Comparative Effectiveness Review
Number 13

Comparative Effectiveness of Therapies for Clinically Localized Prostate Cancer

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Preface

The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to organize knowledge and make it available to inform decisions about health care. As part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Congress directed AHRQ to conduct and support research on the comparative outcomes, clinical effectiveness, and appropriateness of pharmaceuticals, devices, and health care services to meet the needs of Medicare, Medicaid, and the State Children's Health Insurance Program (SCHIP).

AHRQ has an established network of Evidence-based Practice Centers (EPCs) that produce Evidence Reports/Technology Assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care. The EPCs now lend their expertise to the Effective Health Care Program by conducting Comparative Effectiveness Reviews of medications, devices, and other relevant interventions, including strategies for how these items and services can best be organized, managed, and delivered.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strengths and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about systematic reviews, see http://effectivehealthcare.ahrq.gov/reference/purpose.cfm.

AHRQ expects that Comparative Effectiveness Reviews will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. In addition, AHRQ is committed to presenting information in different formats so that consumers who make decisions about their own and their family's health can benefit from the evidence.

Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input. Comparative Effectiveness Reviews will be updated regularly.

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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.

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

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.*
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).

Table B. Summary of evidence on therapies for localized prostate cancer (continued)

Key question	Quality of evidence	Summary, conclusion, comments
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 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.

Table B. Summary of evidence on therapies for localized prostate cancer (continued)

Key question	Quality of evidence	Summary, conclusion, comments
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. • 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.

Table B. Summary of evidence on therapies for localized prostate cancer (continued)

Key question	Quality of evidence	Summary, conclusion, comments
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 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.

Table B. Summary of evidence on therapies for localized prostate cancer (continued)

Key question	Quality of evidence	Summary, conclusion, comments
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. • 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.

Table B. Summary of evidence on therapies for localized prostate cancer (continued)

Key question	Quality of evidence	Summary, conclusion, comments
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 (4^{th} quartile) vs. fewer than 3 surgeries (1^{st} quartile) per year. • There were no data for volume and other forms of prostate cancer treatment
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.

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	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.
	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.

Introduction

Description of Condition

Prostate cancer is the most common nondermatologic cancer in men. In 2007 an estimated 218,890 men will be diagnosed with, and 27,050 deaths will be attributed to, prostate cancer in the United States. Approximately 90 percent of men have disease considered confined to the prostate gland (clinically localized disease). Prostate cancer incidence has increased coinciding with introduction of the 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.[1]

Autopsy studies indicate that the prevalence of subclinical prostate cancer is high at all ages: 30 percent for men ages 30-39 years and more than 75 percent for men older than 85 years.[2] Clinically-detected prostate cancer is primarily a disease of elderly men.[2] Many prostate cancers have a relatively protracted course if left untreated. Due largely to 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, many men die with, rather than from, prostate cancer. Considerable over detection and treatment may exist.

The primary goal of treatment is to target intervention to men most likely to need intervention in order to prevent prostate cancer death and disability while minimizing intervention-related complications. Common treatments include watchful waiting (expectant management), surgery to remove the prostate gland (radical prostatectomy), external beam radiotherapy, and interstitial radiotherapy (brachytherapy), freezing the prostate (cryotherapy), and androgen deprivation therapy (Table 1). Patient treatment decisions incorporate physician recommendations, estimated likelihood of cancer progression without treatment, as well as treatment-related convenience, costs, and potential for eradication and adverse effects.[3] Patient characteristics, including race/ethnicity, age, and comorbidities, have an important role in predicting mortality, the likelihood of urinary, bowel, and sexual dysfunction, and treatment selection. However, little is known about how these characteristics modify the effect of treatment.

