Number 13

Effective Health Care

Comparative Effectiveness of Therapies for Clinically Localized Prostate Cancer

Executive Summary

Background and Key Questions

Prostate cancer is the most common nondermatologic cancer in men. In 2007 an estimated 218,890 men were diagnosed with, and 27,050 deaths were attributed to, prostate cancer in the United States. Approximately 90 percent of men with prostate cancer have disease considered confined to the prostate gland (clinically localized disease). Reported prostate cancer incidence has increased with introduction of the prostate-specific antigen (PSA) blood test. Disease-specific mortality rates have declined, and an estimated 1.8 million men living in the United States have a diagnosis of prostate cancer.

Clinically detected prostate cancer is primarily a disease of elderly men. Prostate cancer frequently has a relatively protracted course even if left untreated, and many men die with, rather than from, prostate cancer. Largely because of widespread PSA testing, the lifetime risk of being detected with prostate cancer in the United States has nearly doubled to 20 percent. However, the risk of dying of prostate cancer has remained at approximately 3 percent. Therefore, considerable overdetection and treatment may exist.

Effective Health Care Program

The Effective Health Care Program was initiated in 2005 to provide valid evidence about the comparative effectiveness of different medical interventions. The object is to help consumers, health care providers, and others in making informed choices among treatment alternatives. Through its Comparative Effectiveness Reviews, the program supports systematic appraisals of existing scientific evidence regarding treatments for high-priority health conditions. It also promotes and generates new scientific evidence by identifying gaps in existing scientific evidence and supporting new research. The program puts special emphasis on translating findings into a variety of useful formats for different stakeholders, including consumers.

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The primary goal of treatment is to target the men most likely to need intervention in order to prevent prostate cancer death and

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disability while minimizing intervention-related complications. Common treatments include watchful waiting (active surveillance), surgery to remove the prostate gland (radical prostatectomy), external beam radiotherapy (EBRT) and interstitial radiotherapy (brachytherapy), freezing the prostate (cryotherapy), and androgen deprivation therapy (ADT). (Treatment options are outlined in Table A.) All treatments have risks of complications, although frequency and severity may vary. Patient treatment decisionmaking incorporates physician recommendations and estimated likelihood of cancer progression without treatment, as well as treatment-related convenience, costs, and potential for eradication and adverse effects (AEs). Patient characteristics, including race/ethnicity, age, and comorbidities, have an important role in predicting mortality; the likelihood of treatment-related urinary, bowel, and sexual dysfunction; treatment tradeoff preferences; and selection. However, little is known about how these characteristics modify the effect of treatment.

Table A. Treatment options for clinically localized prostate cancer

Treatment option	Treatment description
Radical retropubic or perineal prostatectomy (RP)	Complete surgical removal of prostate gland with seminal vesicles, ampulla of vas, and sometimes pelvic lymph nodes. Sometimes done laparoscopically or with robotic assistance and attempt to preserve nerves for erectile function.
External beam radiotherapy (EBRT)	Multiple doses of radiation from an external source applied over several weeks. Dose and physical characteristics of beam may vary. Conformal radiotherapy uses 3D planning systems to maximize dose to prostate cancer and attempt to spare normal tissue. Intensity modulated radiation therapy (IMRT) provides the precise adjusted dose of radiation to target organs, with less irradiation of healthy tissues than conformal radiation therapy. Proton radiation therapy is a form of EBRT in which protons rather than photons are directed in a conformal fashion to a tumor site. The use of the heavier single proton beam (vs. photon therapy) allows for a low entrance dose and maximal dose at the desired tumor location with no exit dose. This theoretically permits improved dose distribution (delivering higher dose to the tumor with lower dose to normal tissue) than other EBRT techniques. May be used alone or in combination with proton and photon-beam radiation therapy.
Brachytherapy	Radioactive implants placed under anesthesia using radiologic guidance. Lower dose/permanent implants typically used. External beam "boost" radiotherapy and/or androgen deprivation sometimes recommended.
Cryoablation	Destruction of cells through rapid freezing and thawing using transrectal guided placement of probes and injection of freezing/thawing gases.
Androgen deprivation therapy	Oral or injection medications or surgical removal of testicles to lower or block circulating androgens.
Watchful waiting (active surveillance)	Active plan to postpone intervention. May involve monitoring with digital rectal exam/prostate-specific antigen test and repeat prostate biopsy with further therapy (either curative or palliative) based on patient preference, symptoms, and/or clinical findings.
Laparoscopic radical prostatectomy (LRP) and robotic assisted radical prostatectomy (RLRP)	Video-assisted, minimally invasive surgical method to remove the prostate.
High-intensity focused ultrasound therapy (HIFU)	High-intensity focused ultrasound therapy has been used as a primary therapy in patients with localized prostate cancer not suitable for radical prostatectomy. Tissue ablation of the prostate is achieved by intense heat focused on the identified cancerous area.

Prior to the advent of widespread PSA testing, most prostate cancers were detected based on abnormalities on the digital rectal examination (DRE) or incidentally from tissue obtained at surgery for treatment of symptoms due to benign prostatic obstruction. The vast majority of prostate cancers currently detected in the United States are asymptomatic, clinically localized, and found on routine PSA testing. PSA testing detects more tumors, at an earlier stage, with smaller volume within each stage, and at an earlier period in a man's life than nonscreen-detected tumors. The clinical significance, natural history, and comparative effectiveness of treatments in PSA-detected cancers are not known but likely differ from those detected and treated in the pre-PSA era (before the late 1980s to early 1990s).

The primary measure of tumor aggressiveness is the Gleason histologic score, although efforts are underway to identify more reliable prognostic factors. A classification currently recommended incorporates PSA levels, Gleason histologic score, and tumor volume to identify low-, intermediate-, and high-risk tumors based on their likelihood of progressing with no treatment as well as recurring (or failing to be eradicated) following early intervention. In addition to patient and provider factors, it is important to determine how tumor characteristics (e.g., Gleason score, tumor volume, screen vs. clinically detected tumors) affect the outcomes of interventions.

Provider and hospital characteristics may affect treatment selection and outcomes. The effect of provider volumes on clinical outcomes in men with localized prostate cancer is not well established. Specialty and geographical location of providers influence diagnostic strategies and the management of localized prostate cancer. Variability in the management of localized prostate cancer is often based on physician opinions and specialty. Diagnosis of localized disease is based primarily on a screening of asymptomatic patients. Therefore, differences in screening practices may be associated with differences in the stage of tumors detected and recommendations for intervention. Physician recommendations play an important role in patient decisions on treatment preferences. Recent studies showed that patient and physician treatment preferences reflect perceived personal factors more than evidence-based recommendations.

