Comparative Effectiveness Review
Number 230

Therapies for Clinically Localized Prostate Cancer

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This report is based on research conducted by the Minnesota Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 290-2015-0000-81). The findings and conclusions in this document are those of the authors, who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

The information in this report is intended to help healthcare decision makers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of healthcare services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

This report may periodically be assessed for the currency of conclusions. If an assessment is done, the resulting surveillance report describing the methodology and findings will be found on the Effective Health Care Program Web site at www.effectivehealthcare.ahrq.gov. Search on the title of the report.

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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 healthcare in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new healthcare 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

AHRQ expects that these systematic reviews will be helpful to health plans, providers, purchasers, government programs, and the healthcare system as a whole. Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the website (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input.

If you have 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, 5600 Fishers Lane, Rockville, MD 20857, or by email to epc@ahrq.hhs.gov.

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Therapies for Clinically Localized Prostate Cancer

Structured Abstract

Objective. To update findings from previous Agency for Healthcare Research and Quality (AHRQ)- and American Urological Association (AUA)-funded reviews evaluating therapies for clinically localized prostate cancer (CLPC).

Sources. Bibliographic databases (2013–January 2020); ClinicalTrials.gov; systematic reviews

Methods. Controlled studies of CLPC treatments with duration ≥5 years for mortality and metastases and ≥1 year for quality of life and harms. One investigator rated risk of bias (RoB), extracted data, and assessed certainty of evidence; a second checked accuracy. We analyzed English-language studies with low or medium RoB. We incorporated findings from randomized controlled trials (RCTs) identified in the prior reviews if new RCTs provided information on the same intervention comparison.

Results. We identified 67 eligible references; 17 were unique RCTs. Among clinically rather than prostate-specific antigen (PSA) detected CLPC, Watchful Waiting (WW) may increase mortality and metastases versus Radical Prostatectomy (RP) at 20+ years. Urinary and erectile dysfunction were lower with WW versus RP. WW's effect on mortality may vary by tumor risk and age but not by race, health status, comorbidities, or PSA. Active Monitoring (AM) probably results in little to no difference in mortality in PSA-detected CLPC versus RP or external beam radiation (EBR) plus Androgen Deprivation (AD) regardless of tumor risk. Metastases were slightly higher with AM. Harms were greater with RP than AM and mixed between EBR plus AD versus AM. 3D-conformal EBR and AD plus low-dose-rate brachytherapy (BT) provided a small reduction in all-cause mortality versus three-dimensional conformal EBR and AD but little to no difference on metastases. EBR plus AD versus EBR alone may result in a small reduction in mortality and metastases in higher risk disease but may increase sexual harms. EBR plus neoadjuvant AD versus EBR plus concurrent AD may result in little to no difference in mortality and genitourinary toxicity. Conventionally fractionated EBR versus ultrahypofractionated EBR may result in little to no difference in mortality and metastases and urinary and bowel toxicity. Active Surveillance may result in fewer harms than photodynamic therapy and laparoscopic RP may result in more harms than robotic-assisted RP. Little information exists on other treatments. No studies assessed provider or hospital factors of RP comparative effectiveness.

Conclusions. RP reduces mortality versus WW in clinically detected CLPC but causes more harms. Effectiveness may be limited to younger men or to those with intermediate-risk disease and requires many years to occur. AM results in little to no mortality difference versus RP or EBR plus AD. EBR plus AD reduces mortality versus EBR alone in higher risk CLPC but may worsen sexual function. Adding low-dose-rate BT to 3D-conformal EBR and AD may reduce mortality in higher risk CLPC. RCTs in PSA-detected and MRI staged CLPC are needed.

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Evidence Summary

Main Points

- In men with clinically localized prostate cancer (CLPC) detected clinically rather than by prostate-specific antigen (PSA) screening, radical prostatectomy (RP) may reduce mortality and metastases more than watchful waiting (WW) but causes more harms. Mortality reductions may be limited to men age 65 and older and those with intermediate-risk disease.

- Active monitoring (AM) probably results in little to no mortality difference versus RP or external beam radiation (EBR)+androgen deprivation (AD) in PSA-detected CLPC and may result in fewer harms. Effects may not vary by patient or tumor factors.

- 3D Conformal EBR (3D-CRT)+low-dose brachytherapy+AD may slightly reduce all-cause mortality but not metastases more than 3D-CRT+AD in higher risk CLPC.

- EBR plus AD may slightly reduce mortality and metastases versus EBR alone in men with intermediate- and high-risk disease but may worsen sexual function.

- Little long-term information exists on other treatments or the effects of patient, tumor, and provider factors especially in PSA-detected and magnetic resonance imaging (MRI)-staged CLPC. We found no evidence on how biomarkers may modify treatment effects.

Background and Purpose

The American Cancer Society estimates that, in 2020, prostate cancer will be one of the most frequently diagnosed cancers among U.S. men (191,930 new cases) and the second leading cause of cancer death (33,330).[1] In 90 percent of newly diagnosed cancers, the disease is confined to the prostate gland (known as "clinically localized prostate cancer" [CLPC]).[2] Most cases of CLPC grow slowly without symptoms, even if untreated. CLPC treatments thus aim to balance treatment benefits with complications, burden, and costs.

The purpose of this systematic review was to evaluate CLPC treatments by updating prior AHRQ and American Urological Association (AUA) reviews.[3-5] We included controlled studies of CLPC (stages T1–T3a) treatments ≥5 years duration for mortality and metastases, and ≥1 year for quality of life and harms for the following interventions: WW, active surveillance (AS), AM, AD, and focal and whole gland therapies or their combinations. We also evaluated how patient and tumor characteristics, including risk indices and biomarkers, modify treatment effects, and how provider/hospital characteristics modify effects of RP compared with other therapies.

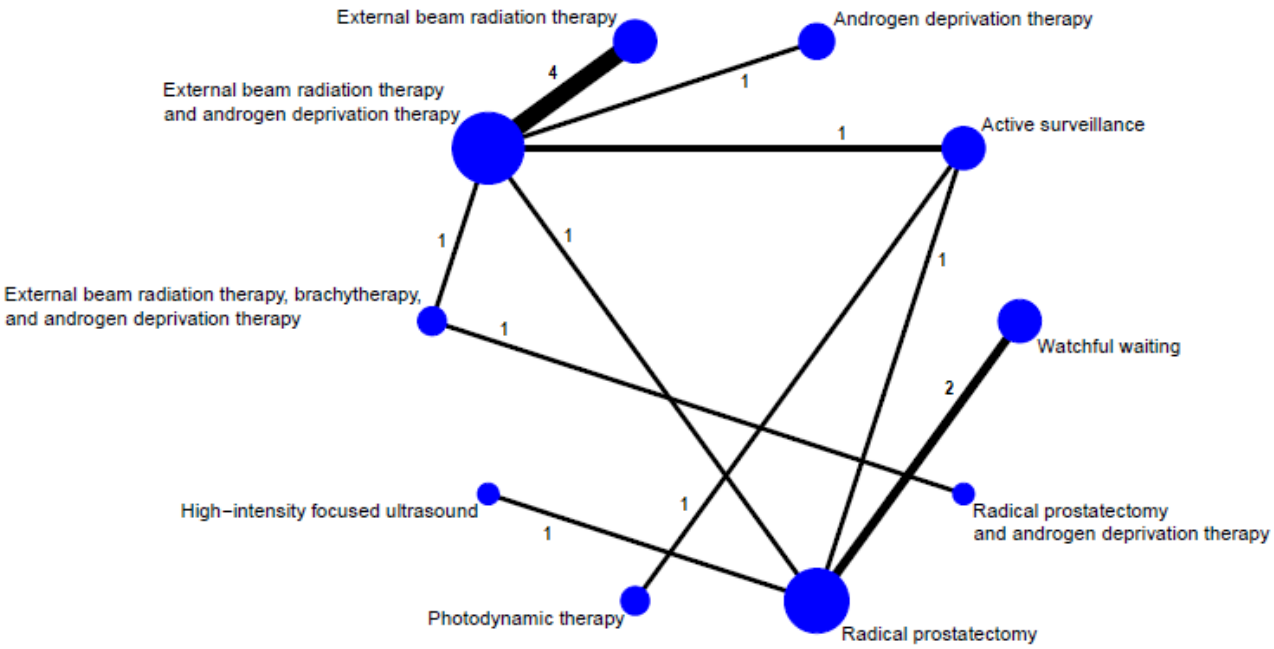
Methods

We employed methods consistent with the AHRQ EPC Program Methods Guidance (https://effectivehealthcare.ahrq.gov/topics/cer-methods-guide/overview). We describe these in the full report. We referenced findings from the 2014 AHRQ- and 2016 AUA-funded reviews and included them in updated analyses if randomized controlled trials (RCTs) provided additional data on similar populations, interventions, comparators, and outcomes. We summarize and compare major findings from our review with those of the prior reports. We derived *a priori* thresholds defining "small," "moderate," and "large" effect sizes for benefits and harms. Our searches covered publication dates from January 2013 to January 2020. We modified AHRQ methods for this review by using GRADE and EPC tools for risk of bias and certainty of evidence assessments.[6-8]

Results

We identified 67 eligible references (citations can be found in the full report), of which 26 were publications from 17 unique RCTs and 41 were publications from 34 unique non-RCTs. The treatment comparisons evaluated in RCTs are illustrated in Figure A.

Figure A. Plot of comparisons addressed in RCTs identified in updated literature search *†‡



*Within-category comparisons are not shown in figure. These include RARP vs. LRP (k=1, n=120), 3D-CRT vs. IMRT (k=1, n=215), ultrahypofractionated EBRT vs. standard EBRT (k=2, n=1,275), and EBRT plus neoadjuvant and concurrent ADT vs. EBRT plus concurrent and adjuvant ADT (k=1, n=432).

†One RCT (ProtecT) was a three-arm trial. ProtecT PSA-based active monitoring group is labeled active surveillance in figure.

‡The node size reflects the sample size. The width of lines reflects the number of RCTs that evaluated that comparison.

Watchful waiting may result in moderate to large increases in overall mortality and small to large increases in prostate cancer mortality compared with RP through 20 years among clinically, rather than PSA screen, detected CLPC. Absolute effects vary by study. WW probably results in small to large increases in metastases through 15–20 years. Effects depend on study population. WW probably results in moderately reduced urinary and erectile dysfunction. Mortality differences may be limited to men age 65 and older or those with intermediate-risk disease.

Active monitoring using PSA-based monitoring probably results in little to no difference in all-cause or prostate cancer mortality compared with RP or EBR plus AD over 10 years. Metastases were infrequent, but AM probably results in a small increase compared with RP and EBR+AD. Effects may not vary by patient or tumor risk factors. Harms were lowest with AM compared with RP or EBR plus AD or AS versus photodynamic therapy.

Radical prostatectomy probably results in little to no difference over 10 years in all-cause or prostate cancer mortality, or metastases compared with EBR plus AD. Results may not vary by patient or tumor risk characteristics. RP probably results in a large increase in urinary incontinence and a moderate increase in erectile dysfunction; fecal incontinence may be slightly decreased compared with EBR plus AD**.**

External beam radiation using a combination of 3D-conformal radiation and AD with low-dose-rate prostate brachytherapy may slightly reduce all-cause mortality compared with 3D-conformal radiation and AD over 5 years but may make little to no difference on metastatic disease. Associated harms were unclear. EBR plus AD probably results in a small reduction in overall mortality and may result in a small reduction in prostate cancer mortality and metastases versus EBR alone over 7 years in men with intermediate- or high-risk disease. However, it may result in a moderate increase in sexual dysfunction. When comparing the sequence of add-on androgen deprivation therapy (ADT), EBR plus neoadjuvant initiation of AD compared with EBR plus concurrent initiation of AD may result in little to no difference in overall mortality and prostate cancer mortality over 12 years and late genitourinary toxicity over 3 years.

Other therapies/comparisons had too little and/or conflicting evidence to draw conclusions.

Limitations

Our review findings have several limitations including—

- Many randomized trials were too short to assess overall or prostate cancer mortality.
- We found few well-designed prospective cohort studies. Retrospective observational studies often had a high risk of bias.
- Varying thresholds to define effect size estimates may alter certainty of evidence and clinical/policy decisions.
- We found few studies of high-intensity focused ultrasound, laser ablation, or photodynamic therapy, and no eligible studies of other focal therapies.
- Few studies reported on how patient, tumor characteristics, or biomarkers modify treatment effect. No studies assessed surgeon or hospital volume treatment effects.

- Metastases were often reported based on radiographic and PSA results in asymptomatic patients rather than as patient-reported outcomes (e.g., bone pain or ureteral obstruction) and should not be interpreted as symptomatic metastases.

- While clinical and policy decision making often incorporate patient and tumor characteristics, evidence certainty to guide decisions based on these characteristics is limited and unlikely to be greater than findings from intervention effects overall.

Implications and Conclusions

An important report contribution lies in its appraisal of longer-term data from two RCTs comparing RP with WW in clinically, rather than PSA, detected CLPC. Extended followup suggests that RP may reduce mortality and probably reduces metastases over a very extended timeframe. Age and tumor risk category may be important effect modifiers. Prostate cancer mortality is infrequent in low-risk disease, and all-cause or prostate cancer mortality reduction due to RP may be limited to intermediate-risk disease or age <65 years. Absolute effects are likely smaller among PSA-detected CLPC due to its more indolent course. Harms are greater with RP.

AM was compared with RP or EBR plus AD in PSA screen–detected CLPC. Prostate cancer mortality and metastases were rare in all three groups. After 10 years, overall and prostate-cancer mortality were similar across all three treatments though EBR and RP resulted in small absolute reductions in metastases. Surgery may have caused worse urinary and sexual function compared with AM, while EBR may have caused worse sexual and bowel function. No RCTs evaluated WW or AS using scheduled prostate biopsies or MRI in CLPC detected by PSA screening alone.

We found additional evidence supporting that EBR plus ADT may reduce mortality and metastases versus EBR alone in men with intermediate- and high-risk disease. However, it may also result in an increase in harms. Additionally, one newly identified RCT showed little difference between conventionally fractionated EBR versus ultra-hypofractionated EBR. Furthermore, combination 3D conformal EBR with low-dose brachytherapy plus neoadjuvant ADT may reduce mortality more than EBR plus neoadjuvant ADT in men with intermediate- to high-risk disease, but harms were unclear.

This report update was motivated, in part, by an increasing interest in focal therapies or whole prostate gland therapy that is suggested to have fewer or less serious harms than RP or EBR. For these modalities, often targeted to lower risk focal CLPC, including cryotherapy, laser ablation, and high-intensity focused ultrasound, evidence was insufficient. We found no evidence for effects of photodynamic therapy on mortality or metastases. We found little additional evidence for within-treatment comparisons between other surgical or EBR approaches.

Our findings have clinical, policy, and research implications. Our results highlight the importance of balancing treatment benefits with harms and the inclusion of patient and tumor characteristics as well as patient preferences into treatment decisions. They reinforce the need for long-term comparative effectiveness RCTs and well-designed prospective cohort studies. They highlight that the more indolent natural history of PSA-detected compared with clinically detected CLPC has important implications on net benefit of treatment options. For most men with CLPC including those with life expectancies of 15–20 years, evidence indicates that WW and AM result in little to no difference in mortality and metastases and fewer harms compared with early intent-to-cure treatments. The absolute benefit of early intervention in PSA-detected

CLPC is likely considerably less and overtreatment greater than studies of WW and AM suggest. For men with PSA-detected CLPC who choose early treatment, RP provides similar effects through 10 years compared with EBR+AD. For men with higher risk disease who select EBR, the addition of AD reduces mortality but may increase harms compared with EBR alone. Our findings provide a cautionary note before incorporating newer treatment modalities (including refinements of RP or EBR) into clinical care as evidence on their effectiveness and harms is very limited. While AS and newer modalities hold promise, we need high-quality studies including assessment of provider, patient, and tumor characteristics on patient important outcomes.

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Chapter 1. Introduction

The American Cancer Society estimates that in 2020 prostate cancer was the most frequently diagnosed non-dermatologic malignancy (191,930 new cases) and the second leading cause of cancer death (33,330 deaths) among men in the U.S.[1] Treatment-related medical costs are projected to rise to $16 billion per year by 2020.[1] In about 90 percent of men diagnosed with prostate cancer, the disease is confined to the prostate gland (referred to as clinically localized prostate cancer [CLPC]).[2] Although disease progression sometimes results in morbidity and mortality, most cases of CLPC grow slowly and remain asymptomatic, even if untreated. Therefore, the potential for over-diagnosis and over-treatment is great, especially when the disease is identified through prostate specific antigen (PSA) screening.

CLPC treatments aim to balance potential benefits with complications, burden and costs. Watchful waiting (WW) monitors patients for signs or symptoms of progression and focuses on avoiding unnecessary or ineffective early interventions, while reserving treatment mainly for palliative purposes. WW is most commonly utilized in men with low-risk CLPC, or with limited life expectancy. Active surveillance and Active monitoring (AS/AM) are other options whereby tumors are not immediately removed, irradiated, or ablated,[9, 10] but instead monitored with delayed active treatment initiated based on varying surveillance and monitoring protocols. Although AS/AM definitions, protocols and intervention recommendations vary, further treatment is typically initiated in response to worsening tumor risk characteristics based on surveillance PSA values, prostate biopsies and/or magnetic resonance imaging (MRI) tests.

Androgen deprivation therapy (luteinizing hormone-releasing hormone [LHRH] agonists, LHRH antagonists, anti-androgens, and orchiectomy), commonly known as ADT, has historically been the first-line treatment for biochemically or clinically progressive, recurrent, and metastatic prostate cancer, even in the absence of symptoms. ADT has been used alone and in combination with radical prostatectomy (RP) or radiation therapies, though its use has declined as primary treatment particularly in men with low risk disease.[4, 11]

Some CLPC treatments are primarily intended to cure disease. These include surgical radical prostatectomy and radiation therapy (RT). RP can be performed with an open or laparoscopic approach. Laparoscopic prostatectomy is now commonly performed with robotic-assisted (RALP) technology. Radiation therapy can be delivered either by external beams (external beam radiation therapy [EBRT]) or by internally placing radioactive sources (brachytherapy). EBRT strategies vary, and include intensity modulated radiation therapy (IMRT), three-dimensional conformal radiation therapy (3D-CRT), stereotactic body radiation therapy (SBRT), and proton beam radiation therapy. These interventions remove or treat the whole prostate gland and can have short and longer-term adverse effects including but not limited to perioperative morbidity and urinary, bowel, and erectile/sexual dysfunction.

Given the complications associated with RP and RT, and the relatively indolent nature of many PSA-screen detected CLPC, more attention is turning to potentially lower-risk focal therapies such as high-intensity focused ultrasound (HIFU) and cryotherapy, that focus treatment on the index lesion.[12-14] Use of these options has also increased in response to advances in MRI technology, which now allows for better detection of limited in size local lesions potentially treatable with “lesion-targeted” interventions rather than whole-gland therapy. In addition, awareness has grown regarding the slow-growing nature of most PSA-detected tumors, and therefore the importance of weighing treatment benefits and harms relative to men’s preferences to avoid treatment-related complications.[15]

The purpose of this review was to identify new information and update previous Agency for Healthcare Research and Quality (AHRQ) and American Urological Association (AUA) funded reviews[3-5] evaluating treatments for CLPC as described in our Analytic Framework (Appendix A), and to inform clinical guideline committees as they update guidelines. We updated the evidence base regarding the Key Questions (KQs) below:

KQ 1: What are the comparative effectiveness and harms of CLPC therapies?

1) Watchful waiting
2) Active surveillance/Active monitoring
3) Androgen deprivation therapy (ADT)
4) Focal therapies
    a) Brachytherapy
    b) Cryotherapy
    c) High-intensity focused ultrasound (HIFU)
    d) Laser ablation
    e) Photodynamic therapy
    f) Irreversible electroporation
5) Whole gland therapies
    a) Brachytherapy
    b) Cryotherapy
    c) External beam radiation therapy
        i) three-dimensional conformal radiation therapy
        ii) intensity-modulated radiation therapy
        iii) proton beam therapy
        iv) stereotactic body radiation therapy
    d) Radical prostatectomy
        i) open
        ii) laparoscopic
            (1) without robotic assistance
            (2) with robotic assistance
6) Combination of above

KQ 2: How do patient characteristics modify comparative effectiveness and harms of CLPC therapies?

1) Age
2) Race/ethnicity
3) Comorbidities
4) Health status

KQ 3: How do tumor characteristics modify comparative effectiveness and harms of CLPC therapies?

1) Baseline PSA
2) Gleason score
3) Tumor index scores (e.g., Cancer of the Prostate Risk Assessment Score [CAPRA], D'Amico Risk Classification for Prostate Cancer, etc.)
4) Biomarker Status
    a) Decipher (Genomic Classifier)
    b) Oncotype Dx (Genomic Prostate Score)
    c) Prolaris (Cell Cycle Progression)

KQ 4: How do provider/hospital characteristics modify comparative effectiveness of RP compared to other therapies?

1) Geographic region
2) Hospital type
3) Provider volume
4) Institutional volume

Table 1. PICOTS

PICOTS	KQ 1-3	KQ 4
Population	Treatment naïve men with CLPC (stages T1-T3a) Studies with 15% or more participants with T3b or unspecified T3 are excluded	Same as KQ 1-3
Intervention	1) Watchful waiting (WW) 2) Active surveillance/active monitoring (AS/AM) 3) Androgen deprivation therapy (ADT) 4) Focal therapies a) Brachytherapy b) Cryotherapy c) High-intensity focused ultrasound (HIFU) d) Laser ablation e) Photodynamic therapy f) Irreversible electroporation 5) Whole gland therapies a) Brachytherapy b) Cryotherapy c) External beam radiation therapy (EBRT) i) Three-dimensional conformal radiation therapy ii) Intensity-modulated radiation therapy iii) Proton beam therapy iv) Stereotactic body radiation therapy d) Radical prostatectomy i) Open ii) Laparoscopic (1) Without robotic assistance (2) With robotic assistance 6) Combination of above	1) Radical prostatectomy i) Open ii) Laparoscopic (1) Without robotic assistance (2) With robotic assistance
Comparison	Any other intervention of listed above except certain within category comparisons (e.g., nerve-sparing vs non-nerve sparing prostatectomy; different dosage/frequency/timing/duration of same therapy)	Same as KQ 1-3
Outcomes	Overall survival/mortality Prostate cancer specific survival/mortality Metastatic-progression free survival Metastases (lymph nodes/distant) Health status Quality of life (measured with validated instruments) Prostate-cancer related quality of life (measured with validated instruments) Harms: Bowel, bladder, and sexual/erectile dysfunction Serious adverse effects associated with ADT such as cognitive impairment, MACE, fractures	Overall survival/mortality Prostate cancer specific survival/mortality Metastatic free survival/metastases (lymph nodes/distant)
Timing	Follow up from treatment initiation: Mortality/survival outcomes/metastases: 5 years or more Health status, quality of life and harms: 1 year or more	Follow up from treatment initiation: Mortality/survival outcomes/metastases: 5 years or more
Setting	All settings	Same as KQ 1-3

PICOTS	KQ 1-3	KQ 4
Study Design	1) RCTs 2) Non-RCT if: a) Comparative b) Concurrent c) Multicenter (enrolling patients treated at multiple locations) d) ≥500 patients e) Some method to control for selection bias (propensity scores, instrumental variables, multivariate regression) f) Prospective data collection	Same as KQ 1-3

Abbreviations: ADT = androgen deprivation therapy; AM = active monitoring; AS = active surveillance; CLPC = clinically localized prostate cancer; EBRT = external beam radiation therapy; HIFU = high-intensity focused ultrasound; KQ = Key Question; MACE = major adverse cardiac events; PICOTS = populations, interventions, comparators, outcomes, timing, setting; RCT = randomized controlled trial; WW = watchful waiting

Chapter 2. Methods

Review Approach

The methods for this systematic review followed the Agency for Healthcare Research Qualtiy (AHRQ) Methods Guide for Effectiveness and Comparative Effectiveness Reviews (available at *https://effectivehealthcare.ahrq.gov/topics/cer-methods-guide/overview*). This systematic review also reports in accordance with the Preferred Items for Reporting in Systematic Reviews and Meta-Analyses (PRISMA).[16] The final protocol was posted online (https://effectivehealthcare.ahrq.gov/products/prostate-cancer-therapies/protocol) and submitted for registration in PROSPERO on October 16, 2019 (ID 154937).

Criteria for Inclusion/Exclusion of Studies in the Review

Studies were included based on the population, intervention, comparison, outcomes, timing, and setting/study design (PICOTS) study-specific inclusion criteria (Table 1).

Searching for the Evidence and Updating Prior Reviews

We searched Medline®, Embase®, and the Cochrane Central trials database incorporating vocabulary and natural language relevant to the Key Questions (KQs) (search strategy in Appendix B). Our search captured publications indexed between 2013 and January 2020. Relevant studies published before 2013 were identified in the previous reports; studies published after 2013 were excluded from our review if they were analyzed in a previous report.

The evidence for this report included: 1) eligible studies published after the 2014 AHRQ and 2016 American Urological Association (AUA) funded reviews; and 2) outcomes from randomized controlled trials (RCTs) included in the 2014 AHRQ and 2016 AUA funded reviews when we also included an RCT of low-moderate risk of bias of the same comparison. It was only applicable to carry forward data for two treatment comparisons (watchful waiting [WW] versus radical prostatectomy [RP] in Chapter 4 and external beam radiation therapy [EBRT] plus androgen deprivation therapy [ADT] versus EBRT in Chapter 6). We refer the reader to findings above insufficient evidence from the 2014 AHRQ and 2016 AUA funded reviews related to treatment comparisons noted previously and that we did not address (Table 2). [4, 5]

Search results were downloaded to EndNote X9 (Clarivate Analytics, 2018) and screened in DistillerSR (Evidence Partners, Ottawa, Canada). Two independent investigators reviewed titles and abstracts using predefined criteria. Two independent investigators conducted full-text screening to determine if inclusion criteria were met. Differences in screening decisions were resolved by consultation between investigators, and, if necessary, with a third investigator.

We supplemented our bibliographic database searches by citation searching relevant systematic reviews and original research. Additionally, we searched ClinicalTrials.gov to identify completed and ongoing studies. Additional grey literature was solicited through Federal Register notification. Information from grey literature was also be used to assess publication and reporting bias and inform future research needs.

Assessment of Methodological Risk of Bias of Individual Studies

We used a hierarchical method to analyze evidence. For each comparison, we first assessed the certainty of evidence (COE) using RCTs rated as low or moderate risk of bias (ROB). If RCT data did not achieve moderate or high COE for an outcome, we next analyzed non-RCT data rated as low or moderate ROB. We did not analyze RCT data rated as high ROB and non-RCT data rated as serious or critical non-RCT data.

Eligible RCTs were assessed for ROB using the Cochrane Risk of Bias Tool[6] and non-RCTs were assessed with the ROBINS-I tool.[7] One investigator independently assessed risk of bias for eligible studies to be analyzed; a second investigator reviewed each risk of bias assessment. Investigators consulted to reconcile any discrepancies. Overall risk of bias assessments for RCTs were classified as low, moderate, or high based on the collective risk of bias across components and confidence that the study results were believable given the study's limitations. Overall risk of bias assessments for non-RCTs were classified as low, moderate, serious, or critical based on ROBINS-I criterion.

Data Abstraction and Data Management

From studies analyzed, we extracted inclusion and exclusion criteria; sample size; participant age, race, clinical stage, and Gleason score; tumor risk classification and score, intervention and comparator characteristics; followup duration; and results for outcomes and adverse effects. We extracted data at one year and the longest followup for quality of life, health status, and harms; we extracted data at five-year intervals for mortality and metastases or at mean/median followup if that was the only way reported. One investigator extracted data to tables with verification by a second reviewer.

Data Synthesis

We summarized results of findings in evidence tables and synthesized evidence for each unique comparison with meta-analysis when appropriate. We assessed clinical and methodological heterogeneity to determine appropriateness of pooling data.[17] When meta-analysis was not appropriate, we summarized findings. We calculated risk ratios (RR) or Peto odds' ratios (OR) and absolute risk differences (RD) with the corresponding 95 percent confidence intervals (CI) for binary outcomes. Weighted mean differences (WMD) and/or standardized mean differences (SMD) with 95 percent CIs were calculated for continuous outcomes. Data were analyzed in Comprehensive Meta-Analysis version 3 (Biostat) or R software (package "meta"), version 3.6.0.

Grading Evidence Certainty

We assessed COE with Grading of Recommendations Assessment, Development and Evaluation (GRADE)[8] approach for key outcomes (overall mortality; prostate-specific mortality; metastatic progression) and harms (bowel, bladder, and sexual function). For each comparison, one investigator rated the certainty of evidence for each outcome as high, moderate, low, or insufficient using GRADEpro GDT.[18] COE was reviewed by a second investigator. We resolved discrepancies by consensus or discussion with a third reviewer. We used suggested language[19] to summarize findings and assessed effect size using prespecified thresholds (Appendix C). For

overall and prostate cancer mortality and metastases we defined absolute risk differences of <2% as “little to no difference”, 2-4.9% as “small”; 5-9.9% as “moderate” and ≥10% as “large” effects regardless of population, intervention, comparison or length of follow-up. For urinary, bowel and sexual function we defined absolute risk differences of 2-4.9% as “small”; 5–19.9% as “moderate” and ≥20% as “large.”

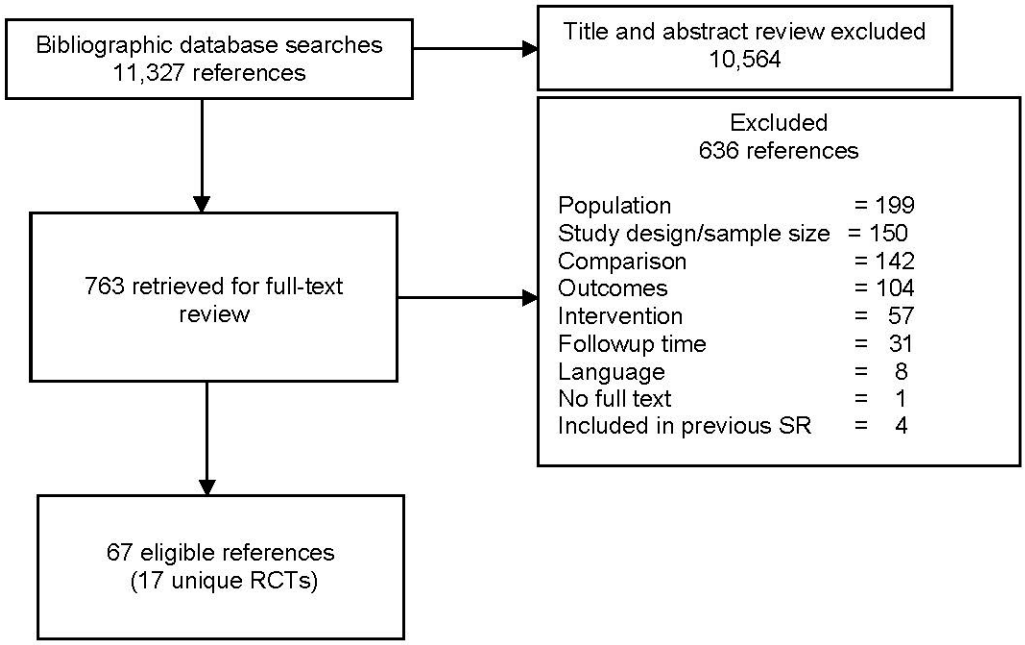
Assessing Applicability

We assessed applicability of results by analyzing whether eligible studies reflected the relevant population according to the PICOTS framework. The population from which the study participants were enrolled, diagnostic approaches, eligibility criteria, patient and intervention characteristics, and other issues that differ from those of the population of treatment naïve men with clinically localized prostate cancer (CLPC) affect applicability.[21]

Chapter 3. Results

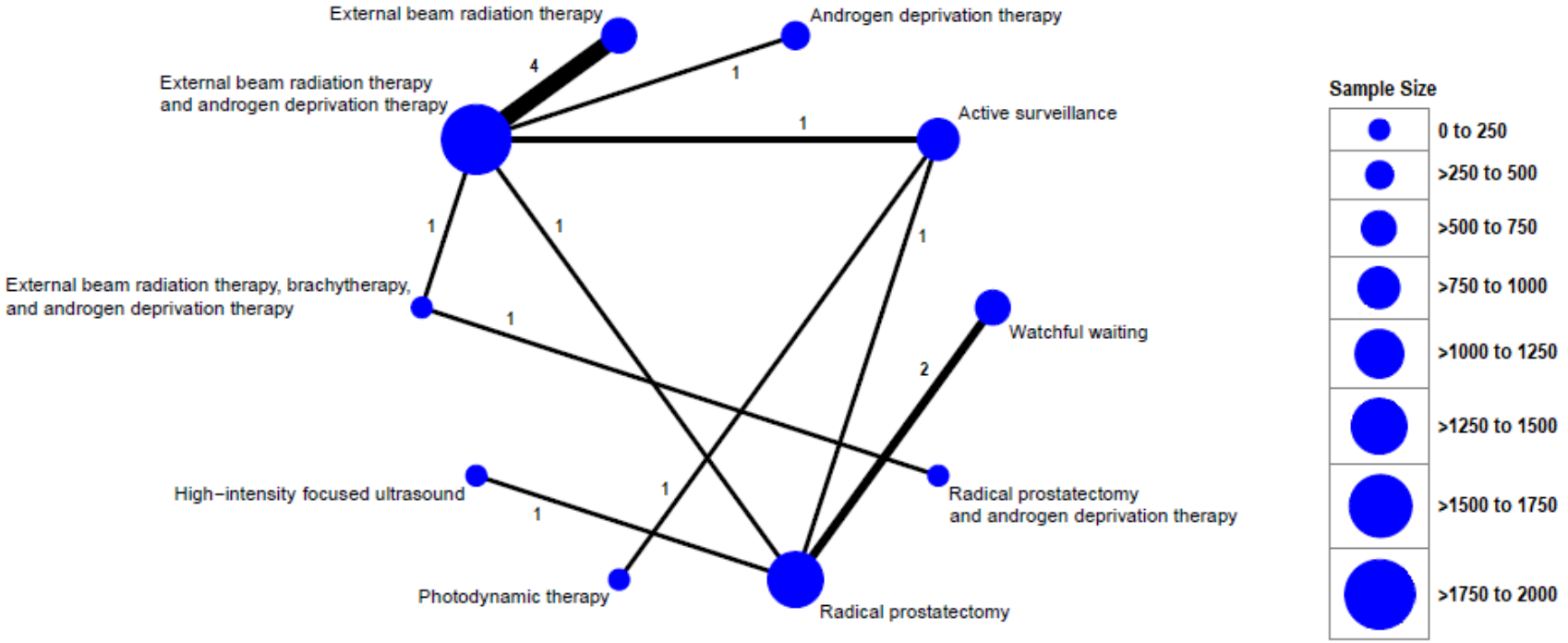
Our search identified 11,327 references (Figure 1). Title and abstract screening eliminated 10,564 references leaving 763 references for full text review. We identified 67 references that were eligible for inclusion to our review, of which 17 were unique randomized controlled trials (RCTs). A list of all eligible publications can be found in Appendix E. A list of all publications excluded at full-text review can be found in Appendix D. Supplemental searches of clinicaltrials.gov and other grey literature sources did not yield any additional published studies that were eligible. Comparisons addressed in eligible RCTs are illustrated in Figure 2. Table 2 summarizes our findings and major intervention and outcomes from past reports.[4, 5]

Figure 1. Literature flow diagram



Abbreviations: RCT = randomized controlled trial; SR = systematic review

Figure 2. Plot of comparisons addressed in RCTs identified in updated literature search *†‡††**



Abbreviation: RCT = randomized controlled trial

*The node size reflects the sample size. The width of lines reflects the number of RCTs that evaluated that comparison.
†Within category comparisons are not shown in figure. These include: RARP vs. LRP (k=1, n=120), 3D-CRT vs. IMRT (k=1, n=215), ultra-hypofractionated EBRT vs. standard EBRT (k=2, n=1,275), and EBRT plus neoadjuvant and concurrent ADT vs. EBRT plus concurrent and adjuvant ADT (k=1, n=432).
‡One RCT (ProtecT) was a three-arm trial.
**The AS protocols varied. One trial evaluated biopsy-based AS vs. photodynamic therapy and a second trial evaluated PSA-based active monitoring vs. RP or EBRT plus ADT.
††We identified 4 RCTs that compared EBRT plus ADT vs. EBRT alone. The old reports identified 3 additional RCTs.

Table 2. Summary updates of comparisons between reviews*

Intervention/ Comparison	Outcome(s)	Previous Findings From 2014 AHRQ- or 2016 AUA-Funded Reviews†	Present Findings Derived From Studies Published After the Prior Reviews and by Incorporating Prior RCT Data When Applicable‡
WW vs. RP in men with clinically detected (SPCG-4) or mainly clinically detected (PIVOT) CLPC ‡	All-cause mortality, PC-specific mortality, Metastases Harms	Insufficient evidence on all-cause mortality, PC-specific mortality, and erectile and bowel harms. RP probably reduces metastases. WW may reduce urinary harms. Insufficient evidence for erectile and bowel harms.§	WW vs. RP in men with clinically detected CLPC: **(SPCG-4)** • probably results in moderate increases in all-cause mortality and large increases in PC-specific mortality and metastases at 25 years. Mortality effects may be limited to men younger than age 65 and intermediate risk CLPC. • No new data for harms. WW versus RP in men with mainly clinically detected CLPC **(PIVOT):** • probably results in a moderate increase in all-cause mortality and large reduction in metastases and small increase in PC-specific mortality and at 20 years. Mortality effects may be limited to men younger than age 65 and intermediate risk CLPC. • probably results in a moderate reduction in erectile and urinary harms at 10 years.
AM (PSA-based) vs. EBRT + ADT	All-cause mortality, PC-specific mortality, Metastases, Harms	Not addressed	AM versus EBRT plus ADT in men with PSA-screen detected CLPC: • probably results in little to no difference in all-cause mortality, may result in little to no difference in PC-specific mortality and probably results in small increases in metastases at 10 years. Results may not vary by patient or tumor characteristics. • may result in a small decrease in erectile dysfunction, probably results in a small increase in urinary incontinence, and may make little to no difference in fecal incontinence at 6 years.
AM (PSA-based) vs. RP	All-cause mortality, PC-specific mortality, Metastases Harms	Not addressed	AM versus RP in men with PSA-screen detected CLPC: • may result in little to no difference in all-cause or PC-specific mortality but probably results in a small increase in metastases at 10 years. Results may not vary by patient or tumor characteristics. • probably results in a large decrease in erectile dysfunction and moderate decrease in urinary incontinence and may make little to no difference in fecal incontinence at 6 years.
AS (Biopsy + PSA based) vs. PDT	Harms	Not addressed	AS versus PDT in men with PSA screen-detected low risk CLPC: • probably results in a large decrease in erectile dysfunction and moderate decrease in urinary retention at 2 years.
RP vs. EBRT + ADT	All-cause mortality, PC-specific mortality, Metastases, Harms	Clinical outcomes not addressed Insufficient evidence on harms. **	RP versus EBRT plus ADT in men with PSA-screen detected CLPC: • may result in little to no difference in all-cause mortality, PC-specific mortality, and metastases at 10 years. Results on PC-specific mortality may not differ by age, PSA level, Gleason score or clinical stage. • probably results in an increase in erectile and urinary harms and a decrease in bowel dysfunction at 6 years.

