



# Effective Health Care Program

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Comparative Effectiveness Review  
Number 146

## **Therapies for Clinically Localized Prostate Cancer: Update of a 2008 Systematic Review**



Agency for Healthcare Research and Quality  
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# *Comparative Effectiveness Review*

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Number 146

## **Therapies for Clinically Localized Prostate Cancer: Update of a 2008 Systematic Review**

**Prepared for:**

Agency for Healthcare Research and Quality  
U.S. Department of Health and Human Services  
540 Gaither Road  
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## Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new health care technologies and strategies.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see [www.effectivehealthcare.ahrq.gov/reference/purpose.cfm](http://www.effectivehealthcare.ahrq.gov/reference/purpose.cfm).

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We welcome comments on this systematic review. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to [epc@ahrq.hhs.gov](mailto:epc@ahrq.hhs.gov).

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## Technical Expert Panel

In designing the study questions and methodology at the outset of this report, the ECRI Institute–Penn Medicine EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

Technical Experts must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The Task Order Officer and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

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# Therapies for Clinically Localized Prostate Cancer: Update of a 2008 Systematic Review

## Structured Abstract

**Objective.** To comprehensively update a 2008 systematic review on treatments for cancer confined to the prostate gland, which is the definition of clinically localized disease.

**Data sources.** We searched MEDLINE<sup>®</sup>, PreMEDLINE, Embase<sup>®</sup>, the Cochrane Library, the Database of Abstracts of Reviews of Effects, the Health Technology Assessment Database, gray literature, and the U.K. National Health Service Economic Evaluation Database for reports published from January 1, 2007, through March 7, 2014.

**Review methods.** We synthesized evidence from randomized controlled trials (RCTs) and nonrandomized comparative studies published in English that evaluated treatments and reported clinical or biochemical outcomes in patients with clinically localized prostate cancer.

**Results.** Eight RCTs and 44 nonrandomized comparative studies evaluating numerous treatment options met inclusion criteria. However, because most comparisons were represented by only one or two studies, the strength of evidence (SOE) was insufficient for the majority of comparisons.

Two RCTs, the Scandinavian Prostate Cancer Group-4 (SPCG-4) and the Prostate Intervention Versus Observation Trial (PIVOT) compared radical prostatectomy (RP) and watchful waiting (WW) in localized prostate cancer patients. No meta-analysis was done because of the heterogeneity of included patients. While the SPCG-4 study found that RP reduced prostate cancer-specific mortality at 12 and 15 years, the PIVOT trial found no statistically significant difference at 12 years. The SPCG-4 study found that RP reduced all-cause mortality at 15 years, but neither the SPCG-4 nor the PIVOT trial found any significant difference at 12 years. The SOE for these outcomes was insufficient. However, both trials found significant reductions in progression to metastases in the RP group compared with the WW group (SOE: moderate). In the SPCG-4 trial, subgroup analyses showed reduced all-cause mortality among patients younger than 65 years and among patients with low tumor risk. In the PIVOT, reduced all-cause mortality was identified among men with prostate-specific antigen >10 ng/mL and among men with intermediate tumor risk.

One RCT that compared three-dimensional conformal radiotherapy (3D-CRT) with 3D-CRT plus androgen-deprivation therapy (ADT) reported an improvement in overall survival and prostate cancer-specific mortality among men who received combined therapy (SOE: low). Six nonrandomized comparison studies reported that all-cause and prostate cancer-specific mortality was lower in patients treated with RP than in patients treated with external beam radiation therapy (SOE: low).

The definition and severity of adverse events varied greatly across studies. Adverse events such as urinary incontinence and erectile dysfunction were reported mostly among men who underwent RP. Additionally, adverse events such as genitourinary toxicity, gastrointestinal toxicity, and erectile dysfunction were reported among men who received radiation therapy.

**Conclusions.** This systematic review update found that the evidence for most treatment comparisons is largely inadequate to determine comparative risks and benefits of therapies for clinically localized prostate cancer. This conclusion is similar to that of the 2008 review, which found that no single therapy can be considered the preferred treatment for localized prostate cancer because of limitations in the body of evidence as well as the likely tradeoffs a patient must make between estimated treatment effectiveness, necessity, and adverse effects. Although limited evidence appears to favor surgery over WW or external beam radiotherapy, or favors 3D-CRT plus ADT over 3D-CRT alone, the patients most likely to benefit and the applicability of these study findings to contemporary patients and practice remain uncertain. More RCTs and better designed observational studies that can control for many of the known and unknown confounding factors that can affect long-term outcomes are needed to evaluate comparative risks and benefits of therapies for clinically localized prostate cancer.



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# Executive Summary

## Background

Prostate cancer is the most common nondermatologic cancer in men.<sup>1,2</sup> The American Cancer Society has estimated that 241,740 men were expected to receive a diagnosis of prostate cancer in 2012, and 28,170 were expected to die from the disease.<sup>1</sup> Approximately 90 percent of those who receive such a diagnosis have cancer confined to the prostate gland, which is the definition of clinically localized disease. Since 2004, the prostate cancer incidence rate has decreased by 2.7 percent annually among men 65 years of age or older and has remained steady among men younger than age 65.<sup>1</sup> The major risk factors for prostate cancer are advanced age, race and ethnicity (the highest incidence is in blacks), and family history.

Many cases of prostate cancer have a protracted course if left untreated. Many men die with prostate cancer rather than from it.<sup>3</sup> During its early stages, clinically localized prostate cancer is usually asymptomatic.<sup>4</sup> However, as the cancer grows, it may cause urinary problems such as blood in the urine, pain or a burning sensation during urination, a weak urine stream, inability to urinate, and frequent urination, especially at night. These presenting symptoms, along with a physical examination, prostate-specific antigen (PSA) levels, and biopsy, may be used to evaluate patients for the presence of prostate cancer.

The PSA test is used to measure blood levels of PSA, a protein produced by the prostate gland.<sup>4</sup> Elevated PSA levels may indicate the presence of prostate cancer, but elevations are also seen in conditions such as benign prostatic hyperplasia and prostatitis. Conversely, some patients with prostate cancer do not have elevated levels of PSA.<sup>5</sup> Moreover, the cutpoint separating a “normal” PSA level from an abnormal level also remains a subject of debate. In recent years, more frequent use of PSA testing has intensified concern about overdiagnosis of prostate cancer (i.e., detection of cancer that would have remained silent and caused the patient no illness throughout his lifetime).<sup>2,4</sup>

In May 2012, the U.S. Preventive Services Task Force recommended against PSA-based screening for prostate cancer in healthy men of all ages, concluding that the harms of screening outweigh the benefits (Grade D recommendation).<sup>6</sup> However, health care professionals and professional societies have continued to debate the merits of PSA-based screening. Potential benefits of regular PSA screening include early cancer detection and reduced mortality rates. Potential harms include anxiety related to abnormal results, pain, infection, bleeding from diagnostic biopsies, and morbidity from definitive treatment in men who may not need such treatment.<sup>7-10</sup> No organization (including the American Urological Association) currently recommends routine PSA-based screening.

Determining which men with clinically localized prostate cancer are most likely to benefit from interventions such as surgery and radiation could potentially improve the balance of benefits and harms, especially in those identified by screening. Current practice is to use tumor grade as the primary prognostic variable in patients with clinically localized prostate cancer.<sup>2</sup> After biopsy confirms the presence of the cancer, pathologists report tumor grade using the Gleason score, which ranges from 2 to 10.<sup>4</sup> Gleason 8 and higher tumors are considered the most aggressive, Gleason 7 tumors are considered somewhat less aggressive, and Gleason 6 or lower tumors are considered potentially indolent.<sup>11</sup>

A biopsy-based Gleason score may not always accurately reflect the real aggressiveness of the prostate cancer. Therefore, efforts are underway to identify more reliable prognostic factors. PSA, PSA kinetics (rate of rise in PSA over time and doubling time for PSA), and digital rectal

examination are still very important when deciding treatment. Additionally, radiographic imaging in high-risk disease is valuable, along with other diagnostic assessments, before making definitive treatment decisions.

Staging is the process of assessing whether the cancer is confined to the prostate gland or has spread and the extent of the spread.<sup>4</sup> Staging of prostate cancer could be clinical (based on a digital rectal examination of the prostate gland, imaging tests, prostate biopsy, and laboratory tests) or pathological (based on surgery and examination of resected prostate tissue). The staging system currently used is the American Joint Committee on Cancer TNM classification.<sup>4</sup> TNM classification is based on the extent of primary tumor (T stages), whether cancer has spread to the adjacent lymph nodes (N stages), and any metastasis (M stages).<sup>4,12</sup> TNM categories are combined with the Gleason histologic score and PSA results (stage grouping) to determine the overall stage, commonly reported as stage I, IIA, IIB, III, or IV, with stage I being the least advanced and stage IV being the most advanced. In the absence of a Gleason histologic score, staging can be based on the TNM classification.

Another categorization—incorporating PSA levels, Gleason histologic score, and TNM stage—stratifies tumors into low, intermediate, and high risk: the concept reflects the likelihood of progressing with no treatment or recurring after early intervention. The levels are defined as follows:<sup>4</sup>

- Low risk (corresponding to stage I): a PSA level of 10 ng/mL or less, a Gleason score of 6 or less, and clinical stage T1c or T2a
- Intermediate risk (roughly corresponding to stage IIA): a PSA level of greater than 10 to 20 ng/mL, a Gleason score of 7, or clinical stage T2b but not qualifying for high risk
- High risk (roughly corresponding to stage IIB): a PSA level of greater than 20 ng/mL, a Gleason score of 8 or higher, or clinical stage T2c

This risk-assessment scheme, although commonly used, has significant limitations in assessing patients in the intermediate- and high-risk groups. A good example of a risk-assessment scheme developed and validated across populations is the University of California, San Francisco, Cancer of the Prostate Risk Assessment (CAPRA). The CAPRA is associated with both overall and cause-specific survival and can be used to predict disease recurrence and mortality after radical prostatectomy (RP).<sup>13-16</sup> These risk-assessment tools may be improved in the future with the use of biomarkers (e.g., actinin alpha 1, derlin 1).

Clinicians make pretreatment assessment of whether prostate cancer is localized by determining tumor stage, basing their decision on clinical examinations (e.g., digital rectal examination, imaging and laboratory tests, prostate biopsy). According to a 2013 clinical practice guideline published by the National Comprehensive Cancer Network, clinically localized prostate cancer includes clinical stage T1–T3a, N0–X, and M0.<sup>17</sup> This expert opinion-based guideline further categorizes clinically localized disease based on the recurrence risk as follows:

- Very low recurrence risk: T1c, Gleason score  $\leq 6$ , PSA  $< 10$  ng/mL, fewer than three prostate biopsy cores positive,  $\leq 50$  percent cancer in each core, PSA density  $< 0.15$  ng/mL/g
- Low recurrence risk: T1–T2a, Gleason score  $\leq 6$ , PSA  $< 10$  ng/mL
- Intermediate recurrence risk: T2b–T2c or PSA 10–20 ng/mL or Gleason score 7
- High recurrence risk: T3a or Gleason score 8–10 or PSA  $> 20$  ng/mL

The focus of this report is clinically localized prostate cancer (T1–T3a). Locally advanced (T3b–T4), metastatic, and recurrent prostate cancer are outside the scope of this report.

## **Therapies for Clinically Localized Prostate Cancer**

The primary goal of treating clinically localized prostate cancer is to target men most likely to need intervention to prevent disability or death while minimizing intervention-related complications. Frequently used treatment options include the following:

- RP, including laparoscopic or robotic-assisted prostatectomy
- External beam radiotherapy (EBRT), including conventional radiation, intensity-modulated radiation (IMRT), three-dimensional conformal radiation therapy (3D-CRT), stereotactic body radiation therapy, and proton beam therapy
- Interstitial brachytherapy (BT)
- Cryotherapy
- Observation or watchful waiting (WW); the two terms are used interchangeably throughout the report
- Active surveillance (AS)
- Hormonal therapy (e.g., androgen-deprivation therapy [ADT])
- High-intensity focused ultrasound (HIFU)

Choice of treatment options may be influenced by numerous factors. These include patient age and health at the time of diagnosis, life expectancy, and estimated likelihood of cancer progression without treatment; surgeon experience and preference; treatment-related convenience and costs; and potential for eradication and adverse effects (e.g., incontinence, sexual dysfunction).<sup>4</sup> Before choosing any intervention, the patient’s overall health status should be assessed because it may influence response to therapy, severity of complications, and life expectancy.<sup>4</sup>

The National Cancer Institute and the Centers for Disease Control and Prevention sponsored a National Institutes of Health (NIH) State-of-the Science Conference in December 2011 to better understand the risks and benefits of AS and other observational management strategies for low-grade localized prostate cancer detected by PSA screening.<sup>3</sup> AS (with curative intent) usually includes hands-on followup in which PSA levels are checked, prostate biopsies may be repeated, and subsequent treatment is planned. The panel concluded that AS should be offered to patients with low-risk prostate cancer.<sup>3</sup>

The NIH panel used the term “watchful waiting” to describe a palliative observational strategy—that is, waiting for symptoms to appear and then intervening to manage the symptoms. In the 2008 Comparative Effectiveness Review “Comparative Effectiveness of Therapies for Clinically Localized Prostate Cancer,” these two approaches were considered together.<sup>18</sup> In the literature, the distinction between AS (with curative intent) and other observational strategies (with palliative intent) has not always been clear; however, for this systematic review update we attempted to separate the two using the definitions proposed at the 2011 NIH State-of-the-Science Conference.<sup>3</sup>

## **Objectives of This Review**

This report updates a 2008 systematic review conducted by the University of Minnesota Evidence-based Practice Center (EPC).<sup>18</sup> This update examines the same four Key Questions

(KQs) as the original report and summarizes the more recent evidence comparing the relative effectiveness and safety of treatment options for clinically localized prostate cancer.

## Key Questions and Scope

### Key Questions

The KQs are as follows:

**Key Question 1:** What are the comparative risks and benefits of the following therapies for clinically localized prostate cancer?

- a. Radical prostatectomy, including open (retropubic and perineal) and laparoscopic (with or without robotic assistance) approaches
- b. External beam radiation therapy, including standard therapy and therapies designed to decrease exposure to normal tissues such as three-dimensional conformal radiotherapy, intensity-modulated radiation therapy, proton beam therapy, and stereotactic body radiation therapy
- c. Interstitial brachytherapy
- d. Cryotherapy
- e. Watchful waiting
- f. Active surveillance
- g. Hormonal therapy
- h. High-intensity focused ultrasound

**Key Question 2:** How do specific patient characteristics (e.g., age, race/ethnicity, presence or absence of comorbid illness, preferences such as tradeoff of treatment-related adverse effects vs. potential for disease progression) affect the outcomes of these therapies overall and differentially?

**Key Question 3:** How do provider/hospital characteristics (e.g., geographic region, case volume, learning curve) affect outcomes of these therapies overall and differentially?

**Key Question 4:** How do tumor characteristics (e.g., Gleason score, tumor volume, screen-detected vs. clinically detected tumors, PSA levels) affect the outcomes of these therapies overall and differentially?

### Scope

An analytic framework showing the populations, interventions, comparators, outcomes, timing, and setting (PICOTS) in diagram form is shown in Figure 1 of the full report.

**Population:** KQs 1–4: The population comprised men considered to have clinically localized prostate cancer (T1–T3a, N0–X, M0–X), regardless of age, histologic grade, or PSA level. Studies were excluded if more than 15 percent of men with disease stage higher than T3a were enrolled and data were not reported separately for men with T1, T2, and/or T3a prostate cancer.

**Interventions:** For KQs 1–4, we included treatment options for men with clinically localized prostate cancer: RP (including retropubic, perineal, laparoscopic, robotic assisted), EBRT (including conventional radiation, IMRT, 3D-CRT, proton beam, and stereotactic body radiation therapy), interstitial BT, cryotherapy, WW, AS, hormonal therapy, and HIFU.

**Comparators:** Comparators were any interventions of interest listed above.

**Outcomes:** The primary outcome is overall mortality or survival. Additional outcomes include prostate cancer–specific mortality or survival, biochemical (PSA) progression, metastatic and/or clinical progression-free survival, health status, and quality of life (QOL). We focused primarily on common and severe adverse events of treatment, including bowel, bladder, and sexual dysfunction, as well as harms from biopsy such as bleeding and nosocomial infections. For KQ 3, we focus on RP compared with other interventions in association with provider location, case volume, and affiliation with academic centers.

**Timing:** Duration of followup was appropriate for the outcome under consideration.

**Settings:** All settings were considered.

## Methods

### Search Strategy

Medical Librarians in the ECRI Institute–Penn Medicine EPC Information Center performed literature searches following established systematic review protocols. We searched the following databases using controlled vocabulary and text words: Embase<sup>®</sup>, MEDLINE<sup>®</sup>, PubMed<sup>®</sup>, and the Cochrane Library from January 1, 2007, through March 7, 2014.

### Study Selection

We used the same study selection criteria as in the 2008 report. For KQs 1, 2, and 4, we included randomized trials only if the randomized treatment allocation was based on men with clinically localized disease and if clinical outcomes were reported for T1, T2, and T3a disease separately from T3b and T4 disease. We also included large nonrandomized comparative studies ( $N \geq 500$ ) that controlled for potentially confounding variables. For KQ 3, we included multicenter studies that compared RP with another treatment of interest, enrolled 500 or more patients, used appropriate statistical techniques to control for potentially confounding variables, and examined the effect of provider characteristics on survival of patients with localized prostate cancer.

### Data Extraction and Management

We used the DistillerSR<sup>®</sup> (Evidence Partners, Inc., Ottawa, Ontario, Canada) Web-based systematic review software for abstract screening. One team member extracted data directly into a Word document and a second team member reviewed the extractions. The data extracted included study, patient, tumor, and intervention characteristics and predefined outcomes. We calculated standard errors, regression coefficients, and 95% confidence intervals (CIs) from reported means, standard deviations, and sample size when provided and appropriate, if not



already done in the original study.<sup>19</sup> Also, because of the possibility of subjective interpretation, we judged the risk-of-bias items in duplicate. We resolved all discrepancies through discussion. Multiple publications of the same study (e.g., publications reporting subgroups, other outcomes, longer followup) were identified by examining author affiliations, study designs, enrollment criteria, and enrollment dates. Multiple publications were used only when each publication had unique data not reported in the most comprehensive and recent publication.

## **Risk-of-Bias Assessment of Individual Studies**

Because of the possibility of subjective interpretation, two researchers assessed methodologic risk of bias for each study and resolved discrepancies by consensus. When consensus could not be reached, a third researcher adjudicated.

We assessed the risk of bias by following the guidelines in the chapter “Assessing the Risk of Bias of Individual Studies When Comparing Medical Interventions” in the “Methods Guide for Effectiveness and Comparative Effectiveness Reviews.”<sup>20</sup> This involved evaluating several items such as randomization, allocation concealment, intention-to-treat-analysis, and completeness of followup. Additionally, we assessed fidelity to the protocol to address performance bias and blinding of outcome assessors to address detection bias when outcomes were subjective.

To be considered as having low risk of bias, the study must have met all the following conditions: randomization or pseudorandomization (e.g., using instrumental variable analysis) of study participants to treatment groups, concealment of allocation, data analysis based on the intention-to-treat-principle, an outcome that was objective if outcome assessors were not blinded or blinding of outcome assessors was not reported, a difference of 15 percent or less in the length of followup for the comparison groups, data for more than 85 percent of enrolled patients provided at the timepoint of interest, and no clear indication of lack of fidelity to the protocol.

To be considered as having high risk of bias, the study must have met at least one of the following criteria: trial did not randomly or pseudorandomly (i.e., using instrumental variables) assign patients to study groups and did not blind outcome assessors, trial had a difference of 15 percent or more in the length of followup for comparison groups, or trial stated that there was not good fidelity to the protocol. To be considered as having medium risk of bias, the study met neither the criteria for low risk of bias nor the criteria for high risk of bias.

## **Data Synthesis**

Because of the differences in study designs, treatments, patient and tumor characteristics, and reporting of outcomes, the 2008 report did not pool studies for KQs 1, 2, and 4. For the same reason, we performed only qualitative analysis in this update.

Because randomized controlled trials (RCTs) and nonrandomized comparative studies differed substantially in average risk of bias, we performed separate qualitative analyses and present results separately for these study designs. The findings from the RCTs and nonrandomized comparative studies were included in our discussion and formed the basis of our overall conclusion. We further stratified the results from the RCTs based on comparisons across and within primary treatment categories.

Generally, we report summaries of effectiveness and adverse event outcomes with ranges according to treatment option, tumor characteristics, and group sample size. For KQ 1, we summarize and discuss comparative risks, benefits, and outcomes of therapies. For KQ 2, we summarize how patient characteristics affect outcomes. For KQ 4, we summarize how tumor

characteristics affect outcomes. For KQ3, we were unable to identify any studies that met our inclusion criteria.

## **Strength-of-Evidence Grading**

We provided evidence grades for the following patient-oriented outcomes: overall mortality or survival, prostate cancer-specific survival, progression to metastases, and QOL. We assessed strength of evidence by following the guidelines from the article “Grading the Strength of a Body of Evidence When Comparing Medical Interventions” by Owens and colleagues.<sup>21</sup> We graded the strength of evidence based on the following domains: risk of bias (low, medium, or high), consistency (consistent, inconsistent, or unknown/not applicable), directness (direct or indirect), and precision (precise or imprecise). Two independent graders assessed each domain, and differences were resolved by consensus.

We assigned the strength of evidence an overall grade of high, moderate, low, or insufficient, as outlined by Owens and colleagues.<sup>21</sup> Briefly, a high grade reflects high confidence that the effect estimate lies close to the true effect; a moderate grade reflects moderate confidence; a low grade reflects limited confidence; and an insufficient grade reflects either no evidence, inability to estimate an effect, or no confidence in the effect estimate. The decision to grade an evidence base as insufficient rather than low often reflected an imprecise effect estimate (a non-statistically significant effect with 95% CIs wide enough to allow the possibility of a significant benefit for one treatment compared with another) in an evidence base with only one or two studies. However, we also graded as insufficient evidence from a single study with medium risk of bias or from fewer than three consistent studies with high risk of bias, even when findings were direct and precise. Because multiple factors other than treatment can influence apparent differences between interventions, we placed a high value on replication of findings, even more so for studies with high risk of bias. Further explanation of this conservative approach to evidence grading appears in the Discussion.

When evidence came from subgroup analyses (KQs 2 and 4), we lowered the strength-of-evidence grade by one level. For example, when the strength of evidence for a primary analysis in KQ 1 was low, strength of evidence for subgroup analyses from the same studies was considered insufficient. We adopted this approach because subgroup analyses were usually underpowered to detect differences between treatments and sometimes not prespecified at the beginning of the study. In general, subgroup analyses should be considered as hypothesis generating rather than definitive analyses.

## **Applicability**

Applicability assessment refers to how generalizable findings from this report are to other populations and settings. We assessed applicability by following the guidelines in the article “Assessing the Applicability of Studies When Comparing Medical Interventions” by Atkins and colleagues.<sup>22</sup> The applicability of the evidence involves the following five aspects: patients, interventions, comparisons, outcomes, and settings.<sup>22</sup>

We addressed factors relevant to the applicability of the evidence by evaluating patient selection in both observational studies and clinical trials. We considered the primary biology and epidemiology (grade and stage of the prostate cancer) and the present-day clinical practice setting. The typical interventions, comparisons, outcomes (e.g., overall mortality, prostate cancer-specific survival), and settings of care were also used to specify more clearly the most

applicable study characteristics (i.e., most typical of care for patients with localized prostate cancer in the United States).

## **Peer Review and Publication**

Peer reviewers were invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. The EPC considered peer review comments on the preliminary draft of the report in preparation of the final report. The dispositions of the peer review comments are documented and will be published 3 months after the publication of the evidence report.

## **Results**

### **Evidence Base**

Our searches of the literature identified 5,210 potentially relevant articles. We excluded 1,508 articles by reviewing the titles, 3,420 by reviewing the abstracts, and 221 by reviewing the full-length articles. Figure 2 in the full report is a flow chart that describes in detail the exclusion process and the reasons for exclusion at each review level. The remaining 61 publications, describing 52 unique studies, made up the evidence base for this review.

All 52 studies met the inclusion criteria for review for KQ 1. Thirteen of these studies also met the inclusion criteria for KQ 2, and 20 of them met the inclusion criteria for KQ 4. Studies that addressed KQ 1 reported data for patient-oriented outcome measures such as overall survival, all-cause mortality, prostate cancer–specific mortality, QOL, and adverse events. Evidence addressing KQ 2 or 4 came solely from subgroup analyses of some larger studies that addressed KQ 1. Although these subgroup analyses reported data on overall survival, all-cause mortality, or prostate cancer–specific mortality for specific patient subgroups, they did not report adverse events that occurred in these subgroups.

### **KQ 1: Comparative Risks and Benefits of Therapies for Clinically Localized Prostate Cancer**

Eight RCTs in 16 publications addressed comparative risks and benefits for various therapies. Our risk-of-bias assessments for the eight trials appear in Table C-1 of Appendix C. Of these eight RCTs, seven were categorized as medium risk of bias for all outcomes excluding the QOL outcome. One study received a rating of low risk of bias.<sup>23</sup> Because QOL is subjectively interpreted, studies that did not blind outcome assessors received a lower rating for this outcome.

Table A summarizes our findings from RCTs on the major health outcomes for KQ 1. These outcomes include overall survival, all-cause mortality, prostate cancer–specific mortality, QOL, and progression to metastases, for which we assessed the strength of evidence. For the comparison of RP versus WW, the Scandinavian Prostate Cancer Group-4 (SPCG-4) trial reported that all-cause and prostate cancer–specific mortality at the end of the 15-year followup period favored RP, but the strength of evidence was insufficient. Both the Prostate Cancer Intervention Versus Observation Trial (PIVOT) and SPCG-4 studies reported data on all-cause and prostate cancer–specific mortality at the end of the 12-year followup period, but we found that the evidence on these outcomes at this timepoint was insufficient to draw any conclusion (based mostly on imprecision in the statistically nonsignificant effect sizes). However, both trials found that progression to metastases was significantly lower among patients in the RP group than

in the WW group; the strength of evidence was moderate due to consistent and precise findings in medium risk-of-bias trials. The evidence on other patient-oriented outcomes based on the two trials is insufficient to permit conclusions.

For the comparison of 3D-CRT alone versus 3D-CRT combined with ADT,<sup>23</sup> data on overall survival, all-cause mortality, and prostate cancer–specific mortality reported in the trial favor the combined treatments. Although a single trial, the study was precise with a low risk of bias, which allowed a low strength-of-evidence grade. For the comparison of EBRT alone versus EBRT combined with ADT, data on overall survival, all-cause mortality, and prostate cancer–specific mortality reported in the trial favor the combined treatments with an insufficient strength-of-evidence grade.

**Table A. Summary of the main findings from randomized controlled trials for Key Question 1**

Comparison and Outcome	Evidence Base	Findings	Risk of Bias	Consistency	Directness and Precision	SOE Grade
RP vs. WW, all-cause mortality	2 trials SPCG-4 <sup>24-26</sup> PIVOT <sup>27</sup> (N = 1,426)	SPCG-4: Favors RP at 15 years. ARR, 6.6%; 95% CI, -1.3% to 14.5%. Cumulative incidence: 46.1% vs. 52.7%; RR, 0.75; 95% CI, 0.61 to 0.92 No significant difference between the interventions at 12 years. ARR, 7.1%; 95% CI, -0.5 to 14.7%. Cumulative incidence: 32.7% vs. 39.8% (137 vs. 156 deaths); RR, 0.82; 95% CI, 0.65 to 1.03 PIVOT: No significant difference between the interventions at 12 years. ARR, 2.9%; 95% CI, -4.1% to 10.3% (171 [47.0%] vs. 183 [49.9%] deaths); HR, 0.88; 95% CI, 0.71 to 1.08	Medium	Consistent	Direct Imprecise	Insufficient
RP vs. WW, PCSM	2 trials SPCG-4 <sup>24-26</sup> PIVOT <sup>27</sup> (N = 1,426)	SPCG-4: Favors RP at 12 and 15 years. ARR, 6.1%; 95% CI, 0.2% to 12.0%. Cumulative incidence: 14.6% vs. 20.7%; RR, 0.62; 95% CI, 0.44 to 0.87 PIVOT: No significant difference between the interventions. ARR, 2.6%; 95% CI, -1.1 to 6.5 (21 [5.8%] vs. 31 [8.7%] deaths); HR, 0.63; 95% CI, 0.36 to 1.09	Medium	Inconsistent	Direct Imprecise	Insufficient
RP vs. WW, QOL	1 trial SPCG-4 <sup>24-26</sup> (N = 695)	No significant difference between the interventions at median followup of 12.2 years	High	Consistency unknown (single study)	Direct Imprecise	Insufficient

**Table A. Summary of the main findings from randomized controlled trials for Key Question 1 (continued)**

Comparison and Outcome	Evidence Base	Findings	Risk of Bias	Consistency	Directness and Precision	SOE Grade
RP vs. WW, QOL (urinary leakage)	2 trials SPCG-4 <sup>24-26</sup> PIVOT <sup>27</sup> (N = 1,426)	Favors WW for urinary leakage (2–4 years)  SPCG-4: OR, 2.3; 95% CI, 1.6 to 3.2 PIVOT: RR, 2.69; 95% CI, 1.61 to 4.51	Medium <sup>a</sup>	Consistent	Direct Precise	Low <sup>a</sup>
RP vs. WW, QOL (erectile dysfunction at 4 years)	2 trials SPCG-4 <sup>24-26</sup> PIVOT <sup>27</sup> (N = 1,426)	SPCG-4: No significant difference between interventions for erectile dysfunction at 4 years PIVOT: RR, 1.84; 95% CI, 1.59 to 2.11. Favors WW at 2 years	Medium	Inconsistent	Direct Imprecise	Insufficient
RP vs. WW, QOL (bowel dysfunction)	1 trial PIVOT <sup>27</sup> (N = 731)	No significant difference between interventions for bowel dysfunction	Medium	Consistency unknown (single study)	Direct Imprecise	Insufficient
RP vs. WW, progression to metastases	2 trials SPCG-4 <sup>24-26</sup> PIVOT <sup>27</sup> (N = 1,426)	Favors RP SPCG-4: RR, 0.65; 95% CI, 0.47 to 0.88 PIVOT: HR, 0.40; 95% CI, 0.22 to 0.70	Medium	Consistent	Direct Precise	Moderate
RALRP vs. LRP, QOL (urinary continence, erectile function)	1 trial <sup>28</sup> (N = 120)	Favors RALRP at 1 year Urinary continence: 95% vs. 83.3%; p = 0.042 Erectile function: 80% vs. 54.2%; p = 0.02	High	Consistency unknown (single study)	Direct Precise	Insufficient
RRP vs. BT, QOL	1 trial <sup>29</sup> (N = 200)	No significant difference between the interventions at 5-year followup	High	Consistency unknown (single study)	Direct Imprecise	Insufficient
RPP vs. RRP, QOL (urinary continence, erectile function)	1 trial <sup>30</sup> (N = 200)	Favors RRP for erectile function (60% vs. 42%; p = 0.032) at 2 years; no significant between-group difference in urinary continence	High	Consistency unknown (single study)	Direct Precise (erectile function) Imprecise (urinary continence)	Insufficient
3D-CRT vs. 3D-CRT plus ADT, overall survival	1 trial <sup>23</sup> (N = 206)	Favors 3D-CRT plus ADT at median 7.6-year followup HR, 3.0; 95% CI, 1.5 to 6.4 (44 vs. 30 deaths)	Low	Consistency unknown (single study)	Direct Precise	Low
3D-CRT vs. 3D-CRT plus ADT, all-cause mortality	1 trial <sup>23</sup> (N = 206)	Favors 3D-CRT plus ADT at median 7.6-year followup HR, 1.8; 95% CI, 1.1 to 2.9	Low	Consistency unknown (single study)	Direct Precise	Low
3D-CRT vs. 3D-CRT plus ADT, PCSM	1 trial <sup>23</sup> (N = 206)	Favors 3D-CRT plus ADT at median 7.6-year followup HR, 4.1; 95% CI, 1.4 to 12.14 (14 vs. 4 deaths)	Low	Consistency unknown (single study)	Direct Precise	Low

**Table A. Summary of the main findings from randomized controlled trials for Key Question 1 (continued)**

Comparison and Outcome	Evidence Base	Findings	Risk of Bias	Consistency	Directness and Precision	SOE Grade
EBRT vs. EBRT plus ADT, overall survival	1 trial <sup>31</sup> (N = 1,979)	Favors EBRT plus ADT at median 9.1-year followup HR, 1.17; 95% CI, 1.10 to 1.35 (57% vs. 62% survival rate)	Medium	Consistency unknown (single study)	Direct Precise	Insufficient
EBRT vs. EBRT plus ADT, PCSM	1 trial <sup>31</sup> (N = 1,979)	Favors EBRT plus ADT at median 9.1-year followup HR, 1.87; 95% CI, 1.27 to 2.74 (8 vs. 4 deaths)	Medium	Consistency unknown (single study)	Direct Precise	Insufficient
EBRT vs. EBRT plus ADT, QOL (sexual function)	1 trial <sup>31</sup> (N = 1,979)	Favors EBRT at 1 year OR, 1.72; 95% CI, 1.17 to 2.52; p = 0.004	High	Consistency unknown (single study)	Direct Precise	Insufficient
EBRT vs. cryotherapy, overall survival	1 trial <sup>32</sup> (N = 244)	No significant difference between interventions at 5 years. Difference, 1.2 (95% CI, -6.8–9.2)	Medium	Consistency unknown (single study)	Direct Imprecise	Insufficient
EBRT vs. cryotherapy, PCSM	1 trial <sup>32</sup> (N = 244)	No significant difference between interventions at 5 years. Difference, 0.3 (95% CI, -4.8–5.4)	Medium	Consistency unknown (single study)	Direct Imprecise	Insufficient
EBRT vs. cryotherapy, QOL (urinary function)	1 trial <sup>33</sup> (N = 244)	Favors cryotherapy (p-value was statistically significant) at 3 years	High	Consistency unknown (single study)	Direct Precise	Insufficient
EBRT vs. cryotherapy, QOL (bowel function)	1 trial <sup>33</sup> (N = 244)	No significant difference between interventions at 3 years	High	Consistency unknown (single study)	Direct Imprecise	Insufficient
EBRT vs. cryotherapy, QOL (sexual function)	1 trial <sup>33</sup> (N = 244)	Favors EBRT (p-value was statistically significant) at 3 years	High	Consistency unknown (single study)	Direct Precise	Insufficient

<sup>31</sup>The evidence base for this outcome contained 1 medium and 1 high risk-of-bias study; because of this borderline between medium and high risk, the strength of evidence was lowered from moderate to low.

**Note:** For the interpretation of SOE grading, see definitions of evidence grades in the Methods section under Strength-of-Evidence Grading.

**Abbreviations:** 3D-CRT = 3-dimensional conformal radiation therapy; ADT = androgen-deprivation therapy; ARR = absolute risk reduction; BT = brachytherapy; CI = confidence interval; EBRT = external beam radiation therapy; HR = hazard ratio; LRP = laparoscopic radical prostatectomy; OR = odds ratio; PCSM = prostate cancer-specific mortality; PIVOT = Prostate Intervention Versus Observation Trial; QOL = quality of life; RALRP = robotic-assisted laparoscopic radical prostatectomy; RP = radical prostatectomy; RPP = radical perineal prostatectomy; RRP = radical retropubic prostatectomy; RR = relative risk; SOE = strength of evidence; SPCG-4 = Scandinavian Prostate Cancer Group-4; WW = watchful waiting.

Of 44 nonrandomized comparative studies included, we categorized 41 as high risk of bias for all reported outcomes. (See Table 10 in the full report for risk-of-bias assessment criteria and Table C-2 of Appendix C for individual study assessments.) We categorized the three remaining studies as medium risk of bias because all used instrumental variable analysis, which effectively “pseudorandomizes” patients into different groups and can account for both measured and unmeasured confounders.<sup>34</sup>

Table B summarizes our findings from nonrandomized comparative studies on overall survival, overall mortality, prostate cancer–specific mortality, or QOL for each treatment comparison and outcome with evidence from at least three nonrandomized comparative studies. (See the Results section in the full report for a full description of evidence for all comparisons.) Although the majority of studies had a high risk of bias, the evidence base for all-cause mortality and prostate cancer–specific mortality for the comparison of RP and EBRT included six studies with consistent and precise findings that provide low strength of evidence favoring RP. For all other comparisons/outcomes, the strength of evidence was insufficient.

The definition and severity of adverse events varied greatly across the studies. Adverse events such as urinary incontinence and erectile dysfunction were mostly reported among men who underwent RP. Adverse events such as genitourinary toxicity, gastrointestinal toxicity, and erectile dysfunction were reported among men who received radiation therapy.

**Table B. Summary of the main findings from nonrandomized comparative studies for Key Question 1**

Comparison and Outcome	Evidence Base	Findings	Risk of Bias	Consistency	Directness and Precision	SOE Grade
RP vs. EBRT, all-cause mortality	6 studies <sup>35-40</sup> (N = 22,771)	Favors RP Five of 6 studies found that overall mortality was significantly lower after RP (followup, 3–15 years)	High	Consistent	Direct Precise	Low
RP vs. EBRT, PCSM	6 studies <sup>35,37-41</sup> (N = 23,301)	Favors RP All 6 studies found that PCSM was significantly lower after RP (followup 3–15 years)	High	Consistent	Direct Precise	Low
RP vs. BT, PCSM	3 studies <sup>35,39,42</sup> (N = 22,337)	Outcomes between groups did not differ significantly in any study	High	Consistent	Direct Imprecise	Insufficient
RP vs. observation, all-cause mortality	4 studies <sup>34,36,40,43</sup> (N = 131,114)	Favors RP with multivariable regression or propensity score analyses, but 1 study using instrumental variable analysis did not find a significant between-group difference	High	Inconsistent	Direct Imprecise	Insufficient
RP vs. observation, PCSM	3 studies <sup>34,40,43</sup> (N = 63,219)	Favors RP with multivariable regression or propensity score analyses, but 1 study using instrumental variable analysis did not find a significant between-group difference	High	Inconsistent	Direct Imprecise	Insufficient

**Table B. Summary of the main findings from nonrandomized comparative studies for Key Question 1 (continued)**

Comparison and Outcome	Evidence Base	Findings	Risk of Bias	Consistency	Directness and Precision	SOE Grade
RALRP vs. RRP, QOL	3 studies <sup>44-46</sup> (N = 2,108)	In 1 study, RALRP was associated with greater problems with incontinence. The 2 treatment groups did not differ in sexual dysfunction Two studies found no between-group differences for continence or sexual function	High	Inconsistent for continence; consistent for sexual dysfunction	Direct Imprecise	Insufficient

**Abbreviations:** BT = brachytherapy; EBRT = external beam radiation therapy; PCSM = prostate cancer–specific mortality; QOL = quality of life; RALRP = robotic-assisted laparoscopic radical prostatectomy; RP = radical prostatectomy; RRP = radical retropubic prostatectomy; SOE = strength of evidence.

## KQ 2: Specific Patient Characteristics Affecting Outcomes of the Therapies

We identified four RCTs and nine nonrandomized comparative studies that addressed the impact of significant patient characteristics on outcomes. Two RCTs comparing RP and WW and another two RCTs comparing EBRT alone and EBRT plus ADT performed subgroup analysis according to patient characteristics. In the PIVOT trial,<sup>27</sup> investigators reported no differences in all-cause mortality and prostate cancer–specific mortality between RP and WW when patients were stratified according to age. In contrast, investigators in the SPCG-4 trial<sup>24</sup> reported that the advantages of RP over WW in all-cause mortality, prostate cancer–specific mortality, and progression to metastases were statistically significant for patients younger than 65 years of age but not for the older patient group. The SPCG-4 trial investigators noted that the findings of the subgroup analyses should be interpreted with caution because these analyses may misleadingly dismiss differences because of a lack of power.<sup>24</sup>

One study reported that 3D-CRT plus ADT was associated with significantly lower 8-year all-cause mortality compared with 3D-CRT alone for patients with no comorbidity or a minimal comorbidity score. However, for patients with a moderate or severe comorbidity score, all-cause mortality did not differ significantly between the two treatments. For reasons described in the Methods section, all subgroup analyses were considered inconclusive, with insufficient strength of evidence.

Table C summarizes our findings on overall survival, overall mortality, prostate cancer–specific mortality, or QOL from the randomized trials that addressed KQ 2. Results for nonrandomized comparative studies can be found in the Results section of the full report.



**Table C. Summary of the main findings from randomized controlled trials for Key Question 2**

Comparison	Outcome	Evidence Base	Patient Characteristics by Which Data Were Stratified	Findings	SOE Grade
RP vs. WW	All-cause mortality, PCSM, and progression to metastases at 15-year followup	1 trial SPCG-4 <sup>24-26</sup> (N = 695)	Age	There was a significant reduction in all-cause mortality, PCSM, and progression to metastases in the younger than 65 years age category but not in the 65 years or older category.	Insufficient for patient subgroup
RP vs. WW	All-cause mortality and PCSM at 12 years	1 trial PIVOT <sup>27</sup> (N = 731)	Age, race, self-reported performance status	No significant difference between interventions in either younger than 65 years or 65 or older age group, race (white, black, and other), or performance (score 0 or 1–4) category.	Insufficient for patient subgroup
3D-CRT vs. 3D-CRT plus ADT	All-cause mortality at 8 years	1 trial <sup>23</sup> (N = 206)	Comorbidity scores	Among patients with no or minimal comorbidity, all-cause mortality was higher for the EBRT-alone group than for the EBRT plus ADT group. Among men with moderate or severe comorbidity, all-cause mortality was not significantly different between the 2 treatment groups.	Insufficient for patient subgroup
EBRT vs. EBRT plus ADT	Overall survival, PCSM	1 trial <sup>31</sup> (N = 1,979)	Age, race	Age group was unrelated to survival. EBRT plus ADT was associated with a significantly lower PCSM than EBRT alone among men older than 70 years of age, but not among men 70 years of age or younger. EBRT plus ADT was also associated with significantly greater overall survival and significantly lower PCSM among white patients but not among black patients.	Insufficient for patient subgroup

**Abbreviations:** 3D-CRT = 3-dimensional conformal radiation therapy; ADT = androgen-deprivation therapy; EBRT = external beam radiation therapy; PCSM = prostate cancer–specific mortality; PIVOT = Prostate Intervention Versus Observation Trial; RP = radical prostatectomy; SOE = strength of evidence; SPCG-4 = Scandinavian Prostate Cancer Group-4; WW = watchful waiting.

### **KQ 3: Provider/Hospital Characteristics Affecting Outcomes of the Therapies**

We did not identify any comparative study directly examining how provider or hospital characteristics influence the effectiveness of different treatments. As a result, this review does not add new information on this KQ beyond that from the 2008 report. The 2008 report found that results from national administrative databases and surveys suggested that provider/hospital characteristics—including RP procedure volume, physician specialty, and geographic region—affect outcomes. Screening practices can influence the characteristics of patients receiving diagnoses and tumors detected. Screening practices and treatment choices varied by physician specialty and across U.S. regions. Given the diverse readership of this report, we would also like to note a landmark U.S. Government Accountability Office report that found a growing concern

that financial incentives (a provider characteristic) may continue to drive treatment selection and costs.<sup>47</sup>

## KQ 4: Tumor Characteristics Affecting Outcomes of the Therapies

We identified 4 RCTs and 16 nonrandomized comparative studies that addressed the effect of tumor characteristics. Two RCTs compared RP and WW; another RCT compared EBRT alone and EBRT plus ADT and performed subgroup analysis according to tumor characteristics. In the PIVOT trial,<sup>27</sup> investigators reported that RP did not reduce all-cause mortality and prostate cancer–specific mortality among men with PSA levels of less than 10 ng/mL but resulted in a significant reduction in all-cause mortality (but not prostate cancer–specific mortality) among men with PSA levels higher than 10 ng/mL. In contrast, investigators in the SPCG-4 trial<sup>24</sup> reported that the PSA level (<10 vs. ≥10 ng/mL) did not alter RP’s effect in reducing all-cause mortality or prostate cancer–specific mortality. However, the tumor stage differed in these trials. In PIVOT almost 45 percent of the men had T2 prostate cancer, whereas in the SPCG-4 study the figure was almost 75 percent.

In another trial, adding short-term ADT to EBRT led to significantly higher overall survival and lower prostate cancer–specific mortality among patients with intermediate-risk prostate cancer, but not among patients with high- or low-risk prostate cancer, compared with EBRT alone. For reasons described in the Methods section, all subgroup analyses were considered inconclusive, with insufficient strength of evidence.

Table D summarizes our findings on overall survival, overall mortality, prostate cancer–specific mortality, or a global QOL score from the RCTs that addressed KQ 4. Results for nonrandomized comparative studies can be found in the Results section of the full report; all findings had insufficient strength of evidence.

**Table D. Summary of the main findings from randomized controlled trials for Key Question 4**

Comparison	Outcome	Evidence Base	Tumor Characteristics by Which Data Were Stratified	Findings	SOE Grade
RP vs. WW	All-cause mortality and PCSM at median followup of 10 years	1 trial PIVOT <sup>27</sup> (N = 731)	PSA levels	No reduction in all-cause mortality among men with PSA levels of ≤10 ng/mL treated with RP compared with WW. All-cause mortality (but not PCSM) was reduced by 13.2% among men with PSA levels of >10 ng/mL who were treated with RP compared with WW.	Insufficient for patient subgroup
RP vs. WW	All-cause mortality at 15-year followup	1 trial SPCG-4 <sup>24-26</sup> (N = 695)	PSA levels	No reduction in all-cause mortality among men with PSA levels of <10 ng/mL or ≥10 ng/mL treated with RP compared with WW at 15-year followup.	Insufficient for patient subgroup
RP vs. WW	All-cause mortality at 15-year followup	1 trial SPCG-4 <sup>24-26</sup> (N = 695)	Gleason score	No reduction in all-cause mortality among men with Gleason score <7 or ≥7 treated with RP compared with WW at 15-year followup.	Insufficient for patient subgroup

**Table D. Summary of the main findings from randomized controlled trials for Key Question 4 (continued)**

Comparison	Outcome	Evidence Base	Tumor Characteristics by Which Data Were Stratified	Findings	SOE Grade
RP vs. WW	All-cause mortality and PCSM at median followup of 10 years	1 trial PIVOT <sup>27</sup> (N = 731)	Risk level based on PSA levels, Gleason score, or tumor stage	There was a 31% relative reduction in all-cause mortality among men with intermediate tumor risk treated with RP compared with WW. There was a significant reduction in PCSM among men with PSA >10 ng/mL and men with high-risk tumors who were treated with RP compared with WW.	Insufficient for patient subgroup
RP vs. WW	All-cause mortality and distant metastases at 15-year followup	1 trial SPCG-4 <sup>24-26</sup> (N = 695)	Risk level based on PSA levels, Gleason score, or a WHO grade of 1	There were significant absolute between-group reductions of 13.2% for all-cause mortality and 11.4% for distant metastases among men with low-risk tumors who were treated with RP compared with those in WW at 15-year followup.	Insufficient for patient subgroup
EBRT vs. EBRT plus ADT	Overall survival and PCSM at 10 years	1 trial <sup>31</sup> (N = 1,979)	Risk level based on PSA levels, Gleason score, or tumor stage	Among men with intermediate-risk tumors, overall survival was increased to 60% in the EBRT plus ADT group compared with 54% in the EBRT-alone group. Among men with low-risk tumors, overall survival was increased to 67% in the EBRT plus ADT group compared with 60% in the EBRT-alone group. There was no reduction in PCSM among men with low-risk tumors who were treated with EBRT alone compared with EBRT plus ADT.	Insufficient for patient subgroup

**Abbreviations:** ADT = androgen deprivation therapy; EBRT = external beam radiation therapy; PCSM = prostate cancer-specific mortality; PIVOT = Prostate Intervention Versus Observation Trial; PSA = prostate-specific antigen; RP = radical prostatectomy; SOE = strength of evidence; SPCG-4 = Scandinavian Prostate Cancer Group-4; WHO = World Health Organization; WW = watchful waiting.

## Discussion

### Key Findings and Strength of Evidence

Extended followup data from SPCG-4 and the recently published findings from the PIVOT trial add to our understanding of the effects of RP versus WW or observation in subgroups. However, neither study compared RP with active surveillance. The strength of evidence from the SPCG-4 and PIVOT trials is graded as insufficient for all-cause mortality and prostate cancer-specific mortality at 12 or 15 years (meaning that the evidence does not permit a conclusion). However, both trials reported consistent findings regarding a significant reduction in progression to metastases in the RP group compared with the WW group. This consistency, combined with medium risk of bias and precision, means that the strength of evidence is moderate for this outcome. The 2008 report similarly showed a significant reduction in incidence of distant metastases in the RP group compared with the WW group based on 10-year followup of SPCG-4<sup>18</sup> but did not have evidence from PIVOT to support this finding.

We did not perform a meta-analysis on these outcomes, primarily because of differences between the two trials in enrolled patient populations. Compared with the SPCG-4 trial, the PIVOT enrolled a higher percentage of men with nonpalpable tumors (T1c, 50% vs. 12%) and with low PSA values.<sup>26</sup> The SPCG-4 trial used an eligibility criterion of T1 or T2 stage; however, given the lack of widespread PSA screening in the early portion of the study, these tumors are at higher risk of being understaged by digital rectal examination than PSA-screened tumors in the PIVOT. The two trials also differed in their protocol for the observation arms. Both trials reported similar hazard ratios for prostate cancer–specific mortality, but the hazard ratio for all-cause mortality was higher in the PIVOT than the SPCG-4 trial. This suggests that prostate cancer deaths in the PIVOT may have been diluted by deaths from other causes or competing risks. This conjecture, in turn, suggests that the underlying health of men in the two RCTs was different and poses the question of whether the PIVOT data can apply to a healthy cohort. Furthermore, in the PIVOT study, the median survival was assumed to be 15 years in the original study design and 10 years in the updated design. The PIVOT investigators failed to accrue their targeted enrollment of 2,000 patients to surgery or observation.

In our review, we were unable to draw any conclusions about the effect of various treatments on global QOL. Therefore, it is unclear how patients as a whole will balance the tradeoff between the potential benefit in long-term survival and the potential harms (e.g., urinary incontinence, sexual dysfunction) associated with the treatments. Ultimately, personal preferences and values play a significant role in this decisionmaking. This may be particularly true for patients with life expectancies of less than about 15 years.

This review and the 2008 report both attempted to evaluate whether a particular patient group (in terms of age, race, general health status, and various tumor risk factors) might benefit more than another group from compared interventions. Addressing this question would help patients and clinicians make better informed treatment decisions. The SPCG-4 trial reviewed in the 2008 report performed subgroup analysis by age and had already found that survival benefits of RP compared with WW may be limited to men younger than 65 years of age.<sup>48</sup>

The evidence reviewed in this update does not provide any consistent conclusion on this issue. For example, the SPCG-4 trial found that RP led to significantly lower all-cause and cancer-specific mortality compared with WW among patients younger than 65 years of age but not among the older patient group.<sup>27</sup> However, the PIVOT study did not have the same finding regarding age.<sup>24</sup> The PIVOT trial found that RP did not reduce all-cause or cancer-specific mortality among men with PSA levels of 10 ng/mL or less but resulted in a significant reduction among men with PSA of more than 10 ng/mL. However, this finding is not confirmed by the SPCG-4 trial, which found that overall mortality was reduced by RP regardless of PSA level. Despite these differences, the two trials also show some overlap in findings (reduced mortality with RP) for the subgroup of patients with PSA of more than 10 ng/mL. Nevertheless, inconsistency remains in the evidence. The subgroup analyses might have misleadingly dismissed differences because of the lack of statistical power.<sup>24</sup> Therefore, clear guidance regarding the appropriate patient population for RP is difficult to establish. Four observational studies that used multivariable or propensity score analyses to adjust for known confounding factors found a lower overall mortality risk with RP than with WW,<sup>34,36,40,43</sup> but when one of these studies also performed an instrumental variable analysis (which adjusts for known and unknown confounding factors), no significant between-group difference was observed.<sup>34</sup> Given that the patient population in this latter study was derived from a database of patients 65 years or

older, the findings in this analysis are comparable to those of the SPCG-4 trial<sup>24-26</sup> for patients aged 65 years or older.

This current review also evaluated RCTs that compared EBRT alone versus EBRT combined with ADT<sup>31</sup> and 3D-CRT alone versus 3D-CRT combined with ADT.<sup>23</sup> The evidence based on both RCTs<sup>23,31</sup> suggests that the results for overall survival and prostate cancer–specific mortality favored the combined treatments, although only one RCT<sup>23</sup> met the threshold for low strength of evidence. However, in both studies, the dose of radiation therapy was lower than is currently known to be effective. These findings are similar to the findings of two RCTs summarized in the 2008 report.<sup>18</sup> The subgroup analysis in one RCT<sup>23</sup> also suggests that the advantage of 3D-CRT combined with ADT may occur only among patients with no comorbidity or a minimal comorbidity score for the outcome all-cause mortality. The evidence in another RCT<sup>31</sup> suggests that the advantage of EBRT combined with ADT may occur only among white patients for the outcome of overall survival and among white patients and men older than 70 years of age for the outcome of prostate cancer–specific mortality. For both outcomes, the study found a significant benefit for combined therapy among patients with intermediate-risk prostate cancer, but not among patients with high- or low-risk prostate cancer. In this study, the length of ADT (only 4 months) might have been too short for patients with high-risk disease. Therefore, although it appears that men with intermediate-risk prostate cancer may benefit from 4 to 6 months of ADT, this study could not adequately address either of the study endpoints in the cases in which longer term ADT may be needed. Moreover, treating low-risk patients with EBRT plus ADT would be considered substantial overtreatment by most national clinical practice guidelines. For these reasons, this evidence is weak and requires further validation by new studies before it can be used to form clinical guidance for choosing appropriate cases for the treatments.

For a single treatment comparison, we were able to draw a conclusion from observational evidence based on six studies of high risk of bias but with consistent findings. RP was favored over EBRT for both all-cause mortality<sup>35-39</sup> and prostate cancer–specific mortality with low strength of evidence.<sup>35,37-41</sup> However, we note that radiation dosage was not reported in some studies and a proportion of patients received a lower dose than what is currently considered effective. Furthermore, despite attempts to adjust for known confounders, observational studies are vulnerable to bias from unknown confounding factors. Therefore, RCTs are needed to address this comparison.

Similarly, the evidence for other treatment comparisons covered in the current review needs further validation, particularly via rigorously designed RCTs, to form a more reliable foundation for making clinical recommendations.

As noted in the Methods section, we chose a conservative approach when grading strength of evidence in this report, because multiple factors other than treatment can influence apparent differences in clinical outcomes between interventions observed in these studies. Accordingly, we placed a high value on replication of findings and believe that if the evidence was based on a single RCT, it should be considered sufficient evidence (low strength) only if that RCT had precise findings and was rated as low risk of bias. For studies rated as having high risk of bias, we set a higher bar and required at least three studies with consistent and precise findings. End-users of this report can reasonably choose to set a less conservative bar when making clinical or policy decisions.

## Applicability

The evidence-based conclusions are applicable only to the types of patients enrolled in the studies underlying those conclusions, the types of clinical settings in which the studies were conducted, the types of interventions being compared, and the particular outcomes and followup periods reported. Table 37 in the full report summarizes factors that may restrict the applicability of the findings from the RCTs discussed in the previous section.

Although the restrictions on the applicability of the conclusions may vary across the evidence bases for different treatment comparisons, some restrictions may be common to most of these evidence bases. All but one of the RCTs in this review recruited their patients before 2002. Since then, the treatment options compared in many studies have greatly evolved. For example, open surgery was the main treatment technique for RP in the reviewed RCTs. However, in recent years, robotic-assisted surgery has become the dominant technique for RP in the United States. Similarly, for EBRT, BT, and other treatments, advances in technologies and knowledge may allow currently available treatments to better target the cancer, thereby improving the effectiveness and tolerance of treatments. Evidence based on dated medical techniques may not be applicable in current practice.

Additionally, patients studied in the RCTs included in this review may have a different risk profile from patients currently receiving a diagnosis of prostate cancer. Risk profiles may affect the findings of treatment comparisons, although we did not reach any definitive conclusions from the evidence reviewed for KQs 2 and 4 because of the lack of statistical power for detecting between-intervention differences in the subgroup analyses. Ten to 15 years ago, prostate cancers were primarily detected by digital rectal examination or tissue specimens obtained during transurethral resection of the prostate for treating benign prostatic obstruction. Currently, the vast majority of prostate cancers detected in the United States are found by PSA testing. Men often start to receive PSA tests in their 40s and continue taking the test on a regular basis until their 80s. As a result, patients with an established diagnosis can be younger and have a more confined cancer than those studied in the reviewed RCTs, which further restricts the applicability of the reviewed evidence. Because of intensified concern about overdiagnosis of prostate cancer in recent years, the way to use PSA testing for screening prostate cancer and the criteria for establishing an abnormal PSA test result may continue to change. Patient and tumor characteristics of men with prostate cancer in the future are likely to be different from those of men diagnosed in the past as well as those of men diagnosed today.

Finally, we note that even in well-designed RCTs that found an apparent advantage of one intervention over another, subgroup analyses raise the possibility that not all patients in the target population will derive equal or even any benefit from the treatment with the best average outcome. This is of particular importance given the potential morbidities associated with prostate surgery and radiation therapies, which may be avoided if a more conservative intervention such as active surveillance is deemed appropriate.

## Research Gaps

A fundamental research gap involves the development of better methods for staging prostate cancer that is detectable but not metastatic. With current technology, such staging is not straightforward, and choosing treatment based on stage for patients whose prostate cancer is detectable but not metastatic will be difficult until more precise imaging and diagnostic methods are available.

To further address this review's KQs, additional RCTs are needed. In Table G-1 and Table G-2 in Appendix G of the full report, we summarize nine ongoing clinical trials. Ideally, future RCTs should (1) recruit patients with PSA-detected prostate cancer; (2) compare patient-focused outcomes (e.g., all-cause and cancer-specific mortalities, QOL) between treatment options, including AS and techniques used in current practice, and be designed with a long followup. These RCTs should use standardized or validated patient outcome measures, have adequate power to detect significant treatment effects, and define patient subgroups of interest a priori. They should also enroll patients who are representative of current clinical practice using similar enrollment criteria that would allow comparison of the patients' outcomes across studies.

RCTs have had challenges achieving target enrollments for comparing different treatment options. For example, the PIVOT investigators did not achieve their stated target enrollment of 2,000 patients. This suggests that comparative effectiveness research to guide treatment decisions will likely require well-designed observational studies as well.

Observational studies with better design and conduct (e.g., cancer registries and large prospective population-based cohort studies, use of propensity score or instrumental variables, use of validated QOL measures) may provide useful evidence, particularly in cases in which large differences in outcomes might exist. Observational studies may help estimate treatment effectiveness in high-priority patient and tumor subgroups that have not been adequately addressed in RCTs. Findings from observational studies may also help in generating hypotheses and designing better RCTs. We noted and reported that some observational studies conflicted in findings based on analytic methods employed (e.g., instrumental variable analysis vs. propensity scoring vs. multivariable regression analysis). Most of the existing evidence from nonrandomized comparative studies comes with treatment-selection biases.

We did not identify any studies that compared AS with current treatment therapies. Because WW or observation is not AS, more studies are needed to assess the effectiveness of AS. These studies might necessitate adequate consideration of multiparametric magnetic resonance imaging as a tool to enhance observation or AS. Additional research comparing observation or AS with any early intervention is warranted to avoid potential overdiagnosis and overtreatment in men with PSA-detected cancer (especially low PSA/low-risk disease, but possibly intermediate PSA/intermediate-risk disease as well). Future RCTs that compare early intervention versus AS or other early interventions should target patients with higher PSA/higher risk disease, given that the benefits in this group remain uncertain.

Furthermore, because prostate cancer is a significant cause of mortality among men, a research need remains for better prognostic surrogate markers to predict the risk of recurrence among patients with clinically localized prostate cancer.

Finally, some studies discussed in this report suggest that outcomes of surgery and radiation are influenced by center and surgeon case volume and expertise. However, most of these studies did not provide information about practice of care that could have influenced the results. Future studies are needed to fill this gap.

## Conclusions

Overall, the body of evidence for treating prostate cancer continues to evolve, but the evidence for most treatment comparisons is largely inadequate to determine comparative risks and benefits. Although limited evidence appears to favor surgery over WW or EBRT and favors radiotherapy plus ADT over radiotherapy alone, the patients most likely to benefit and the applicability of these study findings to contemporary patients and practice remain uncertain.

More RCTs and better designed observational studies that reflect contemporary practice and can control for many of the known/unknown confounding factors that can affect long-term outcomes may be needed to evaluate comparative risks and benefits of therapies for clinically localized prostate cancer. We also believe that an urgent need exists to provide clinicians an improved way to categorize patients with prostate cancer into different groups based on associated risk factors. All treatments available for clinically localized prostate cancer can cause bothersome complications, including sexual, urinary, and bowel dysfunction. Patients should be informed and actively involved in the decisionmaking process and consider the benefits and harms of the various treatments.

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# Introduction

## Background

Prostate cancer is the most common nondermatologic cancer in men.<sup>1,2</sup> American Cancer Society data show that in 2012, an estimated 241,740 men were expected to receive a diagnosis of prostate cancer and 28,170 were expected to die from the disease.<sup>1</sup> Approximately 90 percent of those who receive such a diagnosis have cancer confined to the prostate gland (clinically localized disease). Since 2004, the prostate cancer incidence rate has decreased by 2.7 percent annually among men 65 years of age or older and has remained steady among men younger than age 65.<sup>1</sup> The major risk factors for prostate cancer are advanced age, race and ethnicity (the highest incidence is in blacks), and family history.

Many cases of prostate cancer have a protracted course if left untreated. Mortality rates have been declining, and many men die with prostate cancer rather than from it.<sup>3</sup> During its early stages, clinically localized prostate cancer is usually asymptomatic.<sup>4</sup> However, as the cancer grows, it may cause urinary problems, such as blood in the urine, pain or a burning sensation during urination, a weak urine stream, inability to urinate, and frequent urination, especially at night. These presenting symptoms along with a physical examination, prostate-specific antigen (PSA) levels, and biopsy may be used to evaluate patients for the presence of prostate cancer.

The PSA test is used to measure blood levels of PSA, a protein produced by the prostate gland.<sup>4</sup> Elevated PSA levels may indicate prostate cancer, but elevations are also seen in conditions such as benign prostatic hyperplasia and prostatitis. Conversely, some patients with prostate cancer do not have elevated PSA levels.<sup>5</sup> Moreover, the cutpoint separating a “normal” PSA level from an abnormal level also remains a subject of debate. In recent years, more frequent use of PSA testing has intensified concern about overdiagnosis of prostate cancer—that is, detection of cancer that would have remained silent and caused the patient no illness throughout his lifetime.<sup>2,4</sup>

In May 2012, the U.S. Preventive Services Task Force (USPSTF) recommended against PSA-based screening for prostate cancer in healthy men of all ages, concluding that the harms of screening outweigh the benefits (Grade D recommendation).<sup>6</sup> However, health care professionals and professional societies have continued to debate the merits of PSA-based screening. Potential benefits of regular PSA screening include early cancer detection and reduced mortality rates. Potential harms include anxiety related to abnormal results, pain, infection, bleeding due to diagnostic biopsies, and the morbidity of definitive treatment in men who may not need such treatment.<sup>7-10</sup>

Landmark trials, including the European Randomized Study of Screening for Prostate Cancer (ERSPC), the Göteborg trial (from the Swedish center in the ERSPC trial), and the U.S.-based Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial have published findings on PSA screening’s effect on prostate cancer mortality. Both the ERSPC and PLCO trials found little effect on mortality after PSA screening.<sup>11</sup> The Göteborg trial reported a 0.40 percent absolute cumulative risk reduction in prostate cancer mortality (from 0.90% in the control group to 0.50% in the screening group) and no difference in overall mortality in men aged 50–64 years over 14 years of screening.<sup>12</sup>

Citing these trials, USPSTF assessed the potential benefit of screening to be zero to one death from prostate cancer prevented for every 1,000 men aged 55–69 years screened by PSA testing every 1–4 years for 10 years. USPSTF also estimated that there would be 100–120 men with false-positive tests and 110 men with true-positive tests; complication rates from treatment

would range from fewer than 1 death per 1,000 men screened to 29 cases of erectile dysfunction per 1,000 men screened.<sup>6</sup> For these reasons, determining which men with clinically localized prostate cancer are most likely to benefit from interventions such as surgery and radiation could potentially improve the balance of benefits and harms, especially in those identified by screening.

Current practice is to use tumor grade as the primary prognostic variable in patients with clinically localized prostate cancer.<sup>2</sup> After biopsy confirms the presence of the cancer, pathologists report tumor grade in terms of the Gleason score, which ranges from 2 to 10.<sup>4</sup> Gleason 8–10 tumors are considered the most aggressive, Gleason 7 tumors are considered somewhat less aggressive, and Gleason 6 or lower tumors are considered potentially indolent.<sup>13</sup> However, the Gleason grade assigned based on a biopsy specimen may differ from the Gleason grade assigned based on a surgical specimen. Although the primary measure of tumor aggressiveness is the Gleason histologic score, efforts are under way to identify more reliable prognostic factors. PSA, PSA kinetics (rate of increase in PSA over time, or PSA velocity, and PSA doubling time), and digital rectal examination (DRE) are still very important when considering treatment options.

Staging is the process of assessing whether the cancer is confined to the prostate gland or has spread beyond it and, if so, to what extent it has spread.<sup>4</sup> Staging of prostate cancer could be clinical (based on a DRE of the prostate gland, prostate biopsy, and laboratory tests) or pathological (based on surgery and examination of resected prostate tissue). The staging system currently used is the American Joint Committee on Cancer (AJCC) TNM classification.<sup>4</sup> TNM classification is based on the extent of primary tumor (T stages), whether cancer has spread to the adjacent lymph nodes (N stages), and any metastasis (M stages).<sup>4,14</sup> These classifications are detailed in Table 1, Table 2, and Table 3.

**Table 1. American Joint Committee on Cancer TNM classification: Tumor (T) stages**

Stage	Description
T1	The tumor cannot be felt or seen using imaging techniques
	T1a. The cancer cells are incidentally found in 5% or less of resected tissue
	T1b. The cancer cells are found in more than 5% of the resected tissue
	T1c. The cancer is identified by needle biopsy, which is performed because of high prostate-specific antigen levels
T2	The cancer is confined to the prostate but can be felt as a small, well-defined nodule
	T2a. The cancer is in half of a prostate lobe
	T2b. The cancer is in more than half of a prostate lobe
	T2c. The cancer is in both prostate lobes
T3	The tumor extends through the prostate capsule
	T3a: The cancer extends outside the prostate but not to the seminal vesicles
	T3b: The cancer has spread to the seminal vesicles
T4	The tumor is fixed or invades adjacent structures

**Table 2. American Joint Committee on Cancer TNM classification: Lymph node (N) stages**

Stage	Description
NX	Nearby lymph nodes were not assessed
N0	The cancer has not spread to any nearby lymph nodes
N1	The cancer has spread to one or more nearby lymph nodes in the pelvis

**Table 3. American Joint Committee on Cancer TNM classification: Metastasis (M) stages**

Stage	Description
M0	The cancer has not spread past nearby lymph nodes
M1	The cancer has spread beyond nearby lymph nodes
	M1a. The cancer has spread to distant (outside the pelvis) lymph nodes
	M1b. The cancer has spread to bone
	M1c. The cancer has spread to other organs such as the lungs, liver, or brain (with or without spread to the bones)

Clinicians usually make pretreatment assessment of prostate cancer tumor stage based on DRE and in some cases, transrectal ultrasound of the prostate (TRUS) and/or magnetic resonance imaging (MRI). The accuracy of clinical staging is affected by tumor size and location as well as the skill of the examiner and the accuracy and interpretation of the imaging study, if performed. Several surgical studies have documented both under- and overstaging by clinical examination when compared with surgical findings. For example, although the Scandinavian Prostate Cancer Group 4 (SPCG-4) trial's eligibility criteria specified clinical stage T1 or T2 disease, nearly half the patients undergoing RP were found to have extracapsular extension (pT3) on resection.<sup>15</sup>

Unfortunately, additional assessments such as radiographs, bone scans, computed tomography, and MRI are of limited use, particularly for detecting small foci of cancer in lymph nodes. Several methods for improving detection via imaging are under study. For detecting cancer in the lymph nodes, an innovative technique called enhanced MRI may help.<sup>14</sup> For identifying prostate cancer in other parts of the body, a new type of positron-emission tomography scan that uses the radioactive tracer carbon acetate as a replacement for fluorodeoxyglucose may be useful. It may also be used to define the effectiveness of the therapy.<sup>14</sup>

Determining tumor anatomy and extent when assigning clinical stage is inherently difficult, but clinical application of current staging criteria is also problematic. Staging errors have been documented in several studies, including one using the Cancer of the Prostate Strategic Urologic Research Endeavor database.<sup>16</sup> This registry included men with prostate cancer from 40 academic and community-based urology practices. Reese et al. examined the clinical T stage reported by clinicians based on their individual interpretation of clinical staging criteria and compared that with the corrected clinical stage based on AJCC staging criteria. They found staging errors in 1,370 of 3,875 men (35.4%); the clinicians assigned a lower stage than was appropriate 55% of the time, and a higher stage 45% of the time.<sup>16</sup>

A number of risk classification schemes have been developed in an attempt to better predict the pathologic stage and the aggressiveness of prostate cancer. The TNM categories are combined with the Gleason histologic score and PSA-level results (stage grouping) to determine the overall stage, which is commonly reported in Roman figures (Stages I, IIA, IIB, III, and IV), with stage I being the least advanced and stage IV being the most advanced. In the absence of a Gleason histologic score, staging can still be based on the TNM classification. The criteria for Stages I, II and III are provided in Table 4.

**Table 4. Anatomic and prognostic prostate cancer staging**

Stage Group	T*	N	M	PSA Levels (ng/mL)	Gleason Score
I	T1a–c	N0	M0	PSA <10	Gleason ≤6
	T2a	N0	M0	PSA <10	Gleason ≤6
	T1–2a	N0	M0	PSA X	Gleason X
IIA	T1a–c	N0	M0	PSA <20	Gleason 7
	T1a–c	N0	M0	PSA ≥10 <20	Gleason ≤6
	T2a	N0	M0	PSA ≥10 <20	Gleason ≤6
	T2a	N0	M0	PSA <20	Gleason 7
IIB	T2b	N0	M0	PSA <20	Gleason ≤7
	T2b	N0	M0	PSA X	Gleason X
	T2c	N0	M0	Any PSA	Any Gleason
	T1–2	N0	M0	PSA ≥20	Any Gleason
III	T1–2	N0	M0	Any PSA	Gleason ≥8
	T3a**–b	N0	M0	Any PSA	Any Gleason

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\*Tumor found in one or both lobes by needle biopsy but not palpable or reliably visible by imaging, is classified as T1c. Invasion into the prostatic apex or into (but not beyond) the prostatic capsule is classified not as T3 but as T2.

\*\*Extracapsular extension (unilateral or bilateral)

**Abbreviations:** PSA=Prostate-specific antigen; X=unknown.

Another categorization, the D’Amico Classification System, also incorporates PSA levels, Gleason histologic score, and TNM stage. It stratifies tumors into low-, intermediate-, and high-risk in terms of their likelihood of progressing with no treatment or of recurring after early intervention.<sup>4</sup>

- Low risk (corresponding to stage I): a PSA level of 10 ng/mL or less, a Gleason score of 6 or less, and a clinical stage of T1c or T2a
- Intermediate risk (roughly corresponding to stage IIA): a PSA level of 10–20 ng/mL, a Gleason score of 7, or a clinical stage of T2b but not qualifying for high risk
- High risk (roughly corresponding to stage IIB): a PSA level of more than 20 ng/mL, a Gleason score of 8–10, or a clinical stage of T2c

The risk assessment scheme described above, although commonly used among men with clinically localized prostate cancer, has significant limitations in assessing patients in the intermediate- and high-risk groups. Another example of a risk assessment scheme that has been developed, validated across populations, and associated with both overall and cause-specific survival is the University of California, San Francisco, Cancer of the Prostate Risk Assessment (CAPRA) score. CAPRA can be used to predict disease recurrence and mortality after radical prostatectomy (RP).<sup>17-20</sup> These risk assessment tools may be improved in the future with the use of biomarkers (e.g., actinin alpha 1, derlin 1).

The term “clinically localized” prostate cancer has most often been used to describe tumors of stages I and II, and the term “locally advanced” has been used for tumors that have spread beyond the prostatic capsule (“extracapsular extension”) but not beyond the seminal vesicles.

However, the National Comprehensive Cancer Network (NCCN) issued a clinical practice guideline in 2013 in which it defined clinically localized prostate cancer as clinical stages T1–

T3a, NX, M0; or stage I–IIIa.<sup>21</sup> This shift reflects the impression that tumors with extracapsular extension (T3a) but without spread into the seminal vesicles (T3b) respond better to therapy. The NCCN guideline, which was based on opinions of individual experts, describes the various categories based on the recurrence risk:<sup>21</sup>

- Clinically localized
  - Very low recurrence risk: T1c, Gleason score 6 or less, PSA of less than 10 ng/mL, fewer than 3 prostate biopsy cores positive, 50% or less cancer in each core, and PSA density (PSA/prostate volume) of less than 0.15 ng/mL/g
  - Low recurrence risk: T1–T2a, Gleason score 2–6, and PSA of less than 10 ng/mL
  - Intermediate recurrence risk: T2b–T2c or PSA 10–20 ng/mL or Gleason score 7
  - High recurrence risk: T3a or Gleason score 8–10 or PSA of more than 20 ng/mL
- Locally advanced
  - Very high recurrence risk: T3b–T4

The focus of this report is clinically localized prostate cancer (T1–T3a). Locally advanced (T3b–T4), metastatic, and recurrent prostate cancer are outside the scope of this report.

## Therapies for Clinically Localized Prostate Cancer

The primary goal of treating clinically localized prostate cancer is to target the men most likely to need intervention to prevent disability or death while minimizing intervention-related complications. Treatment options that are frequently used include the following and are described in Table 5:

- RP, including laparoscopic or robotic-assisted prostatectomy (RALRP)
- External beam radiotherapy (EBRT), including conventional radiation, intensity modulated radiation therapy (IMRT), three-dimensional conformal radiation therapy (3D-CRT), stereotactic body radiation therapy, and proton beam radiation
- Interstitial brachytherapy (BT)
- Cryotherapy
- Observation or watchful waiting (WW) (these terms will be used interchangeably)
- Active surveillance (AS)
- Hormonal therapy (e.g., androgen deprivation therapy [ADT])
- High-intensity focused ultrasound (HIFU)

**Table 5. Treatment options for clinically localized prostate cancer**

Treatment Option	Treatment Description
Radical prostatectomy (open retropubic, open perineal, laparoscopic, robotic-assisted approaches)	Complete surgical removal of prostate gland with seminal vesicles, ampulla of vas, and sometimes pelvic lymph nodes
External beam radiotherapy, including conventional radiation, intensity-modulated radiation therapy, three-dimensional conformal radiation, proton beam, and stereotactic body radiation therapy	Multiple doses of radiation from an external source applied over several days to weeks
Interstitial brachytherapy	Radioactive implants placed using radiologic guidance. Low dose–rate/permanent implants and high dose–rate brachytherapy may be used. Combination therapy comprises external beam radiotherapy with a brachytherapy boost
Hormonal therapy	Oral or injected medications or surgical removal of testicles to lower or block circulating androgens



**Table 5. Treatment options for clinically localized prostate cancer (continued)**

Treatment Option	Treatment Description
Cryotherapy	Destruction of cells through rapid freezing and thawing, using transrectal guided placement of probes and injection of freezing/thawing gases
High-intensity focused ultrasound therapy	Tissue ablation of the prostate by intense heat, focusing on the identified cancerous area
Observation or watchful waiting (these terms will be used interchangeably)	Relatively passive patient followup, with symptom management if and when any symptoms occur <sup>3</sup>
Active surveillance	Usually includes hands-on followup in which prostate-specific antigen levels are checked, prostate biopsies may be repeated, and subsequent treatment is planned <sup>3</sup>

Choice of treatment options may be influenced by factors such as patient age and health at the time of the diagnosis, life expectancy, estimated likelihood of cancer progression without treatment, the surgeon’s experience and preference, and treatment-related convenience, costs, and potential for eradication and adverse effects (e.g., incontinence, sexual dysfunction).<sup>4</sup> Before choosing any intervention, an assessment of the overall health status of patients is important because it may influence response to therapy, severity of complications, and life expectancy.<sup>4</sup>

The treatment for men with clinically localized prostate cancer has been the subject of much debate. As discussed above, identifying those men most likely to benefit from aggressive therapy is challenging. Ideally, those with slowly progressing disease who are more likely to die of other causes would be spared unnecessary treatment, while men with aggressive, localized prostate cancer would be offered curative procedures.<sup>3,10</sup> One option under study for assessing disease progression is an approach called “active surveillance,” or AS, which typically includes monitoring of PSA levels and rate of increase, periodic DRE, and repeat prostate biopsies with curative intent.

The National Cancer Institute and the Centers for Disease Control and Prevention sponsored a National Institutes of Health (NIH) State-of-the Science Conference in December 2011 to better understand the risks and benefits of AS and other observational management strategies for PSA screening–detected, low-grade, localized prostate cancer.<sup>3</sup> The panel concluded that AS should be offered to patients with low-risk prostate cancer.

The NIH panel used the term “watchful waiting”, or WW, to describe a palliative observational strategy—that is, waiting for symptoms to appear and then intervening to manage the symptoms. In the 2008 systematic review, “Comparative Effectiveness of Therapies for Clinically Localized Prostate Cancer,” these two approaches were considered together.<sup>22</sup> In the literature, the distinction between AS (with curative intent) and other observational strategies (with palliative intent) has not always been clear; however, for this systematic review update, we attempted to separate the two using the definitions proposed at the 2011 NIH State-of-the-Science Conference.<sup>3</sup>

## Findings From the Original Report

The 2008 systematic review on therapies for clinically localized prostate cancer, written by the University of Minnesota Evidence-based Practice Center (EPC), included 18 randomized controlled trials (RCTs) and 473 observational studies.<sup>22</sup> None of these included studies enrolled patients with prostate cancer primarily identified by PSA testing. The main findings of the 2008 report include the following:

- No single therapy can be considered the preferred treatment for localized prostate cancer because of limitations in the body of evidence as well as the likely tradeoffs a patient

must make between estimated treatment effectiveness, necessity, and adverse effects. All treatment options result in adverse effects (primarily urinary, bowel, and sexual), although the severity and frequency may vary across treatments.

- No RCT reported head-to-head comparisons of treatment outcomes stratified by race/ethnicity.
- The results from the analysis of national administrative databases and surveys suggested that provider and hospital characteristics, including RP procedure volume, physician specialty, and geographic region, affect outcomes. Patient outcomes varied in different locations and were associated with provider and hospital case volume, independent of patient and disease characteristics. Screening practices and treatment choices varied by physician specialty and across U.S. regions. Clinicians were more likely to recommend procedures they performed regardless of tumor grades and PSA levels.
- Few data exist on the comparative effectiveness of treatments based on stratification of risk into low, intermediate, and high categories using PSA levels, histologic score, and tumor volume.

Overall, the authors concluded that “assessment of the comparative effectiveness and harms of localized prostate cancer treatments is difficult because of limitations in the evidence.”<sup>22</sup> For example, only a few RCTs directly compared the effectiveness between (rather than within) major treatment categories. Additionally, many of these RCTs were inadequately powered to provide long-term survival outcomes, with the majority reporting biochemical progression or recurrence as the primary outcomes. Finally, some RCTs were conducted before prostate cancer detection with PSA testing was available.

Remaining issues and future research needs that were outlined in the 2008 report included the following:<sup>22</sup>

- RCTs should evaluate relative effectiveness and adverse events and stratify their findings based on patient (e.g., age, race, comorbidity) and tumor (e.g., level of PSA, stage, histologic grade) characteristics.
- Comparative trials on technologies that were considered to be “emerging” at the time the report was written—IMRT, proton beam radiation, cryotherapy, and robotic-assisted and laparoscopic prostatectomy—must provide long-term followup data.
- Head-to-head RCTs must be adequately powered to compare primary treatments for localized prostate cancer.
- Trials should standardize reporting of key clinically relevant outcomes and should structure the assessment of outcome measures such as quality of life (QOL) and health status.

## Rationale for Update

A surveillance analysis conducted by the Southern California EPC in May 2012 determined the need for this update. In the analysis, investigators evaluated the Key Questions (KQs) from the 2008 systematic review and conducted a restricted literature search for new evidence.<sup>23</sup> The key finding of the analysis was that the Prostate Cancer Intervention Versus Observation Trial (PIVOT),<sup>23-25</sup> published after the 2008 report, makes the 2008 report’s conclusions out-of-date. Specifically, the analysis suggested re-evaluating KQs 1, 2, and 4 as newly available evidence

from the PIVOT trial and other recent studies may change the conclusions from those of the previous report.<sup>23</sup>

## Scope and Key Questions

This update examined the same four KQs as in the original 2008 report on the comparative effectiveness of treatments for clinically localized prostate cancer. For the original report, these KQs were reviewed and approved by the Agency for Healthcare Research and Quality (AHRQ) and discussed with Technical Expert Panel (TEP) members. For this update, we presented the KQs again for discussion with a newly convened TEP and made changes as necessary. This update summarizes the more recent evidence comparing the relative effectiveness and safety of treatment options for clinically localized prostate cancer. The KQs we addressed are as follows:

### Key Question 1:

What are the comparative risks and benefits of the following therapies for clinically localized prostate cancer?

- a. RP, including open (retropubic and perineal) and laparoscopic (with or without robotic assistance) approaches
- b. EBRT, including standard therapy and therapies designed to decrease exposure to normal tissues such as IMRT, 3D-CRT, proton beam therapy, and stereotactic body radiation therapy
- c. Interstitial BT
- d. Cryotherapy
- e. WW
- f. AS
- g. Hormonal therapy
- h. HIFU

### Key Question 2:

How do specific patient characteristics (e.g., age, race/ethnicity, presence or absence of comorbid illness, preferences such as tradeoff of treatment-related adverse effects vs. potential for disease progression) affect the outcomes of these therapies overall and differentially?

### Key Question 3:

How do provider/hospital characteristics (e.g., geographic region, case volume, learning curve) affect outcomes of these therapies overall and differentially?

### Key Question 4:

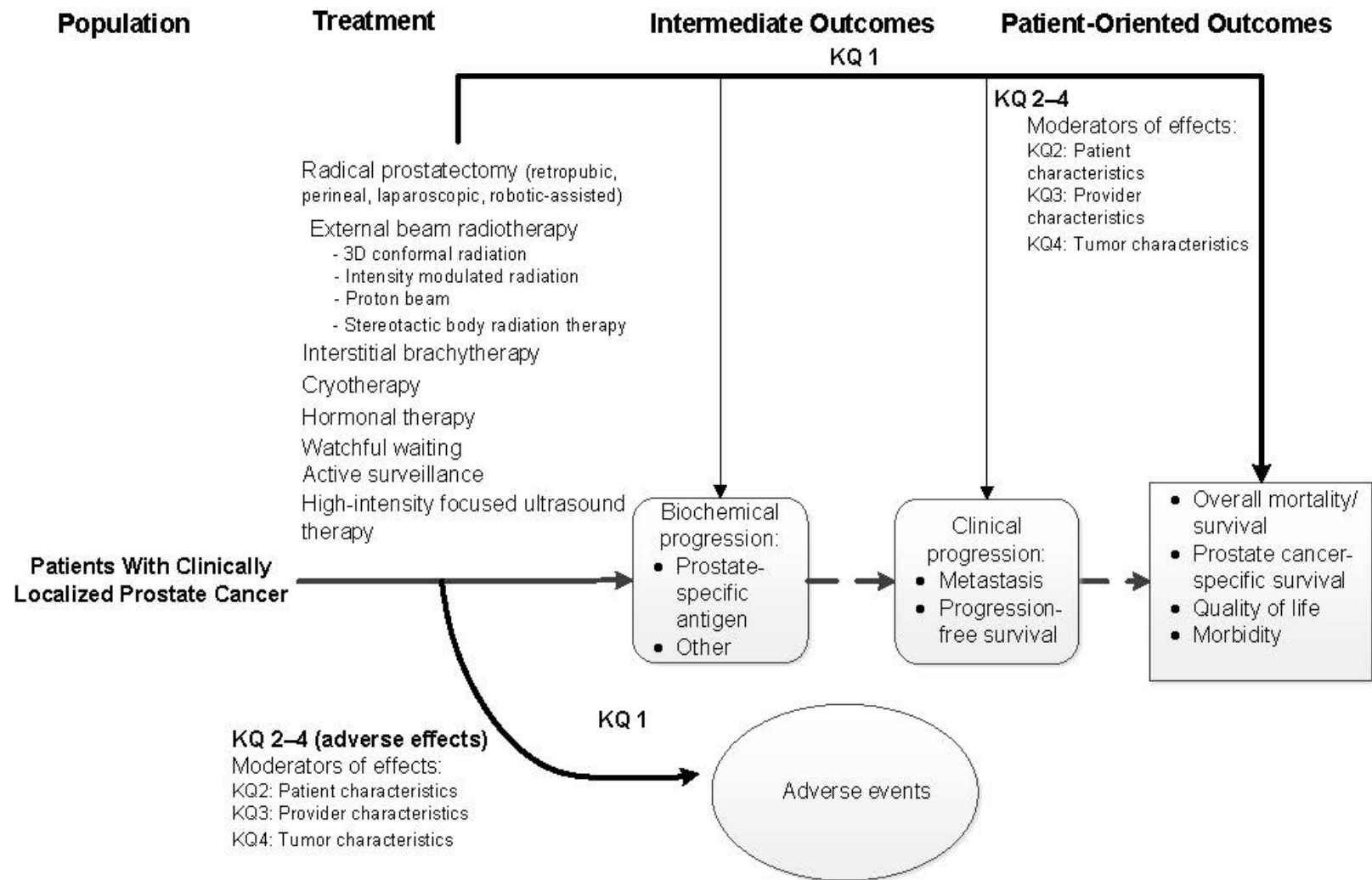
How do tumor characteristics (e.g., Gleason score, tumor volume, screen-detected vs. clinically detected tumors, and PSA levels) affect the outcomes of these therapies overall and differentially?

## Conceptual Framework

An analytic framework illustrating the connections between the population of interest (patients with clinically localized prostate cancer), the treatments, and the outcomes is shown in Figure 1 below. The population of interest enters the diagram at the left, undergo treatment (KQ 1), and outcomes (intermediate and patient-oriented clinical outcomes) are monitored and

recorded. Intermediate outcomes such as biochemical progression require shorter followup for measurement than clinical outcomes such as all-cause or prostate cancer-specific mortality, which require years of followup to accumulate enough events for detection of differences between treatments. When enough outcome data are available, investigators often conduct statistical analyses to detect moderators of treatment effects (KQ 2–4).

Figure 1. Analytic framework



Abbreviations: 3D = three-dimensional; KQ = key question.

## Methods

This section documents the methods we used to conduct and produce this updated systematic review on therapies for clinically localized prostate cancer for the Agency for Healthcare Research and Quality (AHRQ) through its Effective Health Care Program ([www.effectivehealthcare.ahrq.gov](http://www.effectivehealthcare.ahrq.gov)).

The methods used for preparing the 2008 systematic review were developed through a rigorous process by the University of Minnesota Evidence-based Practice Center (EPC) in consultation with AHRQ and a Technical Expert Panel.<sup>22</sup> We incorporated the methods from the original report when possible. However, for this update, our methods were informed by a more recent version of the guidance from the “Methods Guide for Effectiveness and Comparative Effectiveness Reviews,”<sup>26</sup> hereafter referred to as the Methods Guide. The search strategy was based on that composed for the 2008 report, but we incorporated newer search methods and reflected changes in the relevant nomenclature, such as differentiating AS from WW. We used similar criteria and methods as in the 2008 report for study selection, data extraction, and risk-of-bias assessment for studies published since January 2007. The strength of evidence for each outcome was assessed according to more recent guidance from the Methods Guide.<sup>26</sup>

### Literature Search Strategy

Medical Librarians in the ECRI Institute–Penn Medicine EPC Information Center performed literature searches, following established systematic review protocols. We searched the following databases using controlled vocabulary and text words: EMBASE, MEDLINE, PubMed, and The Cochrane Library from January 1, 2007, through March 7, 2014. The literature searches were updated during the peer review process, before finalization of the review. The full search strategy is provided in Appendix A.

Literature screening (for reviews or studies) was performed in duplicate using the database Distiller SR (Evidence Partners, Ottawa, Ontario, Canada). Initially, we screened literature search results in duplicate for relevancy. We screened relevant abstracts again, in duplicate, against the inclusion criteria. Studies that appeared to meet the inclusion criteria were retrieved in full, and we screened them again, in duplicate, against the inclusion criteria. All disagreements were resolved by consensus discussion among the two original screeners and, if necessary, an additional third screener. We used Reference Manager™ software (Thomson Reuters, New York, NY) for managing references.

### Inclusion and Exclusion Criteria

We used the same study selection criteria as in the 2008 report (see Table 6, Table 7, Table 8, and Table 9). For Key Questions (KQs) 1, 2, and 4, we included randomized trials only if the randomized treatment allocation was based on men with clinically localized disease and if clinical outcomes were reported for T1–T3a disease separately from T3b and T4 disease. We also included large nonrandomized comparative studies ( $N \geq 500$ ) that controlled for potentially confounding variables.

For KQ 3, we considered multicenter studies that compared radical prostatectomy (RP) with another treatment of interest, enrolled 500 or more patients, used appropriate statistical techniques to control for potentially confounding variables, and examined the effect of provider characteristics on survival of localized prostate cancer patients.