This report summarizes evidence comparing the relative effectiveness and safety of treatment options for clinically localized prostate cancer. The report addresses the following questions:

1. What are the comparative risks, benefits, short- and long-term outcomes of therapies for clinically localized prostate cancer?
2. How do specific patient characteristics, e.g., age, race/ethnicity, presence or absence of comorbid illness, preferences (e.g., tradeoff of treatment-related adverse effects vs. potential for disease progression), affect the outcomes of these therapies, overall and differentially?
3. How do provider/hospital characteristics affect outcomes overall and differentially (e.g., geographic region and volume)?
4. How do tumor characteristics, e.g., Gleason score, tumor volume, screen vs. clinically detected tumors, affect the outcomes of these therapies, overall and differentially?

Conclusions

The findings covered in this report are summarized in Table B.

Key Question 1. What are the comparative risks, benefits, and outcomes of therapies?

No one therapy can be considered the preferred treatment for localized prostate cancer due to limitations in the body of evidence as well as the likely tradeoffs an individual patient must make between estimated treatment effectiveness, necessity, and adverse effects. All treatment options result in adverse effects (primarily urinary, bowel, and sexual), although the severity and frequency may vary between treatments. Even if differences in therapeutic effectiveness exist, differences in adverse effects, convenience, and costs are likely to be important factors in individual patient decisionmaking. Patient satisfaction with therapy is high and associated with several clinically relevant outcome measures. Data from nonrandomized trials are inadequate to reliably assess comparative effectiveness and adverse effects. Additional randomized controlled trials (RCTs) are needed.

Limitations in the existing evidence include the following:

- Few randomized trials directly compared the relative effectiveness between (rather than within) major treatment categories.

- Many randomized trials are inadequately powered to provide long-term survival outcomes, with the majority reporting biochemical progression or recurrence as the main outcomes.
- Some randomized trials were old, conducted prior to prostate cancer detection with PSA testing (i.e., studies before the current era, when tumors are diagnosed in an earlier stage, giving more lead time, and there is a higher percentage of benign tumors, resulting in length bias and overdiagnosis), and used technical aspects of treatment that may not reflect current practice; therefore, their results may not be generalizable to modern practice settings.
- Wide variation existed in reporting and definitions of outcomes.
- There was little reporting of outcomes according to major patient and tumor characteristics.
- Emerging technologies have not been evaluated in randomized trials.

Randomized comparisons across primary treatment categories

- **Radical prostatectomy compared with watchful waiting (2 RCTs)**. Compared with men who used watchful waiting (WW), men with clinically localized prostate cancer detected by methods other than PSA testing and treated with radical prostatectomy (RP) experienced fewer deaths from prostate cancer, marginally fewer deaths from any cause, and fewer distant metastases. The greater benefit of RP on cancer-specific and overall mortality appears to be limited to men under 65 years of age but is not dependent on baseline PSA level or histologic grade. Two RCTs compared WW with RP. The Scandinavian Prostate Cancer Group (SPCG) trial found significantly lower incidences of all-cause deaths (24 vs. 30 percent), disease-specific deaths (10 vs. 15 percent), and distant metastases (14 vs. 23 percent) for subjects treated with RP than for subjects assigned WW after a median followup of 8.2 years. Surgery was associated with greater urinary and sexual dysfunction than WW. An older trial of 142 men found no significant differences in overall survival between RP and WW after a median followup of 23 years, although small sample size limited study power.
- **Radical prostatectomy vs. external beam radiotherapy (1 RCT)**. One small (N=106), older trial indicated that, compared with EBRT, RP was more effective in preventing progression, recurrence, or distant metastases in men with clinically localized prostate cancer detected by methods other then PSA testing. Treatment failure at 5 years of followup, defined as acid phosphatase elevation on two consecutive followup visits or appearance of bone or parenchymal disease with or without concomitant acid phosphatase elevation, occurred in 39 percent for EBRT compared with 14 percent for RP.
- **Cryotherapy, laparoscopic or robotic assisted radical prostatectomy, primary androgen deprivation therapy, high-intensity focused ultrasound (HIFU), proton beam radiation therapy, or intensity modulated radiation therapy (IMRT) (0 RCTs)**. It is not known whether these therapies are better or worse than other treatments for localized prostate cancer because these options have not been evaluated in RCTs.

Randomized comparisons within primary treatment categories

- **Radical prostatectomy combined with neoadjuvant androgen deprivation therapy (5 RCTs)**. The addition of neoadjuvant hormonal therapy to RP did not improve survival or cancer recurrence rates, defined by PSA recurrence, but increased AEs. One small RCT comparing RP alone and RP combined with neoadjuvant ADT found no overall or disease-specific survival benefit with the addition of neoadjuvant ADT after a median followup of 6 years. The addition of neoadjuvant ADT did not prevent biochemical progression compared with RP alone in any of the four trials. The trial comparing 3 months and 8 months neoadjuvant ADT with RP reported greater AEs in the 8-month group than the 3-month group (4.5 percent vs. 2.9 percent) and higher incidence of hot flashes (87 percent vs. 72 percent).
- **External beam radiotherapy: comparison of EBRT regimens (5 RCTs)**. No RCTs compared EBRT and WW. It is not known if using higher doses of EBRT by increasing either the total amount or type of radiation (e.g., via high-dose intensity modulated or proton beam or by adding

brachytherapy) improves overall or disease-specific survival compared with other therapies. No EBRT regimen, whether conventional, high-dose conformal, dose fractionation, or hypofractionation, was superior in reducing overall or disease-specific mortality. Increasing the total amount of radiation or adding brachytherapy after EBRT decreased cancer recurrence compared with lower doses of radiation. One trial (N=936) found that the probability of biochemical or clinical progression at 5 years was lower in the long-arm group (66 Gy in 33 fractions) than the short-arm group (52.5 Gy in 20 fractions). Conventional-dose EBRT (64 Gy in 32 fractions) and hypofractionated EBRT (55 Gy in 20 fractions) resulted in similar PSA relapse. One trial (N=104) found that brachytherapy combined with EBRT reduced biochemical or clinical progression compared with EBRT alone. One trial (N=303) found that high-dose EBRT (79.2 Gy that included 3D conformal proton 50.4 Gy with 28.8 Gy proton boost) was more effective than conventional-dose EBRT (70 Gy that included 19.8 Gy proton boost) in the percentage of men free from biochemical failure at 5 years (80 percent in the high-dose group and 61 percent in the conventional-dose group). Effectiveness was evident in low-risk disease (PSA <10 ng/ml, stage ≤T2a tumors, or Gleason ≤6) and higher risk disease. Acute combined gastrointestinal (GI) and genitourinary (GU) toxicity was lower in the long arm (7.0 percent) than in the short arm (11.4 percent). Late toxicity was similar. There were no significant differences between conventional and hypofractionated EBRT with the exception of rectal bleeding at 2 years after therapy, which had a higher prevalence in the hypofractionated group. Acute GI or GU symptoms of at least moderate severity were similar in the trial comparing high and conventional doses.

