Therapies for Clinically Localized Prostate Cancer

Research Focus for Clinicians

This is a summary of a systematic review update evaluating the current evidence regarding the comparative effectiveness and harms of treatment options for clinically localized prostate cancer. The systematic review included 61 articles reporting on 52 eligible studies published from January 1, 2007, through March 7, 2014. The full report, listing all studies, is available at *www.effectivehealthcare.ahrq.gov/prostate-cancer.* This summary is provided to assist in informed clinical decisionmaking. However, reviews of evidence should not be construed to represent clinical recommendations or guidelines.

Background

Prostate cancer is the most common nondermatologic cancer in men. Approximately 90 percent of men who are diagnosed with prostate cancer have cancer confined to the prostate gland (clinically localized disease). The percentage of men diagnosed with clinically localized prostate cancer might change as a result of the recent recommendations from the United States Preventive Services Task Force (USPSTF).[1,2] Clinically localized prostate cancer is usually asymptomatic or may be associated with symptoms that overlap with benign lower urinary tract symptoms. Presenting symptoms, a physical examination, a prostate-specific antigen (PSA) test, and a biopsy may be used to diagnose localized prostate cancer.

The National Comprehensive Cancer Network (NCCN) Clinical Guideline for the Treatment of Prostate Cancer, published in 2015, defined clinically localized prostate cancer as clinical stages T1–T3a, which includes tumors confined to the prostate (T1–T2) and tumors with extracapsular extension but without spread into the seminal vesicles (T3a).

Management options for localized prostate cancer that are frequently used include radical prostatectomy (RP), radiation therapy, hormonal therapy, active surveillance (AS), and watchful waiting (WW), as well as other strategies (Table 1). Choice of treatment options may be influenced by factors such as patient age and health at the time of diagnosis, life expectancy, tumor stage, PSA levels, Gleason score, the estimated likelihood of cancer progression without treatment, recommendation of a multidisciplinary health care team, the surgeon's experience if the patient is referred for surgery, treatment-related convenience and costs, patient values and preferences, and adverse effects.

The treatment for men with clinically localized prostate cancer has been the subject of much debate. Identifying those men most likely to benefit from aggressive therapy is challenging. Men with slowly progressing disease who are more likely to die of other causes could be spared unnecessary treatment, while men with aggressive, localized prostate cancer would be offered curative procedures.

A National Institutes of Health (NIH) panel that convened in 2011 recommended that AS—a strategy with curative intent that involves regular monitoring of PSA levels and repeat biopsies—should be offered to patients with low-risk prostate cancer.[3] The NIH panel also used the term "watchful waiting" (WW) to describe a palliative observational strategy that involves waiting for symptoms to appear and then intervening to manage them.[3] WW does not include active monitoring such as performing a PSA test or a biopsy.

The current systematic review updates a 2008 report[4] and summarizes the more recent evidence comparing the effectiveness and safety of management options for clinically localized prostate cancer. In the 2008 report, AS and WW were considered together. For the present systematic review update, however, an attempt was made to separate the two using the definitions proposed at the 2011 NIH Conference.

Table 1. Management Options for Clinically Localized Prostate Cancer

Radical prostatectomy (RP) – Open perineal – Open retropubic – Laparoscopic – Robotic-assisted laparoscopic
Radiation therapy – Conventional external beam radiation therapy (EBRT) – Three-dimensional conformal radiation therapy (3D-CRT) – Intensity-modulated radiation therapy (IMRT) – Proton beam radiation therapy (PBRT) – Stereotactic body radiation therapy (SBRT)
Watchful waiting (WW): a palliative observational strategy that consists of intervening only when symptoms appear
Active surveillance (AS): a strategy with curative intent that involves regular monitoring of PSA levels and repeat biopsies
Hormonal therapy (e.g., androgen deprivation therapy [ADT])
Interstitial brachytherapy: a strategy whereby tumor tissue is specifically targeted by placing seeded radioactive material in or near the tumor
Cryotherapy: a strategy that uses very low temperatures to freeze and kill the tumor cells in the prostate
High-intensity focused ultrasound (HIFU): a procedure that applies high-intensity focused ultrasound energy to locally heat and destroy tumor tissue

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Summary of Key Findings and Strength of Evidence

Table 2. Benefits and Adverse Effects of Therapies for Clinically Localized Prostate Cancer

Treatment*	Outcome
Radical prostatectomy (RP) versus watchful waiting (WW)	Progression to metastases was significantly reduced among patients undergoing RP when compared with those receiving WW (●●○). However, evidence was insufficient to determine the comparative effectiveness of RP and WW for mortality outcomes (○○○), largely because of the lack of replication in two large trials.†
	Urinary incontinence was lower among patients on WW when compared with patients undergoing RP. (●○○)
	Evidence is insufficient to determine the relative impact of RP versus WW on the adverse effects of bowel dysfunction and erectile dysfunction. (○○○)
RP versus external beam radiation therapy (EBRT)	All-cause mortality and prostate cancer–specific mortality were significantly lower in patients undergoing RP when compared with patients treated with EBRT. (●○○)
Three-dimensional conformal radiation therapy (3D-CRT) plus androgen deprivation therapy (ADT) versus 3D-CRT alone	Overall survival was higher in patients treated with 3D-CRT plus ADT when compared with those treated with 3D-CRT alone. (●○○)
	All-cause mortality and prostate cancer–specific mortality were lower in patients treated with 3D-CRT plus ADT when compared with those treated with 3D-CRT alone. (●○○)
All other treatment comparisons	Evidence is insufficient to permit conclusions about the comparative effectiveness or adverse effects of all other treatments (including brachytherapy, cryotherapy, intensity-modulated radiation therapy, proton beam radiation therapy, stereotactic body radiation therapy, and high-intensity focused ultrasound) compared in this review. (○○○)

* Note: Advances in technologies and knowledge may allow some of the currently available treatments to better target prostate cancer when compared with the treatments described in this review and, thereby, improve the effectiveness and patient tolerance of the treatments. Such advances might affect the applicability of some of the findings of this review to contemporary clinical practice.

† Two large randomized controlled trials compared RP and WW and reported health outcomes. The Scandinavian Prostate Cancer Group-4 (SPCG-4) study (N = 695) and the Prostate Cancer Intervention Versus Observation Trial (PIVOT; N = 731) compared RP with WW in patients with localized prostate cancer and reported data on prostate cancer–specific and all-cause mortality.

Prostate cancer–specific mortality: The SPCG-4 study found that RP reduced prostate cancer–specific mortality at 12 and 15 years; however, PIVOT found no statistically significant difference at 12 years.

All-cause mortality: The SPCG-4 study found that RP reduced all-cause mortality at 15 years, but neither the SPCG-4 study nor PIVOT found any significant difference at 12 years.

Strength of Evidence Scale

High:	●●●	High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
Moderate:	●●○	Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.
Low:	●○○	Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of effect and is likely to change the estimate.
Insufficient:	○○○	Evidence either is unavailable or does not permit a conclusion.

Other Findings of the Review

- Evidence was insufficient to determine if patient characteristics (e.g., age, race, preferences, comorbidities) or tumor characteristics (e.g., PSA levels, Gleason score) impacted outcomes of therapies for localized prostate cancer.
- No comparative studies assessed how provider or hospital characteristics (e.g., RP procedure volume, physician specialty, geographic region) might impact the effectiveness of various treatments.

Conclusions

Evidence from two large studies (the SPCG-4 study and PIVOT) showed that metastases can be reduced with RP versus WW. Evidence related to the comparative effectiveness of RP and WW for mortality outcomes was rated as insufficient, largely because of the lack of replication in the two large trials. Evidence for other therapies for clinically localized prostate cancer assessed in this updated systematic review is too limited to determine their comparative effectiveness and adverse effects.

Evidence is insufficient to determine which subgroups of patients might benefit most from these therapies based on patient and disease characteristics.

Clear guidance regarding the appropriate patient population for RP, radiation therapy, hormonal therapy, WW, AS, or one of the other options is difficult to establish. Physicians might take into consideration age, general health status, stage of tumor, PSA level, Gleason score, logistical factors (timing of surgery vs. radiation), use of androgen deprivation therapy (ADT) as a component of the treatment strategy, patient preferences, nuances in patient recovery and quality of life, and other factors in identifying the most appropriate treatment options. Guidelines from NCCN and the American Urological Association may be informative in this regard.

Gaps in Knowledge and Limitations of the Evidence Base

The following gaps in research and/or issues were identified in the updated review:

- The lack of precise methods and tools for clinically staging prostate cancer that is detectable but not metastatic
- A limited number of studies with long followup times
  - With prostate cancer, a key limitation in accruing high-quality data is the long natural history of the disease.
- A limited number of studies that recruit patients with PSA-detected prostate cancer and examine patient-focused outcomes
  - An ongoing clinical trial is comparing the effectiveness of RP, AS, and radiation therapy in men with PSA-detected prostate cancer.
- A dearth of studies that compare AS to current therapeutic approaches for prostate cancer
- A need for continuing ongoing research for prognostic surrogate markers to improve prediction of recurrence risk among patients with clinically localized disease
- A possible restriction in the applicability of the findings of this review based on the following factors:
  - Most studies included in the review recruited participants before 2002. Since diagnostic approaches have evolved in the last 10 to 15 years, patients in the reviewed studies were likely older and had more advanced disease than patients being diagnosed with localized prostate cancer today.
  - For treatments such as EBRT and interstitial brachytherapy, advances in technologies and knowledge may allow many of the currently available treatments to better target prostate cancer and, thereby, improve the effectiveness and patient tolerance of the treatments.

What To Discuss With Your Patients and/or Their Caregivers

- How long the patient may live with his cancer
- If WW or AS is recommended, the estimated likelihood of cancer progression without treatment
- Recommended treatment options based on the patient's age, health status, life expectancy, and tumor stage
- The potential for tumor eradication with treatment
- Available evidence for the efficacy and effectiveness of the various treatment options
- The schedule and logistics of each treatment
- Use of ADT with other treatments
- The patient's quality of life with the various treatments
- The patient's and/or caregiver's values and preferences

Companion Resource for Patients

Treating Localized Prostate Cancer: A Review of the Research for Adults is a free companion to this clinician research summary. It can help patients and their caregivers talk with their health care professionals about the various treatment options that are available for treating clinically localized prostate cancer.

Ordering Information

For electronic copies of this clinician research summary, the companion patient summary, and the full systematic review, visit *www.effectivehealthcare.ahrq.gov/prostate-cancer.*

Source

The information in this summary is based on *Therapies for Clinically Localized Prostate Cancer: Update of a 2008 Systematic Review,* Comparative Effectiveness Review No. 146, prepared by the ECRI Institute–Penn Medicine Evidence-based Practice Center under Contract No. 290-2007-10063 for the Agency for Healthcare Research and Quality, December 2014. Available at *www.effectivehealthcare.ahrq.gov/prostate-cancer.* This summary was prepared by the John M. Eisenberg Center for Clinical Decisions and Communications Science at Baylor College of Medicine, Houston, TX.

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