Strategies for early detection of prostate cancer include the DRE and PSA blood testing. The DRE[4] has not been proven to improve morbidity or mortality. Sensitivity, specificity, and inter-examiner agreement with findings are poor. The DRE requires considerable experience to achieve the tactile sensitivity for detection of early tumors. More than half of subjects with DRE-detected cancer will have disease that has spread beyond the gland at diagnosis.[5]

Prior to the advent of widespread PSA testing, most prostate cancers were detected based on abnormalities on the DRE or incidentally from tissue obtained at surgery for treatment of symptoms due to benign prostatic obstruction. Prostate cancer can cause signs or symptoms due to local (hematuria, urinary obstruction), regional (edema), or metastatic progression (bone pain). However, the vast majority of newly diagnosed prostate cancers in the United States are asymptomatic and detected by elevated levels or rates of changes of PSA tests. Estimates for the lead time associated with PSA-detected tumors range from 5-15 years. Many tumors detected by

PSA testing are found serendipitously and may never cause signs or symptoms. The clinical significance, natural history, and comparative effectiveness of treatments, particularly in PSA-detected cancer, are not known.

In the United States, nearly three-quarters of men over age 50 have had at least one PSA test. PSA testing finds more cancers, shifts detection to tumors of lower stage, smaller volume, and at earlier time periods (stage, lead, and length shift) compared to DRE. Sensitivity and specificity of the PSA test vary with test thresholds of abnormality as well as factors such as family history, age, gland size, findings on DRE, and whether prior biopsies (negative) have been obtained.

The greatest factor leading to a diagnosis of prostate cancer is aggressive testing. The lifetime risk of prostate cancer diagnosis for men in their 50s in the United States was approximately 10 percent prior to widespread PSA testing. This nearly doubled to 19 percent during 2000-2002 with widespread PSA testing. With increasing regular and repeated PSA testing, lower PSA thresholds considered normal, and obtaining a greater numbers of core prostate specimens during biopsy, the lifetime risk of being diagnosed with prostate cancer is likely to exceed 20 percent. An individual's risk of both any prostate cancer and potentially aggressive cancers can be calculated using a risk assessment tool (http://www.compass.fhcrc.org/edrnnci/bin/calculator/main.asp) and may be useful for decisionmaking.[6]

Increased detection of localized disease has resulted in more frequent utilization of interventions that are potentially effective but have adverse effects, thus complicating treatment decisionmaking. This may be particularly problematic in men with a life expectancy <10-15 years due to age or comorbid conditions. For example, among men >75 years, almost half have received PSA screening, including those in poor health.[7] The likelihood of detecting clinically insignificant disease in men over age 75, based on histopathologic criteria, has been estimated to be 56 percent.[8]

Despite widespread testing, there is no conclusive evidence that screening improves morbidity or mortality. Prostate cancer screening is associated with AEs, including anxiety related to abnormal results, pain, infection, and bleeding due to diagnostic prostate biopsies, and detection/treatment of prostate cancers unlikely to cause health problems.[9-11] While prostate cancer mortality rates have been declining in several countries and some age groups, it is not clear if this is due to increased PSA testing.

Pretreatment assessment of whether prostate cancer is localized is determined by tumor stage based on clinical examination; primarily the DRE. Prostate cancer believed confined to the prostate gland (T1-T2, NxM0 or Stage 1-2) is considered “clinically localized,” forms the foundation for treatment decisionmaking, and is the focus of this report. T1 tumors include those with a normal DRE (typically detected by abnormalities of PSA tests but also diagnosed on histopathology from specimens obtained during surgical prostate resection for treatment of benign prostate conditions). T1a and T1b are defined as incidental histologic findings of less than and greater than 5 percent of tissue resected during transurethral resection of the prostate (TURP), respectively. T1c is noted as a nonpalpable tumor identified due to an elevated PSA. T2 stage is described as an abnormal DRE but no evidence of disease spread beyond the prostate. T2a involves a tumor in up to one-half of a lobe, T2b involves more than one-half but is limited to one lobe, and T2c is a tumor in both lobes. Additional tests, including x-rays, bone scans,

computerized tomography (CT), or magnetic resonance imaging (MRI) are of limited use and not typically performed.