Intervention/ Comparison	Outcome(s)	Previous Findings From 2014 AHRQ- or 2016 AUA-Funded Reviews†	Present Findings Derived From Studies Published After the Prior Reviews and by Incorporating Prior RCT Data When Applicable‡
RP + ADT vs. EBRT + HDR Brachytherapy + ADT	All-cause mortality, PC-specific mortality, Harms	Insufficient evidence on harms for RP vs. EBRT plus brachytherapy. **	RP plus ADT versus EBRT plus high-dose-rate brachytherapy plus ADT in men with T1b-T3a PC of any histologic grade: • may result in a small increase in erectile dysfunction at 2 years. • insufficient evidence on urinary or bowel harms at 2 years and all-cause or PC-specific mortality through 10 years.
RP vs. HIFU	Harms	Not addressed	In men with Gleason score 7, <T2b CLPC, insufficient evidence on urinary, erectile, and bowel harms at 1 year.
Laparoscopic RP vs. Robotic Assisted RP	Harms	Insufficient evidence on urinary and erectile harms at 1 year. §	Laparoscopic RP versus robotic RP in men with PSA detected predominately low-intermediate risk CLPC: • may result in a moderate increase in urinary incontinence and a large increase in erectile dysfunction at 5 years.
Robotic-assisted Laparoscopic RP vs. Open Retropubic RP	All-cause mortality, PC-specific mortality, Metastases Harms	Insufficient evidence on all-cause mortality, PC-specific mortality, metastases, and harms. **	In men with predominately low and intermediate D'Amico risk CLPC, insufficient evidence on erectile dysfunction. No data for mortality/metastases.
EBRT vs. Brachytherapy	All-cause mortality, PC-specific mortality, Metastasis-free survival	Insufficient evidence on all-cause mortality and PC-specific mortality. §	In men with Gleason 6 or 7 CLPC, insufficient evidence on overall survival, PC-specific survival, and metastasis-free survival.
EBRT + Brachytherapy vs. Brachytherapy	All-cause mortality, PC-specific mortality	Insufficient evidence on PC-specific mortality. §	In men with intermediate NCCN risk CLPC, insufficient evidence on all-cause mortality in men.
IMRT vs. SBRT	All-cause Mortality	Not addressed	In men with predominately Gleason 6-7, PSA<10, and T1C CLPC, insufficient evidence on all-cause mortality.
Conventionally fractionated EBRT vs. ultra-hypofractionated EBRT	All-cause mortality, PC-specific mortality, Metastasis Harms	Not addressed	Conventionally fractionated EBRT versus ultra-hypofractionated EBRT in men with predominantly intermediate-risk CLPC: • probably results in little to no difference in all-cause mortality and may result in little to no difference in PC-specific mortality and metastasis at 5 years. • may result in little to no differences on urinary and bowel harms (except urinary harms at 1 year). Insufficient evidence on erectile function.
3D-CRT + ADT + low-dose-rate Brachytherapy vs. 3D-CRT + ADT	All-cause mortality, PC-specific mortality, Metastases Harms	Insufficient evidence on PC-specific mortality for EBRT plus BT vs. EBRT. §	3D-CRT and ADT plus low-dose-rate brachytherapy versus 3D-CRT and ADT in men with intermediate and high NCCN risk CLPC: • may result in a small decrease in all-cause mortality and little to no difference in metastases at 5 years. • insufficient evidence on PC-specific mortality, urinary incontinence, and erectile function.

Intervention/ Comparison	Outcome(s)	Previous Findings From 2014 AHRQ- or 2016 AUA-Funded Reviews†	Present Findings Derived From Studies Published After the Prior Reviews and by Incorporating Prior RCT Data When Applicable‡
EBRT + ADT vs. EBRT ‡	All-cause mortality, PC-specific mortality, Metastases Harms	Inconsistent findings on all-cause mortality/survival and metastases but evidence consistently favored combination therapy on PC-mortality. **	EBRT plus ADT versus EBRT in men with predominately intermediate to high risk CLPC (using different risk classifications): • probably results in a small reduction in all-cause mortality and may result in a small reduction in PC-mortality and metastasis at 5 to 10 years. Mortality effects may be limited to intermediate-high risk men and men with no or minimal co-morbidity. • may moderately increase sexual dysfunction. Insufficient evidence on urinary incontinence and rectal bleeding.
EBRT + neoadjuvant and concurrent ADT vs. EBRT plus concurrent and adjuvant ADT	All-cause mortality, PC-specific mortality, Metastasis, Harms	Not addressed	EBRT plus neoadjuvant and concurrent ADT versus EBRT plus concurrent and adjuvant ADT in men with predominantly intermediate-risk CLPC: • may result in little to no difference in all-cause mortality and PC-specific mortality at 12 years. Insufficient evidence on metastasis. • may result in little to no difference in genitourinary toxicity at 3 years.
RP vs. EBRT	All-cause mortality, PC-specific mortality	RP may reduce all-cause mortality and PC-specific mortality vs. EBRT. §	No new data
Retropubic RP vs. Brachytherapy	Harms	Results were similar on erectile and urinary function at 5 years. Retropubic RP may reduce short-term urinary symptoms versus brachytherapy. **	No new data
Retropubic RP vs. Perineal RP	Harms	Retropubic RP may improve erectile function at 2 years versus Perineal RP, but no between-group difference at 6 months. No difference on urinary function. **	No new data
Transperitoneal Robotic-Assisted Laparoscopic RP vs. Extraperitoneal Robotic-Assisted Laparoscopic RP	Harms	Results on incontinence or erection rates at 6 months were similar. **	No new data
EBRT vs. Observation	PC-specific mortality	EBRT may reduce PC-specific mortality versus observation. **	No new data

Intervention/ Comparison	Outcome(s)	Previous Findings From 2014 AHRQ- or 2016 AUA-Funded Reviews†	Present Findings Derived From Studies Published After the Prior Reviews and by Incorporating Prior RCT Data When Applicable‡
EBRT vs. Cryotherapy	All-cause mortality PC-specific mortality, harms	No between-group difference on overall survival or PC-specific mortality. Safety outcomes were inconsistent. **	No new data
EBRT + ADT vs. ADT	PC-specific mortality	EBRT plus ADT may reduce PC-specific mortality versus ADT. **	No new data
IMRT vs. Proton beam	Harms	IMRT may reduce GI adverse events versus proton beam. **	No new data
3D-CRT conventional vs. 3D-CRT high dose	All-cause mortality, PC-specific mortality, metastases, harms	No between-group differences. **	Out of scope for this review
Hypofractionated RT vs. conventionally-fractionated RT	All-cause mortality, PC-specific mortality, Harms	No between-group differences. **	Out of scope for this review
Brachytherapy conventional dose vs. Brachytherapy low dose	All-cause mortality, Urinary symptoms	No between-group difference (except in short-term urinary symptoms). **	Out of scope for this review
ADT plus RP vs. RP	All-cause mortality, PC-specific mortality, Metastasis	No between-group differences. **	No new data
ADT plus SOC (RP or RT) vs. SOC (RP or RT)	All-cause mortality, metastases	No between-group difference. **	Out of scope for this review
ADT plus SOC (WW) vs. SOC (WW) alone	All-cause mortality, metastases	Inconsistent results. **	No new data
ADT short-term plus RT vs. ADT long-term plus RT	All-cause mortality, PC-specific mortality	No between-group difference on mortality. Inconsistent results on PC-specific mortality. **	Out of scope for this review
ADT vs. ADT plus docetaxel and estramustine	All-cause mortality, PC-specific mortality, Metastases	Combination therapy may reduce mortality, PC-specific mortality, and metastases versus ADT, but results considered “inconclusive” in 2016 AUA-funded report. **	No new data

Abbreviations: 3D-CRT = three-dimensional conformal radiation therapy; ADT = androgen deprivation therapy; AHRQ = Agency for Healthcare Research and Quality; AM = active monitoring; AS = active surveillance/ AUA = American Urological Association; BT = brachytherapy; CLPC = clinically localized prostate cancer; EBRT = external beam radiation therapy; GI = gastrointestinal; HDR = high-dose rate; HIFU = high-intensity focused ultrasound; IMRT = intensity-modulated radiation therapy; NCCN = National Comprehensive Cancer Network; PC = prostate cancer; PDT = photodynamic therapy; PIVOT = Prostate Cancer Intervention Versus Observation Trial; PSA = prostate-specific antigen; RCT = randomized controlled trial; RP = radical prostatectomy; RT = radiation therapy; SBRT = stereotactic body radiation therapy; SOC = standard of care; SPCG-4 = Scandinavian Prostate Cancer Group Study Number 4; WW = watchful waiting

*This table shows findings on mortality, PC-specific mortality, metastases, sexual, urinary, and bowel harms from treatment comparisons analyzed in this current systematic review and any comparisons from the 2014 AHRQ-funded and 2016 AUA-funded systematic reviews with findings above insufficient evidence.
†We interpreted findings from the 2016 AUA-funded report with "Level C" evidence to be equivalent to "insufficient evidence".
‡For select treatment comparisons (WW vs. RP and EBRT plus ADT vs. EBRT), our findings incorporate data/outcomes from the prior reviews (see methods).
§Findings from the 2014 AHRQ-funded systematic review
**Findings from the 2016 AUA-funded systematic review

Chapter 4. Watchful Waiting

Key Messages

- Watchful waiting (WW) versus radical prostatectomy (RP) in men with predominately clinically, rather than prostate specific antigen (PSA) screen-detected clinically localized prostate cancer (CLPC):
  - May result in a moderate to large increase in all-cause mortality and a small to large increase in prostate cancer mortality and metastases through 20 years. Absolute effects varied between studies. (Low to moderate certainty of evidence [COE])
  - Mortality effects may not vary based on race or PSA levels but may be limited to men with D'Amico intermediate tumor risk and men younger than age 65
  - Probably results in a moderate reduction in erectile dysfunction and urinary incontinence at 10 years versus RP (moderate COE).
- No RCTs evaluated WW among men with CLPC detected by PSA screening alone.

We identified three reports of two unique RCTs[20-22] and five reports of four unique non-RCTs[23-27] comparing WW to other therapies. Serious risk of bias (ROB) precluded inclusion of non-RCTs in the analysis. Some comparisons were only evaluated in studies rated high ROB (e.g., WW vs. external beam radiation therapy [EBRT][k=3 non-RCTs],[23, 25, 26] WW vs. radiation therapy [either EBRT and/or brachytherapy][k=1 non-RCT],[24, 27] WW vs. active surveillance [k=1 non-RCT],[24, 27] WW vs. androgen deprivation therapy [ADT] [k=1 non-RCT]).[24, 27]

ROB assessments, population characteristics of the analyzed studies, outcomes data, and detailed GRADE rating tables are in Appendix F. Summary of Findings appears in Table 3.

There were several comparisons of WW to other therapies addressed in the 2016 evidence report commissioned by the American Urological Association (AUA) in which we did not identify additional studies that met analysis criteria.[5] A list of these comparisons can be found in Appendix J. The 2016 evidence report contains detailed results, strength of evidence, and evidence tables for these comparisons. Table 3 summarizes major findings of WW versus other comparisons.

Watchful Waiting Versus Radical Prostatectomy

We identified two RCTs that compared WW to RP and reported long-term results.[20-22] The Scandinavian Prostate Cancer Group 4 (SPCG-4) study was conducted in Scandinavia prior to PSA screening, and enrolled men with clinically detected disease. The U.S. Prostate Cancer Intervention Versus Observation Trial (PIVOT) study began during the early period of PSA screening and enrolled approximately 50 percent of men with T1C disease. Because of clinical heterogeneity in the enrolled populations, we did not think pooling of results was appropriate. Instead, we describe and evaluate findings from each study and attempt to note implications for patients with T1C tumors diagnosed primarily through PSA screening. Shorter followup times, development of metastatic disease, and harms have been reported in earlier publications of these trials, and were included in the previous reviews though we note some data here.[28-41] Both trials enrolled men under 75 with clinical T1 or T2 and life expectancy greater than 10 years. Results

reported since the previous review had longer followup periods for mortality and metastases and provided additional information about harms.

At nearly 20 years, prostate cancer mortality as well as the absolute overall and prostate cancer mortality differences in both the RP and WW groups were much larger in SPCG-4 versus PIVOT. Overall mortality and distant metastases were higher with WW versus RP in SPCG-4, but not PIVOT, likely reflecting the greater absolute risk of metastases and prostate cancer death in SPCG-4 compared to PIVOT.

Based on combined results from these two studies, WW may increase overall and prostate-specific mortality (low COE) among men whose prostate disease was mostly detected clinically rather than through PSA screening. Based on findings from SPCG-4, WW probably results in a moderate increase in overall mortality at 25 years (moderate COE) and a large increase in prostate-specific mortality (moderate COE). While the relative effects were similar between the two studies, the absolute effect varied considerably: 12 percentage points in SPCG-4 and 4 percentage points in PIVOT for overall mortality. Based on SPCG-4, at both 20 and 25 years, WW probably resulted in a large increase in metastases (moderate COE). Based on findings from PIVOT, WW may result in a small increase in metastatic disease, defined as systemic progression (low COE). The prior systematic reviews noted that in PIVOT at 10 years followup, incidences of bone metastases were much less frequent overall compared to SPCG-4 but still lower in the RP group (4.7%) compared with WW (10.6%) with an absolute difference of approximately 6 percentage points.[4, 5] No RCTs have assessed WW versus radiation therapy or other interventions among men whose disease was detected solely through PSA screening.

In the PIVOT trial, WW probably resulted in moderately lower erectile dysfunction (defined as unable to have an erection or able to have an erection but the erection was not sufficient for vaginal penetration) and urinary incontinence (defined as >1 pad use per day) versus RP at 2, 5 and 10 years (moderate COE) (personal communication from the study lead author). Satisfaction with sexual functioning was moderately lower with RP vs. WW at two, five and 10 years. While sexual function was low in both groups at 10 years more men in the RP group reported poor sexual functioning compared with men in the WW group at two, five and 10 years. There may be a small increase bowel dysfunction with WW, defined as patient reported dysfunction as a "moderate" or "big" problem, versus RP at 10 years (low COE) (personal communication from the study lead author). No harms data were reported for SPCG-4 trial at the longest-term followup. Prior reviews reported that at 8-year followup, men allocated to WW regularly reported less erection dysfunction and urinary leakage than men allocated to RP.[4, 5] Quality of life data has been previously reported but indicates that WW does not result in worse quality of life.

Variation in Outcomes by Participant or Tumor Characteristics

Outcomes specific to several subgroups were analyzed. Both trials analyzed subgroups defined by age and tumor characteristics at nearly 20 years followup.[20-22] Wilt et al. also analyzed race as a potential effect modifier.[22]

Overall mortality was higher with WW than RP in men younger than 65; this difference was not significant in men 65 and older. Race did not modify treatment effects based on PIVOT results. Age was an important effect modifier for prostate-cancer-specific mortality on SPCG-4, but not PIVOT. SPCG-4 analyzed the effect of age on distant metastases. Distant metastases were higher with WW versus RP in both age groups.

Two tumor characteristics, namely PSA and D'Amico classified prostate cancer risk category, were analyzed for effect modification. The effect of treatment on overall mortality or

prostate-specific mortality did not vary by PSA level (<10 vs. >=10 ng/mL) in PIVOT. Both trials found that D'Amico tumor risk category modified the effect of treatment. In both trials at 20 years followup, WW versus RP was associated with higher mortality among men at intermediate risk but not low- or high-risk disease.

Table 3. Certainty of evidence: watchful waiting

Comparison	Outcome № of Participants (studies)	Relative Effect (95% CI)	Absolute Effects WW	Absolute Effects Comparator	Absolute Effects Difference (95% CI)	Certainty of Evidence:	What Happens
WW versus RP[20-22]	All-cause mortality ~20-years followup 2 RCTs (n=1426)	SPCG-4: RR 1.23 (1.10 to1.38)	70.9% (247/348)	57.6% (200/347)	13.3% (6.3 to 20.4)	⊕⊕◯◯ LOW [a, b]	WW may result in a moderate to large increase in all-cause mortality versus RP
		PIVOT: RR 1.09 (0.98 to1.22)	66.7% (245/367)	61.3% (223/364)	5.5% (-1.45 to 12.4)		
	All-cause mortality ~25-years followup 1 RCT (n=695)	RR 1.12 (1.03 to1.2)	83.9% (292/348)	75.2% (261/347)	8.7 (2.7 to14.6)	⊕⊕⊕◯ MODERATE [b]	WW probably results in a moderate increase in all-cause mortality versus RP
	PC-specific mortality ~20-years followup 2 RCT (n=1426)	SPCG-4: RR 1.57 (1.19 to 2.07)	28.4% (99/348)	18.1% (63/347)	10.3% (4.05 to 16.5)	⊕⊕◯◯ LOW [a, b]	WW may result in a small to large increase in PC-specific mortality versus RP
		PIVOT: RR 1.54 (0.97 to 2.45)	11.4% (42/367)	7.4% (27/364)	4.0% (-0.19 to 8.25)		
	PC-specific mortality ~25-years followup 1 RCT (n=695)	RR 1.54 (1.19 to 2.00)	31.6% (110/348)	20.5% (71/347)	11.1% (4.7 to 17.6)	⊕⊕⊕◯ MODERATE [b]	WW probably results in a large increase in PC-specific mortality versus RP
	Metastases ~20-years followup 1 RCT (n=695)	RR 1.54 (1.24 to1.93)	39.7% (138/348)	25.6% (89/347)	14% (7.1 to 20.9)	⊕⊕⊕◯ MODERATE [b]	WW probably results in a large increase in metastases versus RP
	Metastases ~25-years followup 1 RCT (n=695)	RR 1.63 (1.3 to 2.00)	43.1% (150/348)	26.5% (92/347)	16.6% (9.6 to 23.6)	⊕⊕⊕◯ MODERATE [b]	WW probably results in a large increase in metastases versus RP
	Metastases (Systemic progression) ~20-years followup 1 RCT (n=731)	RR 1.45 (0.98 to 2.14)	14.7% (54/367)	10.2% (37/364)	4.5% (-0.3 to 9.4)	⊕⊕◯◯ LOW [c]	WW may result in a small increase in metastases (systemic progression) versus RP

Comparison	Outcome № of Participants (studies)	Relative Effect (95% CI)	Absolute Effects WW	Absolute Effects Comparator	Absolute Effects Difference (95% CI)	Certainty of Evidence:	What Happens
	Erectile dysfunction 10 years followup 1 RCT (n=293)	RR 0.82 (0.72 to 0.93)	69.9% (102/146)	85.0% (125/147)	-15.2% (-24.6 to -5.8)	⊕⊕⊕◯ MODERATE [b]	WW probably results in a moderate reduction of erectile dysfunction versus RP
	Urinary incontinence (>1 pad per day) 10-years followup 1 RCT (n=295)	RR 0.25 (0.12 to 0.53)	5.4% (8/147)	21.6% (32/148)	-16.2% (-23.8 to -8.6)	⊕⊕⊕◯ MODERATE [b]	WW probably results in a moderate reduction in urinary incontinence versus RP
	Bowel dysfunction 10-years followup 1 RCT (n=299)	RR 1.21 (0.77 to 1.88)	22.7% (34/150)	18.8% (28/149)	3.9% (-5.3 to 13.1)	⊕⊕◯◯ LOW [c]	WW may result in a small increase in bowel dysfunction versus RP

Abbreviations: CI = confidence interval; n = sample size; PC = prostate cancer; PIVOT = Prostate Cancer Intervention Versus Observation Trail; RCT = randomized controlled trial; RP = radical prostatectomy; RR = relative risk; SPCG-4 = Scandinavian Prostate Cancer Group Study Number 4; WW = watchful waiting

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Insufficient: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations
a. Rated down one level for inconsistency
b. Rated down one level for imprecision
c. Rated down two levels for imprecision

Chapter 5. Active Surveillance/Active Monitoring

Key Messages

- Prostate specific antigen (PSA) -based Active Monitoring (AM) versus external beam radiation therapy (EBRT) plus androgen deprivation therapy (ADT) in men with PSA detected clinically localized prostate cancer (CLPC):
  - There may be little to no difference in all-cause mortality (moderate [certainty of evidence] COE) or prostate-specific mortality (low COE) over 10 years with AM versus EBRT plus ADT among men with prostate cancer detected by PSA screening. Metastases were infrequent, but probably slightly higher with AM (moderate COE).
  - Results may not vary by age, PSA level, tumor stage or Gleason score
  - No studies evaluated biopsy based active surveillance/active monitoring (AS/AM) versus radical prostatectomy (RP) or EBRT.
  - Urinary incontinence was higher with AM than with EBRT+ADT.
- AM versus RP over 10 years in men with PSA detected CLPC:
  - There was little to no difference in all-cause (moderate COE) and prostate-cancer-specific mortality (low COE). Metastases were infrequent but slightly increased with AM (moderate COE)
  - Erectile dysfunction (ED) and urinary incontinence were moderately lower with AM versus RP over 6 years (moderate COE)
- Biopsy and PSA-based AS versus Photodynamic Therapy (PDT) over 2 years
  - Data are insufficient to assess the effect of biopsy-based AS versus PDT on all-cause or prostate cancer specific mortality or metastasis in men with low-risk disease.
  - Urinary retention was moderately lower, and hematuria was largely lower with AS than with PDT among men with low risk disease (moderate COE). AS probably results in a large reduction in ED and a moderate reduction in perineal pain with AS versus PTD (moderate COE).

We identified six reports of two unique randomized controlled trials (RCTs)[12, 42-46] and nine reports of four unique non-RCTs[24, 27, 47-53] that compared AS/AM to other therapies. Serious or critical risk of bias (ROB) precluded the inclusion of non-RCTs in the analysis. Some comparisons were only evaluated in studies rated high ROB (e.g., AS vs. watchful waiting [WW][k=1 non-RCT],[24, 27] AS vs. EBRT[k=1 non-RCT],[52] AS vs. brachytherapy [k=1 non-RCT],[52] AS vs. radiation therapy [either EBRT and/or brachytherapy][k=1 non-RCT],[24, 27] and AS vs. ADT[k=1 non-RCT].[24, 27]

ROB assessments, population characteristics of the analyzed studies, outcomes data, and detailed GRADE rating tables are in Appendix G. Summary of Findings appears in Table 4.

Information on AS/AM versus radical prostatectomy can be found in Chapter 7.

There were several comparisons of AS/AM to other therapies addressed in the 2016 evidence report commissioned by the American Urological Association (AUA) in which we did not identify any additional studies that met our analysis criteria.[5] A list of these comparisons can be found in Appendix J. The 2016 evidence report and appendices contain detailed results, strength of evidence, and evidence tables for these comparisons. Table 2 summarizes major findings of AS/AM versus other comparisons.

Active Monitoring Versus External Beam Radiation Therapy Plus Androgen Deprivation Therapy

Four reports of one eligible RCT (ProtecT) compared PSA-based AM to EBRT plus ADT or to RP and reported results for survival, metastases, quality of life, or harms.[42-44, 46] Men with PSA-screen-detected T1c-T2 CLPC were randomized to PSA-based monitoring (which were included under the intervention category of active surveillance) AM (n=545), RP (n=553) or EBRT plus ADT (n=545). Most men had a Gleason score of 6 (77%), followed by scores of 7 (21%) and 8-10 (2%). Eighty-eight percent of men allocated to AM, 71 percent to RP and 74 percent to EBRT received the assigned treatment within 9 months after randomization.

Participants assigned to AM had serum PSA levels measured every 3 months in the first year and every 6 to 12 months thereafter. A 50 percent or greater increase in PSA level initiated a review. Following review, participants could continue AM, undergo further testing (including rebiopsy), or receive radical or palliative interventions as needed. At the 10-year followup, 53 percent (n=291) of men assigned to AM had received radical treatment (surgery 49%, per-protocol EBRT 33%, 8% brachytherapy, 9% non-protocol EBRT, 1% high intensity focused ultrasound). Participants assigned to EBRT received 74 Gy in 37 fractions with neoadjuvant androgen suppression (ADT) given for 3 to 6 months before and concomitantly.[44] Median age was 62 years and the majority were white (98%).[44] ProtecT was conducted in the UK, was non-industry funded, and rated low risk of bias. Prior reviews included no randomized trials that directly compared AS/AM or PSA plus biopsy-based AS/AM to EBRT. No studies enrolled patients based on evaluation, monitoring, or targeted biopsies with MRI.

There probably was little to no difference in all-cause (moderate COE) and prostate-cancer-specific mortality (low COE) with AM versus EBRT plus ADT at 10-years (Table 4).[43] Deaths attributable to prostate cancer were few; 8 (1.5%) and 4 (0.7%) in the AM and EBRT plus ADT groups, respectively.

Metastases were infrequent but probably slightly higher with AM than with EBRT plus ADT over 10 years (33 (6.0%) versus 16 (2.9%)) (moderate COE) (Table 4).[43] There were no differences in the Medical Outcomes Study 12-Item Short-Form General Health Survey (SF-12) physical and mental health subscales and the European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire–Core 30 module (EORTC QLQ-C30) with AM versus EBRT plus ADT at 12 and 72 month followups.[42]

Erectile dysfunction was slightly lower with AM versus EBRT plus ADT (low COE).[42] However, urinary incontinence was higher with AM than with EBRT plus ADT. At 72 months, urinary incontinence (defined as any use of absorbent pads) was reported by 38 of 453 (8.4%) men randomized to AM versus 16 of 452 (3.5%) randomized to EBRT plus ADT (moderate COE). Fecal incontinence at least one time per week was reported for 2.6% with AM versus 4.1% with EBRT plus ADT group at 72 months. The interventions differed little for the outcome of fecal incontinence (low COE).

Variation in Outcomes by Participant or Tumor Characteristics

Pre-specified subgroup analyses found no differences between groups in prostate-cancer-specific mortality when stratified by age, PSA level, Gleason score, or clinical stage, though few events occurred.

Active Surveillance Versus Photodynamic Therapy

One multicenter RCT compared biopsy and PSA-based AS versus PDT in men with low but not very low-risk disease.[12] Azzouzi et al. enrolled men (n=413) with low-risk T1a through T2a CLPC with up to 24 months followup. Men were eligible if one core of cancer that was free of Gleason patterns 4 or 5 was present, provided that the cancer core length was between 3 mm and 5 mm. Eighty-six percent of men had T1c tumors, more than three quarters had unilateral prostate cancer; the baseline PSA was approximately 6 ng/mL. The mean age of enrollees was 63 years. AS included protocol-directed prostate biopsies at 12-month intervals and PSA measurements every 3 months. Photodynamic therapy involved a dedicated magnetic resonance imaging (MRI), intravenous padeliporfin, and transurethral administration of laser light. The co-primary study outcomes were "treatment failure (defined by biopsy determined histological progression of cancer from low to moderate or high risk or death) and absence of definite cancer for 24 months). We did not extract data on mortality or metastases because of the short followup. No eligible non-RCTs or studies in previous reports addressed this comparison.

Certainty was very low for both urinary incontinence and erectile function (Table 4) assessed with the International Index of Erectile Function (IIEF-5) scale (insufficient COE). Urinary retention was probably moderately lower, and hematuria was largely lower with AS (moderate COE). AS probably results in a large reduction in erectile dysfunction (ED) and a moderate reduction in perineal pain versus PDT (moderate COE).

Table 4. Certainty of evidence: active monitoring and active surveillance

Comparison	Outcome № of Participants (studies)	Relative Effect (95% CI)	Absolute Effects AS/AM	Absolute Effects Comparator	Absolute Effects Difference (95% CI)	Certainty of Evidence:	What Happens
PSA-based AM versus EBRT + ADT[42-44]	All-cause mortality 10 years followup 1 RCT (n=1090)	RR 1.07 (0.8 to 1.5)	10.8% (59/545)	10.1% (55/545)	0.7% (-2.9 to 4.4)	⊕⊕⊕◯ MODERATE [a]	AM probably results in little to no difference in all-cause mortality versus EBRT + ADT
	PC-specific mortality 10 years followup 1 RCT (n=1090)	Peto OR 1.96 (0.63 to 6.12)	1.5% (8/545)	0.7% (4/545)	0.7% (-0.5 to 1.9)	⊕⊕◯◯ LOW [b]	AM may result in little to no difference in PC-specific mortality versus EBRT + ADT
	Metastases 10 years followup 1 RCT (n=1090)	RR 2.1 (1.15 to 3.7)	6.0% (33/545)	2.9% (16/545)	3.1% (0.67 to 5.6)	⊕⊕⊕◯ MODERATE [a]	AM probably results in a small increase of metastases versus EBRT + ADT
	Erectile dysfunction 6 years followup 1 RCT (n=908)	RR 0.97 (0.89 to 1.05)	70.4% (318/452)	72.6% (331/456)	-2.4% (-8.2 to 3.5)	⊕⊕◯◯ LOW [b]	AM may result in a small decrease in erectile dysfunction versus EBRT + ADT
	Urinary incontinence 6 years followup 1 RCT (n=903)	RR 2.37 (1.34 to 4.19)	8.4% (38/453)	3.5% (16/452)	4.8% (1.8 to 7.9)	⊕⊕⊕◯ MODERATE [a]	AM probably results in a small increase in urinary incontinence versus EBRT + ADT
	Fecal incontinence 6 years followup 1 RCT (n=927)	RR 0.64 (0.3 to 1.3)	2.6% (12/462)	4.1% (19/465)	-1.5% (-3.8 to 0.82)	⊕⊕◯◯ LOW [b]	AM may result in little to no difference in fecal incontinence versus EBRT + ADT
AS versus PDT[12]	Erectile dysfunction 24-month followup 1 RCT (n=404)	RR 0.31 (0.2 to 0.5)	11.6% (24/207)	37.6% (74/197)	-26% (-34 to -18);	⊕⊕⊕◯ MODERATE [c]	AS probably results in a large decrease in erectile dysfunction versus PDT
	Urinary incontinence 24 months followup 1 RCT (n=404)	RR 0.5 (0.24 to 1.05)	4.8% (10/207)	9.6% (19/197)	-4.8% (-9.9 to 2.4)	⊕◯◯◯ INSUFFICIENT [b, c]	The evidence is very uncertain about the effect of AS on urinary incontinence versus PDT
	Urinary retention 24 months followup 1 RCT (n=404)	RR 0.06 (0.01 to 0.24)	1.0% (2/207)	16.2% (32/197)	-15.3% (-20.6 to -10)	⊕⊕⊕◯ MODERATE [c]	AS probably results in a moderate reduction of urinary retention versus PDT

Abbreviations: ADT = androgen deprivation therapy; AM = active monitoring; AS = active surveillance; CI = confidence interval; EBRT = external beam radiation therapy; n = sample size; PC = prostate cancer; PDT = photodynamic therapy; PSA = prostate-specific antigen; RCT = randomized controlled trial; RR = relative risk

Comparison	Outcome № of Participants (studies)	Relative Effect (95% CI)	Absolute Effects AS/AM	Absolute Effects Comparator	Absolute Effects Difference (95% CI)	Certainty of Evidence:	What Happens

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Insufficient: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations
a. Rated down one level for imprecision
b. Rated down two levels for imprecision
c. Rated down one level for risk of bias

Chapter 6. Whole Gland Therapies- External Beam Radiation Therapy

Key Messages

- 3D-conformal radiation therapy (3D-CRT) and androgen deprivation therapy (ADT) plus low-dose-rate prostate brachytherapy (LDR-prostate brachytherapy) versus 3D-CRT and ADT in men with predominately high National Comprehensive Cancer Network (NCCN) classified risk disease over 5 years:
    - may provide a small reduction in all-cause mortality (low certainty of evidence [COE])
    - may make little to no difference on metastatic disease (low COE).
- External beam radiation therapy (EBRT) plus ADT versus EBRT alone in men with predominantly intermediate or high-risk disease:
    - Probably results in a small reduction in overall mortality over 6 to 9 years (moderate COE)
    - May result in a small reduction in prostate cancer specific mortality over 7 to 9 years (low COE)
    - May result in a small reduction in metastasis over 5 to 10 years (low COE)
    - May result in a moderate increase in sexual impairment over 7 years (low COE)
    - Appears to vary by patient comorbidities for overall mortality.
- EBRT plus neoadjuvant and concurrent ADT versus EBRT plus concurrent and adjuvant ADT in men with predominantly intermediate-risk disease:
    - May result in little to no difference in overall mortality over 12 years (low COE)
    - May result in little to no difference in prostate cancer specific mortality over 12 years (low COE)
    - May result in little to no difference in late genitourinary toxicity grade ≥3 over 3 years (low COE).
- Conventionally fractionated EBRT versus ultra-hypofractionated EBRT in men with predominantly intermediate risk disease:
    - Probably results in little to no difference in overall mortality over 5 years (moderate COE)
    - May result in little to no difference in prostate cancer specific mortality over 5 years (low COE)
    - May result in little to no difference in metastasis over 5 years (low COE)
    - May result in a small reduction in urinary toxicity grade ≥2 at 1 year, but little to no difference at 2 years (low COE)
    - May result in little to no difference in bowel toxicity grade ≥2 at 2 years (low COE)

We identified 12 randomized controlled trials (RCTs) and 18 observational studies comparing EBRT to other therapies or different types of EBRT.[24, 27, 42, 43, 45, 52, 54-84] Among the RCTs, one compared 3D-CRT versus intensity-modulated radiation therapy (IMRT).[70] One RCT compared 3D-CRT and ADT versus 3D-CRT and ADT plus low-dose-rate (LDR) prostate brachytherapy boost.[61, 64, 65] Four RCTs (6 publications) compared EBRT plus ADT versus EBRT alone.[69, 74, 76, 78-80] One RCT compared EBRT plus ADT versus ADT alone.[75] Two RCTs

compared ultra-hypofractionated EBRT versus standard fractionations.[68, 82] One RCT compared EBRT plus neoadjuvant and concurrent ADT versus EBRT plus concurrent and adjuvant ADT.[81] Three of the aforementioned RCTs were rated high risk of bias (ROB) and therefore not analyzed.[68, 69, 75] Two RCTs involving EBRT are described in other sections of the report. Serious or critical ROB precluded the inclusion of most non-RCTs in the analysis.

ROB assessments, population characteristics of the analyzed studies, outcomes data, and detailed GRADE rating tables are in Appendix H. Summary of Findings appears in Table 5.

Information about AS versus EBRT plus ADT can be found in Chapter 5. Information about RP versus EBRT plus ADT and RP plus ADT versus EBRT plus high-dose brachytherapy plus ADT can be found in Chapter 7.

There were several comparisons of radiation therapy to other therapies addressed in the 2016 evidence report commissioned by the American Urological Association (AUA) in which we did not identify any additional studies that met our analysis criteria published after this report.[5] A list of these comparisons can be found in Appendix J. The 2016 evidence report and appendices contain detailed results, strength of evidence, and evidence tables for these comparisons. Table 2 summarizes major findings of EBRT versus other comparisons.

3D-Conformal Radiation Therapy and Androgen Deprivation Therapy Versus 3D-Conformal Radiation Therapy and Androgen Deprivation Therapy Plus Low-Dose-Rate Prostate Brachytherapy

The Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiation Therapy (ASCENDE-RT) Trial (n=398) compared 3D-CRT and ADT with 3D-CRT and ADT plus low-dose-rate prostate brachytherapy (LDR-PB) boost.[61, 64, 65] The trial compared 46 Gray of dose-escalated EBRT delivered in 23 fractions plus an additional 32 Gray/16 fractions 3-dimensional conformal boost versus the same 46 Gray of EBRT plus a low-dose-rate brachytherapy boost using Iodine-125. Approximately two-thirds of patients had high-risk disease; the remainder had intermediate risk disease as per NCCN risk categories. Median followup was 6.5 years. Both arms received 12 months of neoadjuvant ADT initiated 8 months prior to pelvic irradiation. At baseline mean age was 68 years. Race was not reported.

At five years, 3D-CRT and ADT with LDR-PB boost may result in a small reduction in overall mortality versus 3D-CRT and ADT (low COE) (Table 5). 3D-CRT and ADT with LDR-PB boost may result in little to no difference in metastatic disease compared to 3D-CRT and ADT (low COE), while effects on prostate cancer specific mortality were very uncertain (insufficient COE). These outcomes were also reported at 7- and 9-year followup, but groups were not statistically compared or reported in enough detail for us to evaluate.

Evidence was very uncertain about the effect of 3D-CRT plus ADT with or without LDR-PB on urinary incontinence or erectile function (both insufficient COE) after 5 years.

Quality of life (QOL) not extracted due to high ROB of the reporting study.[64]

3D-Conformal Radiation Therapy Versus Intensity-Modified Radiation Therapy

One RCT (n=215) compared 3D-CRT with 70 Gray delivered in 25 fractions versus the same target dose and fractions of IMRT. Followup was over 3 years[70] Mean age was 72 years and 79 percent had clinical stage T1a-T2a tumors. Approximately half of patients had low-risk prostate cancer based on NCCN risk groups, a third had high-risk, and the remainder had intermediate risk disease. Patients with intermediate and high-risk disease received 6 and 24 months of systematic androgen deprivation therapy, respectively. Race was not reported. The only eligible outcome reported was QOL based on the EORTC QLQ-PR25. At 1 year, QOL scores were statistically worse with 3D-CRT versus IMRT for urinary symptoms, bowel symptoms, and treatment-related symptoms, though the clinical significance of these differences is unclear. Neither sexual function nor activity differed between groups. At 3 years, groups did not differ in any QOL domain.

Brachytherapy With External Beam Radiation Therapy Versus Brachytherapy

No randomized trial evidence informed this question. One observational study used propensity score matching to retrospectively analyze a subset of the National Cancer Database (n=5,858).[55] EBRT types were not specified, but EBRT doses ranged from 40 to 50.4 Gy in 1.8-2.0 Gy fractionations. Brachytherapy doses were not reported. In the brachytherapy group, 34.3% of patients received ADT and 48.4% in the combination therapy group received ADT. The duration of ADT was not reported. All patients had intermediate-risk disease per NCCN risk categories. Mean age was 69 years, 61 percent had clinical stage T1, and 83 percent were white. ROB was medium for one analysis which was propensity score matched (overall survival at 7 years). The evidence was very uncertain about the effect of brachytherapy with EBRT on overall survival versus brachytherapy alone (insufficient COE). No effect modifiers were reported for the propensity-score-matched analysis.

Intensity-Modified Radiation Therapy Versus Stereotactic Beam Radiation Therapy

No randomized trial evidence evaluated these interventions, but we identified a propensity-score-matched observational study that retrospectively analyzed the National Cancer Database (n=5,430).[63] and compared overall survival between IMRT versus stereotactic body radiation therapy (SBRT). Subjects were excluded if they received more or less than 72-86.4 Gy IMRT or 35-50 Gy SBRT. Mean age was 69; 87 percent were white. Most men had T1 tumor (80%), followed by T2 (19%). The majority had a prostate specific antigen (PSA) level <10 (82%) and a Gleason score of 6 (56%) or 7 (38%). Approximately 8% had a PSA level >20 and 5% and a Gleason score between 8 and 10. The only outcome reported was overall survival at 8 years. The evidence was very uncertain about the effect of IMRT on overall survival versus SBRT (insufficient COE).

