon-based radiation therapy such as

stereotactic ablative body radiation have become available in the US, but the clinical evidence base for these new modalities is still developing.[36]

Men with newly diagnosed prostate cancer who pursue radiation therapy are faced with many different treatment choices. Although evidence derived from direct comparisons of alternative modalities is optimal for guiding this choice, a 2015 ESP review[37] on PBT concluded that there was not enough evidence on its effectiveness to determine whether it was better, worse, or equivalent to conventional therapies for prostate cancer. There continues to be considerable demand for PBT, however, and this review provides an up-to-date synthesis of evidence on benefits and harms of PBT compared with other radiation modalities, as well as evidence on whether treatment benefits and harms differ for men with certain clinical characteristics.

METHODS

PROTOCOL

A preregistered protocol for this review can be found on the PROSPERO international prospective register of systematic reviews (http://www.crd.york.ac.uk/PROSPERO/; registration number CRD42022310783).

KEY QUESTIONS

The following key questions (KQs) were the focus of this review:

KQ1: What are the benefits and harms of PBT compared to conventional external beam radiation therapy or brachytherapy for the treatment of early stage localized prostate cancer?

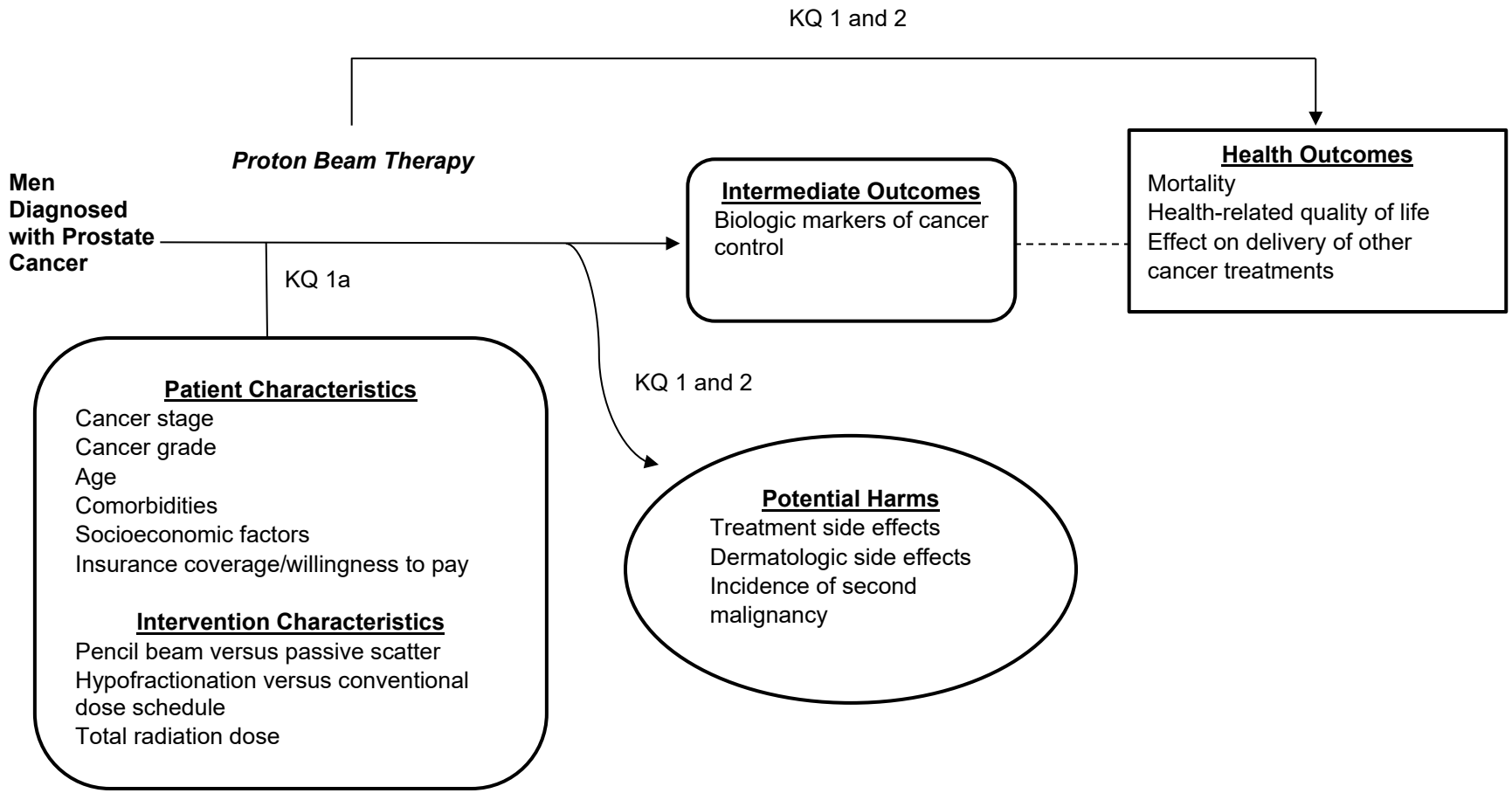
KQ1a: Do benefits or harms of PBT vary according to fractionation schedules, beam targeting modality (passive scattering vs pencil beam scanning), or patient characteristics (*eg*, symptom score, prostate size)?

KQ2: For patients with progression or recurrence of cancer in the prostate who were not previously treated with radiation therapy, what are the benefits and harms of PBT compared to conventional forms of radiation therapy?

ANALYTIC FRAMEWORK

The analytic framework shown in Figure 1 provides a conceptual overview of this review. The population of interest was men who have biopsy-confirmed adenocarcinoma of the prostate. Eligible outcomes were survival, impact of the cancer on quality of life, and treatment harms (Key Questions 1 and 2). The clinical literature also frequently refers to intermediate outcomes related to signs of tumor progression (including tumor size and the level of prostate specific antigen [PSA] in the blood). We examined these intermediate outcomes because of a plausible association of these measures with changes in eligible patient-relevant outcomes. Whether benefits and/or harms of the intervention differ by patient characteristics (*eg*, patient demographics, comorbidities, disease severity) or treatment protocol (*eg*, number of sessions, technical aspects of the delivery of the radiation dose) was also of interest (Key Question 1a).

Figure 1. Analytic Framework



Abbreviations. KQ=key question.

ELIGIBILITY CRITERIA

The review included studies that met the following criteria:

***P**opulation:*	Adults with localized prostate cancer
***I**ntervention:*	Proton beam irradiation therapy
***C**omparators:*	Radiotherapy using X-ray-based external beam modalities or brachytherapy
***O**utcomes:*	• *Benefits:* Survival, quality of life, functional capacity, local tumor control, delivery of planned radiation regimens • *Harms:* Gastrointestinal (GI) and genitourinary (GU) symptoms, second malignancies, soft tissue damage
***T**iming:*	Any
***S**etting:*	Any
***S**tudy Design:*	Any, but we may prioritize studies using a best-evidence approach to accommodate project timeline

DATA SOURCES AND SEARCHES

To identify articles relevant to the key questions, a research librarian searched Ovid MEDLINE, Ovid CENTRAL, and ClinicalTrials.gov, as well as the AHRQ and Cochrane Databases of Systematic Reviews through February 2022 using terms for proton beam and prostate cancer (see Appendix A in Supplemental Materials for complete search strategies). Formal Requests for Scientific Information were sent to manufacturers of proton therapy systems (see Appendix B for list of proton therapy centers). 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 available in the English language. Study selection was based on the eligibility criteria described above. Titles, abstracts, and full-text articles were reviewed by 1 investigator and checked by another. All disagreements were resolved by consensus or discussion with a third reviewer.

Key Questions 1 and 2 are comparative effectiveness questions, so all studies judged to be potentially relevant compared outcomes in 2 or more patient groups (as defined by the type of radiation therapy administered). Studies with comparative data were included in the review if patients in the comparison condition received IMRT or brachytherapy and patients in all conditions were treated for similar durations. Studies comparing PBT to older modalities for delivery of external beam proton therapy were excluded. Studies that examined only PBT (*ie*, without a comparator group receiving another type of radiation therapy) and stratified patients into subgroups defined by patient characteristics or difference in the dosage, schedule, or delivery method of PBT were considered eligible to address Key Question 1a.

DATA ABSTRACTION AND ASSESSMENT

Effect information and population, intervention, and comparator characteristics were abstracted from all included studies. The internal validity (risk of bias) of each included comparative study was rated using the ROBINS-I tool for observational studies.[38] For studies with observational

designs, this tool assesses the risk of bias attributable to confounding. For studies that were not controlled trials but reported data about non-PBT comparator groups, we examined what methodologies were used to improve the comparability of patient groups, such as one-to-one case matching, matching based on propensity scores, or case weighting using inverse probability weighting. All data abstraction and internal validity ratings were first completed by 1 investigator and then checked by 2 others; disagreements were resolved by discussion among the 3 investigators (DHH, JKA, NJP).

We graded the strength of the evidence (SOE) for outcomes based on the AHRQ Methods Guide for Comparative Effectiveness Reviews.[39] This approach provided a rating of confidence in reported findings based on trial methodology (design, quality, and risk of bias), consistency (whether effects are in the same direction and have a consistent magnitude), and directness (whether assessed outcomes are clinically important to patients and providers). When information on precision of findings (*eg*, confidence intervals) was available, certainty of evidence was also evaluated. For this review, we applied the following general algorithm: *high strength* evidence consisted of multiple, large controlled trials with low risk of bias, consistent and precise findings, and clinically relevant outcomes; *moderate strength* evidence consisted of multiple trials or well conducted comparative cohort studies with low risk of bias, consistent and precise findings, and clinically relevant outcomes; *low strength* evidence consisted of a single study, or multiple small studies, with varying risk of bias, inconsistent or imprecise findings, and/or outcomes with limited clinical relevance; and *insufficient* evidence consisted of a single study with moderate or high risk of bias, or no available studies.

SYNTHESIS

Studies were categorized by the characteristics of the patient populations, the types of treatments compared, and the types of clinical outcomes considered. When there were 2 or more studies that examined the same treatment comparisons in similar patient populations and with comparable outcome timing, study results were pooled using meta-analysis. Because the amount of between-study variation in true effects (*ie*, heterogeneity) can be difficult to estimate in meta-analyses of few studies, we employed Bayesian random-effects models to fully account for imprecision in heterogeneity estimates.[40] Models were fitted with limited prior information: For mean effects, a Normal prior with a mean of 0 and standard deviation of 4 was specified.[41] Heterogeneity magnitude was estimated with a half-Normal prior with a scale of 0.5, reflecting possible moderate to high heterogeneity, and sensitivity analyses were conducted at a scale of 1.0 (allowing extreme heterogeneity).[41-44]

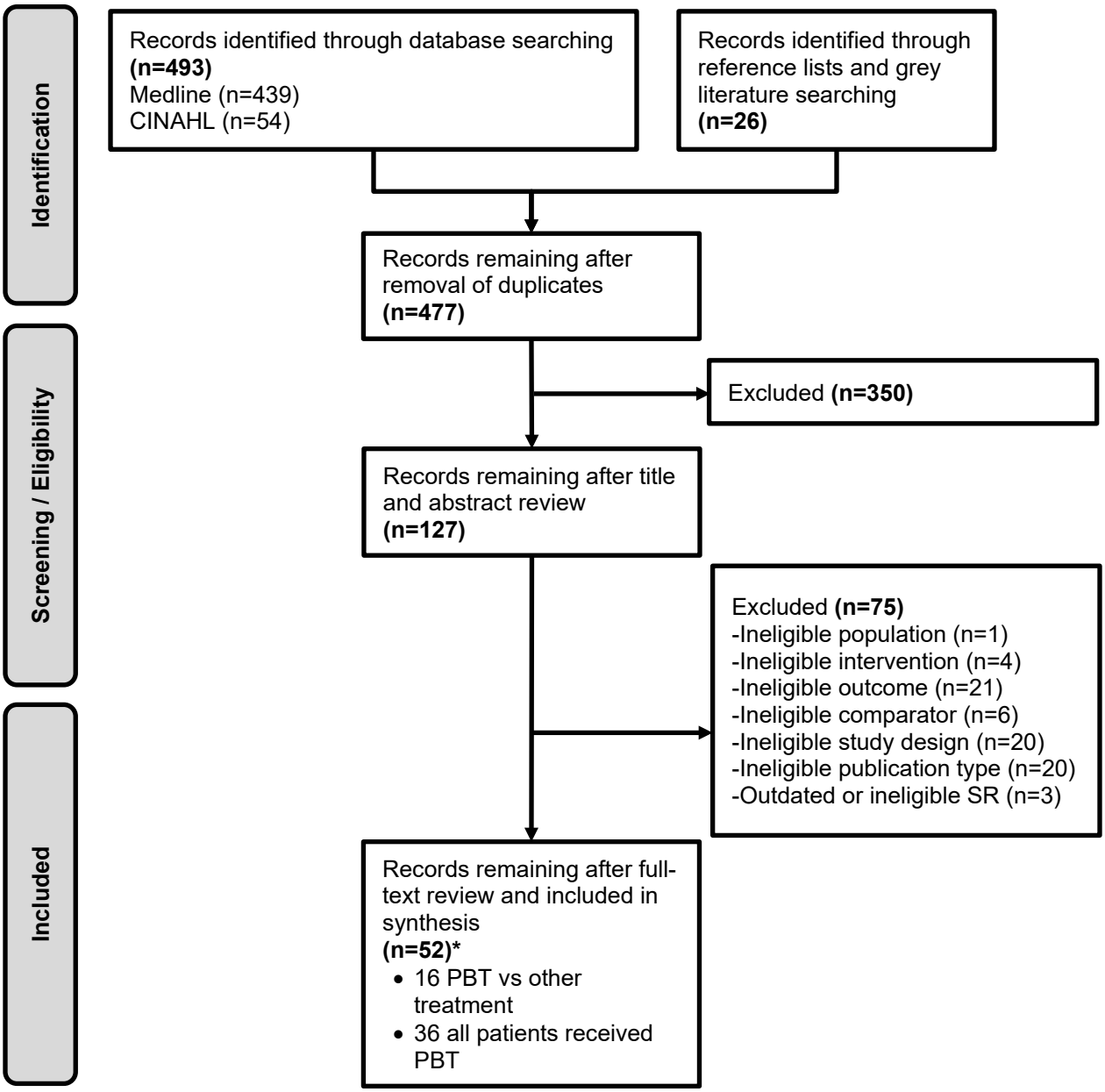
Meta-analysis results are presented with 95% highest posterior density credible intervals (CIs), which were used to evaluate statistical significance (*ie*, whether there was an at least 95% probability that a mean effect estimate differed from 1, or no difference between treatment groups). To assess variation in effects across studies, we report 95% prediction intervals (PIs) for mean effect estimates, which summarize the likely range of true study effects,[45-47] as well as shrinkage estimates and corresponding 95% PIs for individual studies. The latter provide an estimate of each study's underlying true effect (*eg*, toxicity risk) by drawing on information from all available studies,[47] and are useful for investigating heterogeneity. Meta-analyses were carried out using the *bayesmeta*[48] package for R version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

LITERATURE FLOW

The literature flow diagram (Figure 2) summarizes the results of the study selection process (full list of excluded studies available in Appendix C in Supplemental Materials).

Figure 2. Literature Flowchart



Notes. *47 studies in 52 publications.
Abbreviations. CINAHL=Cumulative Index for Nursing and Allied Health Literature; SR=systematic review.

LITERATURE OVERVIEW

Our search identified 477 potentially relevant articles. Of these, 47 studies (in 52 publications)[1-32,36,49-66] reported the results of treatment with PBT and met all inclusion criteria. No proton therapy manufacturers submitted information in response to our formal requests for scientific information. Fifteen studies (in 16 publications)[1-8,32,36,49,53,56,58,65,66] reported data from a comparison population of patients who received IMRT or brachytherapy. All of the included studies were published after 2010 and generally reported data only on patients who were diagnosed with prostate cancer after 2000.

Using the ROBINS-I tool, 10 comparative studies (in 11 publications)[1-8,32,65,66] were rated as low risk of bias, 3 were rated as moderate risk of bias, and 2 were rated as high risk of bias. Studies rated as low risk of bias were cohort studies using propensity score-based matching or weighting to limit selection bias risk. Characteristics of these studies are summarized in Table 1 (see Appendix D in Supplemental Materials for full study details). Seven studies compared PBT to IMRT as initial therapy for newly diagnosed prostate cancer patients,[1-6,66] 2 compared PBT to brachytherapy for initial therapy of prostate cancer,[7,8] and 1 study compared PBT to IMRT as postoperative adjuvant therapy following initial therapy with radical prostatectomy.[32,65]

Patients were followed for at least 12 months, and the most commonly reported outcomes were GI and GU toxicity. Six studies comparing PBT to IMRT as initial therapy for prostate cancer[1-5,66] measured short- and/or intermediate-term GI symptoms (*eg*, rectal bleeding), GU symptoms (*eg*, urinary irritative or incontinence symptoms), or erectile dysfunction (ED). Symptoms were assessed with prospectively administered questionnaires (with results dichotomized into low and high severity) or by diagnosis and procedure codes contained in clinical administrative databases. One study[1] also employed a prospectively measured general quality of life questionnaire. All studies reported intermediate-term outcomes, and 3 studies[1-3] also reported acute GI and GU symptoms (defined as occurring within 90 days of treatment). An additional study[6] examined risk of a new second cancer after primary treatment with PBT or IMRT.

Five comparative cohort studies[36,49,53,56,58] were rated as moderate or high risk of bias mainly because they did not implement methods to sufficiently account for differences between treatment groups (see Appendix D in Supplemental Materials for full study details). These studies were not considered among the evidence addressing Key Questions 1 and 2 due to the risk of uncontrolled confounding. Thirty-two studies (in 36 publications)[9-31,50-52,54,55,57,59-64,67] were case series in which all patients received PBT and provided evidence about whether benefits and harms of PBT vary by patient and/or treatment characteristics (Key Question 1a).

We identified 27 underway studies, 9 of which (5 RCTs) compare PBT to other treatment modalities (see Appendix F in Supplemental Materials for study details).

Table 1. Characteristics of Low Risk of Bias Studies Comparing PBT with IMRT or Brachytherapy

Author, Year ***Sample Size***	**Study Design** ***Country***	**Mean/Median Age** ***Follow-up***	**Prostate Cancer Characteristics**	**PBT Dose (Gy)** ***PBT Details***	**Comparator**	**Outcomes**
Barsky 2021[32] & Santos 2019[65] *N=307*	Retrospective cohort *US*	NR *5 years*	Post-radical prostatectomy prostate cancer	70.2 (median) *NR*	IMRT	Biochemical failure, overall survival, prostate cancer-specific survival
Coen 2012[8] *N=282*	Retrospective cohort *US*	66 *8 years*	Localized prostate cancer	79.2 *Proton boost of 28.8 Gy before 3DCRT (79.2 Gy total)*	Brachytherapy	Overall survival, biochemical failure, freedom from distant-metastasis
Dutz 2019[1] *N=58*	Prospective cohort *Germany*	72.7 *3 months–1 year*	Localized prostate cancer	74–76 *74–76 Gy in 37-38 fractions*	IMRT	GU toxicity, GI toxicity, QoL
Fang 2014[2] *N=188*	Prospective cohort *US*	NR *3 months–2 years*	Localized prostate cancer	79.2 *79.2 Gy in 44 fractions*	IMRT	GU toxicity, GI toxicity
Liu 2021[7] *N=276,880*	Retrospective cohort *US*	68 *10 years*	Localized prostate cancer	≥ 60 *NR*	Brachytherapy	Overall survival
Pan 2018[4] *N=3,434*	Retrospective cohort *US*	<65 *2 years*	Localized prostate cancer	39 (median) *NR*	IMRT	GU toxicity, ED, QoL
Sheets 2012[66] *N=1,368*	Retrospective cohort *US*	NR *1 year*	Localized prostate cancer	NR *NR*	IMRT	GI toxicity, GU toxicity, ED
Vapiwala 2021[3] *N=1,850*	Prospective cohort *US*	67 *1 year*	Localized early prostate cancer	60–72.5 *2.5–3 Gy per fraction*	IMRT	GU toxicity, GI toxicity
Xiang 2020[6] *N=10,700*	Retrospective cohort *US*	59.4 *5.21 years*	Localized prostate cancer	56.4-81.0 *2.5–5 Gy per fraction*	IMRT	Second cancers
Yu 2013[5] *N=942*	Retrospective cohort *US*	NR *1 year*	Localized early prostate cancer	NR *NR*	IMRT	GU toxicity, GI toxicity

Notes. Barksy 2021[32] is a follow-up analysis of Santos 2019.[65]
Abbreviations. 3DCRT=three-dimensional conformal radiation therapy; ED=erectile dysfunction; GI=gastrointestinal; GU=genitourinary; Gy=gray; IMRT=intensity modulated radiation therapy; PBT=proton beam therapy; QoL=quality of life.

PROTON BEAM THERAPY COMPARED TO IMRT

Toxicity

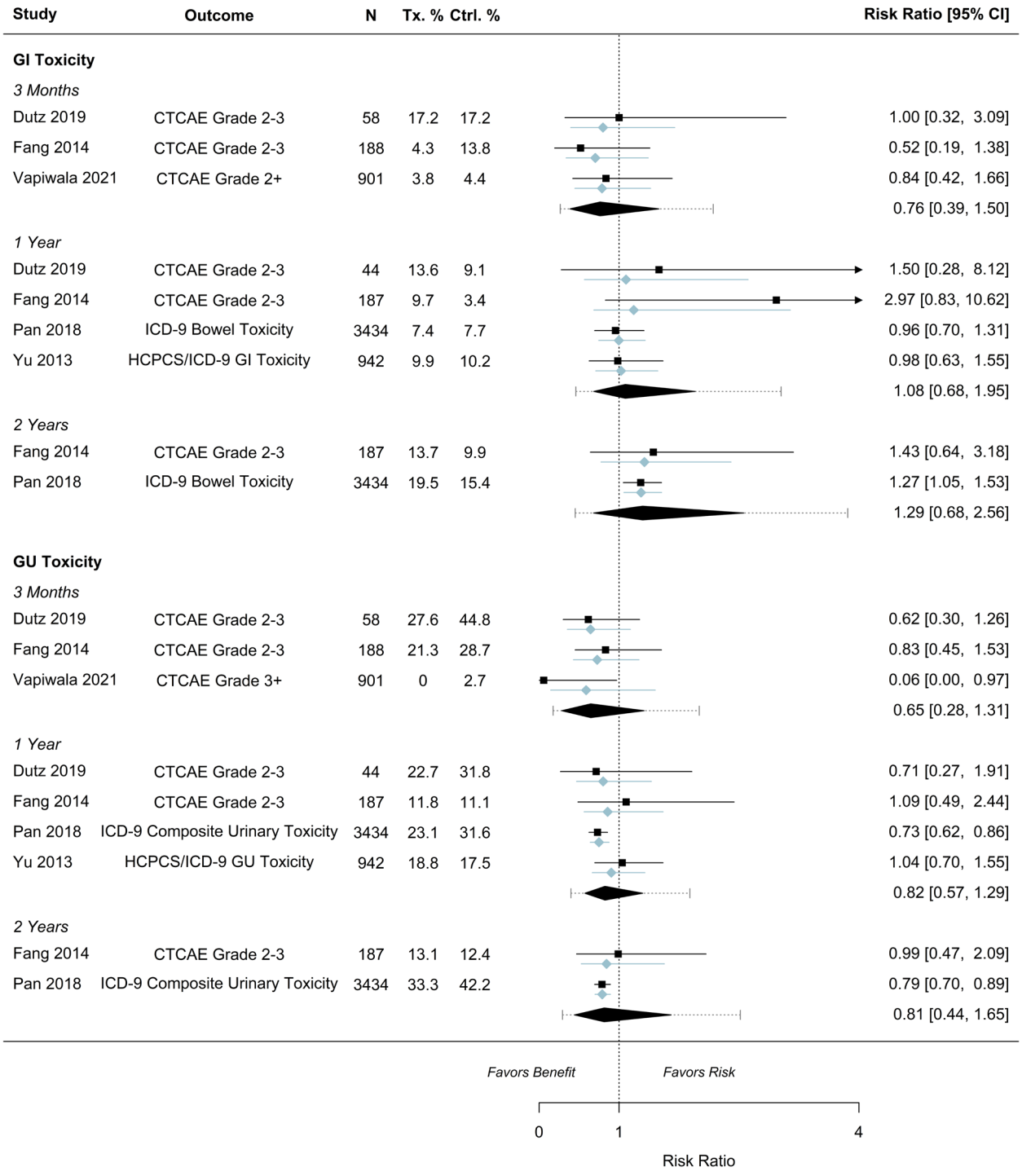
Rates of moderate or severe toxicity symptoms varied across available studies. Early GI toxicity rates ranged from 4% to 17% among both IMRT and PBT patients, but the rates tended to be higher for IMRT patients in the 3 studies[1-3] that reported on early toxicity. Rates of late GI toxicity (defined as symptoms that persist for 12 months or longer) ranged from 5% to 18%, and were lower among IMRT patients (4 studies[1-3,66]) or comparable for IMRT and PBT groups (2 studies[4,5]). Rates of early GU toxicity ranged from 0 to 45% and were consistently higher among patients receiving IMRT.[1-3] Rates of late GU toxicity ranged from 2% to 32%, and were higher among IMRT patients (5 studies[1-4,66]) or comparable for both modalities (1 study[5]).

Studies that were sufficiently similar (see Methods section) were included in meta-analyses. A small number of such studies were available for each analysis after stratifying by trial endpoint. The majority of studies reported outcomes as counts or proportions in statistically matched cohorts, and risk ratios (RRs) were calculated directly for these studies. One study[3] reported no toxicity events in 1 group, and a continuity correction of 0.5 was applied to all cell counts for this outcome. Adjusted odds ratios from 2 studies[2,5] were converted to RRs using the square-root transformation.[68] All synthesized ratios less than 1 indicate benefits (*ie*, reduced risk) for PBT compared to other radiation therapy modalities, and ratios greater than 1 indicate greater risk compared to other radiation therapy modalities. Results of meta-analyses are shown in Figure 3. Findings were not sensitive to prior information specified for heterogeneity in effects.

No pooled estimate of GI or GU toxicity risk reached statistical significance. At 3 months after treatment initiation or completion, results from 3 studies[1-3] (N = 58–901) suggest a possible lower risk of early GI toxicity (RR_{Mean} = 0.76, 95% CI [0.39, 1.50]) and early GU toxicity (RR_{Mean} = 0.65, 95% CI [0.28, 1.34]) after treatment with PBT compared with IMRT. The largest study[3] reported a significant finding for GU toxicity. Observed toxicity risk and estimates of true risk in each study (shown in blue in Figure 3) were consistent in direction (*ie*, at or below an RR of 1.0), and all studies used a similar outcome definition (CTCAE grade 2-3 or 2-3+).

Evidence on toxicity in the first year after treatment is more inconsistent. For GI toxicity, 2 small studies[1,2] (N = 44–187) used the same outcome definition (CTCAE grade 2-3) and reported moderately to substantially greater risk of toxicity 1 year after treatment with PBT compared with IMRT. Risk estimates in these studies were highly imprecise, and in raw counts, differences between groups were minimal (1–6 toxicity events). Results of 2 larger studies[4,5] (N = 942–3,434) were more precise and indicate no difference in risk (measured as ICD-9 bowel/GI toxicity regardless of severity). The pooled estimate also suggests little or no difference in GI toxicity risk between modalities (RR_{Mean} = 1.08, 95% CI [0.68, 1.95]). Estimates of true toxicity risk in each study suggest that the smaller studies may overestimate differences in GI toxicity risk.

Figure 3. Forest Plot of Toxicity Findings of Studies Comparing PBT to IMRT



Notes. Black diamonds indicate results of random-effects meta-analyses (width of diamond corresponds to 95% CI and gray dashed error bars to 95% PIs). Blue diamonds and error bars represent estimates of study-specific true effects (*ie*, shrinkage estimates) and corresponding 95% PIs (reflecting the likely range of true effects in each study). A continuity correction of 0.5 was applied to all 3-month GU toxicity cell counts reported by Vapiwala 2021.
Abbreviations. 95% CI=95% highest posterior density credible interval; CTCAE=Common Terminology Criteria for Adverse Events; Ctrl. %=outcome proportion in control group; HCPCS=Healthcare Common Procedure Coding System; ICD-9=International Classification of Diseases, 9th Revision; Tx. %=outcome proportion in treatment group.

Evidence on GU toxicity 1 year after treatment is also inconsistent. Two studies[1,4] that differ in size and outcome definition reported minimal difference in toxicity after treatment with PBT compared with IMRT. Two other studies[2,5] (again inconsistent in size and outcome definition) observed somewhat lower toxicity risk after PBT. The larger of these studies[4] reported a significant difference in risk, and the pooled result also indicates that GU toxicity risk is possibly lower after treatment with PBT compared with IMRT (RR_{Mean} = 0.82, 95% CI [0.57, 1.29]). Estimates of true GU toxicity risk in each study suggest that the difference in risk in all studies may more consistently favor PBT, while remaining fairly small in magnitude.

Two studies[2,4] (*N* = 187–3,434) reported 24-month GI and GU toxicity outcomes (CTCAE grade 2-3 or ICD-9 bowel or composite urinary toxicity). Both studies reported higher GI toxicity risk after treatment with PBT compared with IMRT (RR_{Mean} = 1.29, 95% CI [0.68, 2.56]). For GU toxicity, studies reported no difference in risk[2] or a somewhat (but significantly) lower risk[4] after treatment with PBT compared with IMRT. Given the much larger size of the second study, pooling estimates from both studies also indicates possibly lower risk of GU toxicity after PBT compared with IMRT (RR_{Mean} = 0.81, 95% CI [0.44, 1.65]). Despite reporting similar GU toxicity risk for both modalities, the underlying risk of GU toxicity in the smaller study may favor PBT according to the estimate of true GU toxicity risk in that study.

Three studies (2 of which provided findings included in meta-analyses) reported on GI and GU toxicity over study observational periods that ranged from 24–80 months (median). All studies (*N* = 187–1,368) carried out statistical adjustment for confounding and excluded toxicity events that occurred in an early or acute period, defined as 3 months[2,3] or 1 year.[66] Studies were not pooled due to differences in outcome definitions, the duration of follow-up, and the excluded acute period. For GI toxicity, 2 studies used similarly defined outcomes (CTCAE grade 2-3 or 2+) and reported greater risk of GI toxicity after treatment with PBT compared with IMRT. Both results were nonsignificant and differed considerably in magnitude (hazard ratio = 1.24, 95% CI [0.53, 2.94];[2] odds ratio = 2.68, 95% CI [0.80, 8.98][3]). The third study[66] assessed ICD-9 GI events of any severity and reported significantly greater GI toxicity risk after treatment with PBT compared with IMRT (RR = 1.52, 95% CI [1.27, 1.82][i]). GU toxicity was reported by the same 3 studies, and estimates were consistent in direction (favoring PBT) and similar in magnitude (ratios ranged from 0.55 to 0.80), although none was significant.

One additional study[32,65] (*N* = 260) examined rates of GI and GU toxicity in matched patients who received PBT or IMRT as "adjuvant" or "salvage" radiation after initial treatment with radical prostatectomy. Few details about the patients' response to the initial prostatectomy were reported. Slightly higher rates of acute and late GI and GU toxicities were observed among IMRT recipients (differences were nonsignificant). Because this patient population differed substantially from those of other studies, this study was not included in meta-analyses.

Based on consistency in direction of reported findings across most comparative studies of GU toxicity—and across meta-analysis results and estimates of study-specific true GU toxicity risk—it is possible that PBT is associated with a somewhat lower risk of GU toxicity compared with IMRT. The magnitude of differences in risk varied across studies, however, and only 2 studies[3,4] reported significantly lower risk among PBT recipients. Consistency in direction is less

[i] Risk ratios reported by this study compared IMRT to PBT (*ie*, values larger than 1 indicate greater risk for IMRT). Results from this study were inverted for consistency with other risk estimates.

evident in findings on GI toxicity, although examining the pattern of available evidence suggests that GI toxicity attributable to PBT may be more likely outside of the early post-treatment period. Two studies reported significantly greater risk for PBT recipients in later periods.

Two retrospective cohort studies[4,66] (N = 1,368–3,434) using clinical administrative data examined rates of ED after PBT and IMRT. Both studies accounted for potential confounders and used the same outcome (ICD-9 ED events) but differed in outcome timing. One study reported a significantly lower risk of ED among PBT recipients compared with those receiving IMRT at 2-year follow-up (hazard ratio = 0.71, 95% CI [0.59, 0.84]). In contrast, the second study observed a somewhat greater risk of ED for PBT recipients at a median of 46–50 months post-treatment (RR = 1.12, 95% CI [0.89, 1.43]).

As noted initially, no meta-analytic findings reached significance. Moreover, despite the consistency in direction of GU findings (and some suggestive trends in GI findings), studies used inconsistent outcome definitions (some restricting to more severe outcomes, others counting toxicity at any severity), varied considerably in size, and may also have differed in PBT dosing. The impact of dosing differences is unclear because not all studies reported dosages. With these considerations in mind, we concluded that available evidence on the comparative risk of GI and GU toxicity following PBT and IMRT is low strength. Evidence is insufficient for reaching a conclusion about differences in risk of post-treatment ED after PBT or IMRT.

Quality of Life and Survival

One small study[1] (29 matched pairs of patients receiving either PBT or IMRT) prospectively administered a general quality of life measure 3 months and 12 months after PBT or IMRT. No subscale scores were significantly different between modalities. Long-term cancer control has been evaluated using patient survival or by elevated post-treatment levels of prostate-specific antigen (PSA; a marker of disease progression). One study[7] examined overall survival among patients enrolled in the National Cancer Database from 2004–2015 who received initial therapy with PBT or external beam photon therapy (either IMRT or 3-dimensional conformal radiation therapy). Ten-year survival rates in 1,860 matched patient pairs were significantly higher in the PBT group (80.1% vs 71.3%). Because study outcomes were not disaggregated by external beam modality, it is unclear to what extent these results correspond to a direct comparison between PBT and IMRT. The study also does not provide information on any changes to PBT techniques over the 10-year study period. Evidence is insufficient to draw conclusions about differences in quality of life or survival after PBT or IMRT.

Incidence of Second Cancers

One study[6] assessed incidence of second cancers among patients who received PBT or IMRT. The study used a retrospective cohort design, and the data were derived from a nationwide cancer registry in the US. A limitation of this data source is that a second cancer was coded only as having occurred, with no information about its timing, location, or histology. The investigators employed propensity scores to match the PBT and IMRT patients with regards to various clinical and sociodemographic characteristics, and statistical models were also adjusted for covariates. A total of 3,566 prostate cancer patients who received PBT as their primary treatment for cancer were matched 2 to 1 to 7,134 patients who received IMRT. We judged this study to have a low risk of bias. The adjusted odds ratio for second cancer was 0.18, 95% CI [0.14, 0.24]. Despite the low risk of bias in this study, there are inherent limitations in the data

used in this study. The time-course of second cancer occurrence was not reported, as well as any data that would provide information about whether second cancers occurred in anatomical locations that plausibly received radiation exposure. Available evidence[ii] is therefore insufficient to reach a conclusion about comparative risk of second cancers after PBT or IMRT.

PROTON BEAM THERAPY COMPARED TO BRACHYTHERAPY

For the direct comparison of PBT to brachytherapy, only 2 comparative studies[7,8] employed adequate methods to control for confounding. Both studies examined markers of long-term disease control. The first[7] assessed overall survival for patients receiving initial therapy with PBT or brachytherapy who were enrolled in the National Cancer Database between 2004 and 2015. In 1,860 matched pairs, 10-year survival rates were similar between the PBT and brachytherapy groups (80.1% and 78.3%, respectively). The second study[8] examined overall survival and cancer progression as measured by PSA levels in 141 matched pairs of men receiving either PBT or brachytherapy. There were no significant differences between the 2 cohorts in either outcome. A limitation of this study was that an older form of combined proton and photon therapy ("proton boost") was used. Evidence that PBT and brachytherapy confer similar impacts on overall survival was rated as low strength.

NONCOMPARATIVE STUDIES OF PROTON BEAM THERAPY

The remaining evidence on the effectiveness of PBT consists of studies based on case series. Thirty-two studies (in 36 publications)[9-31,50-52,54,55,57,59-64,67,70] attempted to compare subgroups of patients who received PBT, and these studies were assessed for whether they provide insight into differences in clinical outcomes between subgroups defined by patient characteristics or by differences in the technical aspects of how the PBT was delivered (Key Question 1a).

Ten studies[9-13,15,16,26,60] (N = 192–2,021) assessed the relationship between patient characteristics and the incidence of late GU or GI toxicity. Factors associated with a higher incidence of GU toxicity were older age[12,15,26] and a history of prior prostate surgery.[16,60] Another case series[54] that used multivariate analysis did not find that age was a predictor of urinary toxicity. For GI toxicity, age was only a weak predictor,[15,26] but use of anticoagulants was associated with a higher rate of rectal bleeding after PBT (low strength of evidence).[11-13]

Three studies[14,55,71] (N = 127–1,005) have examined the relationship between patient characteristics and sexual function following PBT. Pre-existing cardiac disease[55] and older age[71] were associated with ED following PBT. In a study of the relationship between baseline cancer risk scores and sexual function following PBT, low-risk patients had better sexual function prior to treatment but greater decline following treatment.[14] All studies were exploratory and examined different patient characteristics; therefore evidence is insufficient to make conclusions about the effect of patient factors on sexual function.

[ii] Another identified study[69] examined rates of second malignancies for patients who received either PBT or photon-based radiation therapy, but this study was excluded because nearly all PBT patients were treated prior to 2000 at a single proton therapy center, and few photon-treated patients appeared to have received modern external beam modalities such as IMRT.

Single studies have examined other patient factors, including prostate size[52] ($N = 81$), the duration of androgen deprivation therapy[63] ($N = 1,075$), and the time of day that PBT sessions occurred[64] ($N = 168$). These studies did not report data on control groups, and none made a conclusive contribution to the evidence base.

In a study[10] of the effect of patient race on GU and GI toxicity rates after PBT, 92 black patients were matched to 92 white patients. No difference in toxicity rates was found between the 2 groups. These results were similar to another study[9] ($N = 1,066$) that compared racial groups but did not use a matching methodology. Overall, the strength of evidence for race not affecting outcomes is low due to the small number of studies and lack of data on all races/ethnicities.

Thirteen studies have examined the relationship between patient factors and rates of cancer control[9,10,12,15-24,26,71] ($N = 93–1,327$). The most commonly used methods for defining subgroups were measures of risk of cancer recurrence based on baseline data such as patient age, tumor stage, Gleason score, and PSA level. Most studies found that men who had worse baseline risk scores had modestly higher rates of disease progression as measured by PSA levels, though most also found that the rates of 5-year disease progression were generally less than 25% in all risk groups who received PBT as initial therapy for prostate cancer. Two studies[12,23] found very low rates of disease progression and no relationship with risk score. Because of the generally small influence of risk score on disease progression, evidence that baseline risk score predicts the rate of disease progression after PBT is low strength.

EFFECT OF DOSAGE SCHEDULES AND OTHER TECHNOLOGICAL FACTORS ON PATIENT OUTCOMES

Several clinical studies have examined whether dosage schedule (use of hypofractionation), use of pencil beam modality, and total delivered dose influence outcomes. Hypofractionation has been examined in 2 small RCTs.[27,30] The first RCT[27] randomized 82 men to a "moderate hypofractionated" PBT dose schedule or an "extreme hypofractionated" schedule and compared long-term GI and GU toxicity and cancer control. The rates of GI and GU toxicity were slightly different between treatment arms, but these differences were not statistically significant. Cancer progression as measured by PSA levels was significantly higher in the extreme hypofractionation arm. The second RCT[30] ($N = 82$) reported small and nonsignificant differences in GU and GI toxicity between patients on a hypofractionation schedule or conventional dosage schedule.

Two observational studies[28,29] ($N = 289–526$) compared patients receiving hypofractionation to patients receiving conventional dosage schedules. Though there were few baseline differences in demographic characteristics between groups, neither study used statistical methods to control for confounding. Both found only small differences in GU and GI toxicity rates between groups. Despite similar conclusions across all 4 studies on hypofractionation, RCTs were small and employed different comparators, and other studies had critical methodological limitations. For these reasons, the strength of evidence on hypofractionated dosing schedules is low. One of the included RCTs[27] also examined long-term cancer control with hypofractionation, but all patients received some degree of hypofractionation, hindering any conclusion about cancer control.

Pencil beam scanning (PBS) is a newer technique that potentially can deliver more precise dosing in PBT, compared with conventional PBT. A multi-site registry study ($N = 1,343$) has enrolled patients receiving either PBS or conventional PBT and has reported data on toxicity

rates for the 2 alternative modalities.[61,62] Both acute and late GU toxicity were higher in the PBS group, while GI and sexual toxicity did not differ between the groups. The methods for controlling for confounding were limited in this study. Overall, the current evidence is insufficient to draw conclusions about the comparison of PBS to conventional PBT.

Few studies examined the relationship between total radiation dose and outcomes among patients who received PBT. One study[67] ($N = 218$) measured toxicity rates among patients receiving a total dose of either 70 GyE, 74 GyE, or 78 GyE. Significantly higher rates of late GI toxicity were observed in the 78 GyE group compared with the lower dosages. Rates of severe late GU toxicity and sexual function scores did not significantly differ between dosage groups. Another case series found an association between total dose and GI toxicity using a multivariable model.[50] Overall, available evidence is insufficient to draw conclusions about the influence of total radiation dose on toxicity risk.

PROTON BEAM THERAPY FOR PATIENTS WITH RECURRENT PROSTATE CANCER

One study[32,65] ($N = 307$) that used case matching reported on cancer control in patients who received either PBT or IMRT following relapse of prostate cancer and initial therapy with radical prostatectomy. The study reported data from patients who had received "adjuvant" PBT or IMRT, and it is not possible to distinguish between the relapse and adjuvant subgroups. The rates of further disease progression as measured by PSA rise were moderately high (30-45%, depending on the definition used for interpreting PSA rise) and similar between the PBT and IMRT groups. Five-year cancer-specific mortality was low in both PBT and IMRT groups. Two other studies[57,72] ($N = 100$–102) reported cancer control data for patients who received PBT following relapse after initial therapy with radical prostatectomy. These studies did not have comparison groups of patients who received another form of therapy for the relapse. The 5-year rate of disease progression (by PSA rise) was 42% and 39% in these studies, which is similar to the rate reported for the PBT arm of the comparative study. Due to the small number of studies, evidence is insufficient to conclude whether PBT has advantages over other forms of therapy for the treatment of relapsed prostate cancer.

PREVIOUSLY PUBLISHED SYSTEMATIC REVIEWS

The present review updates an evidence synthesis completed in 2015,[37] focusing on use of PBT for prostate cancer. The 2015 review included several studies that were not included in the present review because they compared PBT to older modes of conventional radiation therapy. IMRT is currently the dominant modality used for photon-based radiation therapy in the US, and for the present review, eligible comparison conditions were limited to IMRT and brachytherapy to reflect active treatment options now available to newly diagnosed prostate cancer patients in the US. Risks of bias in these studies was assessed using the ROBINS-I methodology.

The 2015 evidence synthesis reported generally similar outcomes between PBT and photon-based radiation therapy and concluded that there was not enough evidence on the effectiveness of PBT to determine whether it was better, worse, or equivalent to conventional therapies for prostate cancer (low strength of evidence ratings for all conclusions). The present review includes studies published since 2015 that compare GU and GI toxicity risk among patients receiving PBT or IMRT, yet the strength of evidence for these outcomes remains low. In 2021,

Ontario Health released a review of other systematic reviews on PBT,[73] with findings similar to those of the present review and low strength of evidence ratings for all conclusions. Another 2021 systematic review[74] focused on the comparison between PBT and carbon ion radiotherapy, but did not perform meta-analyses on studies comparing PBT to photon-based radiation therapy nor report strength of evidence ratings.

DISCUSSION

Over the last 2 decades, PBT has evolved into a mature technology for treatment of men with recently diagnosed prostate cancer. In this period, the number of PBT treatment centers has greatly increased in the United States. Nonetheless, other types of radiation therapy (particularly IMRT) are used much more frequently than PBT. The evidence base on radiation therapy for the treatment of prostate cancer includes few controlled trials of alternative treatment modalities. Instead, the best available evidence comes from small to medium-sized cohort studies that compare PBT to IMRT. Fewer studies compare PBT to brachytherapy, but those that are available provide some insights.

For men who choose to pursue radiation therapy as initial treatment for prostate cancer, the choice among PBT, IMRT, and brachytherapy can be informed by data about the relative benefits and harms of these modalities. The primary potential benefit of any of these treatments is to provide protection against relapse and progression of the cancer. The available evidence is insufficient to draw a conclusion about the comparative benefits of PBT and IMRT for cancer control. Although uncontrolled studies[9,10,12,15-24,26,71] suggest that relapse rates for PBT are low, there are few data directly comparing PBT to IMRT. The evidence is stronger (though overall low strength) that PBT and brachytherapy confer similar levels of cancer control.

Studies in men who received either radiation therapy, surgical prostatectomy, or active surveillance for prostate cancer have found that radiation therapy is associated with higher rates of undesirable urinary symptoms or bowel problems.[75,76] While a theoretical advantage of PBT is that protons deliver radiation to tissues in a highly targeted fashion, the available evidence has not conclusively shown superiority of PBT for GU and GI toxicities and sexual problems. PBT may be superior to IMRT for one category of treatment toxicity (GU side effects), but the strength of evidence is low and differences in risk between modalities may be modest. Other toxicities (GI and sexual) do not appear to differ substantially between PBT and IMRT, though the strength of evidence for this conclusion is also low. There is insufficient evidence to draw conclusions about differences in toxicity between PBT and brachytherapy.

Hypofractionation can potentially reduce patient burden by requiring fewer sessions to complete a course of radiation therapy. Low-strength evidence from a small number of studies indicates similar GI and GU toxicity rates for hypofractionation and conventional dosing in PBT. Evidence about whether certain patient characteristics lead to differences in clinical outcomes comes mostly from uncontrolled single-arm studies of patients receiving PBT. These results might assist clinicians in increasing patients' understanding of their risk of toxicity when undergoing PBT. However, because of a lack of comparative data for similar patients receiving other forms of radiation therapy, existing studies do not clarify whether specific patient subgroups experience greater treatment benefits or harm—and consequently may be better candidates for PBT than for alternative modalities.

LIMITATIONS

Evidence comparing PBT to IMRT or brachytherapy for initial treatment of prostate cancer is derived from observational studies of patient cohorts receiving either PBT or the alternative modality. Although 10 of these comparative studies were judged to have low risk of bias, various unmeasured confounders (such as the effect of differing patient referral patterns in multiple

participating institutions) could affect the study results. This limitation, among others discussed elsewhere, reduces the strength of available evidence. There are also potential limitations of our review methodology, including use of a second reviewer to check for study selection and data abstraction rather than fully independent dual review.

FUTURE RESEARCH

Prospective randomized trials can avoid biases inherent to studies with observational designs. Several RCTs are underway that will compare clinical outcomes of patients receiving PBT or photon-based radiation therapy, and when reported later this decade, trial findings may resolve open questions about PBT for the treatment of localized prostate cancer.

CONCLUSIONS

The evidence base on comparative benefits and harms of PBT for the initial treatment of prostate cancer continues to grow. Nonetheless, available evidence remains low or insufficient strength. Based on studies published through the end of 2021, it is possible that PBT is associated with lower risk of early and late GU toxicity compared with IMRT. Rates of early and late GI toxicity and sexual side effects appear to be similar between PBT and IMRT. Available evidence is insufficient to determine whether risk of GU and GI toxicity differs between PBT and brachytherapy. Based on a single comparative study using full-dose PBT, relapse rates appear to be similar for PBT and brachytherapy, while evidence on relapse prevention for PBT compared with IMRT is insufficient.

More studies are needed to address evidence gaps, including cancer recurrence rates following PBT and IMRT, toxicity among comparable patients receiving PBT or brachytherapy, and use of PBT in cases of prostate cancer relapse after initial treatment with another therapy. Several controlled clinical trials are currently underway and could address some open questions. Currently available evidence may be useful in patient-provider decisions about the treatment of localized prostate cancer, yet it also reveals important uncertainties that are necessary to consider in the complex and nuanced choice of treatment modality.

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