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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.

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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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To be listed in the Final Report.
Therapies for Clinically Localized Prostate Cancer

Structured Abstract

Objective. To identify new information that updates findings from previous AHRQ and 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 (T1-T3a) treatments with duration ≥5 years for mortality and metastases and ≥1 year for quality of life and harms. Interventions included watchful waiting (WW), active surveillance or monitoring (AS, AM), androgen deprivation (AD), focal and whole gland therapies or combinations. We evaluated how patient and tumor characteristics modify treatment outcomes and how provider/hospital characteristics modify effectiveness of radical prostatectomy (RP) compared to other therapies. 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 RCTs identified in the 2014 AHRQ and 2016 AUA funded reviews if new RCTs provided information on the same intervention comparison. We derived thresholds defining “small”, “moderate” and “large” effect, summarize key findings from prior reviews and the impact of new research.

Results. We identified 67 eligible references; 17 unique RCTs. Among clinically, rather than PSA detected CLPC, WW may increase overall and prostate-cancer mortality, and metastases versus RP at 20+ years. Urinary and erectile dysfunction were lower with WW versus RP. WW’s effect on mortality may have varied by tumor risk and age but not by race, health status, comorbidities or PSA. AM probably results in little to no difference in overall or prostate-cancer mortality in PSA detected CLPC versus RP or EBR plus AD through 10 years regardless of tumor risk. Metastases were infrequent but 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 3D-CRT and AD but little to no difference on metastases. EBR plus AD versus EBR alone may have resulted in a small reduction in overall and prostate-cancer mortality and metastases in higher risk disease but may increase sexual harms. EBR plus initiating neoadjuvant AD versus EBR plus initiating concurrent AD may result in little to no difference in mortality at 12 years and genitourinary toxicity at 3 years. Conventionally fractionated EBR versus ultra-hypofractionated EBR may result in little to no difference in mortality and metastasis at 5 years and urinary and bowel toxicity at 2 years. Limited evidence suggested that AS results in fewer harms than photodynamic therapy and laparoscopic RP resulted in more harms than robotic-assisted RP. There was little to no information on long-term comparative effectiveness of other treatments. No studies evaluated WW or AS in screen detected CLPC or MRI for risk assessment or were conducted since effective pharmacologic therapies for advanced disease. 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, 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. Little information exists on other treatments or the effects of patient, tumor and provider factors. Large, long-term RCTs in PSA-detected and MRI staged CLPC are needed.
Contents

Chapter 1. Introduction ................................................................................................................... 1

Chapter 2. Methods ......................................................................................................................... 6
  Review Approach .......................................................................................................................... 6
  Criteria for Inclusion/Exclusion of Studies in the Review ............................................................. 6
  Searching for the Evidence and Updating Prior Reviews ............................................................... 6
  Assessment of Methodological Risk of Bias of Individual Studies ................................................ 6
  Data Abstraction and Data Management ...................................................................................... 7
  Data Synthesis ............................................................................................................................. 7
  Grading Evidence Certainty ........................................................................................................... 7
  Assessing Applicability .................................................................................................................. 8

Chapter 3. Results ........................................................................................................................... 9
  Search Results ............................................................................................................................... 9

Chapter 4: Watchful Waiting ........................................................................................................ 16
  Key Messages ............................................................................................................................ 16
  Watchful Waiting versus Radical Prostatectomy ...................................................................... 16

Chapter 5: Active Surveillance/Active Monitoring ...................................................................... 20
  Key Messages ........................................................................................................................... 20
  Active Monitoring versus External Beam Radiation Therapy plus Androgen Deprivation Therapy .......................................................................................................................... 21
  Active Surveillance versus Photodynamic Therapy .................................................................... 22

Chapter 6: Whole Gland Therapies- External Beam Radiation Therapy ..................................... 25
  Key Messages ........................................................................................................................... 25
  3D-Conformal Radiation Therapy and Androgen Deprivation Therapy versus 3D-Conformal Radiation Therapy and Androgen Deprivation Therapy plus low-dose-rate Prostate Brachytherapy .......................................................................................................................... 26
  3D-Conformal Radiation Therapy versus Intensity-Modified Radiation Therapy ...................... 27
  Brachytherapy with External Beam Radiation Therapy versus Brachytherapy ........................... 27
  Intensity-Modified Radiation Therapy versus Stereotactic Beam Radiation Therapy ................... 27
  Radiation Therapy versus Androgen Deprivation Therapy ......................................................... 27
  External Beam Radiation Therapy plus Androgen Deprivation Therapy versus External Beam Radiation Therapy .................................................................................................................... 28
  External Beam Radiation Therapy plus Androgen Deprivation Therapy versus Androgen Deprivation Therapy .................................................................................................................... 30
  External Beam Radiation Therapy plus Neoadjuvant and Concurrent Androgen Deprivation Therapy versus External Beam Radiation Therapy plus Concurrent and Adjuvant Androgen Deprivation Therapy .......................................................................................................................... 30
  External Beam Radiation Therapy versus Brachytherapy ........................................................... 30
  Conventionally Fractionated External Beam Radiation Therapy versus Ultra-Hypofractionated External Beam Radiation .......................................................................................................................... 31

Chapter 7: Whole Gland Therapies- Radical Prostatectomy .......................................................... 37
  Key Messages ............................................................................................................................ 37
  Radical Prostatectomy versus Active Monitoring ...................................................................... 38
  Radical Prostatectomy versus External Beam Radiation Therapy plus Androgen Deprivation Therapy .......................................................................................................................... 38
Appendix D. Eligible Studies
Appendix E. Excluded Studies
Appendix F. Watchful Waiting
Appendix G. Active Monitoring and Active Surveillance
Appendix H. External Beam Radiation Therapy
Appendix I. Radical Prostatectomy
Appendix J. Comparisons from Past Reports
Appendix K. Ongoing RCTs for CLPC or Locally Advanced PC
Appendix L. Appendix References
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,\(^3,4\) 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 orchietomy), 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 RP or radiation therapies, though its use has declined as primary treatment particularly in men with low risk disease.\(^5,6\)

Some CLPC treatments are primarily intended to cure disease. These include surgical radical prostatectomy (RP) 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.\(^7,9\) 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.\(^10\)
The purpose of this review was to identify new information and update previous AHRQ and American Urological (AUA) funded reviews 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>
<thead>
<tr>
<th>PICOTS</th>
<th>KQ1-3</th>
<th>KQ4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>Treatment naive men with CLPC (stages T1-T3a) &lt;br&gt;Studies with 15% or more participants with T3b or unspecified T3 are excluded</td>
<td>Same as KQ1-3</td>
</tr>
<tr>
<td>Intervention</td>
<td>1) Watchful waiting (WW) &lt;br&gt;2) Active surveillance/active monitoring (AS/AM) &lt;br&gt;3) Androgen deprivation therapy (ADT) &lt;br&gt;4) Focal therapies  &lt;br&gt; a) Brachytherapy  &lt;br&gt; b) Cryotherapy &lt;br&gt; c) High-intensity focused ultrasound (HIFU) &lt;br&gt; d) Laser ablation &lt;br&gt; e) Photodynamic therapy &lt;br&gt; f) Irreversible electroporation &lt;br&gt;5) Whole gland therapies &lt;br&gt; a) Brachytherapy &lt;br&gt; b) Cryotherapy &lt;br&gt; c) External beam radiation therapy (EBRT)  &lt;br&gt; i) Three-dimensional conformal radiation therapy &lt;br&gt; ii) Intensity-modulated radiation therapy &lt;br&gt; iii) Proton beam therapy &lt;br&gt; iv) Stereotactic body radiation therapy &lt;br&gt; d) Radical prostatectomy &lt;br&gt; i) Open &lt;br&gt; ii) Laparoscopic  &lt;br&gt; (1) Without robotic assistance &lt;br&gt; (2) With robotic assistance</td>
<td>1) Radical prostatectomy  &lt;br&gt; i) Open &lt;br&gt; ii) Laparoscopic  &lt;br&gt; (1) Without robotic assistance &lt;br&gt; (2) With robotic assistance</td>
</tr>
<tr>
<td>Comparison</td>
<td>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)</td>
<td>Same as KQ 1-3</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Overall survival/mortality &lt;br&gt; Prostate cancer specific survival/mortality &lt;br&gt; Metastatic-progression free survival &lt;br&gt; Metastases (lymph nodes/distant) &lt;br&gt; Health status &lt;br&gt; Quality of life (measured with validated instruments) &lt;br&gt; Prostate-cancer related quality of life (measured with validated instruments) &lt;br&gt; Harms: &lt;br&gt; Bowel, bladder, and sexual/erectile dysfunction &lt;br&gt; Serious adverse effects associated with ADT such as cognitive impairment, MACE, fractures</td>
<td>Overall survival/mortality &lt;br&gt; Prostate cancer specific survival/mortality &lt;br&gt; Metastatic free survival/metastases (lymph nodes/distant)</td>
</tr>
<tr>
<td>Timing</td>
<td>Follow up from treatment initiation: &lt;br&gt; Mortality/survival outcomes/metastases: 5 years or more &lt;br&gt; Health status, quality of life and harms: 1 year or more</td>
<td>Follow up from treatment initiation: &lt;br&gt; Mortality/survival outcomes/metastases: 5 years or more</td>
</tr>
<tr>
<td>Setting</td>
<td>All settings</td>
<td>Same as KQ 1-3</td>
</tr>
<tr>
<td>Study Design</td>
<td>1) RCTs &lt;br&gt; 2) Non-RCT if: &lt;br&gt; a) Comparative</td>
<td>Same as KQ 1-3</td>
</tr>
<tr>
<td></td>
<td>PICOTS</td>
<td>KQ1-3</td>
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<tr>
<td>b)</td>
<td>Concurrent</td>
<td></td>
</tr>
<tr>
<td>c)</td>
<td>Multicenter (enrolling patients treated at multiple locations)</td>
<td></td>
</tr>
<tr>
<td>d)</td>
<td>≥500 patients</td>
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<tr>
<td>e)</td>
<td>Some method to control for selection bias (propensity scores, instrumental variables, multivariate regression)</td>
<td></td>
</tr>
<tr>
<td>f)</td>
<td>Prospective data collection</td>
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Chapter 2. Methods

Review Approach

The methods for this systematic review followed the 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). 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 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 KQs (search strategy in Appendix A). 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 AUA funded reviews; and 2) outcomes from 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 (WW versus RP in Chapter 4 and EBRT plus 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).

Search results were downloaded to EndNote X9 and screened in DistillerSR. 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\textsuperscript{16} and non-RCTs were assessed with the ROBINS-I tool.\textsuperscript{17} 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.\textsuperscript{18} 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 certainty of evidence (COE) with Grading of Recommendations Assessment, Development and Evaluation (GRADE)\textsuperscript{19} 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.\textsuperscript{20} COE was reviewed by a second investigator. We resolved discrepancies by consensus or discussion with a third reviewer. We used suggested language\textsuperscript{21} 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 \(\geq 10\%\) 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 \(\geq 20\%\) 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 CLPC affect applicability.21
Chapter 3. Results

Search 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 RCTs. 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.5,12

Figure 1. Literature flow diagram
Figure 2. Plot of comparisons addressed in RCTs identified in updated literature search. *†‡**††

*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*

<table>
<thead>
<tr>
<th>Intervention/Comparison</th>
<th>Outcome(s)</th>
<th>Previous Findings from 2014 AHRQ- or 2016 AUA-Funded Reviews†</th>
<th>Present Findings Derived from Studies Published After the Prior Reviews and by Incorporating Prior RCT Data When Applicable ‡</th>
</tr>
</thead>
</table>
| 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. |
<table>
<thead>
<tr>
<th>Intervention/Comparison</th>
<th>Outcome(s)</th>
<th>Previous Findings from 2014 AHRQ- or 2016 AUA-Funded Reviews†</th>
<th>Present Findings Derived from Studies Published After the Prior Reviews and by Incorporating Prior RCT Data When Applicable ‡</th>
</tr>
</thead>
</table>
| 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. |
| 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. |
| 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. |
| 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 | 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. |
<table>
<thead>
<tr>
<th>Intervention/Comparison</th>
<th>Outcome(s)</th>
<th>Previous Findings from 2014 AHRQ- or 2016 AUA-Funded Reviews†</th>
<th>Present Findings Derived from Studies Published After the Prior Reviews and by Incorporating Prior RCT Data When Applicable ‡</th>
</tr>
</thead>
</table>
| 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. |
<p>| 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 |
| 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 |</p>
<table>
<thead>
<tr>
<th>Intervention/Comparison</th>
<th>Outcome(s)</th>
<th>Previous Findings from 2014 AHRQ- or 2016 AUA-Funded Reviews†</th>
<th>Present Findings Derived from Studies Published After the Prior Reviews and by Incorporating Prior RCT Data When Applicable ‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMRT vs. Proton beam</td>
<td>Harms</td>
<td>IMRT may reduce GI adverse events versus proton beam. **</td>
<td>No new data</td>
</tr>
<tr>
<td>3D-CRT conventional vs. 3D-CRT high dose</td>
<td>All-cause mortality, PC-specific mortality, metastases, harms</td>
<td>No between-group differences. **</td>
<td>Not addressed</td>
</tr>
<tr>
<td>Hypofractionated RT vs. conventionally-fractionated RT</td>
<td>All-cause mortality, PC-specific mortality, Harms</td>
<td>No between-group differences. **</td>
<td>Not addressed</td>
</tr>
<tr>
<td>Brachytherapy conventional dose vs. Brachytherapy low dose</td>
<td>All-cause mortality, Urinary symptoms</td>
<td>No between-group difference (except in short-term urinary symptoms). **</td>
<td>Not addressed</td>
</tr>
<tr>
<td>ADT plus RP vs. RP</td>
<td>All-cause mortality, PC-specific mortality, Metastasis</td>
<td>No between-group differences. **</td>
<td>No new data</td>
</tr>
<tr>
<td>ADT plus SOC (RP or RT) vs. SOC (RP or RT)</td>
<td>All-cause mortality, metastases</td>
<td>No between-group difference. **</td>
<td>No new data</td>
</tr>
<tr>
<td>ADT plus SOC (WW) vs. SOC (WW) alone</td>
<td>All-cause mortality, metastases</td>
<td>Inconsistent results. **</td>
<td>No new data</td>
</tr>
<tr>
<td>ADT short-term plus RT vs. ADT long-term plus RT</td>
<td>All-cause mortality, PC-specific mortality</td>
<td>No between-group difference on mortality. Inconsistent results on PC-specific mortality. **</td>
<td>Not addressed</td>
</tr>
<tr>
<td>ADT vs. ADT plus docetaxel and estramustine</td>
<td>All-cause mortality, PC-specific mortality, Metastases</td>
<td>Combination therapy may reduce mortality, PC-specific mortality, and metastases versus ADT, but results considered &quot;inconclusive&quot; in 2016 AUA-funded report. **</td>
<td>No new data</td>
</tr>
</tbody>
</table>

**Abbreviations:** ADT=androgen deprivation therapy; AHRQ=Agency for Healthcare Research and Quality; AM=active monitoring; AUA=American Urological Association; CLPC=clinically localized prostate cancer; EBRT=external beam radiation therapy; 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; QOL=quality of life; RCT=randomized controlled trial; RP=radical prostatectomy; RT=radiation therapy; SOC=standard of care; SPCG4=Scandinavian Prostate Cancer Group Study Number 4; WW=watchful waiting; 3D-CRT=three-dimensional conformal radiation therapy

*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

- WW versus RP in men with predominately clinically, rather than PSA screen-detected 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 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 clinically localized prostate cancer (CLPC) detected by PSA screening alone.

We identified three reports of two unique RCTs22-24 and five reports of four unique non-RCTs25-29 comparing watchful waiting (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. EBRT25, 27, 28 WW vs. radiation therapy [either EBRT and/or brachytherapy]26, 29 WW vs. active surveillance26, 29 WW vs. ADT26, 29)

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 AUA in which we did not identify additional studies that met analysis criteria.12 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 watchful waiting (WW) to radical prostatectomy (RP) and reported long-term results.22-24 The SPCG-4 study was conducted in Scandinavia prior to PSA screening, and enrolled men with clinically detected disease. The U.S. 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.30-43 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.5, 12 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 and urinary incontinence versus RP at nearly 10 years (moderate COE). There was little to no difference in satisfaction with sexual function at nearly 10 years, although sexual function was low in both groups. However, within the first 5 years of the trial more men in the RP group reported poor sexual functioning compared with men in the WW group. The initial PIVOT trial publication reported no difference in bowel dysfunction at 2 years, defined as patient reported dysfunction as a “moderate” or “big” problem, between the WW and RP groups (11 vs. 12%, p=.74).32 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.5, 12 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.22-24 Wilt et al. also analyzed race as a potential effect modifier.24 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

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Outcome and followup</th>
<th>Relative effect (95% CI)</th>
<th>Absolute effects</th>
<th>Certainty of Evidence:</th>
<th>What happens</th>
</tr>
</thead>
<tbody>
<tr>
<td>WW versus RP&lt;sup&gt;22-24&lt;/sup&gt;</td>
<td>All-cause mortality ~20-years followup 2 RCTs (n=1426)</td>
<td>SPCG-4: RR 1.23 (1.10 to 1.38)</td>
<td>70.9% (247/348)</td>
<td>57.6% (200/347)</td>
<td>13.3% (6.3 to 20.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PIVOT: RR 1.09 (0.98 to 1.22)</td>
<td>66.7% (245/367)</td>
<td>61.3% (223/364)</td>
<td>5.5% (-1.45 to 12.4)</td>
</tr>
<tr>
<td></td>
<td>All-cause mortality ~25-years followup 1 RCT (n=695)</td>
<td>RR 1.12 (1.03 to 1.2)</td>
<td>83.9% (292/348)</td>
<td>75.2% (261/347)</td>
<td>8.7 (2.7 to 14.6)</td>
</tr>
<tr>
<td></td>
<td>PC-specific mortality ~20-years followup 2 RCT (n=1426)</td>
<td>SPCG-4: RR 1.57 (1.19 to 2.07)</td>
<td>28.4% (99/348)</td>
<td>18.1% (63/347)</td>
<td>10.3% (4.05 to 16.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PIVOT: RR 1.54 (0.97 to 2.45)</td>
<td>11.4% (42/367)</td>
<td>7.4% (27/364)</td>
<td>4.0% (-0.19 to 8.25)</td>
</tr>
<tr>
<td></td>
<td>PC-specific mortality ~25-years followup 1 RCT (n=695)</td>
<td>RR 1.54 (1.19 to 2.00)</td>
<td>31.6% (110/348)</td>
<td>20.5% (71/347)</td>
<td>11.1% (4.7 to 17.6)</td>
</tr>
<tr>
<td></td>
<td>Metastases ~20-years followup 1 RCT (n=695)</td>
<td>RR 1.54 (1.24 to 1.93)</td>
<td>39.7% (138/348)</td>
<td>25.6% (89/347)</td>
<td>14% (7.1 to 20.9)</td>
</tr>
<tr>
<td></td>
<td>Metastases ~25-years followup 1 RCT (n=695)</td>
<td>RR 1.63 (1.3 to 2.00)</td>
<td>43.1% (150/348)</td>
<td>26.5% (92/347)</td>
<td>16.6% (9.6 to 23.6)</td>
</tr>
<tr>
<td></td>
<td>Metastases (Systemic progression) ~20-years followup 1 RCT (n=731)</td>
<td>RR 1.45 (0.98 to 2.14)</td>
<td>14.7% (54/367)</td>
<td>10.2% (37/364)</td>
<td>4.5% (-0.3 to 9.4)</td>
</tr>
<tr>
<td></td>
<td>Erectile dysfunction ~10-years followup 1 RCT (n=731)</td>
<td>RR 0.374 (0.23 to 0.61)</td>
<td>5.4% (20/367)</td>
<td>14.6% (53/364)</td>
<td>-9.1% (-13.4 to -4.8)</td>
</tr>
<tr>
<td>Comparison</td>
<td>Outcome</td>
<td>No of participants (studies)</td>
<td>Relative effect (95% CI)</td>
<td>Absolute effects</td>
<td>Certainty of Evidence:</td>
</tr>
<tr>
<td>------------</td>
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<td>-----------------------------</td>
<td>--------------------------</td>
<td>------------------</td>
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</tr>
<tr>
<td></td>
<td>Urinary incontinence (pad use) ~10-years followup</td>
<td>1 RCT (n=731)</td>
<td>RR 0.25 (0.15 to 0.43)</td>
<td>4.4% (16/367)</td>
<td>Comparator 17.3% (63/364)</td>
</tr>
</tbody>
</table>

**Abbreviations:** CI=Confidence interval; n=sample size; PC=prostate cancer; RCT=Randomized controlled trial; RP=radical prostatectomy; RR=relative risk; 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

- **PSA-based Active Monitoring (AM) versus external beam radiation therapy (EBRT) plus androgen deprivation therapy (ADT) in men with PSA detected CLPC:**
  - There may be little to no difference in all-cause mortality (moderate 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 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 erectile dysfunction (ED) and a moderate reduction in perineal pain with AS versus PDT (moderate COE).

We identified six reports of two unique RCTs and nine reports of four unique non-RCTs 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], AS vs. external beam radiation therapy [EBRT][k=1 non-RCT], AS vs. brachytherapy [k=1 non-RCT], AS vs. radiation therapy [either EBRT and/or brachytherapy][k=1 non-RCT], and AS vs. androgen deprivation therapy [ADT][k=1 non-RCT]).

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 AUA in which we did not identify any additional studies that met our analysis criteria. 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. 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. Median age was 62 years and the majority were white (98%). 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). 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). 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.

Erectile dysfunction was slightly lower with AM versus EBRT plus ADT (low COE). 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 photodynamic therapy (PDT) in men with low but not very low-risk disease. 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 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 PTD (moderate COE).
Table 4. Certainty of Evidence: Active Monitoring and Active Surveillance

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Outcome Ne of participants (studies)</th>
<th>Relative effect (95% CI)</th>
<th>Absolute effects</th>
<th>Difference (95% CI)</th>
<th>Certainty of Evidence:</th>
<th>What happens</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PSA-based AM versus EBRT + ADT</strong>&lt;sup&gt;44-46&lt;/sup&gt;</td>
<td>All-cause mortality 10 years followup 1 RCT (n=1090)</td>
<td>RR 1.07 (0.8 to 1.5)</td>
<td>10.8% (59/545)</td>
<td>10.1% (55/545)</td>
<td>0.7% (-2.9 to 4.4)</td>
<td>MODERATE&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>PC-specific mortality 10 years followup 1 RCT (n=1090)</td>
<td>Peto OR 1.96 (0.63 to 6.12)</td>
<td>1.5% (8/545)</td>
<td>0.7% (4/545)</td>
<td>0.7% (-0.5 to 1.9)</td>
<td>LOW&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Metastases 10 years followup 1 RCT (n=1090)</td>
<td>RR 2.1 (1.15 to 3.7)</td>
<td>6.0% (33/545)</td>
<td>2.9% (16/545)</td>
<td>3.1% (0.67 to 5.6)</td>
<td>MODERATE&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Erectile dysfunction 6 years followup 1 RCT (n=908)</td>
<td>RR 0.97 (0.89 to 1.05)</td>
<td>70.4% (318/452)</td>
<td>72.6% (331/456)</td>
<td>-2.4% (-8.2 to 3.5)</td>
<td>LOW&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Urinary incontinence 6 years followup 1 RCT (n=903)</td>
<td>RR 2.37 (1.34 to 4.19)</td>
<td>8.4% (38/453)</td>
<td>3.5% (16/452)</td>
<td>4.8% (1.8 to 7.9)</td>
<td>MODERATE&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Fecal incontinence 6 years followup 1 RCT (n=927)</td>
<td>RR 0.64 (0.3 to 1.3)</td>
<td>2.6% (12/462)</td>
<td>4.1% (19/465)</td>
<td>-1.5% (-3.8 to 0.82)</td>
<td>LOW&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>AS versus PDT</strong>&lt;sup&gt;7&lt;/sup&gt;</td>
<td>Erectile dysfunction 24-month followup 1 RCT (n=404)</td>
<td>RR 0.31 (0.2 to 0.5)</td>
<td>11.6% (24/207)</td>
<td>37.6% (74/197)</td>
<td>-26% (-34 to -18)</td>
<td>MODERATE&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Urinary incontinence 24 months followup 1 RCT (n=404)</td>
<td>RR 0.5 (0.24 to 1.05)</td>
<td>4.8% (10/207)</td>
<td>9.6% (19/197)</td>
<td>-4.8% (-9.9 to 2.4)</td>
<td>INSUFFICIENT&lt;sup&gt;b,c&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Urinary retention 24 months followup 1 RCT (n=404)</td>
<td>RR 0.06 (0.01 to 0.24)</td>
<td>1.0% (2/207)</td>
<td>16.2% (32/197)</td>
<td>-15.3% (-20.6 to -10)</td>
<td>MODERATE&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

**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; RCT=Randomized controlled trial; RR=relative risk
<table>
<thead>
<tr>
<th>Comparison</th>
<th>Outcome</th>
<th>Relative effect (95% CI)</th>
<th>Absolute effects</th>
<th>Difference (95% CI)</th>
<th>Certainty of Evidence:</th>
<th>What happens</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>AS/AM Comparator</td>
<td></td>
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</tbody>
</table>

**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 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).
- 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. Among the RCTs, one compared 3D-CRT versus IMRT. One RCT compared 3D-CRT and ADT versus 3D-CRT and ADT plus low-dose-rate (LDR) prostate brachytherapy boost. Four RCTs (6 publications) compared EBRT plus ADT versus EBRT alone. One RCT compared EBRT plus ADT versus ADT alone. Two RCTs compared ultra-hypofractionated EBRT versus standard fractionations. One RCT compared EBRT plus neoadjuvant and concurrent...
ADT versus EBRT plus concurrent and adjuvant ADT. Three of the aforementioned RCTs were rated high ROB and therefore not analyzed. 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 AUA in which we did not identify any additional studies that met our analysis criteria published after this report. 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. The trial compared 46 Gray of dose-escalated external beam radiation therapy (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. QOL not extracted due to high ROB of the reporting study.
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 intensity-modulated radiation therapy (IMRT). Followup was over 3 years. 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). 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) and compared overall survival between IMRT versus 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 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. The non-RCT (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.\textsuperscript{87-89} 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).\textsuperscript{71, 76, 78, 80 90-92 93, 94} Among the seven total trials, one was rated high ROB.\textsuperscript{71} The analysis focuses on the remaining six. In one trial, the EBRT examined was IMRT,\textsuperscript{78} two trials predominantly used three-dimensional conformal radiation therapy (3D-CRT),\textsuperscript{76, 93} and two trials did not specify EBRT type.\textsuperscript{90, 91} The sixth trial allowed different EBRT techniques to be used across trial centers.\textsuperscript{92} The ADT in four trials consisted of an antiandrogen (flutamide or bicalutamide) with a luteinizing hormone-releasing hormone (LHRH) agonist (goserelin or leuprolide)\textsuperscript{76, 90, 91, 93} and two trials used antiandrogen monotherapy with bicalutamide.\textsuperscript{78, 92} 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).\textsuperscript{92} 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\textsuperscript{76, 78, 91, 94} and two also enrolling patients with higher tumor stages. Patients were eligible for two trials in part by Gleason \(\geq 7\) and a third Gleason 6-8 (three trials specified Gleason in eligibility criteria).\textsuperscript{76, 78, 94} The median PSA at baseline ranged from 7.6 ng/mL to 16.4 (five trials reporting).\textsuperscript{76, 78, 90, 92, 94} 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.\textsuperscript{91, 92} The longest mean/median followups ranged from 5.4 to 18.2 years. We also identified one non-RCT\textsuperscript{95} that reported overall mortality/survival. The 2016 systemic review also included two non-RCTs\textsuperscript{87, 96} 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).\textsuperscript{76, 78, 90, 91, 93} 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).\textsuperscript{76, 93} Mortality reduction persisted at 16.6 years with combination therapy in one 3D-CRT trial that reported longer followup (RD -2.4\%).\textsuperscript{80} 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\%).\textsuperscript{78} 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).\textsuperscript{76, 91, 93} 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\%),\textsuperscript{80} 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\%).\textsuperscript{76} 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).\textsuperscript{76, 90-92} A trial that predominantly used 3D-CRT also reported a small magnitude reduction with combination therapy (RD -3.2\%).\textsuperscript{76} 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. 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. 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. 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). 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). 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). 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. One trial reported little to no difference between groups in hematuria grades 2 to 4, diarrhea, and “complete urinary incontinence”. 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). One trial reported a small decrease in gastrointestinal late toxicity grades 2 to 3 with combination therapy (RD -2.4%).

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). 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). 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). The 2016 systematic review included an earlier follow-up publication of SPCG-7. 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. At median follow-up 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. 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. It was rated serious ROB based on the ROBINS-I tool. The 2016 systematic review included one non-RCT. 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. 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. 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
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 Ultra-Hypofractionated External Beam Radiation**

Two RCTs compared conventionally fractionated EBRT versus ultra-hypofractionated EBRT. One RCT was rated high risk of bias and hereafter, our analysis only focuses on the second trial. 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 fractionated 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>
<thead>
<tr>
<th>Comparison</th>
<th>Outcome</th>
<th>Number of participants (studies)</th>
<th>Relative effect (95% CI)</th>
<th>Anticipated absolute effects</th>
<th>Relative effect (95% CI)</th>
<th>Difference (95% CI)</th>
<th>Certainty of Evidence</th>
<th>What happens</th>
</tr>
</thead>
<tbody>
<tr>
<td>3D-CRT and ADT vs. 3D-CRT and ADT with LDR-PB boost</td>
<td>Mortality 5-year followup 1 RCT study (n=398)</td>
<td>RR 1.25 (0.81 to 1.94)</td>
<td>18.9% (38/200)</td>
<td>15.2% (30/198)</td>
<td>3.8% (-3.5 to 11.2)</td>
<td>LOW a, b</td>
<td>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.</td>
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<tr>
<td>Prostate-specific mortality 5-year followup 1 RCT study (n=398)</td>
<td>RR 1.56 (0.62 to 3.93)</td>
<td>5.5% (11/200)</td>
<td>3.5% (7/198)</td>
<td>2.0% (-2.1 to 6.0)</td>
<td>INSUFFICIENT a, c</td>
<td>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.</td>
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<tr>
<td>Metastatic disease 5-year followup 1 RCT study (n=398)</td>
<td>RR 1.05 (0.56 to 1.97)</td>
<td>9.0% (18/200)</td>
<td>8.6% (17/198)</td>
<td>0.4% (-5.1 to 6.0)</td>
<td>LOW a, b</td>
<td>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.</td>
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<tr>
<td>Urinary incontinence 5-year followup 1 RCT study (n=383)</td>
<td>not estimable</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>INSUFFICIENT a, d</td>
<td>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.</td>
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<tr>
<td>Erectile function 5-year followup 1 RCT study (n=383)</td>
<td>not estimable</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>INSUFFICIENT a, c</td>
<td>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.</td>
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<tr>
<td>Brachytherapy + EBRT vs. Brachytherapy</td>
<td>Overall mortality 7-year followup 1 observational study (n=5858)</td>
<td>not estimable</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>INSUFFICIENT a, d</td>
<td>The evidence is very uncertain about the effect of brachytherapy with EBRT on overall survival versus brachytherapy alone.</td>
<td></td>
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<tr>
<td>IMRT vs. SBRT</td>
<td>Overall mortality 9-year followup 1 observational study (n=5430)</td>
<td>not estimable</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>INSUFFICIENT a, c</td>
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<tr>
<td>EBRT plus ADT versus EBRT</td>
<td>Overall mortality -5.9 to 9.1 years</td>
<td>5 RCTs (n=4047)</td>
<td>RR 0.86 (0.69 to 1.06)</td>
<td>587/2150 (27.3%)</td>
<td>615/1897 (32.4%)</td>
<td>-3.7% (-9.8 to 2.4)</td>
<td>⬤⬤⬤⬤ MODERATE</td>
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<tr>
<td>prostate cancer mortality -7.2 to 9.1 years</td>
<td>3 RCTs (n=3004)</td>
<td>Peto OR 0.51 (0.37 to 0.70)</td>
<td>53/1499 (3.53%)</td>
<td>104/1505 (6.9%)</td>
<td>-3.4% (-4.95 to -1.8)</td>
<td>⬤⬤⬤ ○○ LOW</td>
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<tr>
<td>Metastasis -5 to 10 years</td>
<td>4 RCTs (n=4664)</td>
<td>RR 0.83 (0.71 to 0.97)</td>
<td>284/2461 (11.5%)</td>
<td>289/2203 (13.1%)</td>
<td>-2.3% (-4.1 to -0.4)</td>
<td>⬤⬤⬤ ○○ LOW</td>
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<tr>
<td>Sexual function: severe impairment based on late toxicity scores-measured from six months until end of followup (7.2 years)</td>
<td>1 RCT (n=813)</td>
<td>RR 1.40 (1.08 to 1.80)</td>
<td>110/406 (27.0%)</td>
<td>79/407 (19.4%)</td>
<td>7.7% (1.9 to 13.5)</td>
<td>⬤⬤⬤ ○○ LOW</td>
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<tr>
<td>Sexual function: impotence grade 2-4-4.5 years</td>
<td>1 RCT (n=201)</td>
<td>RR 1.20 (0.79 to 1.84)</td>
<td>32/98 (32.7%)</td>
<td>28/103 (27.2%)</td>
<td>5.5% (-7.2% to 18.1%)</td>
<td>⬤⬤⬤⬤ INSUFFICIENT</td>
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<tr>
<td>Urinary incontinence (stress) grades 2-4-4.5 years</td>
<td>1 RCT (n=201)</td>
<td>RR 0.90 (0.31 to 2.59)</td>
<td>6/98 (6.1%)</td>
<td>7/103 (6.8%)</td>
<td>-0.7% (-7.5 to 6.1)</td>
<td>⬤⬤⬤⬤ INSUFFICIENT</td>
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<tr>
<td>Rectal bleeding grades 2-4-4.5 years</td>
<td>1 RCT (n=201)</td>
<td>RR 1.00 (0.57 to 1.75)</td>
<td>19/98 (19.4%)</td>
<td>20/103 (19.4%)</td>
<td>0.0% (-11.0 to 10.9)</td>
<td>⬤⬤⬤⬤ INSUFFICIENT</td>
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</table>

EBRT plus ADT probably results in a small reduction in overall mortality versus EBRT in higher risk disease.
EBRT and ADT may result in a small reduction in prostate cancer mortality versus EBRT in higher risk disease.
EBRT and ADT may result in a small reduction in metastasis versus EBRT in higher risk disease.
EBRT and ADT may result in a moderate increase in severe impairment in sexual function versus EBRT in higher risk disease.

The evidence is very uncertain about the effect of EBRT plus ADT on impotence grade 2-4 versus EBRT alone.
The evidence is very uncertain about the effect of EBRT plus ADT on urinary incontinence versus EBRT alone.
The evidence is very uncertain about the effect of EBRT plus ADT on rectal bleeding versus EBRT alone.
<table>
<thead>
<tr>
<th>Comparison</th>
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<tbody>
<tr>
<td>EBRT plus neoadjuvant and concurrent ADT vs. EBRT plus concurrent and adjuvant ADT</td>
<td>Overall mortality-12.2 years 1 RCT (n=432)</td>
<td>RR 1.05 (0.81 to 1.37)</td>
<td>75/215 (34.9%)</td>
<td>1.7% (7.2% to 10.6%)</td>
<td>![θθθ◯◯](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</td>
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<tr>
<td></td>
<td>Prostate cancer mortality-12.2 years 1 RCT (n=432)</td>
<td>Peto OR 1.01 (0.35 to 2.93)</td>
<td>7/215 (3.3%)</td>
<td>0% (-3.3% to 3.4%)</td>
<td>![θθθ◯◯](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</td>
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<tr>
<td></td>
<td>Metastasis distant progression-12.2 years 1 RCT (n=432)</td>
<td>Peto OR 1.36 (0.57 to 3.27)</td>
<td>12/215 (5.6%)</td>
<td>1.4% (-2.6% to 5.5%)</td>
<td>![◯◯◯](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</td>
</tr>
<tr>
<td></td>
<td>Late genitourinary toxicity grade ≥3-3 years 1 RCT (428)</td>
<td>Peto OR 1.01 (0.32 to 3.18)</td>
<td>6/213 (2.8%)</td>
<td>0% (-3.1% to 3.2%)</td>
<td>![◯◯◯](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</td>
</tr>
<tr>
<td>EBRT vs. Brachytherapy</td>
<td>Overall survival Median 10 years 1 observational study (n=684)</td>
<td>not estimable</td>
<td>Propensity score adjusted probability 75.5% (CI 71.8 to 79.4)</td>
<td>~ -2.8% (not estimable)</td>
<td>![◯◯◯](INSUFFICIENT e, f) The evidence is uncertain about the effect of EBRT on overall survival versus brachytherapy</td>
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<tr>
<td></td>
<td>Prostate cancer-specific survival Median 10 years 1 observational study (n=684)</td>
<td>not estimable</td>
<td>Propensity score adjusted probability 96.2% (CI 94.3 to 98.1)</td>
<td>~ 0.8% (not estimable)</td>
<td>![◯◯◯](INSUFFICIENT e, f) The evidence is uncertain about the effect of EBRT on prostate cancer-specific survival versus brachytherapy</td>
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<td>EBRT</td>
<td>Comparator</td>
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<tr>
<td>Metastasis-free survival</td>
<td>Median 10 years 1 observational study (n=684)</td>
<td>not estimable</td>
<td>Propensity score adjusted probability 90.6% (CI 87.9 to 93.3)</td>
<td>Propensity score adjusted probability 94.1% (CI 89.5 to 98.9)</td>
<td>~ -3.5% (not estimable)</td>
</tr>
<tr>
<td>Conventionally fractionated EBRT vs. ultra-hypofractionated EBRT</td>
<td>Mortality-5 years 1 RCT (n=1180)</td>
<td>RR 0.93 (0.63 to 1.39)</td>
<td>7.3% (43/591)</td>
<td>7.8% (46/589)</td>
<td>-0.5% (-3.5 to 2.5)</td>
</tr>
<tr>
<td>Prostate cancer mortality-5 years 1 RCT (n=1180)</td>
<td>Peto OR 0.72 (0.29 to 1.79)</td>
<td>1.4% (8/591)</td>
<td>1.9% (11/589)</td>
<td>-0.5% (-2.0 to 0.9)</td>
<td>LOW a, b</td>
</tr>
<tr>
<td>Metastasis-5 years 1 RCT (n=1180)</td>
<td>RR 1.02 (0.66 to 1.58)</td>
<td>6.6% (39/591)</td>
<td>6.5% (38/589)</td>
<td>0.1% (-2.7 to 3.0)</td>
<td>LOW a, b</td>
</tr>
<tr>
<td>Urinary toxicity grade ≥2 based on RTOG morbidity scale-1 and 2 years 1 RCT (n=989 to 1057)</td>
<td>1 year RR 0.41 (0.22 to 0.76)</td>
<td>2.5% (13/529)</td>
<td>1 year 6.1% (32/528)</td>
<td>1 year -3.6% (-6.0 to -1.2)</td>
<td>LOW a, b</td>
</tr>
<tr>
<td>Bowel toxicity grade ≥2 based on RTOG morbidity scale-2 years 1 RCT (n=991)</td>
<td>Peto OR 1.77 (0.80 to 3.92)</td>
<td>3.2% (16/496)</td>
<td>1.8% (9/495)</td>
<td>1.4% (-0.5 to 3.4)</td>
<td>LOW a, b</td>
</tr>
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| Erectile function | 1 and 2 years | not estimable | NR | NR | @@@@ 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 PSA-based AM (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 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 RCTs44-47, 86, 98, 99 and one non-RCT100 that compared RP to other therapies. Serious or critical risk of bias (ROB) precluded the inclusion of eight non-RCTs in the analysis.26, 29, 54, 101-105 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.106-111

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 AUA in which we did not identify any additional studies of low to moderate ROB published after this report.12 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 active monitoring (AM), to RP or EBRT plus ADT in men with PSA-screen detected CLPC and reported results for survival, metastases, quality of life, or harms.44-47 Men with T1c-T2 CLPC were randomized to AM (n=545), RP (n=553) or 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% HIFU). Median age was 62 years and the majority were white (98%).46 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.45 Few deaths were attributable to prostate cancer; five and eight in the RP and AM groups, respectively.

There was probably a small reduction in the development of metastases with RP compared with AM over 10 years (moderate COE).45 At 12- and 72-months, 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).44

Harms associated with urinary and sexual function were worse with RP than AM.44 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;44-47 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. Median age was 62 years, nearly all were white (98%). 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 American Urological Association (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. The 2014 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. The prior AHRQ review also concluded that, in general, urinary incontinence and erectile dysfunction (ED) were commonly reported adverse events among men who underwent RP, and gastrointestinal/genitourinary toxicity and ED 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. 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).

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). ED (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, ED 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 (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 HDR-BT) plus ADT and reported results for survival, quality of life, or harms through 10 years. 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. 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 with longer (5-year) followup of a small RCT previously included in both the 2016 evidence report commissioned by the AUA and the 2014 systematic review conducted by AHRQ, that compared laparoscopic radical prostatectomy (LRP) to robotic-assisted radical prostatectomy (RARP) and reported results for quality of life and harms. 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%. 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. 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. 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.\(^{100}\) 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.\(^{114, 115}\)

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.\(^{12}\) The 2014 systematic review conducted by AHRQ indicated that RALRP versus RRP was the most common comparison.\(^5\) 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 ED 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.\(^{26, 29}\) 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.\(^5, 12\) 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. 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

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Outcome</th>
<th>Relative effect (95% CI)</th>
<th>Absolute effects</th>
<th>Certainty of Evidence</th>
<th>What happens</th>
</tr>
</thead>
<tbody>
<tr>
<td>RP versus AM&lt;sup&gt;44, 45&lt;/sup&gt;</td>
<td>All-cause mortality</td>
<td>RR 0.92 (0.65 to 1.30)</td>
<td>9.9% (55/553)</td>
<td>10.8% (59/545)</td>
<td>-0.9% (-4.5 to 2.7)             MODERATE&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>PC-specific mortality</td>
<td>Peto OR 0.62 (0.20 to 1.87)</td>
<td>0.9% (5/553)</td>
<td>1.5% (8/545)</td>
<td>-0.6% (-1.8 to 0.7)             LOW&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Metastases</td>
<td>Peto OR 0.40 (0.22 to 0.72)</td>
<td>2.4% (13/553)</td>
<td>6.4% (33/545)</td>
<td>-4.0% (-6.1 to -1.3); NNT=25        MODERATE&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Urinary incontinence (pad use)</td>
<td>RR 2.07 (1.44 to 2.98)</td>
<td>17.4% (79/455)</td>
<td>8.4% (38/453)</td>
<td>9% (5 to 13); NNT=11             MODERATE&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Erectile dysfunction</td>
<td>RR 1.19 (1.10 to 1.28)</td>
<td>83.5% (385/461)</td>
<td>70.4% (318/452)</td>
<td>13% (8 to 19); NNT=9              MODERATE&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Fecal incontinence</td>
<td>Peto OR 0.74 (0.31 to 1.75)</td>
<td>1.9% (9/468)</td>
<td>2.6% (12/462)</td>
<td>-0.7% (-2.6 to 1.2);             LOW&lt;sup&gt;a, c&lt;/sup&gt;</td>
</tr>
<tr>
<td>RP versus EBRT plus ADT&lt;sup&gt;44, 45&lt;/sup&gt;</td>
<td>All-cause mortality</td>
<td>RR 0.99 (0.69 to 1.04)</td>
<td>9.9% (55/553)</td>
<td>10.1% (55/545)</td>
<td>-0.1% (-3.7 to 3.7)             MODERATE&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>PC-specific mortality</td>
<td>Peto OR 1.23 (0.33 to 4.58)</td>
<td>0.9% (5/553)</td>
<td>0.7% (4/545)</td>
<td>0.2% (-0.9 to 1.2)              LOW&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Metastases</td>
<td>Peto OR 0.80 (0.38 to 1.67)</td>
<td>2.4% (13/553)</td>
<td>2.9% (16/545)</td>
<td>-0.6% (-2.5 to 1.3)             LOW&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Comparison</td>
<td>Outcome</td>
<td>No of participants (studies)</td>
<td>Relative effect (95% CI)</td>
<td>Absolute effects</td>
<td>Certainty of Evidence</td>
</tr>
<tr>
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<tr>
<td>Urinary incontinence (pad use)</td>
<td>72-month followup</td>
<td>1 RCT (n=907)</td>
<td>RR 4.90 (2.91 to 8.26)</td>
<td>17.4% (79/455)</td>
<td>3.5% (16/452)</td>
</tr>
<tr>
<td>Erectile dysfunction</td>
<td>72-month followup</td>
<td>1 RCT (n=917)</td>
<td>RR 1.15 (1.07 to 1.23)</td>
<td>83.5% (385/461)</td>
<td>72.6% (331/456)</td>
</tr>
<tr>
<td>Fecal incontinence</td>
<td>72-month followup</td>
<td>1 RCT (n=933)</td>
<td>Peto OR 0.48 (0.22 to 1.01)</td>
<td>1.9% (8/468)</td>
<td>4.1% (19/466)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>10-year followup</td>
<td>1 RCT (n=89)</td>
<td>RR 1.30 (0.61 to 2.78)</td>
<td>26.7% (12/45)</td>
<td>20.5% (9/44)</td>
</tr>
<tr>
<td>PC-specific mortality</td>
<td>10-year followup</td>
<td>1 RCT (n=89)</td>
<td>Peto OR 2.89 (0.68 to 12.27)</td>
<td>13.3% (6/45)</td>
<td>4.5% (2/44)</td>
</tr>
<tr>
<td>Urinary incontinence (Grade 3-4*)</td>
<td>24-month followup</td>
<td>1 RCT (n=55)</td>
<td>Peto OR 1.70 (0.35 to 8.23)</td>
<td>16% (4/25)</td>
<td>10% (3/30)</td>
</tr>
<tr>
<td>Erectile dysfunction (Grade 3-4*)</td>
<td>24-month followup</td>
<td>1 RCT (n=71)</td>
<td>RR 1.05 (0.87 to 1.25)</td>
<td>89% (33/37)</td>
<td>85% (29/34)</td>
</tr>
<tr>
<td>Fecal incontinence (Grade 2*)</td>
<td>24-month followup</td>
<td>1 RCT (n=54)</td>
<td>Peto OR 0.32 (0.08 to 1.33)</td>
<td>8% (2/25)</td>
<td>24.1% (7/29)</td>
</tr>
<tr>
<td>Comparison</td>
<td>Outcome (95% CI)</td>
<td>Relative effect (95% CI)</td>
<td>Absolute effects</td>
<td>Certainty of Evidence</td>
<td>What happens</td>
</tr>
<tr>
<td>---------------------------</td>
<td>---------------------------------------------------------------------------------</td>
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<td>------------------------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>LRP versus RARP&lt;sup&gt;99&lt;/sup&gt;</td>
<td>Urinary incontinence (pad use), 60-month followup 1 RCT (n=115)</td>
<td>Peto OR 3.96 (1.15 to 13.65)</td>
<td>15.5% (9/58)</td>
<td>3.5% (2/57)</td>
<td>12% (1.5 to 23) LRP may result in a moderate increase in urinary incontinence versus RARP</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RR 1.89 (0.98 to 3.65)</td>
<td>49% (17/35)</td>
<td>26% (9/35)</td>
<td>23% (1 to 45) LRP may result in a large increase in erectile dysfunction versus RARP</td>
</tr>
<tr>
<td>RALRP versus Open RRP&lt;sup&gt;100&lt;/sup&gt;</td>
<td>Erectile dysfunction (unrecovered erectile function), 24-month followup 1 Obs (n=1702)</td>
<td>Data not presented in usable manner</td>
<td>49%</td>
<td>61%</td>
<td>-12% (CI NA) The evidence is very uncertain about the effect of RALRP on erectile dysfunction versus open RRP</td>
</tr>
<tr>
<td>RP versus HIFU&lt;sup&gt;98&lt;/sup&gt;</td>
<td>Urinary incontinence 12-month followup 1 RCT (n=82)</td>
<td>Data not presented in usable manner</td>
<td>58%</td>
<td>0%</td>
<td>-58% (CI NA) The evidence is very uncertain about the effect of RP on urinary incontinence versus HIFU</td>
</tr>
<tr>
<td></td>
<td>Erectile dysfunction 12-month followup 1 RCT (n=82)</td>
<td>Data not presented in usable manner</td>
<td>50%</td>
<td>20%</td>
<td>-30% (CI NA) The evidence is very uncertain about the effect of RP on erectile dysfunction versus HIFU</td>
</tr>
<tr>
<td></td>
<td>Fecal incontinence 12-month followup 1 RCT (n=82)</td>
<td>Data not presented in usable manner</td>
<td>22%</td>
<td>15%</td>
<td>-7% (CI NA) The evidence is very uncertain about the effect of RP on fecal incontinence versus HIFU</td>
</tr>
</tbody>
</table>

**Abbreviations:** ADT=androgen deprivation therapy; AM=active monitoring; BT=brachytherapy; CI=confidence interval; EBRT=external beam radiation therapy; LRP=laparoscopic radical prostatectomy; HIFU=high intensity focused ultrasound; NA=not available; n=number; NNH=Number-needed-to harm; 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).

**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
- 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 RCT and 1 non-RCT],75, 77 ADT versus RP [k=1 non-RCT],26, 29 ADT versus radiation therapy [either EBRT and/or brachytherapy][k=1 non-RCT],26, 29 ADT versus AS [k=1 non-RCT],26, 29 ADT versus watchful waiting [k=1 non-RCT]).26, 29

There were several comparisons of ADT 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.12 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.12 The 2016 evidence report and appendices contains detailed results, strength of evidence, and evidence tables for this comparison.

Focal Therapies – Photodynamic Therapy

Information about AS versus photodynamic therapy can be found in Chapter 5.

The 2016 evidence report commissioned by the AUA did not report on any eligible comparisons of photodynamic therapy.12

Focal Therapies – Laser Ablation

Laser ablation versus RP was addressed in one non-RCT rated as critical ROB.104 The 2016 evidence report commissioned by the AUA did not report on any eligible comparisons of laser ablation.12
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. 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], AS vs. radiation [either EBRT and/or brachytherapy] [k=1 non-RCT], RP vs. brachytherapy [k=2 non-RCTs], RP vs. radiation [either EBRT and/or brachytherapy] [k=1 non-RCT], ADT vs. radiation [either EBRT and/or brachytherapy] [k=1 non-RCT], and WW vs. radiation [either EBRT and/or brachytherapy] [k=1 non-RCT]).

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. 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 RTC of WW vs. RP in men with mainly clinically detected 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 AM versus either RP or EBRT plus 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 PSA, Gleason score, tumor index scores (such as D’Amico and 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 SPCG-4 than 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 to 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 AHRQ and 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 RP to 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 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 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, AM resulted in similar all-cause and prostate-cancer mortality versus RP or 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 MRI-imaging, 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. 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 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. Functional outcomes at 24 months were also similar. 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.

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 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), 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. {Cancer.net Editorial Board, 2020 #178} 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. {Welch, 2020 #177} 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 EBR + AD. For men with higher risk disease who select EBR, the addition of AD reduces mortality but may increase harms compared to 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 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, EBR plus ADT compared to EBR 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 EBR) 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 NCCN risk categories or the 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 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 J). 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 \textit{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 AHRQ and 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 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 3D-CRT and ADT with low-dose-rate prostate brachytherapy (LDR-prostate brachytherapy) 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 WW in men with 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

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>3D-CRT</td>
<td>three-dimensional conformal radiation therapy</td>
</tr>
<tr>
<td>ACP</td>
<td>American College of Physicians</td>
</tr>
<tr>
<td>ADT</td>
<td>androgen deprivation therapy</td>
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<tr>
<td>AHRQ</td>
<td>Agency for Healthcare Research and Quality</td>
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<td>AM</td>
<td>Active Monitoring</td>
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<tr>
<td>AS</td>
<td>Active Surveillance</td>
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<td>ASCO</td>
<td>American Society of Clinical Oncology</td>
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<tr>
<td>ASTRO</td>
<td>American Society of Therapeutic Radiation Oncology</td>
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<tr>
<td>BT</td>
<td>interstitial brachytherapy</td>
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<tr>
<td>CAPRA</td>
<td>Cancer of the Prostate Risk Assessment Score</td>
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<tr>
<td>CLPC</td>
<td>clinically localized prostate cancer</td>
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<tr>
<td>EAU</td>
<td>European Association of Urology</td>
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<tr>
<td>EBRT</td>
<td>external beam radiation therapy</td>
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<tr>
<td>GRADE</td>
<td>Grading of Recommendations Assessment, Development and Evaluation</td>
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<tr>
<td>FDA</td>
<td>U.S. Food and Drug Administration</td>
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<tr>
<td>HIFU</td>
<td>high-intensity focused ultrasound</td>
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<tr>
<td>IMRT</td>
<td>intensity modulated radiation therapy</td>
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<td>KQ</td>
<td>key question</td>
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<tr>
<td>LHRH</td>
<td>luteinizing hormone-releasing hormone</td>
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<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
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<tr>
<td>NCCN</td>
<td>National Comprehensive Cancer Network</td>
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<tr>
<td>PSA</td>
<td>prostate-specific antigen</td>
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<td>RALP</td>
<td>Robot assisted laparoscopic prostatectomy</td>
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<tr>
<td>RCT</td>
<td>randomized controlled trial</td>
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<td>RD</td>
<td>risk difference</td>
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<tr>
<td>RP</td>
<td>radical prostatectomy</td>
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<tr>
<td>RR</td>
<td>risk ratios</td>
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<tr>
<td>RT</td>
<td>radiation therapy</td>
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<tr>
<td>SBRT</td>
<td>stereotactic body radiation therapy</td>
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<tr>
<td>SEER</td>
<td>NIH Surveillance, Epidemiology, and End Results Program</td>
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<tr>
<td>SUO</td>
<td>Society of Urological Oncology</td>
</tr>
<tr>
<td>T1</td>
<td>tumor Stage 1</td>
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<tr>
<td>T2</td>
<td>tumor Stage 2</td>
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<tr>
<td>WMD</td>
<td>weighted mean differences</td>
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WW watchful waiting
References


20. [Software]. GGDDT. McMaster University: (developed by Evidence Prime, Inc.) Available from gradepro.org; 2015.