Radiation Therapy Versus Androgen Deprivation Therapy

We identified no RCTs and two references of one non-RCT that evaluated radiation therapy (either EBRT and/or brachytherapy) versus ADT.[24, 27] The non-RCT (Hormonal therapy, Active

Surveillance, Radiation, Operation, Watchful Waiting Study [HAROW] study) was rated high ROB based on the ROBINS-I tool. The previous 2014 and 2016 systematic reviews included no RCTs and three non-RCTs for this comparison.[85-87] All three non-RCTs were previously rated low quality.

External Beam Radiation Therapy Plus Androgen Deprivation Therapy Versus External Beam Radiation Therapy

Seven RCTs compared EBRT plus ADT versus EBRT alone (four RCTs in past reviews and three RCTs newly identified).[69, 74, 76, 78 88-90 91, 92] Among the seven total trials, one was rated high ROB.[69] The analysis focuses on the remaining six. In one trial, the EBRT examined was IMRT,[76] two trials predominantly used three-dimensional conformal radiation therapy (3D-CRT),[74, 91] and two trials did not specify EBRT type.[88, 89] The sixth trial allowed different EBRT techniques to be used across trial centers.[90] The ADT in four trials consisted of an antiandrogen (flutamide or bicalutamide) with a luteinizing hormone-releasing hormone (LHRH) agonist (goserelin or leuprolide)[74, 88, 89, 91] and two trials used antiandrogen monotherapy with bicalutamide.[76, 90] In five trials, the duration of ADT ranged from 3 to 6 months. The sixth administered ADT for 2 years or until disease progression (maximum 5 years).[90] Most participants had intermediate-risk disease, high-risk was the next common, and low-risk was least common (defined variably across trials). Tumor stage varied across trials with four only including T1-T2 patients[74, 76, 89, 92] and two also enrolling patients with higher tumor stages. Patients were eligible for two trials in part by Gleason ≥7 and a third Gleason 6-8 (three trials specified Gleason in eligibility criteria).[74, 76, 92]The median PSA at baseline ranged from 7.6 ng/mL to 16.4 (five trials reporting).[74, 76, 88, 90, 92] At baseline, mean/median age ranged from 67 to 73 years (all six trials reporting). Only two trials reported race, and most participants were white.[89, 90] The longest mean/median followups ranged from 5.4 to 18.2 years. We also identified one non-RCT[93] that reported overall mortality/survival. The 2016 systemic review also included two non-RCTs[85, 94] that were previously rated low quality.

After 5.9 to 9.1 years, pooled analysis showed EBRT plus ADT versus EBRT alone probably results in a small reduction in overall mortality (moderate COE).[74, 76, 88, 89, 91] The pooled analysis had minimal heterogeneity (relative effect: I^2=0%; absolute effect: I^2=20%). When stratified by type of EBRT, combination therapy reduced overall mortality with a magnitude ranging from small to large based on two trials of predominantly 3D-CRT plus ADT versus predominantly 3D-CRT alone reporting at 7.2 to 7.6 years (risk difference [RD] -3.5% and RD -12.9%, respectively).[74, 91] Mortality reduction persisted at 16.6 years with combination therapy in one 3D-CRT trial that reported longer followup (RD -2.4%).[78] In contrast, a single trial reported a small increase in overall mortality for IMRT plus ADT versus IMRT alone at 9.1 years (RD 4.6%).[76] Pooled analysis showed EBRT plus ADT versus EBRT alone may result in a small reduction in prostate cancer specific mortality after 7.2 to 9.1 years (low COE).[74, 89, 91] The pooled analysis had minimal to moderate heterogeneity (relative effect: I^2=0%; absolute effect: I^2=55%). In the predominant 3D-CRT trials, one found a moderate reduction in prostate cancer mortality with combination therapy at median followup of 7.6 years (RD -9.5%), with a reduction remaining at 16.6 years (RD -16.2%),[78] while another reported little to no difference between predominantly 3D-CRT plus ADT versus predominantly 3D-CRT alone at median follow up of 7.2 years (RD -1.7%).[74] The IMRT trial did not report prostate cancer mortality.

After 5 to 10 years, pooled analysis showed EBRT plus ADT versus EBRT alone may result in a small reduction in metastasis (low COE).[74, 88-90]. A trial that predominantly used 3D-

CRT also reported a small magnitude reduction with combination therapy (RD -3.2%).[74] For IMRT, distant metastasis was only reported among patients who experienced biochemical relapse and occurred in 51 percent treated with IMRT plus ADT and 68.6 percent with IMRT.[76]

From two trials reporting quality of life, there was generally little to no difference between groups especially at longer followup times, though the results varied by specific scales. McPartlin et al. reported "no marked effect" on the European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire for EBRT plus ADT versus EBRT alone. However, no data were reported.[76] A second trial reported little to no difference between treatment groups in mean change on the global health status/quality of life scale of the EORTC quality of life questionnaire at 1 and 3 years.[74] EBRT plus ADT versus EBRT alone resulted in significant impairment at 1 year in sexual functioning and sexual activity subscales of the EORTC questionnaire, but by three years, groups differed little to not at all on sexual functioning and sexual activity scales. However, also at 3 years, statistically significant impairment remained on the hormonal symptoms scale for EBRT plus ADT versus EBRT alone.

Sexual function may be worse with EBRT plus ADT versus EBRT alone (reported differently across trials). EBRT plus ADT versus EBRT alone may result in a moderate increase in severe impairment in sexual function, based on toxicity scores measured from 6 months until end of followup (low COE).[74] From a second trial, the evidence was insufficient on the effect of EBRT plus ADT versus EBRT alone on impotence grades 2 to 4 (insufficient COE).[92] Evidence was insufficient for adverse effects of EBRT plus ADT versus EBRT alone on urinary incontinence (stress) grades 2 to 4 and rectal bleeding (insufficient COE).[92] One trial also reported that fewer patients who received EBRT plus ADT versus EBRT alone at 1 year were "always or almost always able to have an erection" assessed by the sexual adjustment questionnaire.[89] One trial reported little to no difference between groups in hematuria grades 2 to 4, diarrhea, and "complete urinary incontinence".[92] Two trials reported a small increase in genitourinary late toxicity for EBRT plus ADT versus RT (RD 2.2% for grades 3 to 4; RD 3.0% for grades 2 to 3).[74, 76] One trial reported a small decrease in gastrointestinal late toxicity grades 2 to 3 with combination therapy (RD -2.4%).[76]

Variation in Outcomes by Participant or Tumor Characteristics

A *post hoc* analysis by D'Amico and colleagues suggested that the benefit of EBRT plus ADT versus EBRT alone in D'Amico classified intermediate risk disease on mortality may only be in men with no or minimal comorbidity (mortality interaction test, p<.001 at 7.6 years and p=.01 at 16.6 years).[78, 91] While the effect modification on prostate cancer mortality appeared similar, the eligible references reported no test for interaction. Results from a second RCT reporting a *post hoc* analysis showed possible effect modification by tumor risk level on prostate cancer mortality at 9.1 years (interaction test, p=.08).[89] There were moderate reductions in men with intermediate and high-risk disease with combination treatment versus EBRT alone, but little to no difference in low-risk men. The same RCT reported that the effect on overall survival due to EBRT plus ADT versus EBRT alone did not significantly vary by tumor risk level (interaction test, p=.71), between white and black men (interaction test, p=0.79) or among men aged ≤70 years and >70 years (interaction test, p=0.47). Only the race subgroup analysis was pre-specified.

External Beam Radiation Therapy Plus Androgen Deprivation Therapy Versus Androgen Deprivation Therapy

We identified one publication of the Scandinavian Prostate Cancer Group-7 (SPCG-7).[75] The 2016 systematic review included an earlier followup publication of SPCG-7.[95] That trial randomized mostly men with high-risk disease to total androgen blockade with EBRT versus without EBRT. Based on the prior report, SPCG-7 showed a reduction in 10-year prostate cancer mortality with EBRT plus ADT versus ADT alone in T1b-T2 patients.[95] At median followup of 13.6 years, there was a suggested benefit with combination treatment on prostate-cancer mortality in the T1-T2 patients and no difference on overall mortality.[75] We did not extract the data or rate the COE because the previous report rated the trial as low quality. We identified one non-RCT for this comparison.[73] It was rated serious ROB based on the ROBINS-I tool. The 2016 systematic review included one non-RCT.[85] They rated it low quality.

External Beam Radiation Therapy Plus Neoadjuvant and Concurrent Androgen Deprivation Therapy Versus External Beam Radiation Therapy Plus Concurrent and Adjuvant Androgen Deprivation Therapy

One RCT compared EBRT plus neoadjuvant and concurrent ADT versus EBRT plus concurrent and adjuvant ADT and reported mortality, metastases, and harms.[81] The EBRT approach was image-guided 3D-CRT over 7.5 weeks. Participants assigned to neoadjuvant and concurrent ADT received 6 months ADT starting 4 months before EBRT. Patients in the concurrent and adjuvant ADT treatment group received 6 months ADT starting simultaneously with EBRT. The ADT consisted of an oral antiandrogen (e.g. bicalutamide) and goserelin. Participants were required to have a Gleason score ≤7, clinical tumor stage of T1b to T3a, and serum PSA <30 ng/mL. Patients were excluded if they had low-risk disease (Gleason score ≤6, T1-T2a, and PSA ≤10 ng/mL) or had radiologic evidence of nodal or distant metastasis. At baseline, 95% of men had intermediate risk disease and mean serum PSA was 10.3 ng/mL. Mean age at baseline was 69 years. The trial was conducted at two institutions in Canada and was rated medium risk of bias. We also identified one non-RCT that compared EBRT plus neoadjuvant ADT versus EBRT plus adjuvant ADT.[77] The non-RCT was rated serious ROB. The prior 2014 and 2016 systematic reviews did not identify any studies addressing this comparison.

At a median 12.2 years followup, there may be little to no difference in all-cause mortality (34.9% vs. 33.2% [low COE]). Seven deaths in each treatment group were attributable to prostate cancer. There may be little to no difference in prostate cancer mortality (low COE). The evidence is very uncertain whether metastasis differs for EBRT plus neoadjuvant and concurrent ADT versus EBRT plus concurrent and adjuvant ADT.

Regarding harms, there may be little to no difference in late genitourinary toxicity grade 3 or higher after 3 years (low COE). Lastly, the RCT reported no difference in late gastrointestinal toxicity grade 3 or higher after 3 years (2.5% vs. 3.9%).

External Beam Radiation Therapy Versus Brachytherapy

No randomized trial evidence informed this question. One observational study used propensity score matching to retrospectively analyze data from a multifacility health care system

(n=684).[83] The EBRT patients (n=574) received 3D-CRT with a median dose of 75.3 Gray (range 73.5 to 77.1) over 8.5 weeks. Brachytherapy (n=110) was prescribed as Iodine-125 radioactive seeds with a minimum peripheral dose of 145 Gray. Neoadjuvant ADT (Leuprolide) was administered for a median of 6 months in 59% of the EBRT patients and a median of 4 months in 13% of the brachytherapy patients. Patients in the brachytherapy group were younger compared with the EBRT group with median ages of 65 versus 71, respectively. Most patients had clinical stage T1c (69%). All patients had a Gleason score of 6 (30%) or 7 (70%), mostly 3+4 (48% of all patients). Nearly half were white (49%) followed by black race (25%). ROB was medium. Over a median followup of 10 years, the evidence was uncertain about the effect of EBRT on overall, prostate cancer-specific, and metastases-free survival versus brachytherapy (insufficient COE). Observed deaths and metastases were not reported over the 10-year followup period. No effect modifiers were reported for the propensity-score-matched analysis.

Conventionally Fractionated External Beam Radiation Therapy Versus Ultrahypofractionated External Beam Radiation

Two RCTs compared conventionally fractionated EBRT versus ultra-hypofractionated EBRT.[68, 82] One RCT was rated high risk of bias[68] and hereafter, our analysis only focuses on the second trial.[82] In the trial we analyzed, the EBRT approach was 3D-CRT, volumetric-modulated arc therapy (VMAT), or IMRT (80% of participants received 3D-CRT and 20% VMAT/IMRT). Patients assigned to conventionally fractioned EBRT received 78.0 Gy in 39 fractions 5 days per week for 8 weeks. Patients assigned ultra-hypofractionated EBRT received 42.7 Gy in 7 fractions 3 days per week for 2.5 weeks. No ADT was permitted. At baseline, 89% of men had intermediate risk disease and 11% had high risk. The median PSA values were 8.6 ng/mL and 8.7 in the two arms. Most patients had Gleason score of 7 (76%). The median ages were 69 years and 68 in the two arms. The trial was conducted in Sweden and Denmark. The prior 2016 systematic review did not identify any studies addressing this comparison.

At a median 5-year followup, there is probably little to no difference in all-cause mortality between conventionally fractionated EBRT and ultra-hypofractionated EBRT (7.3% vs. 7.8% [moderate COE]). There may be little to no difference in prostate cancer specific mortality (1.4% vs. 1.9%) and metastasis (low COE).

There was generally little to no difference in harms between conventionally fractionated EBRT and ultra-hypofractionated EBRT, except in urinary toxicity at 1-year followup. Conventionally fractionated EBRT may result in a small reduction in physician-evaluated urinary toxicity grade ≥2 at 1 year, but little to no difference at 2 years versus ultra-hypofractionated EBRT (low COE). There may be little to no difference in physician-evaluated bowel toxicity grade ≥2 at 2 years between treatment groups (low COE). The trial also reported patient-reported urinary and bowel problems with results in line with physician-recorded toxicity. The evidence is very uncertain about the effect of conventionally fractionated EBRT on erectile function versus ultra-hypofractionated EBRT (insufficient COE). Harms reporting from longer-term followup, had substantial missing data and was considered to be at a high ROB.

Table 5. Certainty of evidence: external beam radiation therapy

Comparison	Outcome № of Participants (studies)	Relative Effect (95% CI)	Anticipated Absolute Effects EBRT	Anticipated Absolute Effects Comparator	Anticipated Absolute Effects Difference (95% CI)	Certainty of Evidence	What Happens
3D-CRT and ADT vs. 3D-CRT and ADT with LDR-PB boost[61, 64, 65]	Mortality 5-year followup 1 RCT study (n=398)	RR 1.25 (0.81 to 1.94)	18.9% (38/200)	15.2% (30/198)	3.8% (-3.5 to 11.2)	⊕⊕◯◯ LOW [a, b]	3D-CRT and ADT may result in a small increase in mortality versus 3D-CRT and ADT with LDR-PB boost in higher risk disease
	Prostate-specific mortality 5-year followup 1 RCT study (n=398)	RR 1.56 (0.62 to 3.93)	5.5% (11/200)	3.5% (7/198)	2.0% (-2.1 to 6.0)	⊕◯◯◯ INSUFFICIENT [a, c]	The evidence is very uncertain about the effect of 3D-CRT and ADT with LDR-PB boost on prostate-specific mortality versus 3D-CRT and ADT in higher risk disease
	Metastatic disease 5-year followup 1 RCT study (n=398)	RR 1.05 (0.56 to 1.97)	9.0% (18/200)	8.6% (17/198)	0.4% (-5.1 to 6.0)	⊕⊕◯◯ LOW [a, b]	3D-CRT and ADT with LDR-PB boost may result in little to no difference in metastatic disease versus 3D-CRT and ADT in higher risk disease
	Urinary incontinence 5-year followup 1 RCT study (n=383)	not estimable	-	-	-	⊕◯◯◯ INSUFFICIENT [a, d]	The evidence is very uncertain about the effect of 3D-CRT and ADT with LDR-PB boost on urinary incontinence versus 3D-CRT and ADT
	Erectile function 5-year followup 1 RCT study (n=383)	not estimable	-	-	-	⊕◯◯◯ INSUFFICIENT [a, c, d]	The evidence is very uncertain about the effect of 3D-CRT and ADT with LDR-PB boost on erectile function versus 3D-CRT and ADT
Brachytherapy + EBRT vs. Brachytherapy[55]	Overall mortality 7-year followup 1 observational study (n=5858)	not estimable	-	-	-	⊕◯◯◯ INSUFFICIENT [a, d]	The evidence is very uncertain about the effect of brachytherapy with EBRT on overall survival versus brachytherapy alone
IMRT vs. SBRT[63]	Overall mortality 9-year followup 1 observational study (n=5430)	not estimable	-	-	-	⊕◯◯◯ INSUFFICIENT [a, c, d]	The evidence is very uncertain about the effect of IMRT on overall survival versus SBRT

Comparison	Outcome № of Participants (studies)	Relative Effect (95% CI)	Anticipated Absolute Effects EBRT	Anticipated Absolute Effects Comparator	Anticipated Absolute Effects Difference (95% CI)	Certainty of Evidence	What Happens
EBRT plus ADT versus EBRT[74, 76, 88-92]	Overall mortality-5.9 to 9.1 years 5 RCTs (n=4047)	RR 0.86 (0.69 to 1.06)	587/2150 (27.3%)	615/1897 (32.4%)	-3.7% (-9.8 to 2.4)	⊕⊕⊕◯ MODERATE [b]	EBRT plus ADT probably results in a small reduction in overall mortality versus EBRT in higher risk disease
	Prostate cancer mortality-7.2 to 9.1 years 3 RCTs (n=3004)	Peto OR 0.51 (0.37 to 0.70)	53/1499 (3.53%)	104/1505 (6.9%)	-3.4% (-4.95 to -1.8)	⊕⊕◯◯ LOW [a, b]	EBRT and ADT may result in a small reduction in prostate cancer mortality versus EBRT in higher risk disease
	Metastasis-5 to 10 years 4 RCTs (n=4664)	RR 0.83 (0.71 to 0.97)	284/2461 (11.5%)	289/2203 (13.1%)	-2.3% (-4.1 to -0.4)	⊕⊕◯◯ LOW [a, b]	EBRT and ADT may result in a small reduction in metastasis versus EBRT in higher risk disease
	Sexual function: severe impairment based on late toxicity scores-measured from six months until end of followup (7.2 years) 1 RCT (n=813)	RR 1.40 (1.08 to 1.80)	110/406 (27.0%)	79/407 (19.4%)	7.7% (1.9 to 13.5)	⊕⊕◯◯ LOW [a, b]	EBRT and ADT may result in a moderate increase in severe impairment in sexual function versus EBRT in higher risk disease
	Sexual function: impotence grade 2-4-4.5 years 1 RCT (n=201)	RR 1.20 (0.79 to 1.84)	32/98 (32.7%)	28/103 (27.2%)	5.5% (-7.2% to 18.1%)	⊕◯◯◯ INSUFFICIENT [a, c]	The evidence is very uncertain about the effect of EBRT plus ADT on impotence grade 2-4 versus EBRT alone
	Urinary incontinence (stress) grades 2-4-4.5 years 1 RCT (n=201)	RR 0.90 (0.31 to 2.59)	6/98 (6.1%)	7/103 (6.8%)	-0.7% (-7.5 to 6.1)	⊕◯◯◯ INSUFFICIENT [a, c]	The evidence is very uncertain about the effect of EBRT plus ADT on urinary incontinence versus EBRT alone
	Rectal bleeding grades 2-4-4.5 years 1 RCT (n=201)	RR 1.00 (0.57 to 1.75)	19/98 (19.4%)	20/103 (19.4%)	0.0% (-11.0 to 10.9)	⊕◯◯◯ INSUFFICIENT [a, c]	The evidence is very uncertain about the effect of EBRT plus ADT on rectal bleeding versus EBRT alone

Comparison	Outcome № of Participants (studies)	Relative Effect (95% CI)	Anticipated Absolute Effects EBRT	Anticipated Absolute Effects Comparator	Anticipated Absolute Effects Difference (95% CI)	Certainty of Evidence	What Happens
EBRT plus neoadjuvant and concurrent ADT vs. EBRT plus concurrent and adjuvant ADT[81]	Overall mortality-12.2 years 1 RCT (n=432)	RR 1.05 (0.81 to 1.37)	75/215 (34.9%)	72/217 (33.2%)	1.7% (-7.2% to 10.6%)	⨁⨁◯◯ LOW [c]	EBRT plus neoadjuvant and concurrent ADT may result in little to no difference in overall mortality versus EBRT plus concurrent and adjuvant ADT
	Prostate cancer mortality-12.2 years 1 RCT (n=432)	Peto OR 1.01 (0.35 to 2.93)	7/215 (3.3%)	7/217 (3.2%)	0% (-3.3% to 3.4%)	⨁⨁◯◯ LOW [a, b]	EBRT plus neoadjuvant and concurrent ADT may result in little to no difference in prostate cancer mortality versus EBRT plus concurrent and adjuvant ADT
	Metastasis distant progression-12.2 years 1 RCT (n=432)	Peto OR 1.36 (0.57 to 3.27)	12/215 (5.6%)	9/217 (4.1%)	1.4% (-2.6% to 5.5%)	⨁◯◯◯ INSUFFICIENT [a, c]	The evidence is very uncertain about the effect of EBRT plus neoadjuvant and concurrent ADT on metastasis versus EBRT plus concurrent and adjuvant ADT
	Late genitourinary toxicity grade ≥3-3 years 1 RCT (428)	Peto OR 1.01 (0.32 to 3.18)	6/213 (2.8%)	6/215 (2.8%)	0% (-3.1% to 3.2%)	⨁⨁◯◯ LOW [a, b]	EBRT plus neoadjuvant and concurrent ADT may result in little to no difference in late genitourinary toxicity versus EBRT plus concurrent and adjuvant ADT
EBRT vs. Brachytherapy[83]	Overall survival Median 10 years 1 observational study (n=684)	not estimable	Propensity score adjusted probability 75.5% (CI 71.8 to 79.4)	Propensity score adjusted probability 78.3% (CI 70.1 to 87.4)	~ -2.8% (not estimable)	⨁◯◯◯ INSUFFICIENT [e, f]	The evidence is uncertain about the effect of EBRT on overall survival versus brachytherapy
	Prostate cancer-specific survival Median 10 years 1 observational study (n=684)	not estimable	Propensity score adjusted probability 96.2% (CI 94.3 to 98.1)	Propensity score adjusted probability 95.4% (CI 91.1 to 100)	~ 0.8% (not estimable)	⨁◯◯◯ INSUFFICIENT [e, f]	The evidence is uncertain about the effect of EBRT on prostate cancer-specific survival versus brachytherapy

Comparison	Outcome № of Participants (studies)	Relative Effect (95% CI)	Anticipated Absolute Effects EBRT	Anticipated Absolute Effects Comparator	Anticipated Absolute Effects Difference (95% CI)	Certainty of Evidence	What Happens
	Metastasis-free survival Median 10 years 1 observational study (n=684)	not estimable	Propensity score adjusted probability 90.6% (CI 87.9 to 93.3)	Propensity score adjusted probability 94.1% (CI 89.5 to 98.9)	~ -3.5% (not estimable)	⨁◯◯◯ INSUFFICIENT [e, f]	The evidence is uncertain about the effect of EBRT on metastasis-free survival versus brachytherapy
Conventionally fractionated EBRT vs. ultra-hypofractionated EBRT[82]	Mortality-5 years 1 RCT (n=1180)	RR 0.93 (0.63 to 1.39)	7.3% (43/591)	7.8% (46/589)	-0.5% (-3.5 to 2.5)	⨁⨁⨁◯ MODERATE [b]	Conventionally fractionated EBRT probably results in little to no difference in all-cause mortality versus ultra-hypofractionated EBRT
	Prostate cancer mortality-5 years 1 RCT (n=1180)	Peto OR 0.72 (0.29 to 1.79)	1.4% (8/591)	1.9% (11/589)	-0.5% (-2.0 to 0.9)	⨁⨁◯◯ LOW [a, b]	Conventionally fractionated EBRT may result in little to no difference in prostate cancer mortality versus ultra-hypofractionated EBRT
	Metastasis-5 years 1 RCT (n=1180)	RR 1.02 (0.66 to 1.58)	6.6% (39/591)	6.5% (38/589)	0.1% (-2.7 to 3.0)	⨁⨁◯◯ LOW [a, b]	Conventionally fractionated EBRT may result in little to no difference in metastasis versus ultra-hypofractionated EBRT
	Urinary toxicity grade ≥2 based on RTOG morbidity scale-1 and 2 years 1 RCT (n=989 to 1057)	1 year RR 0.41 (0.22 to 0.76) 2 years RR 1.11 (0.66 to 1.87)	1 year 2.5% (13/529) 2 years 5.6% (28/497)	1 year 6.1% (32/528) 2 years 5.1% (25/492)	1 year -3.6% (-6.0 to -1.2) 2 years 0.6% (-2.3 to 3.4)	⨁⨁◯◯ LOW [a, b]	Conventionally fractionated EBRT may result in a small reduction in urinary toxicity at 1 year, but little to no difference at 2 years versus ultra-hypofractionated EBRT
	Bowel toxicity grade ≥2 based on RTOG morbidity scale-2 years 1 RCT (n=991)	Peto OR 1.77 (0.80 to 3.92)	3.2% (16/496)	1.8% (9/495)	1.4% (-0.5 to 3.4)	⨁⨁◯◯ LOW [a, b]	Conventionally fractionated EBRT may result in little to no difference in bowel toxicity versus ultra-hypofractionated EBRT

Comparison	Outcome № of Participants (studies)	Relative Effect (95% CI)	Anticipated Absolute Effects EBRT	Anticipated Absolute Effects Comparator	Anticipated Absolute Effects Difference (95% CI)	Certainty of Evidence	What Happens
	Erectile function-1 and 2 years 1 RCT (n=944 to 1001)	not estimable	NR	NR	Not significantly different (p=0.59-0.60)	⨁◯◯◯ INSUFFICIENT [a, c]	The evidence is very uncertain about the effect of conventionally fractionated EBRT on erectile function versus ultra-hypofractionated EBRT

Abbreviations: 3D-CRT =3-dimensional conformal radiation therapy; ADT = androgen deprivation therapy; CI = confidence interval; EBRT = external beam radiation therapy; IMRT = intensity modulated radiation therapy; LDR-PB = low dose rate prostate brachytherapy; NR = not reported; OR = odds ratio; RCT = randomized controlled trial; RR = relative risk; RTOG = Radiation Therapy Oncology Group; SBRT = stereotactic body radiation therapy

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Insufficient: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations
a. Rated down one level for risk of bias
b. Rated down one level imprecision
c. Rated down two levels for imprecision
d. Rated down for suspected publication bias
e. Rated down two levels for risk of bias
f. Rated down one level for imprecision (unable to estimate based on data presented)

Chapter 7. Whole Gland Therapies-Radical Prostatectomy

Key Messages

- Radical prostatectomy (RP) versus prostate specific antigen (PSA)-based active monitoring (AM) over 10 years showed:
  - Little to no difference in all-cause (moderate certainty of evidence [COE]) and prostate-cancer-specific mortality (low COE)
  - Small reduction in metastases (moderate COE)
  - Moderate increases in erectile dysfunction (ED) and urinary incontinence over 6 years (moderate COE)
  - Prostate cancer mortality may not vary by age, PSA, tumor stage or Gleason score
- RP versus external beam radiation therapy (EBRT) plus androgen deprivation therapy (ADT) over 10 years showed:
  - Little to no difference in all-cause (moderate COE) or prostate-cancer-specific mortality (low COE) or metastases (low COE).
  - Moderate increases in erectile dysfunction and urinary incontinence at 6-year followup (moderate COE).
  - Small reduction in fecal incontinence over 6 years (low COE)
  - Prostate cancer mortality may not vary by age, PSA, tumor stage or Gleason score
- RP plus ADT versus EBRT plus High-dose-rate Brachytherapy (BT) plus ADT over 2 years showed:
  - Small increase in erectile dysfunction (low COE).
- Laparoscopic RP versus robotic-assisted RP over 5 years showed:
  - Moderate increase in urinary incontinence and large increase in erectile dysfunction and (low COE).
  - Results did not vary by patient or tumor characteristics, but events were few.

We identified seven reports of four eligible randomized controlled trials (RCTs)[42-45, 84, 96, 97] and one non-RCT[98] that compared RP to other therapies. Serious or critical risk of bias (ROB) precluded the inclusion of eight non-RCTs in the analysis.[24, 27, 52, 99-103] Several comparisons were only evaluated in studies rated high ROB (see Appendix I). We identified six articles which were not analyzed due to the inclusion of articles with lower risk of bias of the same comparisons.[104-109]

ROB assessments, population characteristics of the analyzed studies, outcomes data, and detailed GRADE rating tables are in Appendix I. Summary of Findings appears in Table 6.

Information on watchful waiting versus RP can be found in Chapter 4.

There were several comparisons of RP to other therapies addressed in the 2016 evidence report commissioned by the American Urological Association (AUA) in which we did not identify any additional studies of low to moderate ROB published after this report.[5] A list of these comparisons can be found in Appendix J. The 2016 evidence report and appendices contain detailed results, strength of evidence, and evidence tables for these comparisons. Table 2 summarizes major findings of whole gland therapies versus other comparisons.

Radical Prostatectomy Versus Active Monitoring

Four reports of one eligible RCT (ProtecT) compared PSA-based AM, to RP or EBRT plus ADT in men with PSA-screen detected clinically localized prostate cancer (CLPC) and reported results for survival, metastases, quality of life, or harms.[42-45] Men with T1c-T2 CLPC were randomized to AM (n=545), RP (n=553) or radiation therapy (RT) (n=545). Eighty-eight percent of men allocated to AM, 71 percent to RP and 74 percent to EBRT received the assigned treatment within 9 months after randomization. Most men had a Gleason score of 6 (77%), followed by scores of 7 (21%) and 8-10 (2%). Primary RP approach was open retropubic radical. For participants assigned to AM, serum PSA levels were measured every 3 months in the first year and every 6 to 12 months thereafter. Surveillance prostate biopsies were permitted but not performed on a standard protocol. Increases of 50 percent or greater initiated review. Following review, participants could continue monitoring or further testing or receive radical or palliative interventions as needed. At the 10-year followup, 53 percent (n=291) of men assigned AM had received radical treatment (surgery 49%, per-protocol RT 33%, 8% BT, 9% non-protocol RT, 1% high intensity focused ultrasound [HIFU]). Median age was 62 years and the majority were white (98%).[44] ProtecT was conducted in the UK, non-industry funded, and rated low risk of bias. Prior reviews included no randomized trials directly comparing RP with AM.

At 10-year followup there probably was little to no difference in all-cause (moderate COE) and prostate-cancer-specific mortality (low COE) for RP versus AM.[43] Few deaths were attributable to prostate cancer; five and eight in the RP and AM groups, respectively.

There was probably was a small reduction in the development of metastases with RP compared with AM over 10 years (moderate COE).[43] At 12- and 72-month**s**, AM and surgery did not differ in the Medical Outcomes Study 12-Item Short-Form General Health Survey (SF-12) physical and mental health subscales and the European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire–Core 30 module (EORTC QLQ-C30).[42]

Harms associated with urinary and sexual function were worse with RP than AM.[42] Incontinence (defined as any use of absorbent pads) at 12 and 72 months was reported for 26 percent and 17 percent of the participants in the RP group versus 4 percent and 8 percent for AM (moderate COE). Erectile dysfunction (defined as an erection not firm enough for intercourse) was also greater for RP versus AM at both followup periods. At 72 months, 83.5 percent allocated to RP reported ED versus 70 percent allocated to AM (moderate COE). There may be little to no difference for harms associated with bowel function for RP versus AM (low COE). At 12 months, fecal incontinence at least one time per week was reported by approximately 1 percent in both groups; long-term it was reported by 2 percent for RP versus 3 percent for AM.

Variation in Outcomes by Participant or Tumor Characteristics

Prespecified subgroup analyses found no differences between groups in prostate-cancer-specific mortality according to age, PSA level, Gleason score, or clinical stage.

Radical Prostatectomy Versus External Beam Radiation Therapy Plus Androgen Deprivation Therapy

Four reports of one eligible RCT (ProtecT) compared PSA-based AM, RP, and EBRT plus ADT and reported results for survival, metastases, quality of life, or harms;[42-45] Men with PSA screen detected T1c-T2 of any histologic grade CLPC were randomized to AM (n=545), RP (n=553) or EBRT plus ADT (n=545). Most men had a Gleason score of 6 (77%), followed by

scores of 7 (21%) and 8-10 (2%). The primary RP approach was open retropubic radical. Participants assigned EBRT plus ADT received 74 Gy in 37 fractions with neoadjuvant ADT given 3 to 6 months before and concomitantly.[44] Median age was 62 years, nearly all were white (98%).[44] ProtecT was conducted in the UK, non-industry funded, and rated low risk of bias.

Prior reviews included no randomized trials that directly compared RP to EBRT alone or in combination with ADT and reported mortality or metastases outcomes with a followup longer than 5 years. The 2016 evidence report commissioned by the AUA identified one small RCT (n=97) deemed high risk of bias that reported no difference in deaths or measures of metastases between RP versus RT at 5 years.[5] The 2014 Agency for Healthcare Research and Quality (AHRQ) systematic review authors found low-strength evidence favoring RP versus RT for all-cause mortality and prostate-cancer–specific over followup periods ranging from 3 to 15 years, but this was based on nonrandomized studies of mostly high risk of bias.[4] The prior AHRQ review also concluded that, in general, urinary incontinence and erectile dysfunction were commonly reported adverse events among men who underwent RP, and gastrointestinal/genitourinary toxicity and erectile dysfunction were commonly reported harms for men who received RT.

The 10-year followup probably showed little to no difference in all-cause (moderate COE) and prostate-cancer-specific mortality (low COE) for RP versus EBRT plus ADT.[43] Few deaths were attributable to prostate cancer in the RP and RT groups, respectively.

The number of participants who developed metastases may not differ between RP and EBRT plus ADT over 10 years (low COE).[43]

At 12 and 72 months, incontinence (defined as any use of absorbent pads) was reported by 26 percent and 17 percent of participants in the RP group versus approximately 4 percent for RT at both followups (moderate COE). Erectile dysfunction (defined as an erection not firm enough for intercourse) was also greater for RP than EBRT plus ADT at both followup periods. At 72 months, erectile dysfunction was reported by 83.5 percent in the RP group versus 73 percent for RT (moderate COE). Harms associated with bowel function were generally worse with EBRT plus ADT versus RP. At 12 months, fecal incontinence at least once per week was reported for 4 percent in the EBRT plus ADT group and 0.8 percent for the RP group. At 72 months, fecal incontinence did not statistically differ between groups (low COE). Bloody stools half of the time or more were reported for nearly 6 percent of EBRT plus ADT participants versus one percent in the RP group (absolute risk difference [ARD] -5% [95% CI -7 to -2]).

Variation in Outcomes by Participant or Tumor Characteristics

Pre-specified subgroup analyses found no differences between groups in prostate-cancer-specific mortality when stratified by age, PSA level, Gleason score, or clinical stage, but the small number of events limits our interpretation of these findings.

Radical Prostatectomy Plus Androgen Deprivation Therapy Versus External Beam Radiation Therapy Plus High-Dose-Rate Brachytherapy Plus Androgen Deprivation Therapy

We identified one eligible small RCT conducted in Sweden that compared RP plus ADT to high-dose radiation (EBRT plus high dose rate brachytherapy [HDR-BT]) plus ADT and reported results for survival, quality of life, or harms through 10 years.[84] Men with clinically

localized/locally advanced T1b-T3a PC of any histologic grade and a PSA < 50 ng/mL were randomized to primarily nerve sparing RP (n=45) or EBRT plus HDR-BT (n=44). Participants assigned to EBRT received EBRT (25 x 2 Gy) plus HDR-BT (2 x 10 Gy). All patients were treated with neoadjuvant ADT that continued for six months. Median ages ranged from 64 to 66 years. T1 tumors were present in 40% and T2 in 37% of individuals though information was not provided to assess tumor risk status. The trial was originally designed to enroll 360 men but due to recruitment difficulties the study only included 89 and focused on outcomes other than mortality. The trial was non-industry funded and was rated moderate risk of bias.

Prior reviews included no randomized trials that directly compared RP with combined EBRT and HDR-BT. The 2016 evidence report commissioned by the AUA identified three observational studies deemed high risk of bias comparing RP to combination EBRT plus BT that did not report death or metastases outcomes.[5] One study reported a higher rate of urinary incontinence with RP and one study reported that the results for urinary, bowel, and sexual harms were inconclusive for this comparison.

Mortality outcomes were reported at 10-years. The evidence is uncertain whether all-cause and prostate-cancer-specific mortality differ for RP plus ADT versus EBRT plus HDR-BT plus ADT (insufficient COE). The number of participants who developed metastases was not reported. Versus EBRT plus HDR-BT plus ADT, there were no differences in the European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire C33 (EORTC QLQ-C33) with surgery plus ADT at 12- and 24-month followup periods. Harms associated with urinary, bowel, sexual function were reported at 12 and 24 months. Erectile dysfunction, defined as occurring "quite a bit" to "very much" may be slightly higher in the RP plus ADT group (Low COE). It is uncertain whether urinary or fecal incontinence differ for RP plus ADT versus EBRT plus HDR-BT plus ADT (insufficient COE).

Laparoscopic Radical Prostatectomy Versus Robotic-Assisted Radical Prostatectomy

We identified a publication[97] with longer (5-year) followup of a small RCT previously included in both the 2016 evidence report commissioned by the AUA[5] and the 2014 systematic review conducted by AHRQ.[4], that compared laparoscopic radical prostatectomy (LRP) to robotic-assisted radical prostatectomy (RARP) and reported results for quality of life and harms.[97] Men with T1-T2N0M0 PC were randomized to either LRP (n=60) or RARP (n=60). Half of the men had a Gleason score ranging from 2 to 6, 43% had a score of 7, and 7% had a score of 8 to 10. Nerve-sparing procedures were performed in all potent patients with a PSA <10 ng/ml, Gleason score <7, and a positive core (on the same side as the bundle preservation) <30%.[110] Extended lymph node dissections were indicated in men with a preoperative PSA >10 ng/ml, Gleason score ≥7b (4 + 3), and/or a lymph node involvement risk >5% according to Partin tables.[111] Lymph node dissection procedures were conducted for 13 men in each arm (22%). Mean age was 64 years. The trial was conducted in Italy, was non-industry funded, and rated moderate risk of bias. The earlier results indicated higher rates of recovered urinary continence and potency (among potent patients undergoing nerve-sparing techniques) with RARP versus LRP through 1 year of followup.[110] Neither of the previous reports included observational studies directly comparing LRP with RARP.

Authors did not report mortality and metastases outcomes. Participants allocated to LRP were less likely to rate their health status as excellent, very good, or good versus RARP, 86 percent compared with 100 percent, respectively (p=0.003). Harms associated with urinary,

bowel, and sexual function were reported at 12 and 60 months. At 60 months, erectile dysfunction (defined as the inability to achieve an erection sufficient for penetration) may be much higher with LRP versus RARP (low COE). Urinary incontinence, defined as use of any pads or used one safety pad per day, may be moderately higher in the LRP group versus RARP (low COE).