Non-English-language studies were excluded. Moher et al.<sup>27</sup> have demonstrated that exclusion of non-English-language studies from meta-analyses has little impact on the conclusions drawn. Juni et al.<sup>28</sup> found that non-English-language studies typically were of lower methodologic quality and that excluding them had little effect on effect-size estimates in the majority of meta-analyses they examined. Although we recognize that in some situations exclusion of non-English-language studies could lead to bias, we believe that the few instances in which this may occur do not justify the time and cost typically necessary to translate studies to identify those of acceptable quality for inclusion in our review.<sup>27,28</sup>

**Table 6. Inclusion criteria: Key Question 1**

Question Components	Inclusion Criteria
<p><b>Major treatment options of interest:</b></p> <ul style="list-style-type: none"> <li>• Radical prostatectomy (retropubic, perineal, laparoscopic, robotic-assisted)</li> <li>• External beam radiotherapy</li> <li>• Interstitial brachytherapy</li> <li>• Hormonal therapy</li> <li>• Watchful waiting and active surveillance</li> </ul> <p><b>Emerging treatment options of interest:</b></p> <ul style="list-style-type: none"> <li>• Cryotherapy</li> <li>• High-intensity focused ultrasound therapy (premarket approval application for 1 device is under consideration by the U.S. Food and Drug Administration)</li> <li>• Proton beam therapy</li> <li>• Stereotactic body radiation therapy</li> </ul> <p><b>Outcomes of interest:</b></p> <ul style="list-style-type: none"> <li>• Overall mortality and morbidity</li> <li>• Prostate-related mortality and morbidity</li> <li>• Progression to metastasis</li> <li>• Biochemical recurrence</li> <li>• Quality of life</li> <li>• Adverse effects such as urinary incontinence and sexual dysfunction</li> </ul>	<p>RCTs comparing different treatment options that enrolled patients with clinically localized disease and reported outcomes of interest with duration of followup 1 year or more. Trials must have focused on, or provided separate analyses for men with clinically localized prostate cancer (T1–T3a). RCTs that assigned treatments based on pathological staging (i.e., based on intraoperative findings) rather than clinical staging were excluded.</p> <p>Large nonrandomized comparative studies (n≥500) that prospectively enrolled consecutive patients. For any nonrandomized comparative studies, we included only those that used an analytic method to address selection bias (propensity scoring, instrumental variable analysis, or preplanned multivariate regression). The treatments being compared must have been administered during the same time period, so that any observed difference between outcomes were not attributable to differential time frames.</p> <p>For adverse events, we also included large nonrandomized comparative studies (n≥500) that reported relevant data. Studies could be prospective or retrospective; however, to reduce the risk of bias, retrospective studies must have used consecutive enrollment or enrollment of a random sample of eligible participants.</p> <p>Studies must have been published in English. Studies comparing different surgical techniques, such as radical prostatectomy with or without nerve-sparing, or the same type of radiation but at different dosages were outside the scope of this report.</p>

**Abbreviation:** RCT=Randomized controlled trial.

**Table 7. Inclusion criteria: Key Question 2**

Question Components	Inclusion Criteria
Effectiveness outcomes according to patient characteristics (age, race/ethnicity, comorbid conditions, and preferences)	Studies that met the inclusion criteria for Key Question 1 and reported outcomes stratified according to patient characteristics.

**Table 8. Inclusion criteria: Key Question 3**

Question Components	Inclusion Criteria
<ul style="list-style-type: none"> <li>• Association between physician characteristics (specialty, experience) and patient outcomes</li> <li>• Association between geographic region and patient outcomes</li> <li>• Association between hospital characteristics (case volume, university vs. community) and patient outcomes</li> </ul>	Randomized controlled trials or large multicentered nonrandomized studies that compared the effectiveness of radical prostatectomy to another treatment of interest and assessed how the effectiveness of these treatments varied by geographic region, type of hospital (university vs. community), case volume, or physician experience. Studies were excluded if there was insufficient detail regarding provider characteristics to inform this report.

**Table 9. Inclusion criteria: Key Question 4**

Question Components	Inclusion Criteria
Effectiveness outcomes according to tumor characteristics (prostate-specific antigen, tumor stage, histologic grade, tumor risk strata)	Studies that met the inclusion criteria for Key Question 1 and reported outcomes stratified according to tumor characteristics.

## PICOTS Criteria

### Population

- KQs 1–4: Men considered to have clinically localized prostate cancer (T1–T3a, N0–X, M0–X) regardless of age, histologic grade, or prostate-specific antigen (PSA) level. Articles were excluded if more than 15 percent of men with disease stage higher than T3a were enrolled and the study did not specifically report separate data for men with T1, T2, and/or T3a prostate cancer (see Tables 1–3).

### Interventions

- For KQs 1, 2, 4, we included treatment options for men with clinically localized prostate cancer: RP (including retropubic, perineal, laparoscopic, robotic-assisted), external beam radiation therapy (including conventional radiation, intensity-modulated radiation therapy, three-dimensional conformal radiotherapy, proton beam, and stereotactic body radiation therapy), interstitial brachytherapy, cryotherapy, watchful waiting, active surveillance, hormonal therapy, and high-intensity focused ultrasound.
- For KQ 3, we included RP (including retropubic, perineal, laparoscopic, robotic-assisted).

### Comparators

- Any of the interventions of interest above.

### Outcomes

- For KQ 1, 2, and 4, the primary outcome is overall mortality or survival. Additional outcomes include prostate cancer–specific mortality or survival, biochemical (PSA) progression, metastatic and/or clinical progression-free survival, health status, and quality of life. We focused primarily on common and severe adverse events of treatment including bowel, bladder, and sexual dysfunction, as well as harms from biopsy such as bleeding and nosocomial infections.



- For KQ 3, we examined overall-and prostate cancer-specific survival.

## Timing

- Duration of followup was a minimum of 1 year.

## Settings

- No restrictions by setting.

## Data Abstraction

We used the DistillerSR<sup>®</sup> (Evidence Partners, Inc., Ottawa, Ontario, Canada) Web-based systematic review software for abstract screening. Data were extracted directly into a Word document by one team member and reviewed by a second team member. The data extracted included study, patient, tumor, and intervention characteristics and predefined outcomes. Standard errors, regression coefficients, and 95 percent confidence interval (95% CI) were calculated from reported means, standard deviations, and sample size when provided/appropriate.<sup>29</sup> Summary measures included risk ratios, hazard ratios, odds ratios, absolute risk reduction, difference in means, and standardized mean difference. Also, because of the possibility of subjective interpretation, the risk-of-bias items were judged in duplicate. We resolved all discrepancies through discussion. Multiple publications of the same study (e.g., publications reporting subgroups, other outcomes, longer followup) were identified by examining author affiliations, study designs, enrollment criteria, and enrollment dates. Multiple publications were used only when each publication had unique data not reported in the most comprehensive and recent publication.

## Risk-of-Bias Evaluation

As stated above, because of the possibility of subjective interpretation, assessment of methodologic risk of bias of individual studies was performed by two researchers for each study, and discrepancies were resolved by consensus. When consensus could not be reached, a third researcher adjudicated.

We assessed the risk of bias by following the guidelines in the chapter, “Assessing the Risk of Bias of Individual Studies When Comparing Medical Interventions” in the “Methods Guide for Effectiveness and Comparative Effectiveness Reviews.”<sup>30</sup> This involved evaluating several items such as randomization, allocation concealment, intention-to-treat-analysis, and completeness of followup (see Table 10). Additionally, we assessed fidelity to the protocol to address performance bias and blinding of outcome assessors to address detection bias when outcomes were subjective (as defined in Table 10). Each of these items was answered “Yes,” “No,” or “Not reported.”

We used the same checklist to rate the risk of bias for both RCTs and nonrandomized comparative studies. We considered this appropriate because any study with parallel treatment comparisons is subject to the same set of biases, and randomization is a method designed to control for selection bias from both known and unknown confounders. Checklists specific for nonrandomized studies generally do not penalize studies for lack of randomization, which means the risk-of-bias rating tends to be artificially minimized in relation to RCTs that are rated using an RCT-specific checklist. Using the same checklist therefore ensures that both types of studies are judged using the same standards, and the relative ratings are therefore more accurate.

**Table 10. Risk of bias of included studies**

Item	Comment
1. Were patients randomly or pseudorandomly (e.g., using instrumental variable analysis) assigned to the study groups?	Instrumental variable analysis can account for both measured and unmeasured confounders, as long as the chosen variables have a strong association with treatment choice but no association with health outcomes. Studies using this method received a “yes” for this item. Studies using propensity scoring or multivariate regression received a “no”.
2. Was there concealment of group allocation?	—
3. Were data analyzed based on the intention-to-treat-principle?	—
4. Were those who assessed the patient outcomes blinded to the group to which the patients were assigned?	—
5. Was the outcome measure of interest objective and was it objectively measured?	The following were considered objective outcomes: overall mortality or survival, prostate cancer–specific survival, adverse events, biochemical progression–free survival. The following were considered subjective outcomes: quality of life and health status (morbidity).
6. Was there a 15% or less difference in the length of followup for the 2 groups?	—
7. Did 85% or more of enrolled patients provide data at the time point of interest?	—
8. Was there fidelity to the protocol?	

We categorized each study as having low, medium, or high risk of bias using the following method:

- To be considered as having low risk of bias, the study must meet all the following conditions:
  - There was randomization of study participants to treatment groups.
  - There was concealment of allocation.
  - Data analysis was based on the intention-to-treat-principle.
  - If outcome assessors were not blinded (item 4) or blinding of outcome assessors was not reported, then the outcome must have been objective (item 5).
  - There was a difference of 15 percent or less in the length of followup for the two groups.
  - Eighty-five percent or more of enrolled patients provided data at the time point of interest.
  - There was no clear indication of lack of fidelity to the protocol.
- To be considered as having high risk of bias, the study must meet at least one of the following criteria:
  - The trial was not randomized or pseudorandomized (i.e., using instrumental variables) and did not blind outcome assessors.
  - The trial had a difference of 15 percent or more in the length of followup for the two groups.
  - The trial authors specifically reported that they did not have good fidelity to the protocol.
- To be considered as having medium risk of bias, the study neither meets the criteria for low risk of bias nor the criteria for high risk of bias.

## Strength-of-Evidence Grading

We provided evidence grades (see Table 11) for the following outcomes: overall mortality or survival, prostate cancer–specific survival, progression to metastases and quality of life. We assessed strength of evidence by following the guidelines from the publication, “Grading the Strength of a Body of Evidence When Comparing Medical Interventions,” by Owens et al.<sup>31</sup> We graded the strength of evidence for each major health outcome based on the following dimensions:

- Risk of bias (low, medium, or high)
- Consistency (consistent, inconsistent, or unknown/not applicable)
- Directness (direct or indirect)
- Precision (precise or imprecise)

Two independent graders assessed each domain, and differences were resolved by consensus.

We assigned the strength of evidence an overall grade of high, moderate, low, or insufficient, as outlined by Owens et al. (see Table 11).<sup>31</sup> The decision to grade an evidence base as insufficient rather than low often reflected an imprecise effect estimate (a nonstatistically significant effect with 95% CI wide enough to allow the possibility of a significant benefit for one treatment compared with another) in an evidence base with only one or two studies. However, we also graded as insufficient evidence from a single study with medium risk of bias or less than three consistent studies of high risk of bias, even when findings were direct and precise. Because multiple factors other than treatment can influence apparent differences between interventions, we placed a high value on replication of findings, even more so for studies with high risk of bias. Further explanation for this conservative approach to evidence grading appears in the Discussion section of the report.

When evidence came from subgroup analyses (KQs 2 and 4), the strength of evidence was lowered by one level. For example, when the strength of evidence for a primary analysis in KQ 1 was low, strength of evidence for subgroup analyses from the same studies was considered insufficient. We adopted this approach because subgroup analyses were usually underpowered to detect differences between treatments and sometimes not prespecified at the beginning of the study. In general, subgroup analyses should be considered as hypothesis-generating rather than definitive analyses.

**Table 11. Strength-of-evidence grades and definitions**

Grade	Definition
High	<b>We are very confident that the estimate of effect lies close to the true effect for this outcome.</b> The body of evidence has few or no deficiencies. We believe that the findings are stable, that is, another study would not change the conclusions.
Moderate	<b>We are moderately confident that the estimate of effect lies close to the true effect for this outcome.</b> The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains.
Low	<b>We have limited confidence that the estimate of effect lies close to the true effect for this outcome.</b> The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.
Insufficient	<b>We have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome.</b> No evidence is available or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion.

## **Applicability**

Applicability was assessed by following the guidelines in “Assessing the Applicability of Studies When Comparing Medical Interventions,” by Atkins et al.<sup>32</sup> The applicability of the evidence involves the following five aspects: patients, interventions, comparisons, outcomes, and settings.<sup>32</sup> We addressed factors relevant to the applicability of the evidence by evaluating patient selection in both observational studies and clinical trials. We considered the primary biology and epidemiology (grade and stage of the prostate cancer) and the present-day clinical practice setting. The typical interventions, comparisons, outcomes (e.g., overall mortality, prostate cancer–specific survival), and settings of care were also used to more clearly specify the most applicable study characteristics (i.e., most typical of localized prostate cancer care in the United States).

## **Data Synthesis**

Because of the differences in study designs, treatments, patient and tumor characteristics, and reporting of outcomes, the 2008 report did not pool studies for KQs 1, 2, and 4. For the same reason, we performed only qualitative analysis in this update. RCTs and nonrandomized comparative studies differed substantially in average risk of bias, and we performed separate qualitative analyses and presented results separately for these study designs.

Study results were stratified based on study designs, comparisons across primary treatment categories, and comparisons within primary treatment categories.

Generally, we reported summaries of effectiveness and adverse-event outcomes with ranges according to treatment option, tumor characteristics, and group sample size. For KQ 1, we summarized and discussed comparative risks, benefits, and outcomes of therapies. For KQ 2, we summarized how patient characteristics affect outcomes. For KQ 4, we summarized how tumor characteristics affect outcomes. For KQ 3, we were unable to identify any studies that met our inclusion criteria.

## **Peer Review and Publication**

The review protocol was posted on March 29, 2013, at the AHRQ Effective Health Care Program Web site. The full draft report was posted for public and peer review comments from July 10, 2013 to August 6, 2013. Peer reviewers were invited to provide written comments on the draft report based on their clinical, content, or methodologic expertise. Peer review comments on the preliminary draft of the report were considered by the EPC in preparation of the final report. The dispositions of the peer review comments are documented and will be published 3 months after the publication of the evidence report.

# Results

## Introduction

In this chapter, we describe the results of the literature searches, and then present the results of each Key Question (KQ). We were unable to identify any studies that addressed KQ 3 (provider characteristics).

A list of acronyms and abbreviations used in this report is available following the list of references, along with a glossary of selected terms. The Appendices include Appendix A, Literature Search Methods; Appendix B, Full-length Review of Excluded Studies; Appendix C, Risk of Bias Assessments; Appendix D, Study Selection Criteria and Description of Treatment; Appendix E, Baseline Demographic and Tumor Characteristics; Appendix F. Evidence Tables; and Appendix G, Ongoing Clinical Trials.

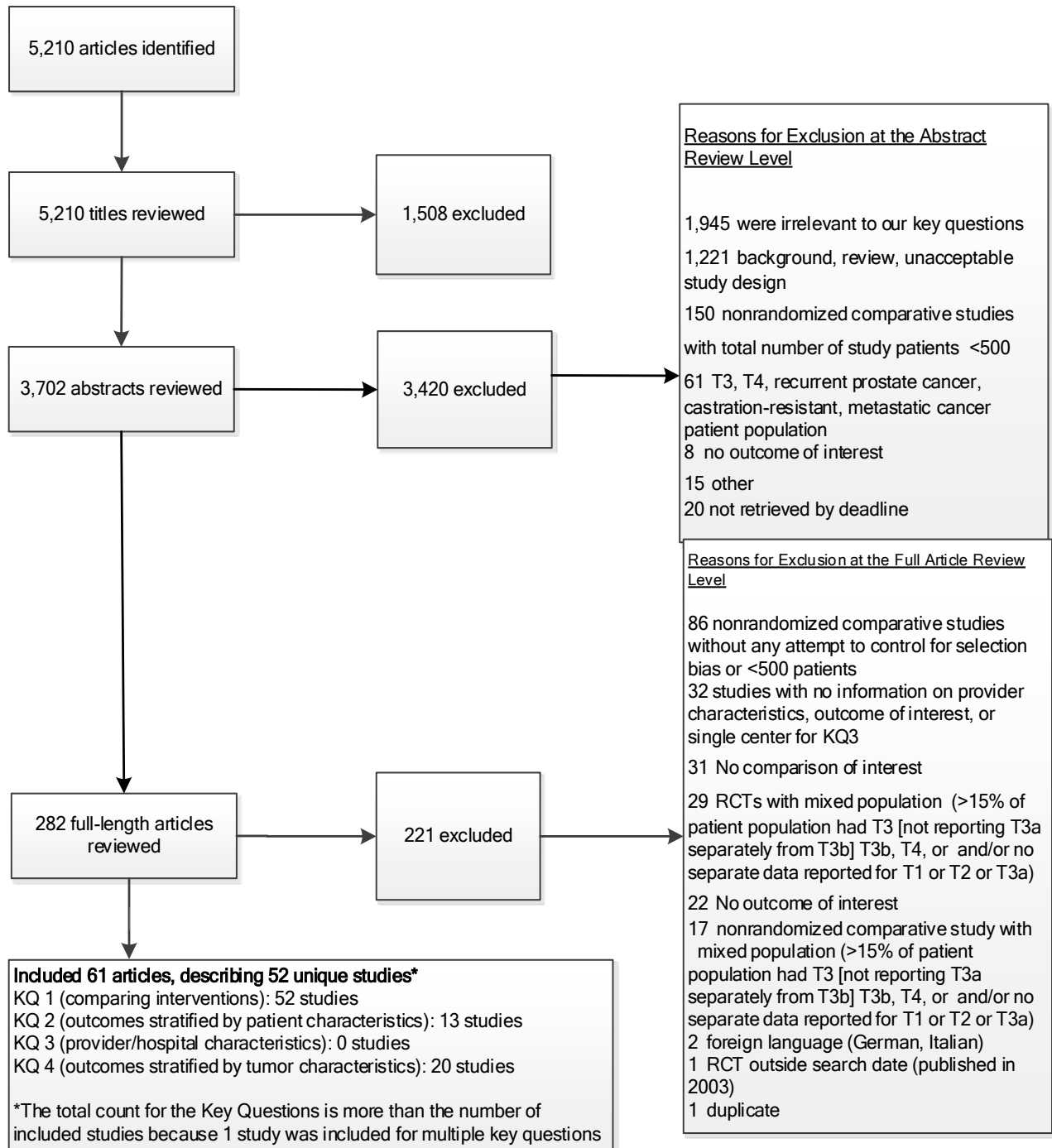
Studies that addressed KQ 1 reported data for patient-oriented outcome measures such as overall survival, all-cause mortality, prostate cancer–specific mortality, quality of life, and adverse events. None of the studies that addressed either KQ 2 or KQ 4 reported on adverse events based on patient subgroups (i.e., patient characteristics or tumor characteristics). All the studies that addressed either KQs 2 or 4 reported data only for outcome measures such as overall survival, all-cause mortality, or prostate cancer–specific mortality. We did not identify any publications of interest that addressed KQ 3 (studies with information on provider or hospital characteristics that evaluated efficacy of the different treatment options in men with clinically localized prostate cancer).

## Results of Literature Searches

Our searches of the literature identified 5,210 potentially relevant articles. We excluded 1,508 articles by reviewing the titles, 3,420 by reviewing the abstracts, and 221 by reviewing the full-length articles. Figure 2 is a flow chart that describes in detail the exclusion process and the reasons for the exclusion at each review level.

The remaining 61 publications describing 52 unique studies made up the evidence base for this review. All 52 studies met the inclusion criteria for review for KQ 1. Thirteen of these studies also met the inclusion criteria for KQ 2, and 20 of them further met the inclusion criteria for KQ 4. Appendix B lists studies excluded after full-length review.

**Figure 2. Literature flow diagram**



## Key Question 1. Comparative Risks and Benefits of Therapies for Clinically Localized Prostate Cancer

### Key Points

- Progression to metastases was reduced at 12 years among patients undergoing radical prostatectomy (RP) compared to those receiving watchful waiting (WW; based on two medium risk-of-bias randomized trials).<sup>15,25,33,34</sup> (Strength of evidence: moderate.)
- Urinary incontinence (as an indirect measure of quality of life [QOL]) was lower among patients receiving WW compared with those undergoing RP (based on 1 medium and 1 high risk-of-bias randomized trial).<sup>15,25,33,34</sup> (Strength of evidence: low.)
- Overall survival was higher in patients treated with three-dimensional conformal radiotherapy (3D-CRT) plus androgen-deprivation therapy (ADT) than in patients treated with 3D-CRT alone (based on a single low risk-of-bias randomized study).<sup>35</sup> (Strength of evidence: low.)
- All-cause mortality was lower in patients treated with 3D-CRT plus ADT compared with patients treated with 3D-CRT alone (based on a single low risk-of-bias randomized study).<sup>35</sup> (Strength of evidence: low.)
- Prostate cancer-specific mortality was lower in patients treated with 3D-CRT plus ADT than in patients treated with 3D-CRT alone (based on a single low risk-of-bias randomized study).<sup>35</sup> (Strength of evidence: low.)
- For other outcomes/comparisons, strength of evidence from the randomized studies is insufficient to draw any conclusion.
- All-cause mortality was significantly lower in patients treated with RP than in patients treated with external beam radiation therapy (EBRT);<sup>36-40, 42</sup> based on consistent evidence from 6 nonrandomized comparison studies with high risk of bias). (Strength of evidence: low.)
- Prostate cancer-specific mortality was significantly lower in patients treated with RP than in patients treated with EBRT<sup>37-42</sup> (based on consistent evidence from 6 nonrandomized comparison studies with high risk of bias). (Strength of evidence: low.)

### Detailed Synthesis

The main treatment options for clinically localized prostate cancer are identified and summarized in Table 5. In this section, we summarize findings from randomized controlled trials (RCTs) and describe additional data from the nonrandomized comparative studies.

### Randomized Controlled Trials

#### Study Characteristics

General information, including detailed baseline demographic and tumor characteristics about the 8 RCTs in 16 unique publications included for this KQ, appears in Table E-1 of Appendix E. The eight RCTs included 4,375 men at enrollment (1,131 underwent RP, 1,114 received EBRT alone, 987 received EBRT plus ADT, 715 were managed by observation or WW, 122 received cryotherapy, 104 received CRT alone, 102 received CRT plus ADT, and 100 received BT). The RCTs enrolled between 120 and 1,979 patients each.

Five studies reported the mean age of patients by treatment group. The mean age ranged from 60.0 to 68.4 years; three studies reported median patient age that ranged from 68.6 to 74.0 years. Five studies did not report the race or ethnicity of enrolled patients. For the three studies reporting this characteristic the percentage of white patients ranged from 60% to 100%.<sup>25,43,44</sup> Four studies did not report the comorbidity status of enrolled patients. One study each reported comorbidity as American Society of Anesthesiology Scores,<sup>45</sup> percentage with a variety of cardiovascular diseases,<sup>25</sup> percentage with any comorbidity,<sup>43</sup> and Adult Comorbidity Evaluation Scores.<sup>35</sup>

All eight trials reported prostate-specific antigen (PSA) levels and Gleason scores of enrolled patients and included at least 85% with clinical T stage T3a or lower as required for inclusion in this comparative effectiveness review. The population for seven studies was patients with T1 and T2 prostate cancer.<sup>15,25,35,43-46</sup> One study<sup>47</sup> included patients with T2a, T2b, T2c, T3a, and T3b,c prostate cancer. Other tumor characteristics were reported inconsistently, including prostate volume, risk category, differentiation, World Health Organization grade, presence of positive margins, and percentage with extracapsular extension at histology. Five studies<sup>35,44-47</sup> reported patient exclusion criteria, four of which excluded patients with a history of radiation exposure.<sup>35,44,45,47</sup>

Two studies were conducted in the United States,<sup>25,35</sup> three in Italy,<sup>44-46</sup> one in Canada<sup>47</sup>; and the remaining two studies were international.<sup>33,43</sup> Three were multicenter RCTs<sup>25,33,43</sup> and five<sup>35,44-47</sup> were single-center RCTs.

One of the included RCTs provided details of expertise of the participating surgeon. The surgeon had performed more than 600 laparoscopic radical prostatectomies (LRPs) and 100 robot-assisted radical prostatectomies before completing the RCT comparing these two surgical techniques.<sup>45</sup> One study<sup>33</sup> reported that radical excision of the tumor was given priority over nerve-sparing, one study<sup>25</sup> reported that the surgical technique was at the discretion of the surgeon, and two studies<sup>44,46</sup> reported that a bilateral nerve-sparing technique was performed on all patients by a single surgeon.

Radiation therapy also varied among the included studies. In one study,<sup>43</sup> radiotherapy was administered in daily 1.8 Gray (Gy) fractions, with 46.8 Gy delivered to the prostate and regional lymph nodes, followed by 19.8 Gy to the prostate. Another study reported a prescribed radiation dose of Gy was increased to 70 Gy in early 2000 and finally to 73.5 Gy in late 2002 in response to changing standards of practice.<sup>47</sup> One study<sup>44</sup> administered brachytherapy (BT) using a transperineal template-guided peripheral loading real-time technique and seeds of iodine 125.

ADT also varied among included studies. One study<sup>43</sup> reported flutamide (250 mg) was administered, and another study<sup>35</sup> did not report the specific dose of the flutamide. Patient enrollment criteria and description of treatment details appear in Table D-1 of Appendix D.

The treatment comparisons assessed in the eight RCTs included RP with observation or WW (2 studies),<sup>25,33</sup> two different forms of RP (2 studies),<sup>45,46</sup> RP with BT,<sup>44</sup> 3D-CRT versus 3D-CRT plus ADT,<sup>35</sup> EBRT versus EBRT plus ADT,<sup>35,43</sup> and EBRT versus cryotherapy.<sup>47</sup> Three studies reported all-cause mortality,<sup>25,33,35</sup> five studies reported prostate cancer-specific mortality,<sup>15,25,35,43,47</sup> three studies reported overall survival,<sup>35,43,47</sup> five studies in six publications measured QOL,<sup>15,43-45,47,48</sup> six studies reported adverse events,<sup>15,25,43,45-47</sup> three studies reported distant metastases,<sup>15,25,43</sup> five studies reported on biochemical failure,<sup>35,43,44,47,49</sup> and two studies reported biochemical disease-free survival.<sup>45,50</sup>

See Table 12 and Table 13 for a summary of the patient characteristics, treatments assessed, outcomes reported, and duration of followup.



**Table 12. Overview of randomized controlled trials across primary treatment categories (4 trials):  
Key Question 1**

Study	Interventions and Number of Patients	Subjects	Outcomes	Duration
Wilt et al. 2012 <sup>25</sup> , Wilt et al. 2009 <sup>24</sup> Prostate Intervention vs. Observation Trial (PIVOT)	RP (364 patients) vs. observation (367 patients)	Age 75 years or younger, T1–T2NxM0, PSA levels <50 ng/mL	All-cause mortality PCSM Distant metastases Adverse events	Median followup of 10 years
Bill-Axelsson et al. 2013 <sup>48</sup> , Bill-Axelsson et al. 2011 <sup>33</sup> , Johansson et al. 2011, <sup>51</sup> Holmberg et al. 2012, <sup>34</sup> and Bill-Axelsson et al. 2008 <sup>15</sup> Scandinavian Prostate Cancer Group-4 (SPCG-4) trial	RP (347 patients) vs. watchful waiting (348 patients)	Age 77 years or younger, T1b, T1c, T2, PSA levels <50 ng/mL	Overall mortality PCSM Distant metastases Adverse events QOL	Median followup of 15 years
Giberti et al. 2009 <sup>44</sup>	RRP (100 patients) vs. brachytherapy using iodine 125 (100 patients)	Caucasian men, T1c or T2a, PSA value ≤10 ng/mL and Gleason sum ≤6)	Biochemical disease-free survival QOL Adverse events	Followup of 5 years
Donnelly et al. 2010 <sup>47</sup> Same study as Robinson et al. 2009 <sup>52</sup>	EBRT (122 patients) vs. cryotherapy (122 patients)	Median age 68.6 years (EBRT) and 69.4 years (cryotherapy), T2a, T2b, T2c, T3a, T3b,c prostate adenocarcinoma, PSA levels ≤20 ng/mL	Overall survival PCSM Biochemical failure QOL Adverse events	3years, 5 years, and 7 years

**Note:** See Tables 1–3 for definitions of T, N, M cancer stages.

**Abbreviations:** EBRT=external beam radiation therapy; PCSM=prostate cancer-specific mortality; PSA=prostate-specific antigen; QOL=quality of life; RP=radical prostatectomy; RRP=radical retropubic prostatectomy.

**Table 13. Overview of randomized controlled trials within primary treatment categories (4 trials): Key Question 1**

Study	Interventions and Number of Patients	Subjects	Outcomes	Duration
Porpiglia et al. 2012 <sup>45</sup>	RARP: 60 patients vs. LRP: 60 patients	Age 40–75 years, PCa T1 through T2N0M0 clinically staged according to TNM 2009	Biochemical recurrence-free survival QOL Adverse events	Followup of 1 year
Jones et al. 2011 <sup>43</sup>	EBRT (992 patients) vs. EBRT plus short-term ADT (987 patients)	Age 71 years or younger, T1b, T1c, T2a, T2b prostate adenocarcinoma, PSA levels ≤20 ng/mL	Overall survival PCSM Biochemical failure Distant metastases QOL Adverse events	Median followup of 9.1 years
D'Amico et al. 2008 <sup>35</sup> , Nguyen et al. 2010 <sup>53</sup>	3D-CRT (104 patients) vs. 3D-CRT plus ADT (102 patients)	Age <70, 70–75, and >75 years, PSA ≤4 up to ≥20, Gleason score ≤6 to 10, T1b–T2b patients (T1, T2 patients who had at least a 10-year life expectancy excluding death from prostate cancer)	Overall survival All-cause mortality PCSM	Median followup of 7.6 years
D'Amico et al. 2008 <sup>49</sup> Study is a subgroup analysis of the 2008 D'Amico study <sup>35</sup> and Nguyen et al. 2010 <sup>53</sup>	3D-CRT (104 patients) vs. 3D-CRT plus 6 months of both LHRH and antiandrogen vs. 3D-CRT (73 patients) plus 6 months of both LHRH and less than 6 months of antiandrogen (29 patients)	Age <70, 70–75, and >75 years, PSA ≤4 up to ≥20, Gleason score ≤6 to 10, T1b–T2b patients (T1, T2 patients who had at least a 10-year life expectancy excluding death from prostate cancer)	Biochemical failure	Median followup 8.2 years
Martis et al. 2007 <sup>46</sup>	Radical retropubic prostatectomy (100 patients) vs. radical perineal prostatectomy (100 patients)	T1, T2	Adverse events	Followup of 2 years

**Abbreviations:** ADT=Androgen-deprivation therapy; EBRT=external beam radiation therapy; 3D-CRT=three-dimensional conformal radiation therapy; LRP=laparoscopic radical prostatectomy; LHRH=luteinizing hormone-releasing hormone; PCSM=prostate cancer-specific mortality; PSA=prostate-specific antigen; QOL=quality of life; RARP=robot-assisted radical prostatectomy.

## Risk of Bias

Our risk-of-bias (ROB) assessments for the eight studies appear in Table C-1 of Appendix C. Seven of the eight RCTs were categorized as medium ROB for all outcomes excluding the QOL outcome. Only D'Amico et al. received a rating of low ROB.<sup>35</sup> Common reasons for assigning a medium rating to the studies were lack of concealment of allocation, failure to use an intent-to-treat analysis, and/or less than 85% of patients had available data at the timepoint of interest. All eight RCTs also reported QOL. Five studies reporting QOL received a rating of high ROB because in addition to the limitations noted above, the study did not blind or failed to report the blinding status of outcome assessors for this subjective outcome.<sup>33,43,45-47</sup> Gilberti et al. and Wilt et al. each received a rating of medium ROB for the QOL outcome because they were blinded RCTs but with an additional flaw such as less than 85% of patients had available data at the

timepoint of interest (Wilt) or intention-to-treat analysis was not reported (Gilberti).<sup>25,44</sup> D'Amico et al. received a low-ROB rating for the QOL outcome.<sup>35</sup>

## **Findings**

All abstracted data for the outcome measures reported by RCTs that address this KQ appear in Table F-1 (all-cause mortality), Table F-3 (overall survival), Table F-5 (prostate cancer–specific mortality), Table F-7 (biochemical failure), Table F-9 (biochemical progression–free survival), Table F-11 (progression to metastasis), Table F-13 (QOL), and Table F-15 (reported adverse events) of Appendix F. Table 14 summarizes major findings reported by the RCTs and is intended to provide a roadmap to the abstracted data, including the key statistics, for each comparison and reported outcome.

**Table 14. Major findings reported by randomized controlled trials for Key Question 1**

Treatments Being Compared	Outcome	Evidence Base	Major Findings Reported in the Study	Detailed Results Abstracted
RP vs. WW	All-Cause Mortality	<p>SPCG-4 Bill-Axelsson et al.<sup>15,33,34</sup></p> <p>PIVOT Wilt et al.<sup>25</sup></p>	<p>SPCG-4: All-cause mortality was lower among men who were treated with RP than those in WW at the 15-year followup. The SPCG-4 reported a statistically significant reduction for all-cause mortality among men who underwent RP (RR 0.75; 95% CI, 0.61 to 0.92) and a 6.6% ARR (95% CI, -1.3 to 14.5; 47.8% deaths in the RP vs. 57.8% deaths in WW) after 15-year followup.</p> <p>At 12-year followup, the all-cause specific mortality was RR 0.84, 95% CI, 0.65 to 1.03 and a 4.6% ARR (-1.1 to 10.5; 39.5% deaths in the RP vs. 44.8% deaths in WW).</p> <p>PIVOT: No significant reduction in all-cause mortality among men who were treated with RP compared with WW after 12-year followup (HR 0.88; 95% CI, 0.71 to 1.08) and an ARR of 2.9 % (95% CI, -4.1% to 10.3; 47% deaths in RP vs.49.9% deaths in WW).</p>	Table F-1 of Appendix F
RP vs. WW	PCSM	<p>SPCG-4 Bill-Axelsson et al.<sup>15,33,34</sup></p> <p>PIVOT Wilt et al.<sup>25</sup></p>	<p>SPCG-4: PCSM was lower among men who were treated with RP than those in WW at 12- and 15-year followup periods in the WW group.</p> <p>The SPCG-4 reported a statistically significant reduction for PCSM among men who underwent RP (RR 0.62; 95% CI, 0.44 to 0.87) and a 6.1% ARR (95% CI, 0.2% to 12.0%; 14.6% deaths in RP vs. 20.7% deaths in WW) after 15-year followup.</p> <p>At 12-year followup, the PCSM was also reduced among men who underwent RP compared with WW (RR 0.65; 95% CI, 0.45 to 0.94). The ARR was 5.4% (95% CI -0.2% to 11.1%) with 12.5% deaths in RP vs. 17.9% deaths in WW.</p> <p>PIVOT: No significant reduction in PCSM among men who were treated with RP compared with WW after 12-year followup (HR 0.63; 95% CI, 0.36 to 1.09) and an ARR of 3.0% (95% CI, -1.1 to 6.5; 4.4% deaths in RP vs. 7.4% deaths in WW).</p>	Table F-5 of Appendix F
RP vs. WW	Progression to metastases	<p>SPCG-4 Bill-Axelsson et al.<sup>15,33,34</sup></p> <p>PIVOT Wilt et al.<sup>25</sup></p>	<p>SPCG-4: The percentage of patients with bone metastases at median followup 12 years (RR 0.65; 95% 0.47 to 0.88) or 15 years (RR 0.59; 95% CI, 0.45 to 0.79) was lower for the RP group than the WW group</p> <p>PIVOT: The percentage of patients with bone metastases at median followup 10 years was lower for the RP group than the WW group (HR 0.40; 95% 0.22 to 0.70)</p>	Table F-11 of Appendix F

**Table 14. Major findings reported by randomized controlled trials for Key Question 1 (continued)**

Treatments Being Compared	Outcome	Evidence Base	Major Findings Reported in the Study	Detailed Results Abstracted
RP vs. WW	QOL	SPCG-4 Johansson et al. <sup>51</sup> Bill-Axelsson et al. <sup>48</sup>  PIVOT Wilt et al. <sup>25</sup>	SPCG-4: At a median followup of 12.2 years (range 7–17 years), no significant differences exist in patient-reported anxiety, depressed mood, well-being, QOL, and sense of meaningfulness between the RP and WW groups. At 8-year followup, men who underwent RP regularly reported more urinary leakage; impaired erection, intercourse, and libido; and fewer obstructive voiding symptoms. At the 4-year followup, the prevalence of urinary leakage was greater after RP than with WW, while erectile function did not differ between groups. Common adverse events in 1 year after RP included urinary leakage and impotence. PIVOT: At 2-year followup, more men in the RP group than in the WW group reported erectile dysfunction and urinary incontinence. Patient-reported bowel dysfunction, however, was comparable in both groups.	Table F-13 in Appendix F
RP vs. WW	Adverse events	PIVOT Wilt et al. <sup>25</sup>	Reported adverse events within 30 days after RP included 1 death, wound infection (4.3%), surgical repair, urinary tract infection, and bleeding requiring blood transfusion.	Table F-15 in Appendix F
RARP vs. LRP	Biochemical recurrence-free survival	Porpiglia et al. <sup>45</sup>	The authors report that there was no difference in PSA values between the 2 groups at any visit through the 1-year followup. PSA values were not reported in the publication. BRFS rates were 98% in the RARP group and 92.5% in the LRP, a non-significant difference.	Table F-7 in Appendix F
RARP vs. LRP	QOL	Porpiglia et al. <sup>45</sup>	Continence rates were significantly higher in the RARP through 1 year of followup, 95% and 83.3%, respectively. Among potent patients undergoing nerve-sparing techniques, 80% of RARP patients and 54.2% of LRP patients experienced a recovery of erections at the 1-year followup.	Table F-13 in Appendix F
RARP vs. LRP	Adverse events	Porpiglia et al. <sup>45</sup>	This study reported Clavien medical and surgical adverse events in the early (30 days) and intermediate (31–90 day) period and graded them as minor or major. No statistical analysis or conclusions could be drawn given how the data were reported.	Table F-15 in Appendix F
RPP vs. RRP	QOL	Martis et al. <sup>46</sup>	At 6 and 24 months, no significant between-group difference for urinary continence; significantly more patients in the RRP group had erectile function at 24 months.	Table F-13 in Appendix F
RRP vs. BT	Biochemical disease-free survival	Giberti et al. <sup>44</sup>	At 5-year followup, the rates of biochemical disease-free survival were comparable for the RRP and BT groups.	Table F-7 in Appendix F

**Table 14. Major findings reported by randomized controlled trials for Key Question 1 (continued)**

Treatments Being Compared	Outcome	Evidence Base	Major Findings Reported in the Study	Detailed Results Abstracted
RRP vs. BT	QOL	Giberti et al. <sup>44</sup>	<p>A deterioration of physical and emotional functions occurred in both groups at the 1-year followup period. No differences between the groups were found in either the physical or emotional functions after 5-year followup.</p> <p>At 6-month followup, commonly reported events include urinary incontinence for the RRP group and urinary irritation and proctitis for the BT group. Both groups reported falling erectile function at 6-month followup. No difference was found in erectile function and urinary disorders at the 5-year followup period in either study group.</p>	Table F-13 in Appendix F
3D-CRT vs. 3D-CRT plus ADT	Overall survival	D'Amico et al. <sup>35</sup> Same study as Nguyen et al. <sup>53</sup>	<p>The study reported that overall survival was higher for men in the 3D-CRT plus ADT group than in men receiving 3D-CRT alone. The Kaplan-Meier 8-year survival estimate was 74% in the 3D-CRT plus ADT group compared with 61% in the 3D-CRT-alone group.</p>	Table F-3 in Appendix F
3D-CRT vs. 3D-CRT Plus ADT	PCSM	D'Amico et al. <sup>35</sup> Same study as Nguyen et al. <sup>53</sup>	<p>The study reported that PCSM at a median followup of 7.6 years favored 3D-CRT plus ADT over 3D-CRT monotherapy: HR: 4.1 (1.4 to 12.1), p=0.01.</p>	Table F-5 of Appendix F
3D-CRT vs. 3D-CRT plus 6 months of both LHRH agonist and antiandrogen flutamide vs. 3D-CRT plus 6 months of both LHRH agonist and less than 6 months of antiandrogen flutamide	Biochemical failure	D'Amico et al. <sup>49</sup> Subgroup analysis of <sup>35,53</sup>	<p>After a median followup of 8.2 years, estimates of PSA recurrence were significantly lower in men who received 6 months of antiandrogen flutamide compared with those who received no ADT.</p> <p>After a median followup of 8.2 years, there was no significant difference in the PSA recurrence between men who received antiandrogen flutamide for 6 months compared with those who received less than 6 months of antiandrogen flutamide.</p> <p>After a median followup of 8.2 years, there was no significant difference in the PSA recurrence between men who received less than 6 months of antiandrogen flutamide compared with those who received no ADT.</p>	Table F-7 of Appendix F
EBRT vs. EBRT plus ADT	Overall survival	Jones et al. <sup>43</sup>	<p>Overall survival was higher for men in the EBRT plus ADT group than in men receiving EBRT alone.</p> <p>The 10-year overall survival was increased to 62% in the EBRT plus short-term ADT group compared with 57% in the EBRT alone group.</p>	Table F-3 in Appendix F

**Table 14. Major findings reported by randomized controlled trials for Key Question 1 (continued)**

Treatments Being Compared	Outcome	Evidence Base	Major Findings Reported in the Study	Detailed Results Abstracted
EBRT vs. EBRT plus ADT	PCSM	Jones et al. <sup>43</sup>	Authors reported a reduction in the PCSM among the men who received EBRT plus ADT compared with EBRT alone.	Table F-5 of Appendix F
EBRT vs. EBRT plus ADT	Biochemical failure	Jones et al. <sup>43</sup>	The 10-year rate of biochemical failure was reduced to 26% in the EBRT plus ADT group from 41% in the EBRT alone group.	Table F-7 of Appendix F
EBRT vs. EBRT plus ADT	Progression to metastases	Jones et al. <sup>43</sup>	The 10-year cumulative incidence of distant metastases was reduced to 6% in the EBRT plus ADT group from 8% in the EBRT alone group.	Table F-11 of Appendix F
EBRT vs. EBRT plus ADT	QOL	Jones et al. <sup>43</sup>	At 1 year, 31% of the patients in the EBRT alone group compared with 21% in the EBRT plus ADT group reported always/almost always (effect of short-term ADT on erectile function) on the Sexual Adjustment Questionnaire.	Table F-13 in Appendix F
EBRT vs. EBRT plus ADT	Adverse events	Jones et al. <sup>43</sup>	The men in the EBRT alone group had an increased incidence of grade 3 or higher acute and late gastrointestinal toxicity occurring up to 90 days after the start of EBRT.	Table F-15 in Appendix F
EBRT vs. cryotherapy	Overall survival	Donnelly et al. <sup>47</sup>	There was no difference in overall survival at 5 years between both groups (EBRT 88.5% vs. cryotherapy 89.7%; difference 1.2 (-6.8–9.2)).	Table F-3 in Appendix F
EBRT vs. cryotherapy	PCSM	Donnelly et al. <sup>47</sup>	There was no difference in PCSM at 5 years between both groups (96.1% vs. 96.4%; Difference 0.3 (-4.8–5.4)).	Table F-5 of Appendix F
EBRT vs. cryotherapy	Biochemical failure	Donnelly et al. <sup>47</sup>	Biochemical failure at 3 years (% reaching end point): 23.7% (EBRT) vs. 23.9% (cryotherapy); Difference 0.2 (-10.8 – 11.2). Biochemical failure at 5 years (% reaching end point): 37.7% (EBRT) vs. 31% (cryotherapy); Difference -6.7 (-19.4 – 6.0) Biochemical failure at 7 years (% reaching end point): 43.9% (EBRT) vs. 33.2% (cryotherapy); Difference -0.7 (-24.4 – 2.9).	Table F-7 of Appendix F
EBRT vs. cryotherapy	QOL	Robinson et al. <sup>52</sup> Same study as Donnelly et al. <sup>47</sup>	At 3 years, men in the EBRT group experienced slightly lower urinary function scores compared with cryotherapy (88.6 vs. 93.0, p=0.049). At 3 years, there was no difference in bowel function scores between men in the EBRT and cryotherapy group (84.1 vs. 88.1, p=0.092). At 3 years, men in the cryotherapy group experienced lower sexual function scores compared with EBRT (16.0 vs. 36.7, p<0.001).	Table F-13 in Appendix F

**Table 14. Major findings reported by randomized controlled trials for Key Question 1 (continued)**

Treatments Being Compared	Outcome	Evidence Base	Major Findings Reported in the Study	Detailed Results Abstracted
EBRT vs. cryotherapy	Adverse events	Donnelly et al. <sup>47</sup>	14 patients suffered 16 grade 3 adverse events in the EBRT group. 12 patients suffered 13 grade 3 adverse events in the cryotherapy group.	Table F-15 in Appendix F

**Abbreviations:** ADT=Androgen-deprivation therapy; ARR=absolute risk reduction; BT=brachytherapy; EBRT=external beam radiation therapy; CI=confidence interval; 3D-CRT=three-dimensional conformal radiation therapy; HR=hazard ratio; LHRH=luteinizing hormone-releasing hormone; LRP=laparoscopic radical prostatectomy; PCSM=prostate cancer-specific mortality; PIVOT=Prostate Cancer Intervention Versus Observation Trial; PSA=prostate-specific antigen; QOL=quality of life; RARP=robot-assisted radical prostatectomy; RP=radical prostatectomy; RPP=radical perineal prostatectomy; RRP=radical retropubic prostatectomy; RR=relative risk; SPCG-4=Scandinavian Prostate Cancer Group-4 study; WW=watchful waiting.



## Nonrandomized Comparative Studies

### Study Characteristics

General information, including baseline demographic and tumor characteristics of the 44 nonrandomized comparative studies in 45 unique publications (of 500 or more patients) that addressed this KQ, appears in Table E-2 of Appendix E. Enrollment ranged from 614 to 275,200 patients. Eleven of the included studies drew their sample from the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) database.

Of the men enrolled and treated with surgery, 164,432 underwent RP, 15,686 received RP plus radiation, 7,537 received radical retropubic prostatectomy (RRP), 5,852 received robotic-assisted laparoscopic radical prostatectomy (RALRP), and 2,208 LRP.

Among the nonsurgical patients enrolled, 1,959 received radiation, 164,203 EBRT monotherapy, 64,116 received BT monotherapy, 24,168 received combination therapy with BT plus EBRT, 924 received combination therapy with BT plus intensity-modulated radiation therapy (IMRT), 13,295 received IMRT monotherapy, 13,815 received 3D-CRT monotherapy, 2,264 received 3D-CRT plus IMRT, 1,039 were treated with external beam image-guided radiation therapy (EB-IGRT), 734 were treated with image-guided radiation therapy (IGRT), 10,820 received ADT monotherapy, 1,024 received cryotherapy monotherapy, 6,775 received BT plus hormone therapy combination therapy, 53,322 were managed by observation, 324 were managed by WW, 685 proton therapy, 260 received high-intensity focused ultrasound (HIFU) monotherapy, and 270 received HIFU plus ADT combination therapy.

Patient followup across the studies ranged from 1.09 years<sup>54</sup> to 15 years.<sup>38,55</sup> Patients ranged in age from 58<sup>56</sup> to 85 years.<sup>57-60</sup> Forty of the 44 studies were conducted in the United States, and one each was conducted in Canada,<sup>41</sup> Spain,<sup>61</sup> France,<sup>62</sup> and Japan.<sup>63</sup>

Regarding specific treatment interventions, the most commonly compared procedures were RALRP versus RRP (10 studies).<sup>54,56,64-71</sup> The remaining studies compared the following:

- RP versus EBRT<sup>38,41,55</sup>
- RP versus observation<sup>72,73</sup>
- RRP versus 3D-CRT versus BT<sup>61</sup>
- RRP versus LRP<sup>74</sup>
- RP versus EBRT (3D-CRT or IMRT) versus BT<sup>37,75</sup>
- RP versus EBRT versus BT<sup>40</sup>
- RRP versus RALRP versus LRP<sup>70</sup>
- BT plus EBRT versus BT plus ADT<sup>76</sup>
- BT plus IMRT vs. IMRT<sup>77</sup>
- RP versus robotic RP versus cryotherapy versus BT<sup>71</sup>
- ADT versus observation<sup>78</sup>
- ADT versus RP<sup>79</sup>
- BT versus cryotherapy<sup>57</sup>
- BT versus image guided-EBRT versus high-dose-rate EBRT<sup>80</sup>
- IMRT versus 3D-CRT<sup>81</sup>
- IMRT versus proton beam therapy versus 3D-CRT<sup>58</sup>
- BT versus BT plus ADT<sup>82,83</sup>
- BT versus EBRT versus BT plus EBRT<sup>84</sup>
- EBRT versus observation or WW<sup>59</sup>

- EBRT versus BT versus conservative management (observation)<sup>60</sup>
- RP versus EBRT versus observation<sup>38,42</sup> or WW<sup>36</sup>
- RP (RRP or LRP or RALRP) versus EBRT (3D-CRT or IMRT) versus BT<sup>85</sup>
- RRP versus LRP versus RALRP<sup>56</sup>
- RALRP versus LRP<sup>62</sup>
- IGRT versus BT<sup>86</sup>
- RP versus EBRT versus ADT<sup>39</sup>
- RRP versus 3D-CRT<sup>87</sup>
- 3D-CRT versus IMRT versus BT versus EBRT plus BT<sup>88</sup>
- HIFU versus HIFU plus ADT<sup>63</sup>
- BT versus BT plus IMRT<sup>89</sup>
- RP versus RP plus radiation versus EBRT versus EBRT plus BT versus BT versus radiation<sup>90</sup>

A great deal of variability existed in the level of detail provided on treatment techniques in the nonrandomized comparative studies. As noted above, studies employed several variations of RP, from open to robot-assisted laparoscopic and with or without nerve-sparing techniques. The only study to describe how cryotherapy was delivered reported that it was delivered with a third-generation delivery system.<sup>71</sup> BT was delivered using a variety of methods, including the following:

- Intraoperative treatment planning with ultrasound guidance with a median dose of 14,400–14,500 cGy<sup>75</sup>
- Either a high-dose or low-dose rate<sup>77,80</sup>
- Either iodine 125 or palladium 103<sup>82</sup>
- A modified peripheral loading dose rate technique with permanent palladium seeds delivering an average of 125 Gray (Gy) dose<sup>71</sup>

Two studies provided details about how EBRT was delivered. In one study, EBRT was delivered at a median dose of 7,400–7,800 cGy; in the other study<sup>75</sup> it was delivered at a median dose of 78 Gy (range 59.4 to 81.5) at 2 Gy per fraction.<sup>37</sup> One study reported the use of a ultra-high-dose IMRT using a five- to seven-field IMRT plan with 15MV photons to a dose of 86.4 Gy in 48 fractions of 1.8 Gy.<sup>77</sup> Study selection criteria and description of treatment appear in Table D-2 of Appendix D.

To be included in this report, a study must have enrolled a minimum of 85 percent of patients with clinically localized prostate cancer clinical T stage T1 through T3a and have reported results separately for these patients compared with patients with higher T stages. Six studies did not report Gleason scores,<sup>57,58,66,73,78,84</sup> seven studies did not report PSA levels,<sup>58,59,66,67,72,78,81</sup> and four studies,<sup>58,66,73,78</sup> did not report either Gleason scores nor PSA levels.

Eleven studies had an outcome measure of all-cause mortality,<sup>36-40,61,65,73,78,79,82</sup> 17 studies had an outcome measure of prostate cancer–specific mortality,<sup>37-42,59,68,72,73,75,76,78,79,84,86,87</sup> five studies had an outcome measure of overall survival,<sup>42,72,75,78,86</sup> six studies reported biochemical failure,<sup>36,56,62,65,86,88</sup> 13 studies reported biochemical progression–free survival,<sup>54,62-65,67-70,74,86,89,91</sup> and three studies reported progression to metastasis,<sup>65,68,88</sup> and 19 studies reported QOL and/or adverse events.<sup>37,55,57,58,62,63,65,66,68,71,77,80,81,83,85,88,90-92</sup> (see Table 15).

**Table 15. Overview of nonrandomized comparative studies (44 studies): Key Question 1**

Study	Number of Patients	Subjects	Outcomes	Duration
Alemezaffar et al. 2014 <sup>68</sup>	RALRP: 132 patients RRP: 468 patients	Mean age at diagnosis: RALRP: 67.2 years RRP: 65.4 years ≥1 of the following: myocardial infarction, coronary artery bypass or coronary angioplasty, confirmed angina, stroke, Parkinson disease, emphysema or chronic bronchitis, or diabetes RALRP: 18.8% Open RRP: 16.8% Median PSA: RALRP: 5.0 ng/mL Open RRP: 5.6 ng/mL	PCSM Progression to metastasis BRFS QOL	A minimum followup of 2 years
Mukherjee et al. 2014 <sup>37</sup>	RP: 5,805 patients EBRT: 2,183 patients BT: 2,936 patients	Median age at diagnosis (range): RP: 60 years (37–87) EBRT: 69 years (40–87) BT: 67 years (41–88) Median (range) PSA ng/mL: RP: 5.6 (0.03–228.5) EBRT: 9.1 (0.37–692.9) BT: 6.0 (0.18–82.91) Gleason: RP: ≤6: 60.4% 7: 30.8% ≥8: 7.7% Unknown: 1.1% EBRT: ≤6: 47.3% 7: 35.3% ≥8: 16.8% Unknown: 0.7% BT: ≤6: 58.5% 7: 36.4% ≥8: 5.0% Unknown: 0%	All-cause mortality PCSM Adverse events	3.05 years median followup

**Table 15. Overview of nonrandomized comparative studies (44 studies): Key Question 1 (continued)**

Study	Number of Patients	Subjects	Outcomes	Duration
DeGroot et al. 2013 <sup>41</sup>	RP: 458 patients (cohort) RP: 36 patients (cases) EBRT: 518 patients (cohort) EBRT: 78 patients (cases)	RP cohort: Mean age (SD): 62.8 years (6.1) PSA: ≤4: 12.5% >4 to ≤10: 57.0% >10 to ≤20: 30.6% Gleason score: 2–4: 23.6% 5–6: 53.3% 7: 23.1% RP cases Mean age (SD): 62.1 years (5.8) PSA <4: 13.9% >4 to <10: 38.9% >10 to <20: 47.2% Gleason score 2–4: 16.7% 5–6: 52.8% 7: 30.6% EBRT cohort Mean age (SD): 69.2 years (5.6) PSA <4: 15.8% >4 to <10: 43.8% >10 to <20: 40.4% Gleason score 2–4: 28.2% 5–6: 48.5% 7: 23.4% EBRT cases Mean age (SD): 67.7 years (5.7) PSA <4: 10.3% >4 to <10: 46.2% >10 to <20: 43.6% Gleason score 2–4: 23.1% 5–6: 38.5% 7: 23.1%	PCSM	Median followup 4.25 years

**Table 15. Overview of nonrandomized comparative studies (44 studies): Key Question 1 (continued)**

Study	Number of Patients	Subjects	Outcomes	Duration
Ferrer et al. 2013 <sup>91</sup> and Ferrer et al. 2008 <sup>61</sup>	RRP: 193 patients 3D-CRT: 194 patients BT: 317 patients	RRP Mean age (SD): 67.6 years (5.2) Mean PSA level (SD): 7.4 (2.7) Mean Gleason score (SD): 5.8 (0.8) 3D-CRT Mean age (SD): 67.1 years (5.2) Mean PSA level (SD): 7.0 (2.7) Mean Gleason score (SD): 5.3 (0.8) BT Mean age (SD): 66.9 years (5.2) Mean PSA level (SD): 6.8 (2.7) Mean Gleason score (SD): 5.1 (0.8)	All-cause mortality BPFS QOL	2- and 5-year followup
Hoffman et al. 2013 <sup>38</sup>	RP: 1,164 patients EBRT: 491 patients	RP Median age (IQR): 64 years (59–68) PSA <4.0: 9.8% 4.0–10.0: 61.0% >10.0: 29.2% Gleason score 2–4: 63.9% 5–7: 18.2% 8–10: 6.5% Unknown: 11.4% EBRT Median age (IQR): 69 years (64–71) PSA <4.0: 9.4% 4.0–10.0: 55.9% >10.0: 34.7% Gleason score: 2–4: 59.3% 5–7: 22.1% 8–10: 9.6% Unknown: 8.9%	All-cause mortality PCSM	15-year followup

**Table 15. Overview of nonrandomized comparative studies (44 studies): Key Question 1 (continued)**

Study	Number of Patients	Subjects	Outcomes	Duration
Liu et al. 2013 <sup>79</sup>	RP: 1,624 patients ADT: 1,624 patients	RP PSA Low ( $\leq 10$ ): 51.79% Median (11–20): 7.76% High ( $> 20$ ): 3.26% Positive: 22.91% Unknown: 14.29% Gleason score risk group: Moderately/well differentiated (Gleason score 2–7): 50.86% Poorly differentiated (Gleason score 8–10): 49.14% ADT PSA Low ( $\leq 10$ ): 51.79% Median (11–20): 7.76% High ( $> 20$ ): 3.26% Positive: 22.91% Unknown: 14.29% Gleason score risk group: Moderately/well differentiated (Gleason score 2–7): 50.12% Poorly differentiated (Gleason score 8–10): 49.88%	All-cause mortality PCSM	Median followup of 2.95 years and 2.87 years, respectively.

**Table 15. Overview of nonrandomized comparative studies (44 studies): Key Question 1 (continued)**

Study	Number of Patients	Subjects	Outcomes	Duration
Marina et al. 2013 <sup>86</sup>	IGRT: 734 BT: 282 patients	IGRT Median age (range): 71 years (47–91) Mean PSA (range): 5.9 (0.1–19.7) PSA <10: 576 (78%) 10–20: 158 (22%) Gleason score <6: 96 (13%) 3+4: 443 (61%) 4+3: 190 (26%) Intermediate risk factors 1=Gleason 7: 499 (68%) 1=PSA >10 ng/mL: 72 (10%) 1=T2b–c stage: 21 (3%) 2: 132 (18%) 3: 10 (1%) BT Median age (range): 66 years (40–83) Mean PSA (range): 6.6 (1.4–19.6) PSA <10: 207 (73%) 10–20: 75 (27%) Gleason score <6: 60 (23%) 3+4: 126 (48%) 4+3: 77 (29%) Intermediate risk factors, n (%) 1=Gleason 7: 146 (52%) 1=PSA >10 ng/mL: 27 (10%) 1=T2b–c stage: 25 (9%) 2: 74 (26%) 3: 10 (4%)	Overall survival Cause-specific mortality Biochemical failure BRFS Clinical progression	Median followup was 3.7 years for the IGRT group and 8.0 years for the BT group.

**Table 15. Overview of nonrandomized comparative studies (44 studies): Key Question 1 (continued)**

Study	Number of Patients	Subjects	Outcomes	Duration
Nepple et al. 2013 <sup>40</sup>	RP: 4,459 patients EBRT: 1,261 patients BT: 972 patients	RP Median age: 60 years Median PSA level: 6.96 Gleason score 5–6: 74% 7: 22% 8–10: 4% EBRT Median age: 68.3 years Median PSA level: 11.1 Gleason score 5–6: 55% 7: 33% 8–10: 12% BT Median age: 66.8 years Median PSA level: 6.66 Gleason score 5–6: 83% 7: 17% 8–10: 0.5%	All-cause mortality PCSM	Median 7.2-year followup
Pierorazio et al. 2013 <sup>70</sup>	RRP: 743 patients RALRP: 105 patients LRP: 65 patients	RRP Median age (range): 60 years (38–74) PSA median level (range): 6.65 (0.2–97) Gleason score 5–6: 19.1% 7: 40.7% 8: 25.8% 9–10: 14.5% RALRP Median age (range): 62 years (41–76) PSA median level (range): 6.4 (2.4–45) Gleason score 5–6: 29.8% 7: 35.6% 8: 22.1% 9–10: 12.5% LRP Median age (range): 60 years (43–74) PSA median level (range): 6.7 (1.6–50) Gleason score 5–6: 30.8% 7: 38.5% 8: 21.5% 9–10: 9.2%	BPFS	3-year followup
Resnick et al. 2013 <sup>55</sup>	RRP: 1,164 patients Radiotherapy: 491 patients	RRP Median age: 64 years Gleason score 2–4: 63.9% Radiotherapy Median age 69 years Gleason score 2–4: 63.9%	QOL	15-year followup



**Table 15. Overview of nonrandomized comparative studies (44 studies): Key Question 1 (continued)**

Study	Number of Patients	Subjects	Outcomes	Duration
Silberstein et al. 2013 <sup>67</sup>	RRP: 961 patients RALRP: 493 patients	RRP Median age (IQR): 5 years (4–8) Gleason score ≤6: 39% 7: 48% ≥8: 13% RALRP Median (IQR): 5 (4–7) Gleason score ≤6: 34% 7: 55% ≥8: 11%	BPFS	3-year followup
Spratt et al. 2013 <sup>77</sup>	IMRT plus BT: 400 patients IMRT: 470 patients	IMRT plus BT Median (IQR) age: 67 (62–72) Gleason score ≤6: 10% 7: 90% IMRT Median (IQR) age: 70 (64–74) Gleason score ≤6: 13% 7: 87%	AEs	Median: 5.3 years
Wirth et al. 2013 <sup>74</sup>	RRP: 600 patients LRP: 244 patients	RRP Age, median (IQR): 59 years (54–64) PSA, median level (IQR): 5.0 (3.8–6.8) Gleason score ≤6: 407 (67.9%) 7: 107 (28.3%) ≥8: 23 (3.8%) T stage T2: 516 (86.0%) T3: 84 (14.0%) LRP Age, median (IQR): 59 years (55–63) PSA, median level (IQR): 5.0 (3.8–6.8) Gleason score ≤6: 166 (68.1%) 7: 72 (29.8%) ≥8: 6 (2.5%) T stage T2: 213 (87.3%) T3: 31 (12.7%)	BPFS	Median followup of 6.6 years and 4.6 years, respectively

**Table 15. Overview of nonrandomized comparative studies (44 studies): Key Question 1 (continued)**

Study	Number of Patients	Subjects	Outcomes	Duration
Abdollah et al. 2012 <sup>59</sup>	EBRT: 46,521 patients Observation: 22,276 patients	EBRT Age 65–69 years: 24.1% 70–74 years: 41.4% 75–80 years: 34.5% Gleason score <6: 5.5% 6–7: 67.8% 8–10: 26.7% Observation Age 65–69 years: 21.8% 70–74 years: 34.0% 75–80 years: 44.2% Gleason score <6: 17.5% 6–7: 67.6% 8–10: 14.8%	PCSM	10-year followup
Abern et al. 2012 <sup>90</sup>	RP: 126,042 patients RP and radiation: 15,686 patients EBRT: 83,110 patients EBRT plus BT: 17,338 patients BT: 32,198 patients Radiation not otherwise specified: 826 patients	Age: not reported For total sample: Well differentiated: 14,861 patients Moderately differentiated: 183,558 patients Poorly differentiated: 76,230 patients Undifferentiated: 550 patients	AEs	Median followup 5.42 years (IQR 3 8.33 years) for entire cohort and 98 months for patients that developed bladder cancer
Barry et al. 2012 <sup>66</sup>	RALRP: 406 patients RRP: 220 patients	RALRP 66–69 years: 41.1%; 70–74 years: 43.8%; 75 years or older: 15.0% RRP 66–69 years: 38.2%; 70–74 years: 46.4%; 75 years or older: 15.5%	QOL	1.67 years
Kibel et al. 2012 <sup>75</sup>	RP: 6,485 patients, 2,843 at site 1 and 3,642 at site 2 3D-CRT plus IMRT: 2,264 patients, 1,638 at site 1 and 626 at site 2 BT: 1,680 patients, 1,330 at site 1 and 350 at site 2	RP Median age at site 1, 2: 60 years and 61 years bGS 2–6 at site 1, 2: 70% and 76% 3D-CRT plus IMRT Median age at site 1, 2: 69 years and 70 years bGS 2–6 at site 1, 2: 47% and 61% BT Median age site 1, 2: 68 years and 69 years bGS 2–6 at site 1, 2: 81% and 89%	Overall survival PCSM	10-year followup

**Table 15. Overview of nonrandomized comparative studies (44 studies): Key Question 1 (continued)**

Study	Number of Patients	Subjects	Outcomes	Duration
Masterson et al. 2012 <sup>69</sup>	RRP: 357 patients RALRP: 669 patients	Age at time of surgery: 61 Gleason sum (%) 5: 105 (10%) 6: 378 (37%) 7: 480 (47%) 3+4: 373 (78%) 4+3: 107 (22%) 8: 15 (1%) 9: 48 (5%) 10: 1 (<1%)	BDFS	5 years
Mohammed et al. 2012 <sup>80</sup>	BT: 417 patients (HDR=210, LDR=207) EB-IGRT: 1,039 patients EBRT plus HDR- BT: 447 patients	BT Mean age: 64.9 years Gleason score 4–6: 89% EB-IGRT Mean age: 70.8 years Gleason score 4–6: 53% EBRT plus HDR Mean age: 67.1 years Gleason score 4–6: 36%	AEs	Median 4.8-year followup
Nanda et al. 2012 <sup>83</sup>	Low-risk: BT without neoadjuvantive HT 3,517 patients BT with neoadjuvantive HT: 1,924 patients Intermediate-risk: BT without neoadjuvantive HT 2,225 patients BT with neoadjuvantive HT 2,140 patients High-risk: BT without neoadjuvantive HT: 353 patients BT with neoadjuvantive HT 1,007 patients Supplemental EBRT was used in 31% of the total sample	All patients Median age 71 years (IQR 66–75 years) Median PSA in ng/mL (IQR) Low-risk without HT: 6.0 (4.8–7.4) Low-risk with HT: 6.1 (4.9–7.6) Intermediate-risk without HT: 9.5 (6.2–12.1) Intermediate-risk with HT: 9.1 (6.0–12.4) High-risk without HT: 20.0 (8.2–26.7) High-risk with HT: 14.9 (7.2–27.0) Gleason score: Low-risk without HT: ≤6: 100% Low-risk with HT: ≤6: 100% Intermediate-risk without HT: ≤6: 42.8% 7: 57.2% Intermediate-risk with HT: ≤6: 38.5% 7: 61.5% High-risk without HT: ≤6: 31.7% 7: 17% 8–10: 51.3% High-risk with HT: ≤6: 18.3% 7: 22.4% 8–10: 59.3%	AEs	Median followup for low-, intermediate-, and high-risk patients was 4.1 years, 4.4 years, and 4.6 years respectively.

**Table 15. Overview of nonrandomized comparative studies (44 studies): Key Question 1 (continued)**

Study	Number of Patients	Subjects	Outcomes	Duration
Ploussard et al. 2012 <sup>62</sup>	LRP: 1377 patients RALRP: 1,009 patients	LRP Mean age 62.7 years Mean number of positive cores: 3.9 Biopsy Gleason score % 6: 65.7% 7: 29.4% 8–10: 4.9% RALRP Mean age 62.7 years Mean number of positive cores: 4.5 Biopsy Gleason score % 6: 60.1% 7: 33.0% 8–10: 6.9%	BRFS Biochemical recurrence QOL AEs	Mean followup LRP: 3.25 years RALRP: 1.28 years
Rosenberg et al. 2012 <sup>76</sup>	BT plus EBRT: 186 patients BT plus ADT: 621 patients	BT plus EBRT Median age: 67.8 years Gleason score ≤6: 24 (12.9%) 3+4: 97 (52.1%) 4+3: 65 (34.9%) BT plus ADT Median age: 72.5 years Gleason score ≤6: 254 (40.9%) 3+4: 252 (40.5%) 4+3: 115 (18.5%)	PCSM	4.4- and 4.8- year followup, respectively

**Table 15. Overview of nonrandomized comparative studies (44 studies): Key Question 1 (continued)**

Study	Number of Patients	Subjects	Outcomes	Duration
Sheets et al. 2012 <sup>58</sup>	IMRT: 6,666 patients 3D-CRT: 6,310 patients PBT: 685 patients	IMRT Age at diagnosis: 66–69 years: 1,338 (20.1%) 70–74 years: 2,415 (36.2%) 75 years or older: 2,913 (43.7%) Tumor grade well/moderately differentiated: 3,390 (50.9%) 3D-CRT Age at diagnosis: 66–69 years: 1,265 (20.1%) 70–74 years: 2,345 (37.2%) 75 years or older: 2,700 (42.8%) Tumor grade well/moderately differentiated: 3,850 (61.0%) PBT Age at diagnosis: 66–69 years: 248 (36.2%) 70–74 years: 233 (34.0%) 75 years or older: 204 (29.8%) Tumor grade well/moderately differentiated: 413 (60.3%)	AEs	Median followup for the IMRT vs. 3D-CRT was 3.67 years and 5.33 years, respectively. Median followup for IMRT vs. PBT was 3.83 years and 4.17 years, respectively.
Shen et al. 2012 <sup>84</sup>	BT: 910 patients BT plus EBRT: 2,466 patients EBRT: 9,369 patients	BT Median age: 70 years T stage T1: 37.4% T2: 59.2% T3: 3.4% BT plus EBRT Median age: 70 years T stage T1: 26.0% T2: 68.6% T3: 5.4% EBRT Median age: 72 years T stage T1: 22.4% T2: 66.8% T3: 10.8%	PCSM	Median 6.4-year followup

**Table 15. Overview of nonrandomized comparative studies (44 studies): Key Question 1 (continued)**

Study	Number of Patients	Subjects	Outcomes	Duration
Zelevsky et al. 2012 <sup>89</sup>	BT: 942 patients BT + IMRT: 524 patients	BT PSA <10: 877 10-20: 63 >20: 2 Gleason score <7: 824 7: 114 >7: 4 T stage T1c: 761 T2a: 149 T2b: 25 T2c: 7 BT plus IMRT PSA <10: 432 10-20: 81 >20: 11 Gleason score <7: 135 7: 331 >7: 58 T stage T1c: 252 T2a: 171 T2b: 77 T2c: 24	BPFS	Median followup 4.08 years (range 1-13 years)
Abdollah et al. 2011 <sup>72</sup>	RP: 22,244 patients Observation: 22,450 patients	RP Mean age: 69.8 years Gleason score 2-5: 4.9% 6-7: 68.2% 8-10: 26.9% Observation Mean age: 73.5 years Gleason score 2-5: 17.6% 6-7: 67.6% 8-10: 14.8%	PCSM Other-cause mortality	10-year followup
Bekelman et al. 2011 <sup>81</sup>	IMRT: 5,845 patients 3D-CRT: 6,753 patients	IMRT Age at diagnosis: 65-74 years: 55% Gleason score 5-7: 70% 3D-CRT Age at diagnosis: 65-74 years: 55% Gleason score 5-7: 68%	AEs	2-year followup

**Table 15. Overview of nonrandomized comparative studies (44 studies): Key Question 1 (continued)**

Study	Number of Patients	Subjects	Outcomes	Duration
Kim et al. 2011 <sup>60</sup>	All EBRT: 19,063 patients BT only: 5,338 patients BT + EBRT: 3,687 patients Conservative management: 13,649 patients	Radiation therapy Age at diagnosis: 66–85 years Charlson comorbidity score: 0: 77% 1: 17% ≥2: 6% <u>Clinical T stage:</u> <u>T1:</u> 52% <u>T2:</u> 48% <u>Conservative management</u> Age at diagnosis: 66–85 years Charlson comorbidity score: 0: 71% 1: 18% ≥2: 11% <u>Clinical T stage:</u> <u>T1:</u> 65% <u>T2:</u> 35%	AEs (GI toxicity)	10 years

**Table 15. Overview of nonrandomized comparative studies (44 studies): Key Question 1 (continued)**

Study	Number of Patients	Subjects	Outcomes	Duration
Rice et al. 2011 <sup>36</sup>	RP: 194 patients vs. EBRT: 252 patients vs. WW without secondary treatment: 214 patients vs. WW with secondary treatment: 110 patients	RP Mean age at diagnosis: 72.2±1.9 years Mean PSA: 5.3±2.2 ng/mL Clinical T stage T1: 111 (57.2%) Clinical T stage T2a: 83 (42.8%) EBRT Mean age at diagnosis: 74.1±3.1 years Mean PSA: 6.0±2.2 ng/mL Clinical T stage T1: 150 (59.5%) Clinical T stage T2a: 102 (40.5%) WW without secondary treatment Mean age at diagnosis: 75.7±3.8 years Mean PSA: 4.7±2.3 ng/mL Clinical T stage T1: 141 (65.9%) Clinical T stage T2a: 73 (34.1%) WW with secondary treatment Mean age at diagnosis: 74.5±3.6 years Mean PSA: 5.6±2.2 ng/mL Clinical T stage T1: 67 (60.9%) Clinical T stage T2a: 43 (39.1%)	Overall survival BRFS PF survival	RP: 7.2±4.2 years EBRT: 7.0±4.0 years WW without secondary treatment: 5.3±3.2 years WW with secondary treatment: 8.4±3.9 years
Williams et al. 2011 <sup>57</sup>	BT: 9,985 patients Cryotherapy: 943 patients	BT 65–69 years: 3,233 (32.4%) 70–74 years: 3,643 (36.5%) 75 years or older: 3,109 (31.1%) Tumor grade well/moderately differentiated: 84.5% Cryotherapy 65–69 years: 218 (23.1%) 70–74 years: 366 (35.6%) ≥75: 389 (41.3%) Tumor grade well/moderately differentiated: 60.6%	AEs	≥2 years
Barocas et al. 2010 <sup>64</sup>	RRP: 491 patients RALRP: 1,413 patients	RRP Mean age: 62 years (7.3) Biopsy Gleason score ≤6: 66.6% RALRP Mean age: 61 years (7.3) Biopsy Gleason score ≤6: 69.9%	BRFS	3 years of followup



**Table 15. Overview of nonrandomized comparative studies (44 studies): Key Question 1 (continued)**

Study	Number of Patients	Subjects	Outcomes	Duration
Cooperberg et al. 2010 <sup>39</sup>	RP: 5,066 patients EBRT: 1,143 patients ADT: 1,329 patients	RP Median age: 62 years PSA, 0-6: 2,673 (52.8%) 6.01-10: 1,452 (28.7%) 10-20: 698 (13.8%) 20.01-30: 129 (2.6%) >30: 114 (2.3%) Gleason score 2-6: 3,573 (52.8%) 3+4: 850 (16.8%) 4+3: 355 (7%) 8+10: 288 (5.7%) EBRT Median age: 72 years PSA 0-6: 322 (28.2%) 6.01-10: 330 (28.9%) 10-20: 302 (26.4%) 20.01-30: 72 (6.3%) >30: 117 (14.9%) Gleason score 2-6: 619 (54.2%) 3+4: 218 (19.1%) 4+3: 136 (11.9%) 8+10: 170 (14.9%) ADT Median age: 74 years PSA 0-6: 301 (22.7%) 6.01-10: 355 (26.7%) 10-20: 305 (23%) 20.01-30: 126 (9.5%) >30: 242 (18.2%) Gleason score 2-6: 622 (46.8%) 3+4: 247 (18.6%) 4+3: 175 (13.2%) 8+10: 285 (21.4%)	All-cause mortality PCSM	Median followup RP: 3.9 years EBRT: 4.5 years ADT: 3.6 years

**Table 15. Overview of nonrandomized comparative studies (44 studies): Key Question 1 (continued)**

Study	Number of Patients	Subjects	Outcomes	Duration
Magheli et al. 2010 <sup>56</sup>	RRP: 522 patients LRP: 522 patients RALRP: 522 patients	RRP Mean age: 58.8 (6.1) Mean PSA: 5.4 (3.2) Gleason score ≤6: 71.1% 7: 26.8% 8-9: 2.1% LRP Mean age: 58.4 (6.4) Mean PSA: 5.4 (3.7) Gleason score: ≤6: 74.7% 7: 21.8% 8-9: 3.4% RALRP Mean age: 58.3 (6.3) Mean PSA: 5.4 (3.2) Gleason score: ≤6: 75.5% 7: 21.8% 8-9: 2.7%	Biochemical recurrence	Mean (SD) followup RRP: 2.5 (1.6) years LRP: 1.47 (0.7) years RALRP: 1.3 (0.6) years
Hadley et al. 2010 <sup>73</sup>	RP: 11,936 patients Observation: 5,879 patients	Not reported	All-cause mortality PCSM	Up to 12 years
Dosoretz et al. 2010 <sup>82</sup>	BT: 1,391 patients BT plus ADT: 1,083 patients	BT Median age was 73 years for all patients enrolled. For patients younger than 73 years Gleason score ≤6: 641 (90%) 7: 60 (8%) 8-10: 10 (1%) BT plus ADT Median age was 73 years for all patients enrolled. For patients younger than 73 years Gleason score ≤6: 426 (86%) 7: 54 (11%) 8-10: 15 (3%)	All-cause mortality	Median 4.8-year followup
Malcolm et al. 2010 <sup>71</sup>	RRP: 135 patients RALRP: 447 patients BT: 122 patients Cryotherapy: 81 patients	RRP Mean age (SD): 59 years (7) Gleason score ≤6: 69% RALRP Mean age (SD): 59 years (6) Gleason score ≤6: 60% BT Mean (SD): 66 (7) Gleason score ≤6: 72% Cryotherapy Mean (SD): 71 (7) Gleason score ≤6: 50%	QOL	3-year followup

**Table 15. Overview of nonrandomized comparative studies (44 studies): Key Question 1 (continued)**

Study	Number of Patients	Subjects	Outcomes	Duration
Wong et al. 2009 <sup>88</sup>	3D-CRT: 270 patients IMRT: 314 patients BT: 225 patients EBRT plus BT: 44 patients	3D-CRT PSA ≤10: 192 (71%) 10.1–20: 52 (19%) ≥20: 26 (10%) Gleason score ≤6: 175 (65%) ≥7: 95 (35%) Risk group Low: 119 (44%) Intermediate: 111 (41%) High: 40 (15%) IMRT PSA ≤10: 238 (76%) 10.1–20: 54 (17%) ≥20: 22 (7%) Gleason score ≤6: 138 (44%) ≥7: 176 (56%) Risk group Low: 109 (35%) Intermediate: 151 (48%) High: 54 (17%) BT PSA ≤10: 193 (86%) 10.1–20: 28 (12%) ≥20: 4 (2%) Gleason score ≤6: 173 (77%) ≥7: 52 (23%) Risk group Low: 158 (70%) Intermediate: 58 (26%) High: 9 (4%) EBRT plus BT PSA ≤10: 29 (65%) 10.1–20: 13 (30%) ≥20: 2 (5%) Gleason score ≤6: 20 (45%) ≥7: 24 (55%) Risk group Low: 14 (32%) Intermediate: 23 (52%) High: 7 (16%)	Biochemical progression Systemic progression AEs	Median followup was 5.17 years, 4.67 years, 4.08 years, and 5.2 years for patients treated with 3D-CRT, IMRT, BT, and EBRT + BT, respectively.

**Table 15. Overview of nonrandomized comparative studies (44 studies): Key Question 1 (continued)**

Study	Number of Patients	Subjects	Outcomes	Duration
Krambeck et al. 2008 <sup>65</sup>	RRP: 588 patients RALRP: 294 patients	RRP Median age at surgery: 61 years (range 41–77) Gleason score <6: 0 (0%) 6: 441 (75.0%) 7: 133 (22.6%) ≥8: 14 (2.3%) RALRP Median age at surgery: 61 years (38–76) Gleason score <6: 2 (0.7%) 6: 212 (72.1%) 7: 70 (23.8%) ≥8: 10 (3.4%)	All-cause mortality PCSM Other-cause mortality Biochemical failure BPFS Progression to metastases Local recurrence Systemic progression QOL AEs	Median followup was 1.3 years
Lu-Yao et al. 2008 <sup>78</sup>	ADT: 7,867 patients Observation: 11,404 patients	ADT Median age (IQR) 79 years (74–83) Cancer grade: Moderately differentiated: 65.0% Observation Median age (IQR) 77 years (72–81) Moderately differentiated: 83.7%	Overall survival PCSS	Median followup for overall survival was 6.75 years
Sanda et al. 2008 <sup>85</sup>	RP (RRP or LRP or RALRP): 603 patients	Median age (range): 59 years (38–79) Mean PSA (SD), median, range: 6.7 (5.7), 5.5, 0.5–71.6 PSA <4: 126 (21%) 4–10: 399 (66%) >10: 78 (13%) Gleason score <7: 371 (62%) 7: 207 (34%) >7: 25 (4%) Overall cancer severity Low risk: 267 (44%) Intermediate risk: 302 (50%) High risk: 25 (4%)	QOL AEs	Median followup of 2.5 years

**Table 15. Overview of nonrandomized comparative studies (44 studies): Key Question 1 (continued)**

Study	Number of Patients	Subjects	Outcomes	Duration
Sanda et al. 2008 <sup>85</sup> (continued)	EBRT (IMRT or 3D-CRT): 292 patients	Median age (range): 69 years (45–84) Mean PSA (SD), median, range: 9.1 (10.1), 6.3, 0.5–99.3 PSA <4: 46 (16%) 4–10: 177 (61%) >10: 69 (24%) Gleason score <7: 129 (44%) 7: 123 (42%) >7: 40 (14%) Overall cancer severity Low risk: 80 (27%) Intermediate risk: 159 (54%) High risk: 53 (18%)		
	BT: 306 patients	Median age (range): 65 years (44–84) Mean PSA (SD), median, range: 5.8 (3.6), 5.1, 0.6–44.0 PSA <4: 67 (22%) 4–10: 217 (71%) >10: 21 (7%) Gleason score <7: 227 (74%) 7: 76 (25%) >7: 2 (1%) Overall cancer severity Low risk: 182 (59%) Intermediate risk: 119 (39%) High risk: 4 (1%)		
Schroeck et al. 2008 <sup>54</sup>	RRP: 435 patients RALRP: 362 patients	RRP Median age 60.3 years Biopsy Gleason score 2–6: 58.8% RALRP Median age 59.2 years Biopsy Gleason score 2–6: 72.2%	Biochemical failure	Mean followup 1.37 and 1.09 years, respectively

**Table 15. Overview of nonrandomized comparative studies (44 studies): Key Question 1 (continued)**

Study	Number of Patients	Subjects	Outcomes	Duration
Sumitomo et al. 2008 <sup>63</sup>	HIFU: 260 patients HIFU plus ADT: 270 patients	HIFU Median age (SD, range): 67.7 (7.2, 45–88) Mean PSA (SD, range) 9.1 (4.4, 2.3–29.4) Mean Gleason score (SD, range) 6.3 (1.1, 3–10) Risk level Low: 93 Intermediate: 102 High: 65 HIFU plus ADT Median age (SD, range): 68.2 (6.7, 52–85) Mean PSA (SD, range) 11.6 (6.2, 2.8–29.5) Mean Gleason score (SD, range) 6.3 (1.3, 2–10) Risk level Low: 70 Intermediate: 113 High: 87	BPFS AEs	3-year followup
Albertsen et al. 2007 <sup>42</sup>	Surgery: 596 patients Radiation: 642 patients Observation: 114 patients	Surgery Median age: 65 years Gleason score 2–4: 3% 5: 5% 6: 53% 7: 27% 8–10: 12% Radiation Median age: 71 years Gleason score 2–4: 3% 5: 6% 6: 46% 7: 25% 8–10: 20% Observation Median age: 70 years Gleason score 2–4: 17% 5: 15% 6: 46% 7: 11% 8–10: 11%	Overall survival PCSM	13-year followup

**Table 15. Overview of nonrandomized comparative studies (44 studies): Key Question 1 (continued)**

Study	Number of Patients	Subjects	Outcomes	Duration
D'Amico et al. 2007 <sup>87</sup>	RRP: 660 patients 3D-CRT: 288 patients	RRP Median age (IQR): 67 years (62–71) PSA <4: 146 (22%) >4–10: 372 (56%) >10–20: 99 (15%) >20: 43 (7%) Gleason score <6: 315 (48%) 7: 271 (41%) 8–10: 74 (11%) 3D-CRT Median age (IQR): 72 years (68–76) PSA <4: 16 (6%) >4–10: 147 (51%) >10–20: 81 (28%) >20: 44 (15%) Gleason score <6: 100 (35%) 7: 148 (51%) 8–10: 40 (14%)	PCSM	7-year followup

**Abbreviations:** 3D-CRT=Three-dimensional conformal radiation therapy; ADT=androgen-deprivation therapy; AEs=adverse events; bGS=baseline Gleason score; BT=brachytherapy; EB-IGRT=external beam image-guided radiation therapy; EBRT=external beam radiation therapy; HDR=high dose rate; HIFU=high-intensity focused ultrasound; HT=hormone therapy; IGRT= image-guided radiation therapy; IMRT=intensity-modulated radiation therapy; IQR=interquartile range; LDR=low dose rate; LRP=laparoscopic radical prostatectomy; PBT=proton beam therapy; PCSM=prostate cancer-specific mortality; PCSS=prostate cancer-specific survival; PSA=prostate-specific antigen; QOL=quality of life; RALRP=robotic-assisted laparoscopic radical prostatectomy; RP=radical prostatectomy; RRP=radical retropubic prostatectomy; T=tumor stage; WW=watchful waiting.

## Risk of Bias

Our risk-of-bias assessments for the 44 nonrandomized comparative studies appear in Table C-2 of Appendix C. Of these 44 nonrandomized studies that applied statistical adjustments for confounding factors, 26 studies<sup>36,37,39,41,54,60,63-71,74,76,77,80,82,85-90</sup> used multivariable regression analysis, 15 studies<sup>38,40,42,55-57,59,72,75,79,81,83,84,91,92</sup> used propensity score analysis, 2 studies<sup>73,78</sup> used instrumental variable analysis, and 1 study<sup>58</sup> used propensity scoring and used an instrumental variable as a sensitivity analysis to control for selection bias.

Forty-one of 44 nonrandomized comparative studies were categorized as high risk of bias for all reported outcomes (see Table 10 for risk-of-bias assessment criteria). Although propensity scoring and multivariable regression analysis can reduce the risk of bias from known or observed confounding factors, they cannot reduce the risk of bias from unknown or unobserved confounding factors. Therefore, these techniques cannot reduce the risk of bias to a level that is equivalent to the risk in a well- or moderately well-designed RCT.

The three remaining nonrandomized comparative studies were categorized as medium risk of bias because all used instrumental variable analysis, which effectively “pseudorandomizes” patients into different groups.<sup>58,73,78</sup> An instrumental variable is a variable that has a statistically significant association with treatment choice but no association with health outcomes or other variables that might affect health outcomes. Unlike propensity scoring and multivariable

analysis, instrumental variable analysis can account for both measured and unmeasured confounders. Although this is not completely equivalent to a true randomization approach, and its effectiveness depends on choosing a variable that demonstrably has the properties noted above, some evidence suggests that it may generate results that are closer to those observed in RCTs than observational studies using other statistical adjustment methods.<sup>73</sup>

Authors were inconsistent in their method of reporting bladder, bowel, and sexual dysfunction. Some authors described these conditions as a measure of QOL while others treated them as adverse events. We categorized them as QOL for the purpose of this report as there seemed to be more subjectivity in evaluating these conditions compared with others, for example, gastrointestinal toxicities.

## **Findings**

All abstracted data for the outcome measures that address this KQ appear in Table F-2 (all-cause mortality), Table F-4 (overall survival), Table F-6 (prostate cancer–specific mortality and cause-specific mortality), Table F-8 (biochemical failure), Table F-10 (biochemical progression–free survival), Table F-12 (progression to metastasis), Table F-14 (QOL), and Table F-16 (reported adverse events) of Appendix F. Table 16 summarizes major findings reported by the non-RCTs and is intended to provide a roadmap to the abstracted data, including the key statistics, for each comparison and reported outcome.