Because of limited sensitivity of pretreatment evaluations, some men with clinically localized disease may have disease that has spread outside of the gland (i.e., pathologically nonlocalized). The risk of pathologically nonlocalized disease is associated with several pretreatment classification factors. Classification includes measures of tumor volume/extent determined by tumor stage, number of biopsy cores with cancer, and extent of cancer in the involved core(s). The primary measure of aggressiveness is the Gleason histologic score. Gleason scores range from 2-10. Gleason 8-10 tumors are considered the most aggressive, Gleason 7 tumors somewhat less, and Gleason ≤6 tumors potentially indolent.[12]

Pretreatment histology is determined based on a pathologist's examination of several small cores of prostate tissue. Typically, six cores are obtained during a prostate biopsy (sextant biopsy that includes both lobes of the prostate). However, the number has increased over time to 12, 24, and even "saturation techniques." This has led to an increasing amount of prostate glands sampled with enhancement in the likelihood of detecting even small volume disease. In addition to the histologic score, the number of biopsy cores that contain prostate cancer and the percent within each core containing tumor is recorded. Risk stratification strategies have incorporated PSA level, biopsy Gleason score, and clinical tumor category because these appear to be associated with risk of PSA failure and prostate cancer-specific mortality. Readily available tables have been designed to help men and their doctors predict the definitive pathological stage (determined after surgery, when a pathologist examines the removed prostate for the presence of cancer) and are often used in treatment decisionmaking.[13] Because Gleason score, tumor volume, and PSA levels do not appear to be complete indicators of an individual tumor risk characteristic, efforts are underway to identify more reliable prognostic factors.

One risk classification currently recommended is:

Low Risk: PSA ≤10 ng/ml, Gleason score ≤6, and clinical stage T1c or T2a
Intermediate Risk: 10 <PSA ≤20 ng/ml, or Gleason score 7, or clinical stage T2b
High Risk: PSA >20 ng/ml or Gleason score 8-10 or clinical stage T2c

The most common Gleason score is 6 or 7 disease.[14,15] Most men diagnosed with prostate cancer have a PSA between 4 and 10 ng/ml; increasingly between 2.5 and 4.0 ng/ml. Therefore, the average man currently diagnosed with prostate cancer and facing uncertainty about the comparative risks, benefits, and outcomes of treatment decisions is between 60 and 70 years of age and has "low-risk" disease. However, changes in the application of the Gleason scoring has resulted in contemporary uropathologists assigning these grades more commonly than in the past when these tumors were more likely to receive a grade one or two scores lower.[14,15] A resultant improved survival relative to historical controls assigned similar scores has been reported. As thresholds to define PSA abnormalities are lowered and a greater number of prostate cores obtained at biopsy, an individual diagnosed with prostate cancer in the future is likely to have a lower PSA level, smaller tumor volume, and better long-term natural tumor history.

Factors incorporated into the decision process include cancer eradication, adverse effects, physician recommendations, convenience, and costs. Patient characteristics, including age, race,

family history, and comorbidities have an important role in predicting the mortality rate of a patient with localized prostate cancer and the likelihood of urinary, bowel, and sexual dysfunction. Little is known regarding how patient characteristics modify the effect of treatment.

Provider/hospital characteristics may affect number and type of detected tumors, patient characteristics, treatment selection, and outcomes. The effect of provider volumes on clinical outcomes in men with localized prostate cancer is not well established. Evidence suggests that provider characteristics, including higher volume,[16] affiliation with academic center,[17,18] and profit status[18,19] are associated with improved quality of care and better outcomes. The association can be partially explained by patient selection, aging and comorbidities, and differences in process of care.[20] One study found substantial differences in published definitions of volume categories and its effects on surgical mortality and complications after urological cancer procedures.[21] Volume thresholds and patient distributions in low and high volume hospitals are defined for several cardiovascular and oncology operations, but not for prostate cancer.[22] The effect size of provider volumes on clinical outcomes in patients with localized prostate cancer is not well established. Because prostate cancer is the second most expensive cancer organ site for Medicare with approximately $8 billion annual expenditure,[23] improved understanding of the role of provider/hospital characteristics is important.