Robotic-Assisted Laparoscopic Radical Prostatectomy Versus Open Retropubic Radical Prostatectomy

We identified one eligible observational study, LAPPRO (n=2,545), that compared robotic-assisted laparoscopic radical prostatectomy (RALRP) to open retropubic radical prostatectomy (open RRP) and reported results for harms.[98] LAPRO recruited men with T1-T3 (T3 3%) PC who underwent RALRP (n=1,792) or open RRP (n=753). Median age was approximately 63 years. The trial was conducted in Sweden, non-industry funded, and rated moderate risk of bias.

One additional RCT among men with CLPC reported findings for urinary, sexual, and erectile function as well as quality of life. This study was excluded because authors did not provide information on tumor stage inclusion or baseline criteria.[112, 113]

Prior reviews included no randomized trials that directly compared RALRP with open RRP. A 2016 evidence report commissioned by the AUA identified four observational studies with mainly inconclusive findings.[5] The 2014 systematic review conducted by AHRQ indicated that RALRP versus RRP was the most common comparison.[4] However, most studies were assessed as high risk of bias and did not report long-term (≥5 years) results for mortality and metastases outcomes. Evidence was insufficient for all outcomes.

Among the subset of men who had preoperative erectile function (n=1702), recovery of erectile function was assessed at 12 and 24 months. At 24 months, more men in the RRP group were classified as having recovered erectile function (defined as being unable to achieve a stiff erection at any time or an erection stiff enough for intercourse at any time) compared with open RALP, 61 percent versus 49 percent (P≤.0014) However, we rated this evidence as insufficient because data were not presented in a useable manner (denominators for each group could not be calculated).

Variation in Outcomes by Participant or Tumor Characteristics

When stratified by D'Amico risk categories, rates for non-recovery of erectile dysfunction in men with low- to moderate-risk disease were comparable to the overall findings, but treatment groups differed little to none for men with high-risk disease (test for subgroup differences not reported).

Radical Prostatectomy Versus Androgen Deprivation Therapy

We identified no RCTs and two references of one non-RCT that evaluated RP versus ADT.[24, 27] The non-RCT (HAROW study) was rated serious ROB based on the ROBINS-I tool. The previous 2014 and 2016 systematic reviews included no RCTs and five non-RCTs for this comparison.[4, 5] All five non-RCTs were previously rated low quality.

Radical Prostatectomy Versus High-Intensity Focused Ultrasound

We identified one small RCT (Partial prostate Ablation versus Radical prosTatectomy [PART], n=82), that compared conventional open, laparoscopic, or robot-assisted laparoscopic radical prostatectomy (RP) to partial ablation using high-intensity focused ultrasound (HIFU) and reported results for harms.[96] PART aimed to assess the feasibility of conducting a similar RCT on a larger scale. PART recruited men with a Gleason score of 7 (3+4 or 4+3) or clinically staged ≤T2b disease from five United Kingdom healthcare centers. Men were randomized to RP (n=41) or HIFU (n=41) and followed for 12 months for harms outcomes. Median age was approximately 66 years. The trial was non-industry funded and rated moderate risk of bias.

Urinary incontinence, erectile dysfunction, and fecal incontinence were assessed at 12 months. Data were not presented in useable manner as only approximate percentages of men reporting each outcome were provided (nominators and denominators for each group could not be calculated). There was an increase in the need to use an absorbent pad at least once per day compared to baseline in the RP group. The percentage of men reporting erectile dysfunction and fecal incontinence was higher in the RP group compared to the HIFU group (insufficient COE).

Table 6. Certainty of evidence: radical prostatectomy

Comparison	Outcome № of Participants (studies)	Relative Effect (95% CI)	Absolute Effects RP	Absolute Effects Comparator	Absolute Effects Difference (95% CI)	Certainty of Evidence	What Happens
RP versus AM[42, 43]	All-cause mortality 10-year followup 1 RCT (n=1098)	RR 0.92 (0.65 to 1.30)	9.9% (55/553)	10.8% (59/545)	-0.9% (-4.5 to 2.7)	⊕⊕⊕◯ MODERATE [a]	RP probably results in little to no difference in all-cause mortality versus AM
	PC-specific mortality 10-year followup 1 RCT (n=1098)	Peto OR 0.62 (0.20 to 1.87)	0.9% (5/553)	1.5% (8/545)	-0.6% (-1.8 to 0.7)	⊕⊕◯◯ LOW [b]	RP may result in little to no difference in PC-specific mortality versus AM
	Metastases 10- year followup. 1 RCT (n=1098)	Peto OR 0.40 (0.22 to 0.72)	2.4% (13/553)	6.4% (33/545)	-4.0% (-6.1 to -1.3); NNT=25	⊕⊕⊕◯ MODERATE [a]	RP probably results in a small reduction in metastases versus AM
	Urinary incontinence (pad use) 72-month followup 1 RCT (n=908)	RR 2.07 (1.44 to 2.98)	17.4% (79/455)	8.4% (38/453)	9% (5 to 13); NNH=11	⊕⊕⊕◯ MODERATE [c]	RP probably results in a moderate increase in urinary incontinence versus AM
	Erectile dysfunction 72-month followup 1 RCT (n=913)	RR 1.19 (1.10 to 1.28)	83.5% (385/461)	70.4% (318/452)	13% (8 to 19); NNH=9	⊕⊕⊕◯ MODERATE [c]	RP probably results in a large increase in erectile dysfunction versus AM
	Fecal incontinence 72-month followup 1 RCT (n=930)	Peto OR 0.74 (0.31 to 1.75)	1.9% (9/468)	2.6% (12/462)	-0.7% (-2.6 to 1.2);	⊕⊕◯◯ LOW [a, c]	RP may result in little to no difference in fecal incontinence versus AM
RP versus EBRT plus ADT[42, 43]	All-cause mortality 10-year followup 1 RCT (n=1098)	RR 0.99 (0.69 to 1.04)	9.9% (55/553)	10.1% (55/545)	-0.1% (-3.7 to 3.7)	⊕⊕⊕◯ MODERATE [a]	RP probably results in little to no difference in all-cause mortality versus AM
	PC-specific mortality 10-year followup 1 RCT (n=1098)	Peto OR 1.23 (0.33 to 4.58)	0.9% (5/553)	0.7% (4/545)	0.2% (-0.9 to 1.2)	⊕⊕◯◯ LOW [b]	RP may result in little to no difference in PC-specific mortality versus EBRT plus ADT
	Metastases 10- year followup. 1 RCT (n=1098)	Peto OR 0.80 (0.38 to 1.67)	2.4% (13/553)	2.9% (16/545)	-0.6% (-2.5 to 1.3)	⊕⊕◯◯ LOW [b]	RP may result in little to no difference in metastases versus EBRT plus ADT

Comparison	Outcome № of Participants (studies)	Relative Effect (95% CI)	Absolute Effects RP	Absolute Effects Comparator	Absolute Effects Difference (95% CI)	Certainty of Evidence	What Happens
	Urinary incontinence (pad use) 72-month followup 1 RCT (n=907)	RR 4.90 (2.91 to 8.26)	17.4% (79/455)	3.5% (16/452)	14% (10 to 18); NNH=7	⊕⊕⊕◯ MODERATE [c]	RP probably results in a large increase in urinary incontinence versus EBRT plus ADT
	Erectile dysfunction 72-month followup 1 RCT (n=917)	RR 1.15 (1.07 to 1.23)	83.5% (385/461)	72.6% (331/456)	11% (6 to 16); NNH=9	⊕⊕⊕◯ MODERATE [c]	RP probably results in a moderate increase in erectile dysfunction versus EBRT plus ADT
	Fecal incontinence-72-month followup 1 RCT (n=933)	Peto OR 0.48 (0.22 to 1.01)	1.9% (9/468)	4.1% (19/465)	-2.2 (-4.4 to 0.02)	⊕⊕◯◯ LOW [a, c]	RP may result in a small reduction in fecal incontinence versus EBRT plus ADT
RP plus ADT versus EBRT plus HDR-BT plus ADT[84]	All-cause mortality-10-year followup 1 RCT (n=89)	RR 1.30 (0.61 to 2.78)	26.7% (12/45)	20.5% (9/44)	6.2% (-11.4 to 23.8)	⊕◯◯◯ INSUFFICIENT [a, b]	The evidence is very uncertain about the effect of RP plus ADT on all-cause mortality versus EBRT plus HDR- BT plus ADT
	PC-specific mortality 10-year followup 1 RCT (n=89)	Peto OR 2.89 (0.68 to 12.27)	13.3% (6/45)	4.5% (2/44)	8.8% (-2.9 to 20.5)	⊕◯◯◯ INSUFFICIENT [a, b]	The evidence is very uncertain about the effect of RP plus ADT on PC-specific mortality versus EBRT plus HDR- BT plus ADT
	Urinary incontinence (Grade 3-4*) 24-month followup 1 RCT (n=55)	Peto OR 1.70 (0.35 to 8.23)	16% (4/25)	10% (3/30)	6% (-11.9 to 23.9)	⊕◯◯◯ INSUFFICIENT [a, b]	The evidence is very uncertain about the effect of RP plus ADT on urinary incontinence versus EBRT plus HDR-BT plus ADT
	Erectile dysfunction (Grade 3-4*) 24-month followup 1 RCT (n=71)	RR 1.05 (0.87 to 1.25)	89% (33/37)	85% (29/34)	4% (-12 to 19)	⊕⊕◯◯ LOW [a, d]	RP plus ADT may result in a small increase of erectile dysfunction versus EBRT plus HDR- BT plus ADT
	Fecal incontinence (Grade 2*) 24-month followup 1 RCT (n=54)	Peto OR 0.32 (0.08 to 1.33)	8% (2/25)	24.1% (7/29)	-16.1% (-35 to 27)	⊕◯◯◯ INSUFFICIENT [a, b]	The evidence is very uncertain about the effect of RP plus ADT on fecal incontinence versus EBRT plus HDR-BT plus ADT

Comparison	Outcome № of Participants (studies)	Relative Effect (95% CI)	Absolute Effects RP	Absolute Effects Comparator	Absolute Effects Difference (95% CI)	Certainty of Evidence	What Happens
LRP versus RARP[97]	Urinary incontinence (pad use), 60-month followup 1 RCT (n=115)	Peto OR 3.96 (1.15 to 13.65)	15.5% (9/58)	3.5% (2/57)	12% (1.5 to 23)	⊕⊕◯◯ LOW [a, b]	LRP may result in a moderate increase in urinary incontinence versus RARP
	Erectile dysfunction (insufficient erections), 60-month followup 1 RCT (n=70)	RR 1.89 (0.98 to 3.65)	49% (17/35)	26% (9/35)	23% (1 to 45)	⊕⊕◯◯ LOW [a, b]	LRP may result in a large increase in erectile dysfunction versus RARP
RALRP versus Open RRP[98]	Erectile dysfunction (unrecovered erectile function), 24-month followup 1 Obs (n=1702)	Data not presented in usable manner	49%	61%	-12% (CI NA)	⊕◯◯◯ INSUFFICIENT [c, d]	The evidence is very uncertain about the effect of RALRP on erectile dysfunction versus open RRP
RP versus HIFU[96]	Urinary incontinence 12-month followup 1 RCT (n=82)	Data not presented in usable manner	58%	0%	-58% (CI NA)	⊕◯◯◯ INSUFFICIENT [c, d]	The evidence is very uncertain about the effect of RP on urinary incontinence versus HIFU
	Erectile dysfunction 12-month followup 1 RCT (n=82)	Data not presented in usable manner	50%	20%	-30% (CI NA)	⊕◯◯◯ INSUFFICIENT [c, d]	The evidence is very uncertain about the effect of RP on erectile dysfunction versus HIFU
	Fecal incontinence 12-month followup 1 RCT (n=82)	Data not presented in usable manner	22%	15%	-7% (CI NA)	⊕◯◯◯ INSUFFICIENT [c, d]	The evidence is very uncertain about the effect of RP on fecal incontinence versus HIFU

Abbreviations: ADT = androgen deprivation therapy; AM = active monitoring; CI = confidence interval; EBRT = external beam radiation therapy; HDR-BT = high dose rate brachytherapy; HIFU = high-intensity focused ultrasound; LRP = laparoscopic radical prostatectomy; n = number; NA = not available; NNH = number needed to harm; NNT = number needed to treat; Obs = observational study; OR = odds ratio; PC = prostate cancer; RALRP = robotic-assisted laparoscopic radical prostatectomy; RARP = robotic-assisted radical prostatectomy; RCT = randomized controlled trial; RP = radical prostatectomy; RR = relative risk; RRP = retropubic radical prostatectomy

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio

Comparison	Outcome № of Participants (studies)	Relative Effect (95% CI)	Absolute Effects RP	Absolute Effects Comparator	Absolute Effects Difference (95% CI)	Certainty of Evidence	What Happens

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Insufficient: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations
a. Rated down by one level for imprecision
b. Rated down by two levels for imprecision and sparse data.
c. Rated down by one level for risk of bias
d. Rated down one level for unknown precision

Chapter 8. Other Therapies

Androgen Deprivation Therapy

Information about active monitoring (AM) versus external beam radiation therapy (EBRT) plus androgen deprivation therapy (ADT) can be found in Chapter 5.

Information about the following comparisons can be found in Chapter 6:

- 3D-conformal radiation therapy (3D-CRT) and ADT versus 3D-CRT and ADT plus low-dose-rate brachytherapy (LDR-BT)
- EBRT plus ADT versus EBRT
- EBRT plus neoadjuvant and concurrent ADT versus EBRT plus concurrent and adjuvant ADT

Information about the following comparisons can be found in Chapter 7:

- Radical prostatectomy (RP) versus EBRT plus ADT
- RP plus ADT versus EBRT plus high-dose-rate brachytherapy plus ADT

Some comparisons of ADT to other therapies were only evaluated in studies rated high risk of bias (ROB) (e.g., ADT versus EBRT plus ADT [k=1 randomized controlled trial [RCT] and 1 non-RCT],[73, 75] ADT versus RP [k=1 non-RCT],[24, 27] ADT versus radiation therapy [either EBRT and/or brachytherapy][k=1 non-RCT],[24, 27] ADT versus AS [k=1 non-RCT],[24, 27] ADT versus watchful waiting [k=1 non-RCT]).[24, 27]

There were several comparisons of ADT to other therapies addressed in the 2016 evidence report commissioned by the American Urological Association (AUA in which we did not identify any additional studies that met our analysis criteria.[5] A list of these comparisons can be found in Appendix J.

The 2016 evidence report and appendices contains detailed results, strength of evidence, and evidence tables for these comparisons. Table 2 summarizes major findings of whole gland therapies versus other comparisons.

Focal Therapies—High-Intensity Focused Ultrasound

Information about radical prostatectomy versus high-intensity focused ultrasound (HIFU) can be found in Chapter 7.

HIFU versus HIFU plus ADT was addressed in the 2016 evidence report commissioned by the AUA.[5] The 2016 evidence report and appendices contains detailed results, strength of evidence, and evidence tables for this comparison.

Focal Therapies—Photodynamic Therapy

Information about active surveillance (AS) versus photodynamic therapy (PDT) can be found in Chapter 5.

The 2016 evidence report commissioned by the AUA did not report on any eligible comparisons of photodynamic therapy.[5]

Focal Therapies—Laser Ablation

Laser ablation versus RP was addressed in one non-RCT rated as critical ROB.[102]
The 2016 evidence report commissioned by the AUA did not report on any eligible comparisons of laser ablation.[5]

Whole Gland Therapies—Cryotherapy

No eligible studies of cryotherapy were identified.

There were several comparisons of cryotherapy to other therapies addressed in the 2016 evidence report commissioned by the AUA in which we did not identify any additional studies of low to moderate ROB published after this report.[5] A list of these comparisons can be found in Appendix J. The 2016 evidence report and appendices contains detailed results, strength of evidence, and evidence tables for these comparisons.

Whole Gland Therapies—Brachytherapy

Information about the following comparisons can be found in Chapter 6:

- 3D-CRT plus ADT versus 3D-CRT plus low-dose-rate brachytherapy plus ADT
- Brachytherapy with EBRT versus brachytherapy alone
- EBRT versus brachytherapy

Information about the following comparison can be found in Chapter 7:

- RP plus ADT versus EBRT plus high-dose-rate brachytherapy plus ADT

Some comparisons of brachytherapy to other therapies were only evaluated in studies rated high ROB (e.g., AS vs. brachytherapy [k=1 non-RCT],[52] AS vs. radiation [either EBRT and/or brachytherapy][k=1 non-RCT],[24, 27] RP vs. brachytherapy [k=2 non-RCTs],[52, 99] RP vs. radiation [either EBRT and/or brachytherapy][k=1 non-RCT],[24, 27] ADT vs. radiation [either EBRT and/or brachytherapy][k=1 non-RCT],[24, 27] and watchful waiting (WW) vs. radiation [either EBRT and/or brachytherapy][k=1 non-RCT]).[24, 27]

There were several comparisons of brachytherapy to other therapies addressed in the 2016 evidence report commissioned by the AUA in which we did not identify any additional studies that met our analysis criteria published after this report.[5] A list of these comparisons can be found in Appendix J. The 2016 evidence report and appendices contains detailed results, strength of evidence, and evidence tables for these comparisons.

Chapter 9. Key Questions 2–4

KQ 2: How do patient characteristics modify comparative effectiveness and harms of CLPC therapies?

We systematically searched for evidence on the patient characteristics that might impact the relative effectiveness of the treatment modalities of interest. We found limited information that met our predefined inclusion criteria related to the characteristic of patients' age. We found limited information from one RCT of watchful waiting (WW) vs. radical prostatectomy (RP) in men with mainly clinically detected clinically localized prostate cancer (CLPC) that the effect of interventions may have varied by age but did not vary by race/ethnicity, comorbidity status or health status. We found limited information that the effects of active monitoring (AM) versus either RP or external beam radiation therapy (EBRT) plus androgen deprivation therapy (ADT) did not vary by age. We found limited information that the benefit of EBRT plus ADT versus EBRT alone on mortality in intermediate risk disease may only be in men with no or minimal comorbidity. Available information for these secondary analyses is presented in the primary analyses of the specific comparisons.

KQ 3: How do tumor characteristics modify comparative effectiveness and harms of CLPC therapies?

We searched for evidence on a potential effect modifying effect of several tumor related prognostic variables including baseline prostate specific antigen (PSA), Gleason score, tumor index scores (such as D'Amico and National Comprehensive Cancer Network [NCCN] risk categories) and biomarkers. We also provide specific information, where available, regarding tumor eligibility criteria and baseline risk status among enrollees from studies to permit interpretation of applicability of the overall study findings. Additionally, when available, findings of secondary analyses were presented in the context of the primary analyses. We found no evidence that met our predefined inclusion criteria for the newer prognostic (proprietary) biomarkers such as Decipher, Oncotype Dx and Prolaris as it relates to comparative effectiveness modification. Evidence suggested that the effect of radical prostatectomy versus watchful waiting on all-cause and prostate cancer mortality among men with mainly clinically detected CLPC may be limited to men with D'Amico intermediate risk disease but that the effect of either RP or EBRT versus AM in men with mostly lower risk PSA-screen detected disease did not vary by baseline tumor stage, PSA level or Gleason score. There was wide variation in the absolute risk of prostate cancer death and the absolute treatment effect overall as well as across similar D'Amico tumor risk characteristics between the two studies. Absolute prostate-cancer and metastatic events and absolute risk differences between WW and RP were much greater in the Scandinavian Prostate Cancer Group-4 (SPCG-4) trial than the Prostate Intervention Versus Observation Trial (PIVOT). Many trials of whole gland therapy with radiation enrolled men with higher risk CLPC but rarely reported subgroup findings by tumor (or patient) factors. *Post-hoc* analysis suggested the benefit of EBRT plus ADT versus EBRT on prostate-cancer mortality may only be in men with intermediate and high-risk disease, but not in low-risk men.

KQ 4: How do provider/hospital characteristics modify comparative effectiveness of RP compared with other therapies?

We found no information about potential effect modification for variables such as geographic region, hospital type, provider volume and institutional volume to inform this review.

Chapter 10. Discussion

Key Findings

We provide information newly published since the previous Agency for Healthcare Research and Quality (AHRQ) and American Urological Association (AUA) funded reviews. We summarize key findings from newly published reports, incorporate information from past reviews when applicable, and refer readers to key findings from prior reports for intervention comparisons addressed previously and not by our report. With few exceptions, these new findings provide little additional information on previously reported comparisons and outcomes to alter previously assessed effect magnitude or certainty. Our report provides new information on longer followup or other outcomes from comparisons published earlier or from different intervention/comparison combinations.

An important contribution of this updated report lies in its' critical appraisal of newer and longer-term data from two trials (SPCG-4 and PIVOT) that have informed the comparison of radical prostatectomy (RP) to watchful waiting (WW). Extended follow-up suggests that RP may reduce mortality and probably reduces metastases over a very extended time frame. Age and tumor risk category may be important effect modifiers. However, these benefits are only realized over a very extended time frame, and tumor risk category appears to be an important effect modifier. Specifically, prostate cancer mortality is infrequent or rare in men with low-risk disease, and the effect of RP on all-cause or prostate cancer mortality may be limited to men with D'Amico intermediate risk disease. Many patients with clinically localized prostate cancer (CLPC) who are treated with WW may avoid prostate-cancer-related morbidity or mortality for an extended period time, thereby also avoiding treatment-related side-effects. Supporting these findings is new information from the ProtecT trial that enrolled prostate specific antigen (PSA)-screen-detected men and, irrespective of treatment arm, observed few prostate cancer related events. ProtecT found that in men with PSA screen detected and primarily lower risk disease, active monitoring (AM) resulted in similar all-cause and prostate-cancer mortality versus RP or external beam radiation therapy (EBRT). Differences in metastases were small in absolute terms.

Comparisons of SPCG-4, PIVOT and ProtecT from the pre-PSA, early PSA, and late PSA era, respectively, illustrate the increasing impact of lead time on baseline risk, as well as the increasing concern related to overdiagnosis and overtreatment. Given prostate cancer is now increasingly diagnosed not by digital rectal examination (as in SPCG-4) but through a combination of PSA and its derivatives, other biochemical markers and magnetic resonance imaging (MRI), the absolute benefits derived from treatment are likely smaller than those observed in the three existing trials that have informed this report. Increasing life expectancy is commonly cited as a reason for aggressive local treatment, but recent epidemiological data for the U.S. population contradicts this reasoning, since average male life expectancy is in fact declining.[114] We recognize that today's surgical approach to prostate cancer has evolved dramatically from past practices, with most patients now undergoing robotic assisted prostatectomy. However, little to no high-quality evidence supports the notion that the benefit-to-risk ratio of radical surgery has fundamentally changed with the widespread adoption of robotic surgery. The only published randomized trial of robotic assisted laparoscopic prostatectomy (RALP) versus open RP reported no oncological outcomes, found little to no difference in urinary and sexual quality of life but did demonstrate lower rates of transfusion and a shorter length of stay.[113] Functional outcomes at 24 months were also similar.[112] These findings stand in contrast to recent developments in field of medical treatment for advanced prostate cancer with

high quality trial evidence supporting an increasing role for newer agents such as apalutamide, enzalutamide and abiraterone as highly effective in prolonging progression and/or all-cause and disease-specific survival.[115]

As noted above, this report is the first to include data on PSA-based AM compared to radiation therapy (RT) and RP in the ProtecT trial. AM included routine PSA measurements but no protocol driven surveillance biopsies or MRI. AM is in the middle of spectrum of monitoring intensity options between WW with additional treatments primarily for palliative/symptomatic care and more intensive approaches that involve surveillance MRI and prostate biopsies. After 10 years, a newly expanded definition of metastatic disease and clinical progression favored surgery and radiation by small absolute amounts, but all-cause and prostate-cancer-specific mortality did not differ. However, surgery resulted in worse urinary and sexual function. A main finding of this study was that prostate cancer mortality was rare irrespective of treatment assignment, and that patients were ten times more likely to die of competing other causes than prostate cancer, thereby again emphasizing the importance of appropriate patient selection and meaningful counseling about short- and long-term treatment outcomes. Furthermore, the effect of AM versus RP or EBRT did not vary by baseline age, PSA, tumor stage or Gleason score.

For radiation therapy, we found similar functional outcomes as AM in the ProtecT trial, yet superior functional outcomes compared with RP. This updated report also provides further support that the addition of systemic androgen deprivation therapy (ADT) to EBRT improves oncological outcomes in men with higher risk disease. However, it may also result in a moderate increase in sexual dysfunction. The duration of ADT varied by study, which could confound generalizability of toxicity data. We also found that 3D-CRT plus low-dose rate brachytherapy plus ADT may slightly reduce all-cause mortality but not metastases more than 3D-CRT plus ADT in higher risk CLPC. We found no eligible studies comparing proton beam therapy to other forms of radiotherapy.

This report update was motivated in part by an increasing interest in novel treatment modalities (other than surgery and radiation) applied as whole prostate gland therapy or as focal therapy. For these modalities, which include cryotherapy of index lesion, which is quite widely used in the U.S., as well as high-intensity focused ultrasound (HIFU), which was cleared for use in 2016 for prostate cancer by the Food and Drug Administration (FDA),[116] we found either no eligible or insufficient evidence. For photodynamic therapy, we found no evidence for oncological outcomes. Although these and other newer modalities hold promise, we need higher quality studies to assess patient important outcomes to guide evidence-based clinical practice.

Our findings have clinical, policy and research implications. Our results highlight the importance of balancing treatment benefits with harms and the inclusion of patient and tumor characteristics as well as patient preferences into treatment decisions. They reinforce the need for long-term comparative effectiveness RCTs and well-designed prospective cohort studies. They highlight that the more indolent natural history of PSA detected compared with clinically detected CLPC has important implications on net benefit of treatment options. For most men with CLPC including those with life expectancies of 15-20 years, evidence indicates that WW and AM result in little to no difference in mortality and metastases and fewer harms compared with early intent-to-cure treatments. Any mortality benefit due to early intervention may be limited to men age <65 years and men with intermediate risk disease. Few men with low risk disease develop systemic spread or die from prostate cancer. Overtreatment and harms could be avoided with greater implementation of WW and/or AM. The absolute benefit of early intervention in PSA detected CLPC is likely considerably less and overtreatment greater than

studies of WW and AM suggest. This is particularly important for practice and policy decisions because most men currently diagnosed with CLPC have PSA-screen detected disease and most are over age 65.[117] Many of these men have lower risk disease or have comorbidities that limit life expectancy to less than 20 years. Furthermore, trials of WW and AM were conducted prior to development of effective pharmacologic treatments for men who develop advanced prostate cancer and thus the net benefit from early intervention may be currently lower than that observed prior to the development of these therapies.[118] For men with PSA detected CLPC who would like to undergo early treatment and who have a long-life expectancy, RP provides similar effects through 10 years compared with EBRT + ADT. For men with higher risk disease who select EBRT, the addition of ADT reduces mortality but may increase harms compared to EBRT alone. Our findings provide a cautionary note before incorporating newer treatment modalities (including refinements of RP or EBRT) into clinical care as evidence on their effectiveness and harms is very limited. While active surveillance (AS) and newer modalities hold promise, we need high quality studies that include an assessment of provider, patient, and tumor characteristics on patient important outcomes.

For men with higher risk disease, while RP may not reduce mortality versus WW, EBRT plus ADT compared to EBRT alone probably reduces mortality but may increase harms. Our updated report also emphasizes the relative lack of, and need for, long-term comparative effectiveness randomized trials and well-designed prospective cohort studies. Particular emphasis should be directed towards evaluating whether known patient and tumor prognostic factors modify comparative treatment outcomes to more accurately guide practice and policy decisions. Our findings also indicate that the incorporation of newer treatment modalities (including refinements of RP or EBRT) into routine clinical care are not convincingly supported by evidence. While AS and newer modalities hold promise, we need additional higher quality studies including assessment of the effect of provider, patient, tumor and biomarker characteristics of these options on patient important outcomes.

Limitations

A central limitation of this updated systematic review lies in the lack of relevant studies. When studies did exist, their value was frequently limited by methodological and clinical limitations. For many important comparisons, especially as related to newer treatment modalities such as HIFU or photodynamic therapy, we found no evidence for oncological outcomes. For comparisons informed by RCTs, followup was often too short to adequately assess long-term prostate-specific and overall mortality as key outcomes. Whereas metastatic disease was assessed more frequently, this outcome was typically a composite of asymptomatic radiographic findings and PSA elevations (> 100 ng/ml) rather than patient-reported, metastases-related complications (such as bone pain or ureteral obstruction). Despite a major interest in focal therapy, we were unable to identify studies that met inclusion criteria for this review. Although we planned to include nonrandomized studies as supplemental evidence for Key Questions since they are usually easier to conduct, most studies were deemed high risk of bias studies, thereby highlighting the importance for future well-designed prospective cohort studies.

Clinical decision-making in the treatment of CLPC is highly influenced by both patient and tumor characteristics, in particular age and comorbidity serving to estimate life expectancy and disease stage most commonly, the D'Amico and National Comprehensive Cancer Network (NCCN) risk categories or the Cancer of the Prostate Risk Assessment Score (CAPRA) score, to predict the natural history of the disease. Evidence for or against any effect modification by these

variables was included in this report as specific Key Questions whenever it was available; however, in accordance with our predefined methods we did not include a formal assessment of the strength of evidence. All subgroup analyses need to be interpreted with caution however, especially those performed post-hoc. Furthermore, it was not possible to construct a treatment flow pattern for a given index patient based off existing data. Patient agreement to enroll in randomized trials was likely often influenced by patient and provider preference for various treatment options. The best that the data can inform relates mainly to the patient and clinical characteristics commonly seen in men with newly diagnosed prostate cancer. That includes men in their 60s in good to excellent health and with low to moderate risk PSA-screen detected prostate cancer. For these men, WW or AM provides similar long-term overall and prostate cancer mortality and metastatic disease spread with fewer harms compared to early intervention. For older men or those with limited life expectancy due to comorbidities or those wishing to avoid harms of early intervention, WW or AM provides even greater net benefit. For younger men or those desiring early intervention for a potential small reduction in mortality despite harms, than either surgery or EBRT + ADT has supporting evidence. For healthy men with long-life expectancy and with higher risk disease EBRT +ADT appears to have benefits that exceed harms versus EBRT alone. Both EBRT + ADT and surgery probably reduced metastases but may not r reduce overall or prostate cancer mortality through at least 10 years. For men with higher risk clinically detected rather than PSA detected CLPC and with long life expectancy surgery may have mortality and metastases benefits that exceed harms. Importantly, we defined effect sizes as small, moderate, or large based on consensus derived thresholds. Varying absolute risk differences to define benefit and harms thresholds as well as patient and provider values on the magnitude of these differences to determine clinical importance may alter certainty of evidence, assessment of net benefit as well as clinical and policy decisions. Furthermore, while clinical and policy decision making often rely on the effects of treatments based on patient and tumor characteristics, evidence certainty to guide these decisions is limited and unlikely to be greater than findings from intervention effects overall. Similar to the 2014 AHRQ report we found no evidence on the impact of geographic region, surgeon and hospital volume for RP versus other treatments modalities.

Future Research Needs

This review update highlights the lack of high-quality research that meet the evidentiary standards predefined in this and prior AHRQ reports protocols. New and updated evidence summarized here stems mainly from a few carefully planned RCTs, in particular SPCG-4, PIVOT and ProtecT, which include long-term followup of 10+ years. Whereas much has there are known challenges of performing clinical trials in CLPC due to its protracted and relatively indolent disease course and the lack of widely accepted surrogate outcome measures, these issues are inherent to the disease itself and therefore relevant to clinical decision making. A search of clinicaltrials.gov failed to find completed trials whose results have not been published in peer-reviewed journals. We also searched for large (planned enrollment >300) ongoing RCTs of nonpharmacological interventions. We identified approximately 30 ongoing trials that may be of sufficient size and duration to provide oncological outcomes in addition to harms and quality of life information (Appendix Table K-1). Fewer than 10 of these studies are scheduled for completion prior to 2025. However, ongoing studies are likely to contribute greatly to our understanding and include comparative effectiveness studies of surgery versus percutaneous radiation implant versus active surveillance for low to intermediate risk CLPC; radical versus

focal therapy plus pharmacological therapies; proton versus photon EBRT; laparoscopic versus conventional RP and other comparative treatments of radical treatments. Almost all are being conducted outside of the United States. Large studies within the US are needed and should include AS and recruit sufficiently to report on subgroups or prognostic factors current interest.

Specific issues for future research include the following:

- What is long-term comparative effectiveness of RP and RT for treating screen-detected men with prostate cancer stratified by tumor risk category and patients' characteristics (such as competing medical comorbidities), and how do outcomes compare with WW?
- What is the comparative effectiveness of contemporary AS, including surveillance biopsies and MRI-imaging, compared with WW stratified by tumor risk category and patient characteristics? Whereas the therapeutic burden of AS for patients should be less than that of surgery and radiation, it may nevertheless contribute to the issue of overtreatment in those men who are unlikely to experience prostate-cancer related morbidity and mortality during their lifetime.
- What is the comparative effectiveness, harms and costs of different radiation therapies, including proton beam therapy, given the variation in treatment time and capital expense of various therapies.
- Evolving newer treatment modalities for CLPC, especially as they relate to the paradigm of focal therapy, should undergo more formal research evaluation up front. Despite the promise of similar outcomes and a potentially more favorable side-effect profile, their current role remains poorly defined.
- Defining clinically meaningful absolute risk difference to set thresholds for small, moderate and large effects and how these might alter clinical and policy decisions.
- A number of commercially available blood, urine, and tissue-based biomarkers have been proposed not only as prognostic tools but also to guide to treatment management decisions and determine comparative effectiveness. However, none met inclusion criteria, thereby emphasizing the importance of their rigorous, prospective evaluation.
- Given the favorable long-term outcomes of deferred management in the form of AS or WW, future research should focus on identifying those men with intermediate- and high-risk disease who are most likely to benefit from treatment.
- Given the importance of patient and tumor characteristics on clinical decision-making, these should be routinely reported in a standardized manner and studies either adequately powered to assess these subgroups or specifically focus on high-priority groups. Secondary analyses based on these variables should considered *a priori*.
- There is an imperative for high quality studies that would meet inclusion criteria of this report to assess the plausible impact of geographic region, provider and institution volume on comparative treatment outcomes.

Conclusion

This systematic review update focused on information newly published since prior Agency for Healthcare Research and Quality (AHRQ) and American Urological Association (AUA) funded reviews. As applicable, we incorporated findings from prior reviews when they and our report identified RCTs that addressed the same comparison and refer readers to past reviews for intervention comparisons only addressed in prior reviews. We also describe how are findings compare and contrast to these two reviews, provide practice and policy implications of the results, and targeted suggestions for future research. We found that compared to watchful waiting, radical prostatectomy may reduce overall and prostate cancer mortality and metastatic spread at 20+ years followup in men with clinically localized prostate cancer not detected by prostate specific antigen (PSA) screening. Mortality benefits may be limited to men under age 65 years and those with intermediate risk disease. Radical prostatectomy probably resulted in increased urinary, sexual, and erectile dysfunction. There is no information on the effect of any early intervention strategies versus watchful waiting in men with PSA-detected prostate cancer. Compared to PSA-based active monitoring, neither radical prostatectomy nor external beam radiation reduce overall or prostate cancer mortality through 10 years regardless of patient or tumor risk characteristic, and both are associated with increased harms. External beam radiation therapy plus androgen deprivation therapy reduces mortality and metastases versus EBRT alone but is associated with worse sexual function. Treatment with three-dimensional conformal radiation therapy (3D-CRT) and androgen deprivation therapy (ADT) with low-dose-rate prostate brachytherapy (LDR-BT) may provide a small reduction in all-cause mortality versus 3D-CRT and ADT in higher risk disease but may have little to no effect on metastatic disease. The evidence is absent or insufficient to assess the comparative effectiveness and harms of many other therapies and comparisons, particularly their effect on long-term outcomes including overall and prostate cancer mortality and metastatic disease. Patient age and tumor risk may modify the effect of radical prostatectomy versus watchful waiting (WW) in men with clinically localized prostate cancer (CLPC) not detected by PSA screening with mortality benefits limited to younger men and those with intermediate-risk disease. The information on comparative effectiveness and harms should be incorporated into practice and policy decisions and patient informed decision materials. Large, long-term randomized trials in men with PSA detected CLPC are needed, particularly in light of the known more indolent nature of PSA detected CLPC, the widespread use of MRI assessment for tumor identification, and characterization, and the availability of effective medical treatments for the minority of men with CLPC who develop advanced disease if not treated with early options.

Abbreviations and Acronyms

3D-CRT	three-dimensional conformal radiation therapy
ADT	androgen deprivation therapy
AHRQ	Agency for Healthcare Research and Quality
AM	Active Monitoring
ARD	absolute risk difference
AS	Active Surveillance
ASCENDE-RT	Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiation Therapy
AUA	American Urological Association BTinterstitial brachytherapy
CAPRA	Cancer of the Prostate Risk Assessment Score
CI	confidence interval
CLPC	clinically localized prostate cancer
COE	certainty of evidence
EBRT	external beam radiation therapy
EORTC	European Organization for Research and Treatment of Cancer
EORTC QLQ-C2	European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire–Core 25 module
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire–Core 30 module
EORTC QLQ-C33	European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire–Core 33 module
FDA	U.S. Food and Drug Administration
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HAROW	Hormonal therapy, Active Surveillance, Radiation, Operation, Watchful Waiting Study
HDR-BT	high dose rate brachytherpay
HIFU	high-intensity focused ultrasound
IIEF-5	International Index of Erectile Function
IMRT	intensity modulated radiation therapy
KQ	Key Question
LDR	low dose rate
LDR-PB	low-dose-rate prostate brachytherapy
LHRH	luteinizing hormone-releasing hormone
LRP	laparoscopic radical prostatectomy
MRI	magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
OR	odds ratio

PART	Partial prostate Ablation versus Radical prosTatectomy
PDT	photodynamic therapy
PICOTS	population, intervention, comparison, outcomes, timing, and setting/study design
PIVOT	Prostate Cancer Intervention Versus Observation Trial
PRIMSA	Preferred Items for Reporting in Systematic Reviews and Meta-Analyses
PSA	prostate-specific antigen
QOL	quality of life
RALP	Robotic assisted laparoscopic prostatectomy
RALRP	robotic-assisted laparoscopic radical prostatectomy
RARP	Robotic assisted radical prostatectomy
RCT	randomized controlled trial
RD	risk difference
ROB	risk of bias
RP	radical prostatectomy
RR	risk ratios
RT	radiation therapy
RRP	open retropubic radical prostatectomy
SBRT	stereotactic body radiation therapy
SF-12	Medical Outcomes Study 12-Item Short-Form General Health Survey
SMD	standardized mean difference
SPCG	Scandinavian Prostate Cancer Group
T1	tumor Stage 1
T2	tumor Stage 2
T3	tumor Stage 3
T4	tumor Stage 4
VMAT	volumetric-modulated arc therapy
WMD	weighted mean differences
WW	watchful waiting

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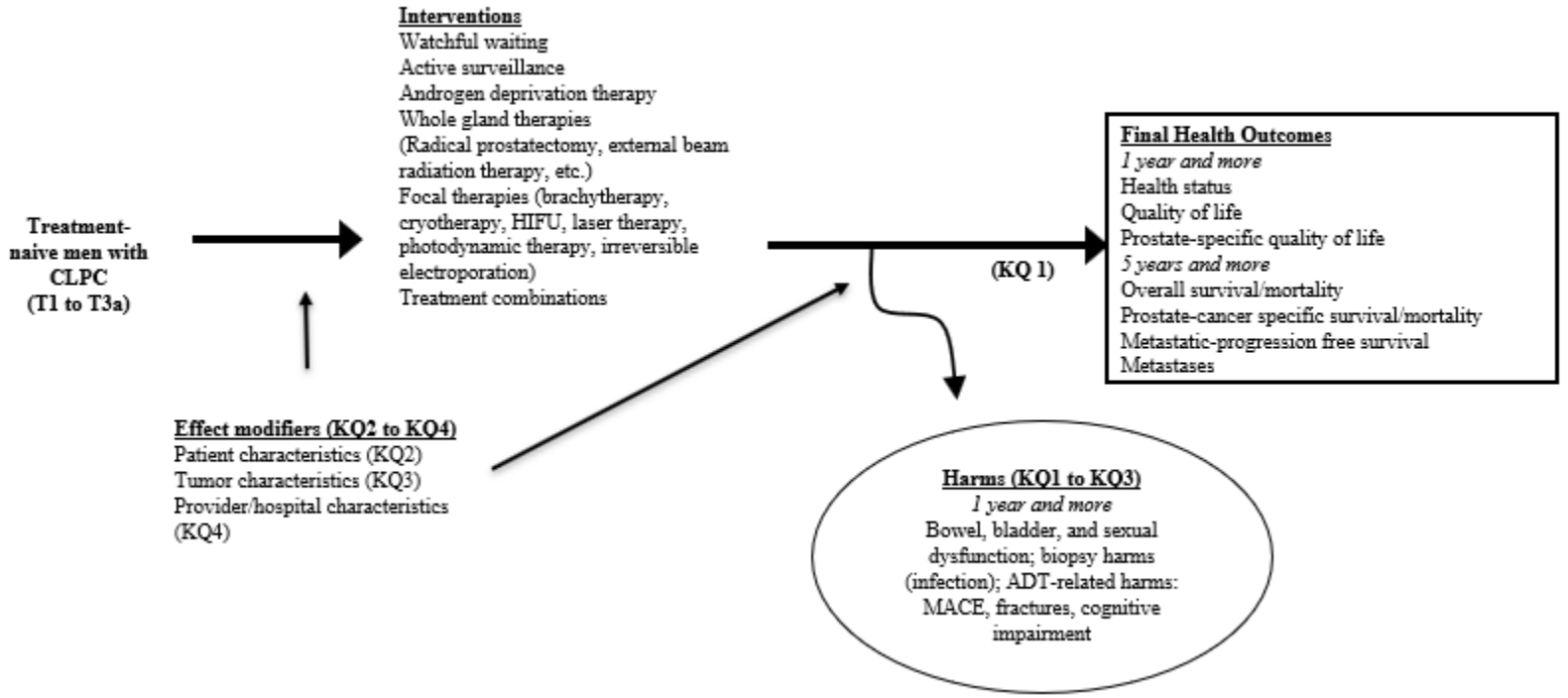
Appendix A. Analytic Framework

Figure A-1. Analytical framework for therapies for clinically localized prostate cancer



Appendix B. Search Strategies

Ovid MEDLINE(R)

1 exp Prostatic Neoplasms/ (118593)

2 (prostat* and (neoplasm* or cancer* or carcinoma*)).ti,ab. (138807)

3 watchful waiting.ti,ab. (2358)

4 active surveillance.ti,ab. (6438)

5 LRP.ti,ab. (3633)

6 RLRP.ti,ab. (48)

7 prostatectom*.ti,ab. (28151)

8 radiotherap*.ti,ab. (156325)

9 EBRT.ti,ab. (2794)

10 IMRT.ti,ab. (8646)

11 proton.ti,ab. (94523)

12 (intensity and modulated and therap*).ti,ab. (7296)

13 brachytherap*.ti,ab. (16219)

14 curietherap*.ti,ab. (455)

15 cryosurger*.ti,ab. (3377)

16 cryotherap*.ti,ab. (6755)

17 cryoablat*.ti,ab. (3229)

18 Cyberknife.ti,ab. (1201)

19 freezing.ti,ab. (32530)

20 androgen deprivation.ti,ab. (6870)

21 HIFU.ti,ab. (2087)

22 (high and intensity and focused and ultrasound*).ti,ab. (2812)

23 1 or 2 (160965)

24 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 (350793)

25 23 and 24 (39445)

26 limit 25 to (clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or evaluation studies or meta analysis or multicenter study or observational study or pragmatic clinical trial or randomized controlled trial) (8330)

27 (clinical trial* or comparative stud* evaluation stud*).tw. (326592)

28 ((singl* or doubl* or trebl* or tripl*) and (mask* or blind*)).tw. (181405)

29 (latin square or placebo or random or control group or prospective* or retrospective* or volunteer* or sham).tw. (2158358)

30 (meta?analysis or cohort or ISRCTN* or ACTRN* or NCT*).tw. (516377)

31 27 or 28 or 29 or 30 (2702617)

32 25 and 31 (12356)

33 26 or 32 (17063)

34 limit 33 to years="2014 -Current" (6117)

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Embase Classic + Embase

1 Prostatic Neoplasms/ (8570)

2 (prostat$.ti,ab. or Prostate/) and (cancer.ti,ab. or Neoplasms/ or neoplasm$.mp. or carcinoma$.mp.) [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (209978)

3 1 or 2 (212135)

4 watchful waiting.ti,ab. or Watchful Waiting/ or active surveillance.ti,ab. or prostatectom$.ti,ab. or Prostatectomy/ or LRP.ti,ab. or RLRP.ti,ab. or exp Radiation therapy/ or radiotherap$.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. (904076)

5 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.mp. 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. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (6606139)

6 3 and 4 and 5 (33678)

7 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.) (32195)

8 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.) (23732)

9 8 not (case report.de. or case reports.pt. or case report.ti. or (year adj old).ti,ab.) (23699)

10 limit 9 to (english language and years="2014 -Current") (8173)
11 10 and compar$.ti,hw. (1454)
12 10 and (clinically adj local$).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (387)
13 10 and (stage 1 or stage one).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (9)
14 10 and (early adj3 stage).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (102)
15 10 and (nonmetastatic or non-metastatic).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (234)
16 10 and (gleason 7 or gleason score 7 or gleason 6 or gleason score 6).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (490)
17 10 and (local$ adj advanced).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (239)
18 10 and (9T3 or T4).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (86)
19 10 and (high adj risk).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (1484)
20 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 (3580)
****

Cochrane

1-prostat* AND (neoplasm* OR cancer* OR carcinoma*)
2-"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*)
3-1 and 2
4- limit 3 to: publication date from 2014 to 2019

Appendix C. Certainty of Evidence Effect Size Language

Table C-1. Effect size and certainty of evidence narrative language

Certainty of Evidence	Size of the Effect Estimate	Absolute Risk Difference Between Groups: Mortality PC Specific Mortality Mets	Absolute Risk Difference Between Groups: Harms (urinary, bowel, sexual dysfunction)	Suggested Statements *(replace X with intervention, replace 'reduce/increase' with direction of effect, replace 'outcome' with name of outcome, include 'when compared with Y' when needed)*
HIGH Certainty of Evidence	Large effect	≥10%	≥20%	X results in a large reduction/increase in outcome
	Moderate effect	5-9.9%	5-19.9%	X results in a moderate reduction/increase in outcome
	Small important effect	2-4.9%	2-4.9%	X results in a small reduction/increase in outcome
	Small unimportant effect	<2.0%	<2.0%	X results in little to no difference in outcome
MODERATE Certainty of Evidence	Large effect	≥10%	≥20%	X probably results in a large reduction/increase in outcome
	Moderate effect	5-9.9%	5-19.9%	X probably results in a moderate reduction/increase in outcome
	Small important effect	2-4.9%	2-4.9%	X probably results in a small reduction/increase in outcome
	Small unimportant effect	<2.0%	<2.0%	X probably results in little to no difference in outcome
LOW Certainty of Evidence	Large effect	≥10%	≥20%	X may result in a large reduction/increase in outcome
	Moderate effect	5-9.9%	5-19.9%	X may result in a moderate reduction/increase in outcome
	Small important effect	2-4.9%	2-4.9%	X may result in a small reduction/increase in outcome
	Small unimportant effect	<2.0%	<2.0%	X may result in little to no difference in outcome
INSUFFICIENT Certainty of Evidence	The evidence is very uncertain about the effect of X on outcome			

Appendix D. Eligible Studies

1. Abugharib AE, Dess RT, Soni PD, et al. External beam radiation therapy with or without low-dose-rate brachytherapy: Analysis of favorable and unfavorable intermediate-risk prostate cancer patients. Brachytherapy. 2017 Jul - Aug;16(4):782-9. PMID: 28499487.
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3. Ansmann L, Winter N, Ernstmann N, et al. Health-related quality of life in active surveillance and radical prostatectomy for low-risk prostate cancer: a prospective observational study (HAROW - Hormonal therapy, Active Surveillance, Radiation, Operation, Watchful Waiting). BJU Int. 2018 Sep;122(3):401-10. PMID: 29603553.
4. Ashamalla H, Guirguis A, McCool K, et al. Brachytherapy improves outcomes in young men (<=60 years) with prostate cancer: A SEER analysis. Brachytherapy. 2017 01 Mar;16(2):323-9. PMID: 614251483.
5. Azzouzi AR, Vincendeau S, Barret E, et al. Padeliporfin vascular-targeted photodynamic therapy versus active surveillance in men with low-risk prostate cancer (CLIN1001 PCM301): an open-label, phase 3, randomised controlled trial. Lancet Oncol. 2017 Feb;18(2):181-91. doi: 10.1016/S1470-2045(16)30661-1. PMID: 28007457.
6. Barocas DA, Alvarez J, Resnick MJ, et al. Association Between Radiation Therapy, Surgery, or Observation for Localized Prostate Cancer and Patient-Reported Outcomes After 3 Years. Jama. 2017 03 21;317(11):1126-40. PMID: 28324093.
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9. Berlin A, Ahmad AE, Chua MLK, et al. Curative Radiation Therapy at Time of Progression Under Active Surveillance Compared With Up-front Radical Radiation Therapy for Prostate Cancer. International Journal of Radiation Oncology, Biology, Physics. 2018 03 01;100(3):702-9. PMID: 29249526.
10. Bill-Axelson A, Holmberg L, Garmo H, et al. Radical prostatectomy or watchful waiting in early prostate cancer. N Engl J Med. 2014 Mar 06;370(10):932-42. PMID: 24597866.
11. Bill-Axelson A, Holmberg L, Garmo H, et al. Radical Prostatectomy or Watchful Waiting in Prostate Cancer - 29-Year Follow-up. N Engl J Med. 2018 12 13;379(24):2319-29. PMID: 30575473.
12. Bolla M, Maingon P, Carrie C, et al. Short Androgen Suppression and Radiation Dose Escalation for Intermediate- and High-Risk Localized Prostate Cancer: Results of EORTC Trial 22991. Journal of Clinical Oncology. 2016 05 20;34(15):1748-56. PMID: 26976418.
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Appendix E. Excluded Studies

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3. Abdel-Rahman O. Outcomes of Prostatectomy versus Radiation Therapy in the Management of Clinically Localized Prostate Cancer Patients Within the PLCO Trial. Clinical Genitourinary Cancer. 2019 Jan 04;04:04. PMID: 30704795. *Ineligible population*
4. Abdollah F, Karnes RJ, Suardi N, et al. Impact of adjuvant radiotherapy on survival of patients with node-positive prostate cancer. Journal of Clinical Oncology. 2014 10 Dec;32(35):3939-47. PMID: 600782396. *Ineligible population*
5. Abdollah F, Sammon JD, Reznor G, et al. Medical androgen deprivation therapy and increased non-cancer mortality in non-metastatic prostate cancer patients aged >=66 years. Eur J Surg Oncol. 2015 Nov;41(11):1529-39. PMID: 26210655. *Ineligible comparison*
6. Abdollah F, Suardi N, Cozzarini C, et al. Selecting the optimal candidate for adjuvant radiotherapy after radical prostatectomy for prostate cancer: a long-term survival analysis. European Urology. 2013 Jun;63(6):998-1008. PMID: 23122664. *Ineligible population*
7. Abelson B, Reddy CA, Ciezki JP, et al. Outcomes after photoselective vaporization of the prostate and transurethral resection of the prostate in patients who develop prostatic obstruction after radiation therapy. Urology. 2014 Feb;83(2):422-7. PMID: 24315301. *Ineligible intervention*
8. Abern MR, Dude AM, Tsivian M, et al. The characteristics of bladder cancer after radiotherapy for prostate cancer. Urol. 2013 Nov;31(8):1628-34. PMID: 22575239. *No eligible outcomes reported*
9. Adam M, Tennstedt P, Lanwehr D, et al. Functional Outcomes and Quality of Life After Radical Prostatectomy Only Versus a Combination of Prostatectomy with Radiation and Hormonal Therapy. European Urology. 2017 03;71(3):330-6. PMID: 27887941. *Ineligible population*
10. Adejoro O, Gupta P, Ziegelmann M, et al. Effect of minimally invasive radical prostatectomy in older men. Urol. 2016 May;34(5):234.e1-11. PMID: 26795606. *Ineligible population*
11. Ahn S, Lee M, Jeong CW. Comparative quality-adjusted survival analysis between radiation therapy alone and radiation with androgen deprivation therapy in patients with locally advanced prostate cancer: a secondary analysis of Radiation Therapy Oncology Group 85-31 with novel decision analysis methods. Prostate International. 2018 December;6(4):140-4. PMID: 620811351. *No eligible outcomes reported*
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14. Alayed Y, Cheung P, Vesprini D, et al. SABR in High-Risk Prostate Cancer: Outcomes From 2 Prospective Clinical Trials With and Without Elective Nodal Irradiation. International Journal of Radiation Oncology Biology Physics. 2019. *Ineligible study design*
15. Albertsen P. Randomised controlled trial: radical prostatectomy reduces prostate cancer-specific mortality among men with intermediate-grade disease, but provides minimal benefit for men with low-grade and high-grade disease. Evidence-based medicine. 2014;19(5):176. PMID: CN-01050592. *Ineligible study design*

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Appendix F. Watchful Waiting

Table F-1. Risk of bias assessments for randomized controlled trials: watchful waiting comparisons

Intervention/ Comparison (Outcomes)	Author Year	Selection Bias	Performance Bias	Detection Bias	Attrition	Reporting Bias	Other Bias	Overall Rating
RP/WW (All-cause mortality, prostate-specific mortality, metastases)	Bill-Axelson 2014[1] Bill-Axelson 2018[2]	Low	Low	Medium	Low	Low	NI	Low
RP/WW (All-cause mortality, prostate-specific mortality, metastases)	Wilt 2017[3]	Low	Low	Medium	Medium	Low	NI	Low

Abbreviations: NI=none identified; RP= radical prostatectomy; WW=watchful waiting

Table F-2. Summary risk of bias assessments for observational studies: watchful waiting

Intervention/ Comparison (Outcomes)	Author, Year	Bias Due to Confounding	Bias in Selection of Participants	Bias in Classification of Interventions	Bias Due to Deviations for Intended Interventions	Bias Due to Missing Data	Bias in Measurement of Outcomes	Bias in Selection of the Reported Result	Overall
WW/RT, AS/ADT, RP, RT	Herden 2016[4]	Moderate	Low	Moderate	Low	Serious	Serious	Low	Serious
WW/RT, RP	Hoffman 2017[5]	Serious	Low	Moderate	Low	Serious	Moderate	Low	Serious
	Lu-Yao 2015[6]	Moderate	Moderate	Low	Low	No Information	Serious	Low	Serious
WW/RT, RT+ADT	Dell'Oglio 2016[7]	Serious	Low	Low	Low	No Information	Moderate	Moderate	Serious

Abbreviations: ADT=androgen deprivation therapy; RP= radical prostatectomy; RT=radiation therapy; WW=watchful waiting

Table F-3. Characteristics of eligible studies: watchful waiting comparisons

Study Design Country ROB	N=	Population	Intervention Frequency Duration	Comparison Frequency Duration	Followup Time(s) Outcome (Instrument)
Bill-Axelson 2014[1] Bill-Axelson 2018[1, 2] RCT Scandinavia (Sweden, Finland and Iceland) Low	695	Men < 75 with life expectancy ≥ 10 years; no other cancers; clinical stage T1, T2; PSA < 50 ng/mL T1b: 12% T2c: 12% T2: 76% Gleason sum 2-4: 13% 5-6: 48% 7: 23% 8-10: 5% Age 65 Race NR	Radical prostatectomy	Watchful waiting: no immediate treatment	*18 years* All-cause mortality Prostate-specific mortality Metastases *29 years* All-cause mortality Prostate-specific mortality Metastases
Wilt 2009[8] Wilt 2017[3] RCT United States Low	731	Men age ≤75 PSA <50 ng/ml with life expectancy ≥ 10 years Stage (T1–T2, Nx, M0) of any grade diagnosed ≤12 months, bone scan negative for metastatic disease T1a: 2% T1b: 2% T1c: 50% T2a: 25% T2b: 12% Gleason sum 2-4: 23% 5-6: 51% 7: 21% 8-10: 7% Age 67 62% White 33% Black Median PSA: 7.8 ng/ml	Radical prostatectomy Surgery	Watchful Waiting No Intervention Closely watching, waiting and treating symptoms if and when cancer progresses	*19.5 years* All-cause mortality Prostate-specific mortality Erectile dysfunction Incontinence

Abbreviations: ng/ml=nanogram per milliliter; NR=not reported; PSA=Prostate-specific antigen; RCT=randomized controlled trial; ROB=risk of bias

Table F-4. Mortality, survival, and metastases: watchful waiting

Intervention/ Comparison	**Study Design (Trial/Registry) Risk of Bias**	***Followup*** **Overall Mortality**	***Followup*** **Prostate Cancer Specific Mortality**	***Followup*** **Metastases**
WW/RP	Bill-Axelson 2014[1] Bill-Axelson 2018[2] RCT (SPCG-4) Low	Cumulative Incidence, % (n/N or 95% CI) *18 years* WW = 71% (247/348) 68.9 (63.8 to 74.3) RP = 58% (200/347) 56.1 (50.9 to 62.0) RR* = 1.23 (1.1 to 1.38) *23.6 years* WW = 84% (292/348) 83.8 (79.8 to 88.1) RP = 75% (261/347) 71.9 (67.0 to 77.0) RR* = 1.1 (1.03 to 1.2) Participant Characteristics, 18 years Participants <65 years: WW = 65.6% (112/170*) RP = 40.0% (69/173*) RR* = 1.65 (1.34 to 2.04) Participants ≥65 years: WW = 71.7% (135/188*) RP = 69.8% (131/188*) RR* = 1.03 (0.90 to 1.17) Risk category: Low: WW = 59.1% (85/144*) RP = 43.4% (51/117*) RR* = 1.35 (1.06 to 1.73) Intermediate: WW = 72.5% (95/120*) RP = 57.1% (87/152*) RR* = 1.38 (1.17 to 1.63)	Cumulative Incidence, % (n/N or 95% CI) *18 years* WW = 28% (99/348) 28.7 (24.2 to 34.2) RP = 18% (63/347) 17.7 (14.0 to 22.4) RR* = 1.56 (1.19 to 2.1) *23.6 years* WW = 32% (110/348) 31.3 (26.8 to 36.6) RP = 20% (71/347) 19.6 (15.8 to 24.4) RR* = 1.55 (1.19 to 2.0) Participant Characteristics, 18 years Participants <65 years: WW = 34.1% (58/170*) RP = 18.3% (31/173*) RR = 1.90 (1.30 to 2.79) Participants ≥65 years: WW = 23.9% (41/188*) RP = 17.3% (32/188*) RR = 1.28 (0.84 to 1.94) Risk category: Low: WW = 14.0% (20/144*) RP = 10.2% (11/117*) RR* = 1.48 (0.73 to 2.96) Intermediate: WW = 39.3% (50/120*) RP = 15.1% (24/152*) RR* = 2.64 (1.73 to 4.03)	Cumulative Incidence, % (n/N or 95% CI) *18 years* WW =40% (138/348) 38.3 (33.4 to 44.0) RP = 26% (89/347) 26.1 (21.7 to 31.4) RR* = 1.55 (1.24 to 1.93) *23.6 years* WW = 43% (150/348) 43.3 (38.3 to 48.9) RP = 27% (92/347) 26.6 (22.3 to 31.7) RR* = 1.63 (1.3 to 2.0) Participant Characteristics, 18 years Participants <65 years: WW = 44.4% (76/170*) RP = 28.7% (45/173*) RR = 1.72 (1.27 to 2.32) Participants ≥65 years: WW = 32.7% (62/188*) RP = 23.8% (44/188*) RR = 1.41 (1.01 to 1.96) Risk category: Low: WW = 24.1% (35/144*) RP = 13.6% (15/117*) RR* = 1.90 (1.09 to 3.30) Intermediate: WW = 44.9% (59/120*) RP = 25.0% (37/152*) RR* = 2.02 (1.45 to 2.82)

Intervention/ Comparison	**Study Design (Trial/Registry) Risk of Bias**	***Followup*** **Overall Mortality**	***Followup*** **Prostate Cancer Specific Mortality**	***Followup*** **Metastases**
		High: WW = 78.8% (67/85*) RP = 73.3% (62/85*) RR* = 1.08 (0.91 to 1.28) Participant Characteristics, 23 years Participants <65 years: WW = 77.6% (129/166) RP = 62.6% (105/157) RR* = 1.16 (1.01 to 1.33) Participants ≥65 years: WW = 87.3% (163/182) RP = 79.2% (156/190) RR* = 1.09 (1.00 to 1.19)	High: WW = 35.7% (29/85*) RP = 33.1% (28/85*) RR* = 1.06 (0.69 to 1.62) Participant Characteristics, 23 years Participants <65 years: WW = 37.9% (63/166) RP = 22.8% (39/157) RR* = 1.52 (1.09 to 2.13) Participants ≥65 years: WW = 25.3% (47/182) RP = 16.9% (32/190) RR* = 1.53 (1.03 to 2.29)	High: WW = 50.8% (44/85*) RP = 45.9% (37/85*) RR* = 1.19 (0.87 to 1.63) Participant Characteristics, 23 years Participants <65 years: WW = 49.4% (81/166) RP = 30.8% (48/157) RR = 1.63 (1.23 to 2.15) Participants ≥65 years: WW = 37.7% (69/182) RP = 23.2% (44/190) RR = 1.67 (1.21 to 2.30)

Intervention/ Comparison	**Study Design (Trial/Registry) Risk of Bias**	***Followup*** **Overall Mortality**	***Followup*** **Prostate Cancer Specific Mortality**	***Followup*** **Metastases**
	Wilt 2017[3] Wilt 2012[9] (median 10 years) RCT PIVOT 19.5 years Low	Cumulative Incidence, % (n/N or 95% CI) *19.5 years* WW = 67% (245/367) 66.8 (61.8 to 71.4) RP = 61% (223/364) 61.3 (56.2 to 66.1) RR* = 1.09 (0.98 to 1.22) Participant Characteristics Participants <65 years: WW = 59.5% (78/131) RP = 47.5% (58/122) RR = 1.25 (0.99 to 1.58) Participants ≥65 years: WW = 70.8% (167/236) RP = 68.2% (165/242) RR = 1.04 (0.92 to 1.17) White participants: WW = 70.5% (155/220) RP = 64.7% (150/232) RR* = 1.08 (0.96 to 1.24) Black participants: WW = 62.0% (75/121) RP = 57.7% (64/111) RR* = 1.13 (0.91 to 1.41) Tumor Characteristics PSA≤10 ng/ml: WW = 62.7% (151/241) RP = 58.8% (140/238) RR* = 1.07 (0.92 to 1.23) PSA>10 ng/ml:: WW = 74.4% (93/125) RP = 65.9% (83/126) RR* = 1.13 (0.96 to 1.33)	Cumulative Incidence, % (n/N or 95% CI) *19.5 years* WW = 11% (42/367) 11.4 (8.6 to 15.1) RP = 7% (27/364) 7.4 (5.2 to 10.6) RR* = 1.54 (0.97 to 2.45) Participant Characteristics Participants <65 years: WW = 11.5% (15/131) RP = 7.4% (9/122) RR = 1.55 (0.71 to 3.42) Participants ≥65 years: WW = 11.4% (27/236) RP = 7.4% (18/242) RR* = 1.54 (0.87 to 2.72) White participants: WW = 12.7% (28/220) RP = 7.3% (17/232) RR* = 1.74 (0.98 to 3.08) Black participants: WW = 9.1% (11/121) RP = 7.2% (8/111) RR* = 1.26 (0.51 to 3.02) Tumor Characteristics PSA≤10 ng/ml: WW = 9.5% (23/241) RP = 6.7% (16/238) RR* = 1.42 (0.77 to 2.62) PSA>10 ng/ml:: WW = 15.2% (19/125) RP = 8.7% (11/126) RR* = 1.74 (0.86 to 3.51)	NR at 19.5 years Bone metastases at 10 years WW = 10.6% (39/367) RP = 4.7% (17/364) HR = 0.40 (0.22 to 0.70)

Intervention/ Comparison	Study Design (Trial/Registry) Risk of Bias	*Followup* Overall Mortality	*Followup* Prostate Cancer Specific Mortality	*Followup* Metastases
		Risk category (locally assessed) Low: WW = 56.1% (83/148) RP = 55.4% (82/148) RR* = 1.01 (0.83 to 1.24) Intermediate: WW = 74.2% (89/120) RP = 59.7% (77/129) RR* = 1.25 (1.05 to 1.48) High: WW = 73.8% (59/80) RP = 71.4% (59/77) RR* = 0.96 (0.80 to 1.15)	Risk category (locally assessed) Low: WW = 5.4% (8/148) RP = 4.1% (6/148) RR* = 1.33 (0.47 to 3.75) Intermediate: WW = 15.8% (19/120) RP = 8.5% (11/129) RR* = 1.85 (0.92 to 3.74) High: WW = 18.8% (15/80) RP = 13.0% (10/77) RR* = 1.44 (0.69 to 3.02)	

*Calculated by EPC

Abbreviations: CI=Confidence Interval; NR=Not Reported; PIVOT=Prostate Cancer Intervention Versus Observation Trial; PSA=Prostate-specific antigen; RCT=randomized controlled trial; RP=radical prostatectomy; RR=relative risk; SPCG-4=Scandinavian Prostatic Cancer Group; WW=watchful waiting

Table F-5. Health status and quality of life: watchful waiting comparisons

Intervention/ Comparison	Study Design (Trial/Registry) Followup Risk of Bias	Health Status	Quality of Life Prostate Cancer Related Quality of Life
WW/RP	Bill-Axelson 2014[1] 18 years Bill-Axelson 2018[2] RCT 23.6 years (SPCG-4) Low	NR	NR
	Wilt 2017[3] RCT PIVOT 19.5 years Low	NR	NR

Abbreviations: NR=Not Reported; PIVOT=Prostate Cancer Intervention Versus Observation Trial; RCT=randomized controlled trial; RP=radical prostatectomy; SPCG-4=Scandinavian Prostatic Cancer Group; WW=watchful waiting

Table F-6. Harms: watchful waiting comparisons

Intervention/ Comparison	Study (Trial) Followup Risk of Bias	Adverse Effects
WW/RP	Bill-Axelson 2014[1] RCT (SPCG-4) 18 years Low	NR
	Bill-Axelson 2018[2] RCT (SPCG-4) 23.6 years Low	NR
	Wilt 2017[3] Wilt 2012[9] Personal communication with author (median 10 years RCT PIVOT 10 years Low	Erectile dysfunction, defined as:1) able to have an erection that is insufficient for vaginal penetration or 2) unable to have erection WW: 102/146 (69.9%) RP: 125/147 (85.0%) Urinary incontinence, defined as >1 pad/day WW: 8/147 (5.4%) RP: 32/148 (21.6%) Bowel dysfunction, defined as moderate or big problem WW 34/150 (22.7%) RP 28/149 (18.8%)

Abbreviations: NR=Not Reported; PIVOT=Prostate Cancer Intervention Versus Observation Trial; RCT=randomized controlled trial; RP=radical prostatectomy; SPCG-4=Scandinavian Prostatic Cancer Group; WW=watchful waiting Group

Table F-7. Evidence certainty: watchful waiting versus RP

Intervention/ Comparison	k= Study Design	Risk of Bias	Incon-sistency	Indirect-ness	Impre-cision	Other Consid-erations	I	C	Relative (95% CI)	Absolute (95% CI)	Certainty
All-cause mortality 20 years	2 RCTs	Not serious	Serious	Not serious	Serious	None	247/348 (71%) 245/367 (67%)	200/347 (58%) 223/364 (61%)	RR 1.23 (1.10 to 1.38) RR 1.09 (0.98 to 1.22)	13.3% (6.3 to 20.4) 5.5% (-1.45 to 12.4)	Low ⨁⨁◯◯[a, b]
All-cause mortality 25 years	1 RCT	Not serious	Not serious	Not serious	Serious	None	292/348 (84%)	261/347 (75%)	RR 1.12 (1.03 to 1.20)	8.7% (2.7 to 14.6)	Moderate ⨁⨁⨁◯[b]

Intervention/ Comparison	k= Study Design	Risk of Bias	Incon-sistency	Indirect-ness	Impre-cision	Other Consid-erations	I	C	Relative (95% CI)	Absolute (95% CI)	Certainty
Prostate Cancer Specific Mortality 20 years	2 RCTs	Not serious	Serious	Not serious	Serious	None	99/348 (28%) 42/367 (11%)	63/347 (18%) 27/364 (7%)	RR 1.57 (1.19 to 2.07) RR 1.54 (0.97 to 2.45)	10.3% (4.05 to 16.5) 4% (-0.19 to 8.25)	Low ⨁⨁◯◯[a, b]
Prostate Cancer Specific Mortality 25 years	1 RCT	Not serious	Not serious	Not serious	Serious	None	110/348 (32%)	71/347 (20%)	RR 1.54 (1.19 to 2.00)	11.1% (4.7 to 17.6)	Moderate ⨁⨁⨁◯[b]
Metastases 20 years	1 RCT	Not serious	Not serious	Not serious	Serious	None	138/348 (40%)	89/347 (26%)	RR 1.54 (1.24 to 1.93)	14% (7.1 to 20.9)	Moderate ⨁⨁⨁◯[b]
Metastases 25 years	1 RCT	Not serious	Not serious	Not serious	Serious	None	150/348 (43%)	92/347 (27%)	RR 1.63 (1.3 to 2.00)	16.6% (9.6 to 23.6)	Moderate ⨁⨁⨁◯[b]
Erectile dysfunction 10 years	1 RCT	Not serious	Not serious	Not serious	Serious	None	102/146 (70%)	125/147 (85%)	RR 0.82 (0.72 to 0.93)	-15.2% (-24.6 to -5.8)	Moderate ⨁⨁⨁◯[b]
Urinary incontinence (>1 pad/day) 10 years	1 RCT	Not serious	Not serious	Not serious	Serious	None	8/147 (5%)	32/148 (22%)	RR 0.25 (0.12 to 0.53)	-16.2% (--23.8 to -8.6)	Moderate ⨁⨁⨁◯[b]
Bowel dysfunction 10 years	1 RCT	Not serious	Not serious	Not serious	Serious	None	34/150 (23%)	28/149 (19%)	RR 1.21 (0.77 to 1.88)	3.9% (-5.3 to 13.1)	Low ⨁⨁◯◯[c]

Abbreviations: C=control; CI=confidence interval; I=intervention; RCT=randomized controlled trial; RP=radical prostatectomy

Explanations
a. Rated down one level for inconsistency
b. Rated down one level for imprecision
c. Rated down two levels for imprecision

Appendix G. Active Surveillance/Active Monitoring

Table G-1. Risk of bias assessments for randomized controlled trials: active surveillance/active monitoring

Intervention/ Comparison (Outcomes) Follow-up Time	Author, Year	Selection Bias	Performance Bias	Detection Bias	Attrition	Reporting Bias	Other Bias	Overall Rating
AS/PDT (QoL) 24 months	Azzouzi 2017[10]	Low	High	Low	High	Medium	None	Medium
AS/PDT (harms) 24 months	Azzouzi 2017[10]	Low	High	Low	Medium	Medium	None	Medium
AM/RT (mortality/metastases) 10 years	Hamdy 2016[11] Donovan 2016[12] Lane 2016[13] Neal 2020[14]	Low	Low	Low	Low	Low	None	Low
AM/RT (harms) 10 years	Hamdy 2016[11] Donovan 2016[12] Lane 2016[13] Neal 2020[14]	Low	Low	Low	Moderate	Low	None	Low

Abbreviations: AS=active surveillance; PDT=photodynamic therapy; QoL=quality of life; RP= radical prostatectomy; RT=radiation therapy

Table G-2. Summary risk of bias assessments for observational studies: active surveillance

Intervention/ Comparison (Outcomes)	Author, Year	Bias Due to Confounding	Bias in Selection of Participants	Bias in Classification of Interventions	Bias Due to Deviations for Intended Interventions	Bias Due to Missing Data	Bias in Measurement of Outcomes	Bias in Selection of the Reported Result	Overall
AS/RP	Thomsen 2019[15]	Moderate	Serious	Critical	No Information	Low	Low	Low	Critical
	Barocas 2013[16]; Barocas 2017[17]; Tyson 2017[18]	Moderate	Low	Moderate	Low	Serious	Moderate	Low	Serious
AS/ADT, RT, RP	Herden 2016[4]; Ansmann 2018[19]	Moderate	Low	Moderate	Low	Serious	Serious	Low	Serious
AS/RP	Tosoian 2016[20]	Serious	Moderate	Moderate	Serious	No Information	Moderate	Low	Critical

Abbreviations: ADT=androgen deprivation therapy; AM=active monitoring; AS=active surveillance; RT=radiation therapy; RP= radical prostatectomy

Table G-3. Characteristics of eligible studies: active surveillance comparisons

Study Design Country ROB	N=	Population	Intervention Frequency Duration	Comparison Frequency Duration	Followup Time(s) Outcome (Instrument)
Azzouzi 2017[10] RCT 10 European countries Medium	413	Adult men with low-risk CLPC (cT2a) diagnosed by transrectal ultrasound - guided biopsy Gleason pattern 3 T1c: 87% T2a: 13% Age 64 99% White	Active Surveillance Biopsy: 1-year intervals PSA & digital rectal exam: 3-month intervals	Photo dynamic therapy Drug + laser padeliporfin (IV)+laser (753nm) energy dose: 200J/cm padeliporfin: 10 min; laser: 22 min	1 year QoL (EQ-5D) 2 years QoL (EQ-5D) Bladder dysfunction Sexual dysfunction (IIEF-15)
Hamdy 2016[11-14, 21] RCT United Kingdom Low	1090	Men with median PSA level of 4.6 ng/milliliter and a Gleason score of 6 (77%) T1c : 76% T2: 23% Gleason sum 6: 78% 7: 20% 8-10: 2% Age 62 99% White	Active Monitoring: PSA at 3-month intervals year 1; 6-month to 1-year intervals thereafter. 50% increase previous 1-year triggered review	3D-CRT 74 Gy in 37 fractions With neoadjuvant ADT for 3 to 6 months before RT	5 years Prostate-specific mortality 10 years Prostate-specific mortality All-cause mortality Metastases

Abbreviations: 3D-CRT=three-dimensional conformal radiation therapy; CLPC=clinically localized prostate cancer; EQ-5D=EuroQoL-5D; Gy=Gray; IIEF-15=International Index of Erectile Function; IV=intravenous; J/cm=Joules per centimeter; min=minutes; ng/ml=nanogram per milliliter; nm=nanometer; PSA=Prostate-specific antigen; RCT=randomized controlled trial; ROB=risk of bias

Table G-4. Mortality, survival, and metastases: active surveillance

Intervention/ Comparison	Study Design (Trial/Registry) Followup Risk of Bias	Overall Survival and Mortality	Prostate Cancer Specific Survival and Mortality	Metastatic Progression Free Survival	Metastases
AS/PDT	Azzouzi 2017[10] RCT CLIN1001 PCM301 2 years Low	NR	NR	NR	NR
AM/RT	Hamdy 2016[11, 12, 14] RCT ProtecT 10 years Low	AM: 11% (59/545) RT: 10% (55/545) RR*=1.07 (0.76 to 1.52)	AM: 1.5% (8/545) RT: 1% (4/545) RR*=2.0 (0.6 to 6.6)	NR	AM: 6% (33/545) RT: 3% (16/545) RR*=2.06 (1.15 to 3.7)

*Calculated by EPC

Abbreviations: AM=active monitoring; AS=active surveillance; NR=Not Reported; PDT=photodynamic therapy; RCT=randomized controlled trial; RP=radical prostatectomy; RR=relative risk; RT=radiation therapy

Table G-5. Health status and quality of life: active surveillance comparisons

Intervention/ Comparison	Study Design (Trial/Registry) Followup Risk of Bias	Health Status	Quality of Life Prostate Cancer Related Quality of Life
AS/PDT	Azzouzi 2017[10] RCT CLIN1001 PCM301 2 years Low	NR	EQ-5D, Adjusted mean change (95% CI) AS: -3.0 (-5.0, -1.0) PDT: -2.3 (-4.2, -0.4) Difference: -0.7

Abbreviations: AS=active surveillance; EQ-5D=EuroQoL-5D; NR=Not Reported; PDT=photodynamic therapy; RCT=randomized controlled trial

Table G-6. Harms: active surveillance comparisons

Intervention/ Comparison	Study (Trial) Followup Risk of Bias	Adverse Effects
AS/PDT	Azzouzi 2017[10] RCT CLIN1001 PCM301 2 years Low	Bladder Dysfunction, RR (95% CI) Urinary incontinence: not defined AS: 5% (10/207) PDT: 10% (19/197) RR*=0.501 (0.24 to 1.05) Urinary retention: not defined, RR (95% CI) AS: 1% (2/207) PDT: 16% (32/197) RR*=0.059 (0.014 to 0.25) Hematuria: not defined, RR (95% CI) AS: 3% (6/207) PDT: 28% (56/197) RR*=0.102 (0.05 to 0.23) Sexual Dysfunction IIEF-15: no difference between groups Erectile dysfunction: not defined, RR (95% CI) AS: 12% (24/207) PDT: 38% (74/197) RR*=0.31 (0.21 to 0.47) Perineal pain: not defined, RR (95% CI) AS: 0.5% (1/207) PDT: 15% (30/197) RR*=0.032 (0.004 to 0.23)

Intervention/ Comparison	Study (Trial) Followup Risk of Bias	Adverse Effects
RT/AM	Hamdy 2016[11-13] RCT ProtecT 6 years Low	Bladder Dysfunction, RR (95% CI) Urinary incontinence: Percent of men reporting more than 1 pad per day in past 4 weeks 1 year AM: 4% (15/357) RT: 4% (13/358) RR*=1.16 (0.56 to 2.40) 6 years AM: 8% (38/453) RT: 4% (16/452) RR*=2.37 (1.34 to 4.19) Sexual Dysfunction, RR (95% CI) Erectile dysfunction: Men unable to have an erection or able to have an erection that is of insufficient strength for vaginal penetration 1 year AM: 51% (173/340) RT: 62% (219/351) RR*=0.82 (0.71 to 0.93) 6 years AM: 70% (318/452) RT: 73% (331/456) RR*=0.97 (0.89 to 1.05) Bowel Dysfunction, RR (95% CI) Fecal incontinence: Percent of men reporting fecal incontinence more than once per week 1 year AM: 1% (4/356) RT: 4% (14/358) RR*=0.64 (0.31 to 1.29) 6 years AM 3% (12/462) RT: 4% (19/465) RR*=0.64 (0.31 to 1.3)

*Calculated by EPC

Abbreviations: AM=active monitoring; AS=active surveillance; IIEF-15=International Index of Erectile Function; PDT=photodynamic therapy; RCT=randomized controlled trial; RR=relative risk; RT=radiation therapy

Table G-7. Evidence certainty: active surveillance comparisons

Intervention/ Comparison Outcome	k= Study Design	Risk of Bias	Inconsist-ency	Indirect-ness	Impre-cisions	Other Consid-erations	I	C	Relative (95% CI)	Absolute (95% CI)	Certainty
AM/EBRT + ADT All-cause mortality 10 years	1 RCT	Not serious	Not serious	Not serious	Serious	None	59/545 (11%)	55/545 (10%)	**RR 1.07** (0.8 to 1.50)	0.7% (-2.9 to 4.4)	Moderate ⊕⊕⊕◯[a]
AM/ EBRT + ADT PC-specific mortality 10 years	1 RCT	Not serious	Not serious	Not serious	Very serious	None	8/545 (1.5%)	4/545 (0.7%)	**Peto OR 1.96** (0.63 to 6.12)	0.7% (-0.5 to 1.9)	Low ⊕⊕◯◯[b]
AM/ EBRT + ADT Metastases 10 years	1 RCT	Not serious	Not serious	Not serious	Serious	None	33/545 (6%)	16/545 (3%)	**RR 2.1** (1.15 to 3.70)	3.1% (0.67 to 5.6)	Moderate ⊕⊕⊕◯[a]
AM/ EBRT + ADT Erectile dysfunction 6 years	1 RCT	Not serious	Not serious	Not serious	Very serious	None	318/452 (70%)	331/456 (73%)	**RR 0.97** (0.89 to 1.05)	-2.4% (-8.2 to 3.5)	Low ⊕⊕◯◯[b]
AM/ EBRT + ADT Urinary incontinence 6 years	1 RCT	Not serious	Not serious	Not serious	Serious	None	38/453 (8%)	16/452 (4%)	**RR 2.37** (1.34 to 4.19)	4.8% (1.8 to 7.9)	Moderate ⊕⊕⊕◯[a]
AM/ EBRT + ADT Fecal incontinence	1 RCT	Not serious	Not serious	Not serious	Very serious	None	12/462 (3%)	19/465 (4%)	**RR 0.64** (0.31 to 1.30)	-1.5 (-3.8 to 0.82)	Low ⊕⊕◯◯[b]
AS/PDT Urinary incontinence 2 years	1 RCT	Serious	Not serious	Not serious	Very serious	None	10/207 (5%)	19/197 (10%)	**RR 0.50** (0.24 to1.05)	-4.8% (-9.9 to 2.4)	Insufficient ⊕◯◯◯[b, c]

Intervention/ Comparison Outcome	k= Study Design	Risk of Bias	Inconsist-ency	Indirect-ness	Impre-cisions	Other Consid-erations	I	C	Relative (95% CI)	Absolute (95% CI)	Certainty
AS/PDT Urinary retention 2 years	1 RCT	Serious	Not serious	Not serious	Not serious	None	2/207 (1%)	32/197 (16%)	**RR 0.06** (0.01 to 0.24)	15.3% (-20.6 to -10)	Moderate ⊕⊕⊕◯[c]
AS/PDT Erectile dysfunction 2 years	1 RCT	Serious	Not serious	Not serious	Not serious	None	24/207 (12%)	74/197 (38%)	**RR 0.31** (0.20 to 0.50)	-26% (-34 to -18)	Moderate ⊕⊕⊕◯[c]

Abbreviations: ADT=androgen deprivation therapy; AM=active monitoring; AS=active surveillance; C=control; CI=confidence interval; EBRT=external beam radiation therapy; I=intervention; PDT=photodynamic therapy; RCT=randomized controlled trial; RR=relative risk

Explanations
a. Rated down one level for imprecision
b. Rated down two levels for imprecision
c. Rated down one level for risk of bias

Appendix H. External Beam Radiation Therapy

Table H-1. Risk of bias assessments for randomized controlled trials: external beam radiation therapy

Intervention/ Comparison (Outcomes)	Author, Year	Selection Bias	Performance Bias	Detection Bias	Attrition	Reporting Bias	Other Bias	Overall
Extreme hypofractionated PBRT/ Standard PBRT	Vargas 2018[22]	Low	Low	Unclear	High	Low	High	High
3D-CRT + ADT/ 3D-CRT + ADT + LDR-PB boost	Morris 2017[23] Rodda 2017[24] Rodda 2017[25]	Low	Low	Low	Low	Low (High for Rodda 2017[25]	High	Medium
3D-CRT/ IMRT	Viani 2016[26]	Low	Unclear	Unclear	High	Low	Low	Medium
EBRT + ADT/EBRT (overall mortality/survival, prostate cancer mortality, distant metastasis, late toxicity, quality of life)	Bolla, 2016[27]	Low	High	High	Low	Low	None	Medium
EBRT + ADT/EBRT (overall survival/mortality, distant metastasis, erectile function, quality of life)	McPartlin, 2016[28]	Low	Unclear	Unclear	Low	Low	None	Medium
EBRT + ADT/EBRT (stratified results reported for ± brachytherapy) (IPSS, EPIC scores, erectile function, adverse events/toxicity)	Vargas, 2019[29]	Low	Unclear	High	High	Unclear	Yes	High
EBRT + ADT/EBRT (overall mortality, prostate cancer mortality)	Phillips, 2014[30] McDuff, 2018[31] Giacalone, 2016[32]	Low	Low	High	Low	High	None	Medium
EBRT + neoadjuvant and concurrent ADT/EBRT + concurrent and adjuvant ADT (overall mortality, prostate cancer mortality, metastasis, late toxicity)	Malone 2019[33]	Low	Unclear	High	Low	Low	None	Medium

Intervention/ Comparison (Outcomes)	Author, Year	Selection Bias	Performance Bias	Detection Bias	Attrition	Reporting Bias	Other Bias	Overall
Conventionally fractionated EBRT/Ultra-hypofractionated EBRT (overall mortality, prostate cancer mortality, metastasis, harms)	Widmark 2019[34]	Low	Unclear	High	Low (except harms at longer follow-up)	Low	None	Medium

Abbreviations: 3D-CRT=3-dimensional conformal radiation therapy; ADT=androgen deprivation therapy; EBRT=external beam radiation therapy; EPIC=Expanded Prostate Cancer Index Composite; IPSS=International Prostate Symptom Score; IMRT=intensity-guided radiation therapy; LBR-PB=low dose rate prostate brachytherapy; NR=not reported; PBRT=proton beam radiation therapy

Table H-2. Summary risk of bias assessments for observational studies: external beam radiation therapy

Intervention/ Comparison (Outcomes)	Author, Year	Bias Due to Confounding	Bias in Selection of Participants	Bias in Classification of Interventions	Bias Due to Deviations for Intended Interventions	Bias Due to Missing Data	Bias in Measurement of Outcomes	Bias in Selection of the Reported Result	Overall
EBRT/ Brachytherapy	Smith 2015[35]	Serious	Serious	Moderate	No information	Low	Moderate	Low	Serious
EBRT ± Brachytherapy	Lee 2018[36]	Moderate	Critical	Moderate	Low	Moderate	Low	Low	Critical
	Abugharib 2017[37]	Serious	Serious	Low	Low	No information	Serious	Moderate	Serious
EBRT/ Brachytherapy + EBRT	Muralidhar 2016[38]	Serious	Serious	Serious	No information	Moderate	Moderate	Moderate	Serious
	Xiang 2015[39]	Serious	Serious	Serious	No information	No information	Moderate	Moderate	Serious
Brachytherapy/ Brachytherapy + EBRT	Yang 2017[40]	Serious	Moderate	Moderate	No information	Moderate	Moderate	Moderate	Serious
	Amini 2016[41]	Moderate	Moderate	Low	No information	No information	Low	Moderate	Moderate (for propensity score-matched analyses)
	Tward 2016[42]	Serious	Serious	Moderate	No information	No information	Moderate	Moderate	Serious
EBRT/ Brachytherapy ± EBRT	Ashmalla 2017[43]	Serious	Serious	Low	No information	No information	Moderate	Moderate	Serious

Intervention/ Comparison (Outcomes)	Author, Year	Bias Due to Confounding	Bias in Selection of Participants	Bias in Classification of Interventions	Bias Due to Deviations for Intended Interventions	Bias Due to Missing Data	Bias in Measurement of Outcomes	Bias in Selection of the Reported Result	Overall
EBRT/ Brachytherapy/ EBRT ± Brachytherapy	Jackson 2017[44]	Serious	Serious	Low	No information	No information	Moderate	Low	Serious
Brachytherapy/ EBRT/ Brachytherapy + EBRT	Jiang 2015[45]	Moderate	Serious	Moderate	No information	No information	Moderate	Low	Serious
IMRT/ SBRT	Ricco 2017[46]	Moderate	Moderate	Low	No information	Low	Low	Moderate	Moderate
IMRT/ SBRT/ Brachytherapy	Evans 2015[47]	Critical	Serious	Moderate	No information	Moderate	Moderate	Low	Critical
EBRT + ADT/ADT (overall mortality and prostate cancer mortality)	Bekelman, 2015[48]	Serious (did not adjust for PSA)	Low	Low	Low	Low	Moderate (except overall mortality)	Moderate	Serious
EBRT + adjuvant ADT/EBRT + neoadjuvant ADT (overall survival and distant metastasis-free survival)	Weller 2015[49]	Serious (did not adjust for age or co-morbidity)	Low	Moderate	Low	Low	Moderate (except overall survival)	Moderate	Serious
EBRT/ Brachytherapy	Goy 2019[50]	Moderate	Moderate	Moderate	No information	No information	Low	Moderate	Moderate

Abbreviations: ADT=androgen deprivation therapy; EBRT=external beam radiation therapy; IMRT=intensity-modulated radiation therapy; PSA=prostate specific antigen; SBRT=stereotactic body radiation therapy

Table H-3. Characteristics of eligible studies: external beam radiation therapy

Study Design Country ROB	N=	Population	Intervention Frequency Duration	Comparison Frequency Duration	Followup Time(s) Outcome (Instrument)
Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiation (ASCENDE-RT) Trial RCT Morris 2017[23] Medium ROB Rodda 2017[24] Medium ROB Rodda 2017[25] High ROB Canada	398 treatment outcomes and harms 357 for QOL	High or intermediate risk according to National Comprehensive Cancer Network criteria; Gleason sum ≥8; PSA >20 ng/mL T1c-T2c: 71% T3a: 29% Gleason sum 6: 5% 7: 54% 8-10: 41% Age 68 Race NR	Dose escalated 3D-CRT 115 Gy (minimal peripheral dose) With 12 months neoadjuvant ADT (depot injection and oral nonsteroidal antiandrogen + pelvic irradiation (46 Gy in 23 fractions) started 8 months before RT	3D-CRT with low dose rate prostate brachytherapy (LDR-PB) boost 32 Gy in 16 fractions With 12 months neoadjuvant ADT (depot injection and oral nonsteroidal antiandrogen) + pelvic irradiation (46 Gy in 23 fractions) started 8 months before RT	5, 9 years Mortality Overall survival Metastasis-free survival Prostate cancer-specific survival 2, 5 years Incontinence pad use 1, 5 years Erectile function 1 year Health-related QOL (SF36) – high ROB
Ricco 2017[46] Retrospective database analysis US Medium	5,430	Propensity-matched subset of the National Cancer Database (2004-2013). Excluded people who received other treatments, or who received RT doses outside the thresholds to the right. T1: 80% T2: 19% Gleason sum 6: 56% 7: 38% 8: 4% 9: 1% Age 69 87% White 11% Black	IMRT 72-86.4 Gy	SBRT 35-50 Gy	8 years Overall survival

Study Design Country ROB	N=	Population	Intervention Frequency Duration	Comparison Frequency Duration	Followup Time(s) Outcome (Instrument)
Amini 2016[41] Retrospective database analysis US Medium (for propensity score-matched analyses)	5,858	Propensity-matched subset of the National Cancer Database (2004-2006). Excluded people with high-risk features (>T3, Gleason 8-10, etc) and people who received other surgical or chemotherapy treatments. Baseline characteristics NR separately for propensity-matched subset. T1: 61% T2: 39% Gleason sum 6: 27% 7: 73% Age 69 83% White 13% Black	Brachytherapy + EBRT EBRT doses 40-50.4 Gy in 1.8-2.0 Gy fractionations	Brachytherapy Dose NR	5, 7 years Overall survival
Viani 2016[26] RCT Brazil Medium	215	Treatment-naïve men with clinically localized prostate cancer; PSA>150 ng/mL Ta1-T2a: 79% T2b: 7% T2c-T3b: 14% Age 72 Race NR	3D-CRT 70 Gy in 25 fractions (single daily dose 2.8 Gy)	IMRT 70 Gy in 25 fractions (single daily dose 2.8 Gy)	1,3 years Prostate-Specific Quality of Life (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire [EORTC QLQPR25])

Study Design Country ROB	N=	Population	Intervention Frequency Duration	Comparison Frequency Duration	Followup Time(s) Outcome (Instrument)
Bolla 2016[27] RCT Multi-national (13 countries in Europe and Israel) Medium	819 randomized	Histologically confirmed prostate adenocarcinoma T1b to T2a (International Union Against Cancer 1997 staging criteria with PSA > 10 ng/mL or Gleason ≥7; no involvement of pelvic lymph nodes as assessed by computed tomography scan, magnetic resonance imaging, or laparoscopic surgery; no clinical evidence of metastatic spread; or clinical tumor stages T2b to T4 and a PSA level of up to 12.5 times the upper limit of the normal range; a WHO performance status ≤2; no previous pelvic irradiation or radical prostatectomy; no previous hormonal therapy; no other malignancy except adequately treated basal cell carcinoma of the skin or another malignancy cured for at least 5 years. T1a (ineligible): 0.1% T1b: 3.3% T1c: 44.8% T2a: 50.9% T2b (ineligible): 0.9% Gleason (sum) <6: 11.2% Gleason (sum) 6: 37.9% Gleason (sum) 7: 40.9% Gleason (sum) 8-10: 10.0% Age (median): 70 years Race: NR	EBRT (predominantly 3D-CRT) plus ADT 3D-CRT or IMRT was performed. The radiation dose was a center-chosen characteristic. RT was delivered once per day, five fractions per day of 2 Gy per week at a dose of 46 Gy for PTV I; 24 Gy for PTV II; and 0, 4, or 8 Gy for PTV III, depending on center policy, resulting in total doses of 70, 74, or 78 Gy, respectively. Median RT duration ranged from 51-57 days. ADT consisted of two subcutaneous injections of every-3 months depot of LHRH analog (goserelin) given the first day of RT, then 3 months later. Flare protection consisted of 1 month of antiandrogen (bicalutamide; 50 mg/d) started 1 week before the first LHRH injection.	EBRT (predominantly 3D-CRT)	*10 years:* Distant metastasis Overall survival *7.2 years (median follow-up):* Prostate cancer mortality Distant metastases Overall survival *From 6 months to end of follow-up (7.2 median):* Late toxicity *5 years:* Distant metastases Overall survival *3 years:* Quality of life scales (EORTC QLQ) *1 year:* Quality of life scales (EORTC QLQ)

Study Design Country ROB	N=	Population	Intervention Frequency Duration	Comparison Frequency Duration	Followup Time(s) Outcome (Instrument)
McPartlin 2006[28] RCT Canada Medium	252 randomized	Prostate carcinoma with T1b through T2 tumors, Gleason scores from 6 to 8, and prostate-specific antigen (PSA) levels ≤20 ng/mL. Patients who had clinical T1b/T2a tumors and a Gleason score of 6 were required to have PSA levels from 10 to 20 ng/mL. All patients who had PSA levels >10 ng/mL had a negative bone scan within 12 months of study entry. No previous hormone or cytotoxic therapy was permitted before study entry. All patients had an Eastern Cooperative Oncology Group performance status ≤2, were aged ≤80 years, and had no contraindication to DE-EBRT. T1b-T2a: 77.59% T2b-T2c: 22.41% Gleason 3+3: 12.45% Gleason 3+4: 57.26% Gleason 4+3: 24.90% Gleason 3+5: 1.24% Gleason 4+4: 3.73% Gleason 5+3: 0.41% Age (median): 71.4 and 70.9 years in the two treatment groups Race: NR	EBRT (IMRT) plus bicalutamide Patients received RT using 6-coplanar, equally weighted 18 MV beams or IMRT, with daily imaging using an electronic portal imaging device and setup verification using fiducial markers. From 1999 to 2001, patients received 75.6 Gy in 42 fractions over 8.5 weeks. Subsequently, the dose was increased up to 79.8 Gy in 42 fractions and then to 78 Gy in 39 fractions as experience with DE-EBRT increased. Bicalutamide was given at 150 mg, 5 months of neoadjuvant and adjuvant starting 3 months before RT.	EBRT (IMRT)	*10 years:* Overall survival *9.1 years (median follow-up):* Overall survival Distant metastases *5 years:* Overall survival *>4 years:* Sexual function (IIEF) Quality of life (EORTC-30) *1 year:* Sexual function (IIEF) Quality of life (EORTC-30) *Timing of outcome not clearly reported:* Late toxicity

Study Design Country ROB	N=	Population	Intervention Frequency Duration	Comparison Frequency Duration	Followup Time(s) Outcome (Instrument)
Phillips, 2014[30] McDuff, 2018[31] Giacalone, 2016;[32] (all secondary references to D'Amico 2008[51]) RCT US Medium	206 randomized	T1B to T2b, NX, MO adenocarcinoma of the prostate. Patients with PSA of at least 10 ng/mL (maximum 40 ng/ML) or a Gleason score of at least 7 (range, 5-10). Low-risk patients were ineligible unless they had radiographic evidence using endorectal coil MRI of extracapsular extension or seminal vesicle invasion. Patients were also considered ineligible if they had a prior history of malignancy except for nonmelanoma skin cancer or any history of hormone therapy use. All patients were required to have a negative bone scan and pelvic lymph node assessment using MRI or CT within 6 months of randomization. Eligible patients also needed to have an Eastern Cooperative Oncology Group performance status of 0 or 1 (range, 0-4), white blood cell count of at least 3000/μL, hematocrit of more than 30%, platelet count of more than $100x10^3$/μL, and a life expectancy of least 10 years, excluding death related to prostate cancer at study entry. T1b: 1.94% T1c: 46.12% T2a: 22.33% T2b: 29.61% Gleason 5 or 6: 27.67% Gleason 3+4: 34.95% Gleason 4+3: 22.82% Gleason 8-10: 14.56% Age (median): 73 and 72 years in the two treatment groups Race: NR	EBRT (3D-CRT) plus ADT EBRT consisted of 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. ADT included a LHRH agonist and the antiandrogen flutamide.	EBRT (3D-CRT)	*16.62 years* Overall mortality Prostate cancer mortality *14.26 years* Prostate cancer mortality

Study Design Country ROB	N=	Population	Intervention Frequency Duration	Comparison Frequency Duration	Followup Time(s) Outcome (Instrument)
Malone, 2019[33] RCT Canada Medium	432 randomized	Men age > 18 years with Eastern Cooperative Oncology Group performance status < 2 and histologically confirmed diagnosis of adenocarcinoma of the prostate, with Gleason score ≤ 7, clinical tumor stage of T1b to T3a, and serum PSA < 30 ng/mL ≤ 4 weeks before enrollment. Patients with baseline PSA ≥ 10 ng/mL underwent a whole-body bone scan ≤ 12 weeks before study entry, whereas those with PSA ≥ 20 ng/mL underwent a contrast-enhanced CT scan of the abdomen and pelvis performed ≤ 12 weeks before study entry. Patients with low-risk PCa (Gleason score ≤ 6, T1-T2a, and PSA ≤ 10 ng/mL) or radiologic evidence of nodal or distant metastasis were excluded. Also excluded were patients with active or prior malignancies, except for nonmelanoma skin carcinoma within 5 years of the diagnosis of PCa; those with contraindications to RT, including inflammatory bowel disease; and those who had received prior pelvic RT, cytotoxic chemotherapy, or ADT. T1b-T1c: 46.3% T2a: 23.8% T2b-T2c: 28.7% T3: 1.2% Gleason < 7: 22.9% Gleason 7: 77.1% Age: 69.1 years Race: NR	EBRT (3D-CRT) plus neoadjuvant and concurrent ADT A total RT dose of 76 Gy in 38 fractions over 7.5 weeks using 3D-CRT and over 2 phases. In the first phase, 56 Gy was delivered to the prostate and proximal 10 mm of seminal vesicles in 28 fractions over 5.5 weeks. An additional boost of 20 Gy in 10 fractions was subsequently delivered to the prostate alone over 2 weeks. 6 months ADT starting 4 months before RT. ADT comprised of an oral antiandrogen (bicalutamide 50 mg once daily) plus goserelin (10.8 mg subcutaneously starting 7 days after bicalutamide with a second injection administered 3 months thereafter).	EBRT (3D-CRT) plus concurrent and adjuvant ADT 6 months ADT starting simultaneously with RT.	*12.17 years* Overall mortality Prostate cancer mortality Distant progression *10 years* Overall survival Prostate cancer mortality Metastatic-free survival *3 years* Late toxicity

Study Design Country ROB	N=	Population	Intervention Frequency Duration	Comparison Frequency Duration	Followup Time(s) Outcome (Instrument)
Goy 2019[50] Retrospective database analysis US Medium (for propensity score-matched analyses	684	Men with intermediate-risk prostate cancer, classified as clinical stage T2b-c, GS 3 + 4 (group 2) or 4 + 3 (group 3), and/or iPSA of 10.1-20.0. The men were clinically staged, with a digital rectal examination for T-stage from the 2002 American Joint Committee Cancer staging. T1a-b: <1% T1c: 69% T2a: 20% T2b: 11% Gleason 6 (3+3): 30% Gleason 7 (3+4): 48% Gleason 7 (4+3): 22% Age (median): EBRT 70.8 years, brachytherapy 65.3 years 49% White 25% Black 17% Hispanic	EBRT (3D-CRT) (+/- neoadjuvant ADT) Median dose to the isocenter was 75.3 Gray (range 73.5-77.1) over 8 1/2 weeks, with 94% receiving 75.3 Gray. Neoadjuvant androgen deprivation therapy was given using Leuprolide for a median 6 months for 59% of the EBRT patients.	Brachytherapy (+/- neoadjuvant ADT) Administered as Iodine-125 radioactive seeds A minimum peripheral dose of 145 Gray was prescribed Neoadjuvant androgen deprivation therapy was given using Leuprolide for a median 4 months in 13% of the patients	*10 years (medians of 9.6 and 9.8 years for EBRT and brachytherapy, respectively)* Overall survival Prostate cancer mortality Metastatic-free survival *5 years:* Overall survival Prostate cancer mortality Metastatic-free survival

Study Design Country ROB	N=	Population	Intervention Frequency Duration	Comparison Frequency Duration	Followup Time(s) Outcome (Instrument)
Widmark, 2019[34] RCT Sweden and Denmark Medium ROB	1200 randomized	Participants were men up to 75 years of age with histologically verified intermediate-to-high risk prostate cancer and WHO performance status between 0 and 2. Intermediate-to-high-risk prostate cancer was categorized according to TNM classification system as T1c-T3a with no evidence of lymph node involvement or distant metastases with one or two of the following risk factors: stage T3a, Gleason score of at least 7, or PSA of at least 10 ng/mL. The maximum PSA allowed was 20 ng/mL and no ADT was permitted. T1c: 51.0% T2: 44.7% T3a: 4.3% Gleason 5: 0.6% Gleason 6: 17.4% Gleason 7: 75.5% Gleason 8: 5.9% Gleason 9: 0.6% Age: median 69 and 68 years in the two treatment groups, respectively Race: NR	EBRT conventional fractionation Radiotherapy was delivered with image-guided 3D-CRT, IMRT, or VMAT with use of fiducial markers. 80% of patients received 3D-CRT and 20% VMAT/IMRT. No ADT was permitted. Patients in the conventional fractionation group received 78.0 Gy in 39 fractions 5 days per week for 8 weeks.	EBRT ultra-hypofractionation Patients in the ultra-hypofractionation arm received 42.7 Gy in 7 fractions 3 days per week for 2.5 weeks inclusive of two weekends.	*5 years* Overall mortality/survival Prostate cancer mortality/survival Distant progression *2 years* Bowel, urinary, and erectile harms *1 year* Bowel, urinary, and erectile harms *harms also reported at longer follow-up but not extracted due to the extent of missing data

Abbreviations: 3D-CRT=3 dimensional conformal radiation therapy; ADT=androgen deprivation therapy; AEs=adverse effects; ASCENDE-RT=Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiation; CT=Computed tomography; DE-EBRT=dose escalated external beam radiation therapy; EBRT=external beam radiation therapy; EPIC=Expanded Prostate Cancer Index Composite; EORTC QLQPR25=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; Gy=Gray units; IIEF=International index of erectile function; IMRT=intensity modulated radiation therapy; IPSS=International Prostate Symptom Score; LDR-PB=low dose rate prostate brachytherapy; LENT-SOMA= Late Effects of Normal Tissue – Somatic, Objective, Management, Analytic scale; LHRH=Luteinizing hormone-releasing hormone; MRI=Magnetic resonance imaging; ml=milliliters; ng=nanograms; NR=not reported; PBRT=proton beam radiation therapy; PCa=prostate cancer; PSA=prostate-specific antigen; QOL=quality of life; RCT=randomized controlled trial; ROB=risk of bias; RT=radiation therapy; SEER=Surveillance, Epidemiology, and End Results; SF36=short form 36 item health survey questionnaire; T=clinical T stage; US=United States; VMAT=volumetric modulated arc therapy; WHO=World Health Organization

Table H-4. Mortality, survival, and metastases outcomes: external beam radiation therapy

Intervention/ Comparison	Study Design (Trial/Registry) Followup Risk of Bias	Overall Survival and Mortality	Prostate Cancer Specific Survival and Mortality	Metastatic Progression Free Survival Metastases
3D-CRT + ADT/3D-CRT + ADT + LDR-PB boost	ASCENDE-RT[23, 24] RCT Median 6.5 years Medium	**Mortality (ITT), % (n/N)** 3D-CRT + ADT: 19% (38/200) LDR-PB: 15% (30/198) RR*=1.25 (95% CI 0.81 to 1.94) p=0.31 **Overall survival, KM Estimate (95% CI)** 5 years 3D-CRT +ADT: 88.7 (4.8) LDR-PB: 91.3 (4.4) 9 years 3D-CRT +ADT: 73.6 (8.4) LDR-PB: 77.9 (8.2)	**Prostate cancer-specific mortality (ITT), % (n/N)** 3D-CRT + ADT: 6% (11/200) LDR-PB: 4% (7/198) RR*=1.56 (95% CI 0.62 to 3.93) p=0.35 **Prostate cancer-specific survival, KM Estimate (±95% CI)** 5 years 3D-CRT + ADT: 97.5 (2.4) LDR-PB: 96.8 (2.8) 9 years 3D-CRT + ADT: 92.1 (5.6) LDR-PB: 94.8 (4.0)	**Metastasis-free survival, KM Estimate (±95% CI)** 5 years 3D-CRT + ADT: 92.5 (4.0) LDR-PB: 93.3 (3.8) 9 years 3D-CRT + ADT: 84.8 (7.6) LDR-PB: 88.6 (5.6) **Metastatic disease** 5 years 3D-CRT + ADT: 9% (18/200) LDR-PB: 9% (17/198) RR*=1.05 (95% CI 0.56 to 1.97) p=0.88
3D-CRT/ IMRT	Viani 2016[26] RCT 3 years Medium	NR	NR	NR
Brachytherapy + EBRT/ Brachytherapy	Amini 2016[41] Observational (National Cancer Database) 7 years Medium	**Overall survival, KM Estimate** Brachytherapy + EBRT: 85.8% Brachytherapy: 83.1% HR=0.85 (95% CI 0.75 to 0.97) p=0.006	NR	NR
IMRT/SBRT	Ricco 2017[46] Observational (National Cancer Database) 8 years Medium	**Overall survival, KM Estimate** IMRT: 77.2% SBRT: 79.4% Log-rank p-value p=0.65	NR	NR

Intervention/ Comparison	Study Design (Trial/Registry) Followup Risk of Bias	Overall Survival and Mortality	Prostate Cancer Specific Survival and Mortality	Metastatic Progression Free Survival Metastases
EBRT + ADT/EBRT	Bolla 2016[27] RCT (EORTC Trial 22991) Median follow-up 7.2 years Medium	<u>Overall survival</u> 5 years: EBRT + ADT: 91.3% (95% CI 88.0 to 93.7) EBRT: 88.4% (95% CI 84.7 to 91.3) 10 years: EBRT + ADT: ~72% (estimated from graph) EBRT: ~67% (estimated from graph) <u>Overall mortality</u> 7.2 years: EBRT + ADT: 69/410 (16.8%) EBRT: 83/409 (20.3%)	<u>Prostate cancer mortality</u> 7.2 years: EBRT + ADT: 9/410 (2.2%) EBRT: 16/409 (3.9%)	<u>Distant metastasis</u> 5 years: EBRT + ADT: ~3% (estimated from graph) EBRT: ~7% (estimated from graph) 7.2 years: EBRT + ADT: 18/410 (4.4%) EBRT: 31/409 (7.6%) 10 years: EBRT + ADT: ~7% (estimated from graph) EBRT: ~10% (estimated from graph)
	McPartlin 2016[28] RCT (PMH 9907) Median follow-up 9.1 years Medium	<u>Overall survival</u> 5 years: EBRT + ADT: ~92% (estimated from graph) EBRT: ~96% (estimated from graph) 9.1 years: EBRT + ADT: 82% (95% CI 75%-90%) EBRT: 86% (95% CI 80%-94%) p=0.37 HR [EBRT vs. EBRT + ADT] =1.33 (95% CI 0.72-2.47) 10 years: EBRT + ADT: ~78% (estimated from graph) EBRT: ~85% (estimated from graph) <u>Overall mortality</u> 9.1 years: EBRT + ADT: 23/119 (19.3%) EBRT: 18/122 (14.8%)	NR	<u>Distant metastasis</u> 9.1 years: Among patients who had biochemical relapse: EBRT + ADT: 24/47 (51.1%) EBRT: 35/51 (68.6%)

Intervention/ Comparison	Study Design (Trial/Registry) Followup Risk of Bias	Overall Survival and Mortality	Prostate Cancer Specific Survival and Mortality	Metastatic Progression Free Survival Metastases
	Phillips, 2014;[30] McDuff, 2018;[31] Giacalone, 2016[32] (all secondary references to D'Amico 2008[51]) RCT (NCT00116220) Median follow-up 14.26 to 18.19 years Medium	Overall mortality 16.62 years: EBRT + ADT: 76/102 (74.5%) EBRT: 80/104 (76.9%) Among patients with no/minimal comorbidity 16.62 years: EBRT + ADT: 53/78 (67.9%) EBRT: 57/79 (72.2%) HRadj=0.87 (95% CI, 0.57 to 1.34) Among patients with moderate/severe comorbidity 16.62 years: EBRT + ADT: 23/24 (95.8%) EBRT: 23/25 (92.0%) HRadj=2.42 (95% CI, 1.19 to 4.94)	Prostate cancer mortality 16.62 years: EBRT + ADT: 6/102 (5.9%) EBRT: 23/104 (22.1%) Among patients with no/minimal comorbidity 14.26 years: EBRT + ADT: 4/73 (5.5%) EBRT: 16/76 (21.1%) HRadj [EBRT vs. EBRT + ADT]=4.12 (95% CI, 1.10 to 15.35) 16.62 years: EBRT + ADT: 5/78 (6.4%) EBRT: 20/79 (25.3%) Among patients with moderate/severe comorbidity 16.62 years: EBRT + ADT: 1/24 (4.2%) EBRT: 3/25 (12.0%)	NR
EBRT + neoadjuvant and concurrent ADT/EBRT + concurrent and adjuvant ADT	Malone, 2019[33] RCT Median follow-up 12.17 years Medium	Overall mortality 12.17 years: EBRT + neoadjuvant and concurrent ADT: 75/215 (34.9%) EBRT + concurrent and adjuvant ADT: 72/217 (33.2%) Overall survival 10 years: EBRT + neoadjuvant and concurrent ADT: 76.4% (95% CI, 70.6% to 82.7%) EBRT + concurrent and adjuvant ADT: 73.7% (95% CI, 67.6% to 80.2%) Stratified log-rank test, p=0.70 HR univariate: 0.94 (95% CI, 0.68 to 1.30) HR multivariate: 1.04 (95% CI, 0.75 to 1.44)	Prostate cancer mortality 12.17 years: EBRT + neoadjuvant and concurrent ADT: 7/215 (3.3%) EBRT + concurrent and adjuvant ADT: 7/217 (3.2%) 10 years: EBRT + neoadjuvant and concurrent ADT: 2% EBRT + concurrent and adjuvant ADT: 1.9% P=0.98	Distant progression 12.17 years: EBRT + neoadjuvant and concurrent ADT: 12/215 (5.6%) EBRT + concurrent and adjuvant ADT: 9/217 (4.1%) Metastatic-free survival 10 years: EBRT + neoadjuvant and concurrent ADT: 94% (95% CI, 90.0% to 98.3%) EBRT + concurrent and adjuvant ADT: 95.1% (95% CI, 91.5% to 98.9%) P=0.60

Intervention/ Comparison	Study Design (Trial/Registry) Followup Risk of Bias	Overall Survival and Mortality	Prostate Cancer Specific Survival and Mortality	Metastatic Progression Free Survival Metastases
EBRT / Brachytherapy	Goy 2019[50] Observational Median follow-up 9.6-9.8 years Medium	<u>Overall survival (10-year propensity score adjusted probability)</u> Median follow-up 9.6-9.8 years EBRT + neoadjuvant ADT: 75.5% (95% CI, 71.8% to 79.4%) Brachytherapy: 78.3% (95% CI 70.1% to 87.4%) Overall mortality 5 years EBRT + neoadjuvant ADT: 26% (150/574) Unadjusted K-M probability for survival 90.6% Brachytherapy: 12% (13/110) Unadjusted K-M probability for survival 98.1%	<u>Overall survival (10-year propensity score adjusted probability)</u> Median follow-up 9.6-9.8 years EBRT + neoadjuvant ADT: 96.2% (95% CI, 94.3% to 98.1%) Brachytherapy: 95.4% (95% CI 91.1% to 100.0%) Prostate cancer-specific mortality 5 years EBRT + neoadjuvant ADT: 2.9% (16/574) Unadjusted K-M probability for survival 99.2% Brachytherapy: 2.7% (3/110) Unadjusted K-M probability for survival 99.0%	<u>Overall survival (10-year propensity score adjusted probability)</u> Median follow-up 9.6-9.8 years EBRT + neoadjuvant ADT: 90.6% (95% CI, 87.9% to 93.3%) Brachytherapy: 94.1% (95% CI 89.5% to 98.9%) Metastases 5 years EBRT + neoadjuvant ADT: 7.1% (41/574) Unadjusted K-M probability for survival 97.8% Brachytherapy: 6.4% (7/110) Unadjusted K-M probability for survival 97.1%

Intervention/ Comparison	Study Design (Trial/Registry) Followup Risk of Bias	Overall Survival and Mortality	Prostate Cancer Specific Survival and Mortality	Metastatic Progression Free Survival Metastases
Conventional fractionated EBRT/ultra-hypofractionated EBRT	Widmark, 2019[34] RCT Median follow-up 5 years Medium ROB	Overall mortality Median 5 years: Conventionally fractionated EBRT: 43/591 (7.3%) Ultra-hypofractioned EBRT: 46/589 (7.8%) Overall survival 5 years: Conventionally fractionated EBRT: 96.4% (95% CI, 94.6 to 98.1) Ultra-hypofractioned EBRT: 93.9% (95% CI, 91.7 to 96.2) Unadjusted HR: 1.11 (95% CI, 0.73 to 1.69) Log-rank test, p=0.951	Prostate cancer mortality Median 5 years: Conventionally fractionated EBRT: 8/591 (1.4%) Ultra-hypofractioned EBRT: 11/589 (1.9%) Prostate cancer specific survival 5 years: Conventionally fractionated EBRT: 99.8% (95% CI, 99.5 to 100) Ultra-hypofractionated EBRT: 98.2% (95% CI, 96.9 to 99.6) Unadjusted HR: 1.40 (95% CI, 0.56 to 3.49) Log-rank test, p=0.46	Distant failure Median 5 years: Conventionally fractionated EBRT: 39/591 (6.6%) Ultra-hypofractionated EBRT: 38/589 (6.5%) Distant failure (free of event) 5 years: Conventionally fractionated EBRT: 94.6% (95% CI, 92.5 to 96.8) Ultra-hypofractionated EBRT: 93.7% (95% CI, 91.5 to 96.0) Unadjusted HR: 0.99 (95% CI, 0.63 to 1.54) Log-rank test, p=0.95

Abbreviations**:** 3D-CRT=3-dimensional conformal radiation therapy; ADJ=adjusted; ADT=androgen deprivation therapy; ASCENDE-RT=Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiation; CI=confidence interval; EBRT=external beam radiation therapy; EORTC=European Organization for Research and Treatment of Cancer; HR=hazard ratio; IMRT=intensity-modulated radiation therapy; IMRT=intensity-modulated radiation therapy; ITT=intent to treat; KM=Kaplan-Meier estimate; LDR-PB=low dose rate prostate brachytherapy; NR=not reported; RCT=randomized controlled trial; ROB=risk of bias; RR=risk ratio; RT=radiation therapy; SBRT=stereotactic body radiation therapy

Table H-5. Health status and quality of life outcomes: external beam radiation therapy

Intervention/ Comparison	Study Design (Trial/Registry) Followup Risk of Bias	Health Status	Quality of Life Prostate Cancer Related Quality of Life
3D-CRT + ADT/3D-CRT + ADT + LDR-PB boost	ASCENDE-RT[23, 24] RCT Median 6.5 years (RT began 8 months after ADT) Medium	NR	NR

