Comparative Effectiveness Review
Number 230

Therapies for Clinically Localized Prostate Cancer

Evidence Summary

Main Points

- In men with clinically localized prostate cancer (CLPC) detected clinically rather than by prostate-specific antigen (PSA) screening, radical prostatectomy (RP) may reduce mortality and metastases more than watchful waiting (WW) but causes more harms. Mortality reductions may be limited to men age 65 and older and those with intermediate risk disease.
- Active monitoring (AM) probably results in little to no mortality difference versus RP or external beam radiation (EBR)+androgen deprivation (AD) in PSA detected CLPC and may result in fewer harms. Effects may not vary by patient or tumor factors.
- 3D Conformal EBR (3D-CRT) + low-dose brachytherapy+AD may slightly reduce all-cause mortality but not metastases more than 3D-CRT+AD in higher risk CLPC.
- EBR plus AD may slightly reduce mortality and metastases versus EBR alone in men with intermediate- and high-risk disease but may worsen sexual function.
- Little long-term information exists on other treatments or the effects of patient, tumor, and provider factors especially in PSA-detected and magnetic resonance imaging (MRI)-staged CLPC. We found no evidence on how biomarkers may modify treatment effects.

Background and Purpose

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

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

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and tumor characteristics, including risk indices and biomarkers, modify treatment effects, and how provider/hospital characteristics modify effects of RP compared with other therapies.

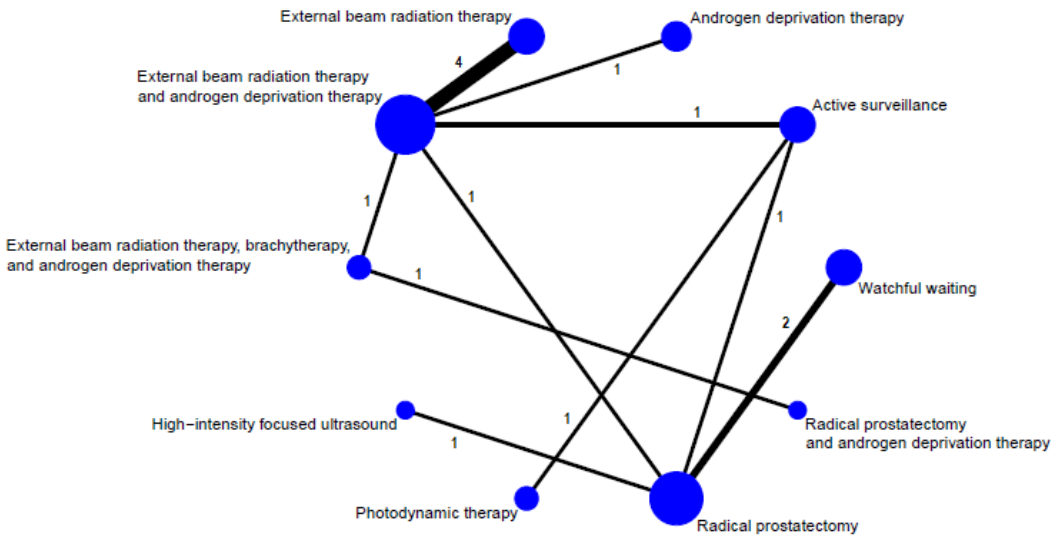
Methods

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

Results

We identified 67 eligible references (citations can be found in the full report); of which 26 were publications from 17 unique RCTs and 41 were publications from 34 unique non-RCTs. The treatment comparisons evaluated in RCTs are illustrated in Figure 1.

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



*Within-category comparisons are not shown in figure. These include RARP vs. LRP (k=1, n=120), 3D-CRT vs. IMRT (k=1, n=215), ultrahypofractionated EBRT vs. standard EBRT (k=2, n=1,275), and EBRT plus neoadjuvant and concurrent ADT vs. EBRT plus concurrent and adjuvant ADT (k=1, n=432).
†One RCT (ProtecT) was a three-arm trial. ProtecT PSA-based active monitoring group is labeled active surveillance in figure.
‡The node size reflects the sample size. The width of lines reflects the number of RCTs that evaluated that comparison.

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

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

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

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

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

Limitations

Our review findings have several limitations including—

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

- Metastases were often reported based on radiographic and PSA results in asymptomatic patients rather than as patient-reported outcomes (e.g., bone pain or ureteral obstruction) and should not be interpreted as symptomatic metastases.
- While clinical and policy decision making often incorporate patient and tumor characteristics, evidence certainty to guide decisions based on these characteristics is limited and unlikely to be greater than findings from intervention effects overall.

Implications and Conclusions

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

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

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

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

Our findings have clinical, policy, and research implications. Our results highlight the importance of balancing treatment benefits with harms and the inclusion of patient and tumor characteristics as well as patient preferences into treatment decisions. They reinforce the need for long-term comparative effectiveness RCTs and well-designed prospective cohort studies. They highlight that the more indolent natural history of PSA-detected compared with clinically detected CLPC has important implications on net benefit of treatment options. For most men with CLPC including those with life expectancies of 15–20 years, evidence indicates that WW

and AM result in little to no difference in mortality and metastases and fewer harms compared with early intent-to-cure treatments. The absolute benefit of early intervention in PSA-detected CLPC is likely considerably less and overtreatment greater than studies of WW and AM suggest. For men with PSA-detected CLPC who choose early treatment, RP provides similar effects through 10 years compared with EBR+AD. For men with higher risk disease who select EBR, the addition of AD reduces mortality but may increase harms compared with EBR alone. Our findings provide a cautionary note before incorporating newer treatment modalities (including refinements of RP or EBR) into clinical care as evidence on their effectiveness and harms is very limited. While AS and newer modalities hold promise, we need high-quality studies including assessment of provider, patient, and tumor characteristics on patient important outcomes.

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Full Report

Dahm P, Brasure M, Ester E, Linskens EJ, MacDonald R, Nelson VA, Ryan C, Saha J, Sultan S, Ullman KE, Wilt TJ. Therapies for Clinically Localized Prostate Cancer. Comparative Effectiveness Review No. 230. (Prepared by the Minnesota Evidence-based Practice Center under Contract No. 290-2015-0000-81) AHRQ Publication No. 20-EHC022. Rockville, MD: Agency for Healthcare Research and Quality; September 2020. DOI: https://doi.org/10.23970/AHRQEPCCER230. Posted final reports are located on the Effective Health Care Program search page.