- **External beam radiotherapy combined with androgen deprivation therapy compared with EBRT alone (3 RCTs)**. ADT combined with EBRT (ADT + EBRT) may decrease overall and disease-specific mortality but increase AEs compared with EBRT alone in high-risk patients defined by PSA levels and Gleason histologic score (PSA >10 ng/ml or Gleason >6). One RCT (N=216) found that conformal EBRT combined with 6 months of ADT reduced all-cause mortality, disease-specific mortality, and PSA failure compared with conformal EBRT alone after a median followup of 4.5 years. There were significant increases in gynecomastia and impotence in the ADT + EBRT group compared with EBRT alone. One RCT (N=206) found that 6 months of ADT + EBRT did not significantly reduce disease-specific mortality compared with conformal EBRT alone in T2b and T2c subjects after a median followup of 5.9 years. Six months of combination therapy reduced clinical failure, biochemical failure, or death from any cause compared with EBRT alone in subjects with T2c disease but not in T2b subjects.
- **Different doses of adjuvant external beam radiotherapy combined with brachytherapy (1 RCT)**. One small trial comparing different doses of supplemental EBRT, 20 Gy (N=83) vs. 44 Gy (N=76), adjuvant to brachytherapy (^{103}Pd) implant found no significant differences in the number of biochemical failure events and freedom from biochemical progression at 3 years.
- **Brachytherapy compared with brachytherapy (1 RCT)**. No RCTs compared brachytherapy alone with other major treatment options. Preliminary results from one small trial (N=126) comparing ^{125}I with ^{103}Pd brachytherapy found similar biochemical control at 3 years. There was a trend toward more radiation proctitis, defined as persistent bleeding, with ^{125}I.
- **Adjuvant androgen deprivation therapy with bicalutamide combined with standard care: RP, EBRT, or WW (3 RCTs)**. Androgen deprivation with bicalutamide alone or in addition to RP or EBRT did not reduce cancer recurrence or mortality. There was no difference in total number of deaths between the bicalutamide and placebo groups for men receiving RP or EBRT at the median followup of 5.4 years. Among WW subjects, there were significantly more deaths with bicalutamide compared with placebo. The addition of bicalutamide to standard care did not reduce progression.

Comparative outcomes data from nonrandomized reports

To supplement RCT findings and summarize the literature on treatment for localized prostate cancer, we used the database of the Clinical Guideline Panel for

Treatment of Clinically Localized Prostate Cancer of the American Urological Association. This work relied on data extracted from 436 articles published between 1991 and April 2004 on T1-T2 prostate cancer. Over 80 percent were case series and only 6 percent were controlled trials. Data interpretation is limited by variability in result reporting, lack of controls, and likelihood that the database contained results from multiple publications using identical or nearly identical populations. Overall and disease-specific mortality were infrequently reported. When reported, there was extremely wide variation within and between treatments, making overall estimates of outcomes difficult. There was not standardized reporting of biochemical outcomes, with more than 200 definitions of "biochemical no evidence of disease (bNED)" reported. Results demonstrated extremely wide and overlapping ranges of outcomes at 5 and 10 years within and between treatments.

Adverse effects were reported, but definitions and severity varied widely. It was not possible to provide precise estimates regarding comparative effectiveness or specific AEs for each treatment option. Urinary dysfunction appeared to be more common in men treated with RP than in men treated with EBRT. Sexual dysfunction was common following all treatments. Impotence rates ranged from less than 5 percent to approximately 60 percent in the few studies reporting on men undergoing nerve-sparing RP.

Additional estimates for U.S. population-based AEs at 5 years following treatment were obtained from a large survey of Medicare-eligible men who had undergone treatment for localized prostate cancer. Urinary dysfunction, defined as no control or frequent leaking of urine, occurred in 14 percent of men undergoing RP and 5 percent undergoing EBRT. Use of pads to stay dry was greater after RP (29 percent) than EBRT (4 percent). Bowel dysfunction was lower in men receiving RP than EBRT, although the only significant difference was related to bowel urgency (18 percent vs. 33 percent). Erection insufficient for intercourse occurred in approximately three-quarters of men regardless of treatment. When adjusting for baseline factors, erectile dysfunction (ED) was greater with RP (odds ratio=2.5, 95-percent confidence interval=1.6, 3.8).

Cryosurgery. No randomized trials evaluated cryosurgery, and the majority of reports included patients with T3-T4 stages. Overall or prostate-cancer-specific survival was not reported. Progression-free survival in patients with T1-T2 stages ranged from 29 to 100 percent. AEs were often not reported but, when described, included bladder outlet obstruction (3 to 21 percent), tissue sloughing (4 to 15 percent), and impotence (40 to 100 percent). Outcomes may be biased by patient and provider characteristics.

Laparoscopic and robotic assisted prostatectomy. Three reviews estimated the effectiveness and AEs of laparoscopic and robotic assisted prostatectomy from 21 nonrandomized trials and case series. Most originated from centers outside of the United States. Median followup was 8 months. Laparoscopic RP had longer operative time but lower blood loss and improved wound healing compared with open retropubic RP. Reintervention rates were similar. Results from eight nonrandomized reports suggested that total complications, continence rates, positive surgical margins, and operative time were similar for robotic assisted and open RP. Median length of hospital stay (1.2 vs. 2.7 days) and median length of catheterization (7 vs. 13 days) were shorter after robotic assisted RP than open RP.

Intensity modulated radiation therapy. There was no direct evidence that IMRT results in better survival or disease-free survival than other therapies for localized prostate cancer. Based on nonrandomized data, the absolute risks of clinical and biochemical outcomes (including tumor recurrence), toxicity, and quality of life after IMRT are comparable with conformal radiation. There is low-level evidence that IMRT provides at least as good a radiation dose to the prostate with less radiation to the surrounding tissues compared with conformal radiation therapy.

Proton EBRT. There were no data from randomized trials comparing EBRT using protons vs. conventional EBRT or other primary treatment options. In one randomized trial, men with localized prostate cancer had statistically significantly lower odds of biochemical failure (increase in PSA) 5 years after the higher dose of EBRT with a combination of conformal photon and proton beams without increased risk of adverse effects. Based on nonrandomized reports, the rates of clinical outcomes and toxicity after proton therapy may be comparable with conformal radiation. There was no direct evidence that proton EBRT results in better overall or disease-free survival than other therapies.

High-intensity focused ultrasound therapy. There were no data from randomized trials comparing HIFU with other primary treatment options. Biochemical

progression-free survival rates of 66 to 87 percent and negative biopsy rates of 66 to 93 percent were reported from noncontrolled studies. The absolute risk of impotence and treatment-related morbidity appeared to be similar to other treatments. Followup duration was <10 years.

Health status, quality of life, and treatment satisfaction. Eight studies of health status and quality of life, including a U.S. population-based survey, were eligible. Bother due to dripping or leaking of urine was more than sixfold greater in RP-treated men than in men treated with EBRT after adjusting for baseline factors. Bother due to bowel dysfunction (4 vs. 5 percent) or sexual dysfunction (47 vs. 42 percent) was similar for RP and EBRT. In a subgroup of men ages 70 and over, bother due to urine, bowel, or sexual dysfunction was 5.1, 2.4, and 2.8 times higher, respectively, for aggressive (RP/EBRT) vs. conservative (WW/ADT) therapy. Satisfaction with treatment was high, with less than 5 percent reporting dissatisfaction, unhappiness, or feeling terrible about their treatment, although the highest percent was among those treated with RP. Treatment satisfaction was highly correlated with bowel, bladder, and erectile function; general health status; belief that the respondent was free of prostate cancer; and whether cancer treatments limited activity or relationships. More than 90 percent said they would make the same treatment decision again, regardless of treatment received.

Key Question 2. How do patient characteristics affect outcomes?

No RCTs reported head-to-head comparisons of treatment outcomes stratified by race/ethnicity, and most did not provide baseline racial characteristics. Available data were largely from case series. Few studies reported head-to-head comparisons, and there was limited adjustment for confounding factors. Modest treatment differences reported in some nonrandomized studies have not been consistently reported in well-powered studies. There was little evidence of a differential effect of treatments based on age. While differences exist in the incidence and morbidity of prostate cancer based on patient age and there are differences in the treatments offered to men at different age ranges, few studies directly compared the treatment effects of different therapies across age groups. Most RCTs did not have age exclusion criteria. The mean/median age ranged from a low of 63 years for trials of RP to 72 years for trials of EBRT. Only one RCT provided subgroup analysis according to age. Results suggest that survival benefits of RP compared with WW may be limited to men under 65 years of age. Practice patterns from observational studies show that RP is the most common treatment option in younger men with localized prostate cancer.

Key Question 3. How do provider and hospital characteristics affect outcomes?

Results from national administrative databases and surveys suggested that provider/hospital characteristics, including RP procedure volume, physician specialty, and geographic region, affect outcomes. (There was no information on volume and outcomes for brachytherapy, cryotherapy, or EBRT.) Patient outcomes varied in different locations and were associated with provider and hospital volume independent of patient and disease characteristics. Screening practices can influence the characteristics of patients diagnosed and tumors detected. Screening practices and treatment choices varied by physician specialty and across regions of the United States. These did not correlate with clinician availability. Clinicians were more likely to recommend procedures they performed regardless of tumor grades and PSA levels.

Regional variation existed in physician availability, ratio of urologists and radiation oncologists per 100,000 adult citizens based on surveys conducted by the American Medical Association, screening practice, incidence, mortality, and treatment selection. The direction of regional variation was not always consistent. Several studies reported geographic variation at the county, State, or U.S. Census region level. Overall, many different methods were used to report geographic variation, so pooling of results was difficult; when results were pooled, the geographic regions used were quite large.

Surgeon RP volume was not associated with RP-related mortality and positive surgical margins. However, the relative risk of surgery-related complications adjusted for patient age, race, and comorbidity and for hospital type and location was lower in patients treated by higher volume surgeons. Urinary complications and incontinence were lower for patients whose surgeons performed more than 40 RPs per year. The length of hospital stay was shorter in patients operated on by surgeons who performed more RPs per year. Cost was not associated with surgeon volume. Surgeon volume of

robotic laparoscopic RP was marginally associated with lower adjusted odds of extensive (but not any or focal) positive margins.

Hospital volume and teaching status were associated with patient outcomes. Despite different definitions of "high" and "low" hospital volumes in individual studies, pooled analysis showed that surgery-related mortality and late urinary complications were lower and length of stay was shorter in hospitals that performed more RPs per year. Hospital readmission rates were lower in hospitals with greater volume. Teaching hospitals had a lower rate of surgery-related complications and higher scores of operative quality. Several studies found differences in treatment and outcome based on whether the patient was seen in an HMO (health maintenance organization) or fee-for-service organization and whether the patient was a Medicare beneficiary. Variability in the use of ADT was more attributable to individual differences among urologists than tumor or patient characteristics.

Key Question 4. How do tumor characteristics affect outcomes?

Little data existed on the comparative effectiveness of treatments based on PSA levels, histologic score, and tumor volume to identify low-, intermediate-, and high-risk tumors. We focused on baseline PSA levels and Gleason histologic score. The natural history of PSA-detected tumors is not known because few men remain untreated for a long period. One report assessed 20-year outcomes in the United States from a cohort of 767 men with prostate cancer detected prior to PSA testing and treated with WW. Histologic grade was associated with overall and prostate-cancer-specific survival. Men with low-grade prostate cancers had a minimal risk of dying from prostate cancer (7 percent with Gleason score 2-4 died due to prostate cancer). Men with high-grade prostate cancers had a high probability of dying from their disease within 10 years of diagnosis, regardless of their age at diagnosis (53 percent with Gleason score 8-10 died due to prostate cancer). Estimates from large ongoing screening trials suggest that PSA increases the time of detection by 5-15 years. Therefore, it is likely that men with PSA-detected tumors will have better 20-year disease-specific survival than this cohort.

Most RCTs did not exclude participants based on PSA levels or tumor histology, and few provided comparative analysis according to these factors. Secondary analysis of one randomized trial concluded that disease-specific mortality at 10 years for men having RP compared with WW differed according to age but not baseline PSA level or Gleason score. Men with Gleason scores 8-10 were more likely to have evidence of biochemical recurrence than men with Gleason scores 2-6, regardless of whether treatment was RP alone or RP combined with neoadjuvant hormonal therapy (NHT). High-dose EBRT was more effective in controlling biochemical failure than conventional dose therapy in both low-risk disease (PSA <10 ng/ml, stage ≤T2a tumors, or Gleason ≤6) and higher risk disease. When the higher risk subjects were further divided into intermediate risk and high-risk groups, the benefit of high-dose therapy remained for the intermediate-risk but not for the high-risk patients.

Based on very limited nonrandomized trial data, disease-specific survival was similar for men treated with EBRT or with RP in men with baseline PSA >10 ng/ml. Men with Gleason scores 8-10 were more likely to have biochemical recurrence than men with Gleason scores 2-6, regardless of type of treatment.

Remaining Issues

Uncertainty about the comparative effectiveness and harms of the primary treatments for localized prostate cancer is the major gap in knowledge. This is mainly due to the paucity of direct head-to-head RCTs and the excess reliance on nonrandomized data to compare the most common treatment options: WW, RP, EBRT, brachytherapy, and ADT. Emerging technologies such as IMRT, proton beam radiation, laparoscopic and robotic assisted prostatectomy, and cryotherapy are increasingly being used despite the absence of long-term comparative RCTs.

Initiation and completion of long-term, adequately powered randomized trials (particularly comparative trials across, rather than within, primary treatment modalities) are needed. Where randomized trials have been conducted, confirmation (or refutation) of findings with additional randomized trials is needed because evidence is often based on results from a single relatively small study. These trials should standardize reporting of key clinically relevant outcomes, including overall, disease-specific, and metastatic-free survival; bNED; adverse effects; and disease-specific quality of life/health status. Ideally, relative effectiveness and adverse effects would be stratified according to tumor

(PSA, stage, histologic grade) and patient (age, race, comorbidity) characteristics. A previous RCT comparing RP and brachytherapy was discontinued due to inadequate recruitment. However, several trials are ongoing, including comparisons of RP vs. WW, RP vs. EBRT or WW, cryotherapy vs. EBRT, and active surveillance with delayed intervention vs. early intervention with RP. Results will not be available for several years. Patients and their support groups, clinicians, researchers, and funders need to ensure successful initiation and completion.

High-quality, large prospective cohort studies or cancer registries that identify men at the time of diagnosis and proceed to collect comprehensive patient, tumor, and treatment decision selection characteristics could help target future RCTs to the most promising research questions. These may be able to provide information related to important patient characteristics (age, race, comorbidities) or tumor characteristics (PSA, stage, histologic grade) that may not be adequately addressed in RCTs currently in progress due to sample size limitations. Nonrandomized studies should report head-to-head comparisons, adjust for confounding factors, and use standardized definitions of disease-specific and biochemical survival, adverse effects, and patient/tumor characteristics.

Identification of biomarkers to provide reliable estimates about prostate cancer aggressiveness and the relative effectiveness of treatments is needed. This would reduce unnecessary interventions while focusing treatment on men most likely to benefit. A new generation of educational materials is required to provide balanced information about the risks and benefits of treatments and assist in patient decisionmaking and incorporation of patient-centric values (tumor eradication, impact of AEs, anxiety, costs, convenience, etc.). It is hoped that these materials incorporate findings from comprehensive systematic reviews that use methods to limit bias and assess quality of evidence. The resulting patient and provider guides can be developed to summarize these findings in a format that is understandable and useful for consumers. Structure and process measures are associated with quality of prostate cancer care. Research across nationally representative databases using methods of risk adjustment is needed to clarify geographical differences in patient outcomes. Identification of factors associated with outcomes and development of systemwide methods for implementation or improvement are needed.

Full Report

This executive summary is part of the following document: Wilt TJ, Shamliyan T, Taylor B, MacDonald R, Tacklind J, Rutks I, Koeneman K, Cho C-S, Kane RL. Comparative Effectiveness of Therapies for Clinically Localized Prostate Cancer. Comparative Effectiveness Review No. 13. (Prepared by Minnesota Evidence-based Practice Center under Contract No. 290-02-0009.) Rockville, MD: Agency for Healthcare Research and Quality. February 2008. Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm.

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Table B. Summary of Evidence on Therapies for Localized Prostate Cancer

Key question	Quality of evidence	Summary, conclusion, comments
Key Question 1. What are the comparative risks, benefits, short- and long-term outcomes of therapies for clinically localized prostate cancer?		
A. Comparisons from randomized controlled trials		
Radical prostatectomy compared with watchful waiting	Medium Low	There were 2 head-to-head comparisons, 1 with an adequate method of allocation and 1 unclear. Few enrolled men had prostate cancers detected by PSA testing. The Veterans Administration Cooperative Urological Research Group (VACURG) trial was underpowered to detect large differences. The Scandinavian Prostate Cancer Group Study 4 (SPCG-4) randomized men with a life expectancy of >10 years. • Overall mortality/survival: In SPCG-4, RP reduced overall mortality compared with WW after a median followup of 8.2 years. In VACURG, there was no significant difference in median overall survival. • Disease-specific mortality: In SPCG-4, RP reduced prostate-cancer-specific mortality compared with WW. • Incidence of distant metastases: In SPCG-4, RP reduced the incidence of distant metastases compared with WW. • Urinary incontinence and sexual dysfunction were greater after RP in SPCG-4. • Relative effectiveness of RP compared with WW for overall and disease-specific survival may be limited to men under 65 years of age based on subgroup analysis from the SPCG-4.
RP with neoadjuvant androgen deprivation therapy compared with RP alone	Medium High High	4 head-to-head comparisons, 1 with an adequate method of allocation. 2 trials enrolled subjects with locally advanced disease. • Overall mortality/survival: RP with ADT did not improve overall survival compared with RP alone after a median followup of 6 years. • Disease-specific survival: RP with ADT did not reduce disease-specific mortality compared with RP alone. • Biochemical/clinical progression or recurrence: RP with ADT did not prevent biochemical progression compared with RP alone in any of 4 RCTs. • Distant metastases: The addition of ADT did not reduce the risk of developing distant metastases in 2 trials reporting.
RP with ADT, comparison of different regimens	Medium	1 trial with an unclear method of allocation. No effectiveness outcomes reported. • Adverse effects and toxicity: There was no difference between 8-month and 3-month ADT in the type and severity of AEs. 8-month ADT resulted in more AEs than 3-month ADT. (AE defined as the first occurrence of an event and higher incidences of hot flashes.)

Table B. Summary of Evidence on Therapies for Localized Prostate Cancer (continued)

Key question	Quality of evidence	Summary, conclusion, comments
RP compared with external beam radiotherapy	Low	1 head-to-head comparison from a small American trial with an unclear method of allocation. • Biochemical/clinical progression or recurrence: RP was more effective than EBRT in preventing progression at 5 years. • Incidence of distant metastases: RP reduced distant metastases compared with EBRT. • *Comment: Only 97 subjects included in analysis; excludes 9 subjects who failed to receive any treatment. Prostate cancers not detected by PSA testing. Refinements in RP and EBRT may make results inapplicable to current practice.*
EBRT, comparison of different regimens	Medium	5 head-to-head comparisons.
a. Long (conventional) arm (66 Gy in 33 fractions) compared with short (hypofractionated) arm (52.5 Gy in 20 fractions)	Medium	1 trial with an adequate method of allocation. • Overall mortality/survival: No difference in overall mortality between groups (median followup of 5.7 years). • Disease-specific survival: No significant difference in PC deaths between groups. • Biochemical/clinical progression or recurrence: At 5 years, biochemical or clinical progression was 53% in the long arm compared with 60% in the short arm. • Distant metastases: No significant difference in distant failure events between groups at the median followup of 5.4 years. • Adverse effects and toxicity: Acute (≤5 months) combined gastrointestinal and genitourinary toxicity was lower in long arm than in short arm. Late toxicity was similar in both arms.
b. Iridium brachytherapy implant + EBRT compared with EBRT alone	Low	1 small trial with an adequate method of allocation. The trial enrolled T3 stage subjects (not included in findings below). • Biochemical/clinical progression or recurrence: Iridium brachytherapy implant combined with EBRT reduced biochemical or clinical progression compared with EBRT alone over a median followup of 8.2 years in T2 subjects.
c. Conventional EBRT (64 Gy in 32 fractions over 6.5 weeks) compared with hypofractionated EBRT group (55 Gy in 20 fractions in 4 weeks)	Medium	1 trial with an adequate method of allocation. • Biochemical/clinical progression or recurrence: No difference in PSA relapse events between conventional and hypofractionated EBRT. • Adverse effects and toxicity: No differences between groups with the exception of rectal bleeding at 2 years, which had a higher prevalence in the hypofractionated group.
d. Trial 1. Conventional-dose (70 Gy) compared with high-dose EBRT (79.2 Gy)	Medium	2 trials: Trial 1, Trial 2 (low-risk subgroup only, defined as T1/2, Gleason ≤6, PSA ≤10), both with an unclear method of allocation. • Trial 1: Overall mortality/survival: No difference in overall survival between conventional- and high-dose EBRT at 5 years.

Table B. Summary of Evidence on Therapies for Localized Prostate Cancer (continued)

Key question	Quality of evidence	Summary, conclusion, comments
e. Trial 2. Conventional dose (68 Gy) compared with high-dose EBRT (78 Gy)	Medium	• Trial 1: Disease-specific survival: No significant reduction in PC deaths noted between groups. • Trial 1: Biochemical/clinical progression or recurrence: High-dose therapy was more effective in controlling biochemical failure than conventional dose. Superior effectiveness was evident in both low-risk disease (PSA <10 ng/ml, stage ≤T2a tumors, or Gleason ≤6) and high-risk disease. Trial 2: There was no benefit with the use of high-dose EBRT among low-risk subjects. Overall, freedom from failure significantly better in the high-dose group. • Trial 1: Adverse effects and toxicity: No differences between treatments in acute and late GU morbidity. Differences remained significant for late Grade 2 GI morbidity.
EBRT with ADT compared with EBRT alone	Medium	2 trials with an adequate method of allocation: • Trial 1: Overall mortality/survival: ADT + EBRT reduced all-cause mortality compared with EBRT alone after a median followup of 4.5 years. • Disease-specific mortality: ADT + EBRT reduced disease-specific mortality compared with EBRT alone. • Biochemical/clinical progression or recurrence: ADT + EBRT reduced PSA failure compared with EBRT. • Adverse effects and toxicity: ADT + EBRT resulted in more AEs, including gynecomastia and impotence, than EBRT alone. • Trial 2, T2 disease only—disease-specific survival: Difference in prostate cancer deaths was not significant with addition of 6 months ADT to EBRT vs. EBRT alone after a median followup of 5.9 years. • Biochemical/clinical progression or recurrence: EBRT + ADT reduced clinical failure at any site, biochemical failure, and death from any cause for subjects with T2c disease but not for T2b. • *Comment: Both trials were underpowered to detect survival differences*.
Shorter (3-months) EBRT with ADT compared with longer (8-months) EBRT with ADT	Low	1 trial (N=378) with an adequate method of allocation. The trial included T3 stage subjects (not included in findings below). • Biochemical/clinical progression or recurrence: The actuarial estimate of freedom from biochemical failure was lower for the 3-month group than the 8-month group among low-risk subjects (N=92, PSA <10 ng/ml, stage T1c to T2a tumors, Gleason ≤6) but not when including T3 subjects.
Brachytherapy: ^{125}I (144 Gy) compared with ^{103}Pd (125 Gy)	Low	1 trial (N=126) with an adequate method of allocation. • Biochemical/clinical progression or recurrence: Biochemical progression was similar for both treatments at 3 years. • Adverse effects and toxicity: No significant difference in radiation proctitis with ^{125}I vs. ^{103}Pd. • *Comment: Preliminary results, only 126 presented (of which 11 were excluded for this report) of a planned total of 600.*

Table B. Summary of Evidence on Therapies for Localized Prostate Cancer (continued)

Key question	Quality of evidence	Summary, conclusion, comments
Adjuvant EBRT combined with brachytherapy, comparison of different regimens	Medium	1 trial with an adequate method of allocation. • Biochemical/clinical progression or recurrence: No significant differences between 20 Gy and 44 Gy in the number of biochemical failure events and the actuarial estimates of freedom from biochemical progression at 3 years. No significant differences in freedom from biochemical progression based on pretreatment PSA levels (<10 ng/ml or >10 ng/ml).
Adjuvant bicalutamide vs. placebo; both treatment arms combined with standard care (RP/EBRT or WW)	Medium	Analysis of 3 RCTs with unclear methods of allocation. The report included T3 stage (not included in findings below). • Overall mortality/survival: At the median followup period of 5.4 years, there was no difference in total number of deaths between the bicalutamide and placebo groups for men receiving RP or EBRT. Among WW subjects, there were more deaths in bicalutamide than placebo group. • Biochemical/clinical progression or recurrence: The addition of bicalutamide to standard care did not reduce objective progression in T2 subjects at 5.4 years.
Vaccine vs. nilutamide	Low	1 very small study: Phase II trial in men with hormone refractory PC. • Overall mortality/survival: Vaccine may reduce overall mortality compared with nilutamide. Fewer overall deaths for vaccine group than nilutamide group. • Disease-specific survival: Vaccine may improve disease-specific survival compared with nilutamide. • Biochemical/clinical progression or recurrence: Vaccine reduces time to treatment failure compared with nilutamide. • Distant metastases: Twice as many metastases on scans for subjects initially treated with vaccine than subjects initially treated with nilutamide. • Adverse effects and toxicity: Both arms reported grade 2 and 3 toxicities – Nilutamide: dyspnea, fatigue, and hot flashes; Vaccine: arthralgia, fatigue, dyspnea, and cardiac ischemia. Grade 2 and 3 toxicities associated with aldesleukin (part of vaccine regimen) included fever, arthralgia, hyperglycemia, lymphopenia, dehydration/anorexia, and diarrhea. • *Comment: Very small trial that may not be applicable to men with clinically localized prostate cancer.*
B. Information from nonrandomized trials	Low to medium	• The variability in reporting of results, lack of controls, and likelihood that the results from case series contain results from multiple publications using identical or nearly identical populations limit data interpretation.
Comparative effectiveness of primary treatments	Low	• Overall and disease-specific mortality were infrequently reported. There was extremely wide variation within and between treatments, making estimates of outcomes difficult. More than 200 definitions of bNED (biological no evidence of disease) were used, with extremely wide and overlapping ranges of outcomes within and between treatments.

Table B. Summary of Evidence on Therapies for Localized Prostate Cancer (continued)

Key question	Quality of evidence	Summary, conclusion, comments
Adverse effects of primary treatments	Medium	• Adverse event definitions and severity varied widely. Baseline tumor and patient characteristics were usually reported, but outcomes were rarely stratified according to prognostic variables. It is not possible to accurately determine the relative adverse effects of treatments from these data. However, urinary dysfunction (especially incontinence) appeared to be more common with RP and bowel dysfunction with EBRT. Sexual dysfunction was common following all treatments. Impotence rates ranged from <5% to approximately 60% in the few studies reporting on men undergoing nerve-sparing RP. • Death within 30 days of RP is approximately 0.5% in Medicare recipients age 65 and over. Major cardiopulmonary complications occurred in 4% to 10%. 30-day mortality, major morbidity, and need for hospitalization appear higher with RP than for other interventions. Need for surgical repairs is 0.5% to 1%. • Population-based surveys of U.S Medicare-eligible men at 5 years following treatment: Urinary dysfunction, defined as no control or frequent leaking of urine, was more common with RP than EBRT. Bowel dysfunction was slightly lower in men receiving RP than EBRT, although the only significant difference was related to bowel urgency. Erection insufficient for intercourse occurred in three-quarters of men regardless of treatment. Adjusting for baseline factors, the odds of ED were greater with RP.
Bother and satisfaction with primary treatments	Medium	• Bother due to urine dripping or leaking was more than sixfold greater in RP than in EBRT after adjusting for baseline factors. Bother due to bowel dysfunction or sexual dysfunction was similar for RP and EBRT. Satisfaction with treatment was high, with <5% reporting dissatisfaction, unhappiness, or feeling terrible about treatment, although the highest percent was among those treated with RP.
Cryosurgery	Low	• No randomized trials evaluated cryosurgery. Overall or prostate-cancer-specific survival was not reported. Progression-free survival in patients with T1-T2 stages ranged from 39% to 100%. Adverse effects, when described, included bladder outlet obstruction (3%-29%), tissue sloughing (1%-26%), and impotence (40%-100%).
Laparoscopic and robotic assisted RP	Low	• No randomized trials evaluated laparoscopic and robotic assisted RP. 3 reviews from 21 nonrandomized trials and case series mostly originated from centers outside the United States. Laparoscopic RP had longer operative time but lower blood loss and improved wound healing vs. open retropubic RP. Reintervention rates were similar. For robotic assisted

Table B. Summary of Evidence on Therapies for Localized Prostate Cancer (continued)		
Key question	**Quality of evidence**	**Summary, conclusion, comments**
Laparoscopic and robotic assisted RP (continued)		laparoscopic RP, total complications, continence rates, positive surgical margins, and operative time were similar to RP. Median length of hospital stay and median length of catheterization were shorter after robotic assisted RP than open RP.
Primary androgen deprivation therapy	Low	• No randomized trials evaluated primary ADT. A previous AHRQ evidence report examined randomized trials of different methods of ADT for advanced prostate cancer. Survival after treatment with a luteinizing hormone-releasing hormone agonist was equivalent to survival after orchiectomy. The available LHRH agonists were equally effective, and no LHRH agonist was superior to others when adverse effects are considered.
	High	• Adverse effects of ADT include ED, loss of libido, breast tenderness, hot flashes, depression and mood changes, memory difficulties, fatigue, muscle and bone loss, and fractures.
High-intensity focused ultrasound	Low	• No randomized trials compared HIFU with other treatments. 2 case series found biochemical progression-free survival ranged from 66%-87%. • 2 studies found mild or moderate urinary incontinence occurred in 1.4%-18.6% of men, and the rate of urethral stenosis differed from 3.6%-27.1%. Impotence was reported by 2%-52.7% in 2 studies.
Proton beam radiation therapy	Low	• No randomized trials compared clinical outcomes after proton beam radiation therapy vs. other treatments. 1 systematic review of nonrandomized studies found no direct evidence of comparative effectiveness of protons vs. photons in men with prostate cancer. 2 nonrandomized clinical trials, Phase II and several case series from 1 center, reported clinical outcomes in patients with localized prostate cancer after combined proton and photon radiation therapy. 86%-97% of subjects were disease free at the end of followup, and 73%-88% did not have biochemical failure. Distant metastases were diagnosed in 2.5%-7.5% of men. Less than 1% had GI and urinary toxicity. Absolute rates of outcomes after proton radiation appear similar to other treatments.
Intensity modulated radiation therapy	Low	• No randomized trials compared clinical outcomes after IMRT vs. other treatments. Case series report similar biochemical-free survival after IMRT compared with conformal radiation. There was no difference in survival without relapse between IMRT and conformal radiation at 25-66 months followup. The rate of distant metastases was 1%-3% after IMRT in case series.

Table B. Summary of Evidence on Therapies for Localized Prostate Cancer (continued)		
Key question	**Quality of evidence**	**Summary, conclusion, comments**
Intensity modulated radiation therapy (continued)		• Acute GI and urinary toxicity were reported in case series. The percents of Grade 1 and 2 acute GI toxicity were 22% and 4%, respectively, and rectal bleeding, 1.6%-10%. Acute urinary toxicity, Grade 1, was detected in 37%-46% after different doses of IMRT. Percentages were 28%-31% for GU toxicity Grade 2. Absolute risk of late toxicity was <20%. • Case series data suggested that IMRT provides at least as good a radiation dose to the tumor with less radiation to the surrounding tissues (where radiation is undesirable) compared with conformal radiation. • Quality of life measures were comparable or better after IMRT vs. conformal radiation.
Key Question 2. How do specific patient characteristics affect the outcomes of therapies?		
Overall	Low	• Data were largely from observational studies. • Mostly based on case series data, with few studies reporting head-to-head comparisons and limited adjustment for confounding factors. • The most commonly reported patient characteristics used as stratifying factors for therapeutic outcomes were age and race/ethnicity.
Race/ethnicity	Low	• No RCTs reported head-to-head comparisons of treatment outcomes stratified by race/ethnicity. Baseline characteristics of populations varied across studies. • While there may be differences in the incidence and morbidity of prostate cancer across racial or ethnic groups, there is little evidence of substantial differences in the effects of treatment by racial or ethnic group. Reports of modest treatment differences in some studies have not been consistently reported in well-powered studies.
Age	Low	• 1 randomized trial evaluated survival with RP vs. WW according to age in men. Subgroup analysis indicated that overall and disease-specific survival benefits of RP when compared with WW were limited to men <65 years of age. Only 5% of enrollees had prostate cancer detected by PSA testing. • 3 observational studies reported results of multiple treatments on sexual function stratified by age group. 1 study compared RP, EBRT, and WW and found no evidence that the effects of the treatments on potency varied by age. 2 observational studies comparing patients with nerve-sparing vs. patients with partial or non-nerve-sparing RP lacked

Table B. Summary of Evidence on Therapies for Localized Prostate Cancer (continued)		
Key question	**Quality of evidence**	**Summary, conclusion, comments**
Age (continued)		adequate sample size and adjusted for baseline characteristics, making it impossible to draw robust conclusions. • While there are differences in the incidence and morbidity of prostate cancer based on patient age and there are differences in the treatments offered to men at different age ranges, few studies directly compare the treatment effects of different therapies across age groups. Practice patterns show RP is the most common treatment option in younger men with localized prostate cancer. However, in older men (>70), radiation therapy and WW become more commonly used treatment options. Differences in practice patterns appear to be based more on differences in preferences of patients and providers related to age, lifestyle, and life expectancy than regarding particular age-independent treatment benefits and side effects.
Key Question 3. How do provider/hospital characteristics affect outcomes?		
Physician specialty and preferences	Medium	• Surveys and large national administrative databases indicate that screening practices varied by physician specialty. • Clinicians were more likely to recommend procedures they performed for patients with the same tumor grades and PSA levels. • Several studies found differences in treatment and outcome based on whether the patient was seen in an HMO or fee-for-service organization and whether the patient was a Medicare beneficiary. • One survey and use of administrative data indicated that variability in use of ADT was more attributable to individual differences among urologists than tumor or patient characteristics.
Regional differences	Medium	• Physician availability, prostate cancer screening, incidence, and mortality varied in U.S. Census regions. The ratio of urologists and radiation oncologists per 100,000 adult citizens was highest in the Middle Atlantic and lowest in the West North, while the prevalence of PSA testing was higher in the South and lower in North East regions. Prostate cancer incidence was highest in the Middle Atlantic and lowest in the Mountain region. Incidence of localized prostate cancer did not differ by regions. The highest age-adjusted mortality was observed among African-American males in the South Atlantic and in the East South.

Table B. Summary of Evidence on Therapies for Localized Prostate Cancer (continued)		
Key question	**Quality of evidence**	**Summary, conclusion, comments**
Regional differences (continued)		• Treatment selection varied substantially among U.S. regions. The probability of receiving EBRT as primary treatment was the lowest in the Mountain region and highest in New England. Less than 11% of patients with localized prostate cancer received brachytherapy, with significant variations between the Middle Atlantic and West South. The lowest prevalence of primary ADT was in the Middle Atlantic, while the West South was highest. WW was most prevalent in the West, Mountain, and Pacific regions. Prevalence of RP was highest in the Mountain region and lowest in the Middle Atlantic. Age-adjusted rates of RP were lower than the national average in the North East and in New England. There was a consistent relative decrease in utilization of RP in the North East and increase in the West compared with the U.S. average.
Hospital volume/type	Medium	• Hospital volume was associated with patient outcomes. Pooled analysis showed a significant relative reduction in surgery-related mortality corresponding to the number of RPs performed annually in hospitals. The number of RPs performed annually in hospitals was associated with significant absolute reduction in complication rates. Patients operated on in hospitals with fewer procedures per year had increased use of adjuvant therapy compared with those treated in hospitals that performed more RPs per year. There was a decrease in length of stay in hospitals above vs. below the mean number of procedures. Hospital readmission rates were also estimated to be lower in hospitals with greater volume. • Teaching hospitals had a lower rate of surgery-related complications and higher scores of operative quality.
Surgeon volume	Medium	• Surgeon volume was not associated with surgery-related mortality and positive surgical margins. • Patients who were operated on by surgeons with higher RP volume experienced lower rates of complications. The relative risk of surgery-related complications adjusted for patient age, race, and comorbidity, and hospital type and location was lower in patients treated by higher volume surgeons (more than 40 vs. 40 or less surgeries per year). • The rate of late urinary complications and incontinence was lower for patients whose surgeons had higher RP volume. • The length of hospital stay was shorter in patients operated on by surgeons who performed more than 15 (4th quartile) vs. fewer than 3 surgeries (1st quartile) per year. • There were no data for volume and other forms of prostate cancer treatment

Table B. Summary of Evidence on Therapies for Localized Prostate Cancer (continued)

Key question	Quality of evidence	Summary, conclusion, comments
Key Question 4. How do tumor characteristics affect outcomes?		
Gleason score	High	• Higher Gleason histologic scores are associated with greater risk of prostate-cancer-related death and disease progression or recurrence, regardless of treatment.
	Medium	• The risk of prostate cancer death over 20 years in non-PSA-detected prostate cancer with Gleason score 2-4 managed with WW is less than 10%.
	Medium	• The risk of prostate cancer death over 10 years in non-PSA-detected prostate cancer with Gleason score 8-10 treated with WW is about 50%.
	Low	• The risk of overall or prostate cancer death over 10 years for PSA-detected prostate cancers according to Gleason histologic grade treated with WW is not adequately known.
	Low	• It is not possible to determine the relative effectiveness of treatments according to Gleason histologic score. Subset analysis from 1 randomized trial found that the relative effectiveness of RP vs. WW was not associated with Gleason score in men whose prostate cancer was detected by methods other than PSA testing.
PSA level	Medium	• The risk of prostate cancer death and disease progression or recurrence is associated with PSA levels and rate of PSA rise. • Evidence is not sufficient to accurately determine the relative effectiveness of treatments according to baseline PSA levels in men with PSA-detected disease. Subset analysis from 1 randomized trial found that the relative effectiveness of RP vs. WW was not associated with baseline PSA in men whose prostate cancer was detected by methods other than PSA testing.
Screen vs. nonscreen detected prostate cancer	Low	• There are no data on the relative effectiveness of treatment options according to screened vs. nonscreen detected prostate cancer.
	High	• The vast majority of men with newly diagnosed prostate cancer are asymptomatic and have clinically localized disease detected by PSA testing.
	High	• Screening with PSA testing detects more prostate cancer and cancers of smaller volume, earlier stage, and at an earlier time period in a man's life compared with digital rectal examination. PSA detects prostate cancer 5-15 years earlier than digital rectal exam.

Table B. Summary of Evidence on Therapies for Localized Prostate Cancer (continued)		
Key question	**Quality of evidence**	**Summary, conclusion, comments**
Screen vs. nonscreen detected prostate cancer (continued)	Low	• Subset analysis of 1 randomized trial found that the relative effectiveness of RP vs. WW for clinically localized prostate cancer did not vary by tumor stage.
Tumor volume	High	• Prostate cancer that has spread locally outside of the prostate gland or metastasizes may cause symptoms such as bone pain, edema, and/or hematuria. Prognosis in men with locally advanced or metastatic disease is not as good as for men with clinically localized disease, and treatment options used for localized prostate cancer (e.g., RP, brachytherapy, prostate-targeted EBRT) are often not feasible.
	High	• A risk classification incorporating Gleason histologic score, PSA level, and tumor stage is associated with the risk of disease progression or recurrence, regardless of treatment.

Abbreviations: ADT=androgen deprivation therapy; AE=adverse effect; EBRT=external beam radiotherapy; ED=erectile dysfunction; GI=gastrointestinal; GU=genitourinary; HIFU=high-intensity focused ultrasound; HMO=health maintenance organization; IMRT=intensity modulated radiation therapy; LHRH=luteinizing hormone-releasing hormone; PC=prostate cancer; PSA=prostate-specific antigen; RCT=randomized controlled trial; RP=radical prostatectomy; SPCG-4=Scandinavian Prostate Cancer Group Study 4; VACURG=Veterans Administration Cooperative Urological Research Group; WW=watchful waiting.

AHRQ Pub. No. 08-EHC010-1
February 2008