3D-CRT/ IMRT	Viani 2016[26] RCT 3 years Medium	NR	**Prostate-specific Quality of Life** **EORTC QLQPR25 items, Mean (SD):** **<u>1 year (n=181/215)</u>** **Urinary symptoms** 3D-CRT: 22 (21) IMRT: 12 (14) p<0.001 **Bowel symptoms** 3D-CRT: 9 (17) IMRT: 4 (10) p=0.02 **Treatment-related symptoms** 3D-CRT: 12 (13) IMRT: 9 (9) p=0.048 **Sexual function** 3D-CRT: 30 (22) IMRT: 27 (22) p=0.42 **Sexual activity** 3D-CRT: 56 (33) IMRT: 53 (35) p=0.55 **<u>3 years (n=175/215)</u>** **Urinary symptoms** 3D-CRT: 14 (15) IMRT: 12 (12) p=0.29 **Bowel symptoms** 3D-CRT: 4 (10) IMRT: 6 (12) p=0.31 **Treatment-related symptoms** 3D-CRT: 6 (8) IMRT: 8 (8) p=0.26 **Sexual function** 3D-CRT: 25 (24) IMRT: 23 (19) p=0.43 **Sexual activity** 3D-CRT: 64 (32) IMRT: 64 (36) p=0.90

Intervention/ Comparison	Study Design (Trial/Registry) Followup Risk of Bias	Health Status	Quality of Life Prostate Cancer Related Quality of Life
Brachytherapy + EBRT/ Brachytherapy	Amini 2016[41] Observational (National Cancer Database) 7 years Medium	NR	NR
IMRT/SBRT	Ricco 2017[46] Observational (National Cancer Database) 8 years Medium	NR	NR

Intervention/ Comparison	Study Design (Trial/Registry) Followup Risk of Bias	Health Status	Quality of Life Prostate Cancer Related Quality of Life
EBRT + ADT/EBRT	Bolla 2016[27] RCT (EORTC Trial 22991) Median Follow-up 7.2 years Medium	(see quality of life)	<u>Mean change in global health status/quality of life scale of EORTC QLQ</u> At 1 year: EBRT + ADT: -0.68 (SD 17.91), n=270 EBRT: 0.52 (SD 20.61), n=255 MD=-1.20 (95% CI, -4.51 to 2.11) At 3 years: EBRT + ADT: -2.29 (SD 19.60), n=262 EBRT: -2.91 (SD 21.08), n=269 MD=0.62 (95% CI, -2.84 to 4.08) <u>Mean change in sexual activity scale of EORTC QLQ</u> At 1 year: EBRT + ADT: -13.54 (SD 26.60), n=229 EBRT: 0.62 (SD 25.41), n=216 MD=-14.16 (95% CI, -18.99 to -9.33) At 3 years: EBRT + ADT: -4.19 (SD 23.96), n=215 EBRT: -1.98 (SD 24.34), n=219 MD=-2.21 (95% CI, -6.75 to 2.33) <u>Mean change in sexual functioning scale of EORTC QLQ</u> At 1 year: EBRT + ADT: -29.25 (SD 38.45), n=143 EBRT: -7.14 (SD 31.98), n=142 MD=-22.11 (95% CI, -30.32 to -13.90) At 3 years: EBRT + ADT: -15.56 (SD 34.95), n=131 EBRT: -13.96 (SD 34.64), n=157 MD=-1.60 (95% CI, -9.67 to 6.47) <u>Mean change in hormonal symptoms scale of EORTC QLQ</u> At 1 year: EBRT + ADT: 11.66 (SD 12.68), n=230 EBRT: 2.83 (SD 10.54), n=216 MD=8.83 (95% CI, 6.67 to 10.99) At 3 years: EBRT + ADT: 7.13 (SD 11.53), n=218 EBRT: 4.42 (SD 13.38), n=221 MD=2.71 (95% CI, 0.38 to 5.05)

Intervention/ Comparison	Study Design (Trial/Registry) Followup Risk of Bias	Health Status	Quality of Life Prostate Cancer Related Quality of Life
	McPartlin 2016[28] RCT (PMH 9907) Median follow-up 9.1 years Medium	NR	EORTC quality of life No data reported. From the article, "EORTC-30 questionnaire similarly identified no marked effect of the addition of bicalutamide, with stable overall QoL reported in both groups through the treatment period."
EBRT + neoadjuvant and concurrent ADT/EBRT + concurrent and adjuvant ADT	Malone, 2019 RCT Median follow-up 12.17 years Medium	NR	NR
EBRT / Brachytherapy	Goy 2019 Observational Median follow-up 9.6-9.8 years Medium	NR	NR
Conventional fractionated EBRT/ultra-hypofractionated EBRT	Widmark, 2019 RCT Median follow-up 5 years Medium ROB	NR	NR

Abbreviations: 3D-CRT=3-dimensional conformal radiation therapy; ADT=Androgen deprivation therapy; ASCENDE-RT=Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiation; CI=confidence interval; EBRT=external beam radiation therapy; EORTC=European Organisation for Research and Treatment of Cancer; HR=hazard ratio; IMRT=intensity-modulated radiation therapy; LDR-PB=low dose rate prostate brachytherapy; MD=Mean difference; NR=not reported; RCT=randomized controlled trial; ROB=risk of bias; RR=risk ratio; RT=radiation therapy; QLQ=Quality of Life Questionnaire; QoL=Quality of life; SBRT=stereotactic body radiation therapy; SD=standard deviation

Table H-6. Harms: external beam radiation therapy

Intervention/ Comparison	Study Design (Trial/Registry) Followup Risk of Bias	Adverse Effects
3D-CRT + ADT/3D-CRT + ADT + LDR-PB boost	ASCENDE-RT[23, 24] RCT Median 6.5 years (RT began 8 months after ADT) Medium	**Urinary incontinence and pad use** **Cumulative incidence at 5 years** 3D-CRT + ADT: 16% LDR-PB: 6% p<0.001 **Prevalence at 2 years** 3D-CRT + ADT: 8% LDR-PB: 1% p=0.003 **Prevalence at 5 years** 3D-CRT + ADT: 7% LDR-PB: 1% p=0.049 **Erectile function (defined as erection adequate for penetration)** **1 year** 3D-CRT + ADT: 7% (NR/195) LDR-PB: 5% (NR/188) p=NR **5 years** 3D-CRT + ADT: 31% (NR/195) LDR-PB: 34% (NR/188) p=0.60
3D-CRT/ IMRT	Viani 2016[26] RCT 3 years Medium	NR at eligible followup time
Brachytherapy + EBRT/ Brachytherapy	Amini 2016[41] Observational (National Cancer Database) 7 years Medium	NR

Intervention/ Comparison	Study Design (Trial/Registry) Followup Risk of Bias	Adverse Effects
IMRT/SBRT	Ricco 2017[46] Observational (National Cancer Database) 8 years Medium	NR
EBRT + ADT/EBRT	Bolla 2016[27] RCT (EORTC Trial 22991) Median Follow-up 7.2 years Medium	<u>Late genitourinary toxicity grade 3 to 4 (measured from 6 months until end of follow-up)</u> EBRT + ADT: 5.9%, calculated 24/406 based on safety sample size EBRT: 3.6%, calculated 15/407 based on safety sample size P=.14 <u>Severe impairment of sexual function (measured from 6 months until end of follow-up)</u> EBRT + ADT: 27.0%, calculated 110/406 based on safety sample size EBRT: 19.4%, calculated 79/407 based on safety sample size P=.01
	McPartlin 2016[28] RCT (PMH 9907) Median follow-up 9.1 years Medium	<u>Late genitourinary toxicity (timing of outcome not clearly reported)</u> Grade 2 EBRT + ADT: 9.6% EBRT: 5.5% Grade 3 EBRT + ADT: 11.4% EBRT: 11% <u>Late gastrointestinal toxicity (timing of outcome not clearly reported)</u> Grade 2 EBRT + ADT: 3.5% EBRT: 4.7% Grade 3 EBRT + ADT: 0% EBRT: 0.8% <u>IIEF</u> Not extracted due to high attrition

Intervention/ Comparison	Study Design (Trial/Registry) Followup Risk of Bias	Adverse Effects
EBRT + neoadjuvant and concurrent ADT/EBRT + concurrent and adjuvant ADT	Malone, 2019 RCT Median follow-up 12.17 years Medium	<u>Late gastrointestinal toxicity grade ≥ 3</u> 3 year cumulative incidence EBRT + neoadjuvant and concurrent ADT: 2.5% EBRT + concurrent and adjuvant ADT: 3.9% P=0.44 <u>Late genitourinary toxicity grade ≥ 3</u> 3 year cumulative incidence EBRT + neoadjuvant and concurrent ADT: 2.9%, calculated 6/213 based on late toxicity sample size EBRT + concurrent and adjuvant ADT: 2.9%, calculated 6/215 based on late toxicity sample size P=0.82
EBRT / Brachytherapy	Goy 2019[50] Observational Median follow-up 9.6-9.8 years Medium	NR
Conventional fractionated EBRT/ultra-hypofractionated EBRT	Widmark, 2019[34] RCT Median follow-up 5 years Medium ROB	<u>Urinary toxicity grade ≥1 (physician evaluated with the RTOG morbidity scale)</u> 2 years Conventional fractionated EBRT: 22.7% (113/497) Ultra-hypofractionated EBRT: 23.6% (116/492) 2 years cumulative incidence Conventional fractionated EBRT: 38.2% (95% CI, 34.4 to 42.4) Ultra-hypofractionated EBRT: 43.1% (95% CI, 39.2 to 47.4) 5 years Data not extracted due to missing data/high attrition <u>Urinary toxicity grade ≥2 (physician evaluated with the RTOG morbidity scale)</u> 1 year Conventional fractionated EBRT: 2.5% (13/529) Ultra-hypofractionated EBRT: 6.1% (32/528) 2 years Conventional fractionated EBRT: 5.6% (28/497) Ultra-hypofractionated EBRT: 5.1% (25/492) 2 years cumulative incidence

Intervention/ Comparison	Study Design (Trial/Registry) Followup Risk of Bias	Adverse Effects
		Conventional fractionated EBRT: 9.4% (95% CI, 7.3 to 12.1) Ultra-hypofractionated EBRT: 13.2% (95% CI, 10.7 to 16.3) 5 years Data not extracted due to missing data/high attrition <u>Urinary toxicity grade ≥3 (physician evaluated with the RTOG morbidity scale)</u> 2 years Conventional fractionated EBRT: 1.0% (5/497) Ultra-hypofractionated EBRT: 0.4% (2/492) 2 years cumulative incidence Conventional fractionated EBRT: 1.9% (95% CI, 1.1 to 3.4) Ultra-hypofractionated EBRT: 3.5% (95% CI, 2.3 to 5.4) 5 years Data not extracted due to missing data/high attrition <u>Urinary problems patient-reported (symptom severity based on PCSS question)</u> 1 year Conventional fractionated EBRT: mean 1.58 (95% CI, 1.37 to 1.78), n=427 Ultra-hypofractionated EBRT: mean 2.06 (95% CI, 1.82 to 2.30), n=425 p=0.0036 2 years Only reported graphically, not significantly different (p=0.18) 4+ years Data not extracted due to missing data/high attrition <u>Bowel toxicity grade ≥1 (physician evaluated with the RTOG morbidity scale)</u> 2 years Conventional fractionated EBRT: 18.3% (91/496) Ultra-hypofractionated EBRT: 19.2% (95/495) 2 years cumulative incidence: Conventional fractionated EBRT: 36.5% (95% CI, 32.8 to 40.6) Ultra-hypofractionated EBRT: 43.7% (95% CI, 39.8 to 48.0) 5 years

Intervention/ Comparison	Study Design (Trial/Registry) Followup Risk of Bias	Adverse Effects
		Data not extracted due to missing data/high attrition <u>Bowel toxicity grade ≥2 (physician evaluated with the RTOG morbidity scale)</u> 2 years Conventional fractionated EBRT: 3.2% (16/496) Ultra-hypofractionated EBRT: 1.8% (9/495) 2 years cumulative incidence: Conventional fractionated EBRT: 5.4% (95% CI, 3.8 to 7.6) Ultra-hypofractionated EBRT: 6.3% (95% CI, 4.6 to 8.6) 5 years Data not extracted due to missing data/high attrition <u>Bowel toxicity grade ≥3 (physician evaluated with the RTOG morbidity scale)</u> 2 years Conventional fractionated EBRT: 0% (0/496) Ultra-hypofractionated EBRT: 0.4% (2/495) 2 years cumulative incidence: Conventional fractionated EBRT: 0.3% (95% CI, 0.1 to 1.4) Ultra-hypofractionated EBRT: 1.1% (95% CI, 0.5 to 2.3) 5 years Data not extracted due to missing data/high attrition <u>Bowel problems patient-reported (symptom severity based on PCSS question)</u> 1 year Only reported graphically, not significantly different (p=0.059) 2 years Only reported graphically, not significantly different (p=0.32) 4+ years Data not extracted due to missing data/high attrition <u>Erectile function (physician recorded)</u> 1 year Only reported graphically, not significantly different (p=0.59)

Intervention/ Comparison	Study Design (Trial/Registry) Followup Risk of Bias	Adverse Effects
		2 years Only reported graphically, not significantly different (p=0.60) 3+ years Data not extracted due to missing data/high attrition <u>Erectile problems patient-reported (symptom severity based on PCSS question)</u> 1 year Only reported graphically, not significantly different (p=0.74) 2 years Only reported graphically, not significantly different (p=0.18) 4+ years Data not extracted due to missing data/high attrition

Abbreviations: 3D-CRT=3-dimensional conformal radiation therapy; ASCENDE-RT=Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiation; CI=confidence interval; EBRT=external beam radiation therapy; EORTC=European Organization for Research and Treatment of Cancer; IIEF: International index of erectile function; HR=hazard ratio; IMRT=intensity-modulated radiation therapy; LDR-PB=low dose rate prostate brachytherapy; NR=not reported; PCSS=Prostate Cancer Symptom Scale; RCT=randomized controlled trial; ROB=risk of bias; RR=risk ratio; RT=radiation therapy; RTOG=Radiation Therapy Oncology Group; SBRT=stereotactic body radiation therapy; SD=standard deviation

Table H-7. Evidence certainty: external beam radiation therapy

Intervention/ Comparison: Outcome	k= Study Design	Risk of Bias	Incon-sistency	Indi-rect-ness	Impre-cision	Other Consid-erations	I	C	Relative (95% CI)	Abso-lute (95% CI)	Certainty
3D-CRT + ADT/3D-CRT +ADT + LDR-PB boost: Mortality (Follow-up: 5 years)	1 RCT	Serious	Not serious	Not serious	Serious	None	38/200 (19.0%)	30/198 (15.2%)	**RR 1.25** (0.81 to 1.94)	3.8% (-3.5 to 11.2)	⨁⨁◯◯[a, b] LOW
3D-CRT + ADT/3D-CRT +ADT + LDR-PB boost: Prostate-specific mortality (Follow-up: 5 years)	1 RCT	Serious	Not serious	Not serious	Very serious	None	11/200 (5.5%)	7/198 (3.5%)	**RR 1.56** (0.62 to 3.93)	2% (-2.1 to 6.0)	⨁◯◯◯ INSUFFICIENT [a, c]

Intervention/ Comparison: Outcome	k= Study Design	Risk of Bias	Incon-sistency	Indi-rect-ness	Impre-cision	Other Consid-erations	I	C	Relative (95% CI)	Abso-lute (95% CI)	Certainty
3D-CRT + ADT/3D-CRT +ADT + LDR-PB boost: Metastatic disease (Follow-up: 5 years)	1 RCT	Serious	Not serious	Not serious	Serious	None	18/200 (9.0%)	17/198 (8.6%)	**RR 1.05** (0.56 to 1.97)	0.4% (-5.1 to 6.0)	⊕⊕◯◯ LOW [a, b]
3D-CRT + ADT/3D-CRT +ADT + LDR-PB boost: Urinary incontinence (Follow-up: 5 years)	1 RCT	Serious	Not serious	Not serious	Serious	Publication bias strongly suspected	-/195	-/188	not estimable	-	⊕◯◯◯ INSUFFICIENT [a, d]
3D-CRT + ADT/3D-CRT + ADT + LDR-PB boost: Erectile function (Follow-up: 5 years)	1 RCT	Serious	Not serious	Not serious	Very serious	Publication bias strongly suspected	-/195	-/188	not estimable	**-**	⊕◯◯◯ INSUFFICIENT [a, e]
Brachytherapy + EBRT/ Brachytherapy: Overall survival (Follow-up: 7 years)	1 observational	Serious	Not serious	Not serious	Not serious	Publication bias strongly suspected	-/2929	-/2929	not estimable	**-**	⊕◯◯◯ INSUFFICIENT [f, g]
IMRT/SBRT: Overall survival (Follow-up: 8 years)	1 observa-tional	Serious	Not serious	Not serious	Very serious	Publication bias strongly suspected	-/2715	-/2715	not estimable	-	⊕◯◯◯ INSUFFICIENT [f, g, h]
EBRT plus ADT vs. EBRT: Overall mortality-5.9 to 9.1 years	5 RCTs	Not serious	Not serious	Not serious	Serious	None	587/2150 (27.3%)	615/1897 (32.4%)	RR 0.86 (0.69 to 1.06)	-3.7% (-9.8 to 2.4)	⊕⊕⊕◯ MODERATE [b]
EBRT plus ADT vs. EBRT: Prostate cancer mortality-7.2 to 9.1 years	3 RCTs	Serious	Not serious	Not serious	Serious	None	53/1499 (3.5%)	104/1505 (6.9%)	Peto OR 0.51 (0.37 to 0.70)	-3.4% (-4.95 to -1.8)	⊕⊕◯◯ LOW [b, j]

Intervention/ Comparison: Outcome	k= Study Design	Risk of Bias	Incon-sistency	Indi-rect-ness	Impre-cision	Other Consid-erations	I	C	Relative (95% CI)	Abso-lute (95% CI)	Certainty
EBRT plus ADT vs. EBRT: Metastasis-5 to 10 years	4 RCTs	Serious	Not serious	Not serious	Serious	None	284/2461 (11.5%)	289/2203 (13.1%)	RR 0.83 (0.71 to 0.97)	-2.3% (-4.1 to -0.4)	⊕⊕◯◯ LOW [b, j]
EBRT plus ADT vs. EBRT: Severe impairment of sexual function based on late toxicity scores-measured from six months until end of follow-up (7.2 years)	1 RCT	Serious	Not serious	Not serious	Serious	None	110/406 (27.0%)	79/407 (19.4%)	RR 1.40 (1.08 to 1.80)	7.7% (1.9 to 13.5)	⊕⊕◯◯ LOW [b, j]
EBRT plus ADT vs. EBRT: sexual function impotence grade 2-4 (4.5 years)	1 RCT	Serious	Not serious	Not serious	Very serious	None	32/98 (32.7%)	28/103 (27.2%)	RR 1.20 (0.79 to 1.84)	5.5% (-7.2 to 18.1)	⊕◯◯◯ INSUFFICIENT[c, j]
EBRT plus ADT vs. EBRT: urinary incontinence (stress) grade 2-4 (4.5 years)	1 RCT	Serious	Not serious	Not serious	Very serious	None	6/98 (6.1%)	7/103 (6.8%)	RR 0.90 (0.31 to 2.59)	-0.7% (-7.5 to 6.1)	⊕◯◯◯ INSUFFICIENT[c, j]
EBRT plus ADT vs. EBRT: rectal bleeding grade 2-4 (4.5 years)	1 RCT	Serious	Not serious	Not serious	Very serious	None	19/98 (19.4%)	20/103 (19.4%)	RR 1.00 (0.57 to 1.75)	0.0% (-11.0 to 10.9)	⊕◯◯◯ INSUFFICIENT[c, j]
EBRT plus neoadjuvant and concurrent ADT vs. EBRT plus concurrent and adjuvant ADT: Overall mortality-12.2 years	1 RCT	Not serious	Not serious	Not serious	Very serious	None	75/215 (34.9%)	72/217 (33.2%)	RR 1.05 (0.81 to 1.37)	1.7% (-7.2% to 10.6%)	⊕⊕◯◯ LOW [c]

Intervention/ Comparison: Outcome	k= Study Design	Risk of Bias	Incon-sistency	Indi-rect-ness	Impre-cision	Other Consid-erations	I	C	Relative (95% CI)	Abso-lute (95% CI)	Certainty
EBRT plus neoadjuvant and concurrent ADT vs. EBRT plus concurrent and adjuvant ADT: Prostate cancer mortality-12.2 years	1 RCT	Serious	Not serious	Not serious	Serious	None	7/215 (3.3%)	7/217 (3.2%)	Peto OR 1.01 (0.35 to 2.93)	0% (-3.3% to 3.4%)	⊕⊕◯◯ LOW [b, j]
EBRT plus neoadjuvant and concurrent ADT vs. EBRT plus concurrent and adjuvant ADT: Metastasis distant progression-12.2 years	1 RCT	Serious	Not serious	Not serious	Very serious	None	12/215 (5.6%)	9/217 (4.1%)	Peto OR 1.36 (0.57 to 3.27)	1.4% (-2.6% to 5.5%)	⊕◯◯◯ INSUFFICIENT [c, j]
EBRT plus neoadjuvant and concurrent ADT vs. EBRT plus concurrent and adjuvant ADT: Late genitourinary toxicity grade ≥ 3-3 years	1 RCT	Serious	Not serious	Not serious	Serious	None	6/213 (2.8%)	6/215 (2.8%)	Peto OR 1.01 (0.32 to 3.18)	0% (-3.1% to 3.2%)	⊕⊕◯◯ LOW [b, j]
EBRT / Brachytherapy Overall survival-median 10 years	1 Obs	Very serious	Not serious	Not serious	Serious	None	KM est. 75.5% (CI 71.8 to 79.4)	KM est. 78.3% (CI 70.1 to 87.4)	NA	~ -2.8% (not estimable)	⊕◯◯◯ INSUFFICIENT [k,l]
EBRT / Brachytherapy	1 Obs	Very serious	Not serious	Not serious	Serious	None	KM est. 96.2% (CI 94.3 to 98.1)	KM est. 95.4% (CI 91.1 to 100)	NA	~ 0.8% (not estimable)	⊕◯◯◯ INSUFFICIENT [k,l]

Intervention/ Comparison: Outcome	k= Study Design	Risk of Bias	Incon-sistency	Indi-rect-ness	Impre-cision	Other Consid-erations	I	C	Relative (95% CI)	Abso-lute (95% CI)	Certainty
EBRT / Brachytherapy	1 Obs	Very serious	Not serious	Not serious	Serious	None	KM est. 90.6% (CI 87.9 to 93.3)	KM est. 94.1% (CI 89.5 to 98.9)	NA	~ -3.5% (not estimable)	⊕◯◯◯ INSUFFICIENT [k,l]
Conventionally fractionated EBRT/ultra-hypofractionated EBRT: overall mortality-5-year follow-up	1 RCT	Not serious	Not serious	Not serious	Serious	None	7.3% (43/591)	7.8% (46/589)	RR 0.93 (0.63 to 1.39)	-0.5% (-3.5 to 2.5)	⊕⊕⊕◯ MODERATE [b]
Conventionally fractionated EBRT/ultra-hypofractionated EBRT: prostate cancer mortality-5-year follow-up	1 RCT	Serious	Not serious	Not serious	Serious	None	1.4% (8/591)	1.9% (11/589)	Peto OR 0.72 (0.29 to 1.79)	-0.5% (-2.0 to 0.9)	⊕⊕◯◯ LOW [b, j]
Conventionally fractionated EBRT/ultra-hypofractionated EBRT: metastasis-5-year-follow-up	1 RCT	Serious	Not serious	Not serious	Serious	None	6.6% (39/591)	6.5% (38/589)	RR 1.02 (0.66 to 1.58)	0.1% (-2.7 to 3.0)	⊕⊕◯◯ LOW [b, j]
Conventionally fractionated EBRT/ultra-hypofractionated EBRT: urinary toxicity grade ≥2 based on RTOG morbidity scale-1 and 2 year follow-up	1 RCT	Serious	Not serious	Not serious	Serious	None	1 year 2.5% (13/529) 2 years 5.6% (28/497)	1 year 6.1% (32/528) 2 years 5.1% (25/492)	1 year RR 0.41 (0.22 to 0.76) 2 years RR 1.11 (0.66 to 1.87)	1 year -3.6% (-6.0 to -1.2) 2 years 0.6% (-2.3 to 3.4)	⊕⊕◯◯ LOW [b, j]

Intervention/ Comparison: Outcome	k= Study Design	Risk of Bias	Incon-sistency	Indi-rect-ness	Impre-cision	Other Consid-erations	I	C	Relative (95% CI)	Abso-lute (95% CI)	Certainty
Conventionally fractionated EBRT/ultra-hypofractionated EBRT: Bowel toxicity grade ≥2 based on RTOG morbidity scale-2-year followup	1 RCT	Serious	Not serious	Not serious	Serious	None	3.2% (16/496)	1.8% (9/495)	Peto OR 1.77 (0.80 to 3.92)	1.4% (-0.5 to 3.4)	⊕⊕◯◯ LOW [b, j]
Conventionally fractionated EBRT/ultra-hypofractionated EBRT: Erectile function-1 and 2-year follow-up	1 RCT	Serious	Not serious	Not serious	Very serious	None	NR	NR	not estimable	Not significantly different (p=0.59 -0.60)	⊕◯◯◯ INSUFFICIENT [j,m]

Abbreviations: 3D-CRT=3-dimensional conformal radiation therapy; C=comparison; CI=confidence interval; EBRT=external beam radiation therapy; I=intervention; KM=Kaplan-Meier estimate, propensity score adjusted; LDR-PB=low-dose rate prostate brachytherapy; NR=not reported; RCT=randomized controlled trial; RR=risk ratio; RTOG=Radiation Therapy Oncology Group

Explanations:

a Downgraded for study limitations (14 people received wrong intervention, 15 people received no intervention).
b. Downgraded for one level imprecision (confidence interval overlapped threshold for small unimportant effect).
c. Downgraded for two levels imprecision (very wide CIs).
d. Downgraded for …p=0.049. Percentages reported without numerators or CIs.
e. p-value NR at 1 year. p-value at 5 years p=0.60. No CI reported.
f. Residual confounding bias expected after adjustment; some selection and reporting bias
g. Very little reported for the propensity-score matched analyses.
h. CI NR; p-value not significant.
i. No CI or relative effect estimate reported.
j. Rated down one level for risk of bias: outcomes except all-cause mortality could be influenced by lack of blinding
k. Rated down two levels for risk of bias (observational study)
l. Rated down one level for imprecision (unable to estimate based on data presented)
m. Rated down two levels for imprecision (difficult to interpret based on graphical display of data only)

Appendix I. Radical Prostatectomy

Table I-1. Risk of bias assessments for randomized controlled trials: radical prostatectomy

Intervention/ Comparison (Outcomes)	Author, Year	Selection Bias	Performance Bias	Detection Bias	Attrition	Reporting Bias	Other Bias	Overall
RP/AM (mortality, metastases, QoL, harms)	Hamdy 2016[11] Donovan 2016[12] Lane 2016[13]	Low	Low	Low	Low for mortality Moderate for harms (15-17%)	Low	None	Low
RP/RT + ADT (mortality, metastases, QoL, harms)	Hamdy 2016[11] Donovan 2016[12] Lane 2016[13]	Low	Low	Low	Low for mortality Moderate for harms (15-17%)	Low	None	Low
RP + ADT/ RT + High-dose brachytherapy + ADT (mortality, metastases, QoL, harms)	Lennernäs 2015[52]	Low	Low	Unclear	Low for mortality Moderate-high for harms (38%)	Unclear n's for harms outcomes	None	Moderate
Laparoscopic RP/RARP (QoL, harms)	Porpiglia 2018[53]	Low	Single surgeon performed all procedures	Unclear	Low	Low	None	Moderate
RP vs. HIFU (urinary and fecal incontinence,erectile dysfunction)	Hamdy 2018[54]	Low	Low	High	Unclear	Low	None	Medium

Abbreviations: ADT=androgen deprivation therapy; AM=active monitoring; HIFU=high intensity focused ultrasound; QoL=quality of life; RARP=robotic-assisted radical prostatectomy; RCT=randomized controlled trial; ROB=risk of bias; RP=radical prostatectomy; RT=radiation therapy

Table I-2. Summary risk of bias assessments for observational studies: radical prostatectomy comparisons

Inter-vention/ Comparison (Outcomes)	Author, Year	Bias Due to Confounding	Bias in Selection of Participants Into the Study	Bias in Classification of Interventions	Bias Due to Deviations From Intended Interventions	Bias Due to Missing Data	Bias in Measurement of Outcomes	Bias in Selection of the Reported Result	Overall
RARP/ Open RRP	Sooriakumaran 2018[55]	Moderate	Moderate	Low	Low	Low	Moderate	Moderate	Moderate
RARP/ Open RRP	Loeb 2016[56]	Serious	Serious	Critical	Low	Low	Moderate	Moderate	Critical

Inter-vention/ Comparison (Outcomes)	Author, Year	Bias Due to Confounding	Bias in Selection of Participants Into the Study	Bias in Classification of Interventions	Bias Due to Deviations From Intended Interventions	Bias Due to Missing Data	Bias in Measurement of Outcomes	Bias in Selection of the Reported Result	Overall
RARP/ Open RP	Herlemann 2018[57]	Moderate	Serious	Moderate	Moderate	Moderate	Moderate	Moderate	Serious
RP (aggregate) /BT	Chang 2017[58]	Moderate	Serious	Moderate	Low	Low	Serious	Moderate	Serious
RP/ADT (quality of life)	Herden, 2016[4] Weissbach, 2016[59]	Moderate	Low	Moderate	Low	Serious	Serious	Low	Serious
RP (aggregate) /Low-dose BT/AS/EBRT	Hoffman 2020[60]	Moderate	Moderate	Serious	Moderate	Moderate	Moderate	Moderate	Serious
RP/FLA	Zheng 2019[61]	Moderate	Moderate	Critical	Moderate	Moderate	Moderate	Moderate	Critical
RP/EBRT	Knipper 2019[62]	Critical	Critical	Serious	No Information	No Information	Low	Low	Critical

Abbreviations: ADT=androgen deprivation therapy; BT=brachytherapy; EBRT=external beam radiation therapy; FLA=focal laser ablation; RCT=randomized controlled trial; RARP=robotic-assisted radical prostatectomy; ROB=risk of bias; RP=radical prostatectomy; RRP=retropubic radical prostatectomy

Table I-3. Characteristics of eligible studies: radical prostatectomy comparisons

Study Design Country ROB	N=	Population	Intervention Frequency Duration	Comparison Frequency Duration	Followup Time(s) Outcome (Instrument)
Hamdy 2016[11, 12, 21] ProtecT trial RCT UK Low	1098 (exclude. AM arm)	Inclusion criteria Men with clinically localized prostate cancer aged 50-69 years, with a PSA ≥3.0 µg/L to <20.0 µg/L without a previous malignancy (apart from skin cancer), renal transplant or on renal dialysis, major CVD or respiratory comorbidities, bilateral hip replacement, or an estimated life expectancy < 10 years. Men with a PSA ≥10 µg/L or a Gleason score >7 points underwent an isotope bone scan to exclude metastatic disease. Clinical Stage (%) T1c 76% T2 24% Gleason score (%) 6 77% 7 21% 8-10 2% Age (median) 62 Race (%) White 99%	Radical prostatectomy predominant approach was open retropubic radical prostatectomy. Participants with a baseline PSA ≥10 µg/L or a biopsy Gleason score ≥7 points received bilateral lymph adenectomy. Postoperatively, PSA levels were measured every 3 months for the first year, every 6 months for 2 years, and then yearly.	Radiation therapy (EBRT+ADT) External beam 3D conformal radiation therapy, Dose 74 Gy in 37 fractions Neoadjuvant androgen suppression was given for 3–6 months before and concomitantly with 3D-conformal radiation therapy.	10 years All-cause mortality Prostate-cancer-specific mortality 6 years Urinary incontinence Erectile dysfunction Fecal incontinence and bloody stools SF-12 physical and mental health subscales and the EORTC QLQ-C30 5 years Prostate-cancer-specific mortality 1 year Urinary incontinence Erectile dysfunction Fecal incontinence and bloody stools SF-12 physical and mental health subscales EORTC QLQ-C30

Study Design Country ROB	N=	Population	Intervention Frequency Duration	Comparison Frequency Duration	Followup Time(s) Outcome (Instrument)
Hamdy 2016[11, 12, 21] ProtecT trial RCT UK Low	1090 (exclude. RT arm)	Inclusion criteria Men with clinically localized prostate cancer aged 50-69 years, with a PSA ≥3.0 µg/L to <20.0 µg/L without a previous malignancy (apart from skin cancer), renal transplant or on renal dialysis, major CVD or respiratory comorbidities, bilateral hip replacement, or an estimated life expectancy < 10 years. Men with a PSA ≥10 µg/L or a Gleason score >7 points underwent an isotope bone scan to exclude metastatic disease. Clinical Stage (%) T1c 77% T2 23% Gleason score (%) 6 77% 7 20% 8-10 2% Age (median) 62 Race (%) White 99%	Radical prostatectomy predominant approach was open retropubic radical prostatectomy. Participants with a baseline PSA ≥10 µg/L or a biopsy Gleason score ≥7 points received bilateral lymph adenectomy. Postoperatively, PSA levels were measured every 3 months for the first year, every 6 months for 2 years, and then yearly.	Active monitoring PSA levels measured and reviewed every 3 months in the first year and twice yearly thereafter. Changes in PSA levels were assessed at each visit, and a rise ≥50% during the previous 12 months triggered repeat testing within 6–9 weeks. If the PSA levels were persistently raised, or the patient had any other concerns, a review appointment was made with the center urologist for discussion of further tests including re-biopsy and all relevant management options.	10 years All-cause mortality Prostate-cancer-specific mortality 6 years Urinary incontinence Erectile dysfunction Fecal incontinence and bloody stools SF-12 physical and mental health subscales and the EORTC QLQ-C30 5 years Prostate-cancer-specific mortality 1 year Urinary incontinence Erectile dysfunction Fecal incontinence and bloody stools SF-12 physical and mental health subscales EORTC QLQ-C30

Study Design Country ROB	N=	Population	Intervention Frequency Duration	Comparison Frequency Duration	Followup Time(s) Outcome (Instrument)
Lennernäs 2015[52] RCT Sweden Moderate	89	Inclusion criteria Men with clinically localized/ locally advanced prostate cancer clinical category T1b – T3a, N0, M0 and a PSA value ≥ 50 ng/ml Clinical Stage (%) T1 39% T2 37% T3 8% Gleason score (%) NR Unknown 16% Age (median) 64 (RP) and 66 (RT) Race (%) NR	Radical prostatectomy recommended RP approach was the nerve sparing method Lymphadenectomy was conducted in participants with stage T1b-T2 PC and PSA ≥20 ng/ml and in all those with either T3 tumors, irrespective of grades, or grade 3 tumors irrespective of stages. All patients were treated with neoadjuvant ADT that continued for six months.	High-dose radiation therapy Combined EBRT (25 x 2 Gy) and high-dose brachytherapy (2 x 10 Gy; minimum radiation dose was 10 Gy). Clinical target volume comprised the tumor and the entire prostate gland All patients were treated with neoadjuvant ADT that continued for six months.	10 years All-cause mortality Prostate-cancer-specific mortality 2 years Urinary incontinence Erectile dysfunction Fecal incontinence and bloody stools EORTC QLQ-C30
Porpiglia 2018[53] RCT Italy Moderate	120	Inclusion criteria Men with clinically staged T1-T2N0M0 aged 40-75 years. Clinical Stage (%) T1-T2 100% Gleason score (%) 2-6 50% 7 43% 8-10 7% Age 64 Race (%) NR	Laparoscopic radical prostatectomy, using transperitoneal anterograde technique. Bilateral nerve-sparing procedure and extended pelvic lymph-node dissection performed when indicated.	Robot-assisted radical prostatectomy, using transperitoneal anterograde technique. Bilateral nerve-sparing procedure and extended pelvic lymph-node dissection performed when indicated.	5 years Urinary incontinence Erectile function (potency) Expanded Prostate Cancer Index Composite questionnaire - Patient satisfaction and health status

Study Design Country ROB	N=	Population	Intervention Frequency Duration	Comparison Frequency Duration	Followup Time(s) Outcome (Instrument)
Sooriakumaran 2018[55] Observational Sweden Moderate	2545, 1702 potent at baseline	Inclusion criteria men aged <75 years, PC staged clinically as T1–T3, PSA<20 ng/ml, no previous malignancy, and no signs of distant metastases. Men who were preoperatively potent (n=1702 using the same definition as for post-operative potency given below) were included in the erectile function analyses. Clinical Stage (%) T1 63% T2 34% T3 3% Gleason score (%) ≤7 93% ≥8 7% Age (median) 63.3-63.5 Race NR	Robot-assisted laparoscopic radical prostatectomy Bilateral to no nerve-sparing procedures were performed when indicated.	Open retropubic radical prostatectomy Bilateral to no nerve-sparing procedures were performed when indicated.	2 years Erectile function (potency) .

Study Design Country ROB	N=	Population	Intervention Frequency Duration	Comparison Frequency Duration	Followup Time(s) Outcome (Instrument)
Hamdy 2018[54] RCT UK (5 centers) Medium	82	Adult men with unilateral, clinically significant intermediate risk PC, Gleason score of 7 or high-volume Gleason score of 6, PSA ≤20 ng/ml, clinical stage ≤T2b, life expectancy ≥10 years, be fit, eligible and normally destined for radical surgery, have no concomitant cancer, no previous treatment of PC, proficiency in English language <u>RP Arm</u> T1c: 1/41 (2.4%) T2: 12/41 (29.3%) T2a: 22/41 (53.7%) T2b: 5/41 (12.2%) T2c: 1/41 (2.4%) Gleason score 3+4: 32 (78%) Gleason score 4+3: 8 (19.5%) High volume 6: 1 (2.4%) Age (median) 65.5 White: 40/41 (97.6%) <u>HIFU Arm</u> T1c: 0 T2: 11/41 (26.8%) T2a: 26/41 (63.4%) T2b: 2/41 (4.9%) T2c: 1/41 (2.4%) Gleason score 3+4: 39 (95%) Gleason score 4+3: 8 (19.5%) High volume 6: 1 (2.4%) Age (median) 66.4 White: 39/41 (95.1%)	Conventional open, laparoscopic or robot-assisted RP	HIFU	12 months Urinary incontinence Fecal incontinence Erectile dysfunction

Abbreviations: ADT=androgen deprivation therapy; AM=active monitoring; CVD=cardiovascular disease; EBRT=external beam radiation therapy; EORTC QLQ-C30=European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire–Core 30 module; Gy=Gray units; HIFU=high-intensity focused ultrasound; NR=not reported; PC=prostate cancer; PSA=prostate specific antigen; ROB=risk of bias; RP=radical prostatectomy; RT=radiation therapy; RCT=randomized controlled trial; SF12=short form 12 item health survey questionnaire; UK=United Kingdom; µg/L=micrograms per liter

Table I-4. Mortality, survival, and metastases outcomes: radical prostatectomy comparisons

Intervention/ Comparison	Study Design (Trial/Registry) Followup Risk of Bias	Overall Survival and Mortality	Prostate Cancer Specific Survival and Mortality	Metastases or Metastatic Progression Free Survival (define)
RP/ AM	Hamdy 2016[11] ProtecT RCT Low	All-cause Mortality at 10 years (median) RP: 9.9% (55/553) 10.1 (95% CI 7.8 to 13.2) deaths per 1000 person-years RT: 10.8% (59/545) 10.9 (95% CI 8.5 to 14.1) deaths per 1000 person-years RR=0.92 (95% CI 0.65 to 1.30); ARD= -0.9 (95% CI -4.5 to 2.7)	Prostate Cancer Specific Survival at 5 years RP: 100% AS: 99% Prostate Cancer Mortality at 10 years RP: 0.9% (5/553) 0.9 (95% CI 0.4 to 2.2) deaths per 1000 person-years AM: 1.5% (8/545) 1.5 (95% CI 0.7 to 3.0) deaths per 1000 person-years P=0.48 between groups (+AS) HR =0.63 (95% CI 0.21 to 1.93) Peto OR =0.62 (95% CI 0.21 to 1.84) ARD= -0.6% (95% CI -1.8 to 0.7)	RP: 2.4% (13/553) 2.4 (95% CI 1.4 to 4.2) metastatic disease per 1000 person-years AM: 6.1% (33/545) 6.3 (95% CI 4.5 to 8.8) metastatic disease per 1000 person-years Peto OR=0.40 (95% CI 0.22 to 0.72) ARD= -4% (95% CI -6.1 to -1.3)
RP/ EBRT+ADT	Hamdy 2016[11] ProtecT RCT Low	All-cause Mortality at 10 years (median) RP: 9.9% (55/553) 10.1 (95% CI 7.8 to 13.2) deaths per 1000 person-years RT: 10.1% (55/545) 10.3 (95% CI 7.9 to 13.4) deaths per 1000 person-years RR=0.99 (95% CI 0.69 to 1.41); ARD= -0.1 (95% CI -3.7-3.4)	Prostate Cancer Specific Survival at 5 years RP: 100% RT: 100% Prostate Cancer Mortality at 10 years RP: 0.9% (5/553) 0.9 (95% CI 0.4 to 2.2) deaths per 1000 person-years EBRT+ADT: 0.7% (4/545) 0.7 (95% CI 0.3 to 2.0) deaths per 1000 person-years P=0.48 between groups (+AS) HR =1.25 (95% CI 0.33 to 4.55) Peto OR =1.23 (95% CI 0.33 to 4.58) ARD=0.2% (95% CI -0.9, 1.2)	RP: 2.4% (13/553) 2.4 (95% CI 1.4 to 4.2) metastatic disease per 1000 person-years EBRT+ADT: 2.9% (16/545) 3.0 (95% CI 1.9 to 4.9) metastatic disease per 1000 person-years Peto OR=0.80 (95% CI 0.38 to 1.67) ARD= -0.6% (95% CI -2.5 to 1.3)
RP + ADT/ High-dose RT (EBRT and BT) + ADT	Lennernäs 2015[52] RCT Moderate	All-cause Mortality at 10 years RP + ADT: 26.7% (12/45) High-dose RT + ADT: 20.5% (9/44) RR=1.30 (95% CI 0.61 to 2.78) ARD=6.2% (95% CI -11.4 to 23.8)	Prostate Cancer Mortality at 10 years RP + ADT: 13.3% (6/45) High-dose RT +ADT: 4.5% (2/44) Peto OR=2.89 (95% CI 0.68 to 12.27) ARD = 8.8% (95% CI -2.9 to 20.52)	NR

Intervention/ Comparison	Study Design (Trial/Registry) Followup Risk of Bias	Overall Survival and Mortality	Prostate Cancer Specific Survival and Mortality	Metastases or Metastatic Progression Free Survival (define)
LRP/RARP	Porpiglia 2018[53] RCT Moderate	NR	NR	NR
RALRP/ Open RRP	Sooriakumaran 2018[55] Observational Moderate	NR	NR	NR
RP vs. HIFU	Hamdy 2018[54] RCT 12 months Medium	NR	NR	NR

Abbreviations: ADT=androgen deprivation therapy; ARD=absolute risk difference; AM=active monitoring; BT=brachytherapy; CI=confidence interval; EBRT=external beam radiation therapy; HIFU=high intensity focused ultrasound; LRP=laparoscopic radical prostatectomy; NR=not reported; OR=odds ratio; RALRP=robotic-assisted laparoscopic radical prostatectomy; RARP=robotic-assisted radical prostatectomy; RP=radical prostatectomy; RR=risk ratio; RRP=retropubic radical prostatectomy; RT=radiation therapy; RCT=randomized controlled trial

Table I-5. Health status and quality of life outcomes: radical prostatectomy comparisons

Intervention/ Comparison	Study Design (Trial/Registry) Followup Risk of Bias	Health Status	Quality of Life Prostate Cancer Related Quality of Life
RP/ AM	Hamdy 2016[11, 12] ProtecT RCT Low	NR	SF-12: Physical health subscale (mean [SD]) At 12 months RP: 49.9 (8.5); n=447 AM: 49.9 (9.1); n=453 At 72 months RP: 48.8 (9.1); n=428 AM: 46.9 (10.6); n=428 SF-12: Mental health subscale (mean [SD]) At 12 months RP: 53.7 (8.3); n=447 AM: 53.6 (8.1); n=453 At 72 months RP: 53.5 (8.3); n=428 AM: 53.0 (8.8); n=428 Cancer-specific quality of life: EORTC-QLQ-C30 at 5 years, Global health status (mean [SD]) RP: 78.4 (17.7); n=386 AM: 76.8 (17.6); n=394

Intervention/ Comparison	Study Design (Trial/Registry) Followup Risk of Bias	Health Status	Quality of Life Prostate Cancer Related Quality of Life
RP/ EBRT+ADT	Hamdy 2016[11, 12] ProtecT RCT Low	NR	<u>SF-12: Physical health subscale (mean [SD])</u> At 12 months RP: 49.9 (8.5); n=447 RT: 50.2 (8.6); n=440 At 72 months RP: 48.8 (9.1); n=428 RT: 48.4 (9.4); n=428 <u>SF-12: Mental health subscale (mean [SD])</u> At 12 months RP: 53.7 (8.3); n=447 RT: 53.3 (8.5); n=440 At 72 months RP: 53.5 (8.3); n=428 RT: 53.8 (7.8); n=428 <u>Cancer-specific quality of life: EORTC-QLQ-C30 at 5 years, Global health status (mean [SD])</u> RP: 78.4 (17.7); n=386 RT: 77.4 (19.0); n=400

Intervention/ Comparison	Study Design (Trial/Registry) Followup Risk of Bias	Health Status	Quality of Life Prostate Cancer Related Quality of Life
RP +ADT/ High-dose RT (EBRT and BT) + ADT	Lennernäs 2015[52] RCT Moderate	NR	EORTC QLQ-C33 subscales Global quality of life at 12 months RP + ADT: 77 (16); n=31 High-dose RT + ADT: 76 (22); n=24 Global quality of life at 24 months RP + ADT: 77 (21); n=31 High-dose RT + ADT: 75 (20); n=24 Physical functioning at 12 months RP + ADT: 96 (9); n=33 High-dose RT + ADT: 94 (14); n=25 Physical functioning at 24 months RP + ADT: 96 (12); n=33 High-dose RT + ADT: 94 (17); n=25 Emotional functioning at 12 months RP + ADT: 89 (15); n=33 High-dose RT + ADT: 86 (19); n=25 Emotional functioning at 24 months RP + ADT: 88 (16); n=33 High-dose RT + ADT: 87 (17); n=25
LRP/RARP	Porpiglia 2018[53] RCT Moderate	Health status, self-rated as excellent, very good, or good (from the Expanded Prostate Cancer Index Composite (EPIC) questionnaire) at 5 years LRP: 86% (50/58) RARP: 100% (57/57), P=.003	NR
RALRP/ Open RRP	Sooriakumaran 2018[55] Observational Moderate	NR	NR
RP vs. HIFU	Hamdy 2018[54] RCT 12 months Medium	NR	NR

Abbreviations: ADT=androgen deprivation therapy; AM=active monitoring; BT=brachytherapy; EBRT=external beam radiation therapy; EORTC QLQ-C30=European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire–Core 30 module; HIFU=high intensity focused ultrasound; LRP=laparoscopic radical prostatectomy; NR=not reported; RALRP=robotic-assisted laparoscopic radical prostatectomy; RARP=robotic-assisted radical prostatectomy; RP=radical prostatectomy; RRP=retropubic radical prostatectomy; RT=radiation therapy; RCT=randomized controlled trial; SD=standard deviation; SF12=short form 12 item health survey questionnaire

Table I-6. Harms: radical prostatectomy comparisons

Intervention/ Comparison	Study (Trial) Followup Risk of Bias	Common Treatment Related Side Effects
RP/ AM	Hamdy 2016; Donovan 2016; Lane 2016[11-13] ProtecT RCT Low	SEXUAL Erection not firm enough for intercourse At 12 months RP: 85% (304/356) AM: 51%; (173/340) At 72 months (last assessment) RP: 84% (385/461) AM: 70.4% (318/452) RR = 1.19 (95% CI 1.10 to 1.28) ARD = 13% (95% CI 8 to 19) URINARY Urinary incontinence, defined as ≥1 pad/day over past 4 weeks (from EPIC) At 12 months RP: 26% (95/362) AM: 4% (15/357) At 72 months (last assessment) RP: 17.4% (79/455) AM: 8.4% (38/453) RR = 2.07 (95% CI 1.44 to 2.98) ARD = 9% (95% CI 5 to 13) BOWEL Fecal incontinence ≥1 time/week (from EPIC) At 12 months RP: 0.8% (3/363) AM: 1% (4/356) At 72 months (last assessment) RP: 2% (9/468) AM: 3% (12/462) RR = 0.74 (95% CI 0.31 to 1.74) ARD = -1% (95% CI -3 to 1) Bloody stools about half the time or more frequently (from EPIC) At 12 months RP: 0.6% (2/364) AM: 1% (5/357) At 72 months (last assessment) RP: 1% (5/470)

Intervention/ Comparison	Study (Trial) Followup Risk of Bias	Common Treatment Related Side Effects
		AM: 1% (6/465) RR = 0.82 (95% CI 0.25 to 2.68) ARD = 0% (95% CI -2 to 1)

RP/ EBRT+ADT	Hamdy 2016; Donovan 2016; Lane 2016[11-13] ProtecT RCT Low	SEXUAL <u>Erection not firm enough for intercourse</u> At 12 months RP: 85% (304/356) EBRT+ADT: 62% (219/351) At 72 months (last assessment) RP: 83.5% (385/461) EBRT+ADT: 72.6% (331/456) RR = 1.15 (95% CI 1.07 to 1.23) ARD = 11% (95% CI 5.6 to 16.2) URINARY <u>Urinary incontinence, defined as ≥1 pad/day over past 4 weeks (from EPIC)</u> At 12 months RP: 26% (95/362) EBRT+ADT: 4% (13/358) At 72 months (last assessment) RP: 17.4% (79/455) EBRT+ADT: 3.5% (16/452) RR = 4.90 (95% CI 2.91 to 8.26) ARD = 13.8% (95% CI 9.9 to 17.7) BOWEL <u>Fecal incontinence ≥1 time/week (from EPIC)</u> At 12 months RP: 0.8% (3/363) EBRT+ADT: 4% (14/358) At 72 months (last assessment) RP: 2% (9/468) EBRT+ADT: 4% (19/465) Peto OR = 0.48 (95% CI 0.22 to 1.01) ARD = -2% (95% CI -4.4 to 0.02) <u>Bloody stools about half the time or more frequently (from EPIC)</u> At 12 months RP: 0.6% (2/364) EBRT+ADT: 4% (14/357) At 72 months (last assessment) RP: 1% (5/470) EBRT+ADT: 6% (26/466) Peto OR = 0.24 (95% CI 0.12 to 0.50) ARD = -5% (95% CI -7 to -2)
RP +ADT/ High-dose RT (EBRT and BT) +ADT	Lennernäs 2015[52] RCT Moderate	SEXUAL <u>Grade 3 (quite a bit)-4 (very much) Erectile dysfunction at 24 months:</u> RP + ADT: 89% (33/37)

Intervention/ Comparison	Study (Trial) Followup Risk of Bias	Common Treatment Related Side Effects
		High-dose-RT + ADT: 85% (29/34) RR = 1.05 (95% CI 0.87 to 1.25) ARD = 4% (95% CI -11.7 to 19.4) <u>Erectile dysfunction; 2 (response=little), 3 (quite a bit) and 4 (very much)</u> - *<u>ns unclear for each timepoint</u>* At 12 months RP + ADT: response 2: 5%, response 3: 11% and response 4: 81% High-dose-RT + ADT: response 2: 19%, response 3: 19% and response 4: 57% At 24 months RP + ADT: response 2: 5%, response 3: 16% and response 4: 74% High-dose-RT + ADT: response 2: 11%, response 3: 27% and response 4: 59% URINARY <u>Grade 3 (quite a bit)-4 (very much) Urinary incontinence at 24 months:</u> RP + ADT: 16% (4/25) High-dose-RT + ADT: 10% (3/30) Peto OR 1.70 (95% CI 0.35 to 8.23) ARD = 6% (95% CI to 11.9-23.9) <u>Urinary incontinence; 2 (response=little), 3 (quite a bit) and 4 (very much)</u> - *<u>ns unclear for each timepoint</u>* At 12 months RP + ADT: response 2: 41%, response 3: 5% and response 4: 8% High-dose-RT + ADT: response 2: 19%, response 3: 5% and response 4: 0% At 24 months RP + ADT: response 2: 39%, response 3: 11% and response 4: 5% High-dose-RT + ADT: response 2: 29%, response 3: 5% and response 4: 5% BOWEL <u>Fecal incontinence at 24 months:</u> RP + ADT: 8% (2/25) High-dose-RT + ADT: 24% (7/29) Peto OR = 0.32 (95% CI 0.08 to 1.33) ARD = -16% (95% CI -35 to 2.7) <u>Fecal incontinence; 2 (response=little), 3 (quite a bit) and 4 (very much)</u> - *ns unclear for each timepoint* At 12 months RP + ADT: response 2: 10%, response 3: 0% and response 4: 0% High-dose-RT + ADT: response 2: 14%, response 3: 5% and response 4: 0% At 24 months RP + ADT: response 2: 8%, response 3: 0% and response 4: 0%

Intervention/ Comparison	Study (Trial) Followup Risk of Bias	Common Treatment Related Side Effects
		High-dose-RT + ADT: response 2: 24%, response 3: 0% and response 4: 0% Bloody stools; 2 (response=little), 3 (quite a bit) and 4 (very much) - *ns unclear for each timepoint* At 12 months RP + ADT: response 2: 8%, response 3: 0% and response 4: 0% High-dose-RT + ADT: response 2: 8%, response 3: 3% and response 4: 0% At 24 months RP + ADT: response 2: 3%, response 3: 3% and response 4: 0% High-dose-RT + ADT: response 2: 15%, response 3: 3% and response 4: 3%
LRP/RARP	Porpiglia 2018[53] RCT Moderate	SEXUAL (Patients who underwent nerve-sparing only) Erectile dysfunction, an erection not sufficient for penetration At 12 months LRP: 45.7% (16/35) RARP: 20% (7/35) At 60 months LRP: 48.6% (17/35) RARP: 25.7% (9/35) ARD = 22.9% (95% CI 0.9 to 44.9) URINARY Urinary incontinence defined as ≥1 pad/day or use of ≥1 safety pad/day (from EPIC) At 12 months LRP: 16.7% (10/60) RARP: 5% (3/60) At 60 months LRP: 15.5% (9/58) RARP: 3.5% (2/57) ARD = 12% (95% CI 1.5 to 22.5) BOWEL NR
RALRP/ Open RRP	Sooriakumaran 2018[55] Observational Moderate	SEXUAL Postoperative erectile dysfunction was defined as when a patient answered they could not achieve a stiff erection at any time or an erection stiff enough for intercourse at any time At 12 months RARP: 57% Open RRP: 69% At 24 months RARP: 49% Open RRP: 61%

Intervention/ Comparison	Study (Trial) Followup Risk of Bias	Common Treatment Related Side Effects
RP vs. HIFU	Hamdy 2018[54] RCT 12 months Medium	Urinary incontinence (need to use absorbent pad at least once per day) RP ~58% HIFU 0% Fecal incontinence (half of the time or more within last 4 weeks of questionnaire) RP ~50% HIFU ~20% Erectile dysfunction RP ~22% HIFU ~15%

Abbreviations: ADT=androgen deprivation therapy; ARD=absolute risk difference; AM=active monitoring; BT=brachytherapy; EBRT=external beam radiation therapy; EPIC=Expanded Prostate Cancer Index Composite questionnaire; HIFU=high-intensity focused ultrasound; LRP=laparoscopic radical prostatectomy; NR=not reported; OR=odds ratio; RALRP=robotic-assisted laparoscopic radical prostatectomy; RARP=robotic-assisted radical prostatectomy; RP=radical prostatectomy; RR=risk ratio; RRP=retropubic radical prostatectomy; RT=radiation therapy; RCT=randomized controlled trial;

Table I-7. Evidence certainty: radical prostatectomy comparisons

Intervention/ Comparison	Outcome	k= Study Design	Risk of Bias	Inconsis-tency	Indirect-ness	Imprecision	Other	I	C	Relative (95% CI)	Abso-lute (95% CI)	Certainty
RP vs. AM	All-cause mortality 10 years	1 RCT	Low	Single study	Direct	Imprecise	None	(55/553) 10%	(59/545) 11%	RR 0.92 (0.65 to 1.30)	-0.9% (-4.5 to 2.7)	Moderate [a] ⊕⊕⊕◯
	PC-specific mortality 10 years	1 RCT	Low	Single study	Direct	Very imprecise	None	(5/553) 0.9%	(8/545) 1.5%	Peto OR 0.62 (0.20 to 1.87)	-0.6% (-1.8 to 0.7)	Low [b] ⊕⊕◯◯
	Metastases 10 years	1 RCT	Low	Single study	Direct	Imprecise	None	(13/553) 2.4%	(33/545) 6.4%	Peto OR 0.40 (0.22 to 0.72)	-4.0% (-6.1 to -1.3)	Moderate [a] ⊕⊕⊕◯
	ED 6 years	1 RCT	Moderate (attrition)	Single study	Direct	Precise	None	(385/461) 83.5%	(318/452) 70.4%	RR 1.19 (1.10 to 1.28)	13% (8 to 19)	Moderate ⊕⊕⊕◯ [c]
	Urinary Incontinence 6 years	1 RCT	Moderate (attrition)	Single study	Direct	Precise	None	(79/455) 17.4%	(38/453) 8.4%	RR 2.07 (1.44 to 2.98)	9% (5 to 13)	Moderate ⊕⊕⊕◯ [c]
	Fecal incontinence 6 years	1 RCT	Moderate (attrition)	Single study	Direct	Imprecise	None	(9/468) 1.9%	(12/462) 2.6%	Peto OR 0.74 (0.31 to 1.75)	-0.7% (-2.6 to 1.2)	Low ⊕⊕◯◯ [a,c]
RP vs. EBRT+ADT	All-cause mortality 10 years	1 RCT	Low	Single study	Direct	Imprecise	None	(55/553) 10%	(55/545) 10%	RR 0.99 (0.69 to 1.04)	-0.1% (-3.7 to 3.4)	Moderate [a] ⊕⊕⊕◯
	PC-specific mortality 10 years	1 RCT	Low	Single study	Direct	Very imprecise	None	(5/553) 0.9%	(4/545) 0.7%	Peto OR 1.23 (0.33 to 4.58)	0.2% (-0.9 to 1.2)	Low [b] ⊕⊕◯◯

Intervention/ Comparison	Outcome	k= Study Design	Risk of Bias	Inconsis-tency	Indirect-ness	Imprecision	Other	I	C	Relative (95% CI)	Abso-lute (95% CI)	Certainty
	Metastases 10 years	1 RCT	Low	Single study	Direct	Imprecise	None	(13/553) 2.4%	(16/545) 2.9%	Peto OR 0.80 (0.38 to 1.67)	-0.6% -2.5 to 1.3)	Low [b] ⊕⊕◯◯
	ED 6 years	1 RCT	Moderate (attrition)	Single study	Direct	Precise	None	(385/461) 83.5%	(331/456) 72.6%	RR 1.15 (1.07 to 1.23)	11% (6 to 16)	Moderate ⊕⊕⊕◯ [c]
	Urinary Incontinence 6 years	1 RCT	Moderate (attrition)	Single study	Direct	Precise	None	(79/455) 17.4%	(16/452) 3.5%	RR 4.90 (2.91 to 8.26)	14% (10 to 18)	Moderate ⊕⊕◯◯ [c]
	Fecal incontinence 6 years	1 RCT	Moderate (attrition)	Single study	Direct	Imprecise	None	(9/468) 1.9%	(19/465) 4.1%	Peto OR 0.48 (0.22 to 1.01)	-2.2 (-4.4 to 0.02)	Low ⊕⊕◯◯ [a,c]
RP plus ADT vs. EBRT plus High-dose BT plus ADT	All-cause mortality 10 years	1 RCT	Moderate	Single study	Direct	Very imprecise	None	(12/45) 26.7%	(9/44) 20.4%	RR 1.30 (0.61 to 2.78)	6.2% (-11.4 to 23.8)	Insufficient ⊕◯◯◯ [a,b]
	PC-specific mortality 10 years	1 RCT	Moderate	Single study	Direct	Very imprecise	None	(6/45) 13.3%	(2/44) 4.5%	Peto OR 2.89 (0.68 to 12.27)	8.8% (-2.9 to 20.5)	Insufficient ⊕◯◯◯ [a, b]
	Urinary Incontinence 2 years	1 RCT	High	Single study	Direct	Very imprecise	None	(4/25) 16%	(3/30) 10%	Peto OR 1.70 (0.35 to 8.23)	6% (-11.9 to 23.9)	Insufficient [a,b] ⊕◯◯◯
	Fecal incontinence 2 years	1 RCT	High	Single study	Direct	Very imprecise	None	(2/25) 8%	(7/29) 24%	Peto OR 0.32 (0.08 to 1.33	-16.1% (-35 to 27)	Insufficient [a,b] ⊕◯◯◯
	ED 60 months	1 RCT	Medium	Single study	Direct	Imprecise	None	(17/35) 49%	(9/35) 26%	RR 1.89 (0.98 to 3.65)	23% (1 to 45)	Low [a,d] ⊕⊕◯◯

Intervention/ Comparison	Outcome	k= Study Design	Risk of Bias	Inconsis-tency	Indirect-ness	Imprecision	Other	I	C	Relative (95% CI)	Abso-lute (95% CI)	Certainty
LRP vs. RARP	Urinary Incontinence-60 months	1 RCT	Medium	Single study	Direct	Imprecise	None	(9/58) 15.5%	(2/57) 3.5%	Peto OR 3.96 (1.15 to 13.65)	12% (1.5 to 22.5)	Low [a,b] ⊕⊕◯◯
	ED 2 years	1 RCT	Moderate	Single study	Direct	Imprecise	None	(33/37) 90%	(29/34) 85%	RR 1.05 (0.87 to 1.25)	4% (-12 to 19)	Low [a,d] ⊕⊕◯◯
RALRP vs. Open RRP	ED	1 Obs.	Medium	Single study	Direct	Unclear, data not presented in usable manner	None	Unclear	Unclear	-	-12% (CI NA)	Insufficient [c,d] ⊕◯◯◯
RP vs. HIFU	Urinary Incontinence-12 months	1 RCT	Medium	Single study	Direct	Unclear, data not presented in usable manner	None	58%	0%	-	-58% (CI NA)	Insufficient [c,d] ⊕◯◯◯
	ED 12 months	1 RCT	Medium	Single study	Direct	Unclear, data not presented in usable manner	None	50%	20%	-	-30% (CI NA)	Insufficient [c,d] ⊕◯◯◯
	Fecal incontinence 12 months	1 RCT	Medium	Single study	Direct	Unclear, data not presented in usable manner	None	22%	15%	-	-7% (CI NA)	Insufficient [c,d] ⊕◯◯◯

Abbreviations: ADT=androgen deprivation therapy; AM=active monitoring; BT=brachytherapy; CI=confidence interval; EBRT=external beam radiation therapy; ED=erectile dysfunction; LRP=laparoscopic radical prostatectomy; OR=odds ratio; PC=prostate cancer; RALRP=robotic-assisted laparoscopic radical prostatectomy; RARP=robotic-assisted radical prostatectomy; RP=radical prostatectomy; RR=risk ratio; RRP=retropubic radical prostatectomy; RT=radiation therapy

Explanations

a. Rated down by one level for imprecision

b. Rated down by two levels for imprecision and sparse data.

c. Rated down by one level for risk of bias

d. Rated down one level for unknown precision

Appendix J. Comparisons From Past Reports

The following is a list of the comparisons which were analyzed in the 2016 evidence report commissioned by AUA which we did not identify any additional studies of low or moderate risk of bias (ROB) published after this report.*

- Transperitoneal robot assisted laparoscopic radical prostatectomy (RALRP) vs. Extraperitoneal RALRP: 1 randomized controlled trial (RCT).
- Androgen deprivation therapy (ADT) vs. ADT plus Docetaxel and Estramustine: 1 RCT.
- External beam radiation therapy (EBRT) vs. Cryotherapy: 1 RCT and 1 non-RCT.
- Radical retropubic prostatectomy (RRP) vs. brachytherapy (BT): 1 RCT and 2 non-RCTs.
- ADT vs. ADT plus EBRT: 1 RCT.
- RRP vs. radical perineal prostatectomy (RPP): 1 RCT.
- Three-dimensional conformal radiotherapy (3D-CRT) conventional dose vs. 3D-CRT high dose: 2 RCTs.
- Hypofractionated radiation therapy (RT) vs. conventionally-fractionated RT: 2 RCTs.
- EBRT vs. EBRT plus BT: 1 RCT and 5 non-RCTs.
- ADT plus radical prostatectomy (RP) vs. RP alone: 4 RCTs and 3 non-RCTs.
- ADT plus standard of care (SOC) (watchful waiting [WW]) vs. SOC (WW): 1 RCT and 7 non-RCTs.
- ADT plus SOC (either RP or RT) versus SOC (either RP or RT): 1 RCT.
- BT conventional dose vs. BT low dose: 1 RCT.
- ADT short-term plus RT vs. ADT long-term plus RT: 2 RCTs.
- RP vs. RALRP: 1 non-RCT.
- ADT short duration vs. ADT long duration: 1 non-RCT.
- RP vs. BT: 10 non-RCTs.
- RRP vs. 3D-CRT: 2 non-RCTs.
- 3D-CRT vs. BT: 3 non-RCTs.
- ADT vs. RP: 5 non-RCTs.
- Intensity modulated radiation therapy (IMRT) BT vs. IMRT: 1 non-RCT.
- EBRT vs. Observation: 3 non-RCTs.
- BT with ADT/HT (hormone therapy) versus BT alone: 4 non-RCTs.
- Laparoscopic radical prostatectomy (LRP) vs. RALRP: 1 non-RCT.
- BT plus EBRT vs. BT plus ADT: 2 non-RCTs.
- 3D-CRT vs. conservative management: 1 non-RCT.
- IMRT vs. conservative management: 1 non-RCT.
- Proton Beam vs. conservative management: 1 non-RCT.
- BT alone vs. conservative management: 1 non-RCT.
- Proton Beam vs. 3D-CRT: 2 non-RCTs.
- IMRT vs. Proton Beam: 2 non-RCTs.
- IMRT vs. BT: 2 non-RCTs.
- BT vs. Cryotherapy: 3 non-RCTs.
- EBRT vs. ADT: 1 non-RCT.

- HIFU (high-intensity focused ultrasound) vs. HIFU plus ADT: 1 non-RCT.
- RT vs. expectant management (EM)/WW: 2 non-RCTs.
- Cryotherapy vs. RP: 2 non-RCTs.
- Cryotherapy vs. RT: 1 non-RCT.
- Cryotherapy vs. EM: 1 non-RCT.
- Cryotherapy vs. ADT: 1 non-RCT.
- RT vs. ADT: 2 non-RCTs.
- RRP vs. Cryotherapy: 1 non-RCT.
- RALRP vs. BT: 1 non-RCT.
- RALRP vs. Cryotherapy: 1 non-RCT.
- 3D-CRT vs. EBRT plus BT: 1 non-RCT.
- IMRT vs. EBRT plus BT: 1 non-RCT.
- RP vs. RP plus RT: 2 non-RCTs.
- RP plus RT vs. EBRT: 1 non-RCT.
- RP plus RT vs. EBRT plus BT: 1 non-RCT.
- RP plus RT vs. BT: 1 non-RCT.
- RP plus RT vs. RT: 1 non-RCT.
- BT vs. RT: 1 non-RCT.
- RT vs. EBRT: 1 non-RCT.
- RT vs. EBRT plus BT: 1 non-RCT.
- RP vs. RP plus EBRT: 2 non-RCTs.
- RP plus EBRT vs. BT: 2 non-RCTs.
- RP plus EBRT vs. EBRT: 2 non-RCTs.
- RP plus EBRT vs. BT plus EBRT: 2 non-RCTs.
- RP plus EBRT vs. Cryotherapy: 1 non-RCT.
- BT plus EBRT vs. Cryotherapy: 1 non-RCT.
- WW vs. RP plus RT: 1 non-RCT.
- WW vs. RP plus ADT: 1 non-RCT.
- WW vs. RT plus ADT: 1 non-RCT.
- WW vs. RP plus RT plus ADT: 1 non-RCT.
- RP vs. RP plus RT plus ADT: 1 non-RCT.
- RT vs. RP plus ADT: 1 non-RCT.
- RT vs. RP plus RT plus ADT: 1 non-RCT.
- RP plus RT vs. ADT: 1 non-RCT.
- RP plus RT vs. RP plus ADT: 1 non-RCT.
- RP plus RT vs. RT plus ADT: 1 non-RCT.
- RP plus RT vs. RP plus RT plus ADT: 1 non-RCT.
- ADT vs. RP plus ADT: 1 non-RCT.
- ADT vs. RT plus ADT: 1 non-RCT.
- ADT vs. RP plus RT plus ADT: 1 non-RCT.
- RP plus ADT vs. RT plus ADT: 1 non-RCT.
- RP plus ADT vs. RP plus RT plus ADT: 1 non-RCT.
- RT vs. RP plus RT plus ADT: 1 non-RCT.
- RP vs. BT plus ADT: 1 non-RCT.

- RP vs. BT plus EBRT plus ADT: 1 non-RCT.
- RP plus ADT vs. RP plus EBRT: 1 non-RCT.
- RP plus ADT vs. BT: 1 non-RCT.
- RP plus ADT vs. BT plus ADT: 1 non-RCT.
- RP plus ADT vs. BT plus EBRT: 1 non-RCT.
- RP plus ADT vs. EBRT: 1 non-RCT.
- RP plus ADT vs. EBRT plus ADT: 1 non-RCT.
- RP plus EBRT vs. BT plus ADT: 1 non-RCT.
- RP plus EBRT vs. BT plus EBRT plus ADT: 1 non-RCT.
- RP plus EBRT vs. EBRT plus ADT: 1 non-RCT.
- BT vs. BT plus EBRT plus ADT: 1 non-RCT.
- BT vs. EBRT plus ADT: 1 non-RCT.
- BT plus ADT vs. EBRT: 1 non-RCT.
- BT plus ADT vs. EBRT plus ADT: 1 non-RCT.
- BT plus EBRT vs. BT plus EBRT plus ADT: 1 non-RCT.
- BT plus EBRT vs. EBRT plus ADT: 1 non-RCT.
- BT plus EBRT plus ADT vs. EBRT: 1 non-RCT.

*The 2016 evidence report included several comparisons that we would have excluded, such as comparisons of ADT duration, select EBRT techniques/doses, and chemotherapy.

Appendix K. Ongoing RCTs for CLPC or Locally Advanced PC

Table K-1. Ongoing RCTs of nonpharmacological interventions for CLPC or locally advanced PC with large planned enrollment (n>300)

Title	Interventions	Planned Completion Planned Enrollment Countries Conducted	NCT Number
Evaluation of Four Treatment Modalities in Prostate Cancer With Low or "Early Intermediate" Risk	Radical prostatectomy vs. percutaneous radiation therapy vs. permanent seed implantation radiation vs. active surveillance	December 2030 N=7600 Germany	NCT01717677
Intensity-Modulated Radiation Therapy in Treating Patients With Localized Prostate Cancer	Conventional radiotherapy (74 Gy delivered in 37 fractions) vs. hypofractionated radiation therapy (60 Gy in 20 fractions) vs. hypofractionated radiation therapy (57 Gy in 19 fractions)	June 2021 N=3216 England, Ireland, Scotland, Wales	NCT00392535
Androgen-Deprivation Therapy and Radiation Therapy in Treating Patients With Prostate Cancer	Radiation therapy vs. Whole-pelvic radiotherapy	July 2031 N=2592 United States, Canada, Hong Kong, Israel, Singapore, Switzerland	NCT01368588
Comparative Health Research Outcomes of NOvel Surgery in Prostate Cancer	A: Radical therapy (radiotherapy or prostatectomy [radiotherapy can be external beam or brachytherapy]) vs. Focal therapy (either high intensity focused ultrasound or cryotherapy) B: Focal therapy vs. focal therapy after finasteride 5 Mg for 12 weeks vs. focal therapy after Bicalutamide 50 Mg for 12 weeks	May 2027 N=2450 England	NCT04049747
Prostate Advances in Comparative Evidence	A: Laproscopic prostatectomy vs. prostate stereotactic body radiotherapy B: Conventionally fractionated prostate radiotherapy vs. prostate stereotactic body radiotherapy	September 2026 N=1716 England	NCT01584258
Role of Lymph node Dissection in Men With Prostate Cancer Treated With Radical Prostatectomy	lymph node dissection vs. standardized surgical technique without extensive lymph node dissection	October 2025 N=1610 Germany	NCT04269512

Title	Interventions	Planned Completion Planned Enrollment Countries Conducted	NCT Number
Surgery Versus Radiotherapy for Locally Advanced Prostate Cancer	Prostatectomy/surgery vs. radiotherapy with adjuvant androgen deprivation therapy	December 2027 N=1200 Denmark, Finland, Norway, Sweden	NCT02102477
Extended Pelvic Lymph Node Dissection vs. no Pelvic Lymph Node Dissection at Radical Prostatectomy for intermediate-and High-risk Prostate Cancer	Radical prostatectomy followed by extended pelvic lymph node dissection vs. radical prostatectomy only	December 2038 N=900 Switzerland	NCT03921996
Prostate Cancer Patients Treated With Alternative Radiation Oncology Strategies	Hypofractionated radiotherapy with photons vs. hypofractionated radiotherapy with protons vs. normofractionated radiotherapy with photons	January 2028 N=897 Germany	NCT04083937
Laparoscopic and Robot-Assisted Radical Prostatectomy - a Comparative Study	Robot-assisted laparoscopic prostatectomy vs. conventional radical laparoscopic prostatectomy	June 2020 N=782 Germany	NCT03682146
Stereotactic Body Radiation Therapy or Intensity-Modulated Radiation Therapy in Treating Patients With Stage IIA-B Prostate Cancer	Intensity-Modulated Radiation Therapy vs. Stereotactic Body Radiation Therapy	December 2030 N=622 United States, Canada, Ireland	NCT03367702
Radical Prostatectomy Versus Radical Radiotherapy for Locally Advanced Prostate Cancer	Radical Prostatectomy vs. Radical Radiotherapy	December 2026 N=600 China	NCT04093375
Study on the Role of Hormonal Treatment for Two Dosage Levels of Prostate Radiation Therapy Versus Prostate Radiation Therapy Alone	Androgen blockade for 6 months plus radiotherapy 70 Gy vs. androgen blockage for 6 months plus radiotherapy 76 Gy vs. Radiotherapy alone with 76 Gy	December 2020 N=600 Canada	NCT00223145
Radiation Therapy in Treating Patients Receiving Hormone Therapy for Prostate Cancer (GETUG-AFU 18)	80 Gy of 3-dimensional conformal radiation therapy or intensity-modulated radiation therapy vs. 70 Gy of 3-dimensional conformal radiation therapy or intensity-modulated radiation therapy	October 2026 N=500 France	NCT00967863

Title	Interventions	Planned Completion Planned Enrollment Countries Conducted	NCT Number
Prostate Cancer Active Surveillance Trigger Trial (PCASTT-UK): Comparing Current Practice for Men With Prostate Cancer on Active Surveillance to an Active Surveillance Protocol With Standardised Triggers for Transitioning to Curative Treatment	Current practice for active surveillance vs. standardized triggers for treatment	December 2030 N=500 England, Sweden	NCT04029714
Neoadjuvant Chemo-hormonal Therapy Combined With Radical Prostatectomy for Locally Advanced Prostate Cancer	Neoadjuvant chemotherapy combined with hormone therapy and radical prostatectomy with extended lymph node dissection vs. neoadjuvant hormonal therapy and radical prostatectomy with extended lymph node dissection vs. radical prostatectomy with extended lymph node dissection	December 2024 N=475 China	NCT04220398
Radiation Hypofractionation Via Extended Versus Accelerated Therapy (HEAT) For Prostate Cancer	Extended hypofractionation radiotherapy vs. accelerated hypofractionation radiotherapy	March 2023 N=456 United States, Australia, Italy	NCT01794403
Evaluating the Effects of Frozen Section Technology on Oncological and Functional Outcomes at Radical Prostatectomy.	NeuroSAFE robotic assisted radical prostatectomy vs. standard robotic assisted radical prostatectomy	June 2022 N=454 England, Scotland,	NCT03317990
Comparison of Irreversible Electroporation and Radical Prostatectomy in Treating Prostate Cancer	Irreversible electroporation vs. radical prostatectomy	September 2027 N=438 China	NCT04278261
Proton Therapy vs. Intensity Modulated Radiation Therapy for Low or Intermediate Risk Prostate Cancer	Proton beam therapy vs. intensity modulated radiation therapy	December 2026 N=400 United States	NCT01617161
Hypofractionated, Dose Escalation Radiotherapy for High Risk Adenocarcinoma of the Prostate	Hypofractionation radiation vs. conventional radiation	January 2023 N=329 Canada	NCT01444820
Early Deep Venous Complex Ligation and Urinary Continence Recovery After Robot-Assisted Radical Prostatectomy	Early deep venous complex ligation during robot-assisted radical prostatectomy vs. standard technique	August 2020 N=312 Italy	NCT03368378

Abbreviations: CLPC=clinically localized prostate cancer; Mg=milligram; NCT=national clinical trial; PC=prostate cancer; RCT=randomized controlled trial

Appendix L. References

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