Specialty and geographical location of providers influence diagnostic strategies and the management of localized prostate cancer.[24-26] Variability in the management of localized prostate cancer is often based on physician opinions and specialty.[25,26] Diagnosis of localized disease is based primarily on screening of asymptomatic patients. Therefore, differences in screening practices lead to length bias in the stage of tumors detected and referral onward to more likely recommend intervention. Physician recommendations play an important role in patient decisions on treatment preferences.[27] A systematic review of treatment choices for localized prostate cancer concluded that variations in treatment decisions are attributable to differences in physician recommendations more than on patient and tumor characteristics.[3] Recent studies showed that patient and physicians treatment preferences reflect perceived personal factors more than evidence-based recommendations.[3,28]

Scope and Key Questions

This report was conducted for the Agency for Healthcare Research and Quality (AHRQ) under Section 1013 of the Medicare Modernization Act to address the following questions:

1. What are the comparative risks, benefits, short- and long-term outcomes of the following therapies for clinically localized prostate cancer?
    a. Radical prostatectomy, including perineal and retropubic approaches, and open vs. laparoscopic vs. no lymphadenectomy
    b. External beam radiotherapy, including standard therapy, and therapies designed to decrease exposure to normal tissues such as 3D conformal radiation therapy and Intensity Modulated Radiation Therapy
    c. Interstitial brachytherapy
    d. Cryosurgery
    e. Expectant management ("watchful waiting")
    f. Hormonal therapy as primary therapy, adjuvant or neoadjuvant to other therapies

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, and PSA levels, affect the outcomes of these therapies, overall and differentially?
5. What are the gaps in our knowledge that would allow patients to better understand the comparative risks, benefits, and outcomes of these treatment options for clinically localized prostate cancer, including for those with and without screen-detected disease?

Table 1. Treatment options for clinically localized prostate cancer

Treatment Option	Treatment Description	Potential Benefits	Potential Risks
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 laparascopically or with robotic assistance and attempt to preserve nerves for erectile function.	May eliminate cancer; generally well tolerated. 1 RCT showed improved overall, prostate cancer survival and metastasis vs. surveillance.	Hospitalization for major surgery; operative-related death, peri-operative cardiovascular complications and bleeding. May not eradicate cancer. Long-term urinary incontinence, urethral stricture, bladder neck contracture, erectile dysfunction.
External-beam radiation (EBRT)	Multiple doses of radiation from an external source applied over several weeks. Dose and physical characteristics of beam may vary. Conformal radiotherapy uses 3 dimensional planning systems to maximize dose to prostate cancer and attempt to spare normal tissue.	May eliminate cancer; generally well tolerated, and avoids operative risk.	Does not remove prostate gland and may not eradicate cancer; 6-8 weeks of outpatient therapy; treatment related death, incontinence, proctitis, cystitis, impotence, urethral stricture, bladder neck contracture, bleeding. Not indicated in men with inflammatory bowel disease because of risk of bowel injury.
	Intensity modulated radiation therapy (IMRT) provides the precise adjusted dose of radiation to target organs with less irradiation of healthy tissues compared to conformal radiation therapy (moderate quality of evidence).	Absolute risk of clinical outcomes, toxicity, and quality of life after IMRT may be comparable to conformal radiation.	Does not remove prostate gland and may not eradicate cancer; 6-8 weeks of outpatient therapy; treatment related death, incontinence, proctitis, cystitis, impotence, urethral stricture, bladder neck contracture, bleeding. No long-term randomized trials comparing IMRT with EBRT or other primary therapies. Accurate absolute risks and benefits not well established.
	Proton radiation therapy is a form of EBRT in which protons rather than photons are directed in a conformal fashion to a tumor site. May be used alone or in combination with proton and photon-beam radiation therapy.	Heavier single proton beam allows low entrance dose, maximal dose at tumor location with no exit dose. May permit improved dose-distribution (delivering higher dose to the tumor with lower dose to normal tissue).	Does not remove prostate gland and may not eradicate cancer; 6-8 weeks of outpatient therapy; treatment related death, incontinence, proctitis, cystitis, impotence, urethral stricture, bladder neck contracture, bleeding. No long-term randomized trials comparing proton beam with other forms of EBRT or other primary therapies. Accurate absolute risks and benefits not well established.
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.	May eliminate cancer; generally well tolerated; avoids operative risk; single outpatient session	Does not remove prostate gland and may not eradicate cancer. May not be effective for larger prostate glands or more aggressive tumors; urinary retention, incontinence, impotence, cystitis/urethritis, proctitis; long-term outcomes from representative national sample not reported. Not indicated in patients with prior TURP.
Cryoablation	Destruction of cells through rapid freezing and thