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Therapies for Clinically Localized Prostate Cancer: A Comparative Effectiveness Review

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Purpose: We sought to identify new information evaluating clinically localized prostate cancer therapies.

Materials and Methods: Bibliographic databases (2013–January 2020), ClinicalTrials.gov and systematic reviews were searched for controlled studies of treatments for clinically localized prostate cancer with duration ≥5 years for mortality and metastases, and ≥1 year for harms.

Results: We identified 67 eligible references. Among patients with clinically, rather than prostate specific antigen, detected localized prostate cancer, watchful waiting may increase mortality and metastases but decreases urinary and erectile dysfunction vs radical prostatectomy. Comparative mortality effect may vary by tumor risk and age but not by race, health status, comorbidities or prostate specific antigen. Active monitoring probably results in little to no mortality difference in prostate specific antigen detected localized prostate cancer vs radical prostatectomy or external beam radiation plus androgen deprivation regardless of tumor risk. Metastases were slightly higher with active monitoring. Harms were greater with radical prostatectomy than active monitoring and mixed between external beam radiation plus androgen deprivation vs active monitoring. 3-Dimensional conformal radiation and androgen deprivation plus low dose rate brachytherapy provided small mortality reductions vs 3-dimensional conformal radiation and androgen deprivation but little to no difference on metastases. External beam radiation plus androgen deprivation vs external beam radiation alone may result in small mortality and metastasis reductions in higher risk disease but may increase sexual harms. Few new data exist on other treatments.

Conclusions: Radical prostatectomy reduces mortality vs watchful waiting in clinically detected localized prostate cancer but causes more harms. Effectiveness may be limited to younger men and those with intermediate risk disease. Active monitoring results in little to no mortality difference vs radical prostatectomy or external beam radiation plus androgen deprivation. Few new data exist on other treatments.

Key Words: male, prostate-specific antigen, prostatic neoplasms, brachytherapy, androgen antagonists

Abbreviations and Acronyms

3D-CRT = 3-dimensional conformal radiation therapy

ADT = androgen deprivation therapy

AHRQ = Agency for Healthcare Research and Quality

AM = active monitoring

AUA = American Urological Association

BT = brachytherapy

CLPC = clinically localized prostate cancer

COE = certainty of evidence

EBRT = external beam radiation therapy

HIFU = high intensity focused ultrasound

LDR-PB = low dose rate prostate brachytherapy

MRI = magnetic resonance imaging

PCa = prostate cancer

PDT = photodynamic therapy

PIVOT = Prostate Cancer Intervention vs Observation Trial

PSA = prostate specific antigen

RCT = randomized controlled trial

ROB = risk of bias

RP = radical prostatectomy

SPCG4 = Scandinavian Prostate Cancer Group Study Number 4

WW = watchful waiting

Accepted for publication December 2, 2020.

Prepared by the Minnesota Evidence-Based Practice Center under Contract No. HHSA290201500008I/Task Order 75Q80119F32008; AHRQ Publication No. 20-EHC022. Rockville, Maryland: Agency for Healthcare Research and Quality September 2020.

This project was funded under Contract No. HHSA290201500008I/Task Order 75Q80119F32008 from the Agency for Healthcare Research and Quality (AHRQ), U.S. Department of Health and Human Services (HHS). The authors of this article are responsible for its content. Statements in the article do not necessarily represent the official views of or imply endorsement by AHRQ or HHS.

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† Financial interest and/or other relationship with Prostate Cancer Intervention versus Observation Trial. The results of this study were included in the evidence report.

0022-5347/21/2054-0967/0
THE JOURNAL OF UROLOGY®

https://doi.org/10.1097/JU.0000000000001578
Vol. 205, 967-976, April 2021
Printed in U.S.A.

In 2020, prostate cancer was estimated to be the most frequently diagnosed nondermatological malignancy (191,930 new cases) and the second leading cause of cancer death (33,330) among men in the United States.[1] Treatment related medical costs were projected to rise to $16 billion per year by the end of 2020. In about 90% of men diagnosed with prostate cancer, the disease is confined to the prostate gland (clinically localized prostate cancer).[2] Although disease progression can result in morbidity and mortality, most cases of clinically localized prostate cancer grow slowly and remain asymptomatic, even if untreated. Attention is turning to potentially lower risk focal therapies that focus treatment on the index lesion, such as HIFU and cryotherapy.[3–5] Use of these options has also increased in response to advances in MRI technology, which allow for better detection of local lesions potentially treatable with "lesion targeted" interventions rather than whole-gland therapy. Awareness has increased regarding the slow growing nature of most prostate specific antigen detected tumors and the importance of weighing treatment benefits and harms to avoid treatment related complications.[6] Thus, treatments for clinically localized prostate cancer aim to balance benefits with complications, burden and costs.

The purpose of this review was to identify new information and update previous Agency for Healthcare Research and Quality and American Urological Association funded reviews[7–9] evaluating treatments for CLPC. Findings can inform clinical guideline committees as they update guidelines.

MATERIALS AND METHODS

We employed methods consistent with the AHRQ Evidence-Based Practice Center Program Methods Guidance (https://effectivehealthcare.ahrq.gov/topics/cer-methods-guide/overview). We describe these in the full report (https://effectivehealthcare.ahrq.gov/products/prostate-cancer-therapies/report). Randomized controlled trials ere assessed for risk of bias using the Cochrane ROB tool.[10] The tool includes domains for random sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and other sources of bias. RCTs were classified as low, moderate or high ROB based on the collective ROBs across domains. We assessed observational studies using the ROBINS-1 tool.[11] Observational studies were rated as low, moderate, serious or critical ROB based on the ROBIN-1 criterion. We referenced findings from the 2014 AHRQ[8] and 2016 AUA[9] funded reviews and included them in updated analyses if RCTs provided additional data on similar populations, interventions, comparators, and outcomes. We summarized and compared major findings from our review with those of the prior reports. We derived a priori thresholds defining "small," "moderate" and "large" effect sizes for benefits and harms (supplementary Appendix 1, https://www.jurology.com). Our searches covered publication dates from January 2013 to January 2020. We modified Grading of Recommendations Assessment, Development and Evaluation and Evidence-Based Practice Center tools for ROB and COE assessments (supplementary Appendix 2, https://www.jurology.com).

We included controlled studies of CLPC (stages T1−T3a) treatments with duration $\geq$5 years for mortality and metastases and $\geq$1 year for quality of life and harms (supplementary Appendix 3, https://www.jurology.com). We extracted inclusion and exclusion criteria; sample size; participant age, race, clinical stage, Gleason score, and tumor risk classification and score; intervention and comparator characteristics; followup duration; and results for outcomes and adverse effects. We extracted data at 1 year and the longest followup for quality of life, health status, and harms; and we extracted data at 5-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. One investigator rated ROB, extracted data and assessed COE, and a second checked accuracy. We analyzed English-language studies with low or medium ROB.

We compiled results 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.[12] When able to pool data, the Hartung-Knapp-Sidik-Jonkman method for random effects models was applied when there were at least 5 trials, and a fixed effect model was used when there were fewer than 5 trials and no between-study variance (tau^2 at or near 0). When meta-analysis was not appropriate, we summarized findings. We calculated RRs or Peto ORs and absolute risk differences with the corresponding 95% CIs for binary outcomes. Mean differences and/or standardized mean differences with 95% CIs were calculated for continuous outcomes. Data were analyzed in Comprehensive Meta-Analysis™ version 3 or R software (package "meta") version 3.6.0 (R Project for Statistical Computing, Vienna, Austria).

We assessed COE using the Grading of Recommendations Assessment, Development and Evaluation approach for key outcomes.[13] This included assessing the applicability of results by analyzing the study population, diagnostic approaches, eligibility criteria, patient and intervention characteristics and other potential factors that may differ from current populations of treatment-naïve men with CLPC. For each comparison, one investigator rated the COE for each outcome as high, moderate, low or insufficient. COE was reviewed by a second investigator. We resolved discrepancies by consensus.

RESULTS

Our search identified 11,327 references (fig. 1). Title and abstract screening eliminated 10,564 references leaving 763 references for full text review. We identified 67 eligible references, of which 17 were unique RCTs. A list of all eligible publications can be found in supplementary Appendix 4 (https://www.jurology.com). Supplemental searches of ClinicalTrials.gov and other grey literature sources did not yield

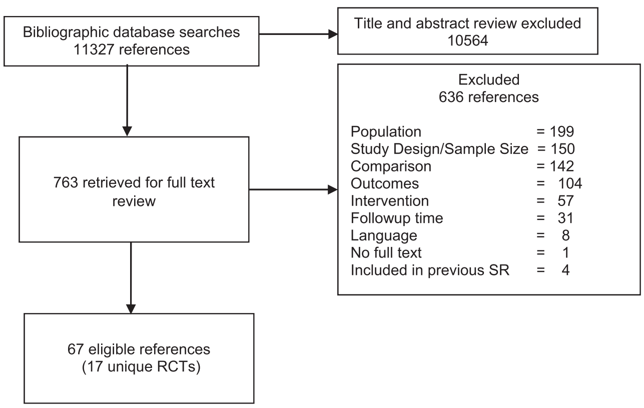

Figure 1. Literature flow diagram. *SR*, systematic review.

additional eligible studies. Figure 2 illustrates intervention comparisons addressed in eligible RCTs according to study sample size. Table 1 summarizes findings by interventions and outcomes from the prior AHRQ and AUA funded reviews, and updated findings derived from our report. Intervention comparisons considered either "out of scope" for this review, or where we found no new data, are summarized in supplementary Appendix 5 (https://www.jurology.com). We provide a narrative summary of benefits and harms according to intervention and comparison. Additional information on effect estimates for individual studies and COE for all-cause mortality, prostate cancer mortality, and metastases are provided in tables 2–5. Effect estimates and COE for harms and quality of life data are provided in supplementary Appendix 6 (https://www.jurology.com).

Watchful waiting: Two studies provided long-term results comparing WW with RP (table 2).[14–16] One RCT enrolled patients with clinically detected CLPC and was initiated prior to widespread PSA testing. The other was conducted in the U.S. during the early PSA screening era, and approximately 50% of individuals had T1c or PSA detected CLPC. We did not conduct pooled analyses due to clinical differences in the enrolled populations. Watchful waiting may result in a moderate to large increase in overall mortality, and small to large increase in prostate cancer mortality compared to RP through 20 years among clinically detected CLPC (rather than PSA screen; low COE). Absolute effects varied by study. WW probably results in small to large increases in metastases through 15–20 years (moderate COE). Effects depended on study population. WW probably resulted in moderately increased urinary and erectile dysfunction (moderate COE, supplementary Appendix 6.1, https://www.jurology.com). Mortality differences may be limited to men age 65 and older or those with intermediate risk disease.

Active monitoring: One RCT enrolled men with PSA screen detected CLPC.[17,18] AM using PSA based monitoring probably resulted in little to no difference in all-cause or prostate cancer mortality compared with RP or EBRT plus ADT over 10 years (moderate COE, table 3). Metastases were infrequent but AM probably resulted in a small increase compared with RP and EBRT plus ADT (moderate COE). Effects may not vary by patient or tumor risk factors. Harms were lowest with AM compared with RP or EBRT plus ADT or AS vs PDT,[3] which was

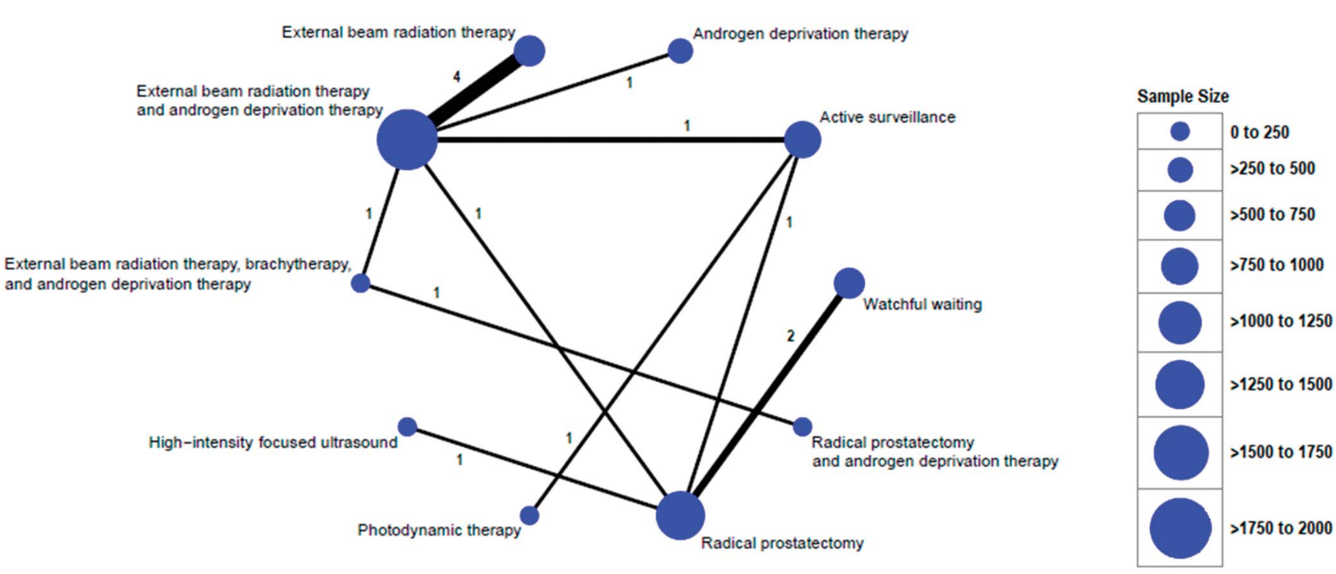

Figure 2. Plot of comparisons addressed in RCTs identified in updated literature search. Node size reflects sample size. Width of lines reflects number of RCTs that evaluated that comparison. Within-category comparisons are not shown in figure. One RCT (ProtecT) was 3-arm trial. Active surveillance protocols varied. Prior systematic reviews identified 3 additional trials that compared external beam radiation alone with add-on androgen deprivation therapy.

Table 1. *Summary updates of comparisons between reviews*

Intervention/Comparison	Outcome(s)	Previous Findings from 2014 AHRQ or 2016 AUA Funded Reviews*	Present Findings Derived from Studies Published after Prior Reviews and by Incorporating Prior RCT Data when Applicable†
WW vs RP in men with clinically detected (SPCG4) or mainly clinically detected (PIVOT) CLPC†	All-cause mortality, PCa-specific mortality, metastases harms	Insufficient evidence on all-cause mortality, PCa-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 (SPCG4)—probably results in moderate increases in all-cause mortality and large increases in PCa-specific mortality and metastases at 25 yrs; mortality effects may be limited to men younger than age 65 yrs and men with intermediate risk CLPC; no new data for harms WW vs RP in men with mainly clinically detected CLPC (PIVOT)—probably results in moderate increase in all-cause mortality and large reduction in metastases, and small increase in PCa-specific mortality and at 20 yrs; mortality effects may be limited to men younger than age 65 yrs and men with intermediate risk CLPC; probably results in moderate reduction in erectile and urinary harms at 10 yrs
AM (PSA based) vs EBRT+ADT	All-cause mortality, PCa-specific mortality, metastases, harms	Not addressed	AM vs EBRT+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 PCa-specific mortality and probably results in small increases in metastases at 10 yrs; results may not vary by patient or tumor characteristics; may result in small decrease in erectile dysfunction, probably results in small increase in urinary incontinence and may make little to no difference in fecal incontinence at 6 yrs
AM (PSA based) vs RP	All-cause mortality, PCa-specific mortality, metastases, harms	Not addressed	AM vs RP in men with PSA screen detected CLPC—may result in little to no difference in all-cause or PCa-specific mortality but probably results in small increase in metastases at 10 yrs; results may not vary by pt or tumor characteristics; probably results in large decrease in erectile dysfunction and moderate decrease in urinary incontinence, and may make little to no difference in fecal incontinence at 6 yrs
AS (biopsy+PSA based) vs PDT	Harms	Not addressed	AS vs PDT in men with PSA screen detected low risk CLPC—probably results in large decrease in erectile dysfunction and moderate decrease in urinary retention at 2 yrs
RP vs EBRT+ADT	All-cause mortality, PCa-specific mortality, metastases, harms	Clinical outcomes not addressed Insufficient evidence on harms§	RP vs EBRT+ADT in men with PSA screen detected CLPC—may result in little to no difference in all-cause mortality, PCa-specific mortality and metastases at 10 yrs; results on PCa-specific mortality may not differ by age, PSA level, Gleason score or clinical stage; probably results in increase in erectile and urinary harms and decrease in bowel dysfunction at 6 yrs
RP+ADT vs EBRT+HDR BT+ADT	All-cause mortality, PCa-specific mortality, harms	Insufficient evidence on harms for RP vs EBRT+BT§	RP+ADT vs EBRT+high dose rate BT+ADT in men with T1b—T3a PCa of any histological grade—may result in small increase in erectile dysfunction at 2 yrs; insufficient evidence on urinary or bowel harms at 2 yrs and all-cause or PCa-specific mortality through 10 yrs
RP vs HIFU	Harms	Not addressed	In men with Gleason score 7, <T2b CLPC, insufficient evidence on urinary, erectile and bowel harms at 1 yr
Laparoscopic RP vs robot-assisted RP	Harms	Insufficient evidence on urinary and erectile harms at 1 yr‡	Laparoscopic RP vs robotic RP in men with PSA detected predominantly low to intermediate risk CLPC—may result in moderate increase in urinary incontinence and large increase in erectile dysfunction at 5 yrs
Robot-assisted laparoscopic RP vs open retropubic RP	All-cause mortality, PCa-specific mortality, metastases, harms	Insufficient evidence on all-cause mortality, PCa-specific mortality, metastases and harms§	In men with predominantly low and intermediate D'Amico risk CLPC, insufficient evidence on erectile dysfunction; no data for mortality/ metastases
EBRT vs BT	All-cause mortality, PCa-specific mortality, metastasis-free survival	Insufficient evidence on all-cause mortality and PCa-specific mortality‡	In men with Gleason 6 or 7 CLPC, insufficient evidence on overall survival, PCa-specific survival and metastasis-free survival

(continued)

Table 1. (*continued*)