**Table 16. Major findings reported by nonrandomized comparative studies for Key Question 1**

Treatments Being Compared	Outcome	Evidence Base	Major Findings Reported in the Study	Detailed Results Abstracted
RALRP vs. RRP	All-cause mortality	Krambeck et al. <sup>65</sup>	At a median followup time 1.3 years, 0.7% of patients died in the RRP group and 1.4% of patients died in the RALRP group.	Table F-2 of Appendix F
RALRP vs. RRP	PCSM	Krambeck et al. <sup>65</sup> Alemozaffar et al. <sup>68</sup>	No deaths in either treatment group were attributable to prostate cancer during the study period. No significant difference in number of deaths (0 deaths RALRP, 2 deaths RRP)	Table F-6 of Appendix F
RALRP vs. RRP	Biochemical failure	Krambeck et al. <sup>65</sup>	During the study, 32/588 (5.4%) cases of PSA progression were found in the RRP group and 14/294 (4.8%) cases of PSA progression were found in the RALRP group. There were also 5 cases of clinical local recurrence in the RRP group and 3 cases in the RALRP group. The groups were similar on margin positivity.	Table F-8 of Appendix F
RALRP vs. RRP	Biochemical progression-free survival	Krambeck et al. <sup>65</sup> , Barocas et al. <sup>64</sup> , Schroek et al. <sup>54</sup> , Silberstein et al. <sup>67</sup> , Alemozaffar et al. <sup>68</sup> , Masterson et al. <sup>69</sup> , Pierorazio et al. <sup>70</sup>	6 studies did not find a significant between-group difference in biochemical progression-free survival. Pierorazio et al. <sup>70</sup> found a significant difference favoring RALRP at a mean followup of 3 years.	Table F-7 in Appendix F
RALRP vs. RRP	Biochemical failure	Magheli et al. <sup>56</sup>	No difference was found in the RRP-vs.-LRP comparison or the RRP-vs.-RALRP comparison.	Table F-8 of Appendix F
RALRP vs. RRP	Progression to metastasis	Krambeck et al. <sup>65</sup> Alemozaffar et al. <sup>68</sup>	In 1 study, 1 patient in the RALRP progressed to metastasis during the study. In the other study, 4 patients, all in the RRP group, progressed to metastases.	Table F-12 of Appendix F
RALRP vs. RRP	Adverse events	Krambeck et al. <sup>65</sup>	Wound herniation was more common after RALRP than with RRP, and development of bladder neck contracture was more common after RRP than with RALRP.	Table F-16 of Appendix F
RALRP vs. RRP	QOL	Barry et al. <sup>66</sup> Krambeck et al. <sup>65</sup> Alemozaffar et al. <sup>68</sup> Malcolm et al. <sup>71</sup>	Barry et al. <sup>66</sup> RALRP was found to be associated with greater problems with incontinence. No difference in sexual dysfunction was found between the 2 treatment groups. Krambeck et al. <sup>65</sup> and Alemozaffar et al. <sup>68</sup> No between-group differences for continence or sexual function. Malcolm et al. <sup>71</sup> Could not be determined from data presented.	Table F-14 of Appendix F

**Table 16. Major findings reported by nonrandomized comparative studies for Key Question 1 (continued)**

Treatments Being Compared	Outcome	Evidence Base	Major Findings Reported in the Study	Detailed Results Abstracted
LRP vs. RRP	Biochemical progression-free survival	Wirth et al. <sup>74</sup> Pierorazio et al. <sup>70</sup>	Wirth et al. <sup>74</sup> At 6 years, the Kaplan–Meier estimates of survival were 83% and 86% for patients treated by LRP and RRP, respectively (log-rank p=0.18). Pierorazio et al. <sup>70</sup> There was a significant difference favoring RRP over LRP at the 3 year followup.	Table F-7 in Appendix F
LRP vs. RRP	Biochemical recurrence	Magheli et al. <sup>56</sup>	No significant difference was found.	Table F-8 of Appendix F
RRP vs. 3D-CRT	Overall survival	Ferrer et al. <sup>91</sup>	No significant difference at a median followup of 6.02 years.	Table F-4 of Appendix F
RRP vs. 3D-CRT	PCSM	D'Amico et al. <sup>87</sup>	At 7-year followup, 29 men (4.45%) in the RRP had died compared with 32 men (11.1%) in the 3D-CRT group (RR 0.4, 95% CI, 0.24 to 0.64).	Table F-6 of Appendix F
RRP vs. 3D-CRT	Biochemical failure	Ferrer et al. <sup>91</sup>	At a mean followup of 5.23 years, the relapse rate was significantly higher in the 3D-CRT group (24.7%) than in the RRP group (17.1%).	Table F-7 in Appendix F
RRP vs. 3D-CRT	QOL	Ferrer et al. <sup>91</sup>	No significant difference at the 2-year followup on any dimension of QOL as measured by the SF-36, FACT-G, FACT-P, or AUA-7.	Table F-14 of Appendix F
3D-CRT vs. BT	Overall survival	Ferrer et al. <sup>91</sup>	At median followup of 6.02 years, no statistically significant difference between the treatment groups was found.	Table F-4 of Appendix F
3D-CRT vs. BT	Progression to metastasis	Wong et al. <sup>88</sup>	Percentage distant metastases was 96% and 99% for patients treated with 3D-CRT and BT respectively.	Table F-12 of Appendix F
3D-CRT vs. BT	Biochemical progression-free survival	Ferrer et al. <sup>61,91</sup>	Percentage with biochemical relapse at 5.23 years was 24.7% and 16.1% respectively.	Table F-7 in Appendix F
3D-CRT vs. BT	QOL	Ferrer et al. <sup>61,91</sup>	A worsening in the EPIC score for sexual function was reported among men who received 3D-CRT (mean change -7.5; 95% CI -12.5 to -2.5). <sup>91</sup> However, data were not reported in a way that directly compared 3D-CRT to BT.	Table F-14 of Appendix F
3D-CRT vs. BT	Adverse events (GI toxicity)	Wong et al. <sup>88</sup> Kim et al. <sup>60</sup>	1 study reported that BT alone and EBRT + BT caused significantly more grade 2 and 3 acute and late GU toxicity compared with 3D-CRT. The other study reported significantly less GI toxicity in the BT group compared with the 3D-CRT group.	Table F-16 of Appendix F

**Table 16. Major findings reported by nonrandomized comparative studies for Key Question 1 (continued)**

Treatments Being Compared	Outcome	Evidence Base	Major Findings Reported in the Study	Detailed Results Abstracted
RP vs. EBRT	All-cause mortality	Nepple et al. <sup>40</sup> Rice et al. <sup>36</sup> Cooperberg et al. <sup>39</sup> Hoffman et al. <sup>38</sup> Mukherjee et al. <sup>37</sup> Albertsen et al. <sup>42</sup>	Nepple et al. <sup>40</sup> EBRT was associated with an increase in all-cause mortality compared with RP at median followup of 7.2 years. Rice et al. <sup>36</sup> There was no significant difference between RP and EBRT at 6.8-year followup in overall mortality, p=0.18. Cooperberg et al. <sup>39</sup> HR 2.21 (95% CI 1.50 to 3.24) in favor of RP at between 3 and 4 year followup visits. Hoffman et al. <sup>38</sup> After 15 years of followup, all-cause mortality was more favorable for men who underwent RP than with EBRT (HR 0.35; 95% CI, 0.26 to 0.49) Mukherjee et al. <sup>37</sup> All-cause mortality was 3.6% in the RP group and 28.8% in the EBRT group, p<0.001 at 3-year followup. Albertsen et al. <sup>42</sup> At an average of 13.3-year followup, RP was associated with improved overall survival compared with overall survival in the radiation group.	Table F-2 of Appendix F

**Table 16. Major findings reported by nonrandomized comparative studies for Key Question 1 (continued)**

Treatments Being Compared	Outcome	Evidence Base	Major Findings Reported in the Study	Detailed Results Abstracted
RP vs. EBRT	PCSM	Nepple et al. <sup>40</sup> Cooperberg et al. <sup>39</sup> Hoffman et al. <sup>38</sup> DeGroot et al. <sup>41</sup> Mukherjee et al. <sup>37</sup> Albertsen et al. <sup>42</sup>	Nepple et al. <sup>40</sup> At median followup of 7.2 years, EBRT was associated with an increase in PCSM compared with RP. Cooperberg et al. <sup>39</sup> HR 1.58 (95% CI 1.32 to 1.89) in favor of RP at between 3- and 4-year followup visits. Hoffman et al. <sup>38</sup> After 15 years of followup, PCSM was more favorable for the men who underwent RP than for the men who received EBRT. DeGroot et al. <sup>41</sup> At median followup of 51 months, adjusted HRs for risk of prostate cancer death were higher for EBRT compared with RP in the entire study population. HRs were 1.62 (95% CI, 1.00 to 2.61) analyzing by intent-to-treat and 2.02 (95% CI, 1.19 to 3.43) analyzing by treatment received. Mukherjee et al. <sup>37</sup> PCSM was 23.7% in the RP group and 28.8% in the EBRT group at 3 year followup. Albertsen et al. <sup>42</sup> The prostate cancer mortality ratio was 2.5 times higher (95% CI, 1.7 to 3.5) in EBRT patients compared with RP patients.	Table F-6 of Appendix F
RP vs. EBRT	Adverse events	Mukherjee et al. <sup>37</sup>	Myodysplastic syndrome occurred in 6 RP patients and 16 EBRT patients, p=0.35.	Table F-16 of Appendix F
RP vs. EBRT	Biochemical recurrence	Rice et al. <sup>36</sup>	HR: 1.38 (95% CI 0.88 to 2.16), no between-group difference for biochemical recurrence at 6.8-year followup.	Table F-8 of Appendix F
RP vs. EBRT	QOL	Sanda et al. <sup>85</sup>	At 24 months followup, reported problem (using the EPIC survey): Overall urinary problems: RP, 7%; EBRT, 11% (p=not significant) Overall bowel problems: RP, 1%; EBRT, 11% (p=0.001); Overall sexual problems: RP, 43%; EBRT, 37% (p=not significant)	Table F-14 of Appendix F
RP vs. BT	Overall survival	Kibel et al. 2012 <sup>75</sup>	10 year overall survival was 88.9% for RP and 81.7% for BT.	Table F-4 of Appendix F
RP vs. BT	All-cause mortality	Nepple et al. <sup>40</sup> Mukherjee et al. <sup>37</sup>	Nepple et al. <sup>40</sup> BT was associated with an increase in all-cause mortality compared with RP at median followup of 7.2 years. Mukherjee et al. <sup>37</sup> All-cause mortality at 3 years was 3.6% for RP and 4.6% for BT.	Table F-2 of Appendix F

**Table 16. Major findings reported by nonrandomized comparative studies for Key Question 1 (continued)**

Treatments Being Compared	Outcome	Evidence Base	Major Findings Reported in the Study	Detailed Results Abstracted
RP vs. BT	PCSM	Nepple et al. <sup>40</sup> Kibel et al. <sup>75</sup> Mukherjee et al. <sup>37</sup>	Nepple et al. <sup>40</sup> At median followup of 7.2 years, there was no statistically significant increase with BT vs. RP. Kibel et al. 2012 <sup>75</sup> 10 year PCSM was 1.8% for RP and 2.3% for BT. Mukherjee et al. <sup>37</sup> At 3-year followup, PCSM was 0.9% for RP and 0.6% for BT	Table F-6 of Appendix F
RP vs. BT	Adverse events	Abern et al. <sup>90</sup> Mukherjee et al. <sup>37</sup>	Abern et al. <sup>90</sup> The authors found that patients receiving radiation had a 70% increased risk of subsequent bladder cancer. After BT with or without EBRT the risks were highest. Mukherjee et al. <sup>37</sup> Myodysplastic syndrome occurred in 6 RP patients and 9 BT cases patients.	Table F-16 of Appendix F
RP vs. BT	QOL	Sanda et al. <sup>85</sup>	Patients in the BT group had significantly more urinary and bowel problems than those treated with RP. There was no between-group difference in sexual problems.	Table F-16 of Appendix F
EBRT vs. BT	All-cause mortality	Mukherjee et al. <sup>37</sup>	All-cause mortality was 28.8% in EBRT and 4.6% in BT at 3 year followup.	Table F-2 of Appendix F
EBRT vs. BT	PCSM	Shen et al. <sup>84</sup> Mukherjee et al. <sup>37</sup>	Shen et al. <sup>84</sup> There was a significant difference in PCSM in favor of BT at a median followup of 6.4 years (HR 0.66; 95% CI, 0.49 to 0.86). The 10-year PCSM rate was 21.1% for EBRT and 11.3% for BT alone. Mukherjee et al. <sup>37</sup> PCSM was 8.3% in EBRT and 0.6% in BT at 3 year followup.	Table F-6 of Appendix F
EBRT vs. BT	Adverse events	Abern et al. <sup>90</sup> Mukherjee et al. <sup>37</sup> Wong et al. <sup>88</sup> Kim et al. <sup>60</sup>	Abern et al. <sup>90</sup> The authors found that patients receiving radiation had a 70% increased risk of subsequent bladder cancer. After BT with or without EBRT the risks were highest. Mukherjee et al. <sup>37</sup> Myodysplastic syndrome occurred in 16 EBRT patients and 9 BT cases. Wong et al. <sup>88</sup> BT caused a lower incidence of acute or late GI toxicity than EBRT. Kim et al. <sup>60</sup> BT had a significantly lower rate of GI toxicity than EBRT.	Table F-16 of Appendix F
EBRT vs. BT	QOL	Sanda et al. <sup>85</sup>	No treatment-related deaths occurred in either treatment group. There was no significant difference in urinary, bowel or sexual problems.	Table F-16 of Appendix F
EBRT vs. BT	Biochemical failure	Wong et al. <sup>88</sup>	94% in both groups.	Table F-8 of Appendix F

**Table 16. Major findings reported by nonrandomized comparative studies for Key Question 1 (continued)**

Treatments Being Compared	Outcome	Evidence Base	Major Findings Reported in the Study	Detailed Results Abstracted
EBRT vs. BT	Distant metastases	Wong et al. <sup>88</sup>	96% for 3D-CRT, 97% IMRT, BT 99%.	Table F-12 of Appendix F
RALRP vs. LRP	Biochemical progression-free survival	Pierorazio et al. <sup>70</sup>	67.8% for RALRP, 41.7% for LRP, but data presentation does not allow determination of statistical significance.	Table F-7 in Appendix F
RALRP vs. LRP	Biochemical recurrence	Magheli et al. <sup>56</sup> Ploussard et al. <sup>62</sup>	Magheli et al. <sup>56</sup> Data were not presented in useable manner. Ploussard et al. <sup>62</sup> Biochemical recurrence rates were 18% for LRP and 10.3% for RALRP, a significant difference favoring RALRP.	Table F-8 of Appendix F
RALRP vs. LRP	QOL	Ploussard et al. <sup>62</sup>	No significant between-group difference for continence at 1-year followup but by the 2-year followup continence rates favored RALRP. Rates of potency recovery favored RALRP at 1- and 2-year followup periods.	Table F-14 of Appendix F
RALRP vs. LRP	Adverse events	Ploussard et al. <sup>62</sup>	Clavien 0–5 adverse events did not differ significantly between groups. Anastomosis leakage occurred significantly more in LRP treated patients. Overall, 6.8% of LRP vs. 10.5% of RALRP patients experienced an event (a nonsignificant difference).	Table F-16 of Appendix F
RP vs. observation	All-cause mortality	Abdollah et al. <sup>72</sup> Hadley et al. <sup>73</sup> Rice et al. <sup>36</sup> Albertsen et al. <sup>42</sup>	Abdollah et al. <sup>72</sup> RP was associated with a significant reduction in all-cause mortality compared with observation. Hadley et al. <sup>73</sup> Using the traditional multivariable survival analysis method or the propensity score adjustment method, the authors found that observation was associated with greater risk of all-cause mortality than was radical prostatectomy. But using the instrumental variable approach, the study found no significant difference between the 2 treatment groups. Rice et al. <sup>36</sup> RP vs. WW without secondary treatment p=0.008; RP vs. WW with secondary treatment p=0.44, favoring RP over WW without secondary treatment at 6.8-year followup. Albertsen et al. <sup>42</sup> Overall survival rates were 78%, 71%, and 61% for low-, intermediate- and high-risk groups, respectively, for RP for 13-year followup. Comparable rates for observation were 58%, 55%, and 37%, favoring surgery.	Table F-2 of Appendix F

**Table 16. Major findings reported by nonrandomized comparative studies for Key Question 1 (continued)**

Treatments Being Compared	Outcome	Evidence Base	Major Findings Reported in the Study	Detailed Results Abstracted
RP vs. observation	PCSM	Abdollah et al. <sup>72</sup> Hadley et al. <sup>73</sup> Albertsen et al. <sup>42</sup>	Abdollah et al. <sup>72</sup> RP was associated with a significant reduction in PCSM compared with that outcome in the observation group. Hadley et al. <sup>73</sup> Using the traditional multivariable survival analysis method or the propensity score adjustment method, the authors found that observation was associated with greater risk of PCSM than RP. But using the instrumental variable approach, the study did not find a significant difference between the 2 treatment groups. Albertsen et al. <sup>42</sup> Cause-specific survival rates were 96%, 92%, and 90% for low-, intermediate- and high-risk groups, respectively, for RP for 13-year followup. Comparable rates for observation were 83%, 89%, and 60%, favoring surgery.	Table F-6 of Appendix F
RP vs. observation	Biochemical recurrence	Rice et al. <sup>36</sup>	RP vs. WW without secondary treatment p=0.01 and RP vs. WW with secondary treatment p=0.05, favoring RP over WW without secondary treatment at 6.8-year followup.	Table F-8 of Appendix F
BT vs. BT plus IMRT	Biochemical progression-free survival	Zelevsky et al. <sup>89</sup>	Study authors only reported that there was no tumor control advantage with BT or BT + IMRT.	Table F-7 in Appendix F
RRP vs. cryotherapy	QOL	Malcolm et al. <sup>71</sup>	Cryotherapy patients had better rates of returning to baseline urinary function than RRP treated patients. Sexual function and bowel function and bother were not significantly different in the 2 treatment groups.	Table F-14 of Appendix F
Cryotherapy vs. BT	QOL	Malcolm et al. <sup>71</sup> Williams et al. <sup>57</sup>	Malcolm et al. Sexual function was better in the BT group compared with sexual function in the cryotherapy group. Urinary function was better in the cryotherapy group. Bowel function and bother were not significantly different in the 2 groups. Williams et al. Cryotherapy was associated with more urinary and erectile complications but fewer bowel complications than BT.	Table F-14 of Appendix F
Cryotherapy vs. BT	Adverse events	Williams et al. <sup>57</sup>	Overall, BT patients had significantly more complications than patients receiving cryotherapy (63.6% vs. 48.8%, respectively, p<0.001).	Table F-16 of Appendix F
RALRP vs. cryotherapy	QOL	Malcolm et al. <sup>71</sup>	Cryotherapy patients had better rates of returning to baseline urinary function than RALRP treated patients. Sexual function, bowel function and bother were not significantly different in the 2 groups.	Table F-14 of Appendix F

**Table 16. Major findings reported by nonrandomized comparative studies for Key Question 1 (continued)**

Treatments Being Compared	Outcome	Evidence Base	Major Findings Reported in the Study	Detailed Results Abstracted
RALRP vs. BT	QOL	Malcolm et al. <sup>71</sup>	BT patients had better rates of returning to baseline urinary function than RALRP treated patients. Sexual function was better in the BT group than sexual function in the RALRP group. Bowel function and bother were not significantly different by treatment group.	Table F-14 of Appendix F
ADT vs. observation	All-cause mortality	Lu-Yao et al. <sup>78</sup>	The overall mortality rate was higher in the ADT group than in the observation group.	Table F-2 of Appendix F
ADT vs. observation	PCSM	Lu-Yao et al. <sup>78</sup>	The PCSM rate was higher in the ADT group than in the observation group.	Table F-6 of Appendix F
IMRT vs. 3D-CRT	Biochemical failure	Wong et al. <sup>88</sup>	The 5-year biochemical failure rates were 74% and 87% for patients treated with 3D-CRT and IMRT, favoring 3D-CRT.	Table F-8 of Appendix F
IMRT vs. 3D-CRT	Progression to metastasis	Wong et al. <sup>88</sup>	Percentage distant metastases was 96% and 97% for patients treated with 3D-CRT and IMRT, respectively, with no significant difference between the 2 treatments.	Table F-12 of Appendix F
IMRT vs. 3D-CRT	Adverse events	Bekelman et al. <sup>81</sup> Sheets et al. <sup>58</sup> Wong et al. <sup>88</sup> Kim et al. <sup>60</sup>	Bekelman et al. <sup>81</sup> IMRT was associated with a reduction in bowel complications and proctitis and hemorrhage compared with 3D-CRT. Sheets et al. <sup>58</sup> No significant difference for GI procedures, urinary nonincontinence diagnoses or procedures, urinary incontinence procedures, or erectile dysfunction procedures. Hip fractures occurred significantly more in the 3D-CRT group. Wong et al. <sup>88</sup> Acute GI toxicity was similar in both groups. There were more grade 2 acute toxicities (49% vs. 39%) and late (27% vs. 16%) GU toxicities but no increase in grade 3 toxicities from high-dose IMRT vs. conventional 3D-CRT. Kim et al. <sup>60</sup> IMRT was associated with a lower rate of GI toxicity than 3D-CRT.	Table F-16 of Appendix F
IMRT vs. 3D-CRT	QOL	Sheets et al. <sup>58</sup>	There was no significant between-group difference in urinary incontinence diagnoses. For erectile dysfunction diagnoses, more patients in the IMRT group received this diagnosis, favoring 3D-CRT for this outcome.	Table F-14 of Appendix F
IMRT vs. proton beam therapy	QOL	Sheets et al. <sup>58</sup>	There was no significant between-group difference in urinary incontinence diagnoses or erectile function diagnoses.	Table F-14 of Appendix F
IMRT vs. proton beam therapy	Adverse events	Sheets et al. <sup>58</sup> Kim et al. <sup>60</sup>	In both studies, proton beam therapy was associated with more GI morbidity than IMRT.	Table F-16 of Appendix F



**Table 16. Major findings reported by nonrandomized comparative studies for Key Question 1 (continued)**

Treatments Being Compared	Outcome	Evidence Base	Major Findings Reported in the Study	Detailed Results Abstracted
3D-CRT vs. proton beam therapy	QOL	Sheets et al. <sup>58</sup>	Urinary incontinence diagnoses occurred at a rate of 3.7 per 100 person-years in the 3D-CRT group and 3.3 in the proton beam therapy group. Erectile dysfunction diagnoses occurred at a rate of 5.3 in the 3d-CRT group vs. 7.4 in the proton therapy group.	Table F-14 of Appendix F
3D-CRT vs. proton beam therapy	Adverse events	Sheets et al. <sup>58</sup> Kim et al. <sup>60</sup>	Sheets et al. <sup>58</sup> GI event diagnoses occurred at a rate of 14.7% in the 3D-CRT group and 17.8% in the proton therapy group. Hip fracture occurred in 1% of the 3D-CRT group and 0.7% of the proton therapy group. Kim et al. <sup>60</sup> Proton therapy was associated with a higher rate of GI toxicity than was 3D-CRT (HR 2.13, 95% CI 1.45-3.13).	Table F-16 of Appendix F
Proton beam therapy vs. conservative management	Adverse events	Kim et al. <sup>60</sup>	Proton beam therapy was associated with greater GI toxicity than conservative management (HR 13.7, 95% CI 9.09-20.8).	Table F-16 of Appendix F
BT vs. BT plus ADT	Adverse events	Nanda et al. <sup>83</sup>	Neoadjuvant hormone therapy was associated with a significantly increased risk of all-cause mortality in patients with low-risk prostate cancer compared with patients treated with only BT. This association was not seen in other risk groups.	Table F-16 of Appendix F
BT vs. BT plus EBRT	PCSM	Shen et al. <sup>84</sup>	There was no significant difference in PCSM between groups. The 10-year PCSM rate was 11.3% for BT alone, and 13.4% for BT plus EBRT.	Table F-6 of Appendix F
BT vs. BT plus EBRT	QOL	Mohammed et al. <sup>80</sup>	Late incontinence greater than or equal to grade 3 occurred in 0.3% of BT group and 1% of EBRT plus BT group.	Table F-14 of Appendix F
BT vs. BT plus EBRT	Adverse events	Abern et al. <sup>90</sup> Mohammed et al. <sup>80</sup>	Abern et al. <sup>90</sup> The authors found that patients receiving radiation had a 70% increased risk of subsequent bladder cancer. After BT with or without EBRT the risks were highest. Mohammed et al. <sup>80</sup> Some adverse events which occurred more often with combination therapy included acute dysuria, late urethral stricture, late genitourinary events, and late rectal bleeding.	Table F-16 of Appendix F
BT vs. conservative management	Adverse events	Kim et al. <sup>60</sup>	BT was associated with greater GI toxicity than with conservative management (HR 3.62, 95% CI 2.85-4.61).	Table F-16 of Appendix F
Surgery vs. radiation	Adverse events	Abern et al. <sup>90</sup>	The authors found that patients receiving radiation had a 70% increased risk of subsequent bladder cancer. After BT with or without EBRT the risks were highest.	Table F-16 of Appendix F
EBRT vs. observation	All-cause mortality	Albertsen et al. <sup>42</sup>	The mortality rate ratio was 1.2 (95% CI, 0.9 to 1.5) times higher in the observation vs. radiation group.	Table F-4 of Appendix F

**Table 16. Major findings reported by nonrandomized comparative studies for Key Question 1 (continued)**

Treatments Being Compared	Outcome	Evidence Base	Major Findings Reported in the Study	Detailed Results Abstracted
EBRT vs. observation	PCSM	Albertsen et al. <sup>42</sup> Abdollah et al. <sup>59</sup>	Albertsen et al. <sup>42</sup> In the EBRT group at 5-, 10-, and 15-year followup 4%, 9%, and 17% of patients, respectively, died of prostate cancer in the EBRT group. In the observation group the percentage mortality was 6%, 14% and 25% at each time point, respectively. Abdollah et al. <sup>59</sup> There was no between-group difference in the clinical effectiveness of observation vs. radiotherapy for patients with low to intermediate risk prostate cancer on 10-year PCSM (4.1% vs. 3.7%, respectively, p=0.10). For patients in the high-risk group, 10-year PCSM was 14.4% in the observation group vs. 8.8% in the radiotherapy group (p=0.001) in favor of radiotherapy.	Table F-6 of Appendix F
RP vs. ADT	Overall survival	Liu et al. <sup>79</sup>	The 8-year survival rate was 79.62% among men who underwent RP cohort compared with 43.39% in the ADT group using Kaplan-Meier estimation. In the RP group, the Kaplan-Meier estimate for 3-year and 5-year survival rate was 96.06% and 92.05%, respectively. In the ADT group, 3-year and 5-year survival rates were 89.66% and 74.81%, respectively.	Table F-4 of Appendix F
RP vs. ADT	All-cause mortality	Liu et al. <sup>79</sup> Cooperberg et al. <sup>39</sup>	Liu et al. <sup>79</sup> There were 56 deaths (3.45%) among men who underwent RP compared with 266 deaths (16.38%) in the ADT group. ADT was associated with an increased risk of all-cause mortality. Cooperberg et al. <sup>39</sup> Adjusted HR 2.25 (95% CI, 1.86-2.71), indicating increased risk with ADT	Table F-2 of Appendix F
RP vs. ADT	PCSM	Liu et al. <sup>79</sup> Cooperberg et al. <sup>39</sup>	Liu et al. <sup>79</sup> There were 4 deaths (0.25%) among men who underwent RP compared with 60 deaths (3.69%) in the ADT group. ADT was associated with an increased risk of PCSM. Cooperberg et al. <sup>39</sup> Adjusted HR 3.22 (95% CI, 2.16 to 4.81), indicating increased risk with ADT	Table F-6 of Appendix F
IGRT vs. BT	Overall survival	Marina et al. <sup>86</sup>	Both 5-year and 8-year overall survival rates were higher among men who underwent high-dose rate BT than with IGRT.	Table F-4 of Appendix F
IGRT vs. BT	Cause-specific survival	Marina et al. <sup>86</sup>	No difference between the treatment groups in 5- or 8-year cause-specific survival rates.	Table F-6 of Appendix F
IGRT vs. BT	Biochemical failure	Marina et al. <sup>86</sup>	No difference between the treatment groups in 5- or 8-year biochemical failure.	Table F-8 of Appendix F

**Table 16. Major findings reported by nonrandomized comparative studies for Key Question 1 (continued)**

Treatments Being Compared	Outcome	Evidence Base	Major Findings Reported in the Study	Detailed Results Abstracted
IGRT vs. BT	Biochemical progression-free survival	Marina et al. <sup>86</sup>	Both 5-year and 8-year biochemical disease-free survival rates were higher among men who underwent high-dose rate BT than with IGRT.	Table F-7 in Appendix F
IGRT vs. BT	Progression to metastasis	Marina et al. <sup>86</sup>	No difference between the treatment groups in 5- or 8-year progression to metastases.	Table F-12 of Appendix F
EBRT vs. ADT	All-cause mortality	Cooperberg et al. <sup>39</sup>	The HR for ADT relative to EBRT was 1.45 (95% CI, 1.02 to 2.07)	Table F-2 of Appendix F
EBRT vs. ADT	PCSM	Cooperberg et al. <sup>39</sup>	Relative to EBRT, the HR for ADT was 1.43 (95% CI, 1.21 to 1.69).	Table F-6 of Appendix F
3D-CRT vs. BT	Biochemical failure	Wong et al. <sup>88</sup>	The 5-year biochemical failure rate was 74%, and 94%, for patients treated with 3D-CRT and BT, respectively.	Table F-8 of Appendix F
3D-CRT vs. BT	Progression to metastases	Wong et al. <sup>88</sup>	Percentage distant metastases was 96% and 99% for patients treated with 3D-CRT and BT, respectively.	Table F-12 of Appendix F
3D-CRT vs. BT	Adverse events	Wong et al. <sup>88</sup> Kim et al. <sup>60</sup>	Wong et al. <sup>88</sup> BT caused significantly more grade 2 and 3 acute and late GU toxicity compared with 3D-CRT. Kim et al. <sup>60</sup> BT was associated with significantly lower GI toxicity than 3D-CRT (HR 0.62, 95% CI 0.51-0.75).	Table F-16 of Appendix F
3D-CRT vs. conservative management	Adverse events	Kim et al. <sup>60</sup>	3D-CRT was associated with significantly greater GI toxicity than conservative management (HR 5.44, 95% CI, 4.52-6.54)	Table F-16 of Appendix F
IMRT vs. EBRT plus BT	Biochemical failure	Wong et al. <sup>88</sup>	The 5-year biochemical failure rate was 87% and 94% for patients treated with IMRT and EBRT + BT, respectively.	Table F-8 of Appendix F
IMRT vs. EBRT plus BT	Progression to metastasis	Wong et al. <sup>88</sup>	Percentage distant metastasis was 97% and 97% for patients treated with IMRT and EBRT + BT, respectively.	Table F-12 of Appendix F
IMRT vs. EBRT plus BT	Adverse events	Wong et al. <sup>88</sup>	EBRT+ BT caused significantly more grade 2 and 3 acute and late GU toxicity compared with IMRT.	Table F-16 of Appendix F
IMRT vs. BT	Biochemical failure	Wong et al. <sup>88</sup>	The 5-year biochemical failure rate was 87% and 94% for patients treated with IMRT and BT, respectively.	Table F-8 of Appendix F
IMRT vs. BT	Progression to metastasis	Wong et al. <sup>88</sup>	Percentage distant metastases was 97% and 99% for patients treated with IMRT and BT, respectively.	Table F-12 of Appendix F
IMRT vs. BT	Adverse events	Wong et al. <sup>88</sup> Kim et al. <sup>60</sup>	Wong et al. BT caused significantly more grade 2 and 3 acute and late GU toxicity than IMRT. Kim et al. <sup>60</sup> GI toxicity did not differ significantly between treatments.	Table F-16 of Appendix F

**Table 16. Major findings reported by nonrandomized comparative studies for Key Question 1 (continued)**

Treatments Being Compared	Outcome	Evidence Base	Major Findings Reported in the Study	Detailed Results Abstracted
IMRT vs. conservative management	Adverse events	Kim et al. <sup>60</sup>	IMRT was associated with greater GI toxicity than conservative management (HR 4.33, 95% CI, 3.32 to 5.63)	Table F-16 of Appendix F
3D-CRT vs. EBRT plus BT	Biochemical failure	Wong et al. <sup>88</sup>	The 5-year biochemical failure rate was 74% and 94% for patients treated with 3D-CRT and EBRT + BT, respectively.	Table F-8 of Appendix F
3D-CRT vs. EBRT plus BT	Progression to metastasis	Wong et al. <sup>88</sup>	Percentage distant metastases was 96% and 97% for patients treated with 3D-CRT and EBRT + BT, respectively.	Table F-12 of Appendix F
3D-CRT vs. EBRT plus BT	Adverse events	Wong et al. <sup>88</sup>	EBRT + BT caused significantly more grade 2 and 3 acute and late GU toxicity compared with 3D-CRT.	Table F-16 of Appendix F
HIFU vs. HIFU plus ADT	Biochemical progression-free survival	Sumitomo et al. <sup>63</sup>	3-year biochemical progression-free survival among whole study population (53.8% vs. 78.0%)	Table F-7 in Appendix F
HIFU vs. HIFU plus ADT	QOL	Sumitomo et al. <sup>63</sup>	Transient grade 1 and 2 incontinence: 6 patients (2.3%) vs. 3 patients (1.1%)	Table F-14 of Appendix F
HIFU vs. HIFU plus ADT	Adverse events	Sumitomo et al. <sup>63</sup>	Grade 3 or 4 bladder neck/urethra stricture: 39 patients (15.0%) vs. 38 patients (14.1%) Rectourethral fistula: 4 patients (1.5%) vs. 3 patients (1.1%)	Table F-16 of Appendix F
IMRT plus BT vs. IMRT	QOL	Spratt et al. <sup>77</sup>	No difference in the percent of patients who retained full potency at the final followup visit.	Table F-14 of Appendix F
IMRT plus BT vs. IMRT	Adverse events	Spratt et al. <sup>77</sup>	GI toxicities and GU toxicities were similar for 7-year actuarial followup but were significantly higher in the IMRT plus BT group acutely.	Table F-16 of Appendix F
RP plus radiation vs. RP	Adverse events	Abern et al. <sup>90</sup>	The authors found that patients receiving radiation had a 70% increased risk of subsequent bladder cancer. After BT with or without EBRT, the risks were highest.	Table F-16 of Appendix F
RP vs. EBRT plus BT	Adverse events	Abern et al. <sup>90</sup>	The authors found that patients receiving radiation had a 70% increased risk of subsequent bladder cancer. After BT with or without EBRT, the risks were highest.	Table F-16 of Appendix F
RP vs. EBRT	Adverse events	Abern et al. <sup>90</sup>	The authors found that patients receiving radiation had a 70% increased risk of subsequent bladder cancer. After BT with or without EBRT the risks were highest.	Table F-16 of Appendix F
EBRT plus BT vs. radiation NOS	Adverse events	Abern et al. <sup>90</sup>	The authors found that patients receiving radiation had a 70% increased risk of subsequent bladder cancer. After BT with or without EBRT, the risks were highest.	Table F-16 of Appendix F
EBRT vs. radiation NOS	Adverse events	Abern et al. <sup>90</sup>	The authors found that patients receiving radiation had a 70% increased risk of subsequent bladder cancer. After BT with or without EBRT, the risks were highest.	Table F-16 of Appendix F

**Table 16. Major findings reported by nonrandomized comparative studies for Key Question 1 (continued)**

Treatments Being Compared	Outcome	Evidence Base	Major Findings Reported in the Study	Detailed Results Abstracted
EBRT vs. EBRT plus BT	PCSM	Shen et al. <sup>84</sup>	There was a significant difference in PCSM in favor of BT plus EBRT at a median followup of 6.4 years (HR 0.77; 95% CI, 0.66 to 0.90). The 10-year prostate cancer–specific mortality rate was 21.1% for EBRT and 13.4% for BT plus EBRT.	Table F-6 of Appendix F
EBRT vs. EBRT plus BT	Adverse events	Abern et al. <sup>90</sup>	The authors found that patients receiving radiation had a 70% increased risk of subsequent bladder cancer. After BT with or without EBRT, the risks were highest.	Table F-16 of Appendix F
3D-CRT plus IMRT vs. BT	Overall survival	Kibel et al. <sup>75</sup>	Adjusted 10-year survival rates were 82.6% and 81.7%, respectively.	Table F-4 of Appendix F
3D-CRT plus IMRT vs. BT	PCSM	Kibel et al. <sup>75</sup>	Adjusted 10-year PCSM 2.9% and 3%, respectively.	Table F-6 of Appendix F
RP vs. 3D-CRT plus IMRT	Overall survival	Kibel et al. <sup>75</sup>	HR with RP as referent is 1.6 (95% CI, 1 to 1.9), adjusted 10-year overall survival was 88% for RP and 82.6% for 3D-CRT plus IMRT	Table F-4 of Appendix F
RP vs. 3D-CRT plus IMRT	PCSM	Kibel et al. <sup>75</sup>	Adjusted 10-year PCSM was 1.8% and 2.9%, respectively, HR 1.5 (95% CI, 1.0 to 2.3)	Table F-6 of Appendix F
RRP vs. radiotherapy NOS	QOL	Resnick et al. <sup>55</sup>	No-control or frequent urinary leakage was significantly higher at the 2- and 5-year followup for RRP treated patients but by the 15-year followup this significant difference disappeared. The same pattern held for erectile dysfunction, with RRP treated patients faring worse. Bowel urgency was significantly worse for the radiotherapy group at the 2- and 5- year followup but this significant between-group difference ceased by the 15-year followup visit.	Table F-14 of Appendix F
BT vs. EB-IGRT	QOL	Mohammed et al. <sup>80</sup>	Late incontinence greater or equal to grade 3 was 0.3% for BT and 0.4% for EB-IGRT	Table F-14 of Appendix F
BT vs. EB-IGRT	Adverse events	Mohammed et al. <sup>80</sup>	The incidence of any acute grade 2 or higher GI or GU toxicities was lower in the BT group. Dysuria was most common among men who received BT alone. Rectal bleeding occurred at a higher rate in the EB-IGRT group.	Table F-16 of Appendix F
EB IGRT vs. EBRT plus BT	QOL	Mohammed et al. <sup>80</sup>	Late incontinence greater or equal to grade 3 was 0.4% for EB-IGRT and 1% for EBRT plus HDR-BT	Table F-14 of Appendix F
EB IGRT vs. EBRT plus BT	Adverse events	Mohammed et al. <sup>80</sup>	The incidence of urethral stricture and urinary retention was higher among men who received EBRT plus HDR-BT. Rectal bleeding occurred at a higher rate in the EB-IGRT group.	Table F-16 of Appendix F
BT vs. BT plus ADT	All-cause mortality	Dosoretz et al. <sup>82</sup>	There was a significant between-group difference in rates of all-cause mortality in favor of BT plus ADT (HR 1.24; 95% CI, 1.10 to 1.53).	Table F-2 of Appendix F
RRP vs. BT	Overall survival	Ferrer et al. <sup>91</sup>	At median followup of 6.02 years, no statistically significant difference between the treatment groups was found.HR 1.17; 95%, CI 0.47 to 2.94.	Table F-4 of Appendix F

**Table 16. Major findings reported by nonrandomized comparative studies for Key Question 1 (continued)**

Treatments Being Compared	Outcome	Evidence Base	Major Findings Reported in the Study	Detailed Results Abstracted
RRP vs. BT	Biochemical recurrence	Ferrer et al. <sup>91</sup>	Percentage of patients with biochemical relapse at 5.23 years was 17.1% and 16.1% for RRP and BT, respectively.	Table F-8 of Appendix F
RRP vs. BT	QOL	Ferrer et al. <sup>91</sup>	QOL was similar for both groups as measured by SF-36 and AUA-7. For the FACT-G, and FACT-P, there were significant between-group differences with RRP scoring lower on both scales.	Table F-14 of Appendix F

**Abbreviations:** 3D-CRT=Three-dimensional conformal radiation therapy; ADT=androgen-deprivation therapy; BT=brachytherapy; CI=confidence interval; EB-IGRT=external beam image-guided radiation therapy; EBRT=external beam radiation therapy; EPIC= Expanded Prostate Cancer Index Composite; FACT-G= Functional Assessment of Cancer Therapy–General questionnaire; FACT-P=Functional Assessment of Cancer Therapy–Prostate questionnaire; GI=gastrointestinal; GU=genitourinary; HDR-EBRT=high dose–rate external beam radiation therapy; HIFU=high-intensity focused ultrasound; HR=hazard ratio; IGRT= image-guided radiation therapy; IMRT= intensity-modulated radiation therapy; LRP=laparoscopic radical prostatectomy; NOS=not otherwise specified; PSM=prostate cancer–specific mortality; QOL=quality of life; RALRP=robotic-assisted laparoscopic radical prostatectomy; RP=radical prostatectomy; RRP=radical retropubic prostatectomy; WW=watchful waiting.

## Conclusions for KQ 1

A summary of the comparisons and outcomes we examined for KQ 1 is in Table 12. The overall evidence based on RCTs alone was sufficient to permit a conclusion for the following treatment comparisons and outcomes:

- Progression to metastases was reduced at 12 years among patients undergoing RP compared to those receiving WW (based on statistically significant differences between interventions in 2 medium risk-of-bias randomized trials).<sup>15,25,33,34</sup> (Strength of evidence: moderate.)
- Urinary incontinence (as an indirect measure of QOL) was lower among patients receiving WW than for those undergoing RP (based on 1 medium and 1 high risk-of-bias randomized trial).<sup>15,25,33,34</sup> (Strength of evidence: low.)
- Overall survival was higher in 3D-CRT plus ADT treated patients than in patients treated with 3D-CRT alone (based on 1 statistically significant difference between treatments in a single low risk-of-bias randomized study).<sup>35</sup> (Strength of evidence: low.)
- All-cause mortality was lower in patients treated with 3D-CRT plus ADT than in patients treated with 3D-CRT alone (based on a statistically significant difference between treatments in a single low risk-of-bias randomized study).<sup>35</sup> (Strength of evidence: low.)
- Prostate cancer–specific mortality was lower in patients treated with 3D-CRT plus ADT than in patients treated with 3D-CRT alone (based on a statistically significant difference between treatments in a single low risk-of-bias randomized study).<sup>35</sup> (Strength of evidence: low.)

Our strength-of-evidence grades for these patient-oriented outcomes also appear in Table 17 for RCTs across treatment categories and Table 18 from RCTs within treatment categories. The majority of the studies reviewed had medium risk of bias (see the pertinent section above) for objective outcomes and a rating of high for QOL-related outcomes, the only subjective outcomes reported by any of the included studies. Strength of evidence was assessed for overall mortality, overall survival, progression to metastases, prostate cancer–specific mortality and QOL. The strength-of-evidence grades for the nonrandomized comparative studies are reported in Table 19.

Based on consistent evidence from six nonrandomized comparison studies with high risk of bias, we drew two additional conclusions:

- All-cause mortality was significantly lower in patients treated with RP than in patients treated with EBRT.<sup>36-40,42</sup> (Strength of evidence: low.)
- Prostate cancer–specific mortality was significantly lower in patients treated with RP than in patients treated with EBRT.<sup>37-42</sup> (Strength of evidence: low.)

**Table 17. Key Question 1: Strength-of-evidence grades for randomized controlled trials across primary treatment categories**

Comparison	Outcome	Overall Risk of Bias	Consistency	Directness	Precision	Evidence Favors	SOE Grade
RP vs. WW <sup>33</sup> (1 study, n=695) SPCG-4 trial	All-cause mortality at the end of the 15-year followup period	Medium	Consistency unknown (single study)	Direct	Precise RR 0.75 (95% CI, 0.61 to 0.92) Effect size was statistically significant.	RP	Insufficient
RP vs. WW <sup>33</sup> (1 study, n=695) SPCG-4 trial	PCSM at the end of the 15-year followup period	Medium	Consistency unknown (single study)	Direct	Precise RR 0.62 (95% CI, 0.44 to 0.87) Effect size was statistically significant.	RP	Insufficient
RP vs. WW <sup>15,25</sup> (2 studies, n=1,426) SPCG-4 trial, PIVOT	All-cause mortality at the end of the 12-year followup period	Medium	Consistent	Direct	Imprecise SPCG-4: RR 0.82 (95% CI, 0.65 to 1.03) PIVOT: HR 0.88 (95% CI, 0.71 to 1.08) Neither effect size was statistically significant.	No significant difference between the interventions	Insufficient
RP vs. WW <sup>15,25</sup> (2 studies, n=1,426) SPCG-4 trial, PIVOT	PCSM at the end of the 12-year followup period	Medium	Inconsistent	Direct	Imprecise SPCG-4: RR 0.65 (95% CI, 0.45 to 0.94) PIVOT: HR 0.63 (95% CI, 0.36 to 1.09) 1 effect size was not statistically significant.	RP	Insufficient
RP vs. WW <sup>15</sup> (1 study, n=695) SPCG-4 trial	QOL (QOL high) at median followup of 12.2 years (range 7–17)	High	Consistency unknown (single study)	Direct	Imprecise OR: 1.01 (95% CI, 0.65 to 1.58), p=0.96	No significant difference between the interventions	Insufficient
RP vs. WW <sup>15,25</sup> (2 studies, n=1,426) SPCG-4 trial, PIVOT	QOL (urinary leakage at 2–4 year followup)	Medium <sup>a</sup>	Consistent	Direct	Precise SPCG-4: OR 2.3 (95% CI, 1.6 to 3.2), p <0.001 PIVOT: RR 2.69 (95% CI 1.61 to 4.51), p <0.001	WW	Low
RP vs. WW <sup>15,25</sup> (2 studies, n=1,426) SPCG-4 trial, PIVOT	QOL (erectile dysfunction at 2-4 year followup)	Medium	Inconsistent	Direct	Imprecise SPCG-4: OR: 0.86 (95% CI, 0.64–1.15), p=0.30 PIVOT: RR 1.84 (95% CI, 1.59 to 2.11), p <0.001	Unclear	Insufficient



**Table 17. Key Question 1: Strength-of-evidence grades for randomized controlled trials across primary treatment categories (continued)**

Comparison	Outcome	Overall Risk of Bias	Consistency	Directness	Precision	Evidence Favors	SOE Grade
RP vs. WW <sup>25</sup> (1 study, n=731) PIVOT	QOL (bowel dysfunction at 2 year followup)	Medium	Consistency unknown (single study)	Direct	Imprecise RR 1.08 (95% CI, 0.69 to 1.69), p=0.74	No significant difference between the interventions	Insufficient
RP vs. WW <sup>15</sup> (1 study, n=695) SPCG-4 trial	Progression to metastases at 15 years	Medium	Consistency unknown (single study)	Direct	Precise RR 0.59 (95% CI, 0.45 to 0.79)	RP	Insufficient
RP vs. WW <sup>15,25</sup> (2 studies, n=1,426) SPCG-4 trial, PIVOT	Progression to metastases at 12 years	Medium	Consistent	Direct	Precise SPCG-4: RR 0.65 (95% CI, 0.47 to 0.88) PIVOT: HR 0.40 (95% CI, 0.22 to 0.70)	RP	Moderate
RARP vs. LRP <sup>45</sup> (1 study, n=120)	QOL (urinary continence, erectile function at 1 year)	High	Consistency unknown (single study)	Direct	Precise Urinary continence: 95% vs. 83.3%, p = 0.042 Erectile function: 80% vs. 54.2%, p=0.02	RARP	Insufficient
RRP vs. BT <sup>44</sup> (1 study, n=200)	QOL at 5-year followup (global health, sexual function, bowel symptoms)	High	Consistency unknown (single study)	Direct	Imprecise (p-value was not statistically significant)	No significant difference between the interventions	Insufficient
EBRT vs. cryotherapy <sup>47</sup> (1 study, n=244)	Overall survival	Medium	Consistency unknown (single study)	Direct	Imprecise OR: 0.92 (95% CI 0.41 to 2.05), p=0.84.	No significant difference between the interventions	Insufficient
EBRT vs. cryotherapy <sup>47</sup> (1 study, n=244)	PCSM	Medium	Consistency unknown (single study)	Direct	Imprecise OR: 0.79 (95% CI 0.21 to 3.03), p=0.73	No significant difference between the interventions	Insufficient

**Table 17. Key Question 1: Strength-of-evidence grades for randomized controlled trials across primary treatment categories (continued)**

Comparison	Outcome	Overall Risk of Bias	Consistency	Directness	Precision	Evidence Favors	SOE Grade
EBRT vs. cryotherapy <sup>52</sup> (1 study, n=244)	QOL (bowel function)	High	Consistency unknown (single study)	Direct	Imprecise Bowel function scores at 3 years (84.1 vs. 88.1, p=0.092).	No significant difference between the interventions	Insufficient
EBRT vs. cryotherapy <sup>52</sup> (1 study, n=244)	QOL (urinary function)	High	Consistency unknown (single study)	Direct	Precise Urinary function scores at 3 years (88.6 vs. 93.0, p=0.043).	Cryotherapy	Insufficient
EBRT vs. cryotherapy <sup>52</sup> (1 study, n=244)	QOL (sexual function)	High	Consistency unknown (single study)	Direct	Precise Sexual function scores at 3 years (16.0 vs. 36.7, p<0.001).	EBRT	Insufficient

<sup>a</sup>The evidence base for this outcome contained one medium and one high risk-of-bias study; because of this borderline between medium and high risk the strength of evidence was lowered from moderate to low.

**Abbreviations:** BT=Brachytherapy; CI=confidence interval; EBRT=external beam radiation therapy; LRP=laparoscopic radical prostatectomy; OR=odds ratio; PCSM=prostate cancer-specific mortality; PIVOT=Prostate Cancer Intervention Versus Observation Trial; QOL=quality of life; RALRP=robotic-assisted laparoscopic radical prostatectomy; RP=radical prostatectomy; RR=relative risk; RRP=radical retropubic prostatectomy; SOE=strength of evidence; SPCG-4=Scandinavian Prostate Cancer Group Study 4; WW=watchful waiting.

**Table 18. Key Question 1: Strength-of-evidence grades for randomized controlled trials within primary treatment categories**

Comparison	Outcome	Overall Risk of Bias	Consistency	Directness	Precision	Evidence Favors	SOE Grade
RARP vs. LRP <sup>45</sup> (1 study, n=120)	QOL (continence recovery at 1 year)	High	Consistency unknown (single study)	Direct	Imprecise 95% vs. 83.3%, p=0.04 by chi-square but p=0.075 (not significant) by Fisher's exact test	RARP	Insufficient
RARP vs. LRP <sup>45</sup> (1 study, n=120)	QOL (sexual recovery at 1 year in nerve sparing cohort)	High	Consistency unknown (single study)	Direct	Precise 80% vs. 54.2%, p=0.02	RARP	Insufficient
RPP vs. RRP <sup>46</sup> (1 study, n=200)	QOL (continence recovery at 2 years)	High	Consistency unknown (single study)	Direct	Imprecise (p-value not statistically significant)	No significant difference between the interventions	Insufficient

**Table 18. Key Question 1: Strength-of-evidence grades for randomized controlled trials within primary treatment categories (continued)**

Comparison	Outcome	Overall Risk of Bias	Consistency	Directness	Precision	Evidence Favors	SOE Grade
RPP vs. RRP <sup>46</sup> (1 study, n=200)	QOL (erectile function at 2 years)	High	Consistency unknown (single study)	Direct	Precise 60% vs 42%, p=0.032	RRP	Insufficient
3D-CRT vs. 3D-CRT plus ADT <sup>35</sup> (1 study, n=206)	Overall survival at 8-year followup	Low	Consistency unknown (single study)	Direct	Precise Adjusted HR 3.0; 95% CI, 1.5 to 6.4	3D-CRT plus ADT	Low
3D-CRT vs. 3D-CRT plus ADT <sup>35</sup> (1 study, n=206)	All-cause mortality at median followup of 7.6 years	Low	Consistency unknown (single study)	Direct	Precise HR 1.8 (95% CI, 1.1 to 2.9) (44 vs. 30 deaths)	3D-CRT plus ADT	Low
3D-CRT vs. 3D-CRT plus ADT <sup>35</sup> (1 study, n=206)	PCSM at median 7.6-year followup	Low	Consistency unknown (single study)	Direct	Precise HR 4.1; 95% CI, 1.4 to 12.14 (14 vs. 4 deaths)	3D-CRT plus ADT	Low
EBRT vs. EBRT plus ADT <sup>43</sup> (1 study, n=1,979)	Overall survival at median 9.1-year followup	Medium	Consistency unknown (single study)	Direct	Precise HR 1.17; 95% CI, 1.10 to 1.35 (57% vs. 62% survival rate)	EBRT plus ADT	Insufficient
EBRT vs. EBRT plus ADT <sup>43</sup> (1 study, n=1,979)	PCSM at median 9.1-year followup	Medium	Consistency unknown (single study)	Direct	Precise HR 1.87; 95% CI, 1.27 to 2.74 (8 vs. 4 deaths)	EBRT plus ADT	Insufficient
EBRT vs. EBRT plus ADT <sup>43</sup> (1 study, n=558, subset of full sample)	QOL (always or almost always functioning sexually) at 1 year	High	Consistency unknown (single study)	Direct	Precise OR: 1.72 (1.17 to 2.52), p=0.004	EBRT	Insufficient

**Abbreviations:** ADT=Androgen-deprivation therapy; 3D-CRT=three-dimensional conformal radiation therapy; CI=confidence interval; EBRT=external beam radiotherapy; HR=hazard ratio; LRP= laparoscopic radical prostatectomy; PCSM=prostate cancer-specific mortality; QOL=quality of life; RALRP=robotic-assisted laparoscopic radical prostatectomy; RPP=radical perineal prostatectomy; RRP=radical retropubic prostatectomy; SOE=strength of evidence.

**Table 19. Key Question 1: Strength-of-evidence grades for nonrandomized comparative studies**

Comparison	Outcome	Overall Risk of Bias	Consistency	Directness	Precision	Evidence Favors	SOE Grade
RALRP vs.RRP <sup>65</sup> (1 study, n=882)	All-cause mortality	High	Consistency unknown (single study)	Direct	Imprecise	No significant between-group difference	Insufficient
RALRP vs.RRP <sup>65,68</sup> (2 studies, n=1,482)	PCSM	High	Consistent	Direct	Imprecise	No significant between-group difference	Insufficient
RALRP vs.RRP <sup>65,68</sup> (2 studies, n=1,482)	Progression to distant metastases	High	Consistent	Direct	Imprecise	No significant between-group difference	Insufficient
RALRP vs.RRP <sup>65,66,68</sup> (3 studies, n=2,108)	QOL	High	Inconsistent for continence, consistent for sexual dysfunction	Direct	Imprecise	No significant between-group difference for sexual function	Insufficient
RRP vs. 3D-CRT <sup>91</sup> (1 study, n=387)	Overall survival	High	Consistency unknown (single study)	Direct	Imprecise	No significant between-group difference	Insufficient
RRP vs. 3D-CRT <sup>87</sup> (1 study, n=948)	PCSM	High	Consistency unknown (single study)	Direct	Precise	RRP	Insufficient
RRP vs. 3D-CRT <sup>91</sup> (1 study, n=387)	QOL	High	Consistency unknown (single study)	Direct	Imprecise	No significant between-group difference	Insufficient
3D-CRT vs. BT <sup>91</sup> (1 study, n=511)	Overall survival	High	Consistency unknown (single study)	Direct	Imprecise	No significant between-group difference	Insufficient
3D-CRT vs. BT <sup>88</sup> (1 study, n=495)	Progression to metastases	High	Consistency unknown (single study)	Direct	Imprecise	No significant between-group difference	Insufficient

**Table 19. Key Question 1: Strength-of-evidence grades for nonrandomized comparative studies (continued)**

Comparison	Outcome	Overall Risk of Bias	Consistency	Directness	Precision	Evidence Favors	SOE Grade
3D-CRT vs. BT <sup>91</sup> (1 study, n=511)	QOL	High	Consistency unknown (single study)	Direct	Imprecise	No significant between- group difference	Insufficient
RP vs. EBRT <sup>36-40,42</sup> (6 studies, n=22,771)	All-cause mortality	High	Consistent	Direct	Precise	RP	Low
RP vs. EBRT <sup>37-42</sup> (6 studies, n=23,301)	PCSM	High	Consistent	Direct	Precise	RP	Low
RP vs. EBRT <sup>85</sup> (1 study, n=895)	QOL	High	Consistency unknown (1 study)	Direct	Precise	RP	Insufficient
RP vs. BT <sup>75</sup> (1 study, n=8,165)	Overall survival	High	Consistency unknown (1 study)	Direct	Precise	RP	Insufficient
RP vs. BT <sup>37,40</sup> (2 studies, n=14,172)	All-cause mortality	High	Inconsistent	Direct	Imprecise	No between- group difference	Insufficient
RP vs. BT <sup>37,40,75</sup> (3 studies, n=22,337)	PCSM	High	Inconsistent	Direct	Imprecise	No between- group difference	Insufficient
RP vs. BT <sup>85</sup> (1 study, n=909)	QOL	High	Consistency unknown (1 study)	Direct	Precise for urinary and bowel problems Imprecise for sexual problems	RP	Insufficient
EBRT vs. BT <sup>37</sup> (1 study, n=8,741)	All-cause mortality	High	Consistency unknown (1 study)	Direct	Precise	BT	Insufficient
EBRT vs. BT <sup>37,84</sup> (2 studies, n=19,020)	PCSM	High	Consistent	Direct	Precise	BT	Insufficient
EBRT vs. BT <sup>85</sup> (1 study, n=598)	QOL	High	Consistency unknown (1 study)	Direct	Imprecise	No between- group difference	Insufficient
RALRP vs. LRP <sup>62</sup> (1 study, n=2,386)	QOL (urinary, bowel, sexual)	High	Consistency unknown (1 study)	Direct	Precise for continence and sexual function	RALRP	Insufficient

**Table 19. Key Question 1: Strength-of-evidence grades for nonrandomized comparative studies (continued)**

Comparison	Outcome	Overall Risk of Bias	Consistency	Directness	Precision	Evidence Favors	SOE Grade
RP vs. observation <sup>36,42,72,73</sup> (4 studies, n=131,114)	All-cause mortality	High	Inconsistent	Direct	Imprecise	RP	Insufficient
RP vs. observation <sup>42,72,73</sup> (3 studies, n=63,219)	PCSM	High	Inconsistent	Direct	Imprecise	RP	Insufficient
RRP vs. cryotherapy <sup>71</sup> (1 study, n=216)	QOL	High	Consistency unknown (1 study)	Direct	Precise for continence Imprecise for sexual and bowel problems	Cryotherapy	Insufficient
Cryotherapy vs. BT <sup>57,71</sup> (2 studies, n=11,131)	QOL	High	Consistent on sexual function Inconsistent for bowel problems	Direct	Precise for sexual function	BT	Insufficient
RALRP vs. cryotherapy <sup>71</sup> (1 study, n=569)	QOL	High	Consistency unknown (1 study)	Direct	Precise for continence Imprecise for sexual and bowel problems	Cryotherapy	Insufficient
ADT vs. observation <sup>78</sup> (1 study, n=19,271)	All-cause mortality	Medium	Consistency unknown (1 study)	Direct	Precise	Observation	Insufficient
ADT vs. observation <sup>78</sup> (1 study, n=19,271)	PCSM	Medium	Consistency unknown (1 study)	Direct	Precise	Observation	Insufficient
IMRT vs. 3D-CRT <sup>88</sup> (1 study, n=584)	Progression to metastases	High	Consistency unknown (1 study)	Direct	Imprecise	No between-group difference	Insufficient
IMRT vs. 3D-CRT <sup>58</sup> (1 study, n=12,976)	QOL	High	Consistency unknown (1 study)	Direct	Precise for sexual function Imprecise for continence	3D-CRT	Insufficient

**Table 19. Key Question 1: Strength-of-evidence grades for nonrandomized comparative studies (continued)**

Comparison	Outcome	Overall Risk of Bias	Consistency	Directness	Precision	Evidence Favors	SOE Grade
IMRT vs. proton beam therapy <sup>58</sup> (1 study, n=7,351)	QOL	High	Consistency unknown (1 study)	Direct	Imprecise for continence and sexual function	No between-group difference	Insufficient
3D-CRT vs. proton beam therapy <sup>58</sup> (1 study, n=6,995)	QOL	High	Consistency unknown (1 study)	Direct	Imprecise for continence Precise for sexual function	3D-CRT	Insufficient
BT vs. BT plus EBRT <sup>84</sup> (1 study, n=3,376)	PCSM	High	Consistency unknown (1 study)	Direct	Imprecise	No between-group difference	Insufficient
BT vs. BT plus EBRT <sup>80</sup> (1 study, n=864)	QOL	High	Consistency unknown (1 study)	Direct	Imprecise	No between-group difference	Insufficient
Surgery vs. radiation <sup>42</sup> (1 study, n=1,038)	Overall survival	High	Consistency unknown (1 study)	Direct	Precise	RP	Insufficient
Surgery vs. radiation <sup>42</sup> (1 study, n=1,038)	PCSM	High	Consistency unknown (1 study)	Direct	Precise	RP	Insufficient
EBRT vs. observation <sup>42</sup> (1 study, n=756)	All-cause mortality	High	Consistency unknown (1 study)	Direct	Imprecise	No between-group difference	Insufficient
EBRT vs. observation <sup>42,59</sup> (2 studies, n=69,553)	PCSM	High	Consistent	Direct	Precise	EBRT	Insufficient
RP vs. ADT <sup>79</sup> (1 study, n=3,248)	Overall survival	High	Consistency unknown (1 study)	Direct	Precise	RP	Insufficient
RP vs. ADT <sup>39,79</sup> (2 studies, n=9,643)	All-cause mortality	High	Consistent	Direct	Precise	RP	Insufficient
RP vs. ADT <sup>39,79</sup> (2 studies, n=9,643)	PCSM	High	Consistent	Direct	Precise	RP	Insufficient
RRP vs. BT <sup>91</sup> (1 study, n=510)	QOL	High	Consistency unknown (1 study)	Direct	Imprecise	No between-group difference	Insufficient

**Table 19. Key Question 1: Strength-of-evidence grades for nonrandomized comparative studies (continued)**

Comparison	Outcome	Overall Risk of Bias	Consistency	Directness	Precision	Evidence Favors	SOE Grade
RRP vs. BT <sup>91</sup> (1 study, n=510)	Overall survival	High	Consistency unknown (1 study)	Direct	Imprecise	No between-group difference	Insufficient
EB-IGRT vs. EBRT plus BT <sup>80</sup> (1 study, n=1,903)	QOL	High	Consistency unknown (1 study)	Direct	Imprecise	No between-group difference	Insufficient
IGRT vs. BT <sup>86</sup> (1 study, n=1,016)	Overall survival	High	Consistency unknown (1 study)	Direct	Precise	BT	Insufficient
IGRT vs. BT <sup>86</sup> (1 study, n=1,016)	Cause-specific survival	High	Consistency unknown (1 study)	Direct	Imprecise	No between-group difference	Insufficient
IGRT vs. BT <sup>86</sup> (1 study, n=1,016)	Progression to metastases	High	Consistency unknown (1 study)	Direct	Imprecise	No between-group difference	Insufficient
EBRT vs. ADT <sup>39</sup> (1 study, n=2,472)	All-cause mortality	High	Consistency unknown (1 study)	Direct	Precise	EBRT	Insufficient
EBRT vs. ADT <sup>39</sup> (1 study, n=2,472)	PCSM	High	Consistency unknown (1 study)	Direct	Precise	EBRT	Insufficient
3D-CRT vs. BT <sup>88</sup> (1 study, n=495)	Progression to metastases	High	Consistency unknown (1 study)	Direct	Imprecise	No between-group difference	Insufficient
IMRT vs. EBRT plus BT <sup>88</sup> (1 study, n=358)	Progression to metastases	High	Consistency unknown (1 study)	Direct	Imprecise	No between-group difference	Insufficient
IMRT vs. BT <sup>88</sup> (1 study, n=539)	Progression to metastases	High	Consistency unknown (1 study)	Direct	Imprecise	No between-group difference	Insufficient
3D-CRT vs. EBRT plus BT <sup>88</sup> (1 study, n=314)	Progression to metastases	High	Consistency unknown (1 study)	Direct	Imprecise	No between-group difference	Insufficient
HIFU vs. HIFU plus ADT <sup>63</sup> (1 study, n=530)	QOL	High	Consistency unknown (1 study)	Direct	Imprecise	No between-group difference	Insufficient
IMRT plus BT vs. IMRT <sup>77</sup> (1 study, n=870)	QOL	High	Consistency unknown (1 study)	Direct	Imprecise for potency	No between-group difference	Insufficient
EBRT vs. EBRT plus BT <sup>84</sup> (1 study, n=11,835)	PCSM	High	Consistency unknown (1 study)	Direct	Precise	EBRT plus BT	Insufficient



**Table 19. Key Question 1: Strength-of-evidence grades for nonrandomized comparative studies (continued)**

Comparison	Outcome	Overall Risk of Bias	Consistency	Directness	Precision	Evidence Favors	SOE Grade
3D-CRT plus IMRT vs. BT <sup>75</sup> (1 study, n=3,944)	Overall survival	High	Consistency unknown (1 study)	Direct	Imprecise	No between-group difference	Insufficient
3D-CRT plus IMRT vs. BT <sup>75</sup> (1 study, n=3,944)	PCSM	High	Consistency unknown (1 study)	Direct	Imprecise	No between-group difference	Insufficient
RP vs. 3D-CRT plus IMRT <sup>75</sup> (1 study, n=9,749)	Overall survival	High	Consistency unknown (1 study)	Direct	Imprecise	No between-group difference	Insufficient
RP vs. 3D-CRT plus IMRT <sup>75</sup> (1 study, n=9,749)	PCSM	High	Consistency unknown (1 study)	Direct	Imprecise	No between-group difference	Insufficient
RRP vs. radiotherapy NOS <sup>55</sup> (1 study, n=1,655)	QOL	High	Consistency unknown (1 study)	Direct	Precise	Sexual function and incontinence: Radiotherapy NOS Bowel problems: RRP	Insufficient
BT vs. EB-IGRT <sup>80</sup> (1 study, n=1,456)	QOL	High	Consistency unknown (1 study)	Direct	Imprecise for incontinence	No between-group difference	Insufficient

**Abbreviations:** 3D-CRT=Three-dimensional conformal radiation therapy; ADT=androgen-deprivation therapy; BT=brachytherapy; EB-IGRT=external beam image-guided radiation therapy; EBRT=external beam radiation therapy; HIFU=high-intensity focused ultrasound; IGRT=image-guided radiation therapy; IMRT=intensity-modulated radiation therapy; LRP=laparoscopic radical prostatectomy; NOS=not otherwise specified; PCSM=prostate cancer-specific mortality; QOL=quality of life; RALRP=robotic-assisted laparoscopic radical prostatectomy; RP=radical prostatectomy; RRP=radical retropubic prostatectomy; SOE=strength of evidence.

## Key Question 2. Specific Patient Characteristics Affecting the Outcomes of Prostate Cancer Therapies

In this section, we summarize findings from RCTs and nonrandomized comparative studies that stratified data by patient characteristics (Tables 20–27). Table 20 compares major primary treatment options and reports clinical outcome measures for the RCTs across primary treatment categories. Table 21 compares major primary treatment options and reports clinical outcome measures for the RCTs within primary treatment categories. Table 23 compares major primary treatment options and reports clinical outcome measures for the nonrandomized comparative studies.

### Key Points

RCTs that performed subgroup analyses based on patient characteristics reported the following. In all cases, the strength of evidence was insufficient to allow conclusions.

- At 15-year followup, the Scandinavian Prostate Cancer Group-4 (SPCG-4) trial identified a significant reduction in all-cause mortality, prostate cancer–specific mortality (PCSM) and progression to metastases in the younger-than-65 age category but not in the 65-or-older category.
- At 10-year followup, the Prostate Cancer Intervention Versus Observation Trial (PIVOT) found no significant difference between interventions in all-cause mortality and PCSM in either the younger-than-65 age category or in the 65-or-older age group.
- Among patients with no or minimal comorbidity in a single RCT, all-cause mortality was higher for the EBRT-alone group than for the EBRT-plus-ADT group. Among men with moderate or severe comorbidity, all-cause mortality was not significantly different between the two treatment groups.
- In a single RCT, EBRT plus ADT was associated with a significantly lower PCSM than EBRT alone among men older than 70 years of age, but not among men 70 years of age or younger, and among white patients but not among black patients.

### Detailed Synthesis

#### Randomized Controlled Trials

All abstracted data for the outcome measures that address this KQ appear in Appendix F. Table 22 summarizes major findings reported by the RCTs and is intended to provide a roadmap to the abstracted data, including the key statistics, for each comparison and reported outcome. The strength-of-evidence grades for selected outcomes (overall survival, all-cause mortality, progression to metastases, and QOL) for the studies that address this Key Question are provided in Table 25 (RCTs across primary treatment categories) and Table 26 (RCTs within primary treatment categories).

**Table 20. Overview of randomized controlled trials across primary treatment categories (2 trials): Key Question 2**

Study	Interventions and Number of Patients	Patient Characteristics	Outcomes	Duration
Wilt et al. 2012 <sup>25</sup> Prostate Intervention Versus Observation Trial (PIVOT)	RP: 364 patients vs. Observation: 367 patients	Age Race Comorbidity status	All-cause mortality PCSM	Median followup of 10 years
Bill-Axelson et al. 2011 <sup>33</sup> Scandinavian Prostate Cancer Group-4 (SPCG-4) trial	RP: 347 patients vs. WW: 348 patients	Age	All-cause mortality PCSM Progression to metastases	Median followup of 15 years

**Abbreviations:** PCSM=prostate cancer-specific mortality, RP=radical prostatectomy, WW=watchful waiting.

**Table 21. Overview of randomized controlled trials within primary treatment categories (2 trials): Key Question 2**

Study	Interventions and Number of Patients	Patient Characteristics	Outcomes	Duration
Jones et al. 2011 <sup>43</sup>	EBRT: 992 patients vs. EBRT plus short-term ADT: 987 patients	Age Race	Overall survival PCSM Biochemical failure	Median followup of 9.1 years
D'Amico et al. 2008 <sup>35</sup> Same study as Nguyen et al. 2010 <sup>53</sup>	EBRT: 104 patients vs. EBRT plus ADT: 102 patients	Comorbidity status	All-cause mortality	Median followup of 7.6 years

**Abbreviations:** ADT=Androgen-deprivation therapy; EBRT=external beam radiation therapy; PCSM=prostate cancer-specific mortality.

**Table 22. Major findings reported by randomized controlled trials for Key Question 2**

Treatments Being Compared	Outcome	Evidence Base	Major Findings Reported in the Study	Detailed Results Abstracted
RP vs. observation	All-Cause Mortality	PIVOT Wilt et al. <sup>25</sup>	No difference in all-cause mortality was found when stratified according to age (younger than 65 years or 65 years or older), race (white, black, or other), Charlson Comorbidity score (0 or ≥1), self-reported performance status (0, 1–4) or 0=Fully Active; 1=Symptoms but ambulatory and able to do light work, 2=No work but self-care and active 50% of waking hours, 3=Limited self-care, confined to bed or chair >50% of waking hours, 4=Completely disabled.	Table F-1 in Appendix F
RP vs. WW	All-Cause Mortality	SPCG-4 Bill-Axelson et al. <sup>15,33,34</sup>	The authors evaluated the interaction between treatment and age (<65 years vs. ≥65 years) and reported a significant reduction in all-cause mortality among men who were <65 years of age treated with RP (p=0.003).	Table F-1 in Appendix F

**Table 22. Major findings reported by randomized controlled trials for Key Question 2 (continued)**

Treatments Being Compared	Outcome	Evidence Base	Major Findings Reported in the Study	Detailed Results Abstracted
RP vs. observation	PCSM	PIVOT Wilt et al. <sup>25</sup>	No difference in PCSM was found when stratified according to age (<65 years or ≥65 years), race (white, black, or other), Charlson Comorbidity score (0 or ≥1), self-reported performance status between both groups (0, 1–4) or 0=Fully Active, 1=Symptoms but ambulatory and able to do light work, 2=No work but self-care and active 50% of waking hours, 3=Limited self-care, confined to bed or chair >50% of waking hours, 4=Completely disabled.	Table F-5 in Appendix F
RP vs. WW	PCSM	SPCG-4 Bill-Axelsson et al. <sup>15,33,34</sup>	The authors evaluated the interaction between treatment and age (<65 years vs. ≥65 years) and reported a significant reduction in PCSM among men <65 years treated with RP relative to those treated with WW.	Table F-5 in Appendix F
RP vs. WW	Progression to metastases	SPCG-4 Bill-Axelsson et al. <sup>15,33,34</sup>	The author evaluated the interaction between treatment and age (<65 years vs. ≥65 years) and reported a significant reduction in progression to metastases among RP treated men in the <65 years age group.	Table F-11 in Appendix F
EBRT vs. EBRT plus ADT	Overall survival	Jones et al. <sup>43</sup>	The statistically significant advantage of EBRT plus ADT over EBRT alone in overall survival was observed among the white patients but not among the black patients. When the patients were stratified by age, no statistically significant advantage of EBRT plus ADT over EBRT alone in overall survival was observed among the ≤70 years of age or the >70 years of age category.	Table F-3 in Appendix F
EBRT vs. EBRT plus ADT	PCSM	Jones et al. <sup>43</sup>	EBRT plus ADT was associated with significantly lower PCSM in comparison with EBRT alone among the white patients, but not among the black patients. EBRT plus ADT was associated with significantly lower cancer-specific mortality in comparison with EBRT alone among men >70 years of age, but not among men ≤70 years of age.	Table F-5 in Appendix F
EBRT vs. EBRT plus ADT	Biochemical failure	Jones et al. <sup>43</sup>	EBRT plus ADT was associated with significantly lower biochemical failure rates in all subgroup analyses (age ≤70, age >70 years, white, and black) in comparison with EBRT alone.	Table F-7 in Appendix F

**Table 22. Major findings reported by randomized controlled trials for Key Question 2 (continued)**

Treatments Being Compared	Outcome	Evidence Base	Major Findings Reported in the Study	Detailed Results Abstracted
3D-CRT vs. 3D-CRT plus ADT	All-cause mortality	D'Amico et al. <sup>35</sup> Same study as Nguyen et al. <sup>53</sup>	Among patients with no or minimal comorbidity, all-cause mortality was higher for the EBRT alone group than for the EBRT plus ADT group. Among men with moderate or severe comorbidity, all-cause mortality was not significantly different between the 2 treatment groups.	Table F-1 in Appendix F

**Abbreviations:** 3D-CRT=Three-dimensional conformal radiation therapy; ADT=androgen-deprivation therapy; EBRT=external beam radiation therapy; PCSM=prostate cancer specific mortality, PIVOT= Prostate Intervention Versus Observation Trial. RP=radical prostatectomy; SPCG-4= Scandinavian Prostate Cancer Group-4; WW=watchful waiting.

## Nonrandomized Comparative Studies

All abstracted data for the outcome measures that address this KQ appear in Appendix F. Table 24 summarizes major findings reported by the non-RCTs and is intended to provide a roadmap to the abstracted data, including the key statistics, for each comparison and reported outcome. The strength-of-evidence grades for the nonrandomized studies that address this Key Question are provided in Table 27. The grades are only for the selected outcomes measures, including overall or prostate cancer-specific mortalities and QOL reported using general health status scores.

**Table 23. Overview of nonrandomized comparative studies (9 studies): Key Question 2**

Study	Number of Patients	Patient Characteristics	Outcomes	Duration
Mukherjee et al. 2014 <sup>37</sup>	RP: 5,805 patients vs. EBRT: 2,183 patients vs. BT: 2,936 patients	Age	AEs (myodysplastic syndrome)	Median 3.05 years
DeGroot et al. 2013 <sup>41</sup>	RP: 458 patients (cohort) vs. RP: 36 patients (cases) vs. EBRT: 518 patients (cohort) vs. EBRT: 78 patients (cases)	Comorbidity status	PCSM	Median 51 months' followup
Ferrer et al. 2013 <sup>91</sup>	RRP: 193 patients vs. 3D-CRT: 194 patients vs. BT: 317 patients	Age	Overall survival	Median 6.06-year followup
Hoffman et al. 2013 <sup>38</sup>	RP: 1,164 patients vs. EBRT: 491 patients	Age Comorbidity status	All-cause mortality PCSM	15-year followup
Wirth et al. 2013 <sup>74</sup>	RRP: 600 patients vs. LRP: 244 patients	Age	BPFS	Median followup of 6.6 years and 4.6 years respectively

**Table 23. Overview of nonrandomized comparative studies (9 studies): Key Question 2 (continued)**

Study	Number of Patients	Patient Characteristics	Outcomes	Duration
Abdollah et al. 2012 <sup>59</sup>	EBRT: 46,521 patients vs. Observation: 22,276 patients	Age Comorbidity status	PCSM	10-year followup
Kibel et al. 2012 <sup>75</sup>	RP: 6,485 patients 3D-CRT: 2,264 patients BT: 1,680 patients	Age Race Comorbidity status	Overall survival PCSM	10 year followup
Rice et al. 2011 <sup>36</sup>	RP: 194 patients vs. EBRT: 252 patients vs. WW without secondary treatment: 214 patients vs. WW with secondary treatment: 110 patients	Age Race Comorbidity status	Overall mortality BPFS (active treatment groups), progression-free survival (WW without secondary treatment)	Mean followup time 6.8±4.0 years
Dosoretz et al. 2010 <sup>82</sup>	BT: 1,391 patients vs. BT plus ADT: 1,083 patients	Age	All-cause mortality	Median followup 4.8 years

**Abbreviations:** 3D-CRT=Three-dimensional conformal radiation therapy; ADT=androgen deprivation therapy; AEs=adverse events; BPFS=biochemical progression-free survival; BT=brachytherapy; EBRT=external beam radiation therapy; LRP=laparoscopic radical prostatectomy; PCSM=prostate cancer-specific mortality; RP=radical prostatectomy; RRP=radical retropubic prostatectomy; WW=watchful waiting.

**Table 24. Major findings reported by nonrandomized comparative studies for Key Question 2**

Treatments Being Compared	Outcome	Evidence Base	Major Findings Reported in the Study	Detailed Results Abstracted
RP vs. WW with and without secondary treatment	All-cause mortality	Rice et al. <sup>36</sup>	Rice et al. <sup>36</sup> compared RP, EBRT, and WW with or without secondary treatment and found age was a significant predictor of overall mortality but race was not a significant predictor of overall mortality. Compared to patients with no comorbidities, overall mortality was significantly higher for those with 2 or more comorbidities.	Table F-4 in Appendix F
RP vs. EBRT	Hoffman et al. <sup>38</sup> All-cause mortality PCSM DeGroot et al. <sup>41</sup> PCSM Mukherjee et al. 2014 <sup>37</sup> AEs Rice et al. <sup>36</sup> All-cause mortality	Hoffman et al. <sup>38</sup> DeGroot et al. <sup>41</sup> Mukherjee et al. <sup>37</sup> Rice et al. <sup>36</sup>	Hoffman et al. <sup>38</sup> For the 2 age groups (55–64 and 65–74 years) analyzed, overall mortality was lower among men who underwent RP compared with EBRT. In the 2 comorbidity categories (men with no comorbidity or with any reported comorbidity) analyzed, all-cause mortality was lower in the RP group than with EBRT. For the 2 age groups (55–64 and 65–74 years) analyzed, PCSM was lower among men who underwent RP than with EBRT. In the 2 comorbidity categories (no comorbidity vs. any comorbidity) analyzed, PCSM was lower in the RP group compared with EBRT. DeGroot et al. <sup>41</sup> The study authors reported that they investigated whether the competing risk of death from comorbid illness could explain their findings and found that none of their results were statistically significant. Mukherjee et al. <sup>37</sup> compared RP, EBRT, and BT and found advanced age was a significant risk factor for developing MDS. Rice et al. <sup>36</sup> compared RP, EBRT, and WW with or without secondary treatment and found age was a significant predictor of overall mortality but race was not a significant predictor of overall mortality. Compared to patients with no comorbidities, overall mortality was significantly higher for those with two or more comorbidities.	Table F-2 in Appendix F
RP vs. 3D-CRT	Overall survival PCSM	Kibel et al. <sup>75</sup>	Age, race, and comorbidity status were all significantly related to OS. No between-treatment group differences were noted. Age, race, and comorbidity status were not significantly associated with PCSM.	Table F-4 in Appendix F Table F-6 in Appendix F

**Table 24. Major findings reported by nonrandomized comparative studies for Key Question 2 (continued)**

Treatments Being Compared	Outcome	Evidence Base	Major Findings Reported in the Study	Detailed Results Abstracted
BT vs. 3D-CRT	Kibel et al. <sup>75</sup> Overall survival PCSM Ferrer et al. <sup>91</sup> Overall survival	Kibel et al. <sup>75</sup> Ferrer et al. <sup>91</sup>	Kibel et al. <sup>75</sup> compared RP, 3D-CRT, and BT and found age, race, and comorbidity status were all significantly related to OS. No between-treatment-group differences were noted. Age, race, and comorbidity status were not significantly associated with PCSM. Ferrer et al. <sup>91</sup> compared RRP, 3D-CRT, and BT and found no significant effect among treatments when comparing age younger than 65 years vs. 65–70 years (HR 1.96; 95% CI, 0.89 to 4.30). They reported a significant effect when patients younger than 65 years were compared with those older than 70 years: (HR 2.95; 95% CI, 1.34 to 6.47).	Table F-4 in Appendix F Table F-6 in Appendix F
EBRT vs. BT	AEs	Mukherjee et al. <sup>37</sup>	Advanced age was a significant risk factor for developing MDS.	Table F-16 in Appendix F
RP vs. BT	Mukherjee et al. <sup>37</sup> AEs Kibel et al. <sup>75</sup> Overall survival PCSM	Mukherjee et al. <sup>37</sup> Kibel et al. <sup>75</sup>	Mukherjee et al. <sup>37</sup> Compared RP, EBRT, and BT and reported advanced age was a significant risk factor for developing MDS. Kibel et al. <sup>75</sup> RP, 3D-CRT, and BT and reported age, race, and comorbidity status were all significantly related to OS. No between-treatment-group differences were noted. Age, race, and comorbidity status were not significantly associated with PCSM.	Table F-16 in Appendix F
LRP vs. RRP	Biochemical progression–free survival	Wirth et al. <sup>74</sup>	Age was not a significant prognostic factor in biochemical progression–free survival.	Table F-7 in Appendix F
RRP vs. 3D-CRT	Overall survival	Ferrer et al. <sup>91</sup>	Ferrer et al. <sup>91</sup> evaluated the effect of age on overall survival at median followup of 6.06 years. The authors reported the following using Cox regression models among treatment groups: Age group younger than 65 years vs. 65–70 years: HR 1.96; 95% CI, 0.89 to 4.30. Age group less than 65 years vs. older than 70 years: HR 2.95; 95% CI, 1.34 to 6.47.	Table F-4 in Appendix F
RRP vs. BT	Overall survival	Ferrer et al. <sup>91</sup>	Ferrer et al. <sup>91</sup> evaluated the effect of age on overall survival at median followup of 6.06 years. The authors reported the following using Cox regression models among treatment groups: Age group younger than 65 years vs. 65–70 years: HR 1.96; 95% CI, 0.89 to 4.30. Age group younger than 65 years vs. older than 70 years: HR 2.95; 95% CI, 1.34 to 6.47.	Table F-4 in Appendix F



**Table 24. Major findings reported by nonrandomized comparative studies for Key Question 2 (continued)**

Treatments Being Compared	Outcome	Evidence Base	Major Findings Reported in the Study	Detailed Results Abstracted
BT vs. BT Plus ADT	All-cause mortality	Dosoretz et al. <sup>82</sup>	In the subgroup of men younger than 73 years of age, BT plus ADT was not associated with a significantly increased risk of all-cause mortality. However, BT plus ADT was associated with a significantly increased risk of all-cause mortality in men aged 73 years or older.	Table F-2 in Appendix F
EBRT vs. observation	Abdollah et al. <sup>59</sup> PCSM Rice et al. <sup>36</sup> Overall mortality, biochemical progression-free survival	Abdollah et al. <sup>59</sup> Rice et al. <sup>36</sup>	Abdollah et al. <sup>59</sup> compared EBRT with observation and found that for all three comorbidity subgroups analyzed (Charlson comorbidity index of 0, 1, and >2), the 10-year PCSM rates were lower among patients who underwent EBRT than among those under observation. For 2 age groups (65–69 and 70–74 years), the 10-year prostate cancer–specific mortality rates were not significantly different between the EBRT and the observation groups. But for the age group of 75–80 years, the 10-year prostate cancer–specific mortality rate was significantly lower for the EBRT group than the observation group. Rice et al. <sup>36</sup> found that age and presence of 2 or more comorbidities were significant predictors of overall mortality, but not biochemical progression-free survival. Race was not a significant predictor for any outcome.	Table F-6 in Appendix F

**Abbreviations:** 3D-CRT=Three-dimensional conformal radiation therapy; ADT=androgen-deprivation therapy; AEs=adverse events, BT=brachytherapy; CI=confidence interval; EBRT=external beam radiation therapy; HR=hazard ratio; LRP=laparoscopic radical prostatectomy; MDS=myelodysplastic syndromes; OS=overall survival; PCSM=prostate cancer–specific mortality, RP=radical prostatectomy, RRP=radical retropubic prostatectomy, WW=watchful waiting.

**Table 25. Key Question 2: Strength-of-evidence grades for randomized controlled trials across primary treatment categories**

Comparison	Outcome	Overall Risk of Bias	Consistency	Directness	Precision	Evidence Favors	SOE Grade
RP vs. WW <sup>25</sup>	All-cause mortality for patients (age younger than 65 years [n=93] and 65 years or older [n=261]; white [n=236], black [n=99], other [n=19]; Charlson score 0 [n=168] or ≥1 [n=186]; performance score 0 [n=285] or 1–4 [n=69]) at 10-year followup	Medium	Consistency unknown (single study)	Direct	Imprecise (reported p-values for interaction were not significant for all subgroups)	No significant difference between the interventions for any of the subgroups assessed (age, race, comorbidity status, performance status)	Insufficient for all patient subgroups
	PCSM for patients (age younger than 65 years [n=18] and 65 years or older [n=34]; white [n=37], black [n=12], other [n=3]; Charlson score 0 [n=33] or ≥1 [n=19]; Performance score 0 [n=43] or 1–4 [n=9]) at 10-year followup	Medium	Consistency unknown (single study)	Direct	Imprecise (reported p-values for interaction were not significant for all subgroups)	No significant difference between the interventions for any of the subgroups assessed (age, race, comorbidity status, performance status)	Insufficient for all patient subgroups
RP vs. WW <sup>33</sup>	Overall mortality for patients age younger than 65 years at 8- and 12-year followup was approximately doubled among the WW patients compared to the RP treated patients.	Medium	Consistency unknown (single study)	Direct	Precise ARR: 11.4 (3.1 to 19.6) and 18.3 (7.8 to 28.8) for 8- and 12-year followup, respectively.	RP	Insufficient for patient subgroup*
	PCSM for patients younger than 65 years at 8- and 12-year followup was approximately doubled in the WW patients compared to RP treated patients.	Medium	Consistency unknown (single study)	Direct	Precise ARR: 8.2 (1.9 to 14.4) and 11.2 (2.6 to 19.8) for 8- and 1-year followup, respectively RR 0.49 (95% CI, 0.31 to 0.79)	RP	Insufficient for patient subgroup*
	Progression to metastases for patients younger than 65 years at 8- and 12-year follow was reduced among those treated with RP compared to those treated with WW.	Medium	Consistency unknown (single study)	Direct	Precise ARR: 12.1 (4.0 to 20.1) for 8-year followup and RR 0.52 (0.34 to 0.81), p=0.006 for 12-year followup	RP	Insufficient for patient subgroup*

\*SOE grading reduced by one level based on subgroup analysis (see methods section for further details).

**Abbreviations:** ARR=Absolute risk reduction, CI=confidence interval; PCSM=prostate cancer-specific mortality; RP=radical prostatectomy; RR=relative risk; SOE=strength of evidence; WW=watchful waiting.

**Table 26. Key Question 2: Strength-of-evidence grades for randomized controlled trials within primary treatment categories**

Comparison	Outcome	Overall Risk of Bias	Consistency	Directness	Precision	Evidence Favors	SOE Grade
EBRT vs. EBRT plus short-term ADT <sup>43</sup>	Overall survival among white patients (n=1,505) at 10-year followup. No significant effect for treatment by age.	Medium	Consistency unknown (single study)	Direct	Precise HR 1.19 (95% CI, 1.01 to 1.41). Effect size was statistically significant.	EBRT plus ADT	Insufficient for patient subgroup
	PCSM among white patients (n=1,505) at 10-year followup.	Medium	Consistency unknown (single study)	Direct	Precise HR 2.33 (95% CI, 1.46 to 3.72). Effect size was statistically significant.	EBRT plus ADT	Insufficient for patient subgroup
	PCSM among patients age older than 70 years (n=1,005) at 10-year followup	Medium	Consistency unknown (single study)	Direct	Precise HR 2.19 (95% CI, 1.31 to 3.64). Effect size was statistically significant.	EBRT plus ADT	Insufficient for patient subgroup
3D-CRT vs. 3D-CRT plus ADT <sup>35</sup>	All-cause mortality among patients with no or minimal comorbidities was tripled among those treated with EBRT alone vs. those treated with combination therapy EBRT plus ADT at 7.6-year followup.	Low	Consistency unknown (single study)	Direct	Precise HR 4.2 (95% CI, 2.1 to 8.5). Effect size was statistically significant.	3D-CRT plus ADT	Insufficient for patient subgroup*
	All-cause mortality among patients with moderate or severe comorbidity (n=49) at a median followup of 7.6 years was similar between treatment groups.	Low	Consistency unknown (single study)	Direct	Imprecise HR 0.54 (95% CI, 0.27 to 1.10), p=0.08. Effect size was not statistically significant.	No significant difference between the interventions	Insufficient for patient subgroup

\*SOE grading reduced by one level based on subgroup analysis (see methods section for further details).

**Abbreviations:** 3D-CRT=three-dimensional conformal radiotherapy; ADT=androgen-deprivation therapy; CI=confidence interval; EBRT=external beam radiation therapy; HR=hazard ratio; PCSM=prostate cancer-specific mortality; SOE=strength of evidence.

**Table 27. Key Question 2: Strength-of-evidence grades for nonrandomized comparative studies**

Comparison	Outcome	Overall Risk of Bias	Consistency	Directness	Precision	Evidence Favors	SOE Grade
RRP vs. 3D-CRT vs. BT <sup>91</sup>	Overall survival among men age group younger than 65 years (n=60) vs. 65–70 years (n=79)	Medium	Consistency unknown (single study)	Direct	Imprecise HR 1.96 (95% CI, 0.89 to 4.30). Effect size was not statistically significant.	No significant difference between the interventions	Insufficient for patient subgroup
	Overall survival among men age group younger than 65 years (n=60) vs. older than 70 years (n=99)	Medium	Consistency unknown (single study)	Direct	Precise HR 2.95 (95% CI, 1.34 to 6.47). Effect size was statistically significant.	RRP	Insufficient for patient subgroup
BT vs. BT plus ADT <sup>82</sup>	All-cause mortality among patients age older than 73 years (n=1,268) at a median followup of 4.8 years	Medium	Consistency unknown (single study)	Direct	Precise HR 1.24 (95% CI, 1.01 to 1.53). Effect size was statistically significant.	BT	Insufficient for patient subgroup
EBRT vs. observation <sup>59</sup>	PCSM among men with a Charlson comorbidity score of 0 (n=17,760), 1 (n=11,545), and ≥2 (n=12,667) at 10-year followup	Medium	Consistency unknown (single study)	Direct	Precise 0 comorbidity: HR 0.81 (95% CI, 0.67 to 0.98) 1 comorbidity: HR 0.87 (95% CI, 0.75 to 0.99) ≥2 comorbidities: HR 0.79 (95% CI, 0.65 to 0.96). Effect size was statistically significant in same direction for each subgroup.	EBRT	Insufficient for all patient subgroups
	PCSM among men aged 75–80 years (n=17,364) at 10-year followup	Medium	Consistency unknown (single study)	Direct	Precise HR 0.7 (95% CI, 0.59 to 0.80). Effect size was statistically significant	EBRT	Insufficient for patient subgroup

**Table 27. Key Question 2: Strength-of-evidence grades for nonrandomized comparative studies (continued)**

Comparison	Outcome	Overall Risk of Bias	Consistency	Directness	Precision	Evidence Favors	SOE Grade
EBRT vs. observation <sup>59</sup> (continued)	PCSM among men aged 65–69 years (n=9,580) and 70–74 (n=15,028) at 10-year followup	Medium	Consistency unknown (single study)	Direct	Imprecise (p-values were not statistically significant for both age groups)	No significant difference between the interventions	Insufficient for patient subgroup
RP vs. EBRT <sup>38</sup>	All-cause mortality among men aged 55–64 years (n=759) at 15-year followup	Medium	Consistency unknown (single study)	Direct	Precise HR 0.41 (95% CI, 0.32 to 0.53). Effect size was statistically significant.	RP	Insufficient for patient subgroup
	All-cause mortality among men aged 65–74 years (n=896) at 15-year followup	Medium	Consistency unknown (single study)	Direct	Precise HR 0.41 (95% CI, 0.32 to 0.53). Effect size was statistically significant.	RP	Insufficient for patient subgroup
	All-cause mortality among men with no comorbidity (n=672) at 15-year followup	Medium	Consistency unknown (single study)	Direct	Precise HR 0.52 (95% CI, 0.41 to 0.65). Effect size was statistically significant.	RP	Insufficient for patient subgroup
	All-cause mortality among men with any reported comorbidity (n=983) at 15-year followup	Medium	Consistency unknown (single study)	Direct	Precise HR 0.67 (95% CI, 0.57 to 0.78). Effect size was statistically significant.	RP	Insufficient for patient subgroup
	PCSM among men aged 55–64 years (n=759) at 15-year followup	High	Consistency unknown (single study)	Direct	Precise HR 0.21 (95% CI, 0.13 to 0.36). Effect size was statistically significant.	RP	Insufficient for patient subgroup
	PCSM among men aged 65–74 years (n=896) at 15-year followup	High	Consistency unknown (single study)	Direct	Precise HR 0.45 (95% CI, 0.31 to 0.65). Effect size was statistically significant.	RP	Insufficient for patient subgroup

**Table 27. Key Question 2: Strength-of-evidence grades for nonrandomized comparative studies (continued)**

Comparison	Outcome	Overall Risk of Bias	Consistency	Directness	Precision	Evidence Favors	SOE Grade
RP vs. EBRT <sup>38</sup> (continued)	PCSM among men with no comorbidity (n=672) at 15-year followup	High	Consistency unknown (single study)	Direct	Precise HR 0.19 (95% CI, 0.12 to 0.31). Effect size was statistically significant.	RP	Insufficient for patient subgroup
	PCSM among men with any reported comorbidity (n=983) at 15-year followup	High	Consistency unknown (single study)	Direct	Precise HR 0.49 (95% CI, 0.34 to 0.72). Effect size was statistically significant.	RP	Insufficient for patient subgroup
RP vs. EBRT <sup>41</sup>	PCSM among men with any reported comorbidity (n=1,090) at 51 months' followup	Medium	Consistency unknown (single study)	Direct	Imprecise (p-value was not statistically significant)	No significant difference between the interventions	Insufficient for patient subgroup
RP vs. EBRT vs. WW with and without secondary treatment <sup>36</sup>	Overall mortality	High	Consistency unknown (single study)	Direct	Precise for age and comorbidities Imprecise for race	Older age and 2 or more comorbidities predicted worse outcome	Insufficient for patient subgroup
RP vs. 3D-CRT vs. BT <sup>75</sup>	Overall survival	Medium	Consistency unknown (single study)	Direct	Precise for age, race, and comorbidities	No differences by treatment group	Insufficient for patient subgroup
RP vs. 3D-CRT vs. BT <sup>75</sup>	PCSM	Medium	Consistency unknown (single study)	Direct	Imprecise	No differences by treatment group	Insufficient for patient subgroup

**Abbreviations:** 3D-CRT=Three-dimensional conformal radiation therapy; ADT=androgen-deprivation therapy; BT=brachytherapy; CI=confidence interval; EBRT=external beam radiation therapy; HR=hazard ratio; PCSM=prostate cancer-specific mortality; RP=radical prostatectomy; RRP=radical retropubic prostatectomy; SOE=strength of evidence; WW=watchful waiting.

### Key Question 3. Provider/Hospital Characteristics Affecting Outcomes of the Therapies

We identified 32 reports that were reviewed for possible inclusion in this report. We found no comparative studies (RCTs or non-RCTs) that examined how provider characteristics influence survival in patients with clinically localized prostate cancer treated with RP compared with another form of RP or RP compared with a nonsurgical treatment. These 32 studies were excluded because they were single-site studies, reported an outcome other than survival, examined management changes but not clinical efficacy, or did not provide any detail on provider characteristics.

We did not identify any studies that addressed this KQ. However, given the diverse readership of this report, we would like to note a landmark U.S. Government Accountability Office report that found a growing concern that financial incentives (a provider characteristic) may continue to drive treatment selection and costs.<sup>93</sup>

### Key Question 4. Tumor Characteristics Affecting the Outcomes of the Therapies

In this section, we summarize findings from RCTs and the nonrandomized comparative studies that stratified data by tumor characteristics (Tables 28–35). Table 28 compares major primary treatment options and reports clinical outcome measures for the randomized controlled trials across primary treatment categories. Table 29 compares major primary treatment options and reports clinical outcome measures for the RCTs within primary treatment categories. Table 31 compares major primary treatment options and reports clinical outcome measures for the nonrandomized comparative studies.

## Key Points

RCTs that performed subgroup analyses based on tumor characteristics reported the following. In all cases, the strength of evidence was insufficient to allow conclusions.

- PSA levels. PIVOT found no reduction in all-cause mortality among men with PSA levels of  $\leq 10$  ng/mL treated with RP compared with WW. All-cause mortality (but not PCSM) was reduced by 13.2% among men with PSA levels of  $>10$  ng/mL who were treated with RP compared with WW.
- PSA levels. The SPCG-4 trial found no reduction in all-cause mortality among men with PSA levels of  $<10$  ng/mL or  $>10$  ng/mL treated with RP compared with WW at 15-year followup.
- Gleason score. SPCG-4 found no reduction in all-cause mortality among men with Gleason score  $<7$  or  $>7$  treated with RP compared with WW at 15-year followup.
- Risk level. PIVOT found a 31% relative reduction in all-cause mortality among men with intermediate tumor risk treated with RP compared with WW. Furthermore, there was a significant reduction in PCSM among men with PSA  $>10$  ng/mL and men with high-risk tumor who were treated with RP compared with WW.
- Risk level. SPCG-4 found a significant absolute between-group difference of 13.2% for all-cause mortality and 11.4% for distant metastases among men with low-risk tumor who were treated with RP than those in WW at 15-year followup.
- Risk level. Among men with intermediate-risk tumors, overall survival was increased to 60% in the EBRT plus ADT group compared with 54% in the EBRT alone group.

Among men with low-risk tumors, overall survival was increased to 67% in the EBRT plus ADT group compared with 60% in the EBRT alone group. The study found no reduction in PCSM among men with low-risk tumor who were treated with EBRT alone compared with EBRT plus ADT.

## Detailed Synthesis

### Randomized Controlled Trials

All abstracted data for the outcome measures that address this KQ appear in Appendix F. Table 30 summarizes major findings reported by the RCTs and is intended to provide a roadmap to the abstracted data, including the key statistics, for each comparison and reported outcome. The strength-of-evidence grades for studies that address this Key Question are provided in Table 33 and Table 34.

**Table 28. Overview of randomized controlled trials across primary treatment categories (2 trials): Key Question 4**

Study	Interventions and Number of Patients	Tumor Characteristics	Outcomes	Duration
Wilt et al. 2012 <sup>25</sup> Prostate Intervention Versus Observation Trial (PIVOT)	RP: 364 patients vs. Observation: 367 patients	PSA level Gleason score Tumor risk	All-cause mortality PCSM	Median followup of 10 years
Bill-Axelsson et al. 2011 <sup>33</sup> Scandinavian Prostate Cancer Group-4 (SPCG-4) trial	RP: 347 patients vs. WW: 348 patients	Tumor risk	All-cause mortality PCSM Progression to metastases	Median followup of 15 years

**Abbreviations:** PCSM=prostate cancer-specific mortality; PSA=prostate-specific antigen, RP=radical prostatectomy; WW=watchful waiting.

**Table 29. Overview of randomized controlled trials within primary treatment categories (2 trials): Key Question 4**

Study	Interventions and Number of Patients	Tumor Characteristics	Outcomes	Duration
Jones et al. 2011 <sup>43</sup>	EBRT: 992 patients vs. EBRT plus short-term ADT: 987 patients	Age 71 years or younger, T1b, T1c, T2a, T2b, PSA ≤20 ng/mL	Overall survival PCSM Biochemical failure	Median followup of 9.1 years
D'Amico et al. 2008 <sup>35</sup> Same study as Nguyen et al. 2010 <sup>53</sup>	3D-CRT (104 patients) vs. 3D-CRT plus 6 months of both LHRH and antiandrogen vs. 3D-CRT (73 patients) plus 6 months of both LHRH and less than 6 months of antiandrogen (29 patients)	PSA level Gleason score Tumor stage	Biochemical failure	Median followup 8.2 years

**Abbreviations:** 3D-CRT=Three-dimensional conformal radiation therapy; ADT=androgen-deprivation therapy; EBRT=external beam radiation therapy; LHRH=luteinizing hormone-releasing hormone, PCSM=prostate cancer specific mortality, PSA=prostate-specific antigen.



**Table 30. Major findings reported by randomized controlled trials for Key Question 4**

Treatments Being Compared	Outcome	Evidence Base	Major Findings Reported in the Study	Detailed Results Abstracted
RP vs. WW	All-Cause Mortality	PIVOT Wilt et al. <sup>25</sup>	No reduction in all-cause mortality among men with PSA levels of 10 ng/mL or less who were treated with RP compared with WW after a median 10-year followup. All-cause mortality was reduced by 13.2% among men with PSA levels of more than 10 ng/mL who were treated with RP compared with WW. After median 10-year followup, there was a 31% relative reduction in all-cause mortality among men with intermediate-risk tumor risk who were treated with RP compared with WW.	Table F-1 in Appendix F
RP vs. WW	All-cause mortality	SPCG-4 Bill-Axelsson et al. <sup>15,33,34</sup>	No reduction in all-cause mortality among men with PSA levels <10 ng/mL or >10 ng/mL who were treated with RP compared with WW at 15-year followup. No reduction in all-cause mortality among men with Gleason score less than 7 or more than 7 who were treated with RP compared with WW at 15-year followup. There was a significant absolute between-group difference of 13.2% for all-cause mortality among men with low-risk tumor who were treated with RP than those in WW at 15-year followup.	Table F-1 in Appendix F
RP vs. WW	PCSM	PIVOT Wilt et al. <sup>25</sup>	After a median 10-year followup, there was a significant reduction in PCSM among men with PSA >10 ng/mL who were treated with RP compared with WW. There was also a significant reduction in PCSM among men with high-risk tumor who were treated with RP compared with WW.	Table F-5 in Appendix F
RP vs. WW	PCSM	SPCG-4 Bill-Axelsson et al. <sup>15,33,34</sup>	No reduction in PCSM among men with PSA levels of less than 10 ng/mL or more than 10 ng/mL who were treated with RP compared with WW at 15-year followup. No reduction in PCSM among men with Gleason score less than 7 or more than 7 who were treated with RP compared with WW at 15-year followup. There was a nonsignificant absolute between-group difference of 4.2% for PCSM among men with low-risk tumor who were treated with RP than those in WW at 15-year followup.	Table F-5 in Appendix F
RP vs. WW	Distant metastases	SPCG-4 Bill-Axelsson et al. <sup>15,33,34</sup>	There was a significant absolute between-group difference of 11.4% for distant metastases among men with low-risk tumor who were treated with RP compared with WW at 15-year followup.	Table F-11 in Appendix F

**Table 30. Major findings reported by randomized controlled trials for Key Question 4 (continued)**

Treatments Being Compared	Outcome	Evidence Base	Major Findings Reported in the Study	Detailed Results Abstracted
EBRT vs. EBRT plus ADT	Overall survival	Jones et al. <sup>43</sup>	Among men with intermediate-risk tumor, the 10-year overall survival was increased to 60% in the EBRT plus short-term ADT group compared with 54% in the EBRT alone group. Among men with low-risk tumor, the 10-year overall survival was increased to 67% in the EBRT plus short-term ADT group compared with 60% in the EBRT alone group.	Table F-3 in Appendix F
EBRT vs. EBRT plus ADT	PCSM	Jones et al. <sup>43</sup>	The risk of PCSM was higher in the EBRT group than in the EBRT plus ADT. But no reduction in PCSM among men with low-risk tumor who were treated with EBRT alone compared with EBRT plus short-term ADT.	Table F-5 in Appendix F
EBRT vs. EBRT plus ADT	Biochemical failure	Jones et al. <sup>43</sup>	The 10-year rate of biochemical failure was significantly reduced in all 3 risk subgroups (i.e., low-, intermediate, and high-risk) among men treated with in the EBRT plus short-term ADT group compared with EBRT alone.	Table F-7 in Appendix F
3D-CRT vs. 3D-CRT plus 6 months of both LHRH and antiandrogen vs. 3D-CRT plus 6 months of both LHRH and less than 6 months of antiandrogen	Biochemical failure	D'Amico et al. <sup>49</sup>	After a median followup of 8.2 years, estimates of PSA recurrence were significantly lower in men with an increasing PSA level (RR 2.07; 95% CI, 1.4 to 3.1), a Gleason score of 8, 9, or 10 (RR 3.2; 95% CI, 1.7 to 6.0), and clinical category T2 disease (RR 1.9; 95% CI, 1.2 to 3.0).	Table F-7 in Appendix F

**Abbreviations:** 3D-CRT=Three-dimensional conformal radiation therapy; ADT=androgen-deprivation therapy; CI=confidence interval; EBRT=external beam radiation therapy; LHRH=luteinizing hormone-releasing hormone; PCSM=prostate cancer-specific mortality, PIVOT= Prostate Intervention Versus Observation Trial, PSA=prostate-specific antigen, RP=radical prostatectomy; RR=relative risk; SPCG-4= Scandinavian Prostate Cancer Group-4, WW=watchful waiting.

## Nonrandomized Comparative Studies

All abstracted data for the outcome measures that address this KQ appear in Appendix F. Table 32 summarizes major findings reported by the non-RCTs and is intended to provide a roadmap to the abstracted data, including the key statistics, for each comparison and reported outcome. The strength-of-evidence grades for nonrandomized comparative studies that address this Key Questions are provided in Table 35.

**Table 31. Overview of nonrandomized comparative studies (16 studies): Key Question 4**

Study	Number of Patients	Tumor Characteristics	Outcomes	Duration
Alemozaffar et al. 2014 <sup>68</sup>	RALRP: 132 patients vs. RRP: 468 patients	Risk level	QOL and satisfaction with cancer care	A minimum followup of 2 years
DeGroot et al. 2013 <sup>41</sup>	RP: 458 patients (cohort) vs. RP: 36 patients (cases) vs. EBRT: 518 patients (cohort) vs. EBRT: 78 patients (cases)	Tumor risk	PCSM	Median 51 months followup
Ferrer et al. 2013 <sup>91</sup>	RRP: 193 patients vs. 3D-CRT: 194 patients vs. BT: 317 patients	Tumor risk	Overall survival	Median 6.06-year followup
Hoffman et al. 2013 <sup>38</sup>	RP: 1,164 patients vs. EBRT: 491 patients	Tumor risk	All-cause mortality PCSM	15-year followup
Wirth et al. 2013 <sup>74</sup>	RRP: 600 patients vs. LRP: 244 patients	PSA level Gleason score Tumor stage	Biochemical progression-free survival	Median followup of 6.6 years and 4.6 years, respectively.
Nanda et al. 2012 <sup>83</sup>	Low-risk: BT without neoadjuvantive HT 3,517 patients vs. BT with neoadjuvantive HT: 1,924 patients Intermediate-risk: BT without neoadjuvantive HT 2,225 patients vs. BT with neoadjuvantive HT 2,140 patients High-risk: BT without neoadjuvantive HT: 353 patients vs. BT with neoadjuvantive HT 1,007 patients	Tumor risk	AEs	Median followup for low-, intermediate-, and high-risk prostate cancer was 4.1 years, 4.4 years, and 4.6 years respectively.
Rosenberg et al. 2012 <sup>76</sup>	BT plus EBRT: 186 patients vs. BT plus ADT: 621 patients	PSA level Gleason score	PCSM	4.4- and 4.8-year followup, respectively
Zelevsky et al. 2012 <sup>89</sup>	BT: 942 patients vs. BT plus IMRT: 524 patients	PSA level Gleason score Clinical T stage	Biochemical progression-free survival	Median followup 49 months (range 1–13 years)
Kibel et al. 2012 <sup>75</sup>	RP: 6,485 patients, 2,843 at site 1 and 3,642 at site 2 vs. 3D-CRT plus IMRT: 2,264 patients, 1,638 at site 1 and 626 at site 2 vs. BT: 1,680 patients, 1,330 at site 1 and 350 at site 2	Tumor risk	Overall survival PCSM	10-year followup

**Table 31. Overview of nonrandomized comparative studies (16 studies): Key Question 4 (continued)**

Study	Number of Patients	Tumor Characteristics	Outcomes	Duration
Abdollah et al. 2012 <sup>59</sup>	EBRT: 46,521 patients vs. Observation: 22,276 patients	Tumor risk	PCSM	10-year followup
Rice et al. 2011 <sup>36</sup>	RP: 194 patients vs. EBRT: 252 patients vs. WW without secondary treatment: 214 patients vs. WW with secondary treatment: 110 patients	PSA level Tumor stage	Biochemical recurrence Overall mortality	Mean 6.8±4.0 years
Dosoretz et al. 2010 <sup>82</sup>	BT: 1,391 patients vs. BT plus ADT: 1,083 patients	PSA level Gleason score Tumor stage	All-cause mortality	Median followup 4.8 years
Magheli et al. 2010 <sup>56</sup>	RRP: 522 patients vs. LRP: 522 patients vs. RALRP: 522 patients	Gleason score	Biochemical recurrence	<u>Mean (SD) followup time</u> RRP: 2.5 (1.6) years LRP: 1.47 (0.7) years RALRP: 1.3 (0.6) years
Lu-Yao et al. 2008 <sup>78</sup>	ADT: 7,867 patients vs. Observation: 11,404 patients	Tumor grade	Overall survival PCSM	Median followup for overall survival was 81 months
Sumitomo et al. 2008 <sup>63</sup>	HIFU: 260 patients vs. HIFU + ADT: 270 patients	Tumor risk	Biochemical recurrence-free survival	3-year followup
D'Amico et al. 2007 <sup>87</sup>	RRP: 660 patients vs. 3D-CRT: 288 patients	PSA level Biopsy Gleason score Tumor stage	PCSM	7-year followup

**Abbreviations:** 3D-CRT=Three-dimensional conformal radiation therapy, ADT=androgen-deprivation therapy; BT=brachytherapy; EBRT=external beam radiation therapy; HIFU=high-intensity focused ultrasound; HT=hormone therapy, IMRT=intensity modulated radiation therapy, PCSM=prostate cancer-specific mortality, LRP=laparoscopic radical prostatectomy; PSA=prostate-specific antigen, RALRP=robotic-assisted laparoscopic radical prostatectomy; RP=radical prostatectomy; RRP=radical retropubic prostatectomy, WW=watchful waiting.

**Table 32. Major findings reported by nonrandomized comparative studies for Key Question 4**

Treatments Being Compared	Outcome	Evidence Base	Major Findings Reported in the Study	Detailed Results Abstracted
RALRP vs. RRP	Expanded Prostate Cancer Index scores (urinary incontinence, urinary obstruction, sexual, bowel, hormonal/vitality)	Alemezaffar et al. <sup>68</sup>	Multivariate regression demonstrated no significant differences on any subscale scores when the analysis was limited to RALRP vs. RRP in the low-risk patients or between RALRP and RRP in the intermediate/high risk patients.	Table F-16 in Appendix F
RALRP vs. RRP	Satisfaction scale for cancer care (outcome satisfaction)	Alemezaffar et al. <sup>68</sup>	Multivariate regression found no significant difference in patient satisfaction when the analysis was limited to RALRP vs. RRP in the low-risk patients or between RALRP and RRP in the intermediate-/high-risk patients.	Table F-16 in Appendix F
RALRP vs. RRP	Biochemical recurrence	Magheli et al. <sup>56</sup>	When stratified by Gleason score, men with Gleason score of 6 or less had lower biochemical recurrence compared to men with Gleason score of 7 (HR 3.35; 95% CI, 1.27 to 8.83) or 8–10 (HR 9.98; 95% CI, 3.07 to 32.42).	Table F-8 in Appendix F
RRP vs. LRP	Biochemical recurrence	Magheli et al. <sup>56</sup>	When stratified by Gleason score, men with Gleason score of 6 or less had lower biochemical recurrence compared to men with Gleason score of 7 (HR 3.35; 95% CI, 1.27 to 8.83) or 8–10 (HR 9.98; 95% CI, 3.07 to 32.42).	Table F-8 in Appendix F
LRP vs. RRP	BPFS	Wirth et al. <sup>74</sup>	There was a significant between-group difference in biochemical progression-free survival when men were stratified by Gleason score, pathological stage, and PSA level. PSA level: HR 1.1; 95% CI, 1.10 to 1.16 Tumor stage: HR, 5.0; 95% CI, 3.44 to 7.16 Gleason score 7: HR 6.6; 95% CI, 4.3 to 10.0 Gleason score of 8 or more: HR 16.4; 9.0 to 29.8	Table F-7 in Appendix F
3D-CRT vs. BT	Overall survival	Ferrer et al. <sup>91</sup>	At median followup of 6.02 years, no statistically significant difference between the treatment groups when men with low-risk tumors were compared with intermediate-risk (HR 1.13; 95% CI, 0.54 to 2.36)	Table F-4 in Appendix F
RRP vs. BT	Overall survival	Ferrer et al. <sup>91</sup>	At median followup of 6.02 years, no statistically significant difference between the treatment groups when men with low-risk tumors were compared with intermediate-risk (HR 1.13; 95% CI, 0.54 to 2.36)	Table F-4 in Appendix F
3D-CRT plus IMRT vs. BT	Overall survival	Kibel et al. <sup>75</sup>	Comparisons were all to RP so no usable data.	Table F-4 in Appendix F
3D-CRT plus IMRT vs. BT	PCSM	Kibel et al. <sup>75</sup>	There were no significant differences in PCSM within each prostate cancer risk group	Table F-6 in Appendix F
RP vs. BT	Overall survival	Kibel et al. <sup>75</sup>	RP was associated with improved survival in all risk groups Low risk: BT vs. RP: (HR 1.7 [1.4 to 2.2]) Intermediate risk BT vs. RP (HR 1.5 [1.1 to 2.1]) High risk BT vs. RP (HR 3.1 [1.7 to 5.9])	Table F-4 in Appendix F

**Table 32. Major findings reported by nonrandomized comparative studies for Key Question 4 (continued)**

Treatments Being Compared	Outcome	Evidence Base	Major Findings Reported in the Study	Detailed Results Abstracted
RP vs. BT	PCSM	Kibel et al. <sup>75</sup>	There were no significant differences in PCSM within each prostate cancer risk group	Table F-6 in Appendix F
RP vs. 3D-CRT plus IMRT	Overall survival	Kibel et al. <sup>75</sup>	RP was associated with improved survival in all risk groups Low risk: EBRT vs. RP (HR 1.7, [1.3 to 2.1]) Intermediate risk EBRT vs. RP (HR 1.5 [1.2 to 1.9])  High risk EBRT vs. RP (HR 1.7 [1.3 to 2.3])	Table F-4 in Appendix F
RP vs. 3D-CRT plus IMRT	PCSM	Kibel et al. <sup>75</sup>	There were no significant differences in PCSM within each prostate cancer risk group	Table F-6 in Appendix F
RRP vs. 3D-CRT	Overall survival	Ferrer et al. <sup>91</sup>	At median followup of 6.02 years, no statistically significant difference between the treatment groups when men with low-risk tumors were compared with intermediate-risk (HR 1.13; 95% CI, 0.54 to 2.36)	Table F-4 in Appendix F
RRP vs. 3D-CRT	PCSM	D'Amico et al. <sup>87</sup>	After 7 years of followup, PCSM was more favorable for men with PSA level >20 ng/mL who underwent RRP compared with 3D-CRT (RR 0.48; 95% CI, 0.23 to 0.99) After 7 years of followup, PCSM was more favorable for men with Gleason score 7 who underwent RRP compared with 3D-CRT (RR 0.38; 95% CI, 0.17 to 0.86) After 7 years of followup, PCSM was more favorable for men with Gleason score 8–10 who underwent RRP compared with 3D-CRT (RR 0.44; 95% CI, 0.2 to 0.98) After 7 years of followup, PCSM was more favorable for men with stage T1c who underwent RRP compared with 3D-CRT (RR 0.23; 95% CI, 0.08 to 0.61)	Table F-6 in Appendix F
RP vs. EBRT	All-cause mortality	Hoffman et al. <sup>38</sup> Rice et al. <sup>36</sup>	Hoffman et al. <sup>38</sup> After 15 years of followup, all-cause mortality was more favorable for men with high-risk tumor who underwent RP compared with EBRT (HR, 0.65; 95% CI, 0.48 to 0.87) Rice et al. <sup>36</sup> PSA at diagnosis was not a significant predictor of overall survival. Clinical T stage was not a significant predictor of overall survival.	Table F-2 in Appendix F
RP vs. EBRT	PCSM	Hoffman et al. <sup>38</sup> and DeGroot et al. <sup>41</sup>	DeGroot et al. <sup>41</sup> At median followup of 51 months, there was no evidence of worse PCSM among men with low-risk or intermediate-risk tumor who underwent EBRT compared with RP (HR 1.57; 95% CI, 0.95 to 2.61). Hoffman et al. <sup>38</sup> After 15 years of followup, PCSM was more favorable for the men with high-risk tumor who underwent RP than for the men who received EBRT (HR, 0.36; 95% CI, 0.20 to 0.64).	Table F-6 in Appendix F

**Table 32. Major findings reported by nonrandomized comparative studies for Key Question 4 (continued)**

Treatments Being Compared	Outcome	Evidence Base	Major Findings Reported in the Study	Detailed Results Abstracted
RP vs. EBRT	Biochemical recurrence	Rice et al. <sup>36</sup>	PSA significantly predicted biochemical recurrence with higher PSA scores experiencing more recurrence. Clinical T stage was not a significant predictor of biochemical recurrence.	Table F-2 in Appendix F Table F-7 in Appendix F
RALRP vs. LRP	Biochemical recurrence	Magheli et al. 2011 <sup>56</sup>	When stratified by Gleason score, men with Gleason score of 6 or less had lower biochemical recurrence than did men with Gleason score of 7 (HR 3.35; 95% CI, 1.27 to 8.83) or 8–10 (HR 9.98; 95% CI, 3.07 to 32.42).	Table F-8 in Appendix F
EBRT vs. observation	Overall mortality	Rice et al. <sup>36</sup>	PSA at diagnosis was not a significant predictor of overall survival. Clinical T stage was not a significant predictor of overall survival.	Table F-2 in Appendix F
EBRT vs. Observation	PCSM	Abdollah et al. <sup>59</sup>	For patients in the high-risk group, 10-year PCSM was 8.8% in the radiotherapy group vs. 14.4% in the observation group (HR 0.59; 95% CI, 0.50 to 0.68) in favor of EBRT. For patients in the low to high-risk group, there was no between-group difference in the same outcome.	Table F-6 in Appendix F
EBRT vs. Observation	Biochemical recurrence	Rice et al. <sup>36</sup>	PSA at diagnosis was not a significant predictor of overall survival. Clinical T stage was not a significant predictor of overall survival. PSA significantly predicted biochemical recurrence with higher PSA scores experiencing more recurrence. Clinical T stage was not a significant predictor of biochemical recurrence.	Table F-7 in Appendix F
BT vs. BT Plus ADT	All-cause mortality	Dosoretz et al. <sup>82</sup>	Study authors only reported no significant difference in all-cause mortality between the interventions when data were stratified by PSA level, biopsy Gleason score, and clinical T stage in either study group.	Table F-2 in Appendix F
BT vs. BT plus HT	AEs	Nanda et al. <sup>83</sup>	Neoadjuvant HT use was associated with a significantly increased risk of all-cause mortality in men with low-risk prostate cancer (adjusted HR 1.27, 95% CI 1.07 to 1.51, p<0.01) but not in men with intermediate-risk prostate cancer (adjusted HR 1.13, 95% CI 0.96 to 1.35, p=0.15) or high-risk prostate cancer (adjusted HR 0.86, 95% CI 0.66 to 1.13, p=0.28) using multivariate regression with propensity score. Among low-risk patients, adjuvant HT was associated with a significantly increased risk of all-cause mortality in men with at least 1 CAD risk factor (adjusted HR 1.36; 95% CI, 1.07 to 1.74, p=0.01) but not in patients with no CAD risk factors (adjusted HR 1.19; 95% CI 0.95 to 1.51, p=0.13). The authors reported all-cause mortality as a possible adverse event of HT use.	Table F-16 in Appendix F
BT plus EBRT vs. BT plus ADT	PCSM	Rosenberg et al. <sup>76</sup>	At 5 years, men with a Gleason score of 4+3 (adjusted HR 8.88; 95% CI, 1.10 to 72.04) and elevated PSA level (adjusted HR 8.03; 95% CI, 2.38 to 28.80) who received BT plus EBRT had an increased risk of PCSM compared with those treated with EBRT plus ADT.	Table F-6 in Appendix F
BT vs. BT plus IMRT	BPFS	Zelevsky et al. <sup>89</sup>	In a multivariate analysis, PSA level and Gleason score were significantly associated with BPFS, while clinical T stage was not significantly associated with BPFS.	Table F-7 in Appendix F

**Table 32. Major findings reported by nonrandomized comparative studies for Key Question 4 (continued)**

Treatments Being Compared	Outcome	Evidence Base	Major Findings Reported in the Study	Detailed Results Abstracted
ADT vs. observation	All-cause mortality	Lu-Yao et al. <sup>78</sup>	The all-cause mortality rate among men with moderately-differentiated cancer was higher in the ADT group than in the observation group (adjusted HR 1.15; 95% CI, 1.10 to 1.21).	Table F-2 in Appendix F
ADT vs. Observation	PCSM	Lu-Yao et al. <sup>78</sup>	The PCSM rate among men with moderately-differentiated cancer was higher in the ADT group than in the observation group (adjusted HR 1.83; 95% CI, 1.58 to 2.12).	Table F-6 in Appendix F
HIFU vs. HIFU plus ADT	BPFS	Sumitomo et al. <sup>63</sup>	PSA level and T stage were significantly associated with BPFS in both groups, while Gleason score was not significantly associated. Patients with HIFU alone had significantly lower BPFS compared to HIFU + ADT only in the intermediate- and high-risk groups: 3-year BPFS among men with low-risk prostate cancer (86.1% vs. 89.7%, p=0.60); intermediate-risk prostate cancer (44.9% vs. 79.3%, p=0.01); high-risk prostate cancer (32.6% vs. 66.8%, p=0.03)	Table F-7 in Appendix F
RP vs. observation	Overall mortality Biochemical recurrence	Rice et al. <sup>36</sup>	PSA at diagnosis was not a significant predictor of overall survival. Clinical T stage was not a significant predictor of overall survival. PSA significantly predicted biochemical recurrence with higher PSA scores experiencing more recurrence. Clinical T stage was not a significant predictor of biochemical recurrence.	Table F-2 in Appendix F Table F-7 in Appendix F

**Abbreviations:** 3D-CRT=Three-dimensional conformal radiation therapy; ADT=androgen-deprivation therapy; BT=brachytherapy; EBRT=external beam radiation therapy; HIFU=high-intensity focused ultrasound; IMRT=intensity-modulated radiation therapy; LRP=laparoscopic radical prostatectomy; PCSM=prostate cancer-specific mortality; RALRP=robotic-assisted laparoscopic radical prostatectomy; RP=radical prostatectomy; RRP=radical retropubic prostatectomy.



**Table 33. Key Question 4: Strength-of-evidence grades for randomized controlled trials across primary treatment categories**

Comparison	Outcome	Overall Risk of Bias	Consistency	Directness	Precision	Evidence Favors	SOE Grade
RP vs. WW <sup>25</sup>	All-cause mortality among patients with PSA levels >10 ng/mL (n=138) at 10-year followup	Medium	Consistency unknown (single study)	Direct	Precise HR 0.67 (95% CI, 0.48 to 0.94). Effect size was statistically significant.	RP	Insufficient for patient subgroup
	All-cause mortality among patients with PSA levels ≤10 ng/mL (n=211); low-risk (n=116), intermediate-risk (n=129), or high-risk (n=91) prostate cancer; Gleason score <7 (n=238) or ≥7 (n=97) at 10-year followup	Medium	Consistency unknown (single study)	Direct	Imprecise Effect size was not statistically significant for all subgroups	No significant difference between the interventions	Insufficient for all patient subgroups
	PCSM among patients with PSA levels ≤10 ng/mL (n=29) or >10 ng/mL (n=23); low-risk (n=10), intermediate-risk (n=19), high-risk (n=21) prostate cancer; Gleason score <7 or ≥7 at 10-year followup	Medium	Consistency unknown (single study)	Direct	Imprecise Effect size was not statistically significant for all subgroups.	No significant difference between the interventions	Insufficient for all patient subgroups
RP vs. WW <sup>33</sup>	Overall mortality among patients with low-risk prostate cancer at 15-year followup (study did not report number of patients in this subgroup)	Medium	Consistency unknown (single study)	Direct	Precise RR (95% CI 0.62, 0.42 to 0.92). Effect size was statistically significant.	RP	Insufficient for patient subgroup*
	PCSM among patients with low-risk prostate cancer at 15-year followup (study did not report number of patients in this subgroup)	Medium	Consistency unknown (single study)	Direct	Imprecise RR 0.53 (95% CI, 0.24 to 1.14). Effect size was not statistically significant.	No significant difference between the interventions	Insufficient for patient subgroup
	Progression to distant metastases in patients with low risk disease at 15-year followup (study did not report number of patients in this subgroup)	Medium	Consistency unknown (single study)	Direct	Precise RR 0.43 (95% CI, 0.23 to 0.79). Effect size was statistically significant.	RP	Insufficient for patient subgroup

\*SOE grading reduced by one level based on subgroup analysis (see methods section for further details).

**Abbreviations:** CI=Confidence interval; HR=hazard ratio; PCSM=prostate cancer-specific mortality; PSA=prostate-specific antigen; RP=radical prostatectomy; RR=relative risk; SOE=strength of evidence; WW=watchful waiting.

**Table 34. Key Question 4: Strength-of-evidence grades for randomized controlled trials within primary treatment categories**

Comparison	Outcome	Overall Risk of Bias	Consistency	Directness	Precision	Evidence Favors	SOE Grade
EBRT vs. EBRT plus short-term ADT therapy <sup>43</sup>	Overall survival among patients with intermediate-risk (n=1,068) prostate cancer at median followup of 9.1 years No treatment by risk category association was found in the low- or high-risk groups.	Medium	Consistency unknown (single study)	Direct	Precise Intermediate risk HR 1.23 (95% CI, 1.02 to 1.49) Effect size was statistically significant.	EBRT plus ADT	Insufficient for patient subgroup
	PCSM among patients with intermediate risk (n=1,068) prostate cancer at 10-year followup No treatment by risk category association was found in the low- or high-risk groups	Medium	Consistency unknown (single study)	Direct	Precise Intermediate risk HR 2.49 (95% CI, 1.50 to 4.11) Effect size was statistically significant.	EBRT plus ADT	Insufficient for patient subgroup

**Abbreviations:** ADT=Androgen-deprivation therapy; CI=confidence interval; EBRT=external beam radiation therapy; HR=hazard ratio; PCSM=prostate cancer-specific mortality; SOE=strength of evidence.

**Table 35. Key Question 4: Strength-of-evidence grades for nonrandomized comparative studies**

Comparison	Outcome	Overall Risk of Bias	Consistency	Directness	Precision	Evidence Favors	SOE Grade
RRP vs. 3D-CRT vs. BT <sup>91</sup>	Overall survival among men with low risk (n=415) vs. men with intermediate risk (n=28) at median followup of 6.06 years	High	Consistency unknown (single study)	Direct	Imprecise HR 1.13 (95% CI, 0.54 to 2.36). Effect size was not statistically significant.	No significant difference between the interventions	Insufficient for patient subgroup
RRP vs. 3D-CRT <sup>87</sup>	PCSM among men with PSA >20 (n=77)	High	Consistency unknown (single study)	Direct	Precise RR 0.48, 95% CI, 0.23 to 0.99. Effect size was statistically significant.	RRP	Insufficient for patient subgroup
RRP vs. 3D-CRT <sup>87</sup>	PCSM among men with Gleason score 7 (n=419)	High	Consistency unknown (single study)	Direct	Precise RR 0.38, 95% CI, 0.17 to 0.86. Effect size was statistically significant.	RRP	Insufficient for patient subgroup
RRP vs. 3D-CRT <sup>87</sup>	PCSM among men with Gleason score 8–10 (n=114)	High	Consistency unknown (single study)	Direct	Precise RR 0.44, 95% CI, 0.2 to 0.98). Effect size was statistically significant.	RRP	Insufficient for patient subgroup
RRP vs. 3D-CRT <sup>87</sup>	PCSM among men with T1c (n=567)	High	Consistency unknown (single study)	Direct	Precise RR 0.23, 95% CI, 0.08 to 0.61. Effect size was statistically significant.	RRP	Insufficient for patient subgroup

**Table 35. Key Question 4: Strength-of-evidence grades for nonrandomized comparative studies (continued)**

Comparison	Outcome	Overall Risk of Bias	Consistency	Directness	Precision	Evidence Favors	SOE Grade
RRP vs. 3D-CRT <sup>87</sup>	PCSM among men with PSA ≤4 (n=162), >4–10 (n=519), >10–12 (n=180), >20 (n=87), biopsy Gleason score ≤6 (n=415), T2a (n=219), T2b (n=107), T2c (n=43), and T3a or T3b (n=12)	High	Consistency unknown (single study)	Direct	Imprecise (p-values were not statistically significant for all sub groups)	No significant difference between the interventions	Insufficient for patient subgroup
BT vs. BT plus ADT <sup>82</sup>	All-cause mortality among patients stratified by PSA level (≤4 [n=247], 4–10 [n=1,783], 10–20 [n=382], >20 [n=69]), biopsy Gleason score (≤6 [n=1,047], 7 [n=181], 8–10 [40], and clinical T classification (T1 [n=787], T2 [n=475], (T3 [n=6]) at a median followup of 4.8 years	High	Consistency unknown (single study)	Direct	Imprecise (p-values were not statistically significant for all sub groups)	No significant difference between the interventions	Insufficient for all patient subgroups
BT plus EBRT vs. BT plus ADT <sup>76</sup>	PCSM among patients with a Gleason score 4+3 (n=180) at median followup of 4.4 years and 4.8 years, respectively	High	Consistency unknown (single study)	Direct	Precise HR 8.88 (95% CI, 1.10 to 72.04) Effect size was statistically significant.	BT plus EBRT	Insufficient for patient subgroup
	PCSM among patients with elevated PSA levels (n=410) at median followup of 4.4 years and 4.8 years, respectively	High	Consistency unknown (single study)	Direct	Precise HR 8.03 (95% CI, 2.38 to 28.80) Effect size was statistically significant.	BT plus EBRT	Insufficient for patient subgroup

**Table 35. Key Question 4: Strength-of-evidence grades for nonrandomized comparative studies (continued)**

Comparison	Outcome	Overall Risk of Bias	Consistency	Directness	Precision	Evidence Favors	SOE Grade
RP vs. EBRT vs. BT <sup>75</sup>	Overall survival among patients with low-risk prostate cancer (n=685) at 10-year followup	High	Consistency unknown (single study)	Direct	RP vs. EBRT Precise HR 1.7 (95% CI, 1.3 to 2.1) Effect size was statistically significant.	RP	Insufficient for patient subgroup
					RP vs. BT Precise HR 1.7 (95% CI, 1.4 to 2.2) Effect size was statistically significant		
	Overall survival among patients with intermediate-risk prostate cancer (n=1,068) at 10-year followup	High	Consistency unknown (single study)	Direct	RP vs. EBRT Precise HR 1.5 (95% CI, 1.2 to 1.9) Effect size was statistically significant		
					RP vs. BT Precise HR 1.5 (95% CI, 1.1 to 2.1) Effect size was statistically significant		

**Table 35. Key Question 4: Strength-of-evidence grades for nonrandomized comparative studies (continued)**

Comparison	Outcome	Overall Risk of Bias	Consistency	Directness	Precision	Evidence Favors	SOE Grade
RP vs. EBRT vs. BT <sup>/5</sup> (continued)	Overall survival among patients with high-risk prostate cancer (n=226) at 10-year followup	High	Consistency unknown (single study)	Direct	RP vs EBRT Precise HR 1.7 (95% CI, 1.3 to 2.3) Effect size was statistically significant RP vs. BT Precise HR 3.1 (95% CI, 1.7 to 5.9) Effect size was statistically significant		
RP vs. EBRT vs. BT <sup>/5</sup>	PCSM among patients with low-risk prostate cancer (n=685) at 10-year followup	High	Consistency unknown (single study)	Direct	RP vs. EBRT Imprecise HR 1.8 (95% CI, 0.5 to 6.2) Effect size was not statistically significant. RP vs. BT Imprecise HR 2.3 (95% CI, 0.8 to 6.9) Effect size was not statistically significant.	No significant difference between the interventions	Insufficient for patient subgroup
	PCSM among patients with intermediate-risk prostate cancer (n=1,068) at 10-year followup	High	Consistency unknown (single study)	Direct	RP vs. EBRT Imprecise HR 1.8 (95% CI, 0.8 to 3.8) Effect size was not statistically significant.		
RP vs. EBRT vs. BT <sup>/5</sup> (continued)					RP vs. BT Imprecise HR 0.6 (95% CI, 0.1 to 2.7) Effect size was not statistically significant.		

**Table 35. Key Question 4: Strength-of-evidence grades for nonrandomized comparative studies (continued)**

Comparison	Outcome	Overall Risk of Bias	Consistency	Directness	Precision	Evidence Favors	SOE Grade
	PCSM among patients with high-risk prostate cancer (n=226) at 10-year followup	High	Consistency unknown (single study)	Direct	RP vs. EBRT Imprecise HR 1.3 (95% CI, 0.8 to 2.1) Effect size was not statistically significant. RP vs. BT Imprecise HR 1.6 (95% CI, 0.4 to 6.6) Effect size was not statistically significant.		
Observation vs. EBRT <sup>59</sup>	PCSM among men with low-to intermediate-risk prostate cancer at 10-year followup (study did not report number of patients in this subgroup)	High	Consistency unknown (single study)	Direct	Imprecise HR 0.91 (0.80 to 1.04) Effect size was not statistically significant.	No significant difference between the interventions	Insufficient for all patient subgroups
	PCSM among men with high risk prostate cancer at 10-year followup (study did not report number of patients in this subgroup)	High	Consistency unknown (single study)	Direct	Precise HR 0.59 (0.50 to 0.60) Effect size was statistically significant.	EBRT	Insufficient for patient subgroup
Observation vs. ADT <sup>78</sup>	All-cause mortality rate per 100 among men with poorly-differentiated prostate cancer (n=4,303) at 81-month followup	Medium	Consistency unknown (single study)	Direct	Imprecise HR 1.04 (95% CI, 0.97 to 1.13) Effect size was not statistically significant.	No significant difference between the interventions	Insufficient for patient subgroup
	All-cause mortality rate per 100 among men with moderately-differentiated prostate cancer (n=14,660) at 81-month followup	Medium	Consistency unknown (single study)	Direct	Precise HR 1.15 (95% CI, 1.10 to 1.21) Effect size was statistically significant.	Observation	Insufficient for patient subgroup
	PCSM rate per 100 among men with poorly-differentiated prostate cancer (n=4,303) at 81-month followup	Medium	Consistency unknown (single study)	Direct	Imprecise HR 1.12 (95% CI, 0.96 to 1.29) Effect size was not statistically significant.	No significant difference between the interventions	Insufficient for patient subgroup

**Table 35. Key Question 4: Strength-of-evidence grades for nonrandomized comparative studies (continued)**

Comparison	Outcome	Overall Risk of Bias	Consistency	Directness	Precision	Evidence Favors	SOE Grade
	PCSM rate per 100 among men with moderately-differentiated prostate cancer (n=14,660) at 81-month followup	Medium	Consistency unknown (single study)	Direct	Imprecise HR 1.83 (95% CI, 1.58 to 2.12) Effect size was statistically significant.	No significant difference between the interventions	Insufficient for patient subgroup
RP vs. EBRT (plus ADT) <sup>38</sup>	All-cause mortality among men with high-risk, diagnostic PSA levels >10 ng/mL or Gleason score ≥8* (n=437) at 15-year followup	High	Consistency unknown (single study)	Direct	Precise HR 0.65 (95% CI, 0.48 to 0.87). Effect size was statistically significant.	RP	Insufficient for patient subgroup
	All-cause mortality among men with low-risk, diagnostic PSA levels <10 ng/mL or Gleason score ≤6* (n=753) at 15-year followup	High	Consistency unknown (single study)	Direct	Precise HR 0.78 (95% CI, 0.63 to 0.96). Effect size was statistically significant.	RP	Insufficient for patient subgroup
RP vs. EBRT (plus ADT) <sup>38</sup> (continued)	PCSM among men with high-risk, diagnostic PSA levels >10 ng/mL or Gleason ≥8* (n=437) at 15-year followup	High	Consistency unknown (single study)	Direct	Precise HR 0.78 (95% CI, 0.63 to 0.96). Effect size was statistically significant.	RP	Insufficient for patient subgroup
	PCSM among men with low-risk, diagnostic PSA levels <10 ng/mL or Gleason score ≤6* (n=753) at 15-year followup	High	Consistency unknown (single study)	Direct	Imprecise HR 0.66 (95% CI, 0.35 to 1.25). Effect size was not statistically significant.	No significant difference between the interventions	Insufficient for patient subgroup
RP vs. EBRT <sup>41</sup>	PCSM for low-risk group (PSA levels ≤10, Gleason score ≤6 and T category ≤T2a) (n=386; 371 cohort and 15 cases)	High	Consistency unknown (single study)	Direct	Imprecise HR 0.87 (95% CI 0.28 to 2.76). Effect size was not statistically significant.	No significant difference between the interventions	Insufficient for patient subgroup
RP vs. EBRT vs. WW with and without secondary treatment <sup>36</sup>	Overall mortality	High	Consistency unknown (single study)	Direct	Imprecise for PSA and clinical T stage	No significant difference	Insufficient for patient subgroup



**Table 35. Key Question 4: Strength-of-evidence grades for nonrandomized comparative studies (continued)**

Comparison	Outcome	Overall Risk of Bias	Consistency	Directness	Precision	Evidence Favors	SOE Grade
RALRP vs. RRP <sup>68</sup>	QOL	High	Consistency unknown (single study)	Direct	Imprecise	No significant difference between the interventions by risk level	Insufficient for patient subgroup

\*Only patients with Gleason score of 8 or more received ADT along with EBRT.

**Abbreviations:** 3D-CRT=Three-dimensional conformal radiotherapy; ADT=androgen-deprivation therapy; BT=brachytherapy; CI=confidence interval; EBRT=external beam radiation therapy; HR=hazard ratio; IMRT=intensity modulated radiotherapy; PCSM=prostate cancer-specific mortality; PSA=prostate-specific antigen; QOL=quality of life; RALRP=robotic-assisted laparoscopic radical prostatectomy; RP=radical prostatectomy; RR=relative risk; RRP=radical retropubic prostatectomy; SOE=strength of evidence.

# Discussion

## Key Findings and Strength of Evidence

This systematic review updates a previous systematic review on treating localized prostate cancer. Fifty-two studies met the inclusion criteria for review for Key Question (KQ) 1 regarding comparative effectiveness of various therapeutic options. Thirteen of the 52 studies also met the inclusion criteria for KQ 2 regarding patient characteristics that impact response to treatment, and 20 of the 52 studies met the inclusion criteria for KQ 4 regarding the impact of tumor characteristics. Studies that addressed KQ 1 reported data for patient-oriented outcome measures such as overall survival, all-cause mortality, prostate cancer–specific mortality, metastases, quality of life (QOL), and adverse events. Evidence addressing KQ 2 or 4 came solely from subgroup analyses of larger studies that addressed KQ 1. Although these subgroup analyses reported data on overall survival, all-cause mortality, or prostate cancer–specific mortality for specific patient subgroups, they did not report adverse events that occurred in these subgroups.

### Key Question 1

For the comparison of radical prostatectomy (RP) versus watchful waiting (WW), the Prostate Cancer Intervention Versus Observation Trial (PIVOT) reported data on all-cause mortality, prostate cancer–specific mortalities, and progression to metastases at the end of the 12-year followup period and the Scandinavian Prostate Cancer Group-4 (SPCG-4) trial reported data on these same outcomes at the end of the 12- and 15-year followup periods. Neither study, however, compared RP to active surveillance.

Although patients with some similarities were enrolled in these two important trials, major differences exist in the enrolled populations. The SPCG-4 trial began in 1989 when prostate-specific antigen (PSA) screening was not widespread; only 5 percent of tumors in SPCG-4 were screen-detected. In contrast, 76 percent of men had prostate cancer detected by screening in PIVOT. Not surprisingly, men with nonpalpable tumors (T1c) comprised 50 percent of the PIVOT population, but only 20 percent of SPCG-4. Although the SPCG-4 trial's eligibility criteria specified clinical stage T1 or T2 disease, nearly half the patients undergoing RP were found to have extracapsular extension (pT3, tumor extending beyond capsule) compared with only 6 percent of patients in the PIVOT study.

In addition to the differences in patient characteristics enumerated above, the protocol for the WW arms differed between the SPCG-4 trial and PIVOT. In the SPCG-4 trial, which included patients in an unscreened population, transurethral resection of the prostate (TURP) was recommended as the initial treatment for men with symptoms suggesting urinary obstruction. Orchidectomy was recommended for symptomatic local recurrence and disseminated disease.

In PIVOT, which primarily included men with screen-detected prostate cancers, patients with symptomatic local progression were treated first with alpha blockers or a mechanical intervention such as TURP or stents. If these measures failed to control local symptoms, prostatectomy was permitted. Hormonal therapy was considered first-line therapy for patients with disease progression requiring nonmechanical therapy, with radiation therapy or chemotherapy permitted when hormonal therapy failed.

While both trials reported similar hazard ratios for prostate cancer–specific mortality, the hazard ratio for all-cause mortality was higher in the PIVOT than the SPCG-4. This suggests that prostate cancer death in the PIVOT may have been diluted by deaths from other causes or

competing risks, which speaks to the underlying health of men in both randomized controlled trials (RCTs) being different and the question of whether the PIVOT data can apply to a healthy cohort. Furthermore, in the PIVOT study, the median survival was assumed to be 15 years in the original study design and 10 years in the updated design. The PIVOT investigators failed to accrue its targeted enrollment of 2,000 patients to surgery or observation.

The SPCG-4 trial reported that both overall and prostate cancer-specific mortalities were statistically significantly lower among men who underwent RP compared with WW at 15-year followup. The SPCG-4 trial also reported that at 12-year followup, prostate cancer-specific mortality was statistically significantly lower among men who underwent RP, but no statistically significant difference in overall mortality was found between the compared interventions. At the 12-year followup, the PIVOT found no statistically significant difference in overall or prostate cancer-specific mortality between RP and WW. The strength-of-evidence grade for each of these reported outcomes is insufficient. The evidence on overall QOL based on the PIVOT<sup>25</sup> and SPCG-4<sup>33</sup> trials is insufficient to permit conclusions, although there was low strength of evidence that one component of QOL (urinary incontinence) occurs more frequently with RP than with WW.

However, both trials reported consistent findings regarding a significant reduction in progression to metastases in the RP group compared to the WW group. This consistency, combined with medium risk of bias and precision, means that the strength of evidence is moderate for this outcome. Given the clinical heterogeneity between these trials, the results suggest that the findings for this outcome may apply to a wide range of patients with clinically localized prostate cancer. Although this is not a QOL assessment, it has serious QOL implications because bone metastasis is a significant determinant of QOL in men with prostate cancer. Nevertheless, we note that these findings should always be interpreted with caution. Potential issues regarding applicability to current clinical practice will be further discussed in the following sections.

For the comparison of radical retropubic prostatectomy (RRP) versus brachytherapy (BT), the evidence on the only reported outcome, QOL at 1-year followup, is insufficient for drawing any conclusion.

For the comparison of three-dimensional conformal radiation therapy (3D-CRT) alone versus 3D-CRT combined with androgen-deprivation therapy (ADT),<sup>35</sup> the data on overall survival, all-cause mortality, and prostate cancer-specific mortality from a single low risk-of-bias trial favor the combined treatments with a low strength-of-evidence grade. For the comparison of external beam radiotherapy (EBRT) alone versus EBRT combined with ADT,<sup>43</sup> a single medium risk-of-bias RCT favored the combined treatments for overall survival, all-cause mortality, and prostate cancer-specific mortality. However, the strength of evidence was insufficient to allow a conclusion. These findings should be interpreted using thorough consideration of the specific patient populations and the treatment methods used in the trials. In both studies, the dose of radiation therapy was lower than is currently known to be effective. The applicability of these trials will be further discussed in the following sections.

Overall, the RCT-based evidence favors the combined therapies. However, the low or insufficient strength-of-evidence grades in the existing evidence suggest that the comparative effectiveness of EBRT versus EBRT plus ADT is still uncertain and will need future studies for validation.

Our review used nonrandomized trials to permit conclusions for treatment comparisons with insufficient RCT-based evidence. As with the RCTs, the strength of evidence from

nonrandomized studies was often insufficient to address the treatment comparisons of interest. The main reasons for the insufficient strength-of-evidence gradings include the medium to high risk of bias in the majority of the individual studies included in the evidence base and the small number of studies addressing each treatment comparison. In two instances we were able to draw a conclusion, based on six studies of high risk of bias but with consistent findings. RP was favored over EBRT for both all-cause mortality<sup>36-40</sup> and prostate cancer-specific mortality.<sup>37-42</sup> However, we note that radiation dosage was not reported in some studies and a proportion of patients received a lower dose than what is currently considered effective. Furthermore, despite statistical attempts to adjust for known confounders, most observational studies are vulnerable to bias from unknown confounding factors.

Adverse events were defined and reported rather differently across the interventions compared and across the studies reviewed. This made synthesis of findings difficult, but some patterns could be discerned. Overall, urinary incontinence and erectile dysfunction were frequently reported among men who underwent RP. Genitourinary toxicity, gastrointestinal toxicity, and erectile dysfunction were frequently reported among men who received radiation therapy.

Table 36 summarizes the main findings and strength of evidence for KQ 1.

**Table 36. Summary of the main findings for Key Question 1**

Comparison and Outcome	Evidence Base	Findings	Risk of Bias	Consistency	Directness and Precision	SOE Grade
RP vs. WW, All-cause mortality	2 trials SPCG-4 <sup>15,33,34</sup> PIVOT <sup>25</sup> (n=1,426)	SPCG-4: Favors RP at 15 years ARR 6.6%; 95% CI, -1.3% to 14.5% Cumulative incidence: 46.1% vs. 52.7% RR 0.75; 95% CI, 0.61 to 0.92 No significant difference between the interventions at 12 years. ARR 7.1%; 95% CI -0.5 to 14.7%; Cumulative incidence: 32.7% vs. 39.8% (137 vs. 156 deaths) RR 0.82; 95% CI 0.65 to 1.03. PIVOT: No significant difference between the interventions at 12 years. ARR 2.9%; 95% CI, -4.1% to 10.3% (171 [47.0%] vs. 183 [49.9%] deaths; HR 0.88; 95% CI, 0.71 to 1.08.	Medium	Consistent	Direct Imprecise	Insufficient

**Table 36. Summary of the main findings for Key Question 1 (continued)**

Comparison and Outcome	Evidence Base	Findings	Risk of Bias	Consistency	Directness and Precision	SOE Grade
RP vs. WW, PCSM	2 trials SPCG-4 <sup>15,33,34</sup> PIVOT <sup>25</sup> (n=1,426)	SPCG-4: Favors RP at 12 and 15 years ARR 6.1%; 95% CI, 0.2% to 12.0% Cumulative incidence: 14.6% vs. 20.7% RR 0.62; 95% CI, 0.44 to 0.87 PIVOT: No significant difference between the interventions. ARR 2.6%; 95% CI, -1.1 to 6.5. (21 [5.8%] vs. 31 [8.7%] deaths; HR 0.63; 95% CI, 0.36 to 1.09.	Medium	Inconsistent	Direct Imprecise	Insufficient
RP vs. WW, QOL	1 trial SPCG-4 <sup>15,33,34</sup> (n=695)	No significant difference between the interventions at median followup of 12.2 years.	High	Consistency unknown (single study)	Direct Imprecise	Insufficient
RP vs. WW, QOL (urinary leakage)	2 trials SPCG-4 <sup>15,33,34</sup> PIVOT <sup>25</sup> (n=1,426)	Favors WW for urinary leakage (2–4 years) SPCG-4: OR 2.3 (95% CI, 1.6 to 3.2) PIVOT: RR 2.69 (95% CI 1.61 to 4.51)	Medium <sup>a</sup>	Consistent	Direct Precise	Low
RP vs. WW, QOL (erectile dysfunction at 4 years)	2 trials SPCG-4 <sup>15,33,34</sup> PIVOT <sup>25</sup> (n=1,426)	SPCG-4: No significant difference between interventions for erectile dysfunction at 4 years). PIVOT: RR 1.84 (95% CI 1.59 to 2.11) (Favors WW at 2 years)	Medium	Inconsistent	Direct Imprecise	Insufficient
RP vs. WW, QOL (bowel dysfunction)	1 trial PIVOT <sup>25</sup> (n=695)	No significant difference between interventions for bowel dysfunction.	Medium	Consistency unknown (single study)	Direct Imprecise	Insufficient
RP vs. WW, Progression to metastases	2 trials SPCG-4 <sup>15,33,34</sup> PIVOT <sup>25</sup> (n=1,426)	Favors RP SPCG-4: RR 0.65 (95% 0.47 to 0.88) PIVOT: HR 0.40 (95% CI 0.22 to 0.70)	Medium	Consistent	Direct Precise	Moderate
RALRP vs. LRP, QOL (urinary continence, erectile function)	1 trial <sup>4b</sup> (n=120)	Favors RALRP at 1 year Urinary continence: 95% vs 83.3%, p=0.042 Erectile function: 80% vs 54.2%, p=0.02	High	Consistency unknown (single study)	Direct Precise	Insufficient
RRP vs. BT, QOL	1 trial <sup>44</sup> (n=200)	No significant difference between the interventions at 5-year followup.	High	Consistency unknown (single study)	Direct Imprecise	Insufficient

**Table 36. Summary of the main findings for Key Question 1 (continued)**

Comparison and Outcome	Evidence Base	Findings	Risk of Bias	Consistency	Directness and Precision	SOE Grade
RPP vs. RRP, QOL (urinary continence, erectile function)	1 trial <sup>46</sup> (n=200)	Favors RRP for erectile function (60% vs 42%, p=0.032) at 2 years; no significant difference in urinary continence	High	Consistency unknown (single study)	Direct Precise (erectile function) Imprecise (urinary continence)	Insufficient
3D-CRT vs. 3D-CRT plus ADT, Overall survival	1 trial <sup>35</sup> (n=206)	Favors 3D-CRT plus ADT at median 7.6-year followup HR 3.0; 95% CI, 1.5 to 6.4 (44 vs. 30 deaths)	Low	Consistency unknown (single study)	Direct Precise	Low
3D-CRT vs. 3D-CRT plus ADT, All-cause mortality	1 trial <sup>35</sup> (n=206)	Favors EBRT plus ADT at median 7.6-year followup HR 1.8 (95% CI, 1.1 to 2.9)	Low	Consistency unknown (single study)	Direct Precise	Low
3D-CRT vs. 3D-CRT plus ADT, PCSM	1 trial <sup>35</sup> (n=206)	Favors 3D-CRT plus ADT at median 7.6-year followup HR 4.1; 95% CI, 1.4 to 12.14 (14 vs. 4 deaths)	Low	Consistency unknown (single study)	Direct Precise	Low
EBRT vs. EBRT plus ADT, Overall survival	1 trial <sup>43</sup> (n=1,979)	Favors EBRT plus ADT at median 9.1-year followup HR 1.17; 95% CI, 1.10 to 1.35 (57% vs. 62% survival rate)	Medium	Consistency unknown (single study)	Direct Precise	Insufficient
EBRT vs. EBRT plus ADT, PCSM	1 trial <sup>43</sup> (n=1,979)	Favors EBRT plus ADT at median 9.1-year followup HR 1.87; 95% CI, 1.27 to 2.74 (8 vs. 4 deaths)	Medium	Consistency unknown (single study)	Direct Precise	Insufficient
EBRT vs. EBRT plus ADT, QOL (sexual function)	1 trial <sup>43</sup> (n=1,979)	Favors EBRT at 1 year OR: 1.72 (1.17 to 2.52), p=0.004	High	Consistency unknown (single study)	Direct Precise	Insufficient
EBRT vs. Cryotherapy, Overall survival	1 trial <sup>47</sup> (n=244)	No significant difference between interventions at 5 years. Difference 1.2 (-6.8–9.2).	Medium	Consistency unknown (single study)	Direct Imprecise	Insufficient
EBRT vs. Cryotherapy, PCSM	1 trial <sup>47</sup> (n=244)	No significant difference between interventions at 5 years. Difference 0.3 (-4.8–5.4).	Medium	Consistency unknown (single study)	Direct Imprecise	Insufficient
EBRT vs. Cryotherapy, QOL (urinary function)	1 trial <sup>52</sup> (n=244)	Favors cryotherapy (p-value was statistically significant) at 3 years.	High	Consistency unknown (single study)	Direct Precise	Insufficient

**Table 36. Summary of the main findings for Key Question 1 (continued)**

Comparison and Outcome	Evidence Base	Findings	Risk of Bias	Consistency	Directness and Precision	SOE Grade
EBRT vs. Cryotherapy, QOL (bowel function)	1 trial <sup>52</sup> (n=244)	No significant difference between interventions at 3 years.	High	Consistency unknown (single study)	Direct Imprecise	Insufficient
EBRT vs. Cryotherapy, QOL (sexual function)	1 trial <sup>52</sup> (n=244)	Favors EBRT at 3 years (p-value was statistically significant)	High	Consistency unknown (single study)	Direct Precise	Insufficient
RP vs. EBRT All-cause mortality	6 studies <sup>36-40,42</sup> (n= 22,771)	Favors RP Five of 6 studies found that overall mortality was significantly lower following RP (followup 3–15 years)	High	Consistent	Direct Precise	Low
RP vs. EBRT PCSM	6 studies <sup>37-42</sup> (n=23,301)	Favors RP All 6 studies found that PCSM was significantly lower following RP (followup 3–15 years)	High	Consistent	Direct Precise	Low

For the interpretation of SOE grading, see definitions of evidence grades in the Methods section under Strength-of-Evidence Grading.

<sup>a</sup>The evidence base for this outcome contained one medium and one high risk-of-bias study; because of this borderline between medium and high risk the strength of evidence was lowered from moderate to low.

**Abbreviations:** ADT=Androgen-deprivation therapy; ARR=absolute risk reduction; BT=brachytherapy; CI=confidence interval; 3D-CRT=three-dimensional radiation therapy; EBRT=external beam radiation therapy; HR=hazard ratio; PCSM=prostate cancer-specific mortality; PIVOT=Prostate Intervention Versus Observation Trial; QOL=quality of life; RP=radical prostatectomy; RPP=radical perineal prostatectomy; RRP=radical retropubic prostatectomy; RR=relative risk; SOE=strength of evidence; SPCG-4=Scandinavian Prostate Cancer Group-4; WW=watchful waiting.

## Key Question 2

For KQ 2, two RCTs that compared RP versus WW and two other RCTs that compared radiotherapy alone versus radiotherapy plus ADT performed subgroup analyses according to patient characteristics.

For the comparison of RP versus WW, both RCTs analyzed data stratified by age. The PIVOT found no significant difference in all-cause or cancer-specific mortality between RP and WW for the age group of younger than 65 years or the group of 65 years or older.<sup>33</sup> We note that the PIVOT was designed to recruit 2,000 patients but enrolled only 731. This may have an impact on the study's results, particularly for the subgroup analysis. The SPCG-4 trial found a significant advantage of RP over WW in all-cause and cancer-specific mortalities for patients younger than 65 years of age but not for the patient group of 65 years or older.<sup>25</sup> A nonrandomized study of a Medicare-linked database of patients age 65 years or older performed an instrumental variable analysis that also found no significant difference between RP and WW regarding all-cause and prostate cancer-specific mortality.<sup>73</sup> The PIVOT performed additional subgroup analysis by race and self-reported performance status. No difference was found in all-cause or cancer-specific mortality between RP and WW for any race or performance score category that was analyzed.<sup>33</sup>

For the comparison of radiotherapy versus radiotherapy plus ADT,<sup>35,43</sup> one RCT found that for patients with no comorbidity or a minimal comorbidity score, 3D-CRT plus ADT was

associated with a significantly higher 8-year survival than EBRT alone.<sup>35</sup> However, for patients with a moderate or severe comorbidity score, overall survival was not significantly different between the two intervention groups. The other RCT<sup>43</sup> compared EBRT versus EBRT plus ADT and found that the combined treatment was associated with a significantly higher overall 10-year survival and lower prostate cancer–specific mortality among the white patients but not among the black patients (this may have been due to lack of statistical power because there were fewer black patients). The study found no statistically significant advantage of EBRT plus ADT over EBRT alone in overall survival among the 70 years of age or younger or the older than 70-years-of- age category.

Overall, the RCTs reviewed in the current report were not well-powered to detect statistical significance in patient-oriented outcomes in subgroup analyses. The strength of the RCT-based evidence body is insufficient for us to draw any conclusion for KQ 2.

In addition to the RCTs, six nonrandomized comparative studies were also reviewed for KQ 2. The strength of the non-RCT-based evidence is also insufficient for drawing any conclusion for KQ 2. Most of the studies addressing KQ2 did not examine the relationship between treatment patient characteristics.

### **Key Question 3**

For KQ 3, we did not identify any comparative study that directly examined how provider characteristics influence the effectiveness of different treatments.

### **Key Question 4**

For KQ 4, two RCTs that compared RP and WW and another RCT that compared radiotherapy alone versus radiotherapy plus ADT performed subgroup analysis by tumor characteristics.

For the comparison of RP versus WW, both RCTs analyzed data stratified by PSA level. The PIVOT study found that RP did not reduce all-cause or prostate cancer–specific mortality among men with PSA of less than 10 ng/mL, but resulted in a significant reduction in the mortalities among men with PSA of more than 10 ng/mL.<sup>33</sup> However, the SPCG-4 trial found that the PSA level (less than 10 ng/mL vs. 10 ng/mL or more) did not affect the superiority of RP in reducing all-cause or prostate cancer–specific mortality.<sup>25</sup>

With respect to tumor risk levels, the PIVOT found that compared with WW, RP led to a significant reduction in overall mortality among patients with intermediate tumor risk (based on PSA, Gleason score, or tumor stage) but not in patients with high or low tumor risk. The SPCG-4 trial found a significant reduction in overall mortality (but not prostate cancer–specific mortality) associated with RP in low-risk patients (based on PSA level less than 10 ng/mL and Gleason score less than 7 or a World Health Organization grade 1 in preoperative biopsy specimens), and no data were reported for men with high-risk cancer. Note that the “low-risk” category was defined differently between the PIVOT and the SPCG-4 trial, and as noted earlier, the percentage of patients with nonpalpable T1c tumors (and by extension the composition of the low risk subgroups) differed between these trials.

The subgroup analysis for other tumor characteristics or outcomes reported in the PIVOT and SPCG-4 trials suggests that those tumor characteristics did not significantly alter the comparative findings. An important context for interpreting these findings is that the majority of men with low-risk cancer in the PIVOT had PSA-detected cancer compared to the low-risk SPCG-4 study.



In PIVOT, almost 45% of the men had T2 prostate cancer compared with almost 75% in the SPCG-4 study.

For the comparison of EBRT alone versus EBRT plus ADT, one RCT<sup>43</sup> performed a subgroup analysis and found that adding short-term ADT to EBRT led to a significantly higher overall survival or lower prostate cancer–specific mortality among patients of intermediate tumor risk (based on PSA, Gleason score, or tumor stage) but not among patients with high- or low-risk cancer. In this study, the radiation dose was low, and the length of ADT (only 4 months) might have been too short for patients with high-risk disease. We therefore highlight that—although it appears that men with intermediate-risk prostate cancers may benefit from 4–6 months of ADT—this study could not adequately address either of the two study endpoints in which longer-term ADT may be needed. Moreover, treating low-risk patients with EBRT plus ADT would be considered substantial overtreatment by most national clinical practice guidelines.

Overall, the RCTs reviewed in the current review were not well-powered to detect statistical significance in patient-oriented outcomes in subgroup analyses, and even significant findings should be viewed as hypothesis-generating rather than definitive evidence. The strength of this RCT-based evidence body is insufficient for drawing any conclusion for KQ 4. Besides the RCTs, eight nonrandomized comparative studies were also reviewed for KQ 4. The strength of the non-RCT-based evidence is also insufficient to allow any conclusion.

As noted in the Methods section, we chose a conservative approach when grading strength of evidence in this report, because multiple factors other than treatment can influence apparent differences in clinical outcomes between interventions observed in these studies. Accordingly, we placed a high value on replication of findings, and felt that if the evidence is based on a single RCT, it should only be considered sufficient evidence (low strength) if that RCT had precise findings and was rated as low risk of bias. For studies rated as having high risk of bias, we set a higher bar and required at least three studies with consistent and precise findings. End-users of this report can reasonably choose to set a less conservative bar when making clinical or policy decisions.

## Findings in Relationship to What Is Already Known

The 2008 systematic review that the current report updates concluded that no single therapy could be considered the preferred treatment for localized prostate cancer because of limitations in the body of evidence as well as the tradeoffs an individual patient must make when considering treatment options. Following publication of the PIVOT, some experts have suggested that patients found to have low- to intermediate-risk localized disease should be encouraged to consider active surveillance and that older patients or those with comorbid conditions should wait for symptoms to appear. Despite the availability of 12-year follow up data from PIVOT and 15-year data from SPCG-4, we believe that uncertainty remains.

The 2008 report also compared RP with WW, primarily based on the evidence at the 10-year followup from the SPCG-4<sup>94</sup> and another small trial.<sup>95</sup> With the 12- and 15-year data from the SPCG-4 trial and the 12-year data from the PIVOT, the RCT-based findings from this comparative effectiveness review extend those from the 2008 report on the same comparison.

For the comparison of radical retropubic prostatectomy (RRP) versus brachytherapy, the 2008 report found no evidence from RCTs.<sup>22</sup> In this report, the evidence on the only reported outcome, QOL at 1-year followup, is insufficient for drawing any conclusion.

Two RCTs<sup>96,97</sup> in the 2008 report compared EBRT plus ADT with EBRT alone. One RCT<sup>96</sup> reported that EBRT plus 6 months of ADT reduced all-cause mortality, prostate cancer–specific

mortality, and PSA failure compared with EBRT alone at 4.5-year followup. Another RCT<sup>97</sup> reported that EBRT plus 6 months of ADT reduced clinical failure, biochemical failure, or death from any cause compared with those outcomes with EBRT alone in men with stage T2c but not T2b prostate cancer.

For the comparison of ADT versus ADT in combination with EBRT, the 2008 report did not identify any evidence from RCTs.<sup>22</sup> In this report, the evidence on the only reported major outcome, prostate cancer–specific mortality, is insufficient for drawing any conclusion.

The only RCT reviewed in the 2008 report that performed a subgroup analysis by any patient characteristics is the SPCG-4 trial. The subgroup analysis of the earlier SPCG-4 trial data found that the difference in prostate cancer mortality between RP and WW appeared to be primarily in patients younger than 65 years. The updated SPCG-4 analysis agrees with this finding and extends it to overall mortality as well, but the PIVOT did not find a difference in these outcomes when stratifying by age. Overall, these RCTs reviewed in the current report and in the 2008 report were not well-powered to detect statistical significance in patient-oriented outcomes in subgroup analyses. The strength of the RCT-based evidence in the current report is insufficient for us to draw any conclusion for KQ 2.

We did not identify any comparative study that directly examined how provider characteristics influence the effectiveness of different treatments. As a result, this review does not add new information to that reported in the 2008 report on the same KQ.

The only RCT reviewed in the 2008 report that performed a subgroup analysis according to any tumor characteristics is the SPCG-4 trial. The subgroup analysis of the earlier SPCG-4 trial data was based on the data at 10-year followup, which is overridden by the undated SPCG-4 trial data reported in this review.

One small RCT in the 2008 report compared RP to EBRT and found that patients undergoing RP had less progression and recurrence and fewer distant metastases. This is supported by low-strength evidence from nonrandomized studies in this update which found lower overall mortality and prostate cancer–specific mortality among patients treated with RP.

## Applicability

We considered applicability of study findings using the PICOTS framework (patients, intervention, comparisons, outcomes, timing, and settings) as described by Atkins et al.<sup>98</sup> The evidence-based conclusions are applicable only to the types of patients enrolled in the studies underlying those conclusions, the types of clinical settings in which the studies were conducted, the types of interventions being compared, and the particular outcomes and followup period reported. Table 37 is a summary of factors that may restrict the applicability of the findings from the RCTs discussed in the previous section. Although the restrictions on the applicability of the conclusions may vary across the evidence bases for different treatment comparisons, some restrictions may be common to most of these evidence bases. All but one of the RCTs included in this review recruited their subjects before 2002. Since then, the treatment options compared in this report have greatly evolved. For example, open surgery was the main treatment for radical prostatectomy in the reviewed RCTs. However, in recent years, robotic-assisted surgery has become the dominant technique for radical prostatectomy in the United States.

Similarly for EBRT, BT, and other treatments, advances in technologies and knowledge may allow many of the currently available treatments to better target the cancer, thereby improving the effectiveness and patient tolerance of the treatments. For example, current radiotherapy dosing protocols are based on patient or tumor characteristics (e.g., age, comorbidity status,

clinical stage of the tumor, Gleason score), thus allowing higher doses than those administered in most of the radiotherapy studies reviewed in this CER update (see Table D-1 and Table D-2 in Appendix D). Because evidence based on dated medical techniques may not apply to current practice, future studies are required for validating the comparative effectiveness and safety of the current and emerging treatment techniques (e.g., robotic-assisted surgery, proton beam therapy, stereotactic body radiation therapy).

Additionally, patients studied in the RCTs included in this review may have a different risk profile from patients currently being diagnosed with prostate cancer. Ten to 15 years ago, prostate cancers were primarily detected by digital rectal examination or tissue specimens obtained during TURP for treating benign prostatic obstruction. Currently, the vast majority of prostate cancers detected in the United States are found via PSA-level testing. Men often start to receive PSA tests in their 40s and continue taking the test on a regular basis until their 80s. As a result, the patients whose diagnosis is established today can be younger and have more confined cancers than those studied in the reviewed RCTs. This trend restricts the applicability of the reviewed evidence, which was based mostly on studies using older and sicker patient populations.

Because of the intensified concern about overdiagnosis of prostate cancer in recent years, the manner in which PSA testing is used for screening prostate cancer and the criteria for establishing an abnormal PSA test result may continue to change. Patient and tumor characteristics among men with prostate cancer diagnosed in the future are likely to be different, not just from those in the past but even from men so diagnosed today.

Finally, we note that even in well-designed RCTs that found an apparent advantage of one intervention over another, subgroup analyses raise the possibility that not all patients in the target population will derive equal or even any observed benefit. This is of particular importance given the potential morbidities associated with prostate surgery and radiation therapies, which may be avoided if a more conservative intervention such as active surveillance is deemed appropriate.

To summarize, most current RCTs were initiated many years ago, and diagnosis and treatment have evolved. Given that it is now possible to detect smaller-volume tumors and that histologic grading is less likely with low-grade tumors than with intermediate-grade tumors, the long-term, patient-oriented outcomes of detected prostate cancer in men managed with observation are likely much better than they were when these studies were initiated and the risk of overdiagnosis and overtreatment greater (this includes the harms of active surveillance with biopsies, which can lead to infection and hospitalization). Therefore, any benefit of early intervention is likely to be less in absolute terms and require a longer time period to accrue and, per se, any harms would carry even more weight.

**Table 37. Factors affecting the applicability of the evidence from randomized controlled trials**

Trial, Setting, Enrollment Period	Population, Demographic, Disease State	Interventions and Comparators	Outcomes and Followup Time points
<p>PIVOT<sup>25</sup>                      A multicenter RCT involving 731 men recruited from 52 medical centers (44 Veterans Affairs and 8 National Cancer Institute sites) across the United States.                      November 1994–January 2002</p>	<p>Age younger than 75 years, T1–T2NxM0, PSA levels &lt;50 ng/mL</p>	<p>RP: The technique used was at the surgeon’s discretion. Additional interventions were determined by each participant and his physician.                      Observation: Men in the WW study arm were offered palliative (noncurative) therapy (e.g., TURP for local progression causing urinary obstruction, ADT and/or targeted radiation therapy for evidence of distant spread).</p>	<p>All-cause mortality, prostate cancer–specific mortality, clinical progression, and adverse events                      Median followup: 10 years</p>
<p>SPCG-4 trial<sup>15,33,34,51</sup>                      A multicenter RCT involving 695 men conducted at 14 centers in Sweden, Finland, and Iceland.                      October 1989–December 1999</p>	<p>Age younger than 77 years, T1b, T1c, T2, PSA levels &lt;50 ng/mL</p>	<p>RP: The surgical procedure started with a lymphadenectomy of the obturator fossa; if no nodal metastases were found in frozen sections, the RP was performed. Radical excision of the tumor was given priority over nerve-sparing surgery.                      WW: Men in the watchful waiting group who had signs of obstructive voiding disorders were treated with TURP. Metastases detected by bone scan were managed with hormonal therapy.</p>	<p>All-cause mortality, prostate cancer–specific mortality, clinical progression, adverse events, and QOL                      Median followup: 15 years</p>
<p>Porpiglia et al. 2012<sup>45</sup>                      A single-center RCT enrolling 120 men was conducted in Italy.                      January 2010–January 2011</p>	<p>Age 40 to 75 years of age, PCa T1 through T2NOMO clinically staged according to TNM 2009</p>	<p>RARP: transperitoneal anterograde approach. When indicated unilateral or bilateral neurovascular bundle preservation and extended lymph node dissection were performed.                      LRP: transperitoneal anterograde approach. When indicated unilateral or bilateral neurovascular bundle preservation and extended lymph node dissection were performed.</p>	<p>Biochemical recurrence-free survival, QOL, adverse events                      Followup: 1 year</p>

**Table 37. Factors affecting the applicability of the evidence from randomized controlled trials (continued)**

Trial, Setting, Enrollment Period	Population, Demographic, Disease State	Interventions and Comparators	Outcomes and Followup Time points
<p>Giberti et al. 2009<sup>44</sup>                      A single-center RCT involving 200 men was conducted in Italy. May 1999–October 2002</p>	<p>Caucasian men, T1c or T2a, PSA levels &lt;10 ng/mL and Gleason sum &lt;6)</p>	<p>RRP: Bilateral nerve-sparing RRP in accordance with Walsh's principles and standard lymph node dissection were performed on all the patients by a single surgeon. Brachytherapy was performed by a team that included a urologist, a radiation therapist, and a primary care physician, through a transperitoneal template-guided peripheral loading real-time technique and seeds of iodine-125. A D90&gt;140 Gy was considered the cut-off value to predict a good-quality implant.</p>	<p>QOL, biochemical progression, adverse events                      5 year followup</p>
<p>Jones et al. 2011<sup>43</sup>                      A multicenter phase III RCT involving 1,979 men was conducted in the United States and Canada. 1994–2001</p>	<p>Age younger than 71 years, T1b, T1c, T2a, T2b prostate adenocarcinoma, PSA levels &lt;20 ng/mL</p>	<p>EBRT: Radiotherapy was administered in daily 1.8 Gy fractions prescribed to the isocenter of the treatment volume, consisted of 46.8 Gy delivered to the pelvis (prostate and regional lymph nodes), followed by 19.8 Gy to the prostate.                      EBRT plus short-term ADT: Flutamide at a dose of 250 mg orally 3 times a day and either monthly subcutaneous goserelin at a dose of 3.6 mg or intramuscular leuprolide at a dose of 7.5 mg for 4 months. Radiotherapy commenced after 2 months of ADT.</p>	<p>Overall survival, prostate cancer-specific mortality, clinical progression, adverse events, biochemical progression, and QOL                      Median followup: 9.1 years</p>

**Table 37. Factors affecting the applicability of the evidence from randomized controlled trials (continued)**

Trial, Setting, Enrollment Period	Population, Demographic, Disease State	Interventions and Comparators	Outcomes and Followup Time points
D'Amico et al. 2008 <sup>35</sup> A single-center RCT involving 206 men was conducted in the United States. December 1, 1995–April 15, 2001	Patients with T1 or T2 tumors who had at least a 10-year life expectancy excluding death from prostate cancer	3D-CRT: Daily dose of 1.8 Gy for initial 25 treatments, totaling 45 Gy, and 2.0 Gy for final 11 treatments, totaling 22 Gy. 3D-CRT plus ADT: 3D-CRT plus ADT which consisted of an LHRH agonist, leuprolide or goserelin, and the antiandrogen flutamide. Leuprolide was delivered intramuscularly each month at a dose 7.5 mg or 22.5 mg every 3 months. Goserelin was administered subcutaneously each month at a dose of 3.6 mg or 10.8 mg every 3 months. Flutamide was taken orally at a dose of 250 mg every 8 hours and starting 1–3 days before leuprolide.	Overall survival, all-cause mortality, and prostate cancer-specific mortality Median followup: 7.6 years

**Abbreviations:** ADT=androgen-deprivation therapy; D90=minimum dose covering 90% of the prostate volume; EBRT=external beam radiation therapy; 3D-CRT=three-dimensional conformal radiation therapy; Gy=gray; LHRH=luteinizing hormone-releasing hormone; PIVOT=Prostate Intervention Versus Observation Trial; PSA=prostate-specific antigen; QOL=quality of life; RCT=randomized controlled trial; RP=radical prostatectomy; RRP=radical retropubic prostatectomy; SPCG-4=Scandinavian Prostate Cancer Group-4; TURP=transurethral resection of the prostate.

## Implications for Clinical and Policy Decisionmaking

Our review suggests that in comparison with WW, RP appears to lead to a reduced all-cause or cancer-specific mortality in at least some patients with localized prostate cancer after a 15-year followup.<sup>33</sup> However, the strength of evidence from the SPCG-4 trial<sup>33</sup> is graded as insufficient (evidence does not permit a conclusion), and the evidence does not clearly identify the subgroup(s) of patients for which this finding is applicable. However, SPCG-4 and PIVOT together provided consistent, moderate-strength evidence that fewer patients treated with RP developed distant metastases at 12 to 15 years compared to patients receiving WW.

Our review was unable to draw any conclusion on global QOL. Therefore, it is unclear how patients as a whole can balance the tradeoff between the potential benefit in long-term survival and the potential harms (e.g., urinary incontinence, sexual dysfunction) associated with RP surgery. In the end, the treatment decision rests with each individual patient and the patient's family and physicians. These stakeholders' personal preferences and values play a significant role in this decisionmaking process. This may be particularly true for patients with life expectancies of less than about 15 years.

This review and the 2008 report both attempted to evaluate whether a particular patient group (in terms of age, race, general health status, and various tumor risk factors) might benefit more from a compared intervention. Addressing this question would help patients and clinicians make better-informed treatment decision. However, the evidence reviewed does not provide any consistent conclusion on this issue. For example, the SPCG-4 trial found that RP led to

significantly lower all-cause and cancer-specific mortalities compared with WW among patients younger than 65 years of age but not among the older patient group.<sup>25</sup> However, the PIVOT study did not have the same finding.<sup>33</sup> The PIVOT study found that RP did not reduce all-cause or cancer-specific mortality among men with PSA levels of less than 10 ng/mL but resulted in a significant reduction among men with PSA levels of more than 10 ng/mL. However, this finding is not confirmed by the SPCG-4 trial, which found a mortality reduction with RP in both subsets of patients. Despite these differences in findings, the two trials also show some overlap in findings (reduced mortality with RP) for the subgroup of patients with PSA levels of more than 10 ng/mL. Given the low prostate cancer–specific mortality in men in PIVOT (early PSA era), the likelihood is very low for more than a small mortality benefit for early intervention, especially in men with low PSA/low-risk disease; moreover, harms are associated with surgery or radiation therapy. Nevertheless, enough inconsistency remains in the evidence that clear guidance regarding the appropriate patient population for RP is difficult to establish.

This current review also evaluated RCTs that compared EBRT alone versus EBRT combined with ADT<sup>43</sup> and 3D-CRT alone versus 3D-CRT combined with ADT.<sup>35</sup> The evidence based on both RCTs<sup>35,43</sup> suggests that the results for overall survival and prostate cancer–specific mortality favored the combined treatments. The subgroup analysis in one RCT<sup>35</sup> also suggests that the advantage of 3D-CRT combined with ADT may only occur among patients with no comorbidity or a minimal comorbidity score for the outcome of all-cause mortality. The evidence in another RCT<sup>43</sup> suggests that the advantage of EBRT combined with ADT may occur only among white patients for the outcome overall survival and among white patients and men older than 70 years of age for the outcome of prostate cancer–specific mortality. However, this evidence is weak and requires further validation by new studies before it can be used to form clinical guidance for choosing appropriate cases for the treatments. Similarly, the evidence for other treatment comparisons covered in the current review also needs further validation, particularly via rigorously designed RCTs, to form a more reliable foundation for making clinical recommendations. The ongoing U.K. trial of RP versus EBRT and AS (ProtectT [Prostate testing for cancer and Treatment] study) when completed could add to the body of evidence (see Table G-2).

## **Limitations of the Comparative Effectiveness Review Process**

This section discusses challenges that we encountered conducting this systematic review and how we addressed them. They included: (1) how to synthesize findings in an evidence base with numerous treatment comparisons and considerable clinical heterogeneity in patient populations even among studies that made the same treatment comparisons; (2) how to handle issues regarding applicability of findings of long-term studies to current clinical practice; and (3) expanding the scope of this update from studies of patients diagnosed with stage T1–T2 prostate cancer to include stage T3a following reviewer input.

After discussion with clinical expert consultants, we decided against conducting meta-analysis of RCTs with similar treatment comparisons and outcomes (e.g. SPCG-4 and PIVOT) because of clinical heterogeneity in the patient populations (see Discussion for more details). The team believes that a meta-analytic summary effect size would provide an illusion of precision regarding differences between interventions when the level of benefit of a given intervention is likely to be affected by patient and tumor characteristics. Instead, we performed a qualitative synthesis of findings from similar RCTs and separately for observational studies that had similar

comparisons and outcomes. This allowed us to reach some conclusions that we could not have reached had we analyzed all individual studies separately.

Issues with lack of applicability of long-term data from RCTs and nonrandomized studies to current clinical practice meant that any conclusions based on findings from such studies needed to be caveated carefully. We have attempted to do this throughout the report.

Although the original scope including patients with stage T1–T2 prostate cancer was agreed on by the Key Informants, comments received by a few reviewers during the draft's public posting led us to expand the scope to include patients with stage T3a prostate cancer. This was supported by a 2013 National Comprehensive Cancer Network guideline that classified clinically localized prostate cancer as stages T1–T3a. We addressed this issue by re-reviewing a large number of abstracts and full publications previously excluded as being outside the original scope of the report. Studies we identified as fitting within the expanded scope were added to the report.

## **Limitations of the Evidence Base**

This current review has several limitations. First, although more RCTs were available for this review than for the 2008 report, the amount of evidence from well-designed RCTs that directly compare different treatments, particularly emerging technologies (e.g., proton beam therapy, high-intensity focused ultrasound [HIFU]), is still small. The few RCTs that met the inclusion criteria for the review compared only a few treatments of interest (e.g., RP vs. WW, EBRT alone vs. EBRT plus ADT, 3D-CRT vs. 3D-CRT plus ADT). Questions about the effectiveness and safety of new and emerging treatment methods are largely unanswered by the RCTs.

Second, all but one of the reviewed RCTs were conducted more than 10 years ago. The manner in which PSA testing was used for detecting prostate cancer and the treatment techniques used may not reflect current practices, so the RCT results may not be generalizable to current practice settings.

Third, there was little reporting of outcomes according to major patient and tumor characteristics. The reviewed RCTs that performed subgroup analyses according to patient or tumor characteristics often do not have adequate power to detect significant effects within the subgroups.

Fourth, wide variation existed in reporting and definitions of outcomes and tumor characteristics (e.g., PSA recurrence level) and patient characteristics (e.g., age, comorbidity status), which make evidence synthesis difficult. We therefore recommend a standardization of definitions of tumor characteristics such as PSA recurrence level and improvement in reporting of clinical outcome data.

Fifth, this review included only studies published in English and also used specific sample-size cutoffs as criteria to exclude small-sized nonrandomized comparative studies. Inclusion of small-sized studies and those published in other languages may have resulted in additional conclusions or may have contradicted some conclusions. Furthermore, this review limited evidence to studies that reported data only for T1–T3a disease separately from T3b or T4 disease. Studies with more than 15 percent of T3/T4 population that did not specifically report data separately for T1–T3a were excluded. As a result, some information potentially relevant to the topic of this review may not have been captured.

Sixth, because prostate cancer–specific mortality is subject to ascertainment bias, all-cause mortality, which is not subject to ascertainment, may be a more consistent outcome measure. A major concern with the outcome all-cause mortality is evaluating comorbidity status using a



validated measure. Most of the included studies reported using various criteria to evaluate comorbidity status.

Seventh, the reported outcomes for the RCTs and non-RCTs in the studies reviewed demonstrate the diversity of the endpoints that study investigators considered, some of which (e.g., biochemical progression) are clinically irrelevant in terms of metastases-free, symptom-free, and overall survival.

Eighth, although evidence from included RCTs suggests that observation should be offered to men with low-risk tumors, it is becoming increasingly clear that some in the intermediate-risk category may also be candidates for such an approach (pointing to the limitations of the risk-assessment scheme described earlier in our Background section). Indeed, some trials we described support the notion that treating some men who have intermediate-risk disease may have little to no impact on prostate cancer-specific survival compared with observation (see nonrandomized comparative study by Abdollah et al.<sup>59</sup>).

Ninth, although our review gave the first priority to evidence from RCTs in drawing conclusions, we also reviewed useable evidence that was available from the nonrandomized comparative studies. However, of all the comparisons that we identified across the 44 nonrandomized comparative studies, only a few nonrandomized studies compared interventions that overlapped with the RCTs. Three of four nonrandomized studies compared RP to WW and reported that RP was associated with a reduction in all-cause and prostate cancer-specific mortality. Although the fourth study agreed using a propensity score analysis, an instrumental variable analysis by the same study did not find a significant difference between interventions.<sup>73</sup> Given that the patient population in this latter study was derived from a database of patients 65 years or older, the findings in this analysis are comparable to those of the SPCG-4 trial<sup>33</sup> for patients aged 65 years or older.

Finally, we acknowledge that tumors in patients with clinically localized prostate cancer undergoing radiation therapy as primary therapy are likely to be understaged and that a fair comparison of radiation with or without androgen deprivation to RP might best be done in a population with nonmetastatic disease. However, that was not the population specified in our review protocol. Until staging systems reframe prostate cancer staging in this way (i.e., metastatic vs. nonmetastatic), we believe that evaluating this comparison will be difficult.

## Research Gaps

A fundamental research gap involves the development of better methods for staging prostate cancer that is detectable but not metastatic. With current technology, such staging is not straightforward, and choosing treatment based on stage for those patients will be difficult until more precise imaging/diagnostic methods are available. As noted earlier, patients who receive radiation therapy are often understaged, which increases the difficulty in judging the relative effectiveness of this treatment in patients with clinically localized prostate cancer.

To further address the KQs of this review, additional RCTs are needed. In Table G-1 and Table G-2 in Appendix G, we summarize nine ongoing clinical trials. Ideally, future RCTs should (1) recruit patients with PSA-detected prostate cancer and (2) compare patient-focused outcomes (e.g., all-cause and cancer-specific mortalities, QOL) between treatment options and techniques used in the current practice with a long followup. To improve applicability, future RCTs should recruit more patients from populations that have been underrepresented in previous trials (e.g., African Americans). Furthermore, new RCTs are needed to evaluate new and emerging technologies such as proton beam therapy and HIFU, because these technologies are

costly and lack an adequate evidence base to assess the balance of benefits and harms. These RCTs should use standardized or validated patient outcome measures, have adequate power to detect significant treatment effect, and define patient subgroups of interest *a priori*. They should also enroll patients that are representative of current clinical practice using similar enrollment criteria that would allow comparison of the patients' outcomes across studies.

However, RCTs have had challenges achieving target enrollments for comparing different treatment options. For example, the PIVOT investigators did not achieve their stated target enrollment of 2,000 patients. This might suggest that comparative-effectiveness research to guide treatment decisions will likely require well-designed observational studies as well.

Observational studies with better design and methodology (e.g., cancer registries and large prospective population-based cohort studies, use of propensity score or instrumental variables, use of validated QOL measures) may provide useful evidence, particularly in cases in which large differences in outcomes might exist. Observational studies may help estimate treatment effectiveness in high-priority patient and tumor subgroups that have not been adequately addressed in RCTs. Findings from observational studies may also help generate hypotheses and design better RCTs. We noted and reported that some observational studies conflicted in their findings based on the analytic methods employed (e.g., instrumental variable analysis vs. propensity scoring vs. multivariable regression analysis). Most of the existing evidence from nonrandomized comparative studies comes with treatment selection biases. These studies also inconsistently defined and reported outcomes.

For this update, we did not identify any studies that compared active surveillance to current treatment therapies. Because WW or observation is not active surveillance, more studies are needed to assess the effectiveness of active surveillance. These studies might necessitate adequate consideration of multiparametric magnetic resonance imaging as a tool to enhance observation or active surveillance. Additional research comparing observation or active surveillance to any early intervention is warranted to avoid potential overdiagnosis and overtreatment in men with PSA-detected cancer (especially low PSA/low-risk disease, but possibly intermediate PSA/intermediate-risk disease as well). Future RCTs that compare early intervention to active surveillance or other early interventions should target patients with higher PSA/higher-risk disease, given that the benefits in this group remain uncertain.

Furthermore, because prostate cancer is a significant cause of mortality among men, a research need remains for better prognostic surrogate markers to predict the risk of recurrence among patients with clinically localized prostate cancer. Finally, some studies discussed in this report suggest that outcomes of surgery and radiation are influenced by center and surgeon case volume and expertise. However, most of these studies did not provide information about practice of care that could have influenced the results. Future studies are needed to fill this gap.

## Conclusions

Overall, the body of evidence for treating prostate cancer continues to evolve, but the evidence for most treatment comparisons is largely inadequate to determine comparative risks and benefits. Although limited evidence appears to favor surgery over WW or EBRT, or favors radiotherapy plus ADT over radiotherapy alone, the patients most likely to benefit and the applicability of these study findings to contemporary patients and practice remain uncertain. More RCTs and better-designed observational studies that reflect contemporary practice and can control for many of the known/unknown confounding factors that can affect long-term outcomes may be needed to evaluate comparative risks and benefits of therapies for clinically localized

prostate cancer. We also believe an urgent need exists for clinicians to provide an improved way to categorize patients with prostate cancer into different groups based on associated risk factors. All of the treatments currently available for clinically localized prostate cancer can cause bothersome complications, including sexual, urinary, and bowel dysfunction. Patients should be informed and have active involvement during the decisionmaking process and consider the benefits and harms of the treatments.

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## Acronyms and Abbreviations

3D-CRT:	three-dimensional conformal radiotherapy
95% CI:	95 percent confidence interval
ADT:	androgen deprivation therapy
AJCC:	American Joint Committee on Cancer
AHRQ:	Agency for Healthcare Research and Quality (U.S. Department of Health and Human Services)
ARR:	absolute risk reduction
BT:	brachytherapy
CAPRA:	UCSF Cancer of the Prostate Risk Assessment
CT:	computed tomography
DRE:	digital rectal exam
EB-IGRT:	external beam image-guided radiation therapy
EBRT:	external beam radiation therapy
EORTC-QLQ:	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
EPC:	Evidence-based Practice Center
EPIC:	Expanded Prostate Cancer Index Composite
ERSPC:	European Randomized Study of Screening for Prostate Cancer
Gy:	gray
HDR-EBRT:	high dose–rate external beam radiation therapy
HDS:	high dose rate
HIFU:	high-intensity focused ultrasound
HR:	hazard ratio
IGRT:	image-guided radiation therapy
IMRT:	intensity-modulated radiation therapy
IQR:	interquartile range
KQ:	Key Question
LDR:	low dose rate
LHRH:	luteinizing hormone–releasing hormone
LRP:	laparoscopic radical prostatectomy
MRI:	magnetic resonance imaging
NCCN:	National Comprehensive Cancer Network
NIH:	National Institutes of Health
OR:	odds ratio
PCSM:	prostate cancer–specific mortality
PICOTS:	Population (patients), Intervention, Comparators, Outcomes, Timing, Setting
PIVOT:	Prostate Cancer Intervention Versus Observation Trial
PLCO:	Prostate, Lung, Colorectal, and Ovarian cancer screening trial
PSA:	prostate-specific antigen
QOL:	quality of life
RALRP:	robotic-assisted laparoscopic radical prostatectomy
RARP:	robot-assisted radical prostatectomy
RCT:	randomized controlled trial
ROB:	risk of bias
RP:	radical prostatectomy

RPP:	radical perineal prostatectomy
RR:	relative risk
RRP:	radical retropubic prostatectomy
SEER:	Surveillance Epidemiology and End Results (National Cancer Institute)
SF-36:	Short Form-36
SOE:	strength of evidence
SPCG-4:	Scandinavian Prostate Cancer Group-4
TEP:	Technical Expert Panel
TNM:	T (tumor) N (lymph node) M (metastases) classification system (American Joint Committee on Cancer)
TOO:	Task Order Officer
TRUS:	transrectal ultrasound of the prostate
TURP:	transurethral resection of the prostate
USPSTF:	U.S. Preventive Services Task Force
WW:	watchful waiting

**Note:** Acronyms and abbreviations used in appendix tables are defined within the tables in which they appear.

# Appendix A. Literature Search Methods

## Electronic Database Searches

ECRI Institute information specialists searched the following databases for relevant information. Search terms and strategies for the bibliographic databases appear below.

**Table A-1. Electronic database searches**

Name	Date Limits	Platform/Provider
The Cochrane Database of Systematic Reviews (Cochrane Reviews) The Cochrane Database of Methodology Reviews (Methodology Reviews) The Cochrane Central Register of Controlled Trials (CENTRAL)	1/01/07–3/7/14	www.thecochranelibrary.com
Cumulative Index of Nursing and Allied Health Literature (CINAHL®)	2007 through current	EBSCOhost
EMBASE (Excerpta Medica)	2007 through current	OVID
Health Technology Assessment Database (HTA)	2007 through current	Wiley
MEDLINE	2007 through current	OVID
PubMed	2007 through current	www.pubmed.gov
ClinicalTrials.gov	1/01/07–3/7/14	NIH
U.K. National Health Service Economic Evaluation Database (NHS EED)	2007 through current	Wiley

Detailed search strategies are presented below.

## Hand Searches of Journal and Nonjournal Literature

Journals and supplements maintained in ECRI Institute’s collections were routinely reviewed. Non-journal publications and conference proceedings from professional organizations, private agencies, and government agencies were also screened. Other mechanisms used to retrieve additional relevant information included review of bibliographies/reference lists from peer-reviewed and gray literature. (Gray literature consists of reports, studies, articles, and monographs produced by federal and local government agencies, private organizations, educational facilities, consulting firms, and corporations. These documents do not appear in the peer-reviewed journal literature.) Select manufacturer websites and a number of organization websites were searched for relevant information, including: ECRI Institute members’ website, CDC, CMS, National Cancer Institute, National Guideline Clearinghouse and the American Cancer Society.

## Medical Subject Headings (MeSH, Emtree and Keywords)

The search strategies employed combinations of free-text keywords as well as controlled vocabulary terms including (but not limited to) the concepts shown in the Topic-specific Search Terms table.

**Table A-2. Topic-specific search terms**

Concept	Controlled Vocabulary	Keywords
Prostate cancer	EMBASE (EMTREE) Neoplasms/ Prostate/ Prostatic Neoplasms/  MeSH (PubMed) Neoplasms Prostate Prostatic Neoplasms	Cancer* Carcinoma* Neoplasm* Prostat*
Treatment options	EMBASE (EMTREE) Brachytherapy/ Cryosurgery/ Cryotherapy/ Freezing/ High-Intensity Focused Ultrasound Ablation/ Prostatectomy/ exp Radiotherapy/ Watchful Waiting/  MeSH (PubMed) Brachytherapy Cryosurgery Cryotherapy Freezing High-Intensity Focused Ultrasound Ablation Prostatectomy exp Radiotherapy Watchful Waiting	Active surveillance Androgen deprivation Brachytherap* Cryoablat* Cryosurger* Cryotherap* Curietherap* EBRT Freez* HIFU High intensity focused ultrasound IMRT LRP Prostatectom* Proton Radiotherap* Radiation RLRP Watchful waiting

## Search Strategies

The strategy below is presented in OVID syntax; the search was simultaneously conducted across EMBASE AND MEDLINE. A similar strategy was used to search the databases comprising the Cochrane Library.

### **OVID Conventions:**

- \$ or \* = truncation character (wildcard)
- ADJ $n$  = search terms within a specified number ( $n$ ) of words from each other in any order
- exp = “explodes” controlled vocabulary term (e.g., expands search to all more specific related terms in the vocabulary’s hierarchy)
- .de. = limit controlled vocabulary heading
- .fs. = floating subheading
- .hw. = limit to heading word
- .mp. = combined search fields (default if no fields are specified)
- .pt. = publication type
- .ti. = limit to title
- .tw. = limit to title and abstract fields

**Table A-3. EMBASE/MEDLINE—OVID syntax**

Set #	Concept	Search Statement
1	Prostate cancer	Prostatic Neoplasms/
2	Prostate cancer	(prostat\$.ti,ab. or Prostate/) AND (cancer.ti,ab. or Neoplasms/ or neoplasm\$ or carcinoma\$)
3	Combine sets	S1 OR S2
4	Treatment options	watchful waiting.ti,ab. or Watchful Waiting/ or active surveillance.ti,ab. or prostatectom\$.ti,ab. or Prostatectomy/ or LRP.ti,ab. or RLRP.ti,ab. or exp Radiotherapy/ or radiotherap\$.ti,ab. or EBRT.ti,ab. or IMRT.ti,ab. or proton.ti,ab. or brachytherap\$.ti,ab. or Brachytherapy/ or curietherap\$.ti,ab. or cryosurger\$.ti,ab. or Cryosurgery/ or cryotherap\$.ti,ab. or Cyberknife.ti,ab. or Cryotherapy/ or cryoablat\$.ti,ab. or Freezing/ or freez\$.ti,ab. or androgen deprivation.ti,ab. or High-Intensity Focused Ultrasound Ablation/ or high intensity focused ultrasound.ti,ab. or HIFU.ti,ab. or (high and intensity and focused and ultrasound).ti,ab.
5	Publication types	(Randomized controlled trial/ or random allocation/ or double-blind method/ or single-blind method/ or placebos/ or cross-over studies/ or crossover procedure/ or cross over studies/ or double blind procedure/ or single blind procedure/ or placebo/ or latin square design/ or crossover design/ or double-blind studies/ or single-blind studies/ or triple-blind studies/ or random assignment/ or exp clinical trial/ or exp comparative study/ or cohort analysis or followup studies/ or intermethod comparison/ or parallel design/ or control group/ or prospective study/ or retrospective study/ or case control study/ or major clinical study/ or evaluation studies/ or followup studies/ or case series.ti,ab. or random\$.hw. or random\$.ti. or placebo\$.ti,ab. or ((singl\$ or doubl\$ or tripl\$ or trebl\$) and (dummy or blind or sham)).ti,ab. or latin square.ti,ab. or ISRCTN\$.ti,ab. or ACTRN\$.ti,ab. or (NCT\$ not NCT).ti,ab.)
6	Combine sets	S3 AND S4 AND S5
7	Limit	6 not ((letter or editorial or news or comment or case reports or note or conference paper).de. or (letter or editorial or news or comment or case reports).pt.)
8	Limit	7 not (book/ or edited book/ or case report/ or case reports/ or comment/ or conference abstract/ or conference paper/ or conference review/ or editorial/ or letter/ or news/ or note/ or proceeding/ or (book or edited book or case report or case reports or comment or conference or editorial or letter or news or note or proceeding).pt. or ("comment/reply" or editorial or letter or review-book).pt.)
9	Limit	8 not (case report.de. OR case reports.pt. OR case report.ti. OR (year ADJ old).ti,ab.)
10	Limit	Limit 9 to English and humans
11	Limit	Limit 10 to yr=" 2007 - 2013"
12	Remove duplicates	Remove duplicates from 11 13
13	Limit	12 and compar\$.ti,hw.
14	Limit	12 and (clinically adj local\$)
15	Limit	12 and (stage 1 or stage one)
16	Limit	12 and (early adj3 stage)
17	Limit	12 and (nonmetastatic or non-metastatic)
18	Limit	12 and (gleason 7 or gleason score 7 or gleason 6 or gleason score 6)
19	Limit	12 and (local\$ adj advanced)
20	Limit	12 and 9T3 orr T4)
21	Limit	12 and (high adj risk) or high-risk
22	Combine	13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21

**Additional Conventions:**

**PubMed**

\* = truncation character (wildcard)

[tiab] = limit to title or abstract

## Cochrane Library

\* = truncation character (wildcard)

Menu-driven

**Table A-4. PubMed**

Set #	Concept	Search Statement
1	Prostate cancer	prostat*[tiab] AND (neoplasm*[tiab] OR cancer*[tiab] OR carcinoma*[tiab])
2	Treatment options	"watchful waiting"[tiab] OR "active surveillance"[tiab] OR LRP[tiab] OR RLRP[tiab] OR prostatectom*[tiab] OR radiotherap*[tiab] OR EBRT[tiab] OR IMRT[tiab] OR proton[tiab] OR (intensity[tiab] AND modulated[tiab] AND therap*[tiab]) OR brachytherap*[tiab] OR curietherap*[tiab] OR cryosurger*[tiab] OR cryotherap*[tiab] OR cryoablat*[tiab] OR Cyberknife[tiab] OR freezing[tiab] OR "androgen deprivation"[tiab] OR HIFU[tiab] OR (high[tiab] AND intensity[tiab] AND focused[tiab] AND ultrasound*[tiab])
3	Publication types	(randomized controlled trial[pt] OR controlled clinical trial[pt] OR clinical trial[pt] OR comparative study[pt] OR evaluation studies [pt] OR meta-analysis[pt] OR multicenter study[pt] OR "clinical trial"[tw] OR "clinical trials"[tw] OR comparative study [tw] OR comparative studies [tw] OR evaluation study[tw] OR evaluation studies [tw] OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw])) OR "latin square" OR placebo* OR random* OR "control group" OR prospective* OR retrospective* OR volunteer* OR sham OR "meta-analysis"[tw] OR cohort OR ISRCTN* OR ACTRN* OR NCT*)
4	Combine sets	1 AND 2 AND 3
5	Limit	4 AND ("in process"[sb] OR publisher[sb] OR pubmednotmedline[sb])
6	Limit	Limit 5 to: Publication date from 2007/01/01 to 2013/12/31

**Table A-5. Cochrane Library**

Set #	Concept	Search Statement
1	Prostate cancer	prostat* AND (neoplasm* OR cancer* OR carcinoma*)
2	Treatment options	"watchful waiting" OR "active surveillance" OR LRP OR RLRP OR prostatectom* OR radiotherap* OR EBRT OR IMRT OR proton OR (intensity AND modulated AND therap*) OR brachytherap* OR curietherap* OR cryosurger* OR cryotherap* OR cryoablat* OR Cyberknife OR freezing OR "androgen deprivation" OR HIFU OR (high AND intensity AND focused AND ultrasound*)
3	Combine sets	1 AND 2
4	Limit	Limit 3 to: Publication date from 2007 to 2013



## Appendix B. Full-Length Review Excluded Studies

**Randomized controlled trials (RCTs) with a mixed population (≥15% of patient population had T3 [not reporting T3a separately from T3b], T3b, or T4, or metastatic cancer and did not report separate data for T1 or T2 or T3a):**

Bolla M, de Reijke TM, Van Tienhoven G, et al. Duration of androgen suppression in the treatment of prostate cancer. *N Engl J Med*. 2009 Jun 11;360(24):2516-27. PMID: 19516032

Bolla M, van Poppel H, Tombal B, et al. Postoperative radiotherapy after radical prostatectomy for high-risk prostate cancer: long-term results of a randomised controlled trial (EORTC trial 22911). *Lancet*. 2012 Dec 8;380(9858):2018-27. PMID: 23084481

Bolla M, Van Tienhoven G, Warde P, et al. External irradiation with or without long-term androgen suppression for prostate cancer with high metastatic risk: 10-year results of an EORTC randomised study. *Lancet Oncol*. 2010 Nov;11(11):1066-73. PMID: 20933466

Creak A, Hall E, Horwich A, et al. Randomised pilot study of dose escalation using conformal radiotherapy in prostate cancer: Long-term follow-up. *Br J Cancer*. 2013;109(3):651-7.

D'Amico AV, Chen MH, Crook J, et al. Duration of short-course androgen suppression therapy and the risk of death as a result of prostate cancer. *J Clin Oncol*. 2011 Dec 10;29(35):4682-7. PMID: 22042952

Danuser H, Pierro GB, Stucki P, et al. Extended pelvic lymphadenectomy and various radical prostatectomy techniques: Is pelvic drainage necessary? *BJU Int*. 2013;111(6):963-9.

Dearnaley DP, Sydes MR, Langley RE, et al. The early toxicity of escalated versus standard dose conformal radiotherapy with neo-adjuvant androgen suppression for patients with localised prostate cancer: results from the MRC RT01 trial (ISRCTN47772397). *Radiother Oncol*. 2007 Apr;83(1):31-41. PMID: 17391791

Denham JW, Nowitz M, Joseph D, et al. Impact of androgen suppression and zoledronic acid on bone mineral density and fractures in the Trans-Tasman Radiation Oncology Group (TROG) 03.04 Randomised Androgen Deprivation and Radiotherapy (RADAR) randomized controlled trial for locally advanced prostate cancer. *BJU Int*. 2013 Oct 15;Epub ahead of print. PMID: 24512527

Denham JW, Steigler A, Tai KH, et al. Paradoxical metastatic progression following 3 months of neo-adjuvant androgen suppression in the TROG 96.01 trial for men with locally advanced prostate cancer. *Radiother Oncol*. 2013 May;107(2):123-8.

Donnelly BJ, Saliken JC, Brasher PM, et al. A randomized trial of external beam radiotherapy versus cryoablation in patients with localized prostate cancer. *Cancer*. 2010 Jan 15;116(2):323-30. PMID: 19937954

Horwitz EM, Bae K, Hanks GE, et al. Ten-year follow-up of radiation therapy oncology group protocol 92-02: a phase III trial of the duration of elective androgen deprivation in locally advanced prostate cancer. *J Clin Oncol*. 2008 May 20;26(15):2497-504. PMID: 18413638

Hoskin PJ, Rojas AM, Bownes PJ, et al. Randomised trial of external beam radiotherapy alone or combined with high-dose-rate brachytherapy boost for localised prostate cancer. *Radiother Oncol*. 2012 May;103(2):217-22. PMID: 22341794

Hoskin PJ, Rojas AM, Ostler PJ, et al. Quality of life after radical radiotherapy for prostate cancer: longitudinal study from a randomised trial of external beam radiotherapy alone or in combination with high dose rate brachytherapy. *Clin Oncol (R Coll Radiol)*. 2013 May;25(5):321-7. PMID: 23384799

Khor R, Duchesne G, Tai KH, et al. Direct 2-arm comparison shows benefit of high-dose-rate brachytherapy boost vs external beam radiation therapy alone for prostate cancer. *Int J Radiat Oncol Biol Phys*. 2013;85(3):679-85.

Klotz L, Miller K, Crawford ED, et al. Disease control outcomes from analysis of pooled individual patient data from five comparative randomised clinical trials of degarelix versus luteinising hormone-releasing hormone agonists. *Eur Urol*. 2014 Jan 9;Epub ahead of print. PMID: 24440304

Lund JA, Kaa SA, Wibe A, et al. Late radiation effects to the rectum and anus after treatment for prostate cancer; Validity of the LENT/SOMA score. *Acta Oncol*. 2013 May;52(4):727-35.

Mason M, Maldonado Pijoan X, Steidle C, et al. Neoadjuvant androgen deprivation therapy for prostate volume reduction, lower urinary tract symptom relief and quality of life improvement in men with intermediate- to high-risk prostate cancer: a randomised non-inferiority trial of degarelix versus goserelin plus bicalutamide. *Clin Oncol*. 2013 Mar;25(3):190-6. PMID: 23257248

Nyarangi-Dix JN, Radtke JP, Hadaschik B, et al. Impact of complete bladder neck preservation on urinary continence, quality of life and surgical margins after radical prostatectomy: a randomized, controlled, single blind trial. *J Urol*. 2013 Mar;189(3):891-8. Epub 2012 Sep 24. PMID: 23017512

Robinson JW, Donnelly BJ, Siever JE, et al. A randomized trial of external beam radiotherapy versus cryoablation in patients with localized prostate cancer: quality of life outcomes. *Cancer*. 2009 Oct 15;115(20):4695-704. PMID: 19691092

Salonen AJ, Taari K, Ala-Opas M, et al. Advanced prostate cancer treated with intermittent or continuous androgen deprivation in the randomised FinnProstate Study VII: quality of life and adverse effects. *Eur Urol*. 2013 Jan;63(1):111-20. PMID: 22857983

Schweizer MT, Huang P, Kattan MW, et al. Adjuvant leuprolide with or without docetaxel in patients with high-risk prostate cancer after radical prostatectomy (TAX-3501): Important lessons for future trials. *Cancer*. 2013;119(20):3610-8.

Taneja SS. Re: Dutasteride treatment over 2 years delays prostate-specific antigen progression in patients with biochemical failure after radical therapy for prostate cancer: Results from the randomised, placebo-controlled avodart after radical therapy for prostate cancer study (ARTS): Editorial comment. *J Urol*. 2013;189(5):1716.

Tombal B, Miller K, Boccon-Gibod L, et al. Additional analysis of the secondary end point of biochemical recurrence rate in a phase 3 trial (CS21) comparing degarelix 80 mg versus leuprolide in prostate cancer patients segmented by baseline characteristics. *Eur Urol*. 2010 May;57(5):836-42. PMID: 19962227

Warde P, Mason M, Ding K, et al. Combined androgen deprivation therapy and radiation therapy for locally advanced prostate cancer: a randomised, phase 3 trial. *Lancet*. 2011 Dec 17;378(9809):2104-11. PMID: 22056152

Widmark A, Klepp O, Solberg A, et al. Endocrine treatment, with or without radiotherapy, in locally advanced prostate cancer (SPCG-7/SFUO-3): an open randomised phase III trial. *Lancet*. 2009 Jan 24;373(9660):301-8. PMID: 19091394

**No outcomes of interest:**

Bellardita L, Rancati T, Valdagni R. Editorial Comment to health-related quality of life after carbon-ion radiotherapy for prostate cancer: A 3-year prospective study. *Int J Urol*. 2014 Apr;21(4):375-6. Epub 2013 Nov 13. PMID: 24224716

Black PC, Basen-Engquist K, Wang X, et al. A randomized prospective trial evaluating testosterone, haemoglobin kinetics and quality of life, during and after 12 months of androgen deprivation after prostatectomy: results from the Postoperative Adjuvant Androgen Deprivation trial. *BJU Int*. 2007 Jul;100(1):63-9. PMID: 17552954

Bratt O, Carlsson S, Holmberg E, et al. The Study of Active Monitoring in Sweden (SAMS): a randomized study comparing two different follow-up schedules for active surveillance of low-risk prostate cancer. *Scand J Urol*. 2013 Oct;47(5):347-55. PMID: 23883427

Chira C, Delouya G, Gruszczynski N, et al. Deferred permanent prostate seed brachytherapy does not affect PSA outcome: results from a large retrospective cohort. *Can J Urol*. 2013 Dec;20(6):7028-34. PMID: 24331344

de la Taille A. Comment on "Secondary chemoprevention of localized prostate cancer by short-term androgen deprivation to select indolent tumors suitable for active surveillance: a prospective pilot study". *World J Urol*. 2014 Jan 11;Epub ahead of print. PMID: 24413818

de Oliveira C, Bremner KE, Ni A, et al. Patient time and out-of-pocket costs for long-term prostate cancer survivors in Ontario, Canada. *J Cancer Surviv*. 2014 Mar;8(1):9-20. Epub 2013 Aug 23. PMID: 23975612

Hansen J, Gandaglia G, Bianchi M, et al. Re-assessment of 30-, 60- and 90-day mortality rates in non-metastatic prostate cancer patients treated either with radical prostatectomy or radiation therapy. *Can Urol Assoc J*. 2014 Jan;8(1-2):E75-80. PMID: 24554978

Hayes JH, Ollendorf DA, Pearson SD, et al. Observation versus initial treatment for men with localized, low-risk prostate cancer: a cost-effectiveness analysis (Provisional abstract). *Ann Intern Med*. 2013;158(12):853-60.

Hernandez V, Blazquez C, de la Pena E, et al. Active surveillance in low-risk prostate cancer. Patient acceptance and results. *Actas Urol Esp*. 2013 Oct;37(9):533-7. Epub 2013 Apr 22. PMID: 23618513

Ko EC, Liu JT, Stone NN, et al. Association of early PSA failure time with increased distant metastasis and decreased survival in prostate brachytherapy patients. *Radiother Oncol*. 2014 Feb;110(2):261-7. Epub 2013

Mostaghel EA, Nelson PS, Lange P, et al. Targeted androgen pathway suppression in localized prostate cancer: a pilot study. *J Clin Oncol*. 2014 Jan 20;32(3):229-37. PMID: 24323034

Norkus D, Karklelyte A, Engels B, et al. A randomized hypofractionation dose escalation trial for high risk prostate cancer patients: interim analysis of acute toxicity and quality of life in 124 patients. *Radiat Oncol*. 2013;8(1):206. PMID: 24007322

Paiva CS, Andreoni C, Cunha GP, et al. Differences among patients undergoing perineal or retropubic radical prostatectomy in pain and perioperative variables: a prospective study. *BJU Int*. 2009 Nov;104(9):1219-26. PMID: 19389007

Parnes HL, Brawley OW, Minasian LM, et al. Phase III prostate cancer chemoprevention trials. *Recent Results Cancer Res*. 2014;202:73-7. PMID: 24531780

Reed DR, Wallner KE, Merrick GS, et al. A prospective randomized comparison of stranded vs. loose 125I seeds for prostate brachytherapy. *Brachytherapy*. 2007 Apr-Jun;6(2):129-34. PMID: 17434106

Sugihara T, Yasunaga H, Horiguchi H, et al. Comparisons of perioperative outcomes and costs between open and laparoscopic radical prostatectomy: a propensity-score matching analysis based on the Japanese Diagnosis Procedure Combination database. *Int J Urol*. 2013 Mar;20(3):349-53.

Sun L, Zhu X, Xu L, et al. Antitumor effects of (32)P-chromic-poly (L-lactide) brachytherapy in nude mice with human prostate cancer. *Oncol Lett*. 2013 Sep;6(3):687-92. PMID: 24137391

Vickers AJ, Thompson IM, Klein E, et al. A commentary on PSA velocity and doubling time for clinical decisions in prostate cancer. *Urology*. 2014 Mar;83(3):592-8. PMID: 24581521

Zumsteg ZS, Spratt DE, Pei I, et al. A new risk classification system for therapeutic decision making with intermediate-risk prostate cancer patients undergoing dose-escalated external-beam radiation therapy. *Eur Urol*. 2013 Dec;64(6):895-902. Epub 2013 Mar 23. PMID: 23541457

**No comparison of interest:**

Cronin-Fenton DP, Antonsen S, Cetin K, et al. Methods and rationale used in a matched cohort study of the incidence of new primary cancers following prostate cancer. *Clin Epidemiol*. 2013;5:429-37. PMID: 24204172

Crook JM. Intermittent and continuous androgen deprivation did not differ for mortality after radiotherapy for prostate CA. *Ann Intern Med*. 2013;158(2):JC9.

Davis JW, Chang DW, Chevray P, et al. Randomized phase II trial evaluation of erectile function after attempted unilateral cavernous nerve-sparing retropubic radical prostatectomy with versus without unilateral sural nerve grafting for clinically localized prostate cancer. *Eur Urol*. 2009 May;55(5):1135-43. PMID: 18783876

Dearnaley DP, Jovic G, Syndikus I, et al. Escalated-dose versus control-dose conformal radiotherapy for prostate cancer: long-term results from the MRC RT01 randomised controlled trial. *Lancet Oncol*. 2014 Apr;15(4):464-73. Epub 2014 Feb 26. PMID: 24581940

Dearnaley DP, Sydes MR, Graham JD, et al. Escalated-dose versus standard-dose conformal radiotherapy in prostate cancer: first results from the MRC RT01 randomised controlled trial. *Lancet Oncol*. 2007 Jun;8(6):475-87. PMID: 17482880

Dearnaley DP, Sydes MR, Langley RE, et al. The early toxicity of escalated versus standard dose conformal radiotherapy with neo-adjuvant androgen suppression for patients with localised prostate cancer: results from the MRC RT01 trial (ISRCTN47772397). *Radiother Oncol*. 2007 Apr;83(1):31-41. PMID: 17391791

Jia Z, Lilly MB, Koziol JA, et al. Generation of “virtual” control groups for single arm prostate cancer adjuvant trials. *PLoS ONE*. 2014 Jan 21;9(1):e85010. PMID: 24465467

Kaushik D, Karnes RJ, Eisenberg MS, et al. Effect of metformin on prostate cancer outcomes after radical prostatectomy. *Urol Oncol*. 2014 Jan;32(1):43.e1-7. Epub 2013 Jun 28. PMID: 23810664

Keizman D, Zahurak M, Sinibaldi V, et al. Lenalidomide in nonmetastatic biochemically relapsed prostate cancer: results of a phase I/II double-blinded, randomized study. *Clin Cancer Res*. 2010 Nov 1;16(21):5269-76. PMID: 20978144

Kellokumpu-Lehtinen PL, Hjälm-Eriksson M, Thellenberg-Karlsson C, et al. Toxicity in patients receiving adjuvant docetaxel + hormonal treatment after radical radiotherapy for intermediate or high-risk prostate cancer: a preplanned safety report of the SPCG-13 trial. *Prostate Cancer Prostatic Dis*. 2012 Sep;15(3):303-7. PMID: 22546837

Lista F, Gimbernat H, Caceres F, et al. Multiparametric magnetic resonance imaging for the assessment of extracapsular invasion and other staging parameters in patients with prostate cancer candidates for radical prostatectomy. *Actas Urol Esp*. 2014 Jun;38(5):290-7. Epub 2014 Jan 1. PMID: 24387827

Mathieu R, Arango JD, Beckendorf V, et al. Nomograms to predict late urinary toxicity after prostate cancer radiotherapy. *World J Urol*. 2014 Jun;32(3):743-51. Epub 2013 Aug 29. PMID: 23990073

Mitsuzuka K, Koie T, Narita S, et al. Is pelvic lymph node dissection required at radical prostatectomy for low-risk prostate cancer. *Int J Urol*. 2013 Nov;20(11):1092-6. Epub 2013 Feb 6. PMID: 23387553

Morris WJ, Spadinger I, Keyes M, et al. Whole prostate D90 and V100: a dose-response analysis of 2000 consecutive (125)I monotherapy patients. *Brachytherapy*. 2014 Jan-Feb;13(1):32-41. PMID: 24126102

Nobes JP, Langley SE, Klopper T, et al. A prospective, randomized pilot study evaluating the effects of metformin and lifestyle intervention on patients with prostate cancer receiving androgen deprivation therapy. *BJU Int*. 2012 May;109(10):1495-502. PMID: 21933330

Pokala N, Trulson JJ, Islam M. Long-term outcome following radical prostatectomy for Gleason 8-10 prostatic adenocarcinoma. *World J Urol*. 2014 Feb 9;Epub ahead of print. PMID: 24510158

Reeve BB, Chen RC, Moore DT, Deal Ms AM, Usinger DS, Lyons JC, Talcott JA. Impact of comorbidity on health-related quality of life after prostate cancer treatment: combined analysis of two prospective cohort studies. *BJU Int*. 2014 Mar 3;Epub ahead of print. Also available: <http://dx.doi.org/10.1111/bju.12723>. PMID: 24588845

Roder MA, Thomsen FB, Berg KD, et al. Risk of biochemical recurrence and positive surgical margins in patients with pT2 prostate cancer undergoing radical prostatectomy. *J Surg Oncol*. 2014 Feb;109(2):132-8. PMID: 24155174

Sfoungaristos S, Kontogiannis S, Perimenis P. Early continence recovery after preservation of maximal urethral length until the level of verumontanum during radical prostatectomy: Primary oncological and functional outcomes after 1 year of follow-up. *Biomed Res Int*. 2013;Epub ahead of print.

Sjoberg C, Lundmark M, Granberg C, et al. Clinical evaluation of multi-atlas based segmentation of lymph node regions in head and neck and prostate cancer patients. *Radiat Oncol.* 2013;8(1):229. PMID: 24090107

Sooriakumaran P, Coley HM, Fox SB, et al. A randomized controlled trial investigating the effects of celecoxib in patients with localized prostate cancer. *Anticancer Res.* 2009 May;29(5):1483-8. PMID: 19443354

Sundi D, Wang VM, Pierorazio PM, et al. Very-high-risk localized prostate cancer: definition and outcomes. *Prostate Cancer Prostatic Dis.* 2014 Mar;17(1):57-63. PMID: 24189998

Sutherland DE, Linder B, Guzman AM, et al. Posterior rhabdosphincter reconstruction during robotic assisted radical prostatectomy: results from a phase II randomized clinical trial. *J Urol.* 2011 Apr;185(4):1262-7. PMID: 21334025

Syndikus I, Morgan RC, Sydes MR, et al, MRC RT01 collaborators. Late gastrointestinal toxicity after dose-escalated conformal radiotherapy for early prostate cancer: results from the UK Medical Research Council RT01 trial (ISRCTN47772397). *Int J Radiat Oncol Biol Phys.* 2010 Jul 1;77(3):773-83. PMID: 19836155

Taneja SS. Re: A phase 3, double-blind, randomised, parallel-group, placebo-controlled study of oral weekly alendronate for the prevention of androgen deprivation bone loss in nonmetastatic prostate cancer: The cancer and osteoporosis research with alendronate and leuprolide (CORAL) study: Editorial comment. *J Urol.* 2013;189(5):1714.

Thornqvist S, Hysing LB, Zolnay AG, et al. Adaptive radiotherapy in locally advanced prostate cancer using a statistical deformable motion model. *Acta Oncol.* 2013 Oct;52(7):1423-9. PMID: 23964658

Wang Y, Liu T, Rossi PJ, et al. Influence of vascular comorbidities and race on erectile dysfunction after prostate cancer radiotherapy. *J Sex Med.* 2013 Aug;10(8):2108-14. Epub 2013 Jun 6. PMID: 23742221

Werahera PN, Crawford ED, La Rosa FG, et al. Anterior tumors of the prostate: diagnosis and significance. *Can J Urol.* 2013 Oct;20(5):6897-906. PMID: 24128826

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**Nonrandomized controlled trials with a mixed population ( $\geq 15\%$  of patient population had T3 [not reporting T3a separately from T3b], T3b, or T4, or metastatic cancer and did not report separate data for T1 or T2 or T3a):**

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## Appendix C. Risk of Bias Assessment for Key Question 1

**Table C-1. Risk-of-bias assessment for Key Question 1 (randomized controlled trials)**

Study	Outcome(s)	Were patients randomly or pseudorandomly (e.g. using instrumental variable analysis) assigned to the study groups?	Q2. Was there concealment of group allocation?	Q3. Were data analyzed based on the intention-to-treat-principle?	Q4. Were those who assessed the patient outcomes blinded to the group to which the patients were assigned?	Q5. Was the outcome measure of interest objective and was it objectively measured?	Q6. Was there a 15% or less difference in the length of followup for the two groups?	Q7. Did 85% or more of enrolled patients provide data at the time point of interest?	Q8. Was there fidelity to protocol?	Overall Risk of Bias Category
Porpiglia et al. 2012 <sup>45</sup>	BRFS AEs	Yes	NR	No	NR	Yes	Yes	Yes	NR	Medium
Porpiglia et al. 2012 <sup>45</sup>	QOL	Yes	NR	No	NR	No	Yes	Yes	NR	High
Wilt et al. 2012 <sup>25</sup> and Wilt et al. 2009 <sup>24</sup> Prostate Intervention Versus Observation Trial (PIVOT)	Overall mortality PCSM Distant metastases AEs	Yes	Yes	Yes	Yes	Yes	Yes	No	NR	Medium
Wilt et al. 2012 <sup>25</sup> and Wilt et al. 2009 <sup>24</sup> Prostate Intervention Versus Observation Trial (PIVOT)	QOL	Yes	Yes	Yes	Yes	No	Yes	No	NR	Medium

Study	Outcome(s)	Were patients randomly or pseudorandomly (e.g. using instrumental variable analysis) assigned to the study groups?	Q2. Was there concealment of group allocation?	Q3. Were data analyzed based on the intention-to-treat-principle?	Q4. Were those who assessed the patient outcomes blinded to the group to which the patients were assigned?	Q5. Was the outcome measure of interest objective and was it objectively measured?	Q6. Was there a 15% or less difference in the length of followup for the two groups?	Q7. Did 85% or more of enrolled patients provide data at the time point of interest?	Q8. Was there fidelity to protocol?	Overall Risk of Bias Category
Bill-Axelsson et al. 2013 <sup>48</sup> , Bill-Axelsson et al. 2011 <sup>33</sup> , Johansson et al. 2011 <sup>51</sup> , Holmberg et al. 2012 <sup>34</sup> , and Bill-Axelsson et al. 2008 <sup>15</sup> Scandinavian Prostate Cancer Group-4 (SPCG-4) Trial	Overall mortality PCSM Distant metastases AEs	Yes	Yes	Yes	Yes for PCSM, NR for other outcomes	Yes	Yes	No	NR	Medium

Study	Outcome(s)	Were patients randomly or pseudorandomly (e.g. using instrumental variable analysis) assigned to the study groups?	Q2. Was there concealment of group allocation?	Q3. Were data analyzed based on the intention-to-treat-principle?	Q4. Were those who assessed the patient outcomes blinded to the group to which the patients were assigned?	Q5. Was the outcome measure of interest objective and was it objectively measured?	Q6. Was there a 15% or less difference in the length of followup for the two groups?	Q7. Did 85% or more of enrolled patients provide data at the time point of interest?	Q8. Was there fidelity to protocol?	Overall Risk of Bias Category
Bill-Axelsson et al. 2013 <sup>48</sup> , Bill-Axelsson et al. 2011 <sup>33</sup> , Johansson et al. 2011 <sup>51</sup> , Holmberg et al. 2012 <sup>34</sup> , and Bill-Axelsson et al. 2008 <sup>15</sup> Scandinavian Prostate Cancer Group-4 (SPCG-4) Trial	QOL	Yes	Yes	Yes	NR	No	Yes	No	NR	High
Jones et al. 2011 <sup>43</sup>	Overall survival PCSM Biochemical failure Distant metastases AEs	Yes	NR	No	No	Yes	Yes	Yes	NR	Medium

Study	Outcome(s)	Were patients randomly or pseudorandomly (e.g. using instrumental variable analysis) assigned to the study groups?	Q2. Was there concealment of group allocation?	Q3. Were data analyzed based on the intention-to-treat-principle?	Q4. Were those who assessed the patient outcomes blinded to the group to which the patients were assigned?	Q5. Was the outcome measure of interest objective and was it objectively measured?	Q6. Was there a 15% or less difference in the length of followup for the two groups?	Q7. Did 85% or more of enrolled patients provide data at the time point of interest?	Q8. Was there fidelity to protocol?	Overall Risk of Bias Category
Jones et al. 2011 <sup>43</sup>	QOL	Yes	NR	No	No	No	Yes	Yes	NR	High
Donnelly et al. 2010 <sup>47</sup> Same study as Robinson et al. 2009 <sup>52</sup>	Overall survival PCSM Biochemical failure AEs	Yes	NR	No	No	Yes	Yes	Yes	NR	Medium
Donnelly et al. 2010 <sup>47</sup> Same study as Robinson et al. 2009 <sup>52</sup>	QOL	Yes	NR	No	No	No	Yes	Yes	NR	High
Giberti et al. 2009 <sup>44</sup>	BDFS	Yes	Yes	NR	Yes	Yes	Yes	Yes	NR	Medium
Giberti et al. 2009 <sup>44</sup>	QOL	Yes	Yes	NR	Yes	No	Yes	Yes	NR	Medium

Study	Outcome(s)	Were patients randomly or pseudorandomly (e.g. using instrumental variable analysis) assigned to the study groups?	Q2. Was there concealment of group allocation?	Q3. Were data analyzed based on the intention-to-treat-principle?	Q4. Were those who assessed the patient outcomes blinded to the group to which the patients were assigned?	Q5. Was the outcome measure of interest objective and was it objectively measured?	Q6. Was there a 15% or less difference in the length of followup for the two groups?	Q7. Did 85% or more of enrolled patients provide data at the time point of interest?	Q8. Was there fidelity to protocol?	Overall Risk of Bias Category
D'Amico et al. 2008 <sup>49</sup> , D'Amico et al. 2008 <sup>35</sup> and Nguyen et al. 2010 <sup>53</sup>	Overall mortality PCSM AEs	Yes	Yes	Yes	NR	Yes	Yes	Yes	NR	Low
D'Amico et al. 2008 <sup>49</sup> , D'Amico et al. 2008 <sup>35</sup> , and Nguyen et al. 2010 <sup>53</sup>	QOL	Yes	Yes	Yes	Yes	No	Yes	Yes	NR	Low
Martis et al. 2007 <sup>46</sup>	AEs	Yes	NR	NR	NR	Yes	Yes	Yes	NR	Medium
Martis et al. 2007 <sup>46</sup>	QOL	Yes	NR	NR	NR	No	Yes	Yes	NR	High

**Abbreviations:** AEs=adverse events, BDFS=biochemical disease free survival, BRFS=biochemical recurrence free survival, NR=not reported, OS=overall survival, PCSM=prostate cancer specific mortality, QOL=quality of life

**Table C-2. Risk-of-bias assessment for Key Question 1 (nonrandomized comparative studies)**

Study	Outcome(s)	Were patients randomly or pseudorandomly (e.g. using instrumental variable analysis) assigned to the study groups?	Q2. Was there concealment of group allocation?	Q3. Were data analyzed based on the intention-to-treat-principle?	Q4. Were those who assessed the patient outcomes blinded to the group to which the patients were assigned?	Q5. Was the outcome measure of interest objective and was it objectively measured?	Q6. Was there a 15% or less difference in the length of followup for the two groups?	Q7. Did 85% or more of enrolled patients provide data at the time point of interest?	Q8. Was there fidelity to protocol?	Overall Risk of Bias Category
Alemozaffar et al. 2014 <sup>68</sup>	PCSM Progression to metastasis BRFS	No	No	No	No	Yes	No	No	NR	High
Alemozaffar et al. 2014 <sup>68</sup>	QOL	No	No	No	No	No	No	No	NR	High
Mukherjee et al. 2014 <sup>37</sup>	All cause mortality PCSM AEs	No	No	No	No	Yes	No	Yes	NR	High
DeGroot et al. 2013 <sup>41</sup>	PCSM	No	No	No	No	Yes	Yes	Yes	NR	High
Ferrer et al. 2013 <sup>91</sup> Same study as Ferrer et al. 2008 <sup>61</sup>	All-cause mortality Biochemical recurrence-free survival	No	No	No	No	Yes	Yes	Yes	NR	High
Ferrer et al. 2013 <sup>91</sup> Same study as Ferrer et al. 2008 <sup>61</sup>	QOL	No	No	No	No	No	Yes	Yes	NR	High

Study	Outcome(s)	Were patients randomly or pseudorandomly (e.g. using instrumental variable analysis) assigned to the study groups?	Q2. Was there concealment of group allocation?	Q3. Were data analyzed based on the intention-to-treat-principle?	Q4. Were those who assessed the patient outcomes blinded to the group to which the patients were assigned?	Q5. Was the outcome measure of interest objective and was it objectively measured?	Q6. Was there a 15% or less difference in the length of followup for the two groups?	Q7. Did 85% or more of enrolled patients provide data at the time point of interest?	Q8. Was there fidelity to protocol?	Overall Risk of Bias Category
Hoffman et al. 2013 <sup>38</sup>	All-cause mortality PCSM	No	No	No	No	Yes	Yes	Yes	NR	High
Liu et al. 2013 <sup>79</sup>	All-cause mortality PCSM	No	No	No	No	Yes	Yes	Yes	NR	High
Marina et al. 2013 <sup>86</sup>	Overall survival Cause-specific survival Biochemical failure Biochemical recurrence-free survival Clinical progression	No	No	No	No	Yes	Yes	Yes	NR	High
Nepple et al. 2013 <sup>40</sup>	All-cause mortality PCSM	No	No	No	No	Yes	Yes	Yes	NR	High
Pierorazio et al. 2013 <sup>70</sup>	BRFS	No	No	No	No	Yes	Yes	Yes	NR	High
Resnick et al. 2013 <sup>55</sup>	QOL (Urinary function, bowel function, sexual function)	No	No	No	No	No	Yes	Yes	NR	High
Silberstein et al. 2013 <sup>67</sup>	BRFS	No	No	No	No	Yes	Yes	Yes	NR	High
Spratt et al. 2013 <sup>77</sup>	AEs	No	No	No	No	Yes	Yes	Yes	NR	High

Study	Outcome(s)	Were patients randomly or pseudorandomly (e.g. using instrumental variable analysis) assigned to the study groups?	Q2. Was there concealment of group allocation?	Q3. Were data analyzed based on the intention-to-treat-principle?	Q4. Were those who assessed the patient outcomes blinded to the group to which the patients were assigned?	Q5. Was the outcome measure of interest objective and was it objectively measured?	Q6. Was there a 15% or less difference in the length of followup for the two groups?	Q7. Did 85% or more of enrolled patients provide data at the time point of interest?	Q8. Was there fidelity to protocol?	Overall Risk of Bias Category
Spratt et al. 2013 <sup>77</sup>	QOL	No	No	No	No	No	Yes	Yes	NR	High
Wirth et al. 2013 <sup>74</sup>	BRFS	No	No	No	No	Yes	Yes	Yes	NR	High
Abdollah et al. 2012 <sup>59</sup>	PCSM	No	No	No	No	Yes	Yes	Yes	NR	High
Abern et al. 2012 <sup>90</sup>	AEs	No	No	No	No	Yes	Yes	Yes	NR	High
Barry et al. 2012 <sup>66</sup>	QOL (Continence, sexual function)	No	No	No	No	No	Yes	Yes	NR	High
Kibel et al. 2012 <sup>75</sup>	Overall survival PCSM	No	No	No	No	Yes	Yes	Yes	NR	High
Mohammed et al. 2012 <sup>80</sup>	AEs	No	No	No	No	Yes	Yes	Yes	NR	High
Mohammed et al. 2012 <sup>80</sup>	QOL	No	No	No	No	No	Yes	Yes	NR	High
Nanda et al. 2012 <sup>83</sup>	AEs	No	No	No	No	Yes	Yes	Yes	NR	High
Ploussard et al. 2012 <sup>62</sup>	BRFS Biochemical recurrence AEs	No	No	No	NR	Yes	No	Yes	NR	High



Study	Outcome(s)	Were patients randomly or pseudorandomly (e.g. using instrumental variable analysis) assigned to the study groups?	Q2. Was there concealment of group allocation?	Q3. Were data analyzed based on the intention-to-treat-principle?	Q4. Were those who assessed the patient outcomes blinded to the group to which the patients were assigned?	Q5. Was the outcome measure of interest objective and was it objectively measured?	Q6. Was there a 15% or less difference in the length of followup for the two groups?	Q7. Did 85% or more of enrolled patients provide data at the time point of interest?	Q8. Was there fidelity to protocol?	Overall Risk of Bias Category
Ploussard et al. 2012 <sup>62</sup>	QOL	No	No	No	NR	No	No	Yes	NR	High
Rosenberg et al. 2012 <sup>76</sup>	PCSM	No	No	No	No	Yes	Yes	Yes	NR	High
Sheets et al. 2012 <sup>58</sup>	AEs	Yes	No	No	No	Yes	Yes	Yes	NR	Medium
Sheets et al. 2012 <sup>58</sup>	QOL	Yes	No	No	No	No	Yes	Yes	NR	High
Shen et al. 2012 <sup>84</sup>	PCSM	No	No	No	No	Yes	Yes	Yes	NR	High
Zelevsky et al. 2012 <sup>89</sup>	BRFS	No	No	No	No	Yes	Yes	Yes	NR	High
Abdollah et al. 2011 <sup>72</sup>	PCSM Other cause mortality	No	No	No	No	Yes	Yes	Yes	NR	High
Bekelman et al. 2011 <sup>81</sup>	AEs	No	No	No	No	Yes	Yes	Yes	NR	High
Kim et al. 2011 <sup>60</sup>	AEs	No	No	No	No	Yes	Yes	No	NR	High
Masterson et al. 2011 <sup>69</sup>	BRFS	No	No	No	No	Yes	No	Yes	NR	High

Study	Outcome(s)	Were patients randomly or pseudorandomly (e.g. using instrumental variable analysis) assigned to the study groups?	Q2. Was there concealment of group allocation?	Q3. Were data analyzed based on the intention-to-treat-principle?	Q4. Were those who assessed the patient outcomes blinded to the group to which the patients were assigned?	Q5. Was the outcome measure of interest objective and was it objectively measured?	Q6. Was there a 15% or less difference in the length of followup for the two groups?	Q7. Did 85% or more of enrolled patients provide data at the time point of interest?	Q8. Was there fidelity to protocol?	Overall Risk of Bias Category
Rice et al. 2011 <sup>36</sup>	Overall mortality Biochemical recurrence	No	No	No	No	Yes	No	Yes	NR	High
Williams et al. 2011 <sup>57</sup>	AEs	No	No	No	No	Yes	Yes	Yes	NR	High
Williams et al. 2011 <sup>57</sup>	QOL	No	No	No	No	No	Yes	Yes	NR	High
Barocas et al. 2010 <sup>64</sup>	BRFS	No	No	No	No	Yes	Yes	Yes	NR	High
Cooperberg et al. 2010 <sup>39</sup>	All-cause mortality PCSM	No	No	No	No	Yes	Yes	Yes	NR	High
Dosoretz et al. 2010 <sup>82</sup>	All-cause mortality	No	No	No	No	Yes	Yes	Yes	NR	High
Hadley et al. 2010 <sup>73</sup>	All cause mortality PCSM	Yes	No	No	No	Yes	Yes	Yes	NR	Medium
Magheli et al. 2010 <sup>56</sup>	Biochemical recurrence	No	No	No	No	Yes	Yes	Yes	NR	High
Wong et al. 2009 <sup>88</sup>	Biochemical recurrence Distant metastases AEs	No	No	No	No	Yes	Yes	Yes	NR	High

Study	Outcome(s)	Were patients randomly or pseudorandomly (e.g. using instrumental variable analysis) assigned to the study groups?	Q2. Was there concealment of group allocation?	Q3. Were data analyzed based on the intention-to-treat-principle?	Q4. Were those who assessed the patient outcomes blinded to the group to which the patients were assigned?	Q5. Was the outcome measure of interest objective and was it objectively measured?	Q6. Was there a 15% or less difference in the length of followup for the two groups?	Q7. Did 85% or more of enrolled patients provide data at the time point of interest?	Q8. Was there fidelity to protocol?	Overall Risk of Bias Category
Malcolm et al. 2009 <sup>71</sup>	QOL	No	No	No	No	No	Yes	No	NR	High
Krambeck et al. 2008 <sup>65</sup>	PCSM Other cause mortality Biochemical progression Systemic progression Clinical local recurrence AEs	No	No	No	No	Yes	Yes	Yes	NR	High
Krambeck et al. 2008 <sup>65</sup>	QOL	No	No	No	No	No	Yes	Yes	NR	High
Lu-Yao et al. 2008 <sup>78</sup>	Overall survival PCSS	Yes	No	No	No	Yes	Yes	Yes	NR	Medium
Sanda et al. 2008 <sup>41</sup>	QOL	No	No	No	No	No	Yes	No	NR	High
Schroeck et al. 2008 <sup>54</sup>	PSA recurrence rate	No	No	No	No	Yes	Yes	Yes	NR	High
Sumitomo et al. 2008 <sup>63</sup>	BPFS AEs	No	No	No	No	Yes	Yes	Yes	NR	High
Sumitomo et al. 2008 <sup>63</sup>	QOL	No	No	No	No	No	Yes	Yes	NR	High

Study	Outcome(s)	Were patients randomly or pseudorandomly (e.g. using instrumental variable analysis) assigned to the study groups?	Q2. Was there concealment of group allocation?	Q3. Were data analyzed based on the intention-to-treat-principle?	Q4. Were those who assessed the patient outcomes blinded to the group to which the patients were assigned?	Q5. Was the outcome measure of interest objective and was it objectively measured?	Q6. Was there a 15% or less difference in the length of followup for the two groups?	Q7. Did 85% or more of enrolled patients provide data at the time point of interest?	Q8. Was there fidelity to protocol?	Overall Risk of Bias Category
Albertsen et al. 2007 <sup>42</sup>	Overall survival PCSM	No	No	No	No	Yes	Yes	Yes	NR	High
D'Amico et al. 2007 <sup>87</sup>	PCSM	No	No	No	No	Yes	Yes	Yes	NR	High

**Abbreviations:** AEs=adverse events, BPFS=biochemical progression free survival, BRFS=biochemical recurrence free survival, NR=not reported, PCSM=prostate cancer specific mortality, PCSS=prostate cancer-specific survival, PSA=prostate specific antigen, QOL=quality of life.

## Appendix D. Key Questions 1–4: Study Selection Criteria and Description of Treatment

**Table D-1. Description of study design and selection criteria and treatment (randomized controlled trials)**

Study	Design and Study Enrollment Period	Patient Inclusion Criteria	Patient Exclusion Criteria	Treatment
Porpiglia et al. 2013 <sup>45</sup>	Single center, single surgeon RCT enrolling 120 men with organ confined prostate cancer. <u>Enrollment Period:</u> January 2010–January 2012	Males 40 to 75 years of age referred to one institution in Italy with prostate cancer T1 to T2N0M0 clinically staged according to TNM 2009 regardless of prostate size and for whom RP was proposed as a treatment.	Patients with prior radiation therapy, hormonal therapy, and/or transurethral resection of the prostate were excluded.	<u>RARP:</u> Transperitoneal anterograde approach. When indicated unilateral or bilateral neurovascular bundle preservation and extended lymph node dissection were performed. <u>LRP:</u> Transperitoneal anterograde approach. When indicated unilateral or bilateral neurovascular bundle preservation and extended lymph node dissection were performed.
Wilt et al. 2012 <sup>25</sup> Same study as Wilt et al. 2009 <sup>24</sup> Prostate Intervention Versus Observation Trial (PIVOT)	A multicenter RCT involving 731 men recruited from 52 medical centers (44 Veterans Affairs and 8 National Cancer Institute sites) across the USA. <u>Enrollment Period:</u> November 1994–January 2002	Eligible men had to have biopsy proven clinically localized prostate cancer (T1–T2NxM0) of any histologic grade, diagnosed within the past 12 months, prostatic specific antigen (PSA) value ≤50 ng/mL, age ≤75 years, bone scan negative for metastatic disease, an estimated life expectancy of at least 10 years and judged to be medically and surgically fit for radical prostatectomy.	Not reported.	<u>Observation:</u> Men were offered palliative (noncurative) therapy (e.g., TURP for local progression causing urinary obstruction, androgen deprivation and/or targeted radiation therapy for evidence of distant spread). <u>RP:</u> The technique was at the surgeon's discretion. Additional interventions were determined by each participant and his physician.

Study	Design and Study Enrollment Period	Patient Inclusion Criteria	Patient Exclusion Criteria	Treatment
Bill-Axelsson et al. 2011 <sup>33</sup> Same study as Johansson et al. 2011 <sup>51</sup> , Holmberg et al. 2012 <sup>34</sup> , and Bill-Axelsson et al. 2008 <sup>15</sup> Scandinavian Prostate Cancer Group-4 (SPCG-4) Trial	A multicenter RCT involving 695 men was conducted at 14 centers in Sweden, Finland, and Iceland. <u>Enrollment Period:</u> October 1989–December 1999	Men were eligible for inclusion if they were younger than 75 years of age and had a life expectancy of more than 10 years, had no other known cancers, and had a localized tumor T0d (later named T1b), T1, or T2. T1c patients were included in 1994. All patients included in the study were required to have a serum PSA <50 ng/mL and a negative bone scan.	NR	<u>WW:</u> Men who had signs of obstructive voiding disorders were treated with transurethral resection. Metastases detected by bone scan were managed with hormonal therapy. <u>RP:</u> The surgical procedure started with a lymphadenectomy of the obturator fossa; if no nodal metastases were found in frozen sections, the RP was performed. Radical excision of the tumor was given priority over nerve-sparing surgery.
Jones et al. 2011 <sup>43</sup>	A multicenter phase 3 RCT involving 1,979 men was conducted in the USA and Canada. <u>Enrollment Period:</u> 1994–2001	Eligible men had to have histologically confirmed prostate cancer stage T1b, T1c, T2a, or T2b, and a PSA ≤20 ng/mL. Other eligibility criteria included a Karnofsky performance score of 70 or more (on a scale of 1 to 100, with higher scores indicating better performance status), an alanine aminotransferase level that was no more than twice the upper limit of the normal range, no evidence of regional lymph node involvement or distant metastatic disease, and no previous chemotherapy, radiotherapy, hormonal therapy, cryosurgery, or definitive surgery for prostate cancer.	NR	<u>EBRT:</u> Radiotherapy was administered in daily 1.8 Gray (Gy) fractions prescribed to the isocenter of the treatment volume, consisted of 46.8 Gy delivered to the pelvis (prostate and regional lymph nodes), followed by 19.8 Gy to the prostate. <u>EBRT plus short-term ADT:</u> Flutamide at a dose of 250 mg orally three times a day and either monthly subcutaneous goserelin at a dose of 3.6 mg or intramuscular leuprolide at a dose of 7.5 mg for 4 months. Radiotherapy commenced after 2 months of ADT.

Study	Design and Study Enrollment Period	Patient Inclusion Criteria	Patient Exclusion Criteria	Treatment
Donnelly et al. 2010 <sup>47</sup> Same study as Robinson et al. 2009 <sup>52</sup>	A single-center RCT involving 244 men was conducted in Canada. <u>Enrollment Period:</u> December 1997–February 2003	Men T2 or T3, no evidence of lymph node or distant metastases and a pretreatment PSA level ≤20 ng/mL	Clinically bulky T3 tumor, received prior pelvic radiation, received previous ADT at any time, and undergone TURP within the previous 3 months	<u>EBRT:</u> Standard 4-field box technique (2 Gy daily, 5 days per week). The prescribed radiation dose was 68 Gy. The dose was increased to 70 Gy in early 2000 and finally to 73.5 Gy in late 2000 and finally to 73.5 Gy in late 2002. <u>Cryotherapy:</u> Thermo sensor monitoring, urethral warming, and saline injection were routinely applied to separate anterior rectal wall from the prostate, and 2 freeze-thaw cycles were used in all cases.
Giberti et al. 2009 <sup>44</sup>	A single center RCT involving 200 men was conducted in Italy. <u>Enrollment Period:</u> May 1999–October 2002	Study included only Caucasian men with low risk prostate cancer (clinical stage T1c or T2a, PSA value ≤10 ng/mL and Gleason sum ≤6)	Previous pelvic irradiation, large median lobes, uroflow-Q max lower than 10 mL/s, history of multiple pelvic surgeries, previous transurethral resection of prostate, prostate volume greater than 60 mL and positive seminal vesicles biopsy.	<u>RRP:</u> Bilateral nerve sparing RRP, in accordance with Walsh's principles, and standard lymph node dissection were performed on all the patients by a single surgeon. <u>BT:</u> BT was performed by a team, which included a urologist, a radiation therapist and a primary care physician, through a transperitoneal template-guided peripheral loading real-time technique and seeds of Iodine-125. A D90 >140 Gy was considered the cut-off value in order to predict a good quality implant.

Study	Design and Study Enrollment Period	Patient Inclusion Criteria	Patient Exclusion Criteria	Treatment
D'Amico et al. 2008 <sup>49</sup> Same study as D'Amico et al. 2008 <sup>35</sup> and Nguyen et al. 2010 <sup>53</sup>	A single center RCT involving 206 men was conducted in USA. <u>Enrollment Period:</u> December 1, 1995– April 15, 2001	Study included men with prostate cancer clinical stage T1b to T2bN0M0 who had at least a 10-year life expectancy excluding death from prostate cancer and an Eastern Cooperative Oncology Group performance status 0 to 1.	Patients with a history of a prior malignancy except for nonmelanoma skin cancer or prior pelvic radiation therapy or ADT.	<u>EBRT:</u> Daily dose of 1.8 Gy for initial 25 treatments, totaling 45 Gy, and 2.0 Gy for final 11 treatments, totaling 22 Gy. <u>EBRT plus ADT:</u> EBRT plus ADT which consisted of a luteinizing hormone-releasing agonist, leuprolide or goserelin and antiandrogen flutamide. Leuprolide was delivered intramuscularly each month at a dose 7.5 mg or 22.5 mg every 3 months. Goserelin was administered subcutaneously each month at a dose of 3.6 mg or 10.8 mg every 3 months. Flutamide was taken orally at a dose of 250 mg every 8 hours and starting 1 to 3 days before leuprolide.
Martis et al. 2007 <sup>46</sup>	A single center RCT involving 200 men was conducted in Italy. <u>Enrollment Date:</u> January 1997–December 2004	Study included men with clinically localized prostate cancer (T1–T2).	For the perineal prostatectomy group, authors reported an exclusion of patients with a prostate weight >80 g, a prominent median lobe and inability to place the patient in an exaggerated lithotomy position because of hip arthrosis, ankylosis, and/or severe coxarthrosis.	Bilateral nerve sparing RP performed by the retropubic or perineal approach by a single surgeon.

**Abbreviations:** ADT=androgen deprivation therapy, BT=brachytherapy, D90=minimum dose covering 90% of the prostate volume, EBRT=external beam radiation therapy, LRP=laparoscopic radical prostatectomy, NR=not reported, PSA=prostate specific antigen, RARP=robot assisted radical prostatectomy, RCT=randomized controlled trial, RP=radical prostatectomy, RRP=radical retropubic prostatectomy, TURP=transurethral resection of the prostate



**Table D-2. Description of study design and selection criteria and treatment (nonrandomized comparative studies)**

Study	Design and Study Enrollment Period	Patient Inclusion Criteria	Patient Exclusion Criteria	Treatment
Alemozaffar et al. 2014 <sup>68</sup>	51,529 male U.S. health professionals complete questionnaires at regular intervals on patients with a diagnosis of prostate cancer. Patient medical records are used to supplement the survey data. <u>Enrollment Period:</u> Patients were diagnosed with prostate cancer after January 1, 2000 and were treated with RP as a primary therapy within one year of diagnosis between 2000 and 2010.	903 men treated with RALP or open RRP for localized prostate cancer.	Patients treated with a pure laparoscopic, perineal approach, or had an unknown type of surgery were excluded.	<u>RALP:</u> Composed 4.5% of procedures in 2003, 28.6% in 2005, 63.9% in 2007, and 85.2% in 2009. <u>Open RRP:</u> Not described.
Mukherjee et al. 2014 <sup>37</sup>	Prospective registry data on 10,924 patients with clinically localized prostate cancer. <u>Enrollment Period:</u> Patients were newly diagnosed between January 1986 and July 2011 at a single clinic in the U.S.	Patients were histopathologically confirmed with locoregional prostate adenocarcinoma (T1–T3) without a history of any cancer before the diagnosis of prostate cancer or in the period between treatment of prostate cancer and diagnosis with myelodysplastic syndrome. Patients had no documented exposure to cytotoxic chemotherapy or use of radiotherapy for any condition other than prostate cancer.	Patients who received combined treatment with EBRT and BT and patients with disease recurrence treated with either salvage radiotherapy or surgery were excluded.	<u>RP:</u> No RP patient received adjuvant radiation, 7.7% received ADT <u>EBRT:</u> Starting in 1998 IMRT became the EBRT method of choice, median radiation dose of all EBRT techniques combined was 78 Gray at 2 Gy per fraction. 45.7% received ADT. <u>BT:</u> Started in 1996 and has been preferred method of radiation since 2002. Patients received 144 Gy using <sup>125</sup> I. 16.4% of patients received ADT.
DeGroot et al. 2013 <sup>41</sup>	Case-cohort study of men with clinically localized prostate cancer. <u>Enrollment Period:</u> 1990 and 1998 in Canada.	NR	NR	<u>RP:</u> Not described. <u>EBRT:</u> Median administered dose was 64 Gray units (Gy)
Ferrer et al. 2013 <sup>91</sup> Same study as Ferrer et al. 2008 <sup>61</sup>	Longitudinal prospective study of consecutive men with clinically localized prostate cancer. <u>Enrollment Period:</u> April 2003 through March 2005 at 10 sites in Spain.	Men with clinically localized prostate cancer, stages T1 or T2 and no previous transurethral prostate resection were enrolled.	NR	<u>RRP:</u> Not described. <u>3D-CRT:</u> Not described. <u>BT:</u> Not described.

Study	Design and Study Enrollment Period	Patient Inclusion Criteria	Patient Exclusion Criteria	Treatment
Hoffman et al. 2013 <sup>38</sup>	<p>This study was a secondary analysis of data from a subset of patients enrolled in the Prostate Cancer Outcomes Study (PCOS), a population-based cohort of men in whom prostate cancer had been diagnosed in the mid-1990s and who had been followed prospectively for 15 years.</p> <p><u>Enrollment Period:</u> Patients were diagnosed in 1994 and 1995.</p>	<p>Men were enrolled in PCOS if they had prostate cancer. Patients were enrolled at six participating research centers throughout the United States. Patients under the age of 60 years, of Hispanic origin, and black men were over-sampled.</p> <p>For the current study, only those men with clinically localized prostate cancer diagnosed between the ages of 55 and 74 years, who had completed a 2-year or 5-year followup survey, and who underwent either prostatectomy or radiotherapy as primary treatment (with or without androgen-deprivation therapy) within one year after diagnosis were included.</p>	NR	<p><u>RP:</u> Not described. <u>Radiotherapy:</u> Not described.</p>
Liu et al. 2013 <sup>79</sup>	<p>This was a U.S. population-based study using Surveillance, Epidemiology, and End Results- (SEER) Medicare-linked data from 2000 to 20009 for patients with nonmetastatic prostate cancer.</p> <p><u>Enrollment Period:</u> Patients received a diagnosis of prostate cancer between 2000 and 2007.</p>	<p>Men with a diagnosis of prostate cancer, no additional cancers, no metastatic disease, no disease diagnosis at autopsy, with the month and year of their prostate cancer diagnosis recorded, and at least one year of claims data before their diagnosis were included.</p>	<p>Men enrolled in a health maintenance organization within one year of diagnosis or not enrolled in Medicare Part A and Part B for the study duration were excluded. Patients who received combination therapy of radiation and either brachytherapy of prostatectomy were also excluded.</p>	<p><u>RP:</u> Not described. <u>ADT:</u> Not described.</p>
Marina et al. 2013 <sup>86</sup>	<p>A review of charts of intermediate-risk prostate cancer patients.</p> <p><u>Enrollment Period:</u> Not reported by study authors</p>	<p>Men with intermediate-risk (prostatic specific antigen [PSA] <math>\geq 10</math> and <math>&lt; 20</math> ng/mL, Gleason score 7, or clinical stage T2b–c) prostate cancer.</p>	NR	<p><u>IGRT:</u> Not described. <u>BT:</u> High dose rate BT.</p>

Study	Design and Study Enrollment Period	Patient Inclusion Criteria	Patient Exclusion Criteria	Treatment
Nepple et al. 2013 <sup>40</sup>	Data from 10,361 men with clinically localized prostate cancer at two academic centers in the U.S. <u>Enrollment Period:</u> Patients were treated between 1995 and 2007.	NR	NR	<u>RRP</u> : RRP or minimally invasive approach. <u>EBRT</u> : Dosage was consistent with the standard of care at the time of treatment, with doses gradually escalated from 68.4 to 79.2 Gy. <u>BT</u> : Administered with intraoperative ultrasound guidance.
Pierorazio et al. 2013 <sup>70</sup>	A secondary data analysis of 10,690 men with clinically localized prostate cancer at one academic center in the U.S. <u>Enrollment Period:</u> Patients were treated between 2002 and 2011.	NR	NR	<u>RALRP</u> : Not described. <u>LRP</u> : Not described.
Resnick et al. 2013 <sup>55</sup>	This study was a secondary analysis of data from a subset of patients enrolled in the Prostate Cancer Outcomes Study (PCOS), a U.S. population-based cohort of men in whom prostate cancer had been diagnosed in the mid-1990s and who had been followed prospectively for 15 years. <u>Enrollment Period:</u> Patients were diagnosed in 1994 and 1995.	Men were enrolled in PCOS if they had prostate cancer. Patients were enrolled at six participating research centers throughout the United States. Patients under the age of 60 years, of Hispanic origin, and black men were over-sampled. For the current study, only those men with clinically localized prostate cancer diagnosed between the ages of 55 and 74 years, who had completed a 2-year or 5-year followup survey, and who underwent either prostatectomy or radiotherapy as primary treatment (with or without androgen-deprivation therapy) within one year after diagnosis were included.	NR	<u>RP</u> : Not described. <u>Radiotherapy</u> : Not described.

Study	Design and Study Enrollment Period	Patient Inclusion Criteria	Patient Exclusion Criteria	Treatment
Silberstein et al. 2013 <sup>67</sup>	Data from 3,005 men with clinically localized prostate cancer at one academic center in the U.S. <u>Enrollment Period:</u> Patients were treated between 2007 and 2010.	NR	NR	<u>RRP:</u> Not described. <u>RALRP:</u> Not described.
Spratt et al. 2013 <sup>77</sup>	870 consecutive patients with intermediate-risk prostate cancer treated with IMRT plus BT or IMRT alone at one site in the U.S. <u>Enrollment Period:</u> Patients were treated between 1997 and 2010.	Patients with intermediate risk disease according to the National Comprehensive Cancer Network risk groupings were included.	Patients were excluded if they had any evidence of extraprostatic extension, lymph node involvement, or distant metastases.	<u>IMRT plus BT:</u> IMRT was dose escalated and BT was either high- or low-dose rate. ADT was prescribed at the discretion of the treating physician in 120 men in this group. <u>IMRT alone:</u> IMRT was dose escalated and ADT was prescribed at the discretion of the treating physician in 229 men in this group.
Wirth et al. 2013 <sup>74</sup>	Cohort study of 1,000 men with T2 and T3 prostate cancer. <u>Enrollment Period:</u> Patients were treated between 2001 and 2005 at one U.S. site.	NR	NR	<u>RRP:</u> Not described. <u>LRP:</u> Not described.
Abdollah et al. 2012 <sup>59</sup>	This was a U.S. population-based cohort study of men with localized, cT1 to T2 prostate cancer treated between 1992 and 2005. This study used the SEER registries-Medicare insurance program linked database. <u>Enrollment Period:</u> Patients were treated between 1992 and 2005.	Men ≥65 years diagnosed with nonmetastatic prostate cancer as their first malignant disease between 1992 and 2005. Patients had Medicare Part A and Part B claims available and were not enrolled in a health maintenance organization throughout the duration of the study.	Patients were excluded if their original or current reason for Medicare entitlement was listed as disability or had a Medicare status code including disability, their PC was diagnosed at autopsy or using the death certificate only, if they were treated surgically or with initial hormonal therapy, they had T3/T4 tumors, anaplastic or unknown grade, unknown stage, had missing socioeconomic data, or were >80 years at the time of diagnosis.	<u>Radiotherapy:</u> Not described. <u>Observation:</u> Not described.

Study	Design and Study Enrollment Period	Patient Inclusion Criteria	Patient Exclusion Criteria	Treatment
Abern et al. 2012 <sup>90</sup>	<p>This was a U.S. population-based cohort study of men (N=275,200) with clinically localized prostate cancer. The study used the SEER registries-Medicare insurance program linked database.</p> <p><u>Enrollment Period:</u> Patients were treated between 1988 and 2007.</p>	<p>Men diagnosed with clinically localized prostate cancer (T1-T2N0M0) treated with RP, RP plus radiation therapy, EBRT alone, EBRT plus BT, BT alone, or radiation not otherwise specified with a minimum of one year of followup data were included in this study.</p>	<p>Patients without complete stage data were excluded.</p>	<p><u>RP:</u> Not described.  <u>RP plus radiation therapy:</u> Not described.  <u>EBRT alone:</u> Not described.  <u>EBRT plus BT:</u> Not described.  <u>BT alone:</u> Not described.  <u>Radiation NOS:</u> Not described.</p>
Barry et al. 2012 <sup>66</sup>	<p>A U.S. population-based random sample was drawn from the 20% Medicare claims files for August 2008 through December 2008.</p> <p><u>Enrollment Period:</u> November 2009–March 2010</p>	<p>Men with the following were included: had an inpatient claim for radical prostatectomy (ICD-9 SX code of 605 in any position); a prostate cancer diagnosis during the admission when the prostatectomy was performed (ICD-9 185, 1850, 2365, 2395, 2334, 19882, V1046, or V1045); a surgeon's claim for the procedure (CPT codes 55810, 55812, 55815, 55840, 55842, 55845, 55866, 55899, or 55899); ≥66 years of age at the time of surgery (to have 12 months of preoperative claims available); no health maintenance organization participation during 2008; and lived in the United States.</p>	<p>Patients who had died before selection or were residents of a nursing home were excluded.</p>	<p><u>RRP:</u> Not described.  <u>RALRP:</u> Not described.</p>

Study	Design and Study Enrollment Period	Patient Inclusion Criteria	Patient Exclusion Criteria	Treatment
Kibel et al. 2012 <sup>65</sup>	<p>Data were gathered retrospectively on a cohort of 10,429 consecutive men with clinically localized prostate cancer treated between 1995 and 2005 at two sites in the United States.</p> <p><u>Enrollment Period:</u> Patients were treated between 1995 and 2005.</p>	NR	NR	<p><u>RP:</u> The procedure was either RRP or LRP.</p> <p><u>EBRT:</u> The procedure was 3D-CRT, IMRT, or 4-field conventional EBRT. The median cGy dose 7800 (IQR 7,400 to 8,000) at site 1, 7,400 (7,070 to 7,544) at site 2.</p> <p><u>BT:</u> BT was delivered using intraoperative treatment planning with ultrasound guidance. The median cGy dose 14,400 at site 1, 14,500 at site 2.</p> <p>In addition, 34% (N=1,348) patients treated with EBRT and BT also received neoadjuvant, concurrent and/or adjuvant ADT.</p>
Mohammed et al. 2012 <sup>80</sup>	<p>Cohort study of 1,903 men with clinical stage II to III adenocarcinoma of the prostate.</p> <p><u>Enrollment Period:</u> Patients were treated between 1992 and 2006 at one U.S. site.</p>	Men with clinical stage II to III adenocarcinoma of the prostate.	NR	<p><u>BT with either high-dose or low-dose rate:</u> Patients were clinical stage II.</p> <p><u>IG-EBRT:</u> Not described.</p> <p><u>EBRT with high-dose rate (HDR) BT boost (EBRT plus HDR):</u> Patients were intermediate or high-risk disease.</p>

Study	Design and Study Enrollment Period	Patient Inclusion Criteria	Patient Exclusion Criteria	Treatment
Nanda et al. 2012 <sup>83</sup>	Retrospective cohort of men with low-risk (N=5,441), intermediate risk (N=4,365) and high risk (N=1,360) adenocarcinoma of the prostate. <u>Enrollment Period:</u> Patients were consecutively treated between September 1991 and September 2006 at the Chicago Prostate Cancer Center or at one of 20 community based medical centers in the U.S.	The men had no or at least a single risk factor and no documented history of CAD. The extent of cardiovascular comorbidity ranged from a single CAD risk factor including diabetes mellitus, hypercholesterolemia or hypertension alone to any two or three of these risk factors. Low, moderate and high-risk disease were defined as: PSA <10 ng/mL, clinical stage T1 or T2a, and Gleason=6 (low), PSA 10 to 20 ng/mL or clinical stage <T3 or Gleason <8 (intermediate), PSA ≥20 ng/mL, or Gleason ≥8 or clinical stage ≥T3.	NR	<u>BT without neoadjuvantive HT:</u> Supplemental EBRT was used in 16% of cases. <u>BT with neoadjuvantive HT:</u> Supplemental EBRT was used in 49% of cases.
Ploussard et al. 2012 <sup>62</sup>	Cohort study of 2386 men at one high-volume laparoscopy referenced center in France. <u>Enrollment Period:</u> Patients were treated between July 2001 and December 2011.	Consecutive cases of men with localized prostate cancer were included. No other details were provided.	NR	<u>LRP:</u> Extraperitoneal approach. Potent low and intermediate risk patients underwent a nerve-sparing procedure. <u>RALP:</u> Using an extraperitoneal approach. Potent low and intermediate risk patients underwent a nerve sparing procedure.
Rosenberg et al. 2012 <sup>76</sup>	Cohort study of men treated for intermediate risk adenocarcinoma of the prostate at one site in the United States. <u>Enrollment Period:</u> Patients were treated between 1997 and 2007.	Men were included in the study if they were treated with either BT plus EBRT or BT plus ADT; had an intermediate risk adenocarcinoma of the prostate; a Gleason score of ≤7 and PSA <20 ng/mL, or Gleason score of 7; or a Gleason score of 6 and PSA >10.	Men with low risk prostate cancer and those treated with BT alone were excluded.	<u>BT plus EBRT:</u> Not described. <u>BT plus ADT:</u> Not described.

Study	Design and Study Enrollment Period	Patient Inclusion Criteria	Patient Exclusion Criteria	Treatment
Sheets et al. 2012 <sup>58</sup>	This was a U.S. population-based study using Surveillance, Epidemiology, and End Results- (SEER) Medicare-linked data from 2000 to 2009 for patients with nonmetastatic prostate cancer. <u>Enrollment Period:</u> Patients received a diagnosis of prostate cancer between 2000 and 2007.	Men with a diagnosis of prostate cancer, no additional cancers, no metastatic disease, no disease diagnosis at autopsy, with the month and year of their prostate cancer diagnosis recorded, and at least one year of claims data before their diagnosis were included.	Men enrolled in a health maintenance organization within one year of diagnosis or not enrolled in Medicare Part A and Part B for the study duration were excluded. Patients who received combination therapy of radiation and either brachytherapy or prostatectomy were also excluded.	<u>IMRT</u> : 50% of patients had concurrent ADT. <u>3D-CRT</u> : 50% of patients had concurrent ADT. <u>Proton Therapy</u> : 31% of patients had concurrent ADT.
Shen et al. 2012 <sup>84</sup>	U.S. population based study of a cohort of patients with high-risk prostate cancer from the SEER database. <u>Enrollment Period:</u> Patients were diagnosed between 1998 and 2002.	Men who were diagnosed with T1 to T3N0M0 prostate adenocarcinoma, received nonsurgical treatment with BT alone, BT plus EBRT, or EBRT alone, and had a Gleason score of 4 or 5 if only a single pattern was reported or a combined Gleason score of 8 to 10.	Patients with a surgery other than biopsy were excluded.	<u>BT</u> : Not described. <u>BT plus EBRT</u> : Not described. <u>EBRT</u> : Not described.
Zelevsky et al. 2012 <sup>89</sup>	Cohort study of patients undergoing RP for clinically localized prostate cancer at one institution in the United States. <u>Enrollment Period:</u> Patients were treated between 1998 and 2009.	Men who were diagnosed with T1 to T3a higher.	NR	<u>BT</u> : Not described. <u>BT plus IMRT</u> : Not described.
Abdollah et al. 2011 <sup>72</sup>	U.S. population based cohort study using the SEER database. <u>Enrollment Period:</u> Patients were diagnosed between 1992 and 2005.	Men ≥65 years with nonmetastatic prostate cancer and both Part A and Part B Medicare claims available and not enrolled in a health maintenance organization were included.	Patients with prostate cancer diagnosed at autopsy or on death certificate only, or if their original or current reason for Medicare entitlement was listed as disability or a Medicare status code including disability were excluded.	<u>RP</u> : Not described. <u>Observation</u> : Not described.
Bekelman et al. 2011 <sup>81</sup>	A U.S. observational cohort study based on the SEER database. <u>Enrollment Period:</u> Men were diagnosed between 2002 and 2004.	Men ≥65 years of age with non-metastatic prostate cancer diagnosed between 2002 and 2004 with followup through 2006 in the Medicare database.	NR	<u>IMRT</u> : Not described. <u>3D-CRT</u> : Not described.



Study	Design and Study Enrollment Period	Patient Inclusion Criteria	Patient Exclusion Criteria	Treatment
Kim et al. 2011 <sup>60</sup>	A U.S. observational cohort study using Medicare claims data linked to the SEER database. <u>Enrollment Period:</u> Men were diagnosed between 1992 and 2005.	Men ≥65 years of age with stage T1 or T2 prostate cancer diagnosed between 1992 and 2005, treated either with radiation therapy or conservative management (no surgery, radiation therapy, or hormone therapy for at least a year after prostate cancer diagnosis).	NR	<u>Radiation therapy, including EBRT (subcategorized into 3D CRT, IMRT, and proton beam therapy), BT, or a combination (EBRT plus BT):</u> The protocols were not described. <u>Conservative management:</u> See description under patient inclusion criteria.
Masterson et al. 2011 <sup>69</sup>	A retrospective review of a cohort of 1026 patients treated by one surgeon with RRP or RALP. <u>Enrollment Period:</u> Men were treated between 1999 and 2010.	Men with clinically localized prostate cancer treated by a single surgeon from April 1999 through October 2010 with RP.	Patients treated with neoadjuvant or adjunctive therapy with androgen deprivation, radiation, or chemotherapy were excluded. Patients undergoing radical perineal, open salvage, and pure laparoscopic RP without robot assistance were excluded.	<u>RRP:</u> Not described <u>RALP:</u> Not described
Rice et al. 2011 <sup>36</sup>	A cohort of men diagnosed with prostate cancer between 1989 and 2009 were identified from the Center for Prostate Disease Research database.	A cohort of men ≥70 years of age diagnosed with prostate cancer between 1989 and 2009 were identified from the Center for Prostate Disease Research database. The men met D'Amico criteria for low risk disease and were treated with RP, EBRT or WW (with or without secondary treatment). 770 men were enrolled.	Patients were excluded if any of the risk stratification data were missing or if there was less than 6 months followup since the primary treatment.	<u>RP:</u> Not described. <u>WW with or without secondary treatment):</u> Once patients progressed to intermediate risk (≥T2b, PSA >10, Gleason score ≥7) they were counseled about secondary treatment.

Study	Design and Study Enrollment Period	Patient Inclusion Criteria	Patient Exclusion Criteria	Treatment
Williams et al. 2011 <sup>57</sup>	A U.S. population-based study patients with localized prostate cancer using the SEER database. <u>Enrollment Period:</u> Men were diagnosed between 2001 and 2005.	Men ≥65 diagnosed with prostate cancer between 2001 and 2005. Prostate cancer was their only cancer diagnosis.	Men enrolled in health maintenance organizations, those not enrolled in Medicare part A and B at diagnosis, patients undergoing combined therapy for prostate cancer or salvage cryotherapy, those with clinical stage T4 disease, distant metastasis or with insufficient followup, and those treated >9 months after diagnosis were excluded.	<u>Cryotherapy:</u> Not described. <u>BT:</u> Not described.
Barocas et al. 2010 <sup>64</sup>	Cohort study of patients undergoing RP for clinically localized prostate cancer at one institution in the United States. <u>Enrollment Period:</u> Patients were treated between June 2003 and January 2008.	Men undergoing RP for clinically localized prostate cancer.	Patients with prior hormonal therapy, radiation therapy, patients with positive lymph nodes, and those missing followup data were excluded.	<u>RRP:</u> Performed in the anatomic fashion described by Walsh and Partin with modifications based on individual surgeon experience. <u>RALRP:</u> Performed by standard techniques with small modifications on 1 to 3 da Vinci surgical robots.
Cooperberg et al. 2010 <sup>99</sup>	Data was abstracted from the cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE), a national disease registry that accrues men with biopsy-proven prostate adenocarcinoma who receive treatment at any of the 40 (primarily community-based) urology practices across the United States.	Men with prostate adenocarcinoma	NR	<u>RP:</u> Not described. <u>EBRT:</u> Not described. <u>ADT:</u> Not described.
Dosoretz et al. 2010 <sup>82</sup>	Retrospective review of medical records of men treated with brachytherapy for localized prostate cancer at 20 sites within the 21 <sup>st</sup> Century Oncology Consortium in the United States. <u>Enrollment Period:</u> Patients received treatment from May 1991–September 2005. Followup ended January 2007.	Men with localized prostate cancer treated with ultrasound guided BT using iodine 125 or palladium 103 sources were enrolled.	Patients were excluded if they received supplemental external-beam radiation nor had <2 years of followup.	<u>BT:</u> Using iodine 125 or palladium 103. <u>BT plus ADT:</u> Using iodine 125 or palladium 103.

Study	Design and Study Enrollment Period	Patient Inclusion Criteria	Patient Exclusion Criteria	Treatment
Hadley et al. 2010 <sup>73</sup>	A U.S. population based cohort study using the SEER database. <u>Enrollment Period:</u> Patients were diagnosed between 1995 and 2003.	Men aged 66–74 years with newly diagnosed and previously untreated prostate cancer and whose tumor state was T1 or T2	Patients with unusual histology, identified as having cancer through a death certificate or autopsy, not from a SEER registry, month of diagnosis or date of death unknown, aged 65 years and no data for previous year, incomplete Medicare Part A and Part B data because of managed care enrollment or only Part A enrollment for 1 year before or after diagnosis, distant stage or not clinical stage T1 or T2 disease, and treatment with chemotherapy, radiation therapy, or hormone therapy but without surgery.	<u>RP:</u> Within 6 months of diagnosis from SEER surgery codes and International Classification of Diseases, Ninth Edition (ICD-9), and Current Procedural Terminology, Fourth Edition (CPT-4), codes from the Medicare claims. <u>Observation:</u> Authors described observation as conservative management in which men did not receive any treatment which was defined as no radiation, surgery, hormonal treatment, or chemotherapy within 6 months of diagnosis
Magheli et al. 2010 <sup>56</sup>	Retrospective matched comparison study of men with prostatic adenocarcinoma treated with RRP or LRP or RALRP. <u>Enrollment Period:</u> Patients were treated between June 2000 and January 2008.	Men with clinically localized prostate cancer	NR	<u>RRP:</u> Not described. <u>LRP:</u> Not described. <u>RALRP:</u> Not described.
Malcolm et al. 2009 <sup>71</sup>	Cohort study of patients treated with open radical prostatectomy, robot assisted laparoscopic prostatectomy, brachytherapy, or cryotherapy. Patients completed a health-related QOL questionnaire before treatment and at 3, 6, 12, 18, 24, 30, and 36 months post-treatment. <u>Enrollment Period:</u> February 2000–December 2008	Men undergoing operative treatment for localized prostate cancer at one institution were invited to participate. Those who completed the baseline and at least one followup questionnaire were included.	Patients receiving multimodal treatments were excluded.	<u>RRP:</u> 132 men underwent retropubic and 3 men underwent perineal. Nerve sparing techniques were used where appropriate. <u>RALRP:</u> Nerve sparing techniques were used where appropriate. <u>BT:</u> Modified peripheral loading low dose rate technique was used with permanent palladium seeds delivering an average dose of 125 Gy. <u>Cryotherapy:</u> Third generation cryotherapy delivery system.

Study	Design and Study Enrollment Period	Patient Inclusion Criteria	Patient Exclusion Criteria	Treatment
Wong et al. 2009 <sup>88</sup>	Patients treated with radiotherapy at a clinic in the United States <u>Enrollment Period:</u> May 1993-July 2004	Men diagnosed localized prostate cancer (T1c–T3, N0, M0)	NR	<u>3D-CRT</u> : Adjuvant ADT was administered to 28% who received 3D-CRT or IMRT. <u>IMRT</u> : Adjuvant ADT was administered to 28% who received 3D-CRT or IMRT. <u>BT</u> : Not described. <u>EBRT plus BT</u> : Not described.
Krambeck et al. 2008 <sup>65</sup>	Retrospective matched comparison study of men with prostatic adenocarcinoma treated with RRP or RALRP in the United States. <u>Enrollment Period:</u> August 2002–December 2005	Men with clinically localized prostate cancer treated between August 2002 and December 2005 at one institution in the United States were enrolled.	NR	<u>RRP</u> : Not described. <u>RALRP</u> : Not described.
Lu-Yao et al. 2008 <sup>78</sup>	A U.S population-based cohort study of men ≥66 receiving Medicare who did not receive definitive local therapy for clinical stage t1 to T2 prostate cancer using the SEER database. <u>Enrollment Period:</u> Patients were diagnosed between 1992 and 2002.	Men ≥66 years of age who were SEER residents and diagnosed with T1 to T2 cancer in 1992 to 2002.	Men who died or received definitive local therapy within 180 days of diagnosis and those without both Medicare Part A and Part B as their primary healthcare insurance coverage during the study period were excluded. Patients with missing data, unknown cancer, or initiation of ADT before the cancer diagnosis were also excluded.	<u>ADT</u> : Luteinizing hormone-releasing hormone agonists and orchiectomy were combined. <u>Observation</u> : Authors reported conservative management and started that these patients did not have surgery, radiation or ADT.
Sanda et al. 2008 <sup>85</sup>	Cohort study of men with clinically localized prostate cancer treated at one site in the United States. <u>Enrollment Period:</u> Patients were treated between March 2003 and March 2006.	Men with previously untreated stage T1 and T2 prostate cancer.	NR	<u>RP</u> : The procedure was either RRP or LRP or RALRP <u>EBRT</u> : The procedure was 3D-CRT or IMRT. <u>BT</u> : Not described.
Schroeck et al. 2008 <sup>54</sup>	Cohort study of men with clinically localized prostate cancer treated at one site in the United States. <u>Enrollment Period:</u> Patients were treated between August 2003 and January 2007.	Consecutive men with clinically localized prostate cancer treated between August 2003 and January 2007 with either RRP or RALRP.	Patients who had a RALRP converted to an open procedure were excluded.	<u>RRP</u> : Not described. <u>RALRP</u> : Procedure was done using the Vattikuti institute technique and the three-arm da Vinci surgical system.

Study	Design and Study Enrollment Period	Patient Inclusion Criteria	Patient Exclusion Criteria	Treatment
Sumitomo et al. 2008 <sup>63</sup>	Cohort study of men with clinically localized prostate cancer treated at seven sites in Japan. <u>Enrollment Period:</u> Patients were treated between April 1999 and March 2006.	Men with prostate cancer with PSA $\leq$ 30 ng/mL and a followup period of 12 months or more after high-intensity focused ultrasound (HIFU) treatment.	Patients who received ADT before HIFU for longer than 6 months. T stage was based on digital rectal examination, needle biopsy and transrectal ultrasound findings.	<u>ADT:</u> With a luteinizing hormone-releasing hormone analogue with or without an antiandrogen. <u>HIFU:</u> Not described.
Albertsen et al. 2007 <sup>42</sup>	Retrospective, U.S. population based study using data from the Connecticut Tumor Registry. <u>Enrollment Period:</u> Patients were diagnosed with prostate cancer from 1990 to 1992.	Men diagnosed in a community setting with localized prostate cancer, treated with surgery, radiation, or observation, residing in Connecticut, with age at diagnosis $\leq$ 75 years.	Males with advanced prostate cancer or an initial PSA $\geq$ 50 ng/mL were excluded.	<u>Surgery:</u> Not described. <u>EBRT:</u> Not described. <u>Observation:</u> Not described.
D'Amico et al. 2007 <sup>87</sup>	Men with clinically localized prostate cancer treated at four medical centers in the United States.	Men diagnosed with T1–T3 prostate cancer.	Men with radiographic evidence of pelvic lymph node or distant metastatic disease. Men who received neoadjuvant, concurrent, or adjuvant ADT were also excluded, as men who received postoperative adjuvant radiotherapy.	<u>RRP:</u> Not described. <u>3D-CRT:</u> A dose of 45 Gy with continued treatment to the prostate to total prescription dose of 70.2 Gy in 1.8 Gy fractions.

**Abbreviations:** ADT=androgen deprivation therapy, BT=brachytherapy, EBRT: external beam radiation therapy, HT=hormone therapy, IG-EBRT=image guided external beam radiation therapy, IGRT= image guided radiation therapy, IMRT=intensity modulated radiation therapy, NOS=not otherwise specified, NR=not reported, RALRP=robot assisted laparoscopic radical prostatectomy, RP=radical prostatectomy, RRP=radical retropubic prostatectomy, WW=watchful waiting, 3D-CRT=three dimensional conformal radiation therapy

## Appendix E. Baseline Demographic and Tumor Characteristics

**Table E-1. Baseline demographic and tumor characteristics (randomized controlled trials)**

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
Porpiglia et al. 2013 <sup>45</sup>	RARP: 60 patients	Mean: 63.9 (6.7) years	NR	BMI mean: 26.2 (2.5) American Society of Anesthesiologist's score mean: 2.0 (0.5)	PSA ng/mL mean: 8.3 (6.5) <u>Gleason score at biopsy no. (%)</u> : 2 through 6: 35 (58.3%) 7: 20 (33.3%) 8 through 10: 5 (8.4%) <u>Prostate volume at transrectal ultrasound, ml mean: 36.2 (12.6)</u>
	LRP: 60 patients	Mean: 64.7 (5.9) years	NR	BMI mean: 26.8 (2.9) American Society of Anesthesiologist's score mean: 2.1 (0.5)	PSA ng/mL mean: 6.9 (4.2) <u>Gleason score at biopsy no. (%)</u> : 2 through 6: 25 (41.7%) 7: 32 (53.3%) 8 through 10: 3 (5%) <u>Prostate volume at transrectal ultrasound, mL mean: 37.7 (14.1)</u>

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
Wilt et al. 2012 <sup>25</sup> Same study as Wilt et al. 2009 <sup>24</sup> PIVOT	Observation: 367 patients	Mean 66.8±5.6 years Age ≥65 years: 64.3%	Black: 33% White: 60% Other: 7.1	MI (11.7) CHF (2.2) PVD (5.5) [CVD] (4.4) Stroke (4.9) Diabetes (16.1) COPD (6.8)	PSA (ng/mL; mean [SD]): 10.2 (7.9), Median: 7.7 <u>Clinical stage (% of patients):</u> 1A: 3.0 1B: 2.5 1C: 49.9 2A: 23.2 2B: 12.0 2C: 9.0 <u>Gleason grade (% of patients):</u> Grade 2–4: 21.5 Grade 5–6: 53.1 Grade 7: 18.9 Grade 8–10: 5.6 <u>Mean Gleason grade (SD):</u> 5.5 (1.6) <u>Histologic grade (% of patients):</u> Well differentiated: 24.2 Moderately well differentiated: 64.2 Poorly differentiated: 6.1 Unknown: 5.5 <u>Tumor risk category (based on PSA, Gleason grade and tumor stage) [% of patients]:</u> Low: 44.0 Medium: 34.9 High: 21.1

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
Wilt et al. 2012 <sup>25</sup> Same study as Wilt et al. 2009 <sup>24</sup> PIVOT (continued)	RP: 364 patients	Mean: 67.0±5.2 years Age ≥65 years: 66.5%	Black: 30.5% White: 63.7% Other: 5.9%	MI (10.2) CHF (0.8) PVD (4.1) CVD (1.9) Stroke (3.9) Diabetes (15.4) COPD (10.2)	<u>PSA (ng/mL; mean [SD]):</u> 10.1 (7.4), Median 7.9 <u>Clinical stage (% of patients):</u> 1A: 1.1 1B: 1.4 1C: 50.8 2A: 26.4 2B: 12.9 2C: 6.6 <u>Gleason grade (% of patients):</u> Grade 2–4: 22.9 Grade 5–6: 48.7 Grade 7: 21.5 Grade 8–10: 6.7 <u>Mean Gleason grade (SD):</u> 5.6 (1.5) <u>Histologic grade (% of patients):</u> Well differentiated: 25.1 Moderately well differentiated: 60.5 Poorly differentiated: 8.0 Unknown: 6.4 <u>Tumor risk category (based on PSA, Gleason grade and tumor stage) [% of patients]:</u> Low: 42.6 Medium: 37.2 High: 20.2



Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
Bill-Axelsson et al. 2013 <sup>48</sup> Same study as Bill-Axelsson et al. 2011 <sup>33</sup> , Johansson et al. 2011 <sup>51</sup> , Holmberg et al. 2012 <sup>34</sup> , and Bill-Axelsson et al. 2008 <sup>15</sup> SPCG-4 trial	RP: 347 patients	Mean: 64.6±5.1 years Age <65 years: 60±3.5 Age ≥65 years: 68.4±2.5	NR	NR	<u>Mean PSA, ng/ml:</u> 13.5 <u>Tumor stage, No (%):</u> T1b: 33 (9.5) T1c: 43 (12.4) T2: 270 (77.8) Unknown: 1 (0.3) <u>WHO grade, No (%):</u> Grade 1: 168 (48.4) Grade 2: 178 (51.3) Unknown: 1 (0.3) <u>Gleason score, at biopsy, No (%):</u> Score 2-4: 45 (13.0) Score 5-6: 165 (47.6) Score 7: 77 (22.2) Score 8-10: 14 (4.0) Unknown: 46 (13.3) <u>PSA level, No (%):</u> Level <4 mg/mL: 43 (12.4) Level 4-6.9 ng/mL: 60 (17.3) Level 7-10: 68 (19.6) Level 10.1-20: 100 (28.8) Level ≥20: 69 (19.9) Unknown: 7 (2.0) <u>Positive margins in RPS, No (%):</u> Margin 0 mm: 184 (64.8) Margin 1-9 mm: 50 (17.6) Margin 10-19 mm: 25 (8.8) Margin ≥20 mm: 24 (8.5) Missing data: 1 (0.4) <u>Extracapsular extension in RPS, No (%):</u> Extension 0 mm: 151 (53.2) Extension 1-9 mm: 46 (16.2) Extension 10-19 mm: 38 (13.4) Extension ≥20 mm: 48 (16.9) Missing data: 1 (0.4) <u>Gleason score of RPS, No (%):</u> Score 2-6: 88 (31.0) Score 7; 3+4: 87 (30.6) Score 7; 4+3: 70 (24.6) Score 8-10: 38 (13.4) Missing data: 1 (0.4)

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
Bill-Axelsson et al. 2013 <sup>48</sup> Same study as Bill-Axelsson et al. 2011 <sup>33</sup> , Johansson et al. 2011 <sup>51</sup> , Holmberg et al. 2012 <sup>34</sup> , and Bill-Axelsson et al. 2008 <sup>15</sup> Scandinavian Prostate Cancer Group-4 (SPCG-4) Trial (continued)	WW 348 patients	Mean: 64.5±5.0 years Age <65 years: 60.2±3.4 Age ≥65 years: 68.4±2.4	NR	NR	<u>Mean PSA, ng/ml:</u> 12.3 <u>Tumor stage, No (%):</u> T1b: 50 (14.4) T1c: 38 (10.9) T2: 259 (74.4) Unknown: 1 (0.3) <u>WHO grade, No (%):</u> Grade 1: 166 (47.7) Grade 2: 182 (52.3) Unknown: 0 (0.0) <u>Gleason score, at biopsy, No (%):</u> Score 2-4: 46 (13.2) Score 5-6: 166 (47.7) Score 7: 82 (23.6) Score 8-10: 21 (6.0) Unknown: 33 (9.5) <u>PSA level, No (%):</u> Level <4 mg/mL: 63 (18.1) Level 4-6.9 ng/mL: 60 (17.2) Level 7-10: 67 (19.3) Level 10.1-20: 95 (27.3) Level ≥20: 60 (17.2) Unknown: 3 (0.9)

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
Jones et al. 2011 <sup>43</sup>	EBRT: 992 patients	Median: 71 years (range: 47–88)	White: 756 (76) Black: 197 (20) Hispanic: 26 (3) Other or unknown: 13 (1)	Present: 712 (72) Absent: 275 (28) Unknown: 5 (<1)	<u>PSA [number (%)]:</u> Level <4 ng/mL: 100 (10) Level 4–20 ng/mL: 892 (90) <u>Tumor stage [number (%)]:</u> T1: 476 (48) T2: 516 (52) <u>Nodal stage [number (%)]:</u> NX: 954 (96) NO: 38 (4) <u>Gleason score [number (%)]:</u> Score 2–6: 592 (60) Score 7: 286 (29) Score 8–10: 87 (9) Unknown: 27 (3) <u>Differentiation [number (%)]:</u> Well differentiated: 150 (15) Moderately differentiated: 620 (62) Poorly differentiated or undifferentiated: 222 (22) <u>Risk subgroup [number (%)]:</u> Low risk: 334 (34) Intermediate risk: 544 (55) High risk: 114 (11)

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
Jones et al. 2011 <sup>43</sup> (continued)	EBRT plus ADT: 987 patients	Median: 70 years (range: 47–91)	White: 745 (75) Black: 198 (20) Hispanic: 27 (3) Other or unknown: 17 (2)	Present: 742 (75) Absent: 245 (25) Unknown: 5 (<1)	<u>PSA [number (%)]:</u> Level <4 ng/mL: 109 (11) Level 4–20 ng/mL: 878 (89) <u>Tumor stage [number (%)]:</u> T1: 488 (49) T2: 499 (51) <u>Nodal stage [number (%)]:</u> NX: 944 (96) NO: 43 (4) <u>Gleason score [number (%)]:</u> Score 2–6: 623 (63) Score 7: 252 (26) Score 8–10: 93 (9) Unknown: 19 (2) <u>Differentiation [number (%)]:</u> Well differentiated: 135 (14) Moderately differentiated: 625 (63) Poorly differentiated or undifferentiated: 227 (23) <u>Risk subgroup [number (%)]:</u> Low risk: 351 (36) Intermediate risk: 524 (53) High risk: 112 (11)

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
Donnelly et al. 2010 <sup>47</sup> Same study as Robinson et al. 2009 <sup>52</sup>	EBRT: 122 patients	Median: 68.6 years (range: 53.2–78.6)	NR	NR	<u>PSA, median, interquartile range (IQR):</u> 9.0 (6.6–12.5) <u>PSA, range:</u> 2.5–23.3 <u>Biopsy tumor classification [number (%)]:</u> T2a: 20 (16.4) T2b: 23 (18.9) T2c: 57 (46.7) T3a: 18 (14.8) T3b, c: 4 (3.3) <u>Gleason score [number (%)]:</u> Score 4–5: 2 (1.6) Score 6: 42 (34.4) Score 7: 65 (53.3 ) Score 8–10: 13 (10.7) <u>Risk category [number (%)]:</u> Low risk: 10 (8.2) Intermediate risk: 28 (23) High risk: 84 (68.8)
Donnelly et al. 2010 <sup>47</sup> Same study as Robinson et al. 2009 <sup>52</sup> (continued)	Cryotherapy: 122 patients	Median: 69.4 years (range: 52.8–81.4)	NR	NR	<u>PSA, median, IQR:</u> 8.1 (5.7–10.9) <u>PSA, range:</u> 0.7–19.9 <u>Biopsy tumor classification [number (%)]:</u> T2a: 22 (18) T2b: 28 (23) T2c: 49 (40.2) T3a: 17 (13.9) T3b, c: 6 (4) <u>Gleason score [number (%)]:</u> Score 4–5: 5 (4.1) Score 6: 37 (30.3) Score 7: 69 (56.6 ) Score 8–10: 11 (9) <u>Risk category [number (%)]:</u> Low risk: 10 (8.2) Intermediate risk: 36 (29.5) High risk: 76 (62.3)

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
Giberti et al. 2009 <sup>44</sup>	RRP: 100 patients	Mean: 65.2 years (range: 57–74)	Caucasian: 100 (100)	NR	<u>Mean PSA (ng/mL):</u> 7.8 (3.5–10) <u>Mean Gleason score:</u> 5.9 <u>Prostate volume (mL):</u> 43.9 (19–56) <u>Tumor stage:</u> T1c patients: 64 T2a patients: 36
	Brachytherapy: 100 patients	Mean: 65.6 years (range: 56–74)	Caucasian: 100 (100)	NR	<u>Mean PSA (ng/mL):</u> 7.5 (2.9–9.3) <u>Mean Gleason score:</u> 5.7 <u>Prostate volume (mL):</u> 41.7 (21–60) <u>Tumor stage:</u> T1c patients: 59 T2a patients: 41

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
D'Amico et al. 2008 <sup>49</sup> Same study as D'Amico et al. 2008 <sup>35</sup> , Nguyen et al. 2010 <sup>53</sup>	EBRT: 104 patients	None or minimal comorbidity: 78 patients Median: 73 (Range: 51–81) ≤60: 4 (5%) >60: 75 (95%)	NR	<u>ACE-27 comorbidity score:</u> Score 0 (none): 68 (86) Score 1 (minimal): 11 (14) Score 2 (Moderate): not applicable Score 3 (Severe): not applicable	<u>PSA, median (Range), ng/mL:</u> 11.2 (3.1–40.0) <u>Gleason score, [number (%)]:</u> Score 5–6: 21 (27) Score 7: 50 (63) Score 8–10: 8 (10) <u>Tumor category, [number (%)]:</u> T1b: 1 (1) T1c: 33 (42) T2a: 20 (25) T2b: 25 (32)
		Moderate or severe comorbidity: 25 patients Median: 74 (Range: 61–81) ≤60: 0 (0%) >60: 25 (100%)	NR	<u>ACE-27 comorbidity score:</u> Score 0 (none): not applicable Score 1 (minimal): not applicable Score 2 (Moderate): 22 (88) Score 3 (Severe): 3 (12)	<u>PSA, median (Range), ng/mL:</u> 10.8 (0.9–24.8) <u>Gleason score, [number (%)]:</u> Score 5–6: 6 (24) Score 7: 11 (44) Score 8–10: 8 (32) <u>Tumor category, [number (%)]:</u> T1b: 1 (4) T1c: 8 (32) T2a: 6 (24) T2b: 10 (40)

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
D'Amico et al. 2008 <sup>35</sup> (continued)	EBRT plus ADT: 102 patients	None or minimal comorbidity: 78 patients Median: 72 (Range: 49–82) ≤60: 2 (3%) >60: 76 (97%)	NR	<u>ACE-27 comorbidity score:</u> Score 0 (None): 67 (86) Score 1 (Minimal): 11 (14) Score 2 (Moderate): not applicable Score 3 (Severe): not applicable	<u>PSA, median (Range), ng/mL:</u> 11.5 (3.1–36.0) <u>Gleason score, [number (%)]:</u> Score 5–6: 26 (33) Score 7: 42 (54) Score 8–10: 10 (13) <u>Tumor category, [number (%)]:</u> T1b: 1 (1) T1c: 46 (59) T2a: 13 (17) T2b: 18 (23)
		Moderate or severe comorbidity: 24 patients Median: 72 (Range: 61–79) ≤60: 0 (0%) >60: 24 (100%)	NR	<u>ACE-27 comorbidity score:</u> Score 0 (none): not applicable Score 1 (minimal): not applicable Score 2 (Moderate): 21 (88) Score 3 (Severe): 3 (12)	<u>PSA, median (Range), ng/mL:</u> 10.0 (1.3–21.1) <u>Gleason score, [number (%)]:</u> Score 5–6: 4 (17) Score 7: 16 (67) Score 8–10: 4 (17) <u>Tumor category, [number (%)]:</u> T1b: 1 (4) T1c: 8 (33) T2a: 7 (29) T2b: 8 (33)



Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
Martis et al. 2007 <sup>46</sup>	RPP: 100 patients	64.2±6.5 years	NR	NR	<u>Mean PSA (ng/mL):</u> 7.9 (3.5–11.6) <u>Mean Gleason score:</u> 5.5 (4–7) <u>Clinical stage [number (%)]:</u> T1a: 20 (20) T2a: 60 (60) T2b: 20 (20)
	RRP: 100 patients	65.4±7.2 years	NR	NR	<u>Mean PSA (ng/mL):</u> 9.2 (4.7–12.3) <u>Mean Gleason score:</u> 5.5 (4–7) <u>Clinical stage [number (%)]:</u> T1a: 24 (24) T2a: 58 (58) T2b: 18 (18)

**Abbreviations:** ACE=Adult Comorbidity Evaluation; ADT=androgen-deprivation therapy; BMI=body mass index; CHF=congestive heart failure; CVD=cerebral vascular disease; COPD=chronic obstructive pulmonary disease; EBRT=external beam radiation therapy; IQR=interquartile range; LRP=laparoscopic radical prostatectomy; MI=myocardial infarction; NR=not reported; PIVOT=Prostate Intervention Versus Observation Trial; PSA=prostate-specific antigen; PVD=peripheral vascular disease; RARP=robot-assisted radical prostatectomy; RP=radical prostatectomy; RPP=radical perineal prostatectomy RPS=radical prostatectomy specimen; RRP=radical retropubic prostatectomy; SPCG-4=Scandinavian Prostate Cancer Group-4; WHO=World Health Organization; WW=watchful waiting.

**Table E-2. Baseline demographic and tumor characteristics (nonrandomized comparative studies)**

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
Alemozaffar et al. 2014 <sup>68</sup>	<u>RALP</u> : 282 patients <u>Open RRP</u> : 621 patients	Mean age at diagnosis <u>RALP</u> : 67.2 years <u>RRP</u> : 65.4 years	NR	Presence of at least one of the following: MI, coronary artery bypass or coronary angioplasty, confirmed angina, stroke, Parkinson disease, emphysema or chronic bronchitis, or diabetes <u>RALP</u> : 18.8% <u>Open RRP</u> : 16.8%  Mean BMI kg/m2 <u>RALP</u> : 26.4 kg/m2 <u>Open RRP</u> : 26.0	<u>T Stage</u> : <u>RALP</u> : T1: 79.4% T2: 20.6% T3: 0% <u>Open RRP</u> : T1: 67.0% T2: 32.8% T3: 0.2% <u>Median PSA</u> : <u>RALP</u> : 5.0 ng/mL <u>Open RRP</u> : 5.6 ng/mL <u>Biopsy Gleason score</u> <u>RALP</u> : <6: 0.7% 6: 52.3% 7: 37.0% ≥8: 10.0% <u>Open RRP</u> : <6: 3.9% 6: 58.8% 7: 28.9% ≥8: 8.4% <u>Modified D'Amico risk score</u> <u>RALP</u> : Low: 48.1% Medium: 42.1% High: 9.8% <u>Open RRP</u> : Low: 55.9% Medium: 32.4% High: 11.7% <u>Perineural invasion</u> <u>RALP</u> : 54.7% <u>Open RRP</u> : 51.1%

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
Mukherjee et al. 2014 <sup>37</sup>	<u>RP</u> : 5,805 patients <u>EBRT</u> : 2,183 patients <u>BT</u> : 2,936 patients	Median age at diagnosis (range) RP 60 years (37 to 87) EBRT: 69 years (40 to 87) BT: 67 years (41 to 88)	<u>RP</u> : Black: 9.9% White: 86.4% Other: 2.7% Unknown: 1% <u>EBRT</u> : Black: 28.3% White: 71.0% Other: 0.7% Unknown: 0% <u>BT</u> : Black: 15.5% White: 82.2% Other: 2.2% Unknown: 0%	NR for total population	<u>Median (range) PSA ng/mL</u> <u>RP</u> : 5.6 (0.03 to 228.5) <u>EBRT</u> : 9.1 (0.37 to 692.9) <u>BT</u> : 6.0 (0.18 to 82.91) <u>Gleason</u> : <u>RP</u> : ≤6: 60.4% 7: 30.8% ≥8: 7.7% Unknown: 1.1% <u>EBRT</u> : ≤6: 47.3% 7: 35.3% ≥8: 16.8% Unknown: 0.7% <u>BT</u> : ≤6: 58.5% 7: 36.4% ≥8: 5.0% Unknown: 0%

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
Mukherjee et al. 2014 <sup>37</sup> (continued)	(continued from above)	(continued from above)	(continued from above)	(continued from above)	<p><u>AJCC Clinical Stage:</u>  <u>RP:</u>  T1-T2a: 83.5%  T2b-T2c: 7.3%  T3: 1.4%  Unknown: 7.8%  <u>EBRT:</u>  T1-T2a: 74.5%  T2b-T2c: 17.3%  T3: 8.2%  Unknown: 0%  <u>BT:</u>  T1-T2a: 97.8%  T2b-T2c: 2.0%  T3: 0.1%  Unknown: 0.1%  <u>Risk category:</u>  <u>RP:</u>  Low: 46.9%  Intermediate: 27.6%  High: 17.5%  Unknown: 7.9%  <u>EBRT:</u>  Low: 26.3%  Intermediate: 26.0%  High: 47.1%  Unknown: 0.6%  <u>BT:</u>  Low: 50.7%  Intermediate: 36.5%  High: 12.5%  Unknown: 0.2%</p>

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
DeGroot et al. 2013 <sup>41</sup>	RP: 458 patients (cohort)	Mean age (SD): 62.8 years (61.)	NR	CIRS-G (SD): 4.8 (3.3)	<u>Prostate Specific-Antigen (PSA) %</u> ≤4: 12.5 >4 to ≤10: 57.0 >10 to ≤20: 30.6 <u>Gleason score %</u> 2–4: 23.6 5–6: 53.3 7: 23.1 <u>T category %</u> T1a/b: 5.9 T1c: 37.6 T2a: 37.3 T2b: 19.2
	RP: 36 patients (cases)	Mean age (SD): 62.1 years (5.8)	NR	Average CIRS-G (SD): 3.9 (2.8)	<u>PSA %</u> ≤4: 13.9 >4 to ≤10: 38.9 >10 to ≤20: 47.2 <u>Gleason score %</u> 2–4: 16.7 5–6: 52.8 7: 30.6 <u>T category %</u> T1a/b: 2.8 T1c: 25.0 T2a: 38.9 T2b: 33.3
DeGroot et al. 2013 <sup>41</sup> (continued)	EBRT: 518 patients (cohort)	Mean age (SD): 69.2 years (5.6)	NR	Average CIRS-G (SD): 5.7 (3.7)	<u>PSA %</u> ≤4: 15.8 >4 to ≤10: 43.8 >10 to ≤20: 40.4 <u>Gleason score %</u> 2–4: 28.2 5–6: 48.5 7: 23.4 <u>T category %</u> T1a/b: 9.3 T1c: 20.7 T2a: 32.8 T2b: 37.3

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
	EBRT: 78 patients (cases)	Mean age (SD): 67.7 years (5.7)	NR	Average CIRS-G (SD): 5.1 (4.1)	<u>PSA %</u> ≤4: 10.3 >4 to ≤10: 46.2 >10 to ≤20: 43.6 <u>Gleason score %</u> 2–4: 23.1 5–6: 38.5 7: 23.1 <u>T category %</u> T1a/b: 5.9 T1c: 37.6 T2a: 37.3 T2b: 19.2

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
Ferrer et al. 2013 <sup>91</sup> Same study as Ferrer et al. 2008 <sup>61</sup>	RRP: 193 patients	Mean age (SD): 67.6 years (5.2)	NR	NR	<u>Mean PSA (SD):</u> 7.4 (2.7) <u>Mean Gleason score (SD):</u> 5.8 (0.8) <u>T category %:</u> T1: 74% T2: 25.8% TX: 0% <u>Risk group:</u> Low: 88% Intermediate: 12%
	3D-CRT: 194 patients	Mean age (SD): 67.1 years (5.2)	NR	NR	<u>Mean PSA (SD):</u> 7.0 (2.7) <u>Mean Gleason score (SD):</u> 5.3 (0.8) <u>T category %:</u> T1: 75.1% T2: 24.1% TX: 0.7% <u>Risk group:</u> Low: 87.4% Intermediate: 12.6%
	BT: 317 patients	Mean age (SD): 66.9 years (5.2)	NR	NR	Mean PSA (SD): 6.8 (2.7) Mean Gleason score (SD): 5.1 (0.8) T1: 74.7% T2: 25.1% TX: 0.2% <u>Risk group:</u> Low: 85% Intermediate: 15%

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
Hoffman et al. 2013 <sup>38</sup>	RP: 1,164 patients	Median (IQR): 64 years (59–68)	Non-Hispanic White: 806 (75.9%) Non-Hispanic Black: 170 (11.7%) Hispanic: 188 (12.4%)	Coexisting illnesses: n (%) 0: 513 (42.5) 1: 368 (33.7) 2: 179 (15.2) ≥3: 104 (8.4) Note: self-reported pre-operative health data were gathered post- surgery.	<u>Gleason score n (%)</u> : 2–4: 743 (63.9) 5–7: 216 (18.2) 8–10: 73 (6.5) Unknown: 132 (11.4) <u>PSA n (%)</u> : <4.0 ng/mL: 122 (9.8) 4.0–10.0 ng/mL: 703 (61.0) >10.0 ng/mL: 339 (29.2)
	Radiotherapy: 491 patients	Median (IQR): 69 years (64–71)	Non-Hispanic White: 370 (82.0%) Non-Hispanic Black: 65 (10.4%) Hispanic: 56 (7.7%)	Coexisting illnesses: n (%) 0: 159 (33.3) 1: 160 (33.1) 2: 93 (16.9) ≥3: 79 (16.7) Note: Self-reported pre-operative health data were gathered post- surgery.	<u>Gleason score n (%)</u> : 2–4: 292 (59.3) 5–7: 110 (22.1) 8–10: 46 (9.6) Unknown: 43 (8.9) <u>PSA n (%)</u> : <4.0 ng/mL: 43 (9.4) 4.0–10.0 ng/mL: 252 (55.9) >10.0 ng/mL: 196 (34.7)



Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
Liu et al. 2013 <sup>9</sup>	RP: 1,624 patients	NR	Not white: 296 (18.23%) White: 1,328 (81.77%)	CCI, n (%): 0: 803 (49.45) ≤2: 634 (39.04) >2: 187 (11.51) Hypertension Yes: 1,241 (76.42) No: 383 (23.58) Diabetes Yes: 531 (32.70) No: 1,093 (67.30)	<u>PSA:</u> Low (≤10 ng/mL): 51.79% Median (11–20 ng/mL): 7.76% High (>20 ng/mL): 3.26% Positive: 22.91% Unknown: 14.29% <u>Gleason score risk group:</u> Moderately/well differentiated (Gleason score 2–7): 50.86% Poorly differentiated (Gleason score 8–10): 49.14%
	ADT: 1,624 patients	NR	Not white: 299 (18.41%) White: 1,325 (81.59%)	CCI, n (%): 0: 833 (51.29) ≤2: 609 (37.50) >2: 182 (11.21) Hypertension Yes: 180 (11.08) No: 390 (24.01) Diabetes Yes: 511 (31.47) No: 1,113 (68.53)	<u>PSA:</u> Low (≤10 ng/mL): 51.79% Median (11–20 ng/mL): 7.76% High (>20 ng/mL): 3.26% Positive: 22.91% Unknown: 14.29% <u>Gleason score risk group:</u> Moderately/well differentiated (Gleason score 2–7): 50.12% Poorly differentiated (Gleason score 8–10): 49.88%

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
Marina et al. 2013 <sup>86</sup>	IGRT: 734	Median age (range): 71 (47– 91)	African American, n (%): 91 (13) Caucasian, n (%): 578 (81) Other, n (%): 47 (7)	NR	<u>PSA, mean ng/mL (range):</u> 5.9 (0.1-19.7) <u>PSA by group, n (%):</u> <10: 576 (78) 10–20: 158 (22) <u>Gleason score, n (%):</u> ≤6: 96 (13) 3+4: 443 (61) 4+3: 190 (26) <u>Clinical T stage, n (%):</u> T1: 499 (68) T2a: 145 (20) T2b: 50 (7) T2c: 40 (5) <u>Intermediate risk factors,</u> <u>n (%):</u> 1=Gleason 7: 499 (68) 1=PSA ≥10 ng/mL: 72 (10) 1=T2b–c stage: 21 (3) 2: 132 (18) 3: 10 (1)
Marina et al. 2013 <sup>86</sup> (continued)	BT: 282 patients	Median age (range): 66 (40– 83)	African American, n (%): 30 (11) Caucasian, n (%): 224 (80) Other, n (%): 26 (9)	NR	<u>PSA, mean ng/mL (range):</u> 6.6 (1.4-19.6) <u>PSA by group, n (%):</u> <10: 207 (73) 10–20: 75 (27) <u>Gleason score, n (%):</u> ≤6: 60 (23) 3+4: 126 (48) 4+3: 77 (29) <u>Clinical T stage, n (%):</u> T1: 138 (49) T2a: 65 (23) T2b: 36 (13) T2c: 43 (15) <u>Intermediate risk factors,</u> <u>n (%):</u> 1= Gleason 7: 146 (52) 1= PSA ≥10 ng/mL: 27 (10) 1= T2b–c stage: 25 (9) 2: 74 (26) 3: 10 (4)

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
Nepple et al. 2013 <sup>40</sup>	RP: 4,459 patients	Median: 60 years	African American: 366 (8%)	NR	<u>Median PSA:</u> 6.96 <u>Biopsy Gleason score (n, %):</u> 5–6: 3,316 (74) 7: 976 (22) 8–10: 167 (4) <u>Clinical stage (n, %):</u> T1: 3,480 (78) T2: 951 (21) T3: 28 (0.6) <u>D'Amico risk group (n, %):</u> Low: 2,807 (63) Intermediate: 1,331 (30) High: 321 (7)
Nepple et al. 2013 <sup>40</sup> (continued)	EBRT: 1,261 patients	Median: 68.3 years	African American: 260 (21%)	NR	<u>Median PSA:</u> 11.11 <u>Biopsy Gleason score (n, %):</u> 5–6: 696 (55) 7: 414 (33) 8–10: 151 (12) <u>Clinical stage (n, %):</u> T1: 743 (59) T2: 446 (35) T3: 72 (6) <u>D'Amico risk group (n, %):</u> Low: 707 (73) Intermediate: 248 (26) High: 17 (2)
	BT: 972 patients	Median: 66.8 years	African American: 107 (11%)	NR	<u>Median PSA:</u> 6.66 <u>Biopsy Gleason score (n, %):</u> 5–6: 805 (83) 7: 162 (17) 8–10: 5 (0.5) <u>Clinical stage (n, %):</u> T1: 798 (82) T2: 174 (18) T3: 0 (0) <u>D'Amico risk group (n, %):</u> Low: 707 (73) Intermediate: 248 (26) High: 17 (2)

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
Pierorazio et al. 2013 <sup>70</sup>	RRP: 743 patients	Median (range): 60 (38-74)	African American: 84 (11.5) Caucasian: 609 (83.5) Other: 3 (0.4)	NR	<u>High-risk features, n (%):</u> 1: 659 (91.0) 2: 62 (8.6) 3: 3 (0.4) <u>PSA (ng/mL), median (range):</u> 6.65 (0.2–97) <u>Biopsy Gleason score n, (%):</u> 5–6: 141 (19.1) 7: 301 (40.7) 8: 191 (25.8) 9–10: 107 (14.5) <u>Clinical stage (n, %):</u> T1c or T2a: 547 (75.0) T2b: 105 (14.4) T2c or T3a: 77 (10.6)
	RALRP: 105 patients	Median (range): 62 (41-76)	African American: 12 (12.4) Caucasian: 86 (88.7) Other: 7 (7.2)	NR	<u>High-risk features, n (%):</u> 1: 93 (98.9) 2: 1 (1.1) 3: 0 (0.0) <u>PSA (ng/mL), median (range):</u> 6.4 (2.4–45) <u>Biopsy Gleason score n, (%):</u> 5–6: 31 (29.8) 7: 37 (35.6) 8: 23 (22.1) 9–10: 13 (12.5) <u>Clinical stage (n, %):</u> T1c or T2a: 75 (77.3) T2b: 13 (13.4) T2c or T3a: 9 (9.3)

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
Pierorazio et al. 2013 <sup>70</sup> (continued)	LRP: 65 patients	Median (range): 60 (43–74)	African American: 12 (19.4) Caucasian: 49 (79) Other: 4 (6.5)	NR	<u>High-risk features, n (%)</u> : 1: 53 (88.3) 2: 6 (10) 3: 1 (1.7) <u>PSA (ng/mL), median (range)</u> : 6.7 (1.6–50) <u>Biopsy Gleason score n, (%)</u> : 5–6: 20 (30.8) 7: 25 (38.5) 8: 14 (21.5) 9–10: 6 (9.2) <u>Clinical stage (n, %)</u> : T1c or T2a: 547 (75.0) T2b: 105 (14.4) T2c or T3a: 77 (10.6)
Resnick et al. 2013 <sup>55</sup>	Prostatectomy: 1,164 patients	Median (IQR): 64 years (59–68)	Non-Hispanic White: 806 (75.9%) Non-Hispanic Black: 170 (11.7%) Hispanic: 188 (12.4%)	Coexisting illnesses, n (%): 0: 513 (42.5) 1: 368 (33.7) 2: 179 (15.2) ≥3: 104 (8.4) Note: self-reported preoperative health data were gathered post- surgery.	<u>Gleason score n (%)</u> : 2–4: 743 (63.9) 5–7: 216 (18.2) 8–10: 73 (6.5) Unknown: 132 (11.4) <u>PSA, n (%)</u> : <4.0 ng/mL: 122 (9.8) 4.0–10.0 ng/mL: 703 (61.0) >10.0 ng/mL: 339 (29.2)
	Radiotherapy: 491 patients	Median (IQR): 69 years (64–71)	Non-Hispanic White: 370 (82.0%) Non-Hispanic Black: 65 (10.4%) Hispanic: 56 (7.7%)	Coexisting illnesses, n (%): 0: 159 (33.3) 1: 160 (33.1) 2: 93 (16.9) ≥3: 79 (16.7) Note: Self-reported pre-operative health data were gathered post- surgery.	<u>Gleason score n (%)</u> : 2–4: 292 (59.3) 5–7: 110 (22.1) 8–10: 46 (9.6) Unknown: 43 (8.9) <u>PSA, n (%)</u> : <4.0 ng/mL: 43 (9.4) 4.0–10.0 ng/mL: 252 (55.9) >10.0 ng/mL: 196 (34.7)

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
Silberstein et al. 2013 <sup>67</sup>	RRP: 961 patients	Median age (IQR): 5 (4–8)	NR	NR	<u>NCCN risk, n (%):</u> Low: 322 (34) Intermediate: 445 (46) High: 194 (20) <u>Clinical Gleason score n (%):</u> ≤6: 373 (39) 7: 464 (48) ≥8: 124 (13) <u>Clinical stage n, (%):</u> TX and T1b: 3 (<1) T1c: 613 (64) T2a: 142 (15) T2b: 203 (21)
	RALRP: 493 patients	Median (IQR): 5 (4–7)	NR	NR	<u>NCCN risk, n (%):</u> Low: 148 (30) Intermediate: 270 (55) High: 75 (15) <u>Clinical Gleason score n (%):</u> ≤6: 170 (34) 7: 269 (55) ≥8: 54 (11) <u>Clinical stage n, (%):</u> TX and T1b: 0 (0) T1c: 299 (61) T2a: 107 (22) T2b: 87 (18)
Spratt et al. 2013 <sup>77</sup>	IMRT Brachytherapy: 400 patients	Median (IQR): 67 (62 to 72)	NR	NR	<u>PSA, n (%):</u> ≤10 ng/mL: 331 (82.8) >10 ng/mL: 69 (17.3) <u>Gleason score, n (%):</u> ≤6: 40 (10.0) 7: 360 (90.0) <u>T stage n (%):</u> ≤T1c, T2a: 317 (79.3) T2b-T2c: 83 (20.8)

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
	IMRT: 470 patients	Median (IQR): 70 (64 to 74) years	NR	NR	<u>PSA, n (%):</u> ≤10 ng/mL: 318 (67.7) >10 ng/mL: 152 (32.3) <u>Gleason score, n (%):</u> ≤6: 61 (13.0) 7: 409 (87.0) <u>T stage n (%):</u> ≤T1c, T2a: 384 (81.7) T2b-T2c: 86 (18.3)

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
Wirth et al. 2013 <sup>74</sup>	RRP: 600 patients	Median (IQR): 59 (54–64)	NR	NR	PSA, median (IQR): 5.0 (3.8-6.8) Gleason score, n (%): ≤6: 407 (67.9) 7: 107 (28.3) ≥8: 23 (3.8) T stage: T2: 516 (86.0) T3: 84 (14.0)
	LRP: 244 patients	Median (IQR): 59 (55–63)	NR	NR	PSA, median (IQR): 5.0 (3.8-6.8) Gleason score, n (%): ≤6: 166 (68.03) 7: 72 (29.8) ≥8: 6 (2.5) T stage: T2: 213 (87.3) T3: 31 (12.7)
Abdollah et al. 2012 <sup>59</sup>	Radiotherapy: 46,521 patients	Age n (%) 65–69 years: 11,209 (24.1%) 70–74 years: 19,279 (41.4%) 75–80 years: 16,033 (34.5%)	Race n (%) White: 40,437 (86.9%) Black: 3,716 (8.0%) Other: 2,368 (5.1%)	Charleston comorbidity index (%): 0: 20,100 (43.2%) 1: 13,835 (29.7%) ≥2: 12,586 (27.1%)	Clinical stage n (%): T1: 18,946 (40.7%) T2a/b: 22,127 (47.6%) T2c: 5,448 (11.7%) Gleason score n (%): <6: 2,555 (5.5%) 6–7: 31,544 (67.8%) 8–10: 12,422 (26.7%)
	Observation: 22,276 patients	Age n (%) 65–69 years: 4,866 (21.8%) 70–74 years: 7,563 (34.0%) 75–80 years: 9,847 (44.2%)	Race n (%) White: 18,355 (82.3%) Black: 2,440 (11.0%) Other: 1,501 (6.7%)	CCI (%): 0: 9,584 (43.0%) 1: 5,832 (26.2%) ≥2: 6,860 (30.8%)	Clinical stage n (%): T1: 11,542 (51.8%) T2a/b: 9,222 (41.4%) T2c: 1,512 (6.8%) Gleason score n (%): <6: 3,906 (17.5%) 6–7: 15,067 (67.6%) 8–10: 3,303 (14.8%)



Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
Abern et al. 2012 <sup>90</sup>	RP: 126,042 patients RP and radiation: 15,686 patients EBRT: 83,110 patients EBRT plus BT: 17,338 patients BT: 32,198 patients Radiation NOS: 826 patients	NR	Total sample: White: 230,892 patients Black: 31,098 patients Other: 13,485 patients	NR	For total sample: Well differentiated: 14,861 patients Moderately differentiated: 183,558 patients Poorly differentiated: 76,230 patients Undifferentiated: 550 patients
Barry et al. 2012 <sup>66</sup>	RALRP: 406 patients	66–69 years: 41.1%; 70–74 years: 43.8%; ≥75 years: 15.0%	Non-Hispanic White: 90.5% African American: 4.2% Hispanic: 2.5% Other: 2.7%	Comorbid illness: NR Self-rated overall health poor, fair, or good: 27.9% Self-rated overall health very good: 44.7% Self-rated overall health excellent: 27.4% Note: Self-reported preoperative health data were gathered post-surgery.	NR
	RRP: 220 patients	66–69 years: 38.2%; 70–74 years: 46.4%; ≥75 years: 15.5%	Non-Hispanic White: 91.7% African American: 3.2% Hispanic: 2.3% Other: 2.8%	Comorbid illness: NR Self-rated overall health poor, fair, or good: 34.1% Self-rated overall health very good: 45.8% Self-rated overall health excellent: 20.1% Note: Self-reported pre-operative health data were gathered post-surgery.	NR

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
Mohammed et al. 2012 <sup>80</sup>	BT: 417 patients (HDR=210, LDR=207)	Mean age: 64.9 years (range: 40–83) years	NR	NR	<u>Clinical stage:</u> T1a–T1c: 273 (65%) T2a–T2c: 144 (35%) T3–T4: 0 (0%) <u>Gleason score:</u> 4–6: 371 (89%) 7: 42 (10%) 8–10: 3 (1%) <u>PSA:</u> ≤4: 98 (24%) 4.1–10.0: 301 (72%) >10.0: 18 (4%) <u>Mean % Cores+:</u> 23% <u>Perineural invasion:</u> 3% <u>Mean prostate gland volume:</u> 36.6%
	EB-IGRT: 1,039 patients	Mean age: 70.8 years (range: 45–88) years	NR	NR	<u>Clinical stage:</u> T1a–T1c: 689 (67%) T2a–T2c: 321 (31%) T3–T4: 16 (2%) <u>Gleason score:</u> 4–6: 544 (53%) 7: 377 (36%) 8–10: 110 (11%) <u>PSA</u> ≤4: 155 (15%) 4.1–10.0: 661 (64%) >10.0: 218 (21%) <u>Mean % Cores+:</u> 35% <u>Perineural invasion:</u> 10% <u>Mean prostate gland volume:</u> 50.6%

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
Mohammed et al. 2012 <sup>80</sup> (continued)	EBRT plus HDR: 447 patients	Mean age: 67.1 years (range: 42–85) years	NR	NR	<u>Clinical stage:</u> T1a–T1c: 107 (24%) T2a–T2c: 282 (64%) T3–T4: 54 (12%) <u>Gleason score:</u> 4–6: 163 (36%) 7: 190 (43%) 8–10: 92 (21%) <u>PSA:</u> ≤4: 27 (6%) 4.1–10.0: 228 (52%) >10.0: 187 (42%) Mean % Cores+: 51% Perineural invasion: 25% Mean prostate gland volume: 41.9%
Nanda et al. 2012 <sup>83</sup>	Low-risk without HT: 3,517 patients	Age, no. (%) Low-risk, BT without Neoadjuvant HT ≤60 years: 613 (17.4%) 61 to 70 years: 1399 (39.8%) 71 to 80 years: 1418 (40.3%) >80 years 87 (2.5%) Low-risk, BT with neoadjuvant HT ≤60 years: 131 (6.8%) 61 to 70 years: 758 (39.4%) 71 to 80 years: 954 (49.6%) >80 years 81 (4.2%)	NR	Low-risk without HT No CAD risk factors: 1731 (49.2%) Diabetes only: 89 (2.5%) Hypertension only: 1033 (29.4%) Hypercholesterolemia only: 191 (5.4%) 2 CAD risk factors: 430 (12.2%) 3 CAD risk factors: 43 (1.2%) Low risk with HT: No CAD risk factors: 947 (49.2%) Diabetes only: 66 (3.4%) Hypertension only: 626 (32.5%) Hypercholesterolemia only: 75 (3.9%) 2 CAD risk factors: 193 (10.0%) 3 CAD risk factors: 17 (0.9%)	<u>Median PSA in ng/mL (IQR)</u> <u>Low-risk without HT:</u> 6.0 (4.8 to 7.4) <u>Low-risk with HT:</u> 6.1 (4.9 to 7.6) <u>Intermediate-risk without HT:</u> 9.5 (6.2 to 12.1) <u>Intermediate-risk with HT:</u> 9.1 (6.0 to 12.4) <u>High-risk without HT:</u> 20.0 (8.2 to 26.7) <u>High-risk with HT:</u> 14.9 (7.2 to 27.0) Clinical T stage <u>Low-risk without HT:</u> T1: 76% T2: 24% T3: 0% <u>Low-risk with HT:</u> T1: 77% T2: 23% T3: 0%
Nanda et al. 2012 <sup>83</sup> (continued)	Low-risk with HT: 1,924 patients		—	Intermediate-risk without HT No CAD risk factors: 1105 (49.7%) Diabetes only: 74 (3.3%) Hypertension only: 667 (30.0%) Hypercholesterolemia only: 108	

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
Nanda et al. 2012 <sup>83</sup> (continued)	Intermediate risk No HT: 2,225 patients With HT: 2,140 patients	Age, no. (%) Intermediate-risk, BT without neoadjuvant HT ≤60 years: 250 (11.2%) 61 to 70 years: 775 (34.8%) 71 to 80 years: 1,078 (48.5%) >80 years 122 (5.5%) Intermediate-risk, BT with neoadjuvant HT ≤60 years: 105 (4.9%) 61 to 70 years: 673 (31.5%) 71 to 80 years: 1,207 (56.4%) >80 years 155 (7.2%)	—	(4.9%) 2 CAD risk factors: 250 (11.2%) 3 CAD risk factors: 21 (0.9%) Intermediate-risk with HT: No CAD risk factors: 1097 (51.3%) Diabetes only: 92 (4.3%) Hypertension only: 637 (29.8%) Hypercholesterolemia only: 66 (3.1%) 2 CAD risk factors: 226 (10.6%) 3 CAD risk factors: 22 (1.0%)  High-risk without HT No CAD risk factors: 193 (54.7%) Diabetes only: 16 (4.5%) Hypertension only: 79 (22.4%) Hypercholesterolemia only: 13 (3.7%) Two CAD risk factors: 46 (13.0%) Three CAD risk factors: 6 (1.7%) High-risk with HT: No CAD risk factors: 511 (50.7%) Diabetes only: 51 (5.1%)	<u>Intermediate-risk without HT:</u> T1: 57.6% T2: 42.4% T3: 0% <u>Intermediate-risk with HT:</u> T1: 51% T2: 49% T3: 0% <u>High-risk without HT:</u> T1: 47.0% T2: 45.9% T3: 7.1% <u>High-risk with HT:</u> T1: 39.8% T2: 46.2% T3: 14.0% Gleason score: <u>Low-risk without HT:</u> ≤6: 100% <u>Low-risk with HT:</u> ≤6: 100% <u>Intermediate-risk without HT:</u> ≤6: 42.8%

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
Nanda et al. 2012 <sup>83</sup> (continued)	High risk No HT: 2,225 patients With HT: 2,140 patients	Age, no. (%) High-risk, BT without neoadjuvant HT ≤60 years: 27 (7.7%) 61 to 70 years: 117 (33.1%) 71 to 80 years: 175 (49.6%) >80 years: 34 (9.6%) High-risk, BT with neoadjuvant HT ≤60 years: 85 (8.4%) 61 to 70 years: 290 (28.8%) 71 to 80 years: 547 (54.3%)	—	Hypertension only: 299 (29.7%) Hypercholesterolemia only: 28 (2.8%) 2 CAD risk factors: 108 (10.7%) 3 CAD risk factors: 10 (1.0%)	7: 57.2% <u>Intermediate-risk with HT:</u> ≤6: 38.5% 7: 61.5% <u>High-risk without HT:</u> ≤6: 31.7% 7: 17% 8 to 10: 51.3% <u>High-risk with HT:</u> ≤6: 18.3% 7: 22.4% 8 to 10: 59.3%
Ploussard et al. 2012 <sup>62</sup>	LRP: 1,377 patients	Mean 62.7 years	NR	BMI kg/m <sup>2</sup> mean: 26.6	<u>Mean number of positive cores:</u> 3.9 Clinical stage % T1c: 81.0 T2a,b: 16.2% T2c-T3: 2.8% >T1c: 19.0% Biopsy Gleason score % 6: 65.7% 7: 29.4% 8 to 10: 4.9%
Ploussard et al. 2012 <sup>62</sup> (continued)	RALP: 1,009 patients	Mean: 62.7 years	NR	BMI kg/m <sup>2</sup> mean: 26.5	<u>Mean number of positive cores:</u> 4.5 <u>Clinical stage %</u> T1c: 81.8% T2a,b: 15.6% T2c-T3: 2.6% >T1c: 18.1% <u>Biopsy Gleason score %</u> 6: 60.1% 7: 33.0% 8 to 10: 6.9%

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
Rosenberg et al. 2012 <sup>76</sup>	BT plus EBRT: 186 patients	Median (IQR): 67.8 years (61.2–71.3)	NR	NR	<u>Median (IQR) PSA ng/mL</u> 8.51 (6.5–12.1) <u>AJCC T-category n (%)</u> T1b: 0 (0%) T1c: 78 (41.9%) T2a: 70 (37.6%) T2b: 38 (20.4%) <u>Gleason score n (%)</u> ≤6: 24 (12.9%) 3+4: 97 (52.1%) 4+3: 65 (34.9%)
	BT plus ADT: 621 patients	Median (IQR): 72.5 years (68.2–76.3)	NR	NR	<u>Median (IQR) PSA ng/mL</u> 10.3 (6.7–13.0) <u>AJCC T-category n (%)</u> T1b: 3 (0.5%) T1c: 425 (68.4%) T2a: 143 (23%) T2b: 50 (8%) <u>Gleason score n (%)</u> ≤6: 254 (40.9%) 3+4: 252 (40.5%) 4+3: 115 (18.5%)
Sheets et al. 2012 <sup>58</sup>	IMRT: 6,666 patients	Age at diagnosis: 66 to 69 years: 1,338 (20.1%) 70 to 74 years: 2,415 (36.2%) ≥75 years: 2,913 (43.7)	White: 5,694 (85.4%) Black: 521 (7.8%) Other/unknown: 451 (6.8%)	Diabetes: 1,750 (26.2) Anticoagulation, arrhythmias, or valvular disease: 1,685 (25.3%) Gastrointestinal diagnosis/procedure: 1,359 (20.4%) Urinary nonincontinence diagnosis/procedure: 1,453 (21.8%) Urinary incontinence diagnosis/procedure: 1,475 (22.1%) Erectile dysfunction diagnosis/procedure: 615 (9.2%) Hip fracture: 20 (0.3%)	<u>Tumor grade well/moderately differentiated: 3,390 (50.9%)</u> <u>Poorly differentiated: 3,177 (47.7%)</u> <u>Unknown/not assessed: 99 (1.5%)</u> <u>Clinical stage:</u> T1: 3,375 (50.6%) T2: 3,070 (46.1%) T3/T4: 221 (3.3%)

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
	3D-CRT: 6,310 patients	Age at diagnosis 66 to 69 years: 1,265 (20.1%) 70 to 74 years: 2,345 (37.2%) ≥75 years: 2,700 (42.8)	White: 5,325 (84.4%) Black: 657 (10.4%) Other/unknown: 328 (5.2%)	Diabetes: 1,681 (26.6) Anticoagulation, arrhythmias, or valvular disease: 1,533 (24.3%) Gastrointestinal diagnosis/procedure: 1,238 (19.6%) Urinary nonincontinence diagnosis/procedure: 1,331 (21.1%) Urinary incontinence diagnosis/procedure: 1,032 (16.3%) Erectile dysfunction diagnosis/procedure: 501 (7.9%) Hip fracture: 14 (0.2%)	<u>Tumor grade well/moderately differentiated</u> : 3,850 (61.0%) <u>Poorly differentiated</u> : 2,334 (37.0%) <u>Unknown/not assessed</u> : 126 (2.0%) <u>Clinical stage</u> : T1: 2,502 (39.7%) T2: 3,556 (56.3%) T3/T4: 252 (4.0%)
Sheets et al. 2012 <sup>58</sup> (continued)	Proton beam therapy: 685 patients	Age at diagnosis 66–69 years: 248 (36.2%) 70–74 years: 233 (34.0%) ≥75 years: 204 (29.8%)	White: 634 (92.6%) Black: 20 (2.9%) Other/unknown: 31 (4.5%)	Diabetes: 130 (19.0%) Anticoagulation, arrhythmias, or valvular disease: 144 (21.0%) Gastrointestinal diagnosis/procedure: 148 (21.6%) Urinary nonincontinence diagnosis/procedure: 104 (15.2%) Urinary incontinence diagnosis/procedure: 109 (15.9%) Erectile dysfunction diagnosis/procedure: 83 (12.1%) Hip fracture: 0 (0%)	<u>Tumor grade well/moderately differentiated</u> : 413 (60.3%) <u>Poorly differentiated</u> : 268 (39.1%) <u>Unknown/not assessed</u> : 4 (0.6%) <u>Clinical stage</u> : T1: 348 (50.8%) T2: 314 (45.8%) T3/T4: 23 (3.4%)
Shen et al. 2012 <sup>84</sup>	BT: 910 patients	Median age: 70 years	White: 83.8% Black: 9.4% Asian: 6.3% Other: 0.5% Hispanic: 95.8% Non-Hispanic: 4.2%	Only prostate cancer: 78.7% Prostate first primary: 11.9% Prostate second or later: 9.5%	<u>Post-1998 PSA elevated at diagnosis</u> : 75.5% <u>PSA borderline</u> : 7.0% <u>PSA normal at diagnosis</u> : 3.5% <u>PSA unknown/other</u> : 14.1% <u>Clinical stage</u> : T1: 37.4% T2: 59.2% T3: 3.4%

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
	BT plus EBRT: 2,466 patients	Median age: 70 years	White: 79.1% Black: 13.1% Asian: 6.9% Other: 0.9% Hispanic: 94.2% Non-Hispanic: 7.4%	Only prostate cancer: 78.8% Prostate first primary: 13.5% Prostate second or later: 7.6%	<u>Post-1998</u> <u>PSA elevated at diagnosis:</u> 79.0% <u>PSA borderline:</u> 5.6% <u>PSA normal at diagnosis:</u> 4.7% <u>PSA unknown/other:</u> 10.6% <u>Clinical stage:</u> T1: 26.0% T2: 68.6% T3: 5.4%
Shen et al. 2012 <sup>84</sup> (continued)	EBRT: 9,369 patients	Median age: 72 years	White: 77.7% Black: 11.3% Asian: 10.0% Other: 1.0% Hispanic: 93.9% Non-Hispanic: 6.1%	Only prostate cancer: 76.9% Prostate first primary: 14.5% Prostate second or later: 8.6%	<u>Post-1998</u> <u>PSA elevated at diagnosis:</u> 81.8% <u>PSA borderline:</u> 4.6% <u>PSA normal at diagnosis:</u> 3.6% <u>PSA unknown/other:</u> 10.0% <u>Clinical stage:</u> T1: 22.4% T2: 66.8% T3: 10.8%
Kibel et al. 2012 <sup>85</sup>	RP: 6,485 patients, 2,843 at site 1 and 3,642 at site 2	Median (IQR) at site 1 (Cleveland Clinic): 60 years (56 to 65) Median (IQR) at site 2 (Barnes- Jewish Hospital): 61 years (55 to 66)	N (%) African American at site 1 (Cleveland Clinic): 310 (11%). N (%) African American at site 2 (Barnes-Jewish Hospital): 334 (9%).	Site 1 (Cleveland Clinic) Comorbidity index n (%): None: 2307 (81%) Mild: 377 (13%) Moderate: 150 (5%) Severe: 9 (0.3%). Site 2 (Barnes-Jewish Hospital) Comorbidity index n (%): None: 2,157 (59%) Mild: 1213 (33%) Moderate: 237 (7%) Severe: 35 (1%) Note: Comorbid illness data were prospectively recorded using medical records and the ACE 27 index at site 1 while comorbidity was recorded through retrospective review of medical records using the CCI at site 2.	<u>Site 1 (Cleveland Clinic)</u> <u>Median ng/mL PSA (IQR):</u> 5.9 (4.6 to 8.2) <u>Site 2 (Barnes-Jewish Hospital) Median ng/mL PSA (IQR):</u> 5.4 (4.1 to 7.8) <u>Site 1 (Cleveland Clinic) bGS n (%):</u> 2 to 6: 1,980 (70%) 7: 745 (26%) 8 to 10: 118 (4%) <u>Site 2 (Barnes-Jewish Hospital) bGS n (%):</u> 2 to 6: 2,774 (76%) 7: 710 (20%) 8 to 10: 158 (4%) <u>Site 1 (Cleveland Clinic)</u> <u>clinical stage n (%):</u> T1ab: 15 (0.5%)



Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
					<p>T1c: 2,074 (73%)  T2a: 554 (20%)  T2b: 124 (4%)  T2c: 48 (2%)  T3: 28 (1%)</p> <p><u>Site 2 (Barnes-Jewish Hospital) clinical stage n (%):</u>  T1ab: 40 (1%)  T1c: 2,921 (80%)  T2a: 364 (10%)  T2b: 250 (7%)  T2c: 49 (1%)  T3: 18 (0.5%)</p> <p><u>Site 1 (Cleveland Clinic) D'Amico risk group n (%):</u> low: 1,669 (59%)  Intermediate: 945 (33%)  High: 229 (8%)</p> <p><u>Site 2 (Barnes-Jewish Hospital) D'Amico risk group n (%):</u>  Low: 2,297 (63%)  Intermediate: 1,049 (29%)  High: 296 (8%)</p>
Kibel et al. 2012 <sup>5</sup> (continued)	EBRT: 2,264 patients, 1,638 at site 1 and 626 at site 2	Median (IQR) at site 1 (Cleveland Clinic): 69 years (63 to 73) Median (IQR) at site 2 (Barnes-Jewish Hospital): 70 years (65 to 75)	N (%) African American at site 1 (Cleveland Clinic): 434 (27%). N (%) African American at site 2 (Barnes-Jewish Hospital): 101 (16%).	<p><u>Site 1 (Cleveland Clinic) Comorbidity index n (%):</u>  None: 1084 (66%)  Mild: 317 (19%)  Moderate: 241 (12%)  Severe: 39 (3%).</p> <p><u>Site 2 (Barnes-Jewish Hospital) Comorbidity index n (%):</u>  None: 220 (35%)  Mild: 277 (44%)  Moderate: 107 (17%)  Severe: 22 (3%)</p> <p>Note: Comorbid illness data were prospectively recorded using medical records and the ACE 27 index at site 1 while comorbidity was recorded through retrospective review of medical records using the CCI at site</p>	<p><u>Site 1 (Cleveland Clinic) Median ng/mL PSA (IQR):</u>  8.9 (6.0 to 15.9)</p> <p><u>Site 2 (Barnes-Jewish Hospital) Median ng/mL PSA (IQR):</u>  6.8 (4.7 to 10.7)</p> <p><u>Site 1 (Cleveland Clinic) bGS n (%):</u>  2 to 6: 789 (47%)  7: 606 (37%)  8 to 10: 243 (16%)</p> <p><u>Site 2 (Barnes-Jewish Hospital) bGS n (%):</u>  2 to 6: 390 (61%)  7: 172 (29%)  8 to 10: 64 (10%)</p> <p><u>Site 1 (Cleveland Clinic)</u></p>

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
				2.	<p>clinical stage n (%):  T1ab: 25 (2%)  T1c: 883 (54%)  T2a: 351 (22%)  T2b: 158 (10%)  T2c: 92 (6%)  T3: 129 (8%)  <u>Site 2 (Barnes-Jewish Hospital) clinical stage n (%):</u>  T1ab: 7 (1%)  T1c: 396 (62%)  T2a: 112 (19%)  T2b: 54 (9%)  T2c: 20 (3%)  T3: 37 (6%)  <u>Site 1 (Cleveland Clinic) D'Amico risk group n (%):</u>  Low: 479 (29%)  Intermediate: 619 (37%)  High: 540 (34%)  <u>Site 2 (Barnes-Jewish Hospital) D'Amico risk group n (%):</u>  Low: 283 (44%)  Intermediate: 207 (35%)  High: 136 (21%)</p>
Kibel et al. 2012 <sup>65</sup> (continued)	BT: 1,680 patients, 1,330 at site 1 and 350 at site 2	Median (IQR) at site 1 (Cleveland Clinic): 68 years (62 to 72) Median (IQR) at site 2 (Barnes- Jewish Hospital): 69 years (63 to 73)	N (%) African American at site 1 (Cleveland Clinic): 149 (11%). N (%) African American at site 2 (Barnes-Jewish Hospital): 31 (9%).	<p><u>Site 1 (Cleveland Clinic) Comorbidity index n (%):</u>  None: 809 (61%)  Mild: 322 (24%)  Moderate: 179 (14%)  Severe: 20 (1%).  <u>Site 2 (Barnes-Jewish Hospital) Comorbidity index n (%):</u>  None: 163 (47%)  Mild: 123 (35%)  Moderate: 56 (16%)  Severe: 8 (2%)  Note: Comorbid illness data were prospectively recorded using medical records and the ACE 27 index at site 1 while comorbidity was recorded</p>	<p><u>Site 1 (Cleveland Clinic) Median ng/mL PSA (IQR):</u>  6.1 (4.8 to 8.0)  <u>Site 2 (Barnes-Jewish Hospital) Median ng/mL PSA (IQR):</u>  5.2 (3.8 to 6.8)  <u>Site 1 (Cleveland Clinic) bGS n (%):</u>  2 to 6: 1,080 (81%)  7: 247 (18%)  8 to 10: 13 (1%)  <u>Site 2 (Barnes-Jewish Hospital) bGS n (%):</u>  2 to 6: 313 (89%)  7: 36 (10%)</p>

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
				through retrospective review of medical records using the CCI at site 2.	<p>8 to 10: 1 (1%)</p> <p><u>Site 1 (Cleveland Clinic) clinical stage n (%):</u>  T1ab: 7 (0.5%)  T1c: 1036 (83%)  T2a: 211 (16%)  T2b: 9 (1%)  T2c: 7 (0.5%)  T3: 0 (0%)</p> <p><u>Site 2 (Barnes-Jewish Hospital) clinical stage n (%):</u>  T1ab: 0 (0%)  T1c: 265 (76%)  T2a: 66 (19%)  T2b: 17 (5%)  T2c: 2 (1%)  T3: 0 (0%)</p> <p><u>Site 1 (Cleveland Clinic) D'Amico risk group n (%):</u>  Low: 932 (70%)  Intermediate: 370 (28%)  High: 28 (2%)</p> <p><u>Site 2 (Barnes-Jewish Hospital) D'Amico risk group n (%):</u>  Low: 272 (78%)  Intermediate: 73 (21%)  High: 5 (1%)</p>
Zelevsky et al. 2012 <sup>89</sup>	BT: 942 patients	NR	NR	NR	<p><u>PSA ng/mL, N</u>  &lt;10: 877  10–20: 63  &gt;20: 2</p> <p><u>Gleason score, N</u>  &lt;7: 824  7: 114  &gt;7: 4</p> <p><u>T stage</u>  T1c: 761  T2a: 149  T2b: 25  T2c: 7</p>

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
	BT plus IMRT: 524 patients				<u>PSA ng/mL, N</u> <10: 432 10–20: 81 >20: 11 <u>Gleason score, N</u> <7: 135 7: 331 >7: 58 <u>T stage</u> T1c: 252 T2a: 171 T2b: 77 T2c: 24

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
Abdollah et al. 2011 <sup>72</sup>	RP: 22,244 patients	Mean age: 69.8 years (range: 65–80)	White: 19,926 (89.6%) Black: 1,334 (6.0%) Other: 984 (4.4%)	CCI: 0: 11,249 (50.6%) 1: 6,582 (29.6%) 2: 2,712 (12.2%) ≥3: 1,701 (7.6%)	<u>Clinical stage:</u> T1: 7,448 (33.5%) T2a/b: 11,322 (50.9%) T2c: 3,474 (15.6%) <u>Gleason score:</u> 2–5: 1,089 (4.9%) 6–7: 15,173 (68.2%) 8–10: 5,982 (26.9%)
	Observation: 22,450 patients	Mean age: 73.5 years (range: 65–80)	White: 18,463 (82.2%) Black: 2,466 (11.0%) Other: 1,521 (6.8%)	CCI: 0: 9,642 (42.9%) 1: 5,882 (26.2%) 2: 3,344 (14.9%) ≥3: 3,582 (16.0%)	<u>Clinical stage:</u> T1: 11,629 (51.8%) T2a/b: 9,293 (41.4%) T2c: 1,528 (6.8%) <u>Gleason score:</u> 2–5: 3,941 (17.6%) 6–7: 15,181 (67.6%) 8–10: 3,328 (14.8%)
Bekelman et al. 2011 <sup>81</sup>	IMRT: 5,845 patients	Age at diagnosis: 65–74 years: 3,204 (55%) ≥75 years: 2,641 (45%)	White: 4,851 (83%) Black: 521 (9%) Other: 371 (6%) Unknown: 102 (2%) Non-Hispanic: 5,384 (92%) Hispanic: 311 (5%) Unknown: 150 (3%)	Comorbidity index: 0: 1,470 (25%) 1: 1,759 (30%) ≥2: 2,616 (45%)	<u>AJCC tumor stage:</u> T1: 2,511 (43%) T2: 3,081 (51%) T3: 215 (4%) T4: 38 (1%) <u>Gleason score:</u> 8–10: 1,590 (27%) 5–7: 4,091 (70%) 2–4: 61 (1%) Unknown: 103 (2%) <u>History of transurethral resection of the prostate (TURP):</u> 228 (4%)
Bekelman et al. 2011 <sup>81</sup> (continued)	3D-CRT: 6,753 patients	Age at diagnosis: 65–74 years: 3,684 (55%) ≥75 years: 3,069 (45%)	White: 5,707 (85%) Black: 708 (10%) Other: 249 (4%) Unknown: 89 (1%) Non-Hispanic: 6,207 (92%) Hispanic: 384 (6%) Unknown: 162 (2%)	Comorbidity index: 0: 1,669 (24%) 1: 2,065 (31%) ≥2: 3,019 (45%)	<u>AJCC tumor stage:</u> T1: 2,547 (38%) T2: 3,908 (58%) T3: 230 (3%) T4: 68 (1%) <u>Gleason score:</u> 8–10: 1,937 (29%) 5–7: 4,603 (68%) 2–4: 107 (2%) Unknown: 106 (2%) <u>History of TURP:</u> 321 (5%)

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
Kim et al. 2011 <sup>60</sup>	Radiation therapy: 28,088 patients (All EBRT: 19,063 patients; BT only: 5,338 patients; BT plus EBRT: 3,687 patients)	Age at diagnosis: 66–85 years	White: 81% Black: 11% Other: 8%	CCI: 0: 77% 1: 17% ≥2: 6% Diabetes: 12% MI: 2% Peripheral disease: 2%	<u>Clinical T stage:</u> <u>T1 : 52%</u> <u>T2 : 48%</u>  <u>Cancer grade:</u> <u>Well differentiated: 5%</u> <u>Moderately differentiated: 64%</u> <u>Poorly differentiated: 29%</u> <u>Unknown: 2%</u>
	Conservative management: 13,649 patients	Age at diagnosis: 66–85 years	White: 77% Black: 13% Other: 10%	Charlson comorbidity score: 0: 71% 1: 18% ≥2: 11% Diabetes: 13% MI: 3% Peripheral disease: 3%	<u>Clinical T stage:</u> <u>T1 : 65%</u> <u>T2 : 35%</u>  <u>Cancer grade:</u> <u>Well differentiated: 20%</u> <u>Moderately differentiated: 59%</u> <u>Poorly differentiated: 15%</u> <u>Unknown: 6%</u>

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
Masterson et al. 2011 <sup>69</sup>	RRP: 357 patients	Age at diagnosis (mean): 60 years	NR	NR	<u>Mean PSA:</u> 7.6 ng/mL <u>Mean prostate weight:</u> 44.2 g <u>Mean tumor volume:</u> 2.9 mL <u>Mean largest tumor dimension:</u> 1.8 cm <u>Gleason sum (%):</u> 5: 55 (15%) 6: 112 (31%) 7: 155 (43%) 3+4: 113 (73%) 4+3: 42 (27%) 8: 9 (3%) 9: 25 (7%) 10: 1 (<1%) <u>Pathological T Stage:</u> T2a: 45 (13%) T2b: 211 (59%) T3a: 79 (22%) T3b: 22 (6%) T4: 0 <u>Positive surgical margins (%):</u> 18% <u>Lymph node involvement (%):</u> 1% <u>Benign capsular incision %:</u> 94 (27%)

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
Masterson et al. 2011 <sup>69</sup> (continued)	RALP: 669 patients	Age at diagnosis (mean): 61 years	NR	NR	<u>Mean PSA:</u> 7.1 ng/mL <u>Mean prostate weight:</u> 48.2 g <u>Mean tumor volume:</u> 3.0 mL <u>Mean largest tumor dimension:</u> 1.8 cm <u>Gleason sum (%):</u> 5: 50 (8%) 6: 266 (40%) 7: 324 (48%) 3+4: 259 (80%) 4+3: 65 (20%) 8: 6 (1%) 9: 23 (3%) 10: 0 <u>Pathological T Stage:</u> T2a: 79 (12%) T2b: 406 (60%) T3a: 127 (19%) T3b: 56 (8%) T4: 1 (<1) <u>Positive surgical margins (%):</u> 14% <u>Lymph node involvement (%):</u> 8% <u>Benign capsular incision %:</u> 186 (30%)



Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
Rice et al. 2011 <sup>36</sup>	RP: 194 patients	Age at diagnosis: 72.2±1.9 years	White: 169 (87.1%) Black: 13 (6.7%) Other: 12 (6.2%)	Number of Comorbidities: 0: 54 (27.8%) 1: 63 (32.5%) 2: 49 (25.3%) ≥3: 28 (14.4%)	<u>Mean PSA:</u> 5.3±2.2 ng/mL <u>Clinical T Stage:</u> T1 111 (57.2%) T2a 83 (42.8%)
	EBRT: 252 patients	Age at diagnosis: 74.1±3.1 years	White: 207 (82.1%) Black: 32 (12.7%) Other: 13 (5.2%)	Number of Comorbidities: 0: 54 (21.4%) 1: 73 (29.0%) 2: 79 (31.4%) ≥3: 46 (18.2%)	<u>Mean PSA:</u> 6.0±2.2 ng/mL <u>Clinical T Stage:</u> T1 150 (59.5%) T2a 102 (40.5%)
	WW without secondary treatment: 214 patients	Age at diagnosis: 75.7±3.8 years	White: 183 (85.5%) Black: 20 (9.4%) Other: 11 (5.1%)	Number of Comorbidities: 0: 54 (24.0%) 1: 61 (28.5%) 2: 49 (22.9%) ≥3: 52 (24.3%)	<u>Mean PSA:</u> 4.7±2.3 ng/mL <u>Clinical T Stage:</u> T1 141 (65.9%) T2a 73 (34.1%)
	WW with secondary treatment: 110 patients	Age at diagnosis: 74.5±3.6 years	White: 91 (82.7%) Black: 13 (11.8%) Other: 6 (5.4%)	Number of Comorbidities: 0: 28 (25.4%) 1: 33 (30.0%) 2: 25 (22.7%) ≥3: 24 (21.8%)	<u>Mean PSA:</u> 5.6±2.2 ng/mL <u>Clinical T Stage:</u> T1 67 (60.9%) T2a 43 (39.1%)
Williams et al. 2011 <sup>57</sup>	BT: 9,985 patients	65–69 years: 3,233 (32.4%) 70–74 years: 3,643 (36.5%) ≥75: 3,109 (31.1%)	White: 8,496 (85.1%) Black: 624 (6.3%) Hispanic: 374 (3.8%) Asian: 302 (3.0%) Other/unknown: 189 (1.9%)	CCI score: 0: 7,534 (75.5%) 1: 1,732 (17.4%) ≥2: 563 (5.6%) Unknown: 156 (1.6%) Incontinence diagnosis: 213 (2.1%) ED diagnosis: 967 (9.7%)	<u>Clinical stage:</u> T1: 4,956 (49.6%) T2: 4,811 (48.2%) T3/unknown: 218 (2.2%) <u>Tumor grade:</u> Well/moderately differentiated: 8,433 (84.5%) Poorly differentiated: 1,291 (12.9%) Unknown/missing: 261 (2.6%) <u>PSA:</u> Elevated: 7,051 (70.6%) Normal: 817 (8.2%) Unknown: 2,117 (21.2%) <u>Prior TURP:</u> 208 (2.1%)

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
	Cryotherapy: 943 patients	65 to 69 years: 218 (23.1%) 70 to 74 years: 366 (35.6%) ≥75: 389 (41.3%)	White: 722 (76.6%) Black: 113 (12.0%) Hispanic: 47 (5.0%) Asian: 31 (3.3%) Other/unknown: 30 (3.2%)	Charlson comorbidity score: 0: 666 (70.6%) 1: 201 (21.3%) ≥2: 65 (6.9%) Unknown: 11 (1.2%) Incontinence diagnosis: 34 (3.6%) ED diagnosis: 103 (10.9%)	<u>Clinical stage:</u> T1: 369 (39.1%) T2: 530 (56.2%) T3/unknown: 44 (4.7%) <u>Tumor grade:</u> Well/moderately differentiated: 571 (60.6%) Poorly differentiated: 338 (35.8%) Unknown/missing: 34 (3.6%) <u>PSA:</u> Elevated: 641 (68.0%) Normal: 65 (6.9%) Unknown: 237 (25.1%) <u>Prior TURP:</u> 49 (5.2%)
Hadley et al. 2010 <sup>73</sup>	Conservative management: 5,879 patients	Unweighted sample: 66–69: 44.1% 70–74: 55.9%	Unweighted sample: White non- Hispanic: 70.0% White Hispanic: 6.3% African American: 16.9% All other: 6.8%	Unweighted sample: <u>NCI comorbidity index:</u> 0: 75.4% 1: 10.0% ≥2: 9.3% Unknown: 5.4%	Unweighted sample: <u>Stage:</u> T1: 61.0% T2: 39.0% <u>Grade:</u> Well differentiated: 9.6% Moderately differentiated: 69.6% Poorly differentiated: 14.0% Unknown: 6.9%
	RP: 11,936 patients	Unweighted sample: 66–69: 53.2% 70–74: 46.8%	White non- Hispanic: 80.7% White Hispanic: 6.9% African American: 7.8% All other: 4.6%	Unweighted sample: <u>NCI comorbidity index:</u> 0: 57.8% 1: 8.4% ≥2: 8.9% Unknown: 23.4%	Unweighted sample: <u>Stage:</u> T1: 64.9% T2: 35.1% <u>Grade:</u> Well differentiated: 7.1% Moderately differentiated: 70.8% Poorly differentiated: 21.0% Unknown: 1.1%

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
Barocas et al. 2010 <sup>64</sup>	RRP: 491 patients	Mean age: 62 years (7.3)	N (%) Nonwhite: 47 (9.6%)	NR	<u>Median PSA:</u> 5.8 ng/mL (IQR 4.6 to 8.4) <u>N clinically palpable</u> 144 (29.5%) <u>Biopsy Gleason score</u> ≤6: 327 (66.6%) 7: 116 (23.6%) 8 to 10: 48 (9.8%) <u>Pathological stage</u> pT0: 3 (0.6%) pT2: 342 (69.6%) pT3: 144 (29.3%) pT4: 2 (0.4%) <u>Extraprostatic extension:</u> 133 (27.1%) <u>Positive seminal vesicles:</u> 38 (7.7%) SM+: 148 (30.1%) <u>Pathological Gleason Score:</u> ≤6: 221 (45.3%) 7: 213 (43.6%) 8 to 10: 54 (11.1%)

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
Barocas et al. 2010 <sup>64</sup> (continued)	RALRP: 1,413 patients	Mean age: 61 years (7.3)	N (%) Nonwhite: 92 (6.5%)	NR	<u>Median PSA:</u> 5.4 ng/mL (IQR 4.3 to 7.4) <u>N clinically palpable:</u> 315 (22.4%) <u>Biopsy Gleason score:</u> ≤6: 986 (69.9%) 7: 353 (25.0%) 8 to 10: 72 (5.1%) <u>Pathological stage:</u> pT0: 7 (0.5%) pT2: 1,136 (80.5%) pT3: 268 (19.0%) pT4: 0 (0%) <u>Extraprostatic extension:</u> 253 (17.9%) <u>Positive seminal vesicles:</u> 55 (3.9%) SM+: 281 (19.9%) <u>Pathological Gleason Score:</u> ≤6: 723 (51.5%) 7: 588 (41.8%) 8 to 10: 94 (6.7%)
Coopersburg et al. 2010 <sup>39</sup>	RP: 5,066 patients	Median age: 62 years	African American: 463 (9.1%) Caucasian: 4,439 (87.6%) Other: 164 (3.2%)	NR	<u>PSA, ng/mL (n, [%]):</u> 0–6: 2,673 (52.8) 6.01–10: 1,452 (28.7) 10–20: 698 (13.8) 20.01–30: 129 (2.6) >30: 114 (2.3) <u>Gleason score:</u> 2–6: 3,573 (52.8) 3+4: 850 (16.8) 4+3: 355 (7) 8+10: 288 (5.7) <u>Tumor classification:</u> T1: 2,585 (51) T2a: 1,082 (21.4) T2b: 392 (7.7) T2c: 950 (18.8) T3a: 57 (1.1)

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
	EBRT: 1,143 patients	Median age: 72 years	African American: 157 (13.7%) Caucasian: 955 (83.6%) Other: 31 (2.7%)	NR	<u>PSA, ng/mL:</u> 0–6: 322 (28.2) 6.01–10: 330 (28.9) 10–20: 302 (26.4) 20.01–30: 72 (6.3) >30: 117 (14.9) <u>Gleason score:</u> 2–6: 619 (54.2) 3+4: 218 (19.1) 4+3: 136 (11.9) 8+10: 170 (14.9) <u>Tumor classification:</u> T1: 484 (42.3) T2a: 249 (21.8) T2b: 97 (8.5) T2c: 266 (23.3) T3a: 47 (4.1)
Coopersburg et al. 2010 <sup>39</sup> (continued)	ADT: 1,329 patients	Median age: 74 years	African American: 197 (14.8%) Caucasian: 1,068 (80.4%) Other: 64 (4.8%)	NR	<u>PSA, ng/mL:</u> 0–6: 301 (22.7) 6.01–10: 355 (26.7) 10–20: 305 (23) 20.01–30: 126 (9.5) >30: 242 (18.2) <u>Gleason score:</u> 2–6: 622 (46.8) 3+4: 247 (18.6) 4+3: 175 (13.2) 8+10: 285 (21.4) <u>Tumor classification:</u> T1: 571 (43) T2a: 238 (17.9) T2b: 102 (7.7) T2c: 341 (25.7) T3a: 77 (5.8)

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
Dosoretz et al. 2010 <sup>82</sup>	BT: 1,391 patients	Median age was 73 years for all patients enrolled.	NR	NR	<p><u>For patients &lt;73 years:</u>  Median PSA 5.9  <u>Gleason score:</u>  ≤6: 641(90%)  7: 60 (8%)  8–10: 10 (1%)  <u>AJCC tumor classification:</u>  T1: 496 (70%)  T2: 215 (30%)  T3: NA  <u>D'Amico risk group:</u>  Low: 539 (76%)  Intermediate: 111 (16%)  High: 61 (9%)</p> <p><u>For patients ≥73 years:</u>  Median PSA 6.7  <u>Gleason score:</u>  ≤6: 586 (86%)  7: 77 (11%)  8–10: 17 (3%)  <u>AJCC tumor classification:</u>  T1: 394 (58%)  T2: 285 (42%)  T3: 1 (0.2%)  <u>D'Amico risk group:</u>  Low: 428 (63%)  Intermediate: 143 (21%)  High: 109 (16%)</p>

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
Dosoretz et al. 2010 <sup>82</sup> (continued)	BT plus ADT: 1,083 patients	—	NR	NR	<p><u>For patients &lt;73 years:</u>  Median PSA 6.2  <u>Gleason score:</u>  ≤6: 426 (86%)  7: 54 (11%)  8–10: 15 (3%)  <u>AJCC tumor classification:</u>  T1: 319 (64%)  T2: 176 (36%)  T3: NA  <u>D'Amico risk group:</u>  Low: 323 (65%)  Intermediate: 120 (24%)  High: 52 (11%)</p> <p><u>For patients ≥73 years:</u>  Median PSA 7.6  <u>Gleason score:</u>  ≤6: 461 (78%)  7: 104 (18%)  8–10: 23 (4%)  <u>AJCC tumor classification:</u>  T1: 393 (67%)  T2: 190 (32%)  T3: 5 (1%)  <u>D'Amico risk group:</u>  Low: 320 (54%)  Intermediate: 193 (33%)  High: 75 (13%)</p>
Magheli et al. 2010 <sup>56</sup>	RRP: 522 patients	Mean age: 58.8 (6.1)	Caucasian: 87.0% African-American: 8.8% Other: 4.2%	NR	<p><u>Mean PSA:</u> 5.4 (3.2)  <u>Biopsy Gleason score:</u>  ≤6: 71.1%  7: 26.8%  8–9: 2.1%  <u>Clinical stage</u>  T1: 81.0%  T2: 19.0%</p>

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
	LRP: 522 patients	Mean age: 58.4 (6.4)	Caucasian: 82.2% African-American: 13.8% Other: 4.0%	NR	<u>Mean PSA</u> : 5.4 (3.7) <u>Biopsy Gleason score</u> : ≤6: 74.7% 7: 21.8% 8–9: 3.4% <u>Clinical stage</u> T1: 79.3% T2: 20.7%
	RALRP: 522 patients	Mean age: 58.3 (6.3)	Caucasian: 83.3% African-American: 11.9% Other: 4.8%	NR	<u>Mean PSA</u> : 5.4 (3.2) <u>Biopsy Gleason score</u> : ≤6: 75.5% 7: 21.8% 8–9: 2.7% <u>Clinical stage</u> T1: 79.9% T2: 20.1%



Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
Malcolm et al. 2009 <sup>71</sup>	RRP: 135 patients	Mean: 59±7 years	N (%) White: 102 (76%) Black: 32 (24%) Other: 1 (1%)	NR	<u>No (%) clinical stage:</u> T1c or less: 112 (83%) T2a: 17 (13%) T2b+: 6 (4%) Unknown: 0 (0%) <u>N (%) Gleason score:</u> ≤6: 93 (69%) 7: 34 (25%) ≥8: 8 (6%) <u>Median (IQR) PSA:</u> 5.7 ng/mL (4.7 to 7.3)
	RALRP: 447 patients	Mean: 59±6 years	N (%) White: 341 (76%) Black: 78 (17%) Other: 28 (6%)	NR	<u>No (%) clinical stage:</u> T1c or less: 340 (76%) T2a: 68 (15%) T2b+: 32 (7%) Unknown: 7 (2%) <u>N (%) Gleason score:</u> ≤6: 269 (60%) 7: 154 (34%) ≥8: 24 (5%) <u>Median (IQR) PSA:</u> 5.2 ng/mL (3.9 to 6.8)
	BT: 122 patients	Mean: 66±7 years	N (%) White: 89 (73%) Black: 29 (24%) Other: 4 (3%)	NR	<u>No (%) clinical stage:</u> T1c or less: 98 (80%) T2a: 16 (13%) T2b+: 3 (2%) Unknown: 5 (4%) <u>N (%) Gleason score:</u> ≤6: 88 (72%) 7: 28 (23%) ≥8: 6 (5%) <u>Median (IQR) PSA:</u> 6.0 ng/mL (4.5 to 8.2)

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
	Cryotherapy: 81 patients	Mean: 71±7 years	N (%) White: 60 (74%) Black: 19 (23%) Other: 2 (2%)	NR	<u>No (%) clinical stage:</u> T1c or less: 57 (70%) T2a: 10 (12%) T2b+: 13 (16%) Unknown: 1 (1%) <u>N (%) Gleason score:</u> ≤6: 40 (50%) 7: 34 (41%) ≥8: 7 (9%) <u>Median (IQR) PSA:</u> 6.2 ng/mL (5.0 to 8.6)
Wong et al. 2009 <sup>88</sup>	3D-CRT: 270 patients	NR	NR	NR	<u>Clinical T Stage:</u> T1c: 42 (16%) T2a: 78 (29%) T2b: 59 (21%) T2c: 64 (24%) T3: 27 (10%) <u>PSA:</u> ≤10: 192 (71%) 10.1–20: 52 (19%) ≥20: 26 (10%) <u>Gleason score:</u> ≤6: 175 (65%) ≥7: 95 (35%) <u>Risk group:</u> Low: 119 (44%) Intermediate: 111 (41%) High: 40 (15%)

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
	IMRT: 314 patients				<u>Clinical T Stage:</u> T1c: 109 (35%) T2a: 122 (39%) T2b: 36 (11%) T2c: 33 (11%) T3: 14 (4%) <u>PSA:</u> ≤10: 238 (76%) 10.1–20: 54 (17%) ≥20: 22 (7%) <u>Gleason score:</u> ≤6: 138 (44%) ≥7: 176 (56%) <u>Risk group:</u> Low: 109 (35%) Intermediate: 151 (48%) High: 54 (17%)
Wong et al. 2009 <sup>88</sup> (continued)	BT: 225 patients				<u>Clinical T Stage:</u> T1c: 114 (51%) T2a: 83 (37%) T2b: 24 (11%) T2c: 4 (2%) T3: 0 (0%) <u>PSA:</u> ≤10: 193 (86%) 10.1–20: 28 (12%) ≥20: 4 (2%) <u>Gleason score:</u> ≤6: 173 (77%) ≥7: 52 (23%) <u>Risk group:</u> Low: 158 (70%) Intermediate: 58 (26%) High: 9 (4%)

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
	EBRT plus BT: 44 patients				<u>Clinical T Stage:</u> T1c: 13 (30%) T2a: 10 (23%) T2b: 16 (36%) T2c: 4 (9%) T3: 1 (2%) <u>PSA:</u> ≤10: 29 (65%) 10.1 – 20: 13 (30%) ≥20: 2 (5%) <u>Gleason score:</u> ≤6: 20 (45%) ≥7: 24 (55%) <u>Risk group:</u> Low: 14 (32%) Intermediate: 23 (52%) High: 7 (16%)
Krambeck et al. 2008 <sup>65</sup>	RRP: 588 patients	Median age at surgery: 61 years (range, 41 to 77)	NR	NR	<u>Median PSA level:</u> 5.0 (range 0.6 to 39.7) <u>Clinical stage:</u> T1a/b: 4 (0.7%) T1c: 418 (71.1%) T2a: 130 (22.1%) T2b: 28 (4.8%) T3 or T4: 8 (1.4%) <u>Biopsy Gleason grade:</u> <6: 0 (0%) 6: 441 (75.0%) 7: 133 (22.6%) ≥8: 14 (2.3%) <u>Pathological stage:</u> T2aN0: 206 (35.0%) T2bN0: 315 (53.6%) T3aN0: 35 (6.0%) T3b4N0: 24 (4.1%) TxN+: 8 (1.4%) <u>Pathological Gleason grade:</u> 6: 391 (66.5%) 7: 167 (28.4%) ≥8: 30 (5.1%)

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
	RALRP: 294 patients	Median age at surgery: 61 years (38 to 76)	NR	NR	<u>Median PSA level:</u> 4.9 (range 0.5 to 33.5) <u>Clinical stage:</u> T1a/b: 0 (0%) T1c: 214 (72.8%) T2a: 75 (25.5%) T2b: 4 (1.4%) T3 or T4: 1 (0.3%) <u>Biopsy Gleason grade:</u> <6: 2 (0.7%) 6: 212 (72.1%) 7: 70 (23.8%) ≥8: 10 (3.4%) <u>Pathological stage:</u> T2aN0: 105 (35.8%) T2bN0: 159 (54.3%) T3aN0: 15 (5.1%) T3b4N0: 14 (4.8%) TxN+: 0 (0%) <u>Pathological Gleason grade:</u> 6: 192 (65.5%) 7: 87 (29.7%) ≥8: 14 (4.8%)
Lu-Yao et al. 2008 <sup>78</sup>	ADT: 7,867 patients	Median (IQR): 79 years (74 to 83)	Black: 758 (9.6%)	CCI status: 0 to 1: 7,446 (94.7%) ≥2: 421 (5.3%)	<u>Cancer grade:</u> Well-differentiated: 64 (0.8%) Moderately differentiated: 5,115 (65.0%) Poorly differentiated: 2,688 (34.2%) <u>Clinical stage:</u> T1: 3,915 (49.8%) T2: 3,952 (50.2%)
	Conservative management: 11,404 patients	Median (IQR): 77 years (72 to 81)	Black: 1,307 (11.5%)	CCI status: 0 to 1: 10,664 (93.5%) ≥2: 740 (6.5%)	<u>Cancer grade:</u> Well-differentiated: 244 (2.1%) Moderately differentiated: 9,545 (83.7%) Poorly differentiated: 1,615 (14.2%) <u>Clinical stage:</u> T1: 7,325 (64.2%) T2: 4,079 (35.8%)

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
Sanda et al. 2008 <sup>85</sup>	RP (RRP or LRP or RALRP): 603 patients	Median (range): 59 (38-79)	White, n (%): 548 (91) Black, n (%): 31 (5) Other, n (%): 15 (2) Not reported, n (%): 9 (1)	Mean number of coexisting illnesses, n (SD): 0.9 (1.1)	<u>PSA ng/mL:</u> Mean (SD), median, range: 6.7 (5.7), 5.5, 0.5–71.6 <u>Group, n (%):</u> <4: 126 (21) 4–10: 399 (66) >10: 78 (13) <u>Gleason score, n (%):</u> <7: 371 (62) 7: 207 (34) >7: 25 (4) <u>Clinical stage, n (%):</u> T1: 436 (72) T2: 167 (28) <u>Overall cancer severity, n (%):</u> Low risk: 267 (44) Intermediate risk: 302 (50) High risk: 25 (4)
	EBRT (IMRT or 3D-CRT): 292 patients	Median (range): 69 (45–84)	White, n (%): 238 (82) Black, n (%): 47 (16) Other, n (%): 2 (1) Not reported, n (%): 5 (2)	Mean number of coexisting illnesses, n (SD): 1.5 (1.2)	<u>PSA ng/mL:</u> Mean (SD), median, range: 9.1 (10.1), 6.3, 0.5-99.3 <u>Group, n (%):</u> <4: 46 (16) 4–10: 177 (61) >10: 69 (24) <u>Gleason score, n (%):</u> <7: 129 (44) 7: 123 (42) >7: 40 (14) <u>Clinical stage, n (%):</u> T1: 202 (69) T2: 90 (31) <u>Overall cancer severity, n (%):</u> Low risk: 80 (27) Intermediate risk: 159 (54) High risk: 53 (18)

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
Sanda et al. 2008 <sup>85</sup> (continued)	BT: 306 patients	Median (range): 65 (44–84)	White, n (%): 265 (85) Black, n (%): 36 (12) Other, n (%): 5 (2) Not reported, n (%): 5 (2)	Mean number of coexisting illnesses, n (SD): 1.3 (1.1)	<u>PSA ng/mL:</u> Mean (SD), median, range: 5.8 (3.6), 5.1, 0.6-44.0 <u>Group, n (%):</u> <4: 67 (22) 4–10: 217 (71) >10: 21 (7) <u>Gleason score, n (%):</u> <7: 227 (74) 7: 76 (25) >7: 2 (1) <u>Clinical stage, n (%):</u> T1: 254 (83) T2: 51 (17) <u>Overall cancer severity, n (%):</u> Low risk: 182 (59) Intermediate risk: 119 (39) High risk: 4 (1)

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
Schroeck et al. 2008 <sup>54</sup>	RRP: 435 patients	Median (IQR): 60.3 years (55.3 to 64.7)	African American: 74 (17.1%) Other: 359 (82.9%)	NR	<u>Median PSA (IQR):</u> 5.3 (4.1 to 7.2) <u>Clinical stage:</u> T1: 296 (72.4%) T2: 101 (24.7%) T3: 12 (2.9%) <u>Biopsy Gleason score:</u> 2 to 6: 241 (58.8%) 7: 127 (31.0%) 8 to 10: 42 (10.2%) <u>D'Amico risk classification:</u> Low: 189 (50.9%) Intermediate: 125 (33.7%) High: 57 (15.4%) <u>Median EBL (IQR):</u> 800 (500 to 1200) <u>Lymphadenectomy:</u> 313 (72.0%) <u>Pathological stage:</u> T2: 324 (74.5%) ≥T3: 111 (25.5%) <u>Pathological Gleason score:</u> 2 to 6: 177 (40.7%) 7: 199 (45.7%) 8 to 10: 59 (13.6%) <u>Pathological node status:</u> pN0: 225 (96.6%) pN1: 8 (3.4%) <u>Seminal vesicle invasion:</u> 42 (9.7%) <u>Extracapsular extension:</u> 102 (23.4%) <u>PSM status:</u> 122 (28.0%) <u>Median (IQR) Prostate weight in grams:</u> 41.3 (32.4 to 52.0)



Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
Schroeck et al. 2008 <sup>54</sup> (continued)	RALRP: 362 patients	Median (IQR): 59.2 years (54.5 to 63.8)	African American: 56 (16.6%) Other: 282 (83.4%)	NR	<u>Median PSA (IQR):</u> 5.4 (4.1 to 7.1) <u>Clinical stage:</u> T1: 281 (83.1%) T2: 57 (16.9%) T3: 0 (0%) <u>Biopsy Gleason score:</u> 2 to 6: 254 (72.2%) 7: 89 (25.3%) 8 to 10: 9 (2.6%) <u>D'Amico risk classification:</u> Low: 211 (65.7%) Intermediate: 95 (29.6%) High: 15 (4.7%) <u>Median EBL (IQR):</u> 150 (100 to 173) <u>Lymphadenectomy:</u> 271 (74.9%) <u>Pathological stage</u> T2: 287 (79.3%) ≥T3: 75 (20.7%) <u>Pathological Gleason score:</u> 2 to 6: 168 (46.4%) 7: 176 (48.6%) 8 to 10: 18 (5.0%) <u>Pathological node status:</u> pN0: 163 (99.4%) pN1: 1 (0.6%) <u>Seminal vesicle invasion:</u> 11 (3.0%) <u>Extracapsular extension:</u> 71 (19.6%) <u>PSM status</u> 106 (29.3%) <u>Median (IQR) Prostate weight in grams:</u> 42.9 (34.3 to 55.0)

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
Sumitomo et al. 2008 <sup>63</sup>	HIFU: 260 patients	Median age (SD, range): 67.7 (7.2, 45–88)	NR	NR	<u>Mean PSA ng/mL (SD, range):</u> 9.1 (4.4, 2.3-29.4) <u>Mean Gleason score (SD, range):</u> 6.3 (1.1, 3-10) <u>Clinical T stage, N:</u> T1: 162 T2a: 25 T2b: 35 T2c: 32 T3: 6 <u>Risk level, N:</u> Low: 93 Intermediate: 102 High: 65
	HIFU plus ADT: 270 patients	Median age (SD, range): 68.2 (6.7, 52–85)			<u>Mean PSA ng/mL (SD, range):</u> 11.6 (6.2, 2.8-29.5) <u>Mean Gleason score (SD, range):</u> 6.3 (1.3, 2-10) <u>Clinical T stage, N:</u> T1: 158 T2a: 19 T2b: 44 T2c: 28 T3: 21 <u>Risk level:</u> Low: 70 Intermediate: 113 High: 87

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
Albertsen et al. 2007 <sup>42</sup>	Surgery: 596 patients	Median: 65 years	NR	% CCI score >1: 4%	<u>% DRE finding:</u> 1 nodule: 34% Multiple nodules on one side: 3% Nodule 2 sides: 2% <u>% Gleason score:</u> 2 to 4: 3% 5: 5% 6: 53% 7: 27% 8 to 10: 12% <u>% PSA (ng/mL):</u> 0 to 3.9: 11% 4 to 9.9: 46% 10 to 19: 28% 20 to 49: 15% Median: 9.1 <u>% D'Amico risk category:</u> Low: 35% Intermediate: 39% High: 26%
Albertsen et al. 2007 <sup>42</sup> (continued)	Radiation: 642 patients	Median: 71 years	NR	% CCI score >1: 10%	<u>% DRE finding:</u> 1 nodule: 32% Multiple nodules on one side: 6% Nodule 2 sides: 4% <u>% Gleason score:</u> 2 to 4: 3% 5: 6% 6: 46% 7: 25% 8 to 10: 20% <u>% PSA (ng/mL):</u> 0 to 3.9: 9% 4 to 9.9: 40% 10 to 19: 29% 20 to 49: 22% Median: 10.3 <u>% D'Amico risk category</u> Low: 26% Intermediate: 36% High: 38%

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
Albertsen et al. 2007 <sup>42</sup> (continued)	Observation: 114 patients	Median: 70 years	NR	% Charlson comorbidity score >1: 11%	<u>% DRE:</u> Multiple nodules on one side: 4% Nodule 2 sides: 0% <u>% Gleason score:</u> 2 to 4: 17% 5: 15% 6: 46% 7: 11% 8 to 10: 11% <u>% PSA (ng/mL):</u> 0 to 3.9: 27% 4 to 9.9: 44% 10 to 19: 17% 20 to 49: 12% Median: 6.6 <u>% D'Amico risk category</u> Low: 58% Intermediate: 20% High: 22%
D'Amico et al. 2007 <sup>87</sup>	RRP: 660 patients	Median age (IQR): 67 years (62-71)	NR	NR	<u>PSA:</u> ≤4: 146 (22%) >4 10: 372 (56%) >10–20: 99 (15%) >20: 43 (7%) <u>Gleason score:</u> ≤6: 315 (48%) 7: 271 (41%) 8–10: 74 (11%) <u>T stage:</u> T1c: 451 (68%) T2a: 140 (21%) T2b: 53 (8%) T2c: 16 (2%) T3a or T3b: 0 (0%)

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
D'Amico et al. 2007 <sup>87</sup> (continued)	3D-CRT: 288 patients	Median age (IQR): 72 years (68–76)			<u>PSA:</u> ≤4: 16 (6%) >4–10: 147 (51%) >10–20: 81 (28%) >20: 44 (15%) <u>Gleason score:</u> ≤6: 100 (35%) 7: 148 (51%) 8–10: 40 (14%) <u>T stage:</u> T1c: 116 (40%) T2a: 79 (27%) T2b: 54 (19%) T2c: 27 (9%) T3a or T3b: 12 (4%)

**Abbreviations:** 3D-CRT=Three-dimensional conformal radiotherapy; ACE=Adult Comorbidity Evaluation; ADT=androgen-deprivation therapy; AJCC=American Joint Committee on Cancer; bGS=baseline Gleason score; BMI=body mass index; BT=brachytherapy; CAD=coronary artery disease; CCI=Charlson Comorbidity Index; CIRS-G=Cumulative Illness Rating Scale for Geriatrics; DRE=digital rectal exam; EB-IGRT=external beam image-guided radiation therapy; EBL=estimated blood loss; EBRT=external beam radiation therapy; ED=erectile dysfunction; HDR=high dose rate; HIFU=high-intensity focused ultrasound; HT=hormone therapy; IGRT=image-guided radiation therapy; IMRT=intensity-modulated radiation therapy; IQR=interquartile range; LDR=low dose rate; LRP=laparoscopic radical prostatectomy; MI=myocardial infarction; NCCN=National Comprehensive Cancer Network; NCI=National Cancer Institute; NOS=not otherwise specified; NR=not reported; PSA=prostate-specific antigen; PSM=positive surgical margin; RALP=robotic-assisted laparoscopic prostatectomy; RALRP=robotic-assisted laparoscopic radical prostatectomy; RP=radical prostatectomy; RRP=radical retropubic prostatectomy; T=tumor stage; TURP=transurethral resection of the prostate; WW=watchful waiting.

## Appendix F. Evidence Tables

**Table F-1. All-cause mortality (randomized controlled trials)**

Study Outcomes	Treatment Group 1	Treatment Group 2	Analyses; p-Values
Wilt et al. 2012 <sup>25</sup> Prostate Intervention Versus Observation Trial (PIVOT)	Observation: 364 patients	RP: 364 patients	HR (95% CI), p-value for interaction
Overall death from any cause at median followup of 10 years (number of events/total number of patients)	183/367	171/364	0.88 (0.71–1.08) p=0.22
<i>Age</i>	—	—	p=0.85
<65 years	50/131	43/122	0.89 (0.59–1.34)
>65 years	133/236	128/242	0.84 (0.63–1.08)
<i>Race</i>	—	—	p=0.81
White	119/220	117/232	0.84 (0.65–1.08)
Black	53/121	46/111	0.93 (0.62–1.38)
Other	11/26	8/21	0.85 (0.34–2.11)
<i>Charlson score</i>	—	—	p=0.79
0	86/220	82/224	0.90 (0.66–1.23)
≥1	97/157	89/140	0.84 (0.63–1.13)
<i>Performance score</i>	—	—	p=0.66
0	146/310	139/312	0.89 (0.71–1.13)
1–4	37/57	32/52	0.82 (0.51–1.31)
<i>Prostate specific antigen (PSA)</i>	—	—	p=0.04
≤10	101/241	110/238	1.03 (0.79–1.35)
>10	77/125	61/126	0.67 (0.48–0.94)
<i>Risk</i>	—	—	p=0.07
Low	54/148	62/148	1.15 (0.80–1.66)
Intermediate	70/120	59/129	0.69 (0.49–0.98)
High	49/80	42/77	0.74 (0.49–1.13)
<i>Gleason score</i>	—	—	p=0.87
<7	125/261	113/254	0.86 (0.67–1.12)
≥7	47/86	50/98	0.84 (0.56–1.25)
At 12 years (percentage of men who died). The authors did not provide subgroup data for patients at 12 years followup	43.9	40.9	

Study Outcomes	Treatment Group 1	Treatment Group 2	Analyses; p-Values
Bill-Axelson et al. 2011 <sup>33</sup> Same study as Holmberg et al. 2012 <sup>34</sup> , and Bill-Axelson et al. 2008 <sup>15</sup> Scandinavian Prostate Cancer Group-4 (SPCG-4) Trial	WW: 348 patients	RP: 347 patients	ARR and or RR, 95% CI, p-value for interaction
Total number of deaths, cumulative incidence (number [% [95% CI]) at a median followup of 10.8 years	156 (44.8)	137 (39.5)	p=0.09
All ages at 8 years followup	22.4 (18.4–27.3)	17.9 (14.3–22.4)	ARR with RP, % (95% CI): 4.6 (-1.4–10.5)
All ages at 12 years followup	39.8 (34.7–45.7)	32.7 (27.9–38.4)	ARR with RP: 7.1 (-0.5–14.7) RR with RP: 0.82 (0.65–1.03) p=0.09
Age <65 years at 8 years followup	23.5 (17.8–30.9)	12.1 (7.9–18.5)	ARR with RP: 11.4 (3.1–19.6)
Age <65 years at 12 years followup	40.2 (33.0 – 49.0)	21.9 (16.1–29.9)	ARR with RP: 18.3 (7.8–28.8) RR with RP: 0.59 (0.41–0.85) p=0.004
Age ≥65 years at 8 years followup	21.4 (16.2–28.3)	22.6 (17.4–29.5)	ARR with RP: -1.2 (-9.6–7.30)
Age ≥65 years at 12 years followup	39.3 (32.5–47.7)	42 (35–50.5)	ARR with RP: -2.7 (-13.5–8.0) RR with RP: 1.04 (0.77–1.40) p=0.81
Total number of deaths, cumulative incidence (number [% [95% CI]) at median followup of 12.8 years	201 (57.8)	166 (47.8)	p=0.007
All at 15 years followup	52.7 (47.4–58.6)	46.1 (40.8–52.0)	ARR 6.6% (-1.3–14.5), p=0.007
Low risk cancer at 15 years followup	44.6 (36.6–54.4)	31.4 (23.9–41.3)	ARR with RP: 13.2 (0.9–25.5) RR with RP: 0.62 (0.42–0.92) p=0.02
Age <65 years at 15 years followup	47.4 (40.0–56.1)	33.9 (26.9–42.6)	ARR with RP: 13.2 (0.9–25.5) RR with RP: 0.52 (0.37–0.73) p<0.001
Age <65 years and low risk cancer at 15 years followup	36.2 (26.1–50.2)	16.9 (9.5–30.1)	ARR with RP: 19.3 (4.0–34.7) RR with RP: 0.36 (0.18–0.70) p=0.002
Age ≥65 years at 15 years followup	57.4 (50.2–65.8)	56.7 (49.5–65.0)	ARR with RP: 0.7 (-10.3–11.7) RR with RP: 0.98 (0.75–1.28) p=0.89

Study Outcomes	Treatment Group 1	Treatment Group 2	Analyses; p-Values
Age ≥65 years and low risk cancer at 15 years followup	52.9 (41.3–67.6)	46.8 (35.1–62.3)	ARR with RP: 6.1 (-12.6–24.8) RR with RP: 0.92 (0.57–1.49) p=0.74
Nguyen et al. 2010 <sup>53</sup>	3D-CRT: 104 patients	3D-CRT plus ADT: 102 patients	—
All-cause mortality among healthy men (i.e., with mild or no comorbidity)	Adjusted HR 0.36; 96% CI, 0.13 to 0.98		p=0.046
All-cause mortality among men with moderate or severe comorbidity)	Adjusted HR 5.2; 96% CI, 1.3 to 20.2		p=0.018
D'Amico et al. 2008 <sup>35</sup>	EBRT: 104 patients	EBRT plus ADT: 102 patients	HR (95% CI), p-value for interaction
Overall death in all patients at median followup of 7.6 years (range 0.5–11.0)	44	30	1.8 (1.1– 2.9), p=0.01
Overall death (No or Minimal Comorbidity)	31	11	4.2 (2.1–8.5), p<0.001
Overall death (Moderate or Severe Comorbidity)	13	19	0.54 (0.27–1.10), p=0.08
D'Amico et al. 2008 <sup>35</sup>	Radiation therapy: 103 patients	Radiation therapy plus AST: 98 patients	HR (95% CI)
Overall mortality at a median of 4.52 years followup	23	12	2.07 (1.02–4.20), p=0.04

**Abbreviations:** 3D-CRT=Three-dimensional conformal radiation therapy; ADT=androgen-deprivation therapy; ARR=absolute risk reduction; CI=confidence interval; EBRT=external beam radiation therapy; HR=hazard ratio; RP=radical prostatectomy; RR=relative risk; WW=watchful waiting.



**Table F-2. All-cause mortality (nonrandomized comparative studies)**

Study Outcomes	Treatment Group 1	Treatment Group 2	Treatment Group 3	Analyses; p-Values
Mukherjee et al. 2014 <sup>37</sup>	RP: 5,805 patients	EBRT: 2,183 patients	BT: 2,936 patients	—
All-cause mortality (median followup 3.05 years)	3.6%	28.8%	4.6%	p<0.001
Rice et al. 2011 <sup>36</sup>	RP: 194	EBRT: 252	WW without secondary treatment: 214 patients WW with secondary treatment: 110 patients	—
Overall mortality with a mean followup of 6.8±4.0 years	—	1.355 (0.871 to 2.108)	WW without secondary treatment 1.938 (1.185 to 3.168) WW with secondary treatment HR 0.807 (0.462 to 1.407)	RP vs. EBRT: p=0.1781 RP vs. WW without secondary treatment: p=0.0084 RP vs. WW with secondary treatment: p=0.4494 Multivariable cox proportional hazards model predicting overall mortality using pretreatment variables and treatment-related variables with RP as the comparator group.
Overall mortality with a mean followup of 6.8±4.0 years for age at diagnosis (per year)	HR 1.093 (1.043 to 1.145)			Multivariable cox proportional hazards model predicting overall mortality using pretreatment variables and treatment-related variables, p=0.0002
Overall mortality with a mean followup of 6.8±4.0 years for PSA (per ng/mL)	HR 1.061 (0.990 to 1.136)			Multivariable cox proportional hazards model predicting overall mortality using pretreatment variables and treatment-related variables, p=0.0922
Overall mortality with a mean followup of 6.8±4.0 years for Race/ethnicity	Black: 1.603 (0.924 to 2.782) Other: 0.618 (0.227 to 1.686)			Multivariable cox proportional hazards model predicting overall mortality using pretreatment variables and treatment-related variables with White as the comparator group. White vs. Black: 0.0933 White vs. Other: 0.3474
Overall mortality with a mean followup of 6.8±4.0 years for number of comorbidities	1: HR 1.371 (0.865 to 2.173) 2: 1.778 (1.113 to 2.842) ≥3: 2.392 (1.462 to 3.916)			Multivariable cox proportional hazards model predicting overall mortality using pretreatment variables and treatment-related variables with no comorbidities as the comparator group. 0 vs. 1: 0.1792 0 vs. 2: 0.0161 0 vs. ≥3: 0.0005

Study Outcomes	Treatment Group 1	Treatment Group 2	Treatment Group 3	Analyses; p-Values
Overall mortality with a mean followup of 6.8±4.0 years for clinical T stage	T2a: HR 0.931 (0.676 to 1.282)			Multivariable cox proportional hazards model predicting overall mortality using pretreatment variables and treatment-related variables with T1 as the comparator group. T1 vs. T2a: 0.6602
Hoffman et al. 2013 <sup>38</sup>	RP: 1,164 patients	EBRT with or without ADT: 491 patients	Not applicable (NA)	—
All-cause mortality after 15 years of followup	HR, 0.60; 95% confidence interval (CI), 0.53 to 0.70			p<0.0001
All-cause mortality among men aged 55 to 64 years	RP: 17.7% (111 of 628) vs. EBRT: 38.9% (51 of 131), HR, 0.41; 95% CI, 0.32 to 0.53.			—
All-cause mortality among men aged 65 to 74 years	RP: 39% (209 of 536) vs. EBRT: 54.7% (197 of 360), HR, 0.41; 95% CI, 0.32 to 0.53			p<0.001
All-cause mortality among men who had no comorbidity	RP: 21.6% (111 of 513) vs. EBRT: 45.3% (72 of 159), HR, 0.52; 95% CI, 0.41 to 0.65			—
All-cause mortality among men who reported any comorbidity	RP: 32.1% (209 of 651) vs. EBRT: 53.0% (176 of 332), HR, 0.67; 95% CI, 0.57 to 0.78			p=0.049
All-cause mortality among men with high-risk tumors, diagnostic PSA >10 ng/mL or Gleason score ≥8	RP: 33.3% (127 of 381) vs. EBRT plus ADT: 62.5% (35 of 56), HR, 0.65; 95% CI, 0.48 to 0.87			—
All-cause mortality among men with low-risk tumors, diagnostic PSA <10 ng/mL or Gleason score ≤6	RP: 22.9% (128 of 558), EBRT: 36.9% [72 of 195], HR, 0.78; 95% CI, 0.63 to 0.96			p=0.3
Liu et al. 2013 <sup>79</sup>	RP: 1,624 patients	ADT: 1,624 patients	NA	—
All-cause mortality at median followup of 2.95 years in the RP group and 2.87 years in the ADT group, n (%)	56 (3.45)	266 (16.38)		HR 2.98 (2.35 to 3.79), p<0.001
All-cause mortality among white men at 2.95 years median followup in the RP group and 2.87 years median followup in the ADT group	ADT vs. RP: HR 0.80 (95% CI, 0.62 to 1.02)			p=0.073

Study Outcomes	Treatment Group 1	Treatment Group 2	Treatment Group 3	Analyses; p-Values
All-cause mortality among men with CCI $\leq 2$ at 2.95 years median followup in the RP group and 2.87 years median followup in the ADT group	ADT vs. RP: HR 1.66 (95% CI, 1.27 to 2.17)			p<0.001
All-cause mortality among men with CCI >2 at 2.95 years median followup in the RP group and 2.87 years median followup in the ADT group	ADT vs. RP: HR 2.21 (95% CI, 1.51 to 3.22).			p<0.001
All-cause mortality among men with low PSA at 2.95 years median followup in the RP group and 2.87 years median followup in the ADT group	ADT vs. HR 0.76 (95% CI, 0.43 to 1.33)			p=0.339
All-cause mortality among men with medium PSA at 2.95 years median followup in the RP group and 2.87 years median followup in the ADT group	ADT vs. RP: HR 1.20 (95% CI, 0.61 to 2.36)			p=0.606
All-cause mortality among men with high PSA at 2.95 years median followup in the RP group and 2.87 years median followup in the ADT group	ADT vs. RP: HR 1.30 (95% CI, 0.59 to 2.86)			p=0.516
All-cause mortality among men with unknown PSA at 2.95 years median followup in the RP group and 2.87 years median followup in the ADT group	ADT vs. RP: HR 1.30 (95% CI, 0.89 to 1.89)			p=0.179
All-cause mortality among men with T2 stage at 2.95 years median followup in the RP group and 2.87 years median followup in the ADT group	ADT vs. RP: HR 1.33 (95% CI, 1.00 to 1.76)			p=0.046

Study Outcomes	Treatment Group 1	Treatment Group 2	Treatment Group 3	Analyses; p-Values
All-cause mortality among men with worse Gleason score at 2.95 years median followup in the RP group and 2.87 years median followup in the ADT group	ADT vs. RP: HR 1.29 (95% CI, 1.02 to 1.62)			p=0.032
Nepple et al. 2013 <sup>40</sup>	RP: 4,459 patients	EBRT: 1,261 patients	Brachytherapy (BT): 972 patients	—
All-cause mortality among men after median followup of 7.2 years	Both EBRT (HR, 1.71; 95% CI, 1.40 to 2.08) and BT (HR, 1.78; 95% CI, 1.37 to 2.31) were associated with increased all-cause mortality in comparison with RP.			—
Cooperberg et al. 2010 <sup>39</sup>	RP: 5,066 patients	EBRT: 1,143 patients	ADT: 1,329 patients	—
All-cause mortality at median followup 3.9 years, 4.5 years, and 3.6 years for RP, EBRT, and ADT, respectively.	Relative to RP, the adjusted HRs were 2.21 (95% CI, 1.50 to 3.24) for EBRT and 3.22 (95% CI, 2.16 to 4.81) for ADT. The HR for ADT relative to EBRT was 1.45 (95% CI, 1.02 to 2.07)			—
Dosoretz et al. 2010 <sup>82</sup>	BT: 1,391 patients	Brachytherapy with ADT: 1,083 patients		Cox regression analysis of time to all-cause mortality. HR (95% CI) for adjusted risk of all-cause mortality by patient baseline characteristics.
All-cause mortality – all patients	NA	NA		Cox regression analysis time to all-cause mortality: There was a significant interaction between hormone therapy and increasing age (adjusted HR 1.04 (1.01 to 1.07), p=0.0035). Age and hormone therapy use (p=0.0049) were also significantly associated with risk of ACM whereas known prostate cancer prognostic risk factors, including PSA, biopsy Gleason score, clinical T classification were not associated.
All-cause mortality – all patients	NA	NA		Adjusted HR for age: 1.03 (1.01 to 1.05), p=0.0013
All-cause mortality – all patients	NA	NA		Adjusted HR for PSA: 1.003 (0.996 to 1.010), p=0.4252
All-cause mortality – all patients	NA	NA		Adjusted HR for Gleason score: <7 reference, ≥7 1.186 (0.972 to 1.448), p=0.0937
All-cause mortality – all patients	NA	NA		Adjusted HR for tumor classification: T1 reference, T2 or T3 0.977 (0.831 to 1.149), p=0.7816
All-cause mortality – all patients	NA	NA		Adjusted HR for ADT no reference, ADT=yes 0.049 (0.0006 to 0.403), p=0.0049

Study Outcomes	Treatment Group 1	Treatment Group 2	Treatment Group 3	Analyses; p-Values
All-cause mortality – all patients	NA	NA		Adjusted HR for ADT*age: 1.043 (1.014 to 1.072), p=0.0035
All-cause mortality – <73 years	NA	NA		Adjusted HR for age: 1.03 (0.996 to 1.055), p=0.084
All-cause mortality – <73 years	NA	NA		Adjusted HR for PSA: 1.123 (0.896 to 1.406), p=0.3132
All-cause mortality – <73 years	NA	NA		Adjusted HR for Gleason score: <7 reference, ≥7 0.916 (0.616 to 1.363), p=0.665
All-cause mortality - <73 years	NA	NA		Adjusted HR for tumor classification: T1 reference, T2 or T3 0.904 (0.685 to 1.194), p=0.4769
All-cause mortality – <73 years	NA	NA		Adjusted HR for ADT no reference, ADT=yes 0.874 (0.662 to 1.153), p=0.3402
All-cause mortality – ≥73 years	NA	NA		Adjusted HR for age: 1.055 (1.025 to 1.085), p=0.0022
All-cause mortality – ≥73 years	NA	NA		Adjusted HR for PSA: 1.015 (0.876 to 1.176), p=0.8451
All-cause mortality – ≥73 years	NA	NA		Adjusted HR for Gleason score: <7 reference, ≥7 1.293 (1.026 to 1.630), p=0.0297
All-cause mortality – ≥73 years	NA	NA		Adjusted HR for tumor classification: T1 reference, T2 or T3 1.014 (0.829 to 1.240), p=0.8945
All-cause mortality – ≥73 years	NA	NA		Adjusted HR for ADT no reference, ADT=yes 1.243 (1.013 to 1.1525), p=0.0369
Hadley et al. 2010 <sup>73</sup>	Observation: 5,879 patients	RP: 11,936 patients	NA	Cox proportional hazards model using three approaches: traditional multivariable survival analysis, propensity score adjustment, and instrumental variable analysis
Multivariable survival analysis	0.249 (0.237 to 0.263)	0.177 (0.170 to 0.185)		HR 1.47 (1.35 to 1.59)
Propensity score adjustments (inverse probability of treatment weights)	0.236 (0.223 to 0.248)	0.185 (0.177 to 0.193)		HR 1.54 (1.46 to 1.62)
Propensity score adjustments (standardized mortality ratio weights)	0.250 (0.237 to 0.263)	0.203 (0.195 to 0.211)		HR 1.46 (1.33 to 1.59)
Instrumental variable approach	0.208 (0.199 to 0.218)	0.192 (0.183 to 0.201)		HR 1.09 (0.46 to 2.59)

Study Outcomes	Treatment Group 1	Treatment Group 2	Treatment Group 3	Analyses; p-Values
Krambeck et al. 2008 <sup>65</sup> Death from any cause	Radical retropubic prostatectomy: 4 patients	Robotic-assisted radical laparoscopic prostatectomy: 4 patients	NA	Median followup time was 1.3 years.
Lu-Yao et al. 2008 <sup>78</sup> Overall mortality – all cancer grades combined	ADT: 4,729/39,767 events/person-year, rate per 100=11.9	Observation 6,316/66,567 events/person-year, rate per 100=9.5		Adjusted HR (95% CI) 1.17 (1.12 to 1.21) p<0.05

**Abbreviations:** ADT=Androgen-deprivation therapy; BT=brachytherapy; CCI=Charlson Comorbidity Index; CI=confidence interval; EBRT=external beam radiation therapy; HR=hazard ratio; PSA=prostate-specific antigen; RP=radical prostatectomy; WW=watchful waiting.

**Table F-3. Overall survival (randomized controlled trials)**

Study Outcomes	Treatment Group 1	Treatment Group 2	Analyses; p-Values
Wilt et al. 2012 <sup>25</sup> Prostate Intervention Versus Observation Trial (PIVOT)	Observation: 364 patients	RP: 364 patients	HR (95% CI), p-value for interaction
Median survival (median followup 10 years)	12.4 years (95% CI, 11.4-13.1)	13.0 years (95% CI, 12.2-13.7)	—
Jones et al. 2011 <sup>43</sup>	EBRT: 992 patients	EBRT plus ADT: 987 patients	—
Overall survival at 10 years [number of patients (% reaching end point)]	—	—	—
All patients	992 (57)	62% in the text	1.17 (1.01–1.35), p=0.03
Low risk	334 (64)	—	1.07 (0.83–1.39)
Intermediate risk	544 (54)	—	1.23 (1.02–1.49), p=0.03
High risk	114 (51)	—	1.16 (0.78–1.71)
White	756 (57)	—	1.19 (1.01–1.41), p=0.04
Black	197 (55)	—	1.15 (0.84–1.58)
Age ≤70 years	471 (64)	—	1.23 (0.98–1.54)
Age >70 years	521 (50)	—	1.11 (0.92–1.33)
Donnelly et al. 2010 <sup>47</sup>	EBRT: 122 patients	Cryotherapy: 122 patients	—
Overall survival at 5 years(% reaching end point)	88.5%	89.7%	Difference 1.2 (-6.8–9.2)
D'Amico et al. 2008 <sup>35</sup>	EBRT: 104 patients	EBRT plus ADT: 102 patients	—
Kaplan-Meir estimates of 8-year survival rates, % points (95% CI)	61% (95% CI, 49%–71%)	74% (95% CI, 64%-82%)	—
Rates of survival free of salvage AST at 5 years, % points (95% CI)	57% (46%–69%)	82% (73%–90%)	—
D'Amico et al. 2008 <sup>35</sup>	EBRT: 103 patients	EBRT plus ADT: 98 patients	HR (95% CI)
Survival free of salvage AST at median of 4.52 years followup, number of patients	43	21	2.30 (1.36–3.89), p=0.002

**Abbreviations:** ADT=Androgen-deprivation therapy; AST=aspartate aminotransferase; CI=confidence interval; EBRT=external beam radiation therapy; HR=hazard ratio; RP=radical prostatectomy.

**Table F-4. Overall survival (nonrandomized comparative studies)**

Study Outcomes	Treatment Group 1	Treatment Group 2	Treatment Group 3	Analyses; p-Values
Ferrer et al.2013 <sup>91</sup> Same study as Ferrer et al. 2008 <sup>61</sup>	RRP: 193 patients	3D-CRT: 194 patients	BT: 317 patients	—
Number of patients who died at median duration of 6.02 years followup	12	24	31	—
	Cox regression model: RRP vs. 3D-CRT (HR 1.47; 95% CI, 0.58-3.72)			p=0.417
	Cox regression model: RRP vs. BT (HR 1.17; 95% CI, 0.47-2.94)			p=0.737
Age group <65 years vs. 65–70 years	Cox regression model: HR 1.96; 95% CI, 0.89-4.30			p=0.093
Age group younger than 65 years vs. older than 70 years	Cox regression model: HR 2.95; 95% CI, 1.34-6.47			p=0.007
Low risk vs. intermediate risk	Cox regression model: HR 1.13; 95% CI, 0.54-2.36			p=0.754
Liu et al. 2013 <sup>79</sup>	RP: 1,624 patients	ADT: 1,624 patients	Not applicable (NA)	—
Kaplan-Meier 8-year survival rate (%)	79.62	43.39	—	—
Kaplan-Meier 5-year survival rate (%)	92.08	74.81	—	—
Kaplan-Meier 3-year survival rate (%)	96.06	89.66	—	—
Marina et al. 2013 <sup>86</sup>	IGRT: 734 patients	BT: 282 patients	NA	
5-year overall survival, % (range)	86 (83-89)	92 (89-96)	—	0.009
8-year overall survival, % (range)	75 (70-80)	86 (81-91)	—	
Kibel et al. 2012 <sup>75</sup> Adjusted 10-year overall survival	RP: 88.9% (95% CI, 87.5 to 90.1)	EBRT: 82.6% (95% CI, 79.8 to 85.0)	BT: 81.7% (95% CI, 78.7 to 84.4)	Kaplan-Meier analysis p-value NR.
Overall survival multivariable analysis (treatment group)	1.0 (referent)	1.6 (95% CI, 1.4 to 1.9)	1.7 (95% CI, 1.4 to 2.1)	HR p-value: <0.001
Overall survival multivariable analysis (patient age)	NR	NR	NR	HR 2.2 (95% CI, 1.7–2.9), p<0.001.



Study Outcomes	Treatment Group 1	Treatment Group 2	Treatment Group 3	Analyses; p-Values
Overall survival multivariable analysis (African-American ethnicity)	NR	NR	NR	HR 1.5 (95% CI, 1.2–1.8), p<0.001.
Overall survival multivariable analysis (comorbidity)	NR	NR	NR	HR none=1.0 (referent); mild 1.6 (1.4–1.8), moderate 3.3 (2.8–3.9), severe 5.0 (3.6–7.0), p<0.001.
Overall survival multivariable analysis (pretreatment PSA)	NR	NR	NR	HR 1.5 (95% CI, 1.3 to 1.7), p<0.001.
Overall survival multivariable analysis (bSG)	NR	NR	NR	HR 2 to 6=1.0 (referent), 7=1.4 (1.2–1.6), 8–10=2.2 (1.8–2.8), p<0.001.
Overall survival multivariable analysis (clinical stage)	NR	NR	NR	HR T1c=1.0 (referent), T1ab=1.4 (0.8–2.4), T2a=1.3 (1.1–1.6), T2b=1.3 (1.0–1.6), T2c=1.3 (0.9–1.8), T3=2.3 (1.5–3.3), p-value=0.002.
Overall survival by D'Amico risk classification (low)	NR	NR	NR	HR for EBRT vs. RP: 1.7 (1.3–2.1), p<0.001. HR for BT vs. RP: 1.7 (1.4–2.2), p<0.001.
Overall survival by D'Amico risk classification (intermediate)	NR	NR	NR	HR for EBRT vs. RP: 1.5 (1.2–1.9), p=0.001. HR for BT vs. RP: 1.5 (1.1–2.1), p=0.019.
Overall survival by D'Amico risk classification (high)	NR	NR	NR	HR for EBRT vs. RP: 1.7 (1.3–2.3), p=0.001. HR for BT vs. RP: 3.1 (1.7–5.9), p<0.001.

Study Outcomes	Treatment Group 1	Treatment Group 2	Treatment Group 3	Analyses; p-Values
Albertsen et al. 2007 <sup>42</sup> Overall survival (13 years of followup data)	Surgery: 596 patients	Radiation: 642 patients	Observation: 114 patients	Adjusted overall survival curves for the 3 treatment groups. Patients who had surgery were 5 years younger on average and had less comorbidity than patients in the other 2 treatment groups. However, even after adjusting for differences in patient factors and tumor characteristics overall survival in the surgery group was considerable better than for the other 2 groups. Survival differences for the radiation and observation groups were much smaller. The mortality rate ratio was 1.2 (95% CI, 0.9 to 1.5) times higher in the observation vs. radiation group.
D'Amico risk group low (overall survival at 13 years followup)	78%	59%	58%	—
D'Amico risk group intermediate (overall survival at 13 years followup)	71%	58%	55%	—
D'Amico risk group high (overall survival at 13 years followup)	61%	40%	37%	—
Abdollah et al. 2011 <sup>72</sup>	Radical prostatectomy (RP): 5760 (matched cohort)	Observation: 5,909 patients	NA	Based on the propensity score matched cohort only two estimates were developed: the development cohort (cumulative incidence plots were used) and the external validation cohort (this tested the calibration and discrimination of the multivariate analysis' competing risks nomogram).

Study Outcomes	Treatment Group 1	Treatment Group 2	Treatment Group 3	Analyses; p-Values
Other cause mortality rate at 5 years of followup	7.0% (6.3–7.7)	15.6% (14.6–16.6)	NA	p<0.001
Other cause mortality rate at 10 years of followup	21.5% (20.1–22.9)	37.0% (35.3–38.6)	NA	p<0.001
Other cause mortality multivariate analyses (treatment type)	NA	NA	NA	HR: Observation=1 (reference), RP 0.57 (95% CI, 0.53–0.62), p<0.001
Other cause mortality multivariate analyses (age in years)	NA	NA	NA	HR: 1.10 (95% CI, 1.09–1.11), p<0.001
Other cause mortality multivariate analyses (race Black)	NA	NA	NA	HR: White 1 reference, Black 1.28 (95% CI, 1.12–1.46), p<0.001
Other cause mortality multivariate analyses (race Other)	NA	NA	NA	HR: White 1 reference, Other 0.73 (95% CI, 0.59–0.88), p=0.001
Other cause mortality multivariate analyses (Charlson comorbidity index 1)	NA	NA	NA	HR: 0 reference, 1 1.61 (95% CI, 1.47–1.77), p<0.001
Other cause mortality multivariate analyses (Charlson comorbidity index 2)	NA	NA	NA	HR: 0 reference, 2 1.97 (95% CI, 1.76–2.20), p<0.001
Other cause mortality multivariate analyses (Charlson comorbidity index ≥3)	NA	NA	NA	HR: 0 reference, 3 3.38 (95% CI, 3.03–3.76), p<0.001
Other cause mortality multivariate analyses (clinical stage T2a/b)	NA	NA	NA	HR: T1 reference, T2a/b 1.07 (95% CI, 0.98–1.16), p=0.1
Other cause mortality multivariate analyses (clinical stage T2c)	NA	NA	NA	HR: T1 reference, T2c 1.21 (95% CI, 1.07–1.38), p=0.002
Other cause mortality multivariate analyses (Gleason 6–7)	NA	NA	NA	HR: Gleason score 2–5 reference, Gleason score 6–7 0.84 (95% CI, 0.75–0.94), p=0.002

Study Outcomes	Treatment Group 1	Treatment Group 2	Treatment Group 3	Analyses; p-Values
Other cause mortality multivariate analyses (Gleason 8–10)	NA	NA	NA	HR: Gleason score 2–5 reference, Gleason score 8–10 0.92 (95% CI, 0.80–1.06), p=0.3

**Abbreviations:** 3D-CRT=Three-dimensional conformal radiation therapy; ADT=androgen-deprivation therapy; bGS=baseline Gleason score; BT=brachytherapy; CI=confidence interval; EBRT=external beam radiation therapy; HR=hazard ratio; IGRT=image-guided radiation therapy; NR=not reported; RP=radical prostatectomy; RRP=radical retropubic prostatectomy.

**Table F-5. Prostate cancer–specific mortality (randomized controlled trials)**

Study Outcomes	Treatment Group 1	Treatment Group 2	Analyses; p-Values
Wilt et al. 2012 <sup>25</sup> Prostate Intervention Versus Observation Trial (PIVOT)	Observation: 364 patients	RP: 364 patients	HR (95% CI), p-value for interaction
Overall death from prostate cancer at median followup of 10 years (number of events/total number of patients)	31/367	21/364	0.63 (0.36–1.00)
<i>Age</i>	—	—	p=0.63
<65 years	12/131	6/122	0.52 (0.20–1.39)
>65 years	19/236	15/242	0.68 (0.34–3.33)
<i>Race</i>	—	—	p=0.76
White	22/220	15/232	0.57 (0.30–1.10)
Black	7/121	5/111	0.80 (0.25–2.54)
Other	2/26	1/21	0.56 (0.05–6.17)
<i>Charlson score</i>			p=0.63
0	19/220	14/224	0.69 (0.34–1.37)
≥1	12/147	7/140	0.54 (0.21–1.38)
<i>Performance score</i>	—	—	p=0.57
0	25/310	18/312	0.67 (0.37–1.23)
1–4	6/57	3/52	0.41 (0.10–1.71)
<i>Prostate specific antigen (PSA)</i>	—	—	p=0.11
≤10	15/241	14/238	0.92 (0.44–1.91)
>10	16/125	3/52	0.36 (0.15–0.89)
<i>Risk</i>	—	—	p=0.11
Low	4/148	6/148	1.48 (0.42–5.24)
Intermediate	13/120	6/129	0.50 (0.21–1.21)
High	14/80	7/77	0.40 (0.16–1.00)
<i>Gleason score</i>	—	—	p=0.57
<7	15/261	11/254	0.68 (0.31–1.49)
≥7	15/86	10/98	0.51 (0.23–1.14)
At 12 years, RP was associated with a nonsignificant absolute reduction in mortality of 3.0 percentage points, as compared with WW (4.4 vs. 7.4 percentage points, relative risk, 0.6; 95% CI, 0.33 – 1.09). Study authors did not provide subgroup data for patient at 12 years followup.			

Study Outcomes	Treatment Group 1	Treatment Group 2	Analyses; p-Values
Bill-Axelsson et al. 2011 <sup>33</sup> Bill-Axelsson et al. 2008 <sup>15</sup> SPCG-4 trial	WW: 348 patients	RP: 347 patients	—
Total number of deaths due to prostate cancer, cumulative incidence (number (% [95% CI]) at a median followup of 10.8 years (Bill-Axelsson et al. 2008 <sup>15</sup> ))	68 (19.5)	47 (13.5)	—
All ages at 8 years followup (Bill-Axelsson et al. 2008 <sup>15</sup> )	9.8 (7.1–13.5)	5.5 (3.5–8.5)	ARR with RP, % (95% CI): 4.3 (0.4–8.2)
All ages at 12 years followup (Bill-Axelsson et al. 2008 <sup>15</sup> )	17.9 (14.1–22.7)	12.5 (9.2–16.8)	ARR with RP, % (95% CI): 5.4 (-0.2–1.1) RR with RP, % (95% CI): 0.65 (0.45–0.94) p=0.03
Age <65 years at 8 years followup (Bill-Axelsson et al. 2008 <sup>15</sup> )	13.3 (9.0–19.6)	5.1 (2.6–10.0)	ARR with RP, % (95% CI): 8.2 (1.9–14.4)
Age <65 years at 12 years followup (Bill-Axelsson et al. 2008 <sup>15</sup> )	23.1 (17.2–30.9)	11.9 (7.5–18.7)	ARR with RP, % (95% CI): 11.2 (2.6–19.8) RR with RP, % (95% CI): 0.5 (0.30–0.84) p=0.014
Age ≥65 years at 8 years followup (Bill-Axelsson et al. 2008 <sup>15</sup> )	6.6 (3.8–11.4)	5.8 (3.3–10.3)	ARR with RP, % (95% CI): 0.8 (-4.1–5.7)
Age ≥65 years at 12 years followup (Bill-Axelsson et al. 2008 <sup>15</sup> )	13.2 (8.9–19.6)	13.1 (8.8–19.5)	ARR with RP, % (95% CI): 0.1 (-7.3–7.5) RR with RP, % (95% CI): 0.87 (0.51–1.49) p=0.55
Total number of deaths due to prostate cancer, cumulative incidence (number (% [95% CI]) at 15 years followup (Bill-Axelsson et al. 2011 <sup>33</sup> ))	81 (23.3)	55 (15.9)	—
All at 15 years followup (Bill-Axelsson et al. 2011 <sup>33</sup> )	20.7 (16.7–25.6)	14.6 (11.2–19.10)	ARR with RP, % (95% CI): 6.1 (0.2–12.0) RR with RP, % (95% CI): 0.62 (0.44–0.87) p=0.01

Study Outcomes	Treatment Group 1	Treatment Group 2	Analyses; p-Values
Low risk cancer at 15 years followup (Bill-Axelsson et al. 2011 <sup>33</sup> )	11.0 (6.8–17.8)	6.8 (3.5–13.5)	ARR with RP, % (95% CI): 4.2 (-2.9–11.2) RR with RP, % (95% CI): 0.53 (0.24–1.14) p=0.14
Age <65 years at 15 years followup(Bill-Axelsson et al. 2011 <sup>33</sup> )	25.8 (19.7–33.7)	16.4 (11.3–23.8)	ARR with RP, % (95% CI): 9.4 (0.2–18.6) RR with RP, % (95% CI): 0.49 (0.31–0.79) p=0.008
Age <65 years and low risk at 15 years followup(Bill-Axelsson et al. 2011 <sup>33</sup> )	11.6 (6.0–22.4)	7.1 (2.7–18.6)	ARR with RP, % (95% CI): 4.5 (-5.7– 4.8) RR with RP, % (95% CI): 0.41 (0.14–0.17) p=0.14
Age ≥65 years at 15 years followup (Bill-Axelsson et al. 2011 <sup>33</sup> )	16.0 (11.4–22.6)	13.0 (8.9–18.9)	ARR with RP, % (95% CI): 3.0 (-4.3– 0.4) RR with RP, % (95% CI): 0.83 (0.50–0.39) p=0.41
Age ≥65 years and low risk at 15 years followup (Bill-Axelsson et al. 2011 <sup>33</sup> )	10.3 (5.1–21.0)	6.6 (2.5–17.1)	ARR with RP, % (95% CI): 3.8 (-5.9–13.4) RR with RP, % (95% CI): 0.76 (0.25–2.32) p=0.58

Study Outcomes	Treatment Group 1	Treatment Group 2	Analyses; p-Values
Jones et al. 2011 <sup>43</sup>	EBRT: 992 patients	EBRT plus short-term ADT: 987	HR (95% CI)
Disease-specific mortality at 10 years (% reaching end point)	—	—	—
All patients	8	4	1.87 (1.27–2.74), p=0.001
Low risk	1	3	0.63 (0.21–1.92)
Intermediate risk	10	3	2.49 (1.50–4.11), p=0.004
High risk	14	12	1.53 (0.72–3.26)
White	8	4	2.33 (1.46–3.72), p<0.001
Black	7	5	1.27 (0.59–2.73)
Age ≤70 years	5	4	1.43 (0.79–2.57)
Age >70 years	10	5	2.19 (1.31–3.64), p=0.004
Donnelly et al. 2010 <sup>47</sup>	EBRT: 122 patients	Cryotherapy: 122 patients	—
Prostate cancer–specific mortality at 5 years(% reaching end point)	96.1%	96.4%	difference 0.3 (-4.8 – 5.4)
D'Amico et al. 2008 <sup>35</sup>	3D-CRT: 104 patients	3D-CRT plus ADT: 102 patients	—
Prostate cancer–specific death in all patients at median followup of 7.6 years (range 0.5–11.0)	14	4	OR: 3.81 (1.21 to 12.01), p=0.02
Prostate cancer–specific death (No or Minimal Comorbidity)	14	3	OR: 5.13 (1.43 to 18.45), p=0.01
Prostate cancer–specific death (Moderate or Severe Comorbidity)	0	1	OR 0.48 (0.02 to 14.71), 0=0.68
—	3D-CRT: 103 patients	3D-CRT plus ADT: 98 patients	—
Prostate cancer–specific death in all patients at median of 4.52 years followup, number of patients	6	0	OR: 12.06 (0.67 to 218.92), p=0.09

**Abbreviations:** 3D-CRT=Three-dimensional conformal radiation therapy; ADT=androgen-deprivation therapy; ARR=absolute risk reduction; CI=confidence interval; EBRT=external beam radiation therapy; HR=hazard ratio; OR=odds ratio; RP=radical prostatectomy; RR=relative risk; SPCG-4= Scandinavian Prostate Cancer Group-4; WW=watchful waiting.



**Table F-6. Prostate cancer–specific mortality and cause-specific survival (nonrandomized comparative studies)**

Study Outcomes	Treatment Group 1	Treatment Group 2	Treatment Group 3	Analyses; p-Values
Alemozaffar et al. 2014 <sup>68</sup>	RALP: 282 patients	Open RRP: 621 patients	NA	—
Deaths attributed to prostate cancer	0 cases	2 cases	NA	—
Mukherjee et al. 2014 <sup>37</sup>	RP: 5,805 patients	EBRT: 2,183 patients	BT: 2,936 patients	—
Cause of death prostate cancer (median followup 3.05 years)	23.7%	28.8%	14.2%	—
DeGroot et al. 2013 <sup>41</sup>	RP: 494 patients (458 cohort and 36 cases)	EBRT: 596 patients (518 cohort and 78 cases)	NA	—
Prostate cancer–specific mortality at median followup of 51 months	Adjusted HRs for risk of prostate cancer death for EBRT compared to RP for entire study population were 1.62 (95% CI, 1.00 to 2.61) and 2.02 (95% CI 1.19 to 3.43) analyzing by intent-to-treat and treatment received, respectively.			—
Intent-to-treat analysis for low-risk group (PSA ≤10, Gleason score ≤6 and T category ≤T2a) (n=386; 371 cohort and 15 cases)	EBRT vs. RP: HR 0.87; 95% CI 0.28 to 2.76			—
Intent-to-treat analysis for intermediate-risk group (patients who were not low risk and had a PSA ≤20, Gleason score ≤7 and T category ≤T2b) (n=698: 599 cohort and 99 cases)	EBRT vs. RP; HR 1.57; 95% 0.95 to 2.61			—
Effect of comorbidity on prostate cancer–specific mortality	Authors only reported that they investigated whether the competing risk of death from comorbid illness could explain their findings and found that none of their results were statistically significant.			—

Study Outcomes	Treatment Group 1	Treatment Group 2	Treatment Group 3	Analyses; p-Values
Hoffman et al. 2013 <sup>38</sup>	RP: 1,164 patients	EBRT with or without ADT: 491 patients	NA	—
Prostate cancer–specific mortality after 15 years of followup	HR, 0.35; 95% CI, 0.26 to 0.49			p<0.0001
Prostate cancer–specific mortality among men aged 55 to 64 years	RP: 2.4% (15 of 628) vs. EBRT: 11.5% (15 of 131), HR, 0.21; 95% CI, 0.13 to 0.36.			—
Prostate cancer–specific mortality among men aged 65 to 74 years	RP: 5.6% (30 of 536) vs. EBRT: 12.2% (44 of 360), HR, 0.45; 95% CI, 0.31 to 0.65			p=0.02.
Prostate cancer–specific mortality among men who had no comorbidity	RP: 3.5% (18 of 513) vs. EBRT: 15.1% (24 of 159), HR, 0.19; 95% CI, 0.12 to 0.31			—
Prostate cancer–specific mortality among men who reported any comorbidity	RP: 4.1% (27 of 651) vs. EBRT: 10.5% (35 of 332) men in the EBRT group, HR, 0.49; 95% CI, 0.34 to 0.72			p=0.001
Prostate cancer–specific mortality among men with high-risk tumors, diagnostic PSA >10 ng/mL or Gleason score ≥8,	RP: 6.6% (25 of 381) vs. EBRT plus ADT: 21.4% (12 of 56), HR, 0.36; 95% CI, 0.20 to 0.64			—
Prostate cancer–specific mortality among men with low-risk tumors, diagnostic PSA <10 ng/mL or Gleason score ≤6	RP: 1.8% (10 of 558) vs. EBRT: 3.6% (7 of 195), HR, 0.66; 95% CI, 0.35 to 1.25			p=0.13

Study Outcomes	Treatment Group 1	Treatment Group 2	Treatment Group 3	Analyses; p-Values
Liu et al. 2013 <sup>79</sup>	RP: 1,624 patients	ADT: 1,624 patients		—
Prostate cancer–specific mortality at median followup of 2.95 years in the RP group and 2.87 years in the ADT group, n (%)	4 (0.25)	60 (3.69)		HR 12.47 (4.48 to 34.70), p<0.001
Prostate cancer–specific mortality among white men at 2.95 years median followup in the RP group and 2.87 years median followup in the ADT	ADT vs. RP: HR 0.94 (95% CI, 0.49 to 1.82)			p=0.86
Prostate cancer–specific mortality among men with CCI ≤2 at 2.95 years median followup in the RP group and 2.87 years median followup in the ADT group	ADT vs. RP: HR 0.82 (95% CI, 0.40 to 1.68).			p=0.59
Prostate cancer–specific mortality among men with CCI >2 at 2.95 years median followup in the RP group and 2.87 years median followup in the ADT group	ADT vs. RP: HR 1.12 (95% CI, 0.35 to 3.65)			p=0.85
Prostate cancer–specific mortality among men with low PSA at 2.95 years median followup in the RP group and 2.87 years median followup in the ADT group	ADT vs. RP: HR 2.68 (95% CI, 0.58 to 12.27)			p=0.21
Prostate cancer–specific mortality among men with medium PSA at 2.95 years median followup in the RP group and 2.87 years median followup in the ADT group	ADT vs. RP: HR 2.43 (95% CI, 0.71 to 8.38)			p=0.16

Study Outcomes	Treatment Group 1	Treatment Group 2	Treatment Group 3	Analyses; p-Values
Prostate cancer-specific mortality among men with high PSA at 2.95 years median followup in the RP group and 2.87 years median followup in the ADT group	ADT vs. RP: HR 1.23 (95% CI, 0.15 to 9.96)			p=0.84
Prostate cancer-specific mortality among men with unknown PSA at 2.95 years median followup in the RP group and 2.87 years median followup in the ADT group	ADT vs. RP: HR 2.43 (95% CI, 0.79 to 7.49)			p=0.12
Prostate cancer-specific mortality among men with T2 stage at 2.95 years median followup in the RP group and 2.87 years median followup in the ADT group	ADT vs. RP: HR 1.71 (95% CI, 0.86 to 3.42)			p=0.13
Prostate cancer-specific mortality among men with worse Gleason score at 2.95 years median followup in the RP group and 2.87 years median followup in the ADT group	ADT vs. RP: HR 3.16 (95% CI, 1.77 to 5.64)			p<0.001

Study Outcomes	Treatment Group 1	Treatment Group 2	Treatment Group 3	Analyses; p-Values
Marina et al. 2013 <sup>86</sup>	Image-guided radiation therapy (IGRT): 734 patients	BT: 282 patients	NA	—
5-year overall survival, % (range)	99 (98–100)	100	—	0.55
8-year overall survival, % (range)	99 (97–100)	100	—	
5-year cause-specific survival by patient characteristics <i>In this study, the authors defined cause-specific survival as death attributed to prostate cancer at their institutional cancer registry.</i>	Age <60 years: IGRT 100% vs. BT 100% Age 60–69 years: IGRT 99% vs. BT 100% Age ≥70 years: IGRT 99% vs. BT 100% Race, African American: IGRT 100% vs. BT 100% Race, European American: IGRT 99% vs. BT 100% Race, Other: IGRT 100% vs. BT 100%		—	—
5-year cause-specific survival by tumor characteristics	PSA <10 ng/mL: IGRT 99% vs. BT 100% PSA 10–20 ng/mL: IGRT 99% vs. BT 100% Gleason score ≤6: IGRT 100% vs. BT 100% Gleason score 3+4: IGRT 99% vs. BT 100% Gleason score 4+3: IGRT 98% vs. 100 BT% Stage T1-2a: IGRT 99% vs. BT 100% Stage T2b–2c: IGRT 99% vs. BT 100%		—	—
Nepple et al. 2013 <sup>40</sup>	RP: 4,459 patients	EBRT: 1,261 patients	BT: 972 patients	—
Prostate cancer–specific mortality among men after median followup of 7.2 years	EBRT was associated with an increase in prostate cancer–specific mortality compared with RP (HR, 1.66; 95% CI, 1.05 to 2.63), while there was no statistically significant increase with BT (HR, 1.83; 95% CI, 0.88 to 3.82) compared with RP.			—

Study Outcomes	Treatment Group 1	Treatment Group 2	Treatment Group 3	Analyses; p-Values
Abdollah et al. 2012 <sup>59</sup>	EBRT: 20,986 patients in propensity score matched cohort	Observation: 20,986 patients in propensity score matched cohort	NA	<p>For patients with low-intermediate risk prostate cancer, 10 year prostate cancer-specific mortality was 3.7% for patients treated with radiotherapy vs. 4.1% for patients undergoing observation (p=0.1).</p> <p>For patients with high-risk prostate cancer, 10 year prostate cancer-specific mortality was 8.8% for patients treated with radiotherapy vs. 14.4% for patients undergoing observation (p=0.001).</p> <p>In the multivariate analysis, radiotherapy was not an independent predictor of prostate cancer-specific mortality in patients with low-intermediate risk prostate cancer (HR 0.91 (0.80 to 1.04), p=0.2). Radiotherapy was an independent risk factor in patients with high-risk PC (HR 0.59 (0.50 to 0.68), p&lt;0.001).</p> <p>CCI=0: HR 0.81 (0.67–0.98), 0.03</p> <p>CCI=1: HR 0.87 (0.75–0.99), p=0.04.</p> <p>CCI ≥2: HR 0.79 (0.65–0.96), p=0.01.</p> <p>Age 65 to 69 years: HR 0.93 (0.72–1.19) p=0.6</p> <p>Age 70 to 74 years: HR 0.84 (0.68–1.03) p=0.08</p> <p>Age 65 to 69 years: HR 0.70 (0.59–0.80) p&lt;0.001</p>

Study Outcomes	Treatment Group 1	Treatment Group 2	Treatment Group 3	Analyses; p-Values
Kibel et al. 2012 <sup>75</sup> Adjusted 10-year prostate cancer-specific mortality	RP: 1.8% (95% CI, 1.6–2.1)	EBRT: 2.9% (95% CI, 2.6–3.3)	BT: 2.3% (95% CI, 2.0–2.6)	Kaplan-Meier analysis p-value NR.
Overall prostate cancer-specific mortality multivariable analysis (treatment group)	1.0 (referent)	1.5 (95% CI, 1.0–2.3)	1.3 (95% CI, 0.7–2.4)	HR p-value: 0.13
Overall prostate cancer-specific mortality multivariable analysis (patient age)	NA	NA	NA	HR 0.8 (95% CI, 0.5 to 1.3), p=0.065
Overall prostate cancer-specific mortality multivariable analysis (African-American ethnicity)	NA	NA	NA	HR 0.7 (95% CI, 0.4 to 1.2), p=0.18
Overall prostate cancer-specific mortality multivariable analysis (comorbidity)	NA	NA	NA	HR none=1.0 (referent); mild 1.2 (0.8–1.7), moderate 1.4 (0.9–2.3), severe 0.7 (0.2–2.9), p=0.4.
Overall prostate cancer-specific mortality multivariable analysis (pretreatment PSA)	NA	NA	NA	HR 1.7 (95% CI, 1.1–2.5), p=0.017.
Overall prostate cancer-specific mortality multivariable analysis (bSG)	NA	NA	NA	HR 2 to 6=1.0 (referent), 7=2.9 (1.8–4.5), 8 to 10=11.1 (6.5–18.9), p<0.001
Overall prostate cancer-specific mortality multivariable analysis (clinical stage)	NA	NA	NA	HR T1c=1.0 (referent), T1ab=0.3 (0.1–1.0), T2a=0.4 (0.1–1.5), T2b=0.5 (0.1–1.6), T2c=0.5 (0.1–1.7), T3=0.8 (0.2–2.9), p-value=0.12.
Overall prostate cancer-specific mortality by D'Amico risk classification (low)	NA	NA	NA	HR for EBRT vs. RP: 1.8 (0.5–6.2), p=0.4. HR for BT vs. RP: 2.3 (0.8–6.9), p=0.14.
Overall prostate cancer-specific mortality by D'Amico risk classification (intermediate)	NA	NA	NA	HR for EBRT vs. RP: 1.8 (0.8–3.8), p=0.13. HR for BT vs. RP: 0.6 (0.1–2.7), p=0.5.
Overall prostate cancer-specific mortality by D'Amico risk classification (high)	NA	NA	NA	HR for EBRT vs. RP: 1.3 (0.8–2.1), p=0.2. HR for BT vs. RP: 1.6 (0.4–6.6), p=0.5.

Study Outcomes	Treatment Group 1	Treatment Group 2	Treatment Group 3	Analyses; p-Values
Rosenberg et al. 2012 <sup>76</sup> Prostate cancer-specific mortality	BT plus EBRT: 186 patients	BT plus ADT: 621 patients	NA	HR Adjusted for age and prostate cancer prognostic factors 4.03 (95% CI, 1.17 to 13.89), p=0.027. Estimates of prostate cancer-specific mortality at 5 years was 3.3% (95% CI, 1.020 to 7.772) in men treated with EBRT and BT compared with 1.1% (95% CI, 0.417 to 2.510) those receiving ADT and brachytherapy.
Prostate cancer-specific mortality	NA	NA	NA	Multivariate HR adjusted for age: 1.086 (95% CI, 0.955–1.235), p=0.21
Prostate cancer-specific mortality	NA	NA	NA	Multivariate HR adjusted for PSA: 8.029 (95% CI, 2.38–28.8), p=0.0014
Prostate cancer-specific mortality	NA	NA	NA	Multivariate HR adjusted for AJCC T category: T1a to c, T2a 1.0 referent, T2b 0.681 (0.092–5.036), p=0.71
Prostate cancer-specific mortality	NA	NA	NA	Multivariate HR adjusted for Gleason score: ≤6=1.0 referent, 3+4: 7.463 (95% CI, 0.816–68.23), p=0.075 4+3: 8.882 (1.095–72.04), p=0.041
Shen et al. 2012 <sup>84</sup>	BT: 910 patients	BT plus EBRT: 2,466 patients	EBRT: 9,369 patients	A Log rank test was performed for unadjusted comparisons. For multivariate analysis an adjusted HR using the Cox model was created controlling for diagnosis, age, race, urban residence, income, prior malignancy, stage and PSA.
Prostate cancer-specific mortality- univariate analysis	NA	NA	NA	Log rank test: Prostate cancer-specific mortality after BT alone or BT plus EBRT was significantly different from EBRT (p<0.001) but there was no difference between BT and BT plus EBRT (p=0.18).
Prostate cancer-specific mortality- multivariate model (year of diagnosis 5 years later)	NA	NA	NA	HR 0.70 (95% CI, 0.63–0.78), p<0.01
Prostate cancer-specific mortality – multivariate model (per year older age)	NA	NA	NA	HR 1.02 (95% CI, 1.01–1.04), p=0.01



Study Outcomes	Treatment Group 1	Treatment Group 2	Treatment Group 3	Analyses; p-Values
Prostate cancer-specific mortality – multivariate model (Asian vs. white)	NA	NA	NA	HR 0.62 (95% CI, 0.49–0.76), p<0.01
Prostate cancer-specific mortality – multivariate model (Black vs. white)	NA	NA	NA	HR 0.93 (95% CI, 0.78–1.10), p=0.38
Prostate cancer-specific mortality – multivariate model (Hispanic)	NA	NA	NA	HR 1.18 (95% CI, 0.95–1.44), p=0.13
Prostate cancer-specific mortality – multivariate model (Urban)	NA	NA	NA	HR 0.99 (95% CI, 0.82–1.20), p=0.93
Prostate cancer-specific mortality – multivariate model (lowest quartile vs. highest quartile income)	NA	NA	NA	HR 1.09 (95% CI, 0.93–1.27), p=0.29
Prostate cancer-specific mortality – multivariate model (low-middle quartile vs. highest quartile income)	NA	NA	NA	HR 0.90 (95% CI, 0.78–1.05), p=0.17
Prostate cancer-specific mortality – multivariate model (low-middle quartile vs. highest quartile income)	NA	NA	NA	HR 0.90 (95% CI, 0.78–1.05), p=0.17
Prostate cancer-specific mortality – multivariate model (high-middle quartile vs. highest quartile income)	NA	NA	NA	HR 1.02 (95% CI, 0.89–1.18), p=0.79
Prostate cancer-specific mortality – multivariate model (prior malignancy vs. prostate only primary)	NA	NA	NA	HR 0.99 (95% CI, 0.82–1.19), p=0.93
Prostate cancer-specific mortality – multivariate model (other malignancy after prostate cancer diagnosis vs. none)	NA	NA	NA	HR 0.73 (95% CI, 0.63–0.86), p<0.01

Study Outcomes	Treatment Group 1	Treatment Group 2	Treatment Group 3	Analyses; p-Values
Prostate cancer-specific mortality – multivariate model (T2 vs. T1)	NA	NA	NA	HR 1.62 (95% CI, 1.39–1.90), p<0.01
Prostate cancer-specific mortality – multivariate model (T3 vs. T1)	NA	NA	NA	HR 2.75 (95% CI, 2.27–3.34), p<0.01
Prostate cancer-specific mortality – multivariate model (PSA elevated)	NA	NA	NA	HR 0.85 (95% CI, 0.63–1.17), p=0.28
Prostate cancer-specific mortality – multivariate model (BT alone vs. EBRT)	NA	NA	NA	HR 0.66 (95% CI, 0.49–0.86), p<0.01
Prostate cancer-specific mortality – multivariate model (BT plus EBRT vs. EBRT)	NA	NA	NA	HR 0.77 (95% CI, 0.66–0.90), p<0.01
Abdollah et al. 2011 <sup>72</sup>	RP: 5,760 (matched cohort)	Observation: 5,909 patients	NA	Based on the propensity score matched cohort only two estimates were developed: the development cohort (cumulative incidence plots were used) and the external validation cohort (this tested the calibration and discrimination of the multivariate analysis' competing risks nomogram).
Prostate cancer-specific mortality rate at 5 years of followup	0.6% (0.3–0.8)	1.8% (1.4–2.2)	NA	p<0.001
Prostate cancer-specific mortality rate at 10 years of followup	2.8% (2.3–3.4)	5.8% (5.0–6.6)	NA	p<0.001
Prostate cancer-specific mortality multivariate analyses (treatment type)	NA	NA	NA	HR: Observation=1 (reference), RP 0.48 (95% CI, 0.38–0.59), p<0.001
Prostate cancer-specific mortality multivariate analyses (age in years)	NA	NA	NA	HR: 1.04 (95% CI, 1.01–1.07), p=0.006
Prostate cancer-specific mortality multivariate analyses (race Black)	NA	NA	NA	HR: white 1 reference, Black 1.19 (95% CI, 0.84–1.67), p=0.3

Study Outcomes	Treatment Group 1	Treatment Group 2	Treatment Group 3	Analyses; p-Values
Prostate cancer-specific mortality multivariate analyses (race Other)	NA	NA	NA	HR: white 1 reference, Other 0.88 (95% CI, 0.54–1.45), p=0.6
Prostate cancer-specific mortality multivariate analyses (CCI 1)	NA	NA	NA	HR: 0 reference, 1 1.04 (95% CI, 0.82–1.31), p=0.7
Prostate cancer-specific mortality multivariate analyses (CCI 2)	NA	NA	NA	HR: 0 reference, 2 0.93 (95% CI, 0.67–1.28), p=0.6
Prostate cancer-specific mortality multivariate analyses (CCI ≥3)	NA	NA	NA	HR: 0 reference, 3 0.81 (95% CI, 0.57–1.16), p=0.2
Cooperberg et al. 2010 <sup>39</sup>	RP: 5,066 patients	EBRT: 1,143 patients	ADT: 1,329 patients	—
Prostate cancer-specific mortality at median followup 3.9 years, 4.5 years, and 3.6 years for RP, EBRT, and ADT, respectively.	Relative to RP, the adjusted HRs were 1.58 (95% CI, 1.32 to 1.89) for EBRT and 2.25 (95% CI, 1.86 to 2.72) for ADT. The HR for ADT relative to EBRT was 1.43 (95% CI, 1.21 to 1.69)			—
Prostate cancer-specific mortality multivariate analyses (clinical stage T2a/b)	NA	NA	NA	HR: T1 reference, T2a/b 1.00 (95% CI, 0.80–1.25), p=0.9
Prostate cancer-specific mortality multivariate analyses (clinical stage T2c)	NA	NA	NA	HR: T1 reference, T2c 1.34 (95% CI, 0.99–1.83), p=0.06
Prostate cancer-specific mortality multivariate analyses (Gleason 6–7)	NA	NA	NA	HR: Gleason score 2 to 5 reference, Gleason score 6–7 2.07 (95% CI, 1.30–3.30), p=0.001
Prostate cancer-specific mortality multivariate analyses (Gleason 8–10)	NA	NA	NA	HR: Gleason score 2–5 reference, Gleason score 8–10 5.89 (95% CI, 3.64–9.54), p<0.001

Study Outcomes	Treatment Group 1	Treatment Group 2	Treatment Group 3	Analyses; p-Values
Hadley et al. 2010 <sup>73</sup>	Observation: 5,879 patients	RP: 11,936 patients	NA	Cox proportional hazards model using three approaches: traditional multivariable survival analysis, propensity score adjustment, and instrumental variable analysis
Multivariable survival analysis	0.036 (0.030–0.041)	0.025 (0.022–0.028)	NA	HR 1.59, (1.27–2.00)
Propensity score adjustments (inverse probability of treatment weights)	0.035 (0.029–0.040)	0.026 (0.023–0.030)	NA	HR 1.60, (1.40–1.83)
Propensity score adjustments (standardized mortality ratio weights)	0.036 (0.030–0.041)	0.030 (0.026–0.033)	NA	HR 1.39 (1.10–1.76)
Instrumental variable approach	0.030 (0.026–0.034)	0.027 (0.023–0.031)	NA	HR 0.73 (0.08–6.73)
Krambeck et al. 2008 <sup>65</sup> Death from prostate cancer	RRP: 0	RALRP: 0	NA	Median followup time was 1.3 years.
Lu-Yao et al. 2008 <sup>78</sup> Prostate specific mortality – all cancer grades combined	ADT: 867/32,744 events/person-year, rate per 100=2.6	Observation: 693/55,424 events/person-year, rate per 100=1.3	NA	Adjusted HR (95% CI,) 1.76 (1.59–1.95) p<0.05
Albertsen et al. 2007 <sup>42</sup> Prostate cancer specific survival at 13-years followup	Surgery: 596 patients	Radiation: 642 patients	Observation: 114 patients	Cause specific survival curve for the 3 treatment groups by D'Amico risk category and cause specific survival with standardization via proportional hazards model to average covariate profile in each D'Amico risk group. Competing risk analysis of percent of patients dead of prostate cancer, dead of other causes, and alive in each treatment group 5, 10, and 15 years after diagnosis standardized to age 65 years at diagnosis, average pretreatment comorbidity, Gleason score, PSA and tumor distribution for entire sample.

Study Outcomes	Treatment Group 1	Treatment Group 2	Treatment Group 3	Analyses; p-Values
D'Amico risk category low: Prostate cancer-specific survival at 13-years followup	96%	90%	83%	—
D'Amico risk category intermediate: Prostate cancer-specific survival at 13-years followup	92%	80%	89%	—
D'Amico risk category high: Prostate cancer-specific survival at 13-years followup	90%	70%	60%	—
D'Amico risk category low: Prostate cancer-specific survival at 13-years followup with standardization	96%	90%	83%	—
D'Amico risk category intermediate: Prostate cancer-specific survival at 13-years followup with standardization	90%	80%	70%	—
D'Amico risk category high: Prostate cancer-specific survival at 13-years followup with standardization	85%	70%	55%	—
5-year followup competing risk analysis	Died of prostate cancer: 2% Died of other causes: 6% Alive: 92%	Died of prostate cancer: 4% Died of other causes: 5% Alive: 91%	Died of prostate cancer: 6% Died of other causes: 4% Alive: 90%	—
10-year followup competing risk analysis	Died of prostate cancer: 3% Died of other causes: 14% Alive: 83%	Died of prostate cancer: 9% Died of other causes: 13% Alive: 78%	Died of prostate cancer: 14% Died of other causes: 13% Alive: 73%	—
15-year followup competing risk analysis	Died of prostate cancer: 8% Died of other causes: 24% Alive: 68%	Died of prostate cancer: 17% Died of other causes: 23% Alive: 60%	Died of prostate cancer: 25% Died of other causes: 20% Alive: 55%	—

Study Outcomes	Treatment Group 1	Treatment Group 2	Treatment Group 3	Analyses; p-Values
D'Amico et al. 2007 <sup>87</sup>	RRP: 660 patients	3D-CRT: 288 patients	—	—
Prostate cancer specific mortality, n (%) at median followup of 5.5 years in the RRP group and 4.0 years in the 3D-CRT group.	29 of 660 patients (4.4)	32 of 288 patients (11.1)	—	RR 0.4 (0.24–0.64)
% of patients who died of prostate cancer with PSA level ≤4 ng/mL	3 of 29 patients (10)	0 of 32 patients (0)	—	RR 7.7 (0.42–143)
% of patients who died of prostate cancer with PSA level >4–10 ng/mL	15 of 29 patients (52)	7 of 32 patients (22)	—	RR 2.37 (1.13–4.97)
% of patients who died of prostate cancer with PSA level >10–20 ng/mL	3 of 29 patients (10)	8 of 32 patients (25)	—	RR 0.41 (0.12–1.41)
% of patients who died of prostate cancer with PSA level >20 ng/mL	8 of 29 patients (28)	17 of 32 patients (53)	—	RR 0.52 (0.27–1.02)
% of patients who died of prostate cancer with biopsy Gleason score ≤7	11 of 29 patients (38)	8 of 32 patients (25)	—	RR 1.52 (0.71–3.24)
% of patients who died of prostate cancer with biopsy Gleason score >7	9 of 29 patients (31)	13 of 32 patients (41)	—	RR 0.9 (0.17–0.86)
% of patients who died of prostate cancer with biopsy Gleason score ≤7	9 of 29 patients (31)	11 of 32 patients (34)	—	RR 0.44 (0.44–1.86)
% of patients who died of prostate cancer with T1c	7 of 29 patients (24)	8 of 32 patients (25)	—	RR 0.97 (0.4–2.33)
% of patients who died of prostate cancer with T2a	17 of 29 patients (59)	9 of 32 patients (28)	—	RR 2.08 (1.11–3.92)
% of patients who died of prostate cancer with T2b	54 of 29 patients (19)	5 of 32 patients (16)	—	RR 0.88 (0.26–2.98)
% of patients who died of prostate cancer with T2c	27 of 29 patients (9)	6 of 32 patients (19)	—	RR 0.18 (0.02–1.44)
% of patients who died of prostate cancer with T3a or T3b	12 of 29 patients (4)	4 of 32 patients (13)	—	RR 0.12 (0.01–2.18)

Study Outcomes	Treatment Group 1	Treatment Group 2	Treatment Group 3	Analyses; p-Values
% of patients who died of prostate cancer with any 1 high-risk factor	8 of 29 patients (28)	5 of 32 patients (34)	—	RR 1.77 (0.65–4.79)
% of patients who died of prostate cancer with any 2 high-risk factors	11 of 29 patients (38)	3 of 32 patients (34)		RR 4.05 (1.25–13.08)
% of patients who died of prostate cancer with any 3 high-risk factors	8 of 29 patients (28)	14 of 32 patients (34)		RR 0.63 (0.31–1.28)
% of patients who died of prostate cancer with any 4 high-risk factors	2 of 29 patients (7)	10 of 32 patients (34)		RR 0.22 (0.05–0.93)

**Abbreviations:** 3D-CRT=Three-dimensional conformal radiotherapy; ADT=androgen-deprivation therapy; AJCC=American Joint Committee on Cancer; BT=brachytherapy; CCI=Charlson Comorbidity Index; CI=confidence interval; EBRT=external beam radiation therapy; HR=hazard ratio; IGRT: image-guided radiation therapy; NA=not applicable; PSA=prostate-specific antigen; RALP=robotic-assisted laparoscopic prostatectomy; RALRP=robotic-assisted laparoscopic radical prostatectomy; RP=radical prostatectomy; RR=relative risk; RRP=radical retropubic prostatectomy; T=tumor stage.

**Table F-7. Biochemical failure (randomized controlled trials)**

Study Outcomes	Treatment Group 1	Treatment Group 2	Analyses; p-Values
Jones et al. 2011 <sup>43</sup>	EBRT: 992 patients	EBRT plus short-term ADT: 987 patients	HR (95% CI)
Biochemical failure at 10 years (% reaching end point)	Biochemical failure was defined in the study as an increasing level of prostate specific antigen (PSA)	Biochemical failure was defined in the study as an increasing level of prostate specific antigen (PSA)	—
All patients	41	26	1.74 (1.48–2.04), p<0.001
Low risk	32	22	1.53 (1.13–2.06), p<0.001
Intermediate risk	45	28	1.79 (1.4–2.21), p<0.001
High risk	53	31	1.98 (1.30–3.03), p=0.002
White	42	29	1.62 (1.35–1.93), p<0.001
Black	40	19	2.27 (1.53–3.38), p<0.001
Age ≤70 years	42	27	1.71 (1.37–2.13), p<0.001
Age >70 years	41	25	1.78 (1.41–2.23), p<0.001
Donnelly et al. 2010 <sup>47</sup>	EBRT: 122 patients	Cryotherapy: 122 patients	—
Biochemical failure definition	Two PSA level rises with a final value >1.0 ng/mL	Two PSA level rises with a final value >1.0 ng/mL	—
Biochemical failure at 3 years (% reaching end point)	23.7	23.9	Difference 0.2 (-10.8–11.2)
Biochemical failure at 5 years (% reaching end point)	37.7	31	Difference -6.7 (-19.4–6.0)
Biochemical failure at 7 years (% reaching end point)	43.9	33.2	Difference -10.7 (-24.4–2.9)
Giberti et al. 2009 <sup>44</sup>	RRP: 100 patients	BT: 100 patients	—
5-year biochemical disease-free survival rate (%)	Biochemical failure was defined as two consecutive PSA values ≥0.2 ng/mL. 91%	Biochemical failure was defined as a PSA increase ≥2 ng/mL higher than the PSA nadir value independent of the serum concentration of the nadir. 91.7%	—
D'Amico et al. 2008 <sup>35</sup>	EBRT: 103 patients	EBRT plus ADT: 98 patients	HR (95% CI)
PSA failure at median of 4.52 years followup, number of patients	43	21	2.86 (1.69–4.86), p<0.001

**Abbreviations:** ADT=Androgen-deprivation therapy; BT=brachytherapy; CI=confidence interval; EBRT=external beam radiation therapy; HR=hazard ratio; PSA=prostate-specific antigen; RRP=radical retropubic prostatectomy.



**Table F-8. Biochemical failure (nonrandomized comparative studies)**

Study Outcomes	Treatment Group 1	Treatment Group 2	Analyses; p-Values
Marina et al. 2013 <sup>86</sup>	IGRT: 734 patients	BT: 282 patients	—
5-year biochemical control, % (range)	92 (89–94)	93 (89–96)	0.22
8-year biochemical control, % (range)	86 (82–90)	91 (86–94)	
5-year biochemical failure by patient characteristics	Age <60 years: IGRT 87% vs. BT 92% Age 60–69 years: IGRT 92% vs. BT 90% Age ≥70 years: IGRT 92% vs. BT 96% Race, African American: IGRT 100% vs. BT 82% Race, European American: IGRT 91% vs. 95 BT% Race, Other: IGRT 90% vs. BT 90%		—
5-year biochemical failure by tumor characteristics	PSA <10 ng/mL: IGRT 92% vs. BT 93% PSA 10–20 ng/mL: IGRT 91% vs. BT 91% Gleason score ≤6: IGRT 94% vs. BT 95% Gleason score 3+4: IGRT 93% vs. BT 91% Gleason score 4+3: IGRT 90% vs. 93 BT% Stage T1-2a: IGRT 93% vs. BT 92% Stage T2b–2c: IGRT 84% vs. BT 95%		—
Rice et al. 2011 <sup>36</sup>	RP: 194 patients	EBRT: 252 patients WW without secondary treatment: 214 patients WW with secondary treatment: 110 patients	—
Biochemical recurrence with a mean followup of 6.8±4.0 years	EBRT: HR 1.376 (0.878 to 2.158) WW without secondary treatment; 1.927 (1.163 to 3.193) WW with secondary treatment; 1.876 (0.990 to 3.557)		Multivariable cox proportional hazards model predicting overall mortality using pretreatment variables and treatment-related variables with RP as the comparator group. <u>EBRT</u> : p=0.1640 <u>WW without secondary treatment</u> : p=0.0109 <u>WW with secondary treatment</u> : p=0.0538

Study Outcomes	Treatment Group 1	Treatment Group 2	Analyses; p-Values
Biochemical recurrence with a mean followup of 6.8±4.0 years for age at diagnosis (per year)	HR 1.029 (0.975 to 1.085)		Multivariable cox proportional hazards model predicting overall mortality using pretreatment variables and treatment-related variables, p=0.2948
Biochemical recurrence with a mean followup of 6.8±4.0 years for PSA (per ng/mL)	HR 1.254 (1.163 to 1.354)		Multivariable cox proportional hazards model predicting overall mortality using pretreatment variables and treatment-related variables, p<0.0001
Biochemical recurrence with a mean followup of 6.8±4.0 years for Race/ethnicity	Black: HR 0.900 (0.505 to 1.606) Other: HR 0.878 (0.407 to 1.892)		Multivariable cox proportional hazards model predicting overall mortality using pretreatment variables and treatment-related variables with White as comparator group. Black p=0.7220 Other: p=0.7390
Biochemical recurrence with a mean followup of 6.8±4.0 years for number of comorbidities	1:HR 0.958 (0.642 to 1.429) 2: HR 0.578 (0.357 to 0.937) ≥3: 0.798 (0.476 to 1.338)		Multivariable cox proportional hazards model predicting overall mortality using pretreatment variables and treatment-related variables with no comorbidities as comparator group. 1: p=0.8326 2: p=0.0262 ≥3: 0.3923
Biochemical recurrence with a mean followup of 6.8±4.0 years for clinical T stage	T2a: HR 1.183 (0.845 to 1.656)		Multivariable cox proportional hazards model predicting overall mortality using pretreatment variables and treatment-related variables with clinical T stage T1 as comparator group. T2a: p=0.3272

Study Outcomes	Treatment Group 1	Treatment Group 2			Analyses; p-Values
Magheli et al. 2010 <sup>56</sup>	RRP: 522 patients	LRP: 522 patients	RALRP: 522 patients		Mean (SD) followup time RRP: 2.5 (1.6) years LRP: 1.47 (0.7) years RALRP: 1.3 (0.6) years
Multivariate proportional hazards ratio (HR) of risk of biochemical recurrence	RRP vs. LRP: HR 1.7; 95% CI, 0.69 to 4.42; p= 0.232 RRP vs RALRP: HR 1.02; 0.13 to 8.36; p= 0.979				—
Multivariate proportional HR of risk of biochemical recurrence stratified by Gleason score	Gleason score ≤6 vs. 7: HR 3.35; 95% CI, 1.27 to 8.83; p=0.015 Gleason score ≤6 vs. 8-10: HR 9.98; 95% CI, 3.07 to 32.42; p<0.001				—
Krambeck et al. 2008 <sup>65</sup>	RRP: 588 patients	RALRP: 294 patients			Median followup time was 1.3 years.
PSA progression, number of patients	32	14			—
Clinical local recurrence	RRP: 5	RALRP: 3			Median followup time was 1.3 years. Groups were similar on margin positivity.
Wong et al. 2007 <sup>88</sup>	3D-CRT: 270 patients	IMRT: 314 patients	BT: 225 patients	EBRT plus BT: 44 patients	—
The 5-year biochemical failure rates. Biochemical failure was defined as an increase in the PSA level ≥2 ng/mL above the nadir with no back-dating.	74%	87%	94%	94%	—

**Abbreviations:** 3D-CRT=Three-dimensional conformal radiotherapy; BT=brachytherapy; CI=confidence interval; EBRT=external beam radiation therapy; HR=hazard ratio; IGRT: image-guided radiation therapy; IMRT=intensity-modulated radiation therapy; LRP=laparoscopic radical prostatectomy; PSA=prostate-specific antigen; RALRP=robotic-assisted laparoscopic radical prostatectomy; RP=radical prostatectomy; RRP=radical retropubic prostatectomy; T=tumor stage; WW=watchful waiting.

**Table F-9. Biochemical progression-free survival (randomized controlled trials)**

Study Outcomes	Treatment Group 1	Treatment Group 2	Analyses; p-Values
Martis et al. 2007 <sup>50</sup>	Radical perineal prostatectomy: 100 patients	Radical retropubic prostatectomy: 100 patients	—
Percentage of patients with negative 1-hour pad-test at 6 months followup	74	75	—
Percentage of patients with negative 1-hour pad-test at 24 months followup	96	95	—

**Table F-10. Biochemical progression-free survival (nonrandomized comparative studies)**

Study Outcomes	Treatment Group 1	Treatment Group 2	Treatment Group 3	Analyses; p-Values
Alemozaffar et al. 2014 <sup>68</sup>	RALP: 282 patients	Open RRP: 621 patients	NA	
Biochemical recurrence at median 2.4 years and 6.8 years for RALP and open RRP groups respectively.	24 cases	110 cases	NA	Kaplan-Meier analysis demonstrated no significant difference in recurrence free survival between the two treatment groups (p=0.23) Median time to recurrence was 1.2 years for RALP and 2.5 years in the RRP group.
Biochemical progression-free survival among men with at least 5 years of followup	88.0%	84.7%	NA	Logistic regression adjusted for age, year of surgery, clinical stage, biopsy Gleason score, PSA showed no significant between-group difference OR 0.75 (95% CI 0.18 to 3.11)
Ferrer et al. 2013 <sup>91</sup> Same study as Ferrer et al. 2008 <sup>61</sup>	RRP: 193 patients	3D-CRT: 194 patients	BT: 317 patients	—
Percentage of patients with biochemical relapse patients who died at median duration of 5.23 years followup	17.1	24.7	16.1	—
Cox regression model	Cox regression model: RRP vs. 3D-CRT (HR 2.06; 95% CI, 1.21-3.52) Cox regression model: RRP vs. BT (HR 1.52; 95% CI, 0.90-2.57)			p=0.008  p=0.120
Age group <65 years vs. 65–70 years	Cox regression model: HR 0.80; 95% CI, 0.52-1.24			p=0.330
Age group <65 years vs. >70 years	Cox regression model: HR 0.65; 95% CI, 0.40-1.65			p=0.080
Low risk vs. intermediate risk	Cox regression model: HR 1.88; 95% CI, 1.09-3.25			p=0.024
Marina et al. 2013 <sup>86</sup>	IGRT: 734 patients	BT: 282 patients	NA	—
5-year disease-free survival, % (range)	81 (77-84)	86 (82–91)	—	0.006
8-year disease-free survival, % (range)	67 (62-73)	79 (74–85)	—	—

Study Outcomes	Treatment Group 1	Treatment Group 2	Treatment Group 3	Analyses; p-Values
5-year biochemical progression-free survival by patient characteristics	Age <60 years: IGRT 89% vs. BT 92% Age 60-69 years: IGRT 84% vs. BT 82% Age ≥70 years: IGRT 78% vs. BT 88% Race, African American: IGRT 87% vs. BT 84% Race, European American: IGRT 80% vs. BT 87% Race, Other: IGRT 86% vs. BT 86%		—	—
5-year biochemical progression-free survival by tumor characteristics	PSA <10 ng/mL: IGRT 81% vs. BT 86% PSA 10-20 ng/mL: IGRT 77% vs. BT 87% Gleason score ≤6: IGRT 78% vs. BT 93% Gleason score 3+4: IGRT 83% vs. BT 82% Gleason score 4+3: IGRT 78% vs. 85 BT% Stage T1-2a: IGRT 81% vs. BT 84% Stage T2b-2c: IGRT 76% vs. BT 91%		—	—
Pierorazio et al. 2013 <sup>70</sup>	RRP: 743 patients	RALRP: 105 patients	LRP: 65 patients	—
Biochemical recurrence-free survival at a mean followup of 3 years, (%)	RRP:56.3%, RALRP: 67.8%, and LRP: 41.1% No statistically significant difference for biochemical recurrence-free survival rates in men who underwent both RALRP (HR, 0.70, 95% CI, 0.32 to 1.51) and LRP (HR, 1.17; 95% CI, 0.62 to 2.20) in comparison with RRP.			—
Silberstein et al. 2013 <sup>67</sup>	RRP: 961 patients	RALRP: 493 patients	NA	—
The overall adjusted 2-year probability of recurrence, (%)	RRP: 4.1% and RALRP: 3.3% No significant difference in biochemical recurrence-free survival rates for RALRP compared with RRP (HR, 0.88; 95% CI, 0.56 to 1.39).			p=0.6
Wirth et al. 2013 <sup>74</sup>	RRP: 600 patients	LRP: 244 patients	NA	—
Overall cumulative biochemical recurrence rate, % (n)	14.2 (120)		—	—
Biochemical recurrence rate, % (n) at median followup 6.6 years in the RRP group and 4.6 years in the RALRP group	14.7 (88)	13.1 (32)	—	p=0.56
Univariate analysis for age as prognostic factor	LRP vs. RRP: HR, 1.0; 95% CI, 0.98 to 1.04		—	p=0.513
Univariate analysis for PSA as prognostic factor	LRP vs. RRP: HR 1.1; 95% CI, 1.10 to 1.16		—	p<0.001
Univariate analysis for tumor stage as prognostic factor	LRP vs. RRP: HR, 5.0; 95% CI, 3.44 to 7.16		—	p=0.005

Study Outcomes	Treatment Group 1	Treatment Group 2	Treatment Group 3	Analyses; p-Values
Univariate analysis for Gleason score 7 as prognostic factor	LRP vs. RRP: HR 6.6; 95% CI, 4.3 to 10.0		—	p<0.001
Univariate analysis for Gleason score ≥8 as prognostic factor	LRP vs. RRP: HR 16.4; 9.0 to 29.8		—	p<0.001
Ploussard et al. 2012 <sup>62</sup>	LRP: 1,377 patients	RALP: 1,009 patients	NA	—
Biochemical recurrence free survival for low risk prostate cancer patients	—	—	NA	Log-rank test: p=0.672
Biochemical recurrence free survival for intermediate prostate cancer patients	—	—	NA	Log-rank test: p=0.928
Biochemical recurrence free survival for high risk prostate cancer patients	—	—	NA	Log-rank test: p=0.413
Biochemical recurrence for all patients	18.0%	10.3%	NA	Log rank test: p=0.753
Biochemical recurrence for pT2 patients	7.9%	3.7%	NA	Log rank test: p=0.794
Biochemical recurrence for pT3 patients	33.5%	19.7%	NA	Log rank test: p=0.663
Zelevsky et al. 2012 <sup>89</sup>	BT: 942 patients	BT plus IMRT: 524 patients	—	—
5-year PSA-relapse free survival was only reported among men with intermediate-risk prostate cancer (i.e., those with T3a or higher, a Gleason score of 8 or more, or a pretreatment PSA level higher than 20 ng/mL)	97%	94%	—	p>0.50
Masterson et al. 2011 <sup>69</sup>	RRP: 357 patients	RALP: 669 patients	NA	—
Biochemical recurrence free survival at 24 months	All patients: 87%	All patients: 87%	NA	Cox proportional logistic regression modeling was used for univariate and multivariate analysis for assessing predictors of biochemical recurrence. p=0.97
Biochemical recurrence free survival at 60 months	All patients: 71%	All patients: 73%	NA	
Krambeck et al. 2008 <sup>65</sup>	RRP: 588 patients	RALRP: 294 patients	NA	—
Percentage free of PSA progression	Mean (SEM) 92.2% (1.8%)	Mean 92.4% (2.3%)	—	3 year Kaplan Meier progression free survival. Progression free survival was similar between groups.

Study Outcomes	Treatment Group 1	Treatment Group 2	Treatment Group 3	Analyses; p-Values
Barocas et al. 2010 <sup>64</sup>	RRP: 491 patients	RALRP: 1,413 patients	NA	—
3 year recurrence free survival (95% CI) log rank p value=0.19 showing no between-group difference.	83.5 (78.3 to 87.5)	84.0 (79.4–87.7)	—	—
Schroek et al. 2008 <sup>54</sup> Cox model adjusted for clinical variables (PSA, clinical stage, biopsy, Gleason score, age, race, BMI, and year of surgery). Mean followup was 1.37 years for RRP and 1.09 years for RALRP.	RRP: 435 patients	RALRP: 362 patients	NA	HR and (95% CI) for PSA recurrence free survival Cox regression models. HR 0.82 (0.48 to 1.38), p=0.448 There was no between-group difference in PSA recurrence free survival.
Cox model adjusted for risk category. Mean followup was 1.37 years for RRP and 1.09 years for RALRP.	RRP: 435 patients	RALRP: 362 patients	—	HR and (95% CI) for PSA recurrence free survival Cox regression models. HR 0.87 (0.52–1.47), p=0.610
Cox model adjusted for clinical and pathological variables (PSA, clinical stage, biopsy Gleason score, age, race, BMI, year of surgery, prostate weight, pathological stage, and pathological Gleason score). Mean followup was 1.37 years for RRP and 1.09 years for RALRP.	RRP: 435 patients	RALRP: 362 patients	—	HR and (95% CI) for PSA recurrence free survival Cox regression models. HR 0.94 (0.55–1.61), p=0.824



Study Outcomes	Treatment Group 1	Treatment Group 2	Treatment Group 3	Analyses; p-Values
Sumitomo et al. 2008 <sup>63</sup>	HIFU: 260 patients	HIFU plus androgen-deprivation therapy: 270 patients	NA	—
3-year biochemical progression-free survival among whole study population	53.8%	78.0%	—	p=0.005
3-year biochemical progression-free survival among men with low-risk prostate cancer	86.1%	89.7%	—	p=0.59
3-year biochemical progression-free survival among men with intermediate-risk prostate cancer	44.9%	79.3%	—	p=0.01
3-year biochemical progression-free survival among men with high-risk prostate cancer	36.2%	66.8%	—	p=0.03

**Abbreviations:** BMI=Body mass index; BT=brachytherapy; CI=confidence interval; HIFU=high-intensity focused ultrasound; HR=hazard ratio; IGRT: image-guided radiation therapy; LRP=laparoscopic radical prostatectomy; NA=not applicable; OR=odds ratio; PSA=prostate-specific antigen; RALP=robotic-assisted laparoscopic prostatectomy; RALRP=robotic-assisted laparoscopic radical prostatectomy; RRP=radical retropubic prostatectomy; T=tumor stage.

**Table F-11. Progression to metastasis (randomized controlled trials)**

Study Outcomes	Treatment Group 1	Treatment Group 2	Analyses; p-Values
Wilt et al. 2012 <sup>25</sup> Prostate Intervention Versus Observation Trial (PIVOT)	RP: 364 patients	Observation: 367 patients	—
Number of patients with bone metastases (%) at median followup 10 years	17 (4.7)	39 (10.0)	HR, 0.40; 95% CI, 0.22–0.70; p<0.001.
Bill-Axelsson et al. 2011 <sup>33</sup> Same study as Holmberg et al. 2012 <sup>34</sup> , and Bill-Axelsson et al. 2008 <sup>15</sup> Scandinavian Prostate Cancer Group-4 (SPCG-4) Trial	RP: 347 patients	Watchful waiting: 348 patients	—
Total number of distant metastases, cumulative incidence (number (%),at followup of 12 years	67 (19.3)	96 (27.6)	—
All ages at 8 years followup	11.5 (8.6–15.4)	18.7 (15-23.3)	ARR, 95% CI: 7.2 (1.8–12.5)
All ages at 12 years followup	19.3 (15.3–24.2)	26 (21.6–31.2)	ARR: 6.7 (0.2–13.2) RR: 0.65 (0.47–0.88) p=0.006
Age <65 years at 8 years followup	10.8 (6.9–17)	22.9 (17.3–30.3)	ARR: 12.1 (4.0–20.1)
Age <65 years at 12 years followup	20.7 (15–28.6)	30.3 (23.8–38.5)	ARR: 9.6 (-0.3–19.5) RR: 0.52 (0.34–0.81) p=0.006
Age ≥65 years at 8 years followup	12.1 (8.2–17.8)	14.8 (10.5–21)	ARR: 2.7 (-4.2–9.7)
Age ≥65 years at 12 years followup	17.9 (13–24.6)	22 (16.5–29.3)	ARR: 4.1 (16.5–29.3) RR: 0.80 (0.51–1.27) p=0.28
Total number of distant metastases (number (%) at 15 years followup	81 (23.3)	123 (35.3)	—
All at 15 years followup	21.7 (17.6–26.7)	33.4 (28.6 to 39.0)	ARR: 11.7 (4.8–18.6) RR: 0.59 (0.45–0.79) p<0.001
Low risk cancer at 15 years followup	9.9 (5.8 - 17.1)	21.4 (15.4 to 29.6)	ARR: 11.4 (2.6–20.2) RR: 0.43 (0.23–0.79) p=0.008
Age <65 years at 15 years followup	21.5 (15.9–29.2)	39.8 (32.6 to 48.5)	ARR: 18.3 (8.0–28.5) RR: 0.47 (0.32–0.70) p=0.001

Study Outcomes	Treatment Group 1	Treatment Group 2	Analyses; p-Values
Age <65 years and low risk cancer at 15 years followup	9.5 (4.4–20.4)	20.6 (12.8 to 33.0)	ARR: 11.1 (-1.0–23.2) RR: 0.41 (0.18–0.95) p=0.06
Age ≥65 years at 15 years followup	22.1 (16.6–29.4)	27.5 (21.5 to 35.1)	ARR: 5.4 (-3.9–14.6) RR: 0.77 (0.51–1.15) p=0.14
Age ≥65 years and low risk cancer at 15 years followup	10.5 (4.8–23.0)	21.8 (13.9 to 34.3)	ARR: 11.3 (-1.6–24.1) RR: 0.46 (0.19–1.11) p=0.06
Jones et al. 2011 <sup>43</sup>	EBRT: 992 patients	EBRT plus ADT: 987 patients	HR (95% CI)
Distant metastases at 10 years (% reaching end point)	—	—	—
All patients	8	6	1.45 (1.03–2.06), p=0.04

**Abbreviations:** ADT=androgen-deprivation therapy; ARR=absolute risk reduction; CI=confidence interval; EBRT=external beam radiation therapy; HR=hazard ratio; RP=radical prostatectomy RR=relative risk.

**Table F-12. Progression to metastasis (nonrandomized comparative studies)**

Study Outcomes	Treatment Group 1	Treatment Group 2			Analyses; p-values
Alemozaffar et al. 2014 <sup>68</sup>	RALP: 282 patients	RRP: 621			—
Progression to metastasis. Median followup was 2.4 years for RALP and 6.8 years for RRP.	0 cases	4 cases			—
Marina et al. 2013 <sup>86</sup>	IGRT: 734 patients	BT: 282 patients			—
5-year FFDM, % (range)	98 (97–99)	98 (96–99)			0.96
8-year FFDM, % (range)	97 (95–99)	98 (95–99)			—
5-year FFLR, % (range)	99 (97–100)	99 (97–100)			0.96
8-year FFLR, % (range)	98 (96–99)	98 (96–99)			—
5-year FFDM by patient characteristics	Age <60 years: IGRT 100% vs. BT 98% Age 60–69 years: IGRT 98% vs. BT 98% Age ≥70 years: IGRT 98% vs. BT 99% Race, African American: IGRT 100% vs. BT 100% Race, European American: IGRT 98% vs. BT 98% Race, Other: IGRT 97% vs. BT 96%			—	
5-year FFDM by tumor characteristics	PSA <10 ng/mL: IGRT 99% vs. BT 99% PSA 10–20 ng/mL: IGRT 97% vs. BT 97% Gleason score ≤6: IGRT 100% vs. BT 100% Gleason score 3+4: IGRT 100% vs. BT 98% Gleason score 4+3: IGRT 95% vs. BT 97% Stage T1–2a: IGRT 99% vs. BT 99% Stage T2b–2c: IGRT 96% vs. BT 97%			—	
Krambeck et al. 2008 <sup>65</sup>	RRP: 588 patients	RALRP: 294 patients			Median followup time was 1.3 years.
Systemic progression, number of patients	0	1			—
Wong et al. 2007 <sup>88</sup>	(3D-CRT: 270 patients	IMRT: 314 patients	BT: 225 patients	EBRT plus BT: 44 patients	—
% distant metastases	96%	97%	99%	97%	—

**Abbreviations:** 3D-CRT=Three-dimensional conformal radiotherapy; BT=brachytherapy; EBRT=external beam radiation therapy; FFDM=freedom from distant metastases; FFLR=freedom from local recurrence; IGRT: image-guided radiation therapy; IMRT=intensity-modulated radiation therapy; RALP=robot-assisted laparoscopic prostatectomy; RALRP=robot-assisted laparoscopic radical prostatectomy; RRP=radical retropubic prostatectomy.

**Table F-13. Quality of life (randomized controlled trials)**

Study Outcomes	Treatment Group 1	Treatment Group 2	Analyses; p-Values
Porpiglia et al. 2013 <sup>45</sup>	RARP: 60 patients	LRP: 60 patients	—
Survival, Continence, and Potency classification at 1 year followup	S0: 49 (98%) S1: 1 (2%) C0: 44 (88%) C1: 4 (8%) C2: 2 (4%) P0: 3 (8.6%) P1: 25 (71.4%) P2: 7 (20%)	S0: 49 (92.5%) S1: 4 (7.5%) C0: 36 (67.9%) C1: 6 (11.3%) C2: 11 (20.8%) P0: 3 (8.6%) P1: 16 (45.7%) P2: 16 (45.7%)	— — p=0.014 p=0.571 p=0.010 (C2 vs C0 to C1) p=1.00 p=0.030 p=0.020 (P2 vs. P0 to P1)
Rate of continence recovery at 12 month followup	95.0%	83.3%	OR 3.80 (95% CI 0.99 to 14.58), p=0.04 per author and p=0.052 per ECRI calculation.
Rate of potency recovery at 12 month followup in the nerve-sparing cohort	80%	54.2%	OR could not be calculated as authors were unclear about denominator, per author p=0.02
Wilt et al. 2012 <sup>25</sup> PIVOT	RP: 364 patients	Observation: 367 patients	—
Urinary Incontinence	RP: 49/287 (17.1%)	Observation 18/284 (6.3%)	p<0.001
Erectile dysfunction	RP: 231/285 (81.1%)	Observation: 124/281 (44.1%)	p<0.001
Bowel dysfunction	RP: 35/286 (12.2%)	Observation: 32/282 (11.3)	p=0.74

Study Outcomes	Treatment Group 1	Treatment Group 2	Analyses; p-Values
Johansson et al. 2011 <sup>51</sup> Bill-Axelsson et al. <sup>48</sup> Scandinavian Prostate Cancer Group-4 (SPCG-4) Trial	WW n/total number of patients who provided information for each question	RP n/total number of patients who provided information for each question	Age-adjusted relative risk, RP vs. WW (95% confidence interval [CI])
Anxiety (moderate or high) at median followup of 12.2 years (range 7–17)	69/161 (43%)	77/178 (43%), mean 2.74	0.97 (0.76–1.24)
Depressed mood (moderate or high) at median followup of 12.2 years (range 7–17)	82/159 (52%)	85/180 (47%), mean 2.89	0.92 (0.74–1.14)
Wellbeing (high) at median followup of 12.2 years (range 7–17)	71/161 (44%), mean 5.04	73 /179 (41%), mean 5.11	0.89 (0.70–1.13)
Quality of life (high) at median followup of 12.2 years (range 7–17)	55/160 (34%), mean 5.00	62/179 (35%), mean 4.96	0.98 (0.73–1.31)
Sense of meaningfulness (moderate or high) at median followup of 12.2 years (range 7–17)	79/160 (49%), mean 5.33	83/179 (46%), mean 5.32	0.92 (0.74–1.15)
Distress (urinary leakage at 4 – 9 years) at 8-year followup, least square means	0.25	0.58	Odds ratio (OR) 4.04 (2.33–6.92)
Distress (obstructive voiding) at 8-year followup, least square means	0.18	0.07	OR 0.34 (0.21–0.54)
Distress (difficulties with erection ) at 8-year followup, least square means	0.83	0.54	OR 4.19 (2.63–6.68)
Distress (difficulties with intercourse ) at 8-year followup, least square means	0.52	0.81	OR 3.97 (2.51–6.30)
Distress (decreased libido) at 8-year followup, least square means	0.46	0.64	OR 2.09 (1.37–3.19)
Distress (health-related distress) at 8-year followup, least square means	0.22	0.22	OR 1.00 (0.65–1.55)
Prevalence of erectile dysfunction at 4 year followup	WW: 45%	RP: 49%	OR: 0.86 (0.64–1.15), p=0.30
Prevalence of urinary leakage at 4 year followup	WW: 21%	RP: 49%	OR 3.62 (2.59–5.05), p=0.00

Study Outcomes	Treatment Group 1	Treatment Group 2	Analyses; p-Values
Jones et al. 2011 <sup>43</sup>	EBRT: 274 patients (number/total number (%))	EBRT plus short-term ADT: 284 patients (number/total number (%))	—
Effect of short-term ADT on erectile function, according to responses on the Sexual Adjustment Questionnaire at 1 year [number (%)]	—	—	—
Always or almost always	85 (31)	59 (21)	p=0.004
Sometimes	62 (23)	66 (23)	p=0.95
Almost never or never	69 (25)	94 (33)	p=0.054
Did not try	55 (20)	58 (20)	p=1.00
Not applicable or not answered	4 (1)	13 (5)	p=0.04
Robinson et al. <sup>52</sup> Same study as Donnelly et al. 2010 <sup>47</sup>	EBRT: 122 patients	Cryotherapy: 122 patients	—
Urinary function scores at 3 years	88.6	93.0	p=0.043
Bowel function scores at 3 years	84.1	88.1	p=0.092
Sexual function scores at 3 years	36.7	16.0	p<0.001
Giberti et al. 2009 <sup>44</sup>	RPP: 100 patients	BT: 100 patients	—
European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ)-C30 at 5-year followup	—	—	—
Physical function	90	94	p-value not specified
Role function	90	94	p-value not specified
Emotional function	84	82	p-value not specified
Cognitive function	90	88	p-value not specified
Social function	89	94	p-value not specified
Global health/Quality of life	78	82	p-value not specified
Fatigue	18	18	p-value not specified
Nausea/vomiting	1	1	p-value not specified
Pain	9	8	p-value not specified
Dyspnea	8	11	p-value not specified
Insomnia	22	20	p-value not specified
Appetite loss	3	4	p-value not specified
Constipation	3	0	p-value not specified
Diarrhea	5	6	p-value not specified

Study Outcomes	Treatment Group 1	Treatment Group 2	Analyses; p-Values
Financial problem	3	2	p-value not specified
International Prostate Symptom Score at 5-year followup	4.7	5.1	p-value not specified
EORTC-QLQ-PR25 urinary symptoms	10	17	p-value not specified
Bowel symptoms	2	5	p-value not specified
Treatment-related symptoms	8	8	p-value not specified
Sexual function	7	8	p-value not specified
Sexual activity	8	8	p-value not specified
IIEF at 5-year followup	22.0	21.2	p-value not specified
D'Amico et al. 2008 <sup>35</sup>	EBRT: 103 patients at median followup of 4.52 years	EBRT plus ADT: 98 patients at median followup of 4.52 years	—
Urinary incontinence (complete)	Grade 1: 3 Grade 2: 1 Grade 3: 1 Grade 4: 0	Grade 1: 2 Grade 2: 1 Grade 3: 1 Grade 4: 0	—
Urinary incontinence (stress)	Grade 1: 20 Grade 2: 7 Grade 3: 0 Grade 4: 0	Grade 1: 22 Grade 2: 6 Grade 3: 0 Grade 4: 0	—
Impotence	Grade 1: 4 Grade 2: 7 Grade 3: 21 Grade 4: 0	Grade 1: 1 Grade 2: 6 Grade 3: 26 Grade 4: 0	—
Martis et al. 2007 <sup>46</sup>	RPP: 100 patients	RRP: 100 patients	—
IIEF score at 6 months followup	30% of the patients had an average score of 18.5±0.5	45% of the patients had an average score of 21.7±1.9	—
IIEF score at 24 months followup	42% had a an average score of 19.7±1.1	60% had a an average score of 23.1±2.5	—

**Abbreviations:** ADT=androgen-deprivation therapy; BT=brachytherapy; CI=confidence interval; EBRT=external beam radiation therapy; IIEF= International Index of Erectile Function; LRP=laparoscopic radical prostatectomy; OR=odds ratio; RARP=robot-assisted radical prostatectomy; RP=radical prostatectomy; RPP=radical perineal prostatectomy; RRP=radical retropubic prostatectomy; WW=watchful waiting.



**Table F-14. Quality of life (nonrandomized comparative studies)**

Study Outcomes	Treatment Group 1	Treatment Group 2	Treatment Group 3	Treatment Group 4	Analyses; p-Values
Alemozaffar et al. 2014 <sup>68</sup>	RALP: 132 patients	RRP: 468 patients	NA	NA	—
Expanded Prostate Cancer Index scores (urinary incontinence)	74.4±23.0	74.4±25.3	NA	NA	p=0.93
Expanded Prostate Cancer Index scores (urinary obstruction)	94.5±7.5	93.9±9.6	NA	NA	p=0.94
Expanded Prostate Cancer Index scores (sexual)	36.8±29.5	36.3±29.7	NA	NA	p=0.66
Expanded Prostate Cancer Index scores (bowel)	96.3±9.2	96.3±7.8	NA	NA	p=0.52
Expanded Prostate Cancer Index scores (hormonal/vitality)	93.5±10.6	92.6±11.4	NA	NA	p=0.37
Satisfaction scale for cancer care (outcome satisfaction)	89.3±13.3	89.5±13.6	NA	NA	p=0.41
Ferrer et al. 2013 <sup>91</sup> Same study as Ferrer et al. 2008 <sup>61</sup>	RRP: 134 patients	3D-CRT: 205 patients	BT: 275 patients	NA	One-way analysis of variance of Health related Quality of Life scores (mean and SE) by treatment and risk group at the 5-year followup
Irritative obstructive scale Incontinence scale among men in the BT group compared with RRP and 3D-CRT	Quality of life in men who underwent BT was limited to the urinary domain with Generalized Estimating Equation models showing the following score changes at the 5-year followup compared to RRP and 3D-CRT BT vs. RRP vs. 3D-CRT: mean change -5.3; 95% CI, -7.5 to -3.1 BT vs. RRP vs. 3D-CRT: mean change -12.0; 95% CI, -15.0 to -9.0				—
Irritative obstructive scale and incontinence scale comparing BT to RRP	Favorable irritative obstructive score (mean change 3.3; 95% CI, 0.0 to 6.5) and worse incontinence score (mean change -17.1; 95% CI, -22.7 to -11.5) were reported among men who underwent RRP compared to BT.				—
EPIC - sexual function	A worsening in the EPIC score for sexual function was reported among men who underwent RRP (mean change -19.1; 95% CI, -25.1 to -13.1) and men who received 3D-CRT (mean change -7.5; 95% CI -12.5 to -2.5). <sup>91</sup>				—
Ferrer et al. 2008 <sup>61</sup> Same study as Ferrer et al. 2013 <sup>91</sup>	RRP: 134 patients	3D-CRT: 205 patients	BT: 275 patients	NA	One-way analysis of variance of Health related Quality of Life scores (mean and SE) by treatment and risk group at the 2-year followup
SF-36 physical component summary	50.6 (0.8)	49.2 (0.6)	50.9 (0.5)	NA	p>0.05 at the 24 month followup for all dimensions forming the physical component. p=0.094 for component summary.

<b>Study Outcomes</b>	<b>Treatment Group 1</b>	<b>Treatment Group 2</b>	<b>Treatment Group 3</b>	<b>Treatment Group 4</b>	<b>Analyses; p-Values</b>
SF-36 mental component summary	54.9 (0.8)	56.3 (0.5)	56.3 (0.4)	NA	p>0.05 at the 24 month followup for all dimensions forming the mental component. p=0.373 for component summary.
Functional Assessment of Cancer Therapy General (FACT-G)	76.6 (1.1)	77.5 (0.9)	79.8 (0.6)	NA	One dimension of the FACT-G (physical well-being) showed significant between-group differences for RP vs. BT and BT vs. 3D-CRT (p<0.05) at the 24 month followup. For entire scale, p=0.008 for RP vs. BT.
Functional Assessment of Cancer Therapy Prostate Specific (FACT-P)	37.2 (0.5)	37.5 (0.4)	38.9 (0.3)	NA	For the entire scale, p=0.001 for RP vs. BT and for BT vs. 3D-CRT.
American Urologic Association Symptom Index (AUA-7)	4.9 (0.6)	6.4 (0.5)	5.7 (0.4)	NA	p=0.405

Study Outcomes	Treatment Group 1	Treatment Group 2	Treatment Group 3	Treatment Group 4	Analyses; p-Values
EPIC urinary	88.2 (1.3)	94.2 (0.8)	92.4 (0.8)	NA	For the following subscale scores there was a significant ( $p<0.05$ ) between-group difference at the 24 month follow up for RP vs. BT: irritative obstructive, urinary function, sexual function, incontinence, and sexual bother. For the following subscale scores there was a significant ( $p<0.05$ ) between-group difference at the 24 month follow up for BT vs. 3D-CRT: bowel function, sexual function, and bowel bother. Overall p values for EPIC urinary ( $p<0.001$ RP vs. both other treatments), urinary irritative ( $p=0.005$ for RP vs. BT), urinary incontinence ( $p<0.001$ for RP vs. both other treatments), EPIC bowel ( $p<0.001$ 3D-CRT vs. both other treatments), EPIC sexual ( $p<0.001$ for all comparisons), EPIC hormonal ( $p=0.74$ ).
Urinary irritative	NR	NR	NR	NA	—
Urinary incontinence	NR	NR	NR	NA	—
EPIC bowel	97.9 (0.7)	94.5 (0.9)	97.9 (0.3)	NA	—
EPIC sexual	33.1 (2.1)	43.5 (1.9)	49.8 (1.6)	NA	—
EPIC hormonal	93.7 (1.0)	93.7 (0.9)	95.5 (0.5)	NA	—
Resnick et al. 2013 <sup>55</sup>	Prostatectomy	Radiotherapy	NA	NA	OR (95% CI) for prostatectomy vs. radiotherapy, adjusted for registry, baseline function, race or ethnicity, tumor grade, number of coexisting illnesses, education, and propensity score.

<b>Study Outcomes</b>	<b>Treatment Group 1</b>	<b>Treatment Group 2</b>	<b>Treatment Group 3</b>	<b>Treatment Group 4</b>	<b>Analyses; p-Values</b>
No control or frequent urinary leakage at the 2-year followup	9.6%	3.2%	NA	NA	6.22 (1.92-20.29)
No control or frequent urinary leakage at the 5-year followup	13.4%	4.4%	NA	NA	5.10 (2.29-11.36)
No control or frequent urinary leakage at the 15-year followup	18.3%	9.4%	NA	NA	2.34 (0.88-6.23)
Bothered by dripping or leaking urine at the 2-year followup	10.6%	2.4%	NA	NA	5.86 (1.93-17.64)
Bothered by dripping or leaking urine at the 5-year followup	12.9%	2.9%	NA	NA	7.66 (2.97-19.89)
Bothered by dripping or leaking urine at the 15-year followup	17.1%	18.4%	NA	NA	0.87 (0.41-1.80)
Erection insufficient for intercourse at the 2-year followup	78.8%	60.8%	NA	NA	3.46 (1.93-6.17)
Erection insufficient for intercourse at the 5-year followup	75.7%	71.9%	NA	NA	1.96 (1.05-3.63)
Erection insufficient for intercourse at the 15-year followup	87.0%	93.9%	NA	NA	0.38 (0.12-1.22)
Bothered by sexual dysfunction at the 2-year followup	55.5%	48.2%	NA	NA	1.19 (0.77-1.86)
Bothered by sexual dysfunction at the 5-year followup	46.7%	39.7%	NA	NA	1.48 (0.92-2.39)
Bothered by sexual dysfunction at the 15-year followup	43.5%	35.8%	NA	NA	1.33 (0.58-3.03)
Bowel urgency at the 2-year followup	13.6%	34.0%	NA	NA	0.39 (0.22-0.68)
Bowel urgency at the 5-year followup	16.3%	31.3%	NA	NA	0.47 (0.26-0.84)
Bowel urgency at the 15-year followup	21.9%	35.8%	NA	NA	0.98 (0.45-2.14)

<b>Study Outcomes</b>	<b>Treatment Group 1</b>	<b>Treatment Group 2</b>	<b>Treatment Group 3</b>	<b>Treatment Group 4</b>	<b>Analyses; p-Values</b>
Bothered by frequent bowel movements, pain, or urgency at the 2-year followup	2.9%	7.9%	NA	NA	0.37 (0.14-0.96)
Bothered by frequent bowel movements, pain, or urgency at the 5-year followup	4.4%	5.8%	NA	NA	0.93 (0.27-3.22)
Bothered by frequent bowel movements, pain, or urgency at the 15-year followup	5.2%	16.0%	NA	NA	0.29 (0.11-0.78)

Study Outcomes	Treatment Group 1	Treatment Group 2	Treatment Group 3	Treatment Group 4	Analyses; p-Values
Barry et al. 2012 <sup>66</sup>	RALRP: 406 patients	RRP: 220 patients	NA	NA	—
Percentage of patients with incontinence (moderate or big problem)	RALRP: 33.1% (131/393)	RRP: 27.1% (58/214)	NA	NA	Pearson chi-square p-value=0.113 for the between-group difference in incontinence. A logistic regression model controlling for age and education was performed comparing RALRP to RRP, producing an OR 1.41 (95% CI, 0.97–2.05). A second logistic regression model with mental and overall health factored in in addition to age and education produced an OR of 1.46 (95% CI, 1.00–2.12, p=0.049). Confirmatory ordinal regression models found RALRP to be significantly associated with greater degrees of problems with continence in both the age, education adjusted model (p=0.020) and the four control variable model (p=0.007).

Study Outcomes	Treatment Group 1	Treatment Group 2	Treatment Group 3	Treatment Group 4	Analyses; p-Values
Percentage of patients with sexual dysfunction (moderate or big problem)	RALRP: 87.5% (335/383)	RRP: 89.0% (187/210)	NA	NA	Pearson chi-square p-value=0.57 for the between-group difference in incontinence. A logistic regression model controlling for age and education was performed comparing RALRP to RRP, producing an OR 0.87 (95% CI, 0.51–1.49). A second logistic regression model with mental and overall health factored in in addition to age and education produced an OR of 0.93 (95% CI, 0.54–1.61). Confirmatory ordinal regression models found RALRP not to be significantly associated with greater degrees of sexual dysfunction in both the age and education adjusted model (p=0.605) and the four control variable model (p=0.761).
Mohammed et al. 2012 <sup>80</sup>	BT: 417 patients	EB-IGRT: 1,039 patients	EBRT plus HDR-BT: 447 patients	—	—
Late incontinence ≥Grade 3	BT: 0.3%	EB-IGRT: 0.4%	EBRT plus HDR: 1%	NA	p-value of difference: 0.13
Ploussard et al. 2012 <sup>82</sup>	LRP: 1377 patients	RALP: 1009 patients	NA	NA	—
Rate of continence recovery at 12 months followup for all patients regardless of baseline continence	68.5%	75.4%	NA	NA	p=0.177
Rate of continence recovery at 24 months followup for all patients regardless of baseline continence	78.8%	83.6%	NA	NA	p=0.024
Predictors of continence at 12 month followup (variable = age)	—	—	NA	NA	Multivariate regression for predictors of urinary continence, OR not calculated, p=0.002.

Study Outcomes	Treatment Group 1	Treatment Group 2	Treatment Group 3	Treatment Group 4	Analyses; p-Values
Predictors of continence at 12 month followup (variable = PSA)	—	—	NA	NA	Multivariate regression for predictors of urinary continence, OR not calculated p=0.746.
Predictors of continence at 12 month followup (variable = prostate volume)	—	—	NA	NA	Multivariate regression for predictors of urinary continence, OR not calculated=0.524.
Predictors of continence at 12 month followup (variable = pT2 disease)	—	—	NA	NA	Multivariate regression for predictors of urinary continence, OR 0.78 (95% CI 0.44 to 1.37), p=0.393.
Predictors of continence at 12 month followup (variable = Gleason score)	—	—	NA	NA	Multivariate regression for predictors of urinary continence using Gleason score 6 as the reference. 7: OR 0.915 (0.53 to 1.60), p=0.751 8 to 10: OR 1.24 (0.42 to 3.68), p=0.70
Predictors of potency at 12 month followup (variable = procedure)	—	—	NA	NA	Multivariate regression for predictors of potency using procedure with LRP as the reference. RALP: OR 5.93 (1.04 to 33.82), p=0.045
Rate of potency recovery following bilateral NS surgery at 12 months followup for all patients regardless of baseline potency	31.6%	57.7%	NA	NA	p<0.001
Rate of potency recovery following bilateral NS surgery at 24 months followup for all patients regardless of baseline potency	55.0%	69.0%	NA	NA	p<0.001
Predictors of potency at 12 month followup (variable = age)	—	—	NA	NA	Multivariate regression for predictors of potency, OR not calculated, p=0.001



Study Outcomes	Treatment Group 1	Treatment Group 2	Treatment Group 3	Treatment Group 4	Analyses; p-Values
Predictors of potency at 12 month followup (variable = PSA)	—	—	NA	NA	Multivariate regression for predictors of potency, OR not calculated, p=0.085
Predictors of potency at 12 month followup (variable = prostate volume)	—	—	NA	NA	Multivariate regression for predictors of potency, OR not calculated, p=0.943
Predictors of potency at 12 month followup (variable = pT2 disease)	—	—	NA	NA	Multivariate regression for predictors of potency OR 8.02 (0.33 to 1.97), p=0.630
Predictors of potency at 12 month followup (variable = Gleason score)	—	—	NA	NA	Multivariate regression for predictors of potency using Gleason score 6 as the reference. 7: OR 1.36 (0.57 to 3.24), p=0.49 8 to 10: OR 1.25 (0.19 to 7.98), p=0.82

Study Outcomes	Treatment Group 1	Treatment Group 2	Treatment Group 3	Treatment Group 4	Analyses; p-Values
Sheets et al. 2012 <sup>58</sup>	Urinary incontinence diagnoses	IMRT: 6,438 patients 3D-CRT: 6,478 patients IMRT: 684 (for the propensity score matched comparison to proton therapy) Proton therapy: 684 patients	Adjusted for baseline- and clinical- characteristics. Outcomes are per 100 person-years and are presented as rate ratio (95% CI) for IMRT vs. 3D-CRT: IMRT total events 858, rate 3.5 3D-CRT total events 917, rate 3.7 Rate ratio: 0.94 (0.86 to 1.04) Propensity score matched rates adjusted for baseline- and clinical- characteristics. Outcomes are per 100 person-years and are presented as rate ratio (95% CI) for IMRT vs. Proton therapy: IMRT total events 75, rate 3.1 Proton total events 82, rate 3.3 Rate ratio: 0.96 (0.70 to 1.32)	—	—

Study Outcomes	Treatment Group 1	Treatment Group 2	Treatment Group 3	Treatment Group 4	Analyses; p-Values
Sheets et al. 2012 <sup>58</sup> (continued)	Erectile dysfunction diagnoses	IMRT: 6,438 patients 3D-CRT: 6,478 patients IMRT: 684 (for the propensity score matched comparison to Proton therapy) Proton therapy: 684 patients	Adjusted for baseline- and clinical- characteristics. Outcomes are per 100 person-years and are presented as rate ratio (95% CI) for IMRT vs. 3D-CRT: IMRT total events 1,342, rate 5.9 3D-CRT total events 1,239, rate 5.3 Rate ratio: 1.12 (1.03–1.20) Propensity score matched rates adjusted for baseline- and clinical- characteristics. Outcomes are per 100 person-years and are presented as rate ratio (95% CI) for IMRT vs. Proton therapy: IMRT total events 145, rate 6.6 Proton total events 164, rate 7.4 Rate ratio: 0.89 (0.70 to 1.12)	—	—
Williams et al. 2011 <sup>57</sup>	BT: 9,985 patients	Cryotherapy: 943 patients	NA	NA	Propensity-weighted incidence of complications expressed as percentages.
Incontinence	18.2%	11.3%	—	—	p<0.001
Bowel	12.1%	19.0%	—	—	p<0.001
Erectile dysfunction	34.7%	21.0%	—	—	p<0.001

Study Outcomes	Treatment Group 1	Treatment Group 2	Treatment Group 3	Treatment Group 4	Analyses; p-Values
Malcolm et al. 2010 <sup>1</sup>	RRP	RALRP	BT	Cryotherapy	Cox proportional hazards ratio adjusted for age, race, Gleason score and baseline functioning on this outcome. Results are presented as hazard ratio (95% CI) for returning to 90% of the baseline score. Scores are presented as average (PBS)
Urinary function	PBS at 1 year followup: 79 PBS at 2 year followup: 84 PBS at 3 year followup: 83	PBS at 1 year followup: 74 PBS at 2 year followup: 76 PBS at 3 year followup: 78	PBS at 1 year followup: 94 PBS at 2 year followup: 90 PBS at 3 year followup: 88	PBS at 1 year followup: 106 PBS at 2 year followup: 102 PBS at 3 year followup: 113	RRP plus RALRP: 1.0, BT plus Cryotherapy 2.98 (2.33-3.82)
Urinary bother	PBS at 1 year followup: 84 PBS at 2 year followup: 87 PBS at 3 year followup: 88	PBS at 1 year followup: 81 PBS at 2 year followup: 83 PBS at 3 year followup: 86	PBS at 1 year followup: 88 PBS at 2 year followup: 94 PBS at 3 year followup: 90	PBS at 1 year followup: 97 PBS at 2 year followup: 98 PBS at 3 year followup: 103	RRP plus RALRP 1.0, BT plus Cryotherapy 1.48 (1.17-1.88)
Sexual function	PBS at 1 year followup: 43 PBS at 2 year followup: 46 PBS at 3 year followup: 48	PBS at 1 year followup: 40 PBS at 2 year followup: 45 PBS at 3 year followup: 46	PBS at 1 year followup: 71 PBS at 2 year followup: 74 PBS at 3 year followup: 73	PBS at 1 year followup: 30 PBS at 2 year followup: 36 PBS at 3 year followup: 27	RRP, RALRP, plus cryotherapy 1, BT 5.71 (3.71-8.77)
Sexual bother	PBS at 1 year followup: 40 PBS at 2 year followup: 52 PBS at 3 year followup: 58	PBS at 1 year followup: 47 PBS at 2 year followup: 48 PBS at 3 year followup: 45	PBS at 1 year followup: 63 PBS at 2 year followup: 78 PBS at 3 year followup: 85	PBS at 1 year followup: 59 PBS at 2 year followup: 61 PBS at 3 year followup: 50	RRP plus RALRP 1, BT plus cryotherapy 1.99 (1.49-2.67)
Bowel function	PBS at 1 year followup: 102 PBS at 2 year followup: 104 PBS at 3 year followup: 101	PBS at 1 year followup: 103 PBS at 2 year followup: 101 PBS at 3 year followup: 102	PBS at 1 year followup: 103 PBS at 2 year followup: 110 PBS at 3 year followup: 107	PBS at 1 year followup: 110 PBS at 2 year followup: 108 PBS at 3 year followup: 108	BT 1, RRP, RALRP, plus cryotherapy 1.24 (0.99 to 1.55)

Study Outcomes	Treatment Group 1	Treatment Group 2	Treatment Group 3	Treatment Group 4	Analyses; p-Values
Bowel bother	PBS at 1 year followup: 99 PBS at 2 year followup: 102 PBS at 3 year followup: 99	PBS at 1 year followup: 100 PBS at 2 year followup: 97 PBS at 3 year followup: 94	PBS at 1 year followup: 99 PBS at 2 year followup: 101 PBS at 3 year followup: 99	PBS at 1 year followup: 106 PBS at 2 year followup: 107 PBS at 3 year followup: 92	RRP, BT plus cryotherapy 1, RALRP 1.28 (1.08 to 1.51)
Krambeck et al. 2008 <sup>65</sup>	RRP: 496 patients with one year data for continence and potency	RALRP: 252 patients with one year data for continence and potency	NA	NA	p=0.344
With continence	446 (93.7%)	224 (91.8%)	NA	NA	NA
Continence=No pads	419 (88.0%)	199 (81.6%)	NA	NA	NA
Continence=security pad only	27 (5.7%)	25 (10.3%)	NA	NA	NA
Without continence	30 (6.3%)	20 (8.2%)	NA	NA	NA
Continence=1 to 2 pads per day	23 (4.8%)	17 (7.0%)	NA	NA	NA
Continence=3 pads per day	7 (1.5%)	3 (1.2%)	NA	NA	NA
Previous incontinence	6	1	NA	NA	NA
Continence=unknown	14	7	NA	NA	NA
—	RRP: 496 patients with potency data at one year followup	RALRP: 252 patients with potency data at the one year followup	NA	NA	p=0.081
Impotent	155 (37.2)	61 (30%)	NA	NA	NA
Potent	262 (62.8%)	142 (70%)	NA	NA	NA
Previously impotent	49	32	NA	NA	NA
Potency=unknown	31	17	NA	NA	NA
Sanda et al. 2008 <sup>85</sup>	RP (RRP or LRP or RALRP): 603 patients	EBRT (IMRT or 3D-CRT): 292 patients	BT: 306 patients	NA	—
Overall urinary problem at 24 months followup, (%)	7	11	16	NA	RP vs. BT: OR 0.21 (0.09 to 0.52), p=0.00 RP vs. EBRT OR: 0.30 (0.12 to 0.78), p=0.01 EBRT vs. BT OR: 0.71 (0.32 to 1.56), p=0.39
Overall bowel problem at 24 months followup, (%)	1	11	8	NA	RP vs. BT: OR 0.06 (0.01 to 0.50), p=0.01 RP vs. EBRT OR: 0.04 (0.01 to 0.33), p=0.00 EBRT vs. BT: OR 1.45 (0.58 to 3.68), p=0.42

Study Outcomes	Treatment Group 1	Treatment Group 2	Treatment Group 3	Treatment Group 4	Analyses; p-Values
Overall sexual problem at 24 months followup, (%)	43	37	30	NA	RP vs. BT: OR 0.71 (0.43 to 1.15), p=0.16 RP vs. EBRT: OR 0.53 (0.33 to 0.84), p=0.00 EBRT vs. BT: OR 1.34 (0.80 to 2.23), p=0.27
Sexuality	RP, independent variable Age, p=0.001 RP, independent variable PSA score, p=0.01 EBRT, independent variable Age, p=0.009 BT, independent variable Age, p=0.01 BT, independent variable PSA score, p≤0.001			NA	—
Urinary incontinence	RP, independent variable PSA score, p=0.005 RP, independent variable Black race, p=0.03 BT, independent variable PSA score, p=0.02			NA	—
Urinary irritation or obstruction	BT, independent variable PSA score, p=0.03 BT, independent variable Clinical stage T1c, p=0.05			NA	—
Bowel or rectal function	RP, independent variable >2 Coexisting illnesses, p=0.02 BT, independent variable Gleason score >7, p=0.03			NA	—
Vitality or hormonal function	EBRT, independent variable Coexisting illness, p=0.03 BT, independent variable Age, p=0.03			NA	—
Sumitomo et al. 2008 <sup>63</sup>	High-Intensity Focused Ultrasound (HIFU): 260 patients			HIFU plus ADT: 270 patients	—
Transient grade 1 and 2 incontinence	6 patients (2.3%)			3 patients (1.1%)	p=0.11

**Abbreviations:** 3D-CRT=Three-dimensional conformal radiotherapy; BT=brachytherapy; CI=confidence interval; EB-IGRT=external beam image-guided radiation therapy; EBRT=external beam radiation therapy; EPIC=Expanded Prostate Cancer Index Composite; HDR=high dose rate; IMRT=intensity-modulated radiation therapy; LRP=laparoscopic radical prostatectomy; NA=not available; NR=not reported; NS=nerve sparing; OR=odds ratio; PBS=percent baseline scores; PSA=prostate-specific antigen; RALP=robotic-assisted laparoscopic prostatectomy; RALRP=robotic-assisted laparoscopic radical prostatectomy; RP=radical prostatectomy; RRP=radical retropubic prostatectomy; SF=Short Form (instrument).

**Table F-15. Reported adverse events (randomized controlled trials)**

Study	Adverse Events/Harms Reported	Author calculation if provided	
Porpiglia et al. 2013 <sup>45</sup>	Early <30 days (Clavien system minor 1–2) medical	RARP: UTI (2), transient hypoaesthesia of left arm (1), ileus (1) LRP: UTI (1), fever requiring antipyretics (1), delirium requiring neuroleptics (1)	—
Porpiglia et al. 2013 <sup>45</sup>	Early <30 days (Clavien system major 3–4) - medical	RARP: 0 cases LRP: 0 cases	—
Porpiglia et al. 2013 <sup>45</sup>	Intermediate 31 to 90 days (Clavien system minor 1–2) - medical	RARP: 0 cases LRP: transient leg edema not requiring therapy (1)	—
Porpiglia et al. 2013 <sup>45</sup>	Intermediate 31 to 90 days (Clavien system major 3–4) - medical	RARP: 0 cases LRP: 0 cases	—
Porpiglia et al. 2013 <sup>45</sup>	Early <30 days (Clavien system minor 1–2) surgical	RARP: urine leak requiring catheterization (1), wound infection (1), lymphocele requiring puncture (1), acute urinary retention (2) LRP: urine leak requiring catheterization (1), wound infection (1)	—
Porpiglia et al. 2013 <sup>45</sup>	Early <30 days (Clavien system major 3–4) – surgical	RARP: 0 cases LRP: 0 cases	—
Porpiglia et al. 2013 <sup>45</sup>	Intermediate 31 to 90 days (Clavien system minor 1–2) – surgical	RARP: epididymitis (1) LRP: distal urethral stenosis requiring urethral dilatation (1)	—
Porpiglia et al. 2013 <sup>45</sup>	Intermediate 31 to 90 days (Clavien system major 3–4) - surgical	RARP: 0 cases LRP: 0 cases	—
Wilt et al. 2012 <sup>25</sup> PIVOT	Adverse events occurring within 30 days after surgery	Patients (N=280) N (%)	—
Wilt et al. 2012 <sup>25</sup> PIVOT	Any	60 (21.4)	—
Wilt et al. 2012 <sup>25</sup> PIVOT	Pneumonia	2 (0.7)	—
Wilt et al. 2012 <sup>25</sup> PIVOT	Wound infection	12 (4.3)	—
Wilt et al. 2012 <sup>25</sup> PIVOT	Urinary tract infection	7 (2.5)	—
Wilt et al. 2012 <sup>25</sup> PIVOT	Sepsis	3 (1.1)	—
Wilt et al. 2012 <sup>25</sup> PIVOT	Deep vein thrombosis	2 (0.7)	—

Study	Adverse Events/Harms Reported		Author calculation if provided
PIVOT	Stroke	1 (0.4)	—
Wilt et al. 2012 <sup>25</sup>	Pulmonary embolism	2 (0.7)	—
PIVOT	Myocardial infarction	3 (1.1)	—
Wilt et al. 2012 <sup>25</sup>	Renal failure or dialysis	1 (0.4)	—
PIVOT	Bowel injury requiring surgical repair	3 (1.1)	—
Wilt et al. 2012 <sup>25</sup>	Additional surgical repair	7 (2.5)	—
PIVOT	Bleeding requiring transfusion	6 (2.1)	—
Wilt et al. 2012 <sup>25</sup>	Urinary catheter present >30 days after surgery	6 (2.1)	—
PIVOT	Death	1 (0.4)	—
Wilt et al. 2012 <sup>25</sup>	Other	28 (10.0)	—
PIVOT			
Bill-Axelsson et al. 2011 <sup>33</sup> SPCG-4 trial	Nonfatal Surgical Complications within 1 year after Surgery among Men in the RP (N=289) Group		
Bill-Axelsson et al. 2011 <sup>33</sup> SPCG-4	<i>Complication</i>	<i>Number of Events</i>	<i>1-Year Cumulative Incidence (95% confidence interval [CI])</i>
Bill-Axelsson et al. 2011 <sup>33</sup> SPCG-4	Urinary leakage	93	32.2 (27.2–38.1)
Bill-Axelsson et al. 2011 <sup>33</sup> SPCG-4	Urinary obstruction	6	2.1 (0.9–4.6)
Bill-Axelsson et al. 2011 <sup>33</sup> SPCG-4	Impotence	168	58.1 (52.7–64.1)
Bill-Axelsson et al. 2011 <sup>33</sup> SPCG-4	Pulmonary embolism	4	1.4 (0.5–3.7)
Bill-Axelsson et al. 2011 <sup>33</sup> SPCG-4	Deep vein thrombosis	3	1.0 (0.3–3.2)
Bill-Axelsson et al. 2011 <sup>33</sup> SPCG-4	Myocardial infarction	0	Not applicable
Giberti et al. 2009 <sup>44</sup>	RRP: 100 patients	BT: 100 patients	—
Urinary incontinence	18.4% (severe in 5.4% and mild in 13.0%) at 6-month-followup	Not reported	—
Anastomotic urethral stricture	6.5% at 6-month-followup	Not reported	—



Study	Adverse Events/Harms Reported		Author calculation if provided
Irritative urinary symptoms	5.0% at 6-month-followup	80% at 6-month followup 20% at 1-year followup	—
Erectile function	Significant worsening of the QLQ-PR25 and IIEF was reported by both groups at 6-month-followup		—
Erectile function and urinary disorders at 5-year followup.	There was no differences in erectile function and urinary disorders at the 5-year followup period in both study groups.		—
Jones et al. 2011 <sup>43</sup>	EBRT: 992 patients	EBRT plus ADT: 987	—
Incidence of grade 3 or higher acute and late gastrointestinal toxic effects up to 90 days after the start of EBRT	3%	1%	—
Acute grade 3 of higher genitourinary toxic effects up to 90 days after the start of EBRT	2%	2%	—
Deaths	Colonic obstruction: 2 patients	Colorectal bleeding: 1 patient	—
Donnelly et al. 2010 <sup>47</sup>	EBRT: 122 patients	Cryotherapy: 122 patients	—
Adverse events at 3 years were classified according to the codes of the National Cancer Institute of Canada Common Toxicity Criteria (version 2,0)	14 patients suffered 16 grade 3 adverse events	12 patients suffered 13 grade 3 adverse events	—
D'Amico et al. 2008 <sup>35</sup>	—	EBRT: 103 patients at median followup of 4.52 years	EBRT plus ADT: 98 patients at median followup of 4.52 years

Study	Adverse Events/Harms Reported	Author calculation if provided		
D'Amico et al. 2008 <sup>35</sup>	Hematuria	Grade 1: 6 Grade 2: 5 Grade 3: 3 Grade 4: 0	Grade 1: 7 Grade 2: 6 Grade 3: 3 Grade 4: 0	
D'Amico et al. 2008 <sup>35</sup>	Diarrhea	Grade 1: 19 Grade 2: 8 Grade 3: 3 Grade 4: 0	Grade 1: 18 Grade 2: 9 Grade 3: 1 Grade 4: 0	
D'Amico et al. 2008 <sup>35</sup>	Rectal bleeding	Grade 1: 34 Grade 2: 18 Grade 3: 2 Grade 4: 0	Grade 1: 26 Grade 2: 16 Grade 3: 3 Grade 4: 0	
D'Amico et al. 2008 <sup>35</sup>	Anal fibrosis	Grade 1: 1 Grade 2: 0 Grade 3: 0 Grade 4: 0	Grade 1: 1 Grade 2: 0 Grade 3: 0 Grade 4: 0	
D'Amico et al. 2008 <sup>35</sup>	Gynecomastia	Grade 1: 1 Grade 2: 2 Grade 3: 0 Grade 4: 0	Grade 1: 14 Grade 2: 4 Grade 3: 0 Grade 4: 0	
D'Amico et al. 2008 <sup>35</sup>	Liver dysfunction	Grade 1: 0 Grade 2: 0 Grade 3: 1 Grade 4: 1	Grade 1: 0 Grade 2: 0 Grade 3: 0 Grade 4: 0	
Martis et al. 2007 <sup>46</sup>	—	RPP: 100 patients	RRP: 100 patients	p-value
Martis et al. 2007 <sup>46</sup>	Urinary continence at 6 months (number, %)	74 (74)	76 (76)	p=0.85
Martis et al. 2007 <sup>46</sup>	Urinary continence at 24 months (number, %)	96 (96)	95 (95)	p=1
Martis et al. 2007 <sup>46</sup>	Erectile function at 6 months (number, %)	30 (30)	45 (45)	p=0.07
Martis et al. 2007 <sup>46</sup>	Erectile function at 24 months (number, %)	42 (42)	60 (60)	p=0.03

**Abbreviations:** ADT=Androgen-deprivation therapy; BT=brachytherapy; CI=confidence interval; EBRT=external beam radiation therapy; LRP=laparoscopic radical prostatectomy; PIVOT= Prostate Intervention Versus Observation Trial; RARP= robot-assisted radical prostatectomy; RP=radical prostatectomy; RPP=radical perineal prostatectomy; RRP=radical retropubic prostatectomy; SPCG-4=Scandinavian Prostate Cancer Group-4; UTI=urinary tract infection.

**Table F-16. Reported adverse events (nonrandomized comparative studies)**

Study	Adverse Events/Harms Reported	Author Reported Calculations
Mukherjee et al. 2014 <sup>37</sup>	MDS	RP: 6 cases EBRT: 16 cases BT: 9 cases
Spratt et al. 2013 <sup>77</sup>	Acute genitourinary grade 2 toxicities	IMRT BT: 35.8% IMRT: 18.9%
	Acute genitourinary grade 3 toxicities	IMRT BT: 2.3% IMRT: 0.4%
	7-year actuarial genitourinary grade 2 toxicities	IMRT BT: 21.2% IMRT: 19.4%
	7-year actuarial genitourinary grade 3 toxicities	IMRT BT: 1.4% IMRT: 3.1%
	Acute GI grade 2 toxicities	IMRT BT: 3.0% IMRT: 3.8%
	Acute GI grade 3 toxicities	IMRT BT: 0 IMRT: 0
	7-year actuarial grade 2 GI toxicities	IMRT BT: 4.1% IMRT: 4.6%
	7-year actuarial grade 3 GI toxicities	IMRT BT: 1.4% IMRT: 0.4%
	% patients who retained full potency at last followup visit	IMRT BT: 55.0% IMRT: 57.8%
Abern et al. 2012 <sup>90</sup>	Cases of bladder cancer (N=3,077) occurring ≥ 1 year after treatment for prostate cancer and age adjusted IRR (95% CI) vs. RP	RP: 942; reference Any RT: 2135; 1.60 (1.47 to 1.73) RP plus RT: 302; 1.78 (1.54 to 2.04) EBRT: 1296; 1.60 (1.45 to 1.76) BT: 304; 1.38 (1.20 to 1.58) EBRT plus BT: 224; 1.62 (1.39 to 1.88) RT NOS: 9; 1.55 (0.80 to 2.98)
		Multivariate regression adjusting for age, use of radiation, type of radiation, and body mass index, only advanced age was statistically significant for MDS development (HR 1.13; 95% CI 1.06 to 1.19, p<0.001). Radiation exposure did not increase the risk for MDS (HR 1.63; 95% CI 0.59 to 4.53, p=0.35). Risk was slightly increased in the BT patients (p=0.08). In one of several analyses, conducted on the 1996–2011 cohort, body mass index and age were significant but radiation was not. f
		p<0.01
		p=0.03
		p=0.14
		p=0.74
		p=0.58
		NA
		p=0.89
		p=0.36
	Standardized incidence ratios were computed for each treatment modality by comparing incidence rates in each group to male age-specific incidence rates in the SEER 2003-2007 by 5 year age group and race adjusted to the US standard population. Incident rate ratios were then calculated with RP as the reference group. The authors found that patients receiving radiation had a 70% increased risk of subsequent bladder cancer with the greatest risk more than 5 years after treatment (IRR 1.93 for 5 to 10-year followup). After brachytherapy, with or without external beam radiation, the risks were highest, with a 2-fold increase after 10 years of followup (IRR 2.55).	

Study	Adverse Events/Harms Reported	Author Reported Calculations
Mohammed et al. 2012 <sup>80</sup>	Acute dysuria ≥Grade 2	BT: 9% EB-IGRT: 8% EBRT plus HDR: 25%
	Acute frequency ≥Grade 2	BT: 27% EB-IGRT: 39% EBRT plus HDR: 38%
	Acute retention ≥Grade 2	BT: 13% EB-IGRT: 6% EBRT plus HDR: 6%
	Acute Hematuria ≥Grade 2	BT: 0% EB-IGRT: 3% EBRT plus HDR: 0.6%
	Acute Incontinence ≥Grade 2	BT: 2% EB-IGRT: 2% EBRT plus HDR: 1%
	Any acute genitourinary toxicity ≥Grade 2	BT: 35% EB-IGRT: 43% EBRT plus HDR: 50%
Mohammed et al. 2012 <sup>80</sup> (continued)	Late dysuria ≥Grade 2	BT: 4% EB-IGRT: 0.5% EBRT plus HDR: 3%
	Late frequency/urgency ≥Grade 2	BT: 18% EB-IGRT: 14% EBRT plus HDR: 17%
	Late retention Grade 2	BT: 9% EB-IGRT: 3% EBRT plus HDR: 12%
	Late hematuria ≥Grade 2	BT: 5% EB-IGRT: 7% EBRT plus HDR: 4%
	Late Incontinence ≥Grade 2	BT: 2% EB-IGRT: 3% EBRT plus HDR: 5%
	Late urethral stricture	BT: 4% EB-IGRT: 2% EBRT plus HDR: 11%
	Any late genitourinary toxicity ≥Grade 2	BT: 22% EB-IGRT: 21% EBRT plus HDR: 28%
	Acute dysuria ≥Grade 3	BT: 1% EB-IGRT: 0% EBRT plus HDR: 2%

Study	Adverse Events/Harms Reported	Author Reported Calculations	Author Reported Calculations
	Acute frequency ≥Grade 3	BT: 7% EB-IGRT: 3% EBRT plus HDR: 5%	p-value of difference: 0.002
	Acute retention ≥Grade 3	BT: 2% EB-IGRT: 0.6% EBRT plus HDR: 1%	p-value of difference: 0.11
	Acute hematuria ≥Grade 3	BT: 0% EB-IGRT: 0.3% EBRT plus HDR: 0%	p-value of difference: 0.62
Mohammed et al. 2012 <sup>80</sup> (continued)	Acute incontinence ≥Grade 3	BT: 0.3% EB-IGRT: 0.2% EBRT plus HDR: 0%	p-value of difference: 0.62
	Acute any acute genitourinary ≥Grade 3	BT: 8% EB-IGRT: 4% EBRT plus HDR: 7%	p-value of difference: 0.001
	Acute diarrhea ≥Grade 3	BT: 0.3% EB-IGRT: 0.3% EBRT plus HDR: 1%	p-value of difference: 0.07
	Acute tenesmus ≥Grade 3	BT: 0% EB-IGRT: 0% EBRT plus HDR: 0.2%	p-value of difference: 0.18
	Acute bleeding ≥Grade 3	BT: 0% EB-IGRT: 0.2% EBRT plus HDR: 0%	p-value of difference: 0.45
	Any acute GI ≥Grade 3	BT: 0.2% EB-IGRT: 0.5% EBRT plus HDR: 1%	p-value of difference: 0.19
	Any acute genitourinary/GI toxicity ≥Grade 3	BT: 8% EB-IGRT: 4% EBRT plus HDR: 8%	p-value of difference: 0.6
	Late dysuria ≥Grade 3	BT: 0.6% EB-IGRT: 0.2% EBRT plus HDR: 0.5%	p-value of difference: 0.003
	Late frequency/urgency ≥Grade 3	BT: 2% EB-IGRT: 0.5% EBRT plus HDR: 1%	p-value of difference: 0.09
	Late retention ≥Grade 3	BT: 3% EB-IGRT: 1% EBRT plus HDR: 5%	p-value of difference: 0.002
	Late hematuria ≥Grade 3	BT: 2% EB-IGRT: 3% EBRT plus HDR: 1%	p-value of difference: 0.09

Study	Adverse Events/Harms Reported	Author Reported Calculations	
Mohammed et al. 2012 <sup>80</sup> (continued)	Late incontinence ≥Grade 3	BT: 0.3% EB-IGRT: 0.4% EBRT plus HDR: 1%	p-value of difference: 0.13
	Late urethral stricture ≥Grade 3	BT: 3% EB-IGRT: 2% EBRT plus HDR: 10%	p-value of difference: <0.001
	Any late genitourinary ≥Grade 3	BT: 5% EB-IGRT: 4% EBRT plus HDR: 12%	p-value of difference: <0.001
	Late diarrhea ≥Grade 2	BT: 0.6% EB-IGRT: 2% EBRT plus HDR: 2%	p-value of difference: 0.20
	Late rectal bleeding ≥Grade 2	BT: 0.9% EB-IGRT: 16% EBRT plus HDR: 7%	p-value of difference: <0.001
	Late proctitis ≥Grade 2	BT: 0.3% EB-IGRT: 5% EBRT plus HDR: 3%	p-value of difference: <0.001
	Late rectal incontinence ≥Grade 2	BT: 0.3% EB-IGRT: 3% EBRT plus HDR: 0.8%	p-value of difference: 0.005
	Late nausea ≥Grade 2	BT: 0% EB-IGRT: 0% EBRT plus HDR: 0%	p-value of difference: NA
	Any late GI toxicity ≥Grade 2	BT: 2% EB-IGRT: 20% EBRT plus HDR: 9%	p-value of difference: <0.001
	Late diarrhea ≥Grade 3	BT: 0% EB-IGRT: 0% EBRT plus HDR: 0.2%	p-value of difference: 0.24
	Late rectal bleeding ≥Grade 3	BT: 0.3% EB-IGRT: 2% EBRT plus HDR: 0.5%	p-value of difference: 0.02
Mohammed et al. 2012 <sup>80</sup> (continued)	Late proctitis ≥Grade 3	BT: 0% EB-IGRT: 0.5% EBRT plus HDR: 0.4%	p-value of difference: 0.43
	Late rectal incontinence ≥Grade 3	BT: 0% EB-IGRT: 0.4% EBRT plus HDR: 0%	p-value of difference: 0.37
	Late nausea ≥Grade 3	BT: 0% EB-IGRT: 0% EBRT plus HDR: 0%	p-value of difference: NA

Study	Adverse Events/Harms Reported		Author Reported Calculations
	Any late GI toxicity $\geq$ Grade 3	BT: 0.3% EB-IGRT: 2% EBRT plus HDR: 1%	p-value of difference: 0.01
	Multivariate hazard ratio (95% CI) for decreasing PSA	NA	Cox Regression HR 1.0 (0.98–1.01), p=0.43 for any chronic genitourinary toxicity $\geq 2$
	Multivariate hazard ratio (95% CI) for increasing age	NA	Cox Regression HR 1.03 (1.02–1.05), p<0.001 for any chronic genitourinary toxicity $\geq 2$
	Multivariate hazard ratio (95% CI) for EBRT plus HDR vs. EB-IGRT	NA	Cox Regression HR 0.98 (0.52–1.84), p=0.94 for any chronic genitourinary toxicity $\geq 2$
	Multivariate hazard ratio (95% CI) for BT vs. EB-IGRT	NA	Cox Regression HR 1.40 (1.06–1.86), p=0.02 for any chronic genitourinary toxicity $\geq 2$
	Multivariate hazard ratio (95% CI) for increasing % Core	NA	Cox Regression HR 1.00 (0.99–1.01), p=0.94 for any chronic GI toxicity $\geq 2$
	Multivariate hazard ratio (95% CI) for increasing age	NA	Cox Regression HR 1.03 (1.00–1.06), p=0.05 for any chronic GI toxicity $\geq 2$
	Multivariate hazard ratio (95% CI) for ADT	NA	Cox Regression HR 0.765 (0.49–1.21), p=0.25 for any chronic GI toxicity $\geq 2$
	Multivariate hazard ratio (95% CI) for EBRT plus HDR vs. EB-IGRT	NA	Cox Regression HR 0.19 (0.11–0.35), p<0.001 for any chronic GI toxicity $\geq 2$
	Multivariate hazard ratio (95% CI) for BT vs. EB-IGRT	NA	Cox Regression HR 0.16 (0.02–1.20), p=0.08 for any chronic GI toxicity $\geq 2$
Nanda et al. 2012 <sup>83</sup>	Increased all-cause mortality due to HT increasing risk of CAD in patients who already have risk factors for CAD	Low-risk: 596 deaths Intermediate-risk: 642 deaths High-risk: 293 deaths	Neoadjuvant HT use was associated with a significantly increased risk of all-cause mortality in men with low-risk prostate cancer (adjusted HR 1.27, 95% CI 1.07 to 1.51, p<0.01) but not in men with intermediate risk prostate cancer (adjusted HR 1.13, 95% CI 0.96 to 1.35, p=0.15) or high-risk prostate cancer (adjusted HR 0.86, 95% CI 0.66 to 1.13, p0.28) using multivariate regression with propensity score. Among low-risk patients, adjuvant HT was associated with a significantly increased risk of all-cause mortality in with at least one CAD risk factor (adjusted HR 1.36, 95% CI 1.07 to 1.74, p=0.01) but not in patients with no CAD risk factors (adjusted HR 1.19, 95% CI 0.95 to 1.51, p=0.13).
Ploussard et al. 2012 <sup>82</sup>	Clavien 0	LRP: 96.0% RALP: 95.3%	p=0.756
	Clavien 1	LRP: 0.6% RALP: 0.7%	
	Clavien 2	LRP: 3.1% RALP: 3.6%	
	Clavien 3	LRP: 0 RALP: 0	

Study	Adverse Events/Harms Reported	Author Reported Calculations	
	Clavien 4	LRP: 0.2% RALP: 0.2%	
	Clavien 5	LRP: 0 RALP: 0.1%	
	Anastomosis leakage %	LRP: 9.7% RALP: 2.3%	p<0.001
	Anastomosis stenosis %	LRP: 1.7% RALP: 0.7%	p=0.081
	Death (n)	LRP: 0 RALP: 1	NR
	Urinary infection (n)	LRP: 32 RALP: 32	NR
	Fever (n)	LRP: 1 RALP: 8	NR
Ploussard et al. 2012 <sup>62</sup> (continued)	Phlebitis (n)	LRP: 2 RALP: 0	NR
	Pulmonary embolus (n)	LRP: 1 RALP: 2	NR
	Atelectasia (n)	LRP: 1 RALP: 0	NR
	Pneumonia (n)	LRP: 6 RALP: 4	NR
	Ill-being (n)	LRP: 5 RALP: 3	NR
	Angor (n)	LRP: 1 RALP: 1	NR
	Threat syndrome(n)	LRP: 3 RALP: 1	NR
	Myocardial infarction (n)	LRP: 2 RALP: 3	NR
	Renal insufficiency (n)	LRP: 2 RALP: 3	NR
	Retinal detachment (n)	LRP: 1 RALP: 0	NR
	Overall % surgical complications(n)	LRP: 4.1% RALP: 5.9%	NR
	Hemorrhage (n)	LRP: 6 RALP: 4	NR
	Rectal injury (n)	LRP: 11 RALP: 3	NR
	Epigastric injury (n)	LRP: 4 RALP: 3	NR



Study	Adverse Events/Harms Reported	Author Reported Calculations
	Wound complications (n)	—
	Hematoma (n)	LRP: 9 RALP: 14
	Abscess (n)	LRP: 3 RALP: 9
Ploussard et al. 2012 <sup>62</sup> (continued)	Retzius collection (n)	LRP: 20 RALP: 23
	Lymphorrhoea (n)	LRP: 1 RALP: 2
	Lymphocele (n)	LRP: 5 RALP: 9
	Hematuria (n)	LRP: 13 RALP: 19
	Ileus (n)	LRP: 2 RALP: 4
	Neurapraxia (n)	LRP: 1 RALP: 1
	Bowel injury (n)	LRP: 0 RALP: 1
	Overall %	LRP: 6.8% RALP: 10.5%
Sheets et al. 2012 <sup>58</sup>	Gastrointestinal procedures including colonoscopy	<p>IMRT: 6,438 patients 3D-CRT: 6,478 patients IMRT: 684 (for the propensity score matched comparison to proton radiation) Proton radiation: 684 patients</p> <p>Adjusted for baseline- and clinical- characteristics. Outcomes are per 100 person-years and are presented as rate ratio (95% CI) for IMRT vs. 3D-CRT: IMRT total events 3,011, rate 17.0 3D-CRT total events 2,989, rate 16.6 Rate ratio: 1.02 (0.97–1.07). Propensity score matched rates adjusted for baseline- and clinical- characteristics. Outcomes are per 100 person-years and are presented as rate ratio (95% CI) for IMRT vs. proton: IMRT total events 302, rate 17.7 Proton total events 347, rate 21.4 Rate ratio: 0.82 (0.70–0.97).</p>

Study	Adverse Events/Harms Reported		Author Reported Calculations
Sheets et al. 2012 <sup>58</sup> (continued)	Gastrointestinal diagnoses	IMRT: 6,438 patients 3D-CRT: 6,478 patients IMRT: 684 (for the propensity score matched comparison to proton therapy) Proton therapy: 684 patients	Adjusted for baseline- and clinical- characteristics. Outcomes are per 100 person-years and are presented as rate ratio (95% CI) for IMRT vs. 3D-CRT: IMRT total events 2,594, rate 13.4 3D-CRT total events 2,828, rate 14.7 Rate ratio: 0.91 (0.86–0.96). Propensity score matched rates adjusted for baseline- and clinical- characteristics. Outcomes are per 100 person-years and are presented as rate ratio (95% CI) for IMRT vs. proton therapy: IMRT total events 235, rate 12.2 Proton total events 301, rate 17.8 Rate ratio: 0.66 (0.55–0.79).
	Urinary nonincontinence procedures	IMRT: 6,438 patients 3D-CRT: 6,478 patients IMRT: 684 (for the propensity score matched comparison to Proton radiation) Proton therapy: 684 patients	Adjusted for baseline- and clinical- characteristics. Outcomes are per 100 person-years and are presented as rate ratio (95% CI) for IMRT vs. CRT: IMRT total events 483, rate 1.9 3D-CRT total events 493, rate 1.9 Rate ratio: 0.99 (0.87 to 1.12). Propensity score matched rates adjusted for baseline- and clinical- characteristics. Outcomes are per 100 person-years and are presented as rate ratio (95% CI) for IMRT vs. Proton therapy: IMRT total events 44, rate 1.8 Proton total events 42, rate 1.6 Rate ratio: 1.06 (0.69 to 1.63).
Sheets et al. 2012 <sup>58</sup> (continued)	Urinary nonincontinence diagnoses	IMRT: 6,438 patients 3D-CRT: 6,478 patients IMRT: 684 (for the propensity score matched comparison to Proton radiation) Proton therapy: 684 patients	Adjusted for baseline- and clinical- characteristics. Outcomes are per 100 person-years and are presented as rate ratio (95% CI) for IMRT vs. 3D-CRT: IMRT total events 1,869, rate 8.8 3D-CRT total events 1,941, rate 8.8 Rate ratio: 0.99 (0.93 to 1.06). Propensity score matched rates adjusted for baseline- and clinical- characteristics. Outcomes are per 100 person-years and are presented as rate ratio (95% CI) for IMRT vs. Proton therapy: IMRT total events 161, rate 7.5 Proton total events 144, rate 6.3 Rate ratio: 1.25 (0.99 to 1.58).

Study	Adverse Events/Harms Reported		Author Reported Calculations
	Urinary incontinence procedures	IMRT: 6,438 patients 3D-CRT: 6,478 patients IMRT: 684 (for the propensity score matched comparison to Proton therapy) Proton therapy: 684 patients	Adjusted for baseline- and clinical- characteristics. Outcomes are per 100 person-years and are presented as rate ratio (95% CI) for IMRT vs. 3D-CRT: IMRT total events 1,888, rate 8.9 3D-CRT total events 1,867, rate 8.5 Rate ratio: 1.05 (0.98 to 1.12). Propensity score matched rates adjusted for baseline- and clinical- characteristics. Outcomes are per 100 person-years and are presented as rate ratio (95% CI) for IMRT vs. Proton therapy IMRT total events 161, rate 7.6 Proton total events 173, rate 7.8 Rate ratio: 0.97 (0.77 to 1.20).
Sheets et al. 2012 <sup>58</sup> (continued)	Erectile dysfunction procedures	IMRT: 6,438 patients 3D-CRT: 6,478 patients IMRT: 684 (for the propensity score matched comparison to Proton therapy) Proton therapy: 684 patients	Adjusted for baseline- and clinical- characteristics. Outcomes are per 100 person-years and are presented as rate ratio (95% CI) for IMRT vs. 3D-CRT: IMRT total events 200, rate 0.8 3D-CRT total events 224, rate 0.8 Rate ratio: 0.90 (0.75–1.09) Propensity score matched rates adjusted for baseline- and clinical- characteristics. Outcomes are per 100 person-years and are presented as rate ratio (95% CI) for IMRT vs. Proton therapy: IMRT total events 21, rate 0.8 Proton total events 36, rate 1.4 Rate ratio: 0.61 (0.35 to 1.06)
	Hip fracture	IMRT: 6,438 patients 3D-CRT: 6,478 patients IMRT: 684 (for the propensity score matched comparison to proton therapy) Proton therapy: 684 patients	Adjusted for baseline- and clinical- characteristics. Outcomes are per 100 person-years and are presented as rate ratio (95% CI) for IMRT vs. 3D-CRT: IMRT total events 209, rate 0.8 3D-CRT total events 272, rate 1.0 Rate ratio: 0.78 (0.65 to 0.93) Propensity score matched rates adjusted for baseline- and clinical- characteristics. Outcomes are per 100 person-years and are presented as rate ratio (95% CI) for IMRT vs. Proton therapy: IMRT total events 21, rate 0.8 Proton total events 18, rate 0.7 Rate ratio: Could not be calculated due to small number of events and zero cell counts in some of the covariates.

Study	Adverse Events/Harms Reported		Author Reported Calculations
Bekelman et al. 2011 <sup>91</sup> bowel complications	IMRT: 3,727 patients at risk 24 month cumulative incidence of complication requiring an invasive procedure 18.8% (95% CI, 17.8–19.9)	3D-CRT: 4,614 patients at risk 24 month cumulative incidence of complication requiring an invasive procedure 22.5% (21.5–23.5)	Multivariate HR (95% CI) adjusted for propensity score, year of diagnosis, and area population. HR 0.86 (0.79–0.93)
urinary complications	IMRT: 3,997 patients at risk 24 month cumulative incidence of complication requiring an invasive procedure 10.4% (95% CI, 9.6–11.1)	3D-CRT: 5,145 patients at risk 24 month cumulative incidence of complication requiring an invasive procedure 11.2% (10.4–12.0)	Multivariate HR (95% CI) adjusted for propensity score, year of diagnosis, and area population. HR 0.93 (0.83–1.04)
erectile complications	IMRT: 4,586 patients at risk 24 month cumulative incidence of complication requiring an invasive procedure 1.0% (95% CI, 0.8–1.3)	3D-CRT: 5,946 patients at risk 24 month cumulative incidence of complication requiring an invasive procedure 0.7% (0.5–0.9)	Multivariate HR (95% CI) adjusted for propensity score, year of diagnosis, and area population. HR 1.50 (1.00–2.24)
proctitis, hemorrhage complications	IMRT: 4,472 patients at risk 24 month cumulative incidence of complication requiring an invasive procedure 3.5% (95% CI, 3.0–4.0)	3D-CRT: 5,723 patients at risk 24 month cumulative incidence of complication requiring an invasive procedure 4.5% (4.0–5.0)	Multivariate HR (95% CI) adjusted for propensity score, year of diagnosis, and area population. HR 0.78 (0.64–0.95)
cystitis, hematuria complications	IMRT: 4,226 patients at risk 24 month cumulative incidence of complication requiring an invasive procedure 7.7% (95% CI, 7.0–8.4)	CRT: 5,433 patients at risk 24 month cumulative incidence of complication requiring an invasive procedure 8.3% (7.6–9.0)	Multivariate HR (95% CI) adjusted for propensity score, year of diagnosis, and area population. HR 0.94 (0.83–1.07)

Study	Adverse Events/Harms Reported		Author Reported Calculations
Kim et al. 2011 <sup>60</sup> Any GI toxicity	Events/person-year (rate/ 1000) All EBRT: 936/106,658 (8.8) 3D CRT: 720/77,659 (9.3) IMRT: 134/15,003 (8.9) Proton beam: 28/1390 (20.1) BT only: 137/25,672 (5.3) BT plus EBRT: 148/19,654 (7.5)	Events/person-year (rate/ 1000) Conservative management: 145/70,564 (2.1)	Multivariate HR (95% CI) adjusted for year of cancer diagnosis, comorbidity, age group, clinical stage at diagnosis, SEER regions, race, marital status, poverty, and cancer grade). 3D CRT vs. conservative: 5.44 (4.52-6.54) IMRT vs conservative: 4.33 (3.32-5.63) Proton beam vs conservative: 13.7 (9.09-20.8) BT alone vs. conservative: 3.62 (2.85-4.61) IMRT vs. 3D CRT: 0.67 (0.55-0.82) Proton beam vs. 3D CRT: 2.13 (1.45-3.13) IMRT vs. proton beam: 0.30 (0.19-0.47) IMRT vs. BT alone: 1.14 (0.89-1.48) BT alone vs. 3D CRT: 0.62 (0.51-0.75) Proton beam vs. IMRT: 3.32 (2.13-5.20)
GI bleeding	Events/person-year (rate/ 1000) All EBRT: 801/107,163 (7.5) 3D CRT: 610/78,101 (7.8) IMRT: 124/15,018 (8.3) Proton beam: 28/1390 (20.1) BT only: 114/25,744 (4.4) BT plus EBRT: 125/19,707 (6.3)	Events/person-year (rate/ 1,000) Conservative management: 62/70,779 (0.9)	Chi-square test used to assess association between GI bleeding and any radiation therapy: p <0.001  Chi-square test used to assess the association of GI bleeding across different radiation modality groups (EBRT, BT only, BT plus EBRT): p <0.001
Williams et al. 2011 <sup>57</sup>	BT: 9,985 patients	Cryotherapy: 943 patients	Propensity-weighted incidence of complications expressed as percentages.
Overall complications	63.6%	48.8%	p<0.001
Urinary cystitis	0.5%	2.4%	p<0.001
Urinary retention	24.5%	8.4%	p<0.001
Urethral stricture	5.4%	3.7%	p=0.190
Urethral fistula	0.9%	0.3%	p=0.1445
Proctitis/hemorrhage	11.7%	18.6%	p<0.001
Rectal injury/ulcer	0.8%	2.0%	p<0.001
Sumitomo et al. 2008 <sup>63</sup>	HIFU: 260 patients	HIFU plus ADT: 270 patients	—
Grade 3 or 4 bladder neck/urethra stricture	39 patients (15.0%)	38 patients (14.1%)	p=0.7
Rectourethral fistula	4 patients (1.5%)	3 patients (1.1%)	p=0.28
Krambeck et al. 2008 <sup>65</sup>	RRP: 564 patients	RALRP: 286 patients	N (%) with early (1 month) and late (>1 month) post-surgical complications based on patients treated in the matched comparison study.
Any early complication	27 (4.8%)	23 (8.0%)	p=0.064
Bladder neck contracture	1 (0.2%)	0 (0%)	p=0.476
Hemorrhage/hematoma	10 (1.8%)	10 (3.5%)	p=0.150
Hernia	0 (0%)	3 (1%)	p=0.038

Study	Adverse Events/Harms Reported		Author Reported Calculations		
Renal failure	1 (0.2%)	0 (0%)	p=0.476		
Sepsis	1 (0.2%)	0 (0%)	p=0.476		
Stricture	3 (0.5%)	2 (0.7%)	p=0.763		
Ureteric obstruction	1 (0.2%)	0 (0%)	p=0.476		
Urinary retention	7 (1.2%)	8 (2.8%)	p=0.104		
UTI	6 (1.1%)	3 (1%)	p=0.984		
Deep vein thrombosis	7 (1.2%)	1 (0.3%)	p=0.203		
Drug reaction	7 (1.2%)	2 (0.7%)	p=0.466		
Ileus	10 (1.8%)	5 (1.7%)	p=0.982		
Lymphocele	4 (0.7%)	2 (0.7%)	p=0.987		
Lymphedema	1 (0.2%)	0 (0%)	p=0.476		
Myocardial infarction	0 (0%)	0 (0%)	NA		
Pulmonary embolism	4 (0.7%)	1 (0.3%)	p=0.517		
Respiratory failure	3 (0.5%)	2 (0.7%)	p=0.763		
Requiring transfusion	77 (13.1%)	15 (5.1%)	p<0.001		
Stroke	3 (0.5%)	3 (1%)	p=0.395		
—	RRP: 492 patients with one year followup	RALRP: 248 patients with 1-year followup	—		
Abdominal abscess	2 (0.4%)	0 (0%)	p=0.554		
Bladder neck contracture	23 (4.6%)	3 (1.2%)	p=0.018		
Deep vein thrombosis	6 (1.2%)	1 (0.4%)	p=0.434		
Hernia	14 (2.8%)	10 (4.0%)	p=0.387		
Lymphocele	5 (1.0%)	1 (0.4%)	p=0.670		
Lymphedema	0 (0%)	0 (0%)	NA		
Pulmonary embolism	5 (1.0%)	0 (0%)	p=0.175		
Urethral stricture	6 (1.2%)	8 (3.2%)	p=0.083		
Wong et al. 2007 <sup>88</sup>	3D-CRT: 270 patients	IMRT: 314 patients	BT: 225 patients	EBRT plus BT: 44 patients	—
GI toxicity	—		<p>There was no increase in acute GI toxicity from IMRT compared with 3D-CRT. There were more grade 2 acute toxicity (49% vs. 39%) and late (27% vs. 16%) GU toxicities, but no increase in grade 3 toxicity, from high-dose IMRT compared with conventional dose 3D-CRT. BT alone caused a much lower incidence of acute or late GI toxicity than EBRT. Late grade 3 GI toxicity occurred in 2% of patients treated with 3D-CRT. Of the group of patients treated with EBRT plus BT, 2 patients (5%) had grade 3 late GI toxicities.</p>		
Proctitis	—		<p>For group of patients treated with BT alone, 2 patients developed grade 3 proctitis (1%).</p>		

Study	Adverse Events/Harms Reported	Author Reported Calculations
GU toxicity	—	Both BT alone and EBRT plus BT caused significantly more grade 2 and 3 acute and late GU toxicity compared with 3D-CRT or IMRT alone.

**Abbreviations:** 3D-CRT=Three-dimensional conformal radiotherapy; ADT=androgen-deprivation therapy; BT=brachytherapy; CAD=coronary artery disease; CI=confidence interval; EB-IGRT=external beam image-guided radiation therapy; EBRT=external beam radiation therapy; GI=gastrointestinal; GU=genitourinary; HDR=high dose rate; HIFU=high-intensity focused ultrasound; HR=hazard ratio; HT=hormone therapy; IMRT=intensity-modulated radiation therapy; IRR=incidence rate ratio; LRP=laparoscopic radical prostatectomy; MDS=myelodysplastic syndrome; NA=not available; NOS=not otherwise specified; NR=not reported OR=odds ratio; RALP=robotic-assisted laparoscopic prostatectomy; RALRP=robotic-assisted laparoscopic radical prostatectomy; RP=radical prostatectomy; RRP=radical retropubic prostatectomy; RT=radiation therapy; SEER=Surveillance, Epidemiology, and End Results program (National Cancer Institute); UTI=urinary tract infection.

## Appendix G. Ongoing Clinical Trials

**Table G-1. Ongoing clinical trials retrieved from <http://clinicaltrials.gov/ct2/home>**

Identifier	Sponsor	Design	Purpose	Start Date and Expected Completion Date
NCT00430183	Cancer and Leukemia Group B, USA	RCT	This randomized phase III trial is studying docetaxel and leuprolide or goserelin to see how well they work when given before surgery compared with surgery alone in treating patients with high-risk localized prostate cancer	Start Date: December 2006 Estimated Completion Date: June 2018 Estimated Enrollment: 750
NCT01617161	Massachusetts General Hospital, University of Pennsylvania, National Cancer Institute	RCT	This randomized phase III trial is studying whether men being treated for prostate cancer have the same amount of side effects from either 1 of 2 different external radiation treatments: intensity-modulated radiation therapy or proton beam therapy	Start Date: July, 2012 Estimated Completion Date: June 2016 Estimated Enrollment: 750
NCT01365143	Mayo Clinic, USA	RCT	This study will prospectively randomize patients with localized prostate cancer who are candidates for surgical management to open vs. robotic radical prostatectomy.	Start Date: May 2011 Estimated Completion Date: May 2016 Estimated Enrollment: 454
NCT01492972	Proton Collaborative Group, USA	RCT	This study will compare the use of hypofraction proton therapy (28 treatments) alone to proton therapy with androgen suppression therapy	Start Date: January 2012 Estimated Completion Date: December 2021 Estimated Enrollment: 192
NCT00116220	Dana-Farber Cancer Institute, USA	RCT	To determine if the use of 6 months of total androgen suppression (hormonal therapy) when added to radiation therapy for localized-high risk prostate cancer would improve overall survival.	Start Date: September 1995 Estimated Completion Date: April 2014 Estimated Enrollment: 270
NCT00175383	University of British Columbia, Canada	RCT	This study will compare short vs. long-acting luteinizing hormone–releasing hormone agonist preparation prior to transperineal implantation of the prostate.	Start Date: December 2004 Estimated Completion Date: June 2013 Estimated Enrollment: 100



Identifier	Sponsor	Design	Purpose	Start Date and Expected Completion Date
NCT01584258 Prostate Advances in Comparative Evidence (PACE)	Accuray Inc., Switzerland Study is being conducted in France, Germany, the Netherlands and the United Kingdom	RCT	This study is an international multicenter randomized study of organ confined low and intermediate risk prostate cancer and is composed of 2 parallel randomization schemes based on applicability of surgery as a treatment for the patient. Patients for whom surgery is a consideration are randomized to either laparoscopic or da Vinci prostatectomy or CyberKnife prostate SBRT (also known as CyberKnife radiosurgery). Patients for whom surgery is not a consideration are randomized to either conventionally fractionated radiation therapy or CyberKnife prostate SBRT. Efficacy, toxicity and quality of life outcomes will be compared across the pairs in each randomization.	Start Date: April 2012 Estimated Completion Date: April 2025 Estimated Enrollment: 1,036
NCT01717677 Evaluation of Four Treatment Modalities in Prostate Cancer With Low or "Early Intermediate" Risk (PREFERE)	Association of Urogenital Oncology (AUO), Germany	RCT	4 arms preference based study to compare four therapy options (radical prostatectomy, percutaneous radiation therapy, permanent seed brachytherapy, and active surveillance) in prostate cancer with low or early intermediate risk.	Start Date: October 2012 Estimated Completion Date: December 2030 Estimated Enrollment: 7,600

**Abbreviations:** RCT=Randomized controlled trial; SBRT=stereotactic body radiotherapy.

**Table G-2. Ongoing clinical trial retrieved from [www.epi.bris.ac.uk/protect/](http://www.epi.bris.ac.uk/protect/)**

Identifier	Sponsor	Design	Purpose	Start Date and Expected Completion Date
ProtecT (Prostate testing for cancer and Treatment) Study	Department of Health, United Kingdom	Randomized Controlled Trial	The study aims to evaluate treatments for localized prostate cancer. It is comparing surgery (radical prostatectomy), radiotherapy (radical conformal) and active monitoring (monitoring with regular check-ups).	Start date: June 1999 Estimated Completion Date: June 2013 Between June 2001 and October 2008, approximately 109,750 men have taken part in the ProtecT study.