Intervention/Comparison	Outcome(s)	Previous Findings from 2014 AHRQ or 2016 AUA Funded Reviews*	Present Findings Derived from Studies Published after Prior Reviews and by Incorporating Prior RCT Data when Applicable†
EBRT+BT vs BT	All-cause mortality, PCa-specific mortality	Insufficient evidence on PCa-specific mortality‡	In men with intermediate National Comprehensive Cancer Network risk CLCP, insufficient evidence on all-cause mortality in men
Intensity modulated radiation therapy vs SBRT	All-cause mortality	Not addressed	In men with predominantly Gleason 6–7, PSA<10 and T1C CLPC, insufficient evidence on all-cause mortality
Conventionally fractionated EBRT vs ultrahypofractionated EBRT	All-cause mortality, PCa-specific mortality, metastasis, harms	Not addressed	Conventionally fractionated EBRT vs ultrahypofractionated 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 PCa-specific mortality and metastasis at 5 yrs; may result in little to no differences in urinary and bowel harms (except urinary harms at 1 yr); insufficient evidence on erectile function
3D-CRT+ADT+low dose rate BT vs 3D-CRT+ADT	All-cause mortality, PCa-specific mortality, metastases, harms	Insufficient evidence on PCa-specific mortality for EBRT+BT vs EBRT‡	3D-CRT and ADT+low dose rate BT vs 3D-CRT and ADT in men with intermediate and high National Comprehensive Cancer Network risk CLPC—may result in small decrease in all-cause mortality and little to no difference in metastases at 5 yrs; insufficient evidence on PCa-specific mortality, urinary incontinence and erectile function
EBRT+ADT vs EBRT‡	All-cause mortality, PCa-specific mortality, metastases, harms	Inconsistent findings on all-cause mortality/survival and metastases but evidence consistently favored combination therapy on PCa-mortality§	EBRT+ADT vs EBRT in men with predominantly intermediate to high risk CLPC (using different risk classifications)—probably results in small reduction in all-cause mortality, and may result in small reduction in PCa-mortality and metastasis at 5–10 yrs. Mortality effects may be limited to intermediate to high risk men, and men with no or minimal comorbidity; may moderately increase sexual dysfunction; insufficient evidence on urinary incontinence and rectal bleeding
EBRT+neoadjuvant and concurrent ADT vs EBRT plus concurrent and adjuvant ADT	All-cause mortality, PCa-specific mortality, metastasis, harms	Not addressed	EBRT+neoadjuvant and concurrent ADT vs EBRT+concurrent and adjuvant ADT in men with predominantly intermediate risk CLPC—may result in little to no difference in all-cause mortality and PCa-specific mortality at 12 yrs; insufficient evidence on metastasis; may result in little to no difference in genitourinary toxicity at 3 yrs

This table shows findings on mortality; PCa-specific mortality; metastases; sexual, urinary and bowel harms from treatment comparisons analyzed in this current systematic review; and previous findings from the 2014 AHRQ funded and 2016 AUA funded systematic reviews on those same treatment comparisons.
* 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+ADT vs EBRT), our findings incorporate data/outcomes from the prior reviews (see Methods).
‡ Findings from 2014 AHRQ funded systematic review.
§ Findings from 2016 AUA funded systematic review.

Table 2. *Certainty of evidence: watchful waiting vs radical prostatectomy (k=2 RCTs)*

Outcome (length of followup)	Relative Effect (95% CI)	% Absolute Effects WW (No./trial)	% Absolute Effects RP	% Absolute Effects Difference (95% CI)	Certainty of Evidence	What Happens
All-cause mortality (∼20 yrs)	SPCG4 RR 1.23 (1.10–1.38),[14,15] PIVOT RR 1.09 (0.98–1.22)[16]	SPCG4 70.9 (247/348), PIVOT 66.7 (245/367)	57.6 (200/347) 61.3 (223/364)	SPCG4 13.3 (6.3–20.4), PIVOT 5.5 (−1.45–12.4)	⊕⊕◯◯ Low*,†	WW may result in moderate to large increase in all-cause mortality vs RP
All-cause mortality (∼25 yrs)[15]	RR 1.12 (1.03–1.2)	83.9 (292/348),	75.2 (261/347)	8.7 (2.7–14.6)	⊕⊕⊕◯ Moderate†	WW probably results in moderate increase in all-cause mortality vs RP
PCa-specific mortality (∼20 yrs)	SPCG4 RR 1.57 (1.19–2.07),[14,15] PIVOT RR 1.54 (0.97–2.45)[16]	SPCG4 28.4 (99/348), PIVOT 11.4 (42/367)	SPCG4 18.1 (63/347), PIVOT 7.4 (27/364)	SPCG4 10.3 (4.05–16.5), PIVOT 4.0 (−0.19–8.25)	⊕⊕◯◯ Low*,†	WW may result in small to large increase in PCa-specific mortality vs RP
PCa-specific mortality (∼25 yrs)[15]	RR 1.54 (1.19–2.00)	31.6 (110/348)	20.5 (71/347)	11.1 (4.7–17.6)	⊕⊕⊕◯ Moderate†	WW probably results in large increase in PCa-specific mortality vs RP
Metastases (∼20 yrs)[15]	RR 1.54 (1.24–1.93)	39.7 (138/348)	25.6 (89/347)	14 (7.1–20.9)	⊕⊕⊕◯ Moderate†	WW probably results in large increase in metastases vs RP
Metastases (∼25 yrs)[15]	RR 1.63 (1.3–2.00)	43.1 (150/348)	26.5 (92/347)	16.6 (9.6–23.6)	⊕⊕⊕◯ Moderate†	WW probably results in large increase in metastases vs RP
Metastases/systemic progression (∼20 yrs)[16]	RR 1.45 (0.98–2.14)	14.7 (54/367)	10.2 (37/364)	4.5 (−0.3–9.4)	⊕⊕◯◯ Low‡	WW may result in small increase in metastases (systemic progression) vs RP

* Rated down 1 level for inconsistency.
† Rated down 1 level for imprecision.
‡ Rated down 2 levels for imprecision.

assessed in 1 separate trial (supplementary Appendix 6.2, https://www.jurology.com).

Radical prostatectomy probably resulted in little to no difference over 10 years in all-cause or prostate cancer mortality, or metastases compared with EBRT plus ADT (moderate COE, table 4).[17,18] Results may not vary by patient or tumor risk characteristics. RP probably results in a large increase in urinary incontinence and a moderate increase in erectile dysfunction (moderate COE); fecal incontinence may be slightly decreased compared to EBRT plus ADT (low COE, supplementary Appendix 6.3, https://www.jurology.com).

External beam radiation using a combination of 3D-CRT and ADT with low dose rate prostate BT may slightly reduce all-cause mortality compared with 3D-CRT and ADT over 5 years but may make little to no difference on metastatic disease (low COE, table 5).[19–21] Associated harms were unclear (supplementary Appendix 6.4, https://www.jurology.com). EBRT plus ADT probably results in a small reduction in overall mortality (moderate COE) and may result in a small reduction in prostate cancer mortality and metastases (low COE) vs EBRT alone over 7 years in men with intermediate or high risk disease.[22–28] However, it may result in a moderate increase in sexual dysfunction. When comparing the sequence of add-on ADT, EBRT plus neoadjuvant initiation of ADT compared with EBRT plus concurrent initiation of ADT may result in little to no difference in overall mortality and prostate cancer mortality over 12 years and late genitourinary toxicity over 3 years (low COE).[29] Conventionally fractionated EBRT vs ultrahypofractionated

Table 3. *Certainty of evidence: active monitoring and active surveillance vs control (k=1 RCT)*

Comparison	Outcome (length of followup)	Relative Effect (95% CI)	% Absolute Effects (No. AM/AS)	% Absolute Effects Control (No./trial)	% Absolute Effects Difference (95% CI)	Certainty of Evidence	What Happens
PSA based AM vs EBRT+ADT[17,18]	All-cause mortality (10 yrs)	RR 1.07 (0.8–1.5)	10.8 (59/545)	10.1 (55/545)	0.7 (−2.9–4.4)	⊕⊕⊕◯ Moderate*	AM probably results in little to no difference in all-cause mortality vs EBRT+ADT
	PCa-specific mortality (10 yrs)	Peto OR 1.96 (0.63–6.12)	1.5 (8/545)	0.7 (4/545)	0.7 (−0.5–1.9)	⊕⊕◯◯ Low†	AM may result in little to no difference in PCa-specific mortality vs EBRT+ADT
	Metastases (10 yrs)	RR 2.1 (1.15–3.7)	6.0 (33/545)	2.9 (16/545)	3.1 (0.67–5.6)	⊕⊕⊕◯ Moderate*	AM probably results in small increase of metastases vs EBRT+ADT

* Rated down 1 level for imprecision.
† Rated down 2 levels for imprecision.

Table 4. *Certainty of evidence: radical prostatectomy vs control (k= 1 RCT)*

Comparison	Outcome (length of followup)	Relative Effect (95% CI)	% Absolute Effects RP (No./trial)	% Absolute Effects Control (No./trial)	% Absolute Effects Difference (95% CI)	Certainty of Evidence	What Happens
RP vs AM[17,18]	All-cause mortality (10 yrs)	RR 0.92 (0.65–1.30)	9.9 (55/553)	10.8 (59/545)	−0.9 (−4.5–2.7)	⊕⊕⊕◯ Moderate*	RP probably results in little to no difference in all-cause mortality vs AM
	PCa-specific mortality (10 yrs)	Peto OR 0.62 (0.20–1.87)	0.9 (5/553)	1.5 (8/545)	−0.6 (−1.8–0.7)	⊕⊕◯◯ Low†	RP may result in little to no difference in PCa-specific mortality vs AM
	Metastases (10 yrs)	Peto OR 0.40 (0.22–0.72)	2.4 (13/553)	6.4 (33/545)	−4.0 (−6.1– −1.3)	⊕⊕⊕◯ Moderate*	RP probably results in small reduction in metastases vs AM
RP vs EBRT+ADT[17,18]	All-cause mortality (10 yrs)	RR 0.99 (0.69–1.04)	9.9 (55/553)	10.1 (55/545)	−0.1 (−3.7–3.7)	⊕⊕⊕◯ Moderate*	RP probably results in little to no difference in all-cause mortality vs AM
	PCa-specific mortality (10 yrs)	Peto OR 1.23 (0.33–4.58)	0.9 (5/553)	0.7 (4/545)	0.2 (−0.9–1.2)	⊕⊕◯◯ Low†	RP may result in little to no difference in PCa-specific mortality vs EBRT+ADT
	Metastases (10 yrs)	Peto OR 0.80 (0.38–1.67)	2.4 (13/553)	2.9 (16/545)	−0.6 (−2.5–1.3)	⊕⊕◯◯ Low†	RP may result in little to no difference in metastases vs EBRT+ADT

* Rated down by 1 level for imprecision.
† Rated down by 2 levels for imprecision and sparse data.

EBRT may result in little to no difference in mortality and metastases and urinary and bowel toxicity (low COE).[30]

Other therapies/comparisons: For other therapies including cryotherapy, laser ablation and HIFU, we found no new data or insufficient evidence to draw conclusions.

DISCUSSION

This systematic review provides updated evidence on the comparative effectiveness and harms of treatments for CLPC. Our review extends previous report findings used for development of clinical practice guidelines. Important report contribution lies in its appraisal of longer-term data from 2 RCTs comparing RP to WW in clinically, rather than PSA, detected CLPC. While prior reviews found insufficient evidence on all-cause and prostate cancer mortality, and erectile and bowel dysfunction, extended followup suggests RP may reduce mortality and probably reduces metastases over a very extended time frame compared to WW. Furthermore, age and tumor risk category may be important effect modifiers. Specifically, prostate cancer mortality is infrequent in low risk disease, and all-cause or prostate cancer mortality reduction due to RP may be limited to intermediate risk disease or men age <65 years. Absolute effects are likely smaller among PSA detected CLPC due to its more indolent course. Harms are greater with RP. Also, AM was not addressed in previous reports and there was little evidence comparing RP with EBRT.

This report update was motivated, in part, by an increasing interest in focal therapies or whole prostate gland therapy that are suggested to have fewer or less serious harms than RP or EBRT. However, we either found no data or evidence was insufficient for cryotherapy, laser ablation and HIFU. We found no evidence for effects of PDT on mortality or metastases.

The available evidence to inform our review findings has several limitations, including 1) many randomized trials were too short to assess overall or prostate cancer mortality; 2) relatively few well designed prospective cohort studies exist and they do not provide sufficient new evidence on comparative effectiveness; 3) no validated thresholds exist to define effect size magnitude to determine "clinically important differences" or establish criteria to define "small", "moderate" or "large" effects by intervention or across outcomes; therefore, varying thresholds to define effect size estimates (whether by patients, clinicians, health systems or guideline members) may alter certainty of evidence and clinical/policy decisions; 4) no studies assessed the role of active surveillance or the role of WW in men with screen detected CLPC; additionally, no studies evaluated

Table 5. *Certainty of evidence: external beam radiation therapy vs control (k=9 RCTs)*

Comparison	Outcome (length of followup) No of Participants (studies)	No. RCTs (No. pts)	Relative Effect (95% CI)	% Anticipated Absolute Effects EBRT (No./trial)	% Anticipated Absolute Effects Control (No./trial)	% Anticipated Absolute Effects Difference (95% CI)	Certainty of Evidence	What Happens
3D-CRT and ADT vs 3D-CRT and ADT with LDR-PB boost[19–21]	Mortality (5 yrs)	1 (398)	RR 1.25 (0.81—1.94)	18.9 (38/200)	15.2 (30/198)	3.8 (−3.5—11.2)	⊕⊕◯◯ Low*,†	3D-CRT and ADT may result in small increase in mortality vs 3D-CRT and ADT with LDR-PB boost in higher risk disease
	Prostate-specific mortality (5 yrs)	1 (398)	RR 1.56 (0.62—3.93)	5.5 (11/200)	3.5 (7/198)	2.0 (−2.1—6.0)	⊕◯◯◯ Insufficient*,‡	Evidence is very uncertain about effect of 3D-CRT and ADT with LDR-PB boost on prostate-specific mortality vs 3D-CRT and ADT in higher risk disease
	Metastatic disease (5 yrs)	1 (398)	RR 1.05 (0.56—1.97)	9.0 (18/200)	8.6 (17/198)	0.4 (−5.1—6.0)	⊕⊕◯◯ Low*,†	3D-CRT and ADT with LDR-PB boost may result in little to no difference in metastatic disease vs 3D-CRT and ADT in higher risk disease
EBRT+ADT vs EBRT[22–28]	Overall mortality (5.9—9.1 yrs)	5 (4,047)	RR 0.86 (0.69—1.06)	27.3 (587/2,150)	32.4 (615/1,897)	−3.7 (−9.8—2.4)	⊕⊕⊕◯ Moderate†	EBRT+ADT probably results in small reduction in overall mortality vs EBRT in higher risk disease
	PCa mortality (7.2—9.1 yrs)	3 (3,004)	Peto OR 0.51 (0.37—0.70)	3.53 (53/1,499)	6.9 (104/1,505)	−3.4 (−4.95- −1.8)	⊕⊕◯◯ Low*,†	EBRT and ADT may result in small reduction in prostate cancer mortality vs EBRT in higher risk disease
	Metastasis (5—10 yrs)	4 (4,664)	RR 0.83 (0.71—0.97)	11.5 (284/2,461)	13.1 (289/2,203)	−2.3 (−4.1—−0.4)	⊕⊕◯◯ Low*,†	EBRT and ADT may result in small reduction in metastasis vs EBRT in higher risk disease
EBRT+neoadjuvant and concurrent ADT vs EBRT+concurrent and adjuvant ADT[29]	Overall mortality (12.2 yrs)	1 (432)	RR 1.05 (0.81—1.37)	34.9 (75/215)	33.2 (72/217)	1.7 (−7.2—10.6)	⊕⊕◯◯ Low‡	EBRT+neoadjuvant and concurrent ADT may result in little to no difference in overall mortality vs EBRT+concurrent and adjuvant ADT
	PCa mortality (12.2 yrs)	1 (432)	Peto OR 1.01 (0.35—2.93)	3.3 (7/215)	3.2 (7/217)	0 (−3.3—3.4)	⊕⊕◯◯ Low*,†	EBRT+neoadjuvant and concurrent ADT may result in little to no difference in PCa mortality vs EBRT+concurrent and adjuvant ADT
	Metastasis distant progression (12.2 yrs)	1 (432)	Peto OR 1.36 (0.57—3.27)	5.6 (12/215)	4.1 (9/217)	1.4 (−2.6—5.5)	⊕◯◯◯ Insufficient*,‡	Evidence is very uncertain about effect of EBRT+neoadjuvant and concurrent ADT on metastasis vs EBRT+concurrent and adjuvant ADT
Conventionally fractionated EBRT vs ultrahypofractionated EBRT[30]	Mortality (5 yrs)	1 (1,180)	RR 0.93 (0.63—1.39)	7.3 (43/591)	7.8 (46/589)	−0.5 (−3.5—2.5)	⊕⊕⊕◯ Moderate†	Conventionally fractionated EBRT probably results in little to no difference in all-cause mortality vs ultrahypofractionated EBRT
	PCa mortality (5 yrs)	1 (1,180)	Peto OR 0.72 (0.29—1.79)	1.4 (8/591)	1.9 (11/589)	−0.5 (−2.0—0.9)	⊕⊕◯◯ LOW*,†	Conventionally fractionated EBRT may result in little to no difference in PCa mortality vs ultrahypofractionated EBRT
	Metastasis (5 yrs)	1 (1,180)	RR 1.02 (0.66—1.58)	6.6 (39/591)	6.5 (38/589)	0.1 (−2.7—3.0)	⊕⊕◯◯ Low*,†	Conventionally fractionated EBRT may result in little to no difference in metastasis vs ultrahypofractionated EBRT

* Rated down 1 level for risk of bias.
† Rated down 1 level imprecision.
‡ Rated down 2 levels for imprecision.

the comparative effectiveness of interventions of men diagnosed or undergoing surveillance using MRI assessment and targeted biopsies; and 5) there is limited information to guide clinicians and patients on the use of newer targeted therapies such as high intensity focused ultrasound or laser ablation.

Few studies reported on how patient, tumor characteristics or biomarkers modify treatment effect. While clinical and policy decision-making often incorporate patient and tumor characteristics, evidence certainty for these characteristics was limited and unlikely to be greater than findings from intervention effects overall. We found no information on the effect modification of newer biomarkers that are frequently used to evaluate prognosis and develop treatment recommendations. Metastases were often reported based on radiographic and PSA results in asymptomatic patients, rather than as patient-reported outcomes (eg bone pain or ureteral obstruction), and should not be interpreted as symptomatic metastases.

Our findings have clinical, policy and research implications. They reinforce the need for long-term comparative effectiveness RCTs and well designed prospective cohort studies. Our results highlight the importance of balancing treatment benefits with harms, and the inclusion of incorporating patient and tumor characteristics as well as patient preferences into treatment decisions. For example among men with clinically detected CLPC, WW increased mortality and metastases compared with RP with absolute effects ranging from 4–13 percentage points through 25 years. Harms were fewer with WW and benefits due to RP may be limited to men with intermediate risk disease and younger than age 65 years. Results also highlight that the more indolent natural history of PSA detected CLPC, compared with clinically detected CLPC, has important implications on assessing net benefit of treatment options. The absolute benefit of early intervention in PSA detected CLPC is likely considerably less and overtreatment greater than studies of WW in men with clinically detected CLPC suggest. For men with PSA detected CLPC, prostate cancer mortality and metastases are rare in men treated with AM and are probably little to no different than among men treated with either RP or EBRT plus ADT. However, AM results in fewer harms. Among men who choose early treatment, RP provides similar effects through 10 years compared with EBRT plus ADT. For men with higher risk disease who select EBRT, the addition of ADT reduces mortality but may increase harms compared to EBRT alone.

Overall, our findings provide a cautionary note before incorporating newer treatment modalities (including refinements of RP or EBRT) into clinical care as evidence on their effectiveness and harms is very limited. While AS and newer modalities hold promise, we need high quality studies including assessment of provider, patient and tumor characteristics on patient-important outcomes.

CONCLUSIONS

RP reduces mortality vs WW in clinically detected CLPC but causes more harms. Effectiveness may be limited to younger men and those with intermediate risk disease. AM results in little to no mortality difference vs surgery or EBRT plus ADT. EBRT plus ADT reduces mortality vs EBRT alone in higher risk CLPC but may worsen sexual function. Adding low dose rate BT to 3D-CRT and ADT may reduce mortality in higher risk CLPC. Little information exists on other treatments, the effects of patient and tumor factors, the effects of WW or AS in screen detected CLPC, or use of MRI for detection or surveillance. Large, long-term randomized trials are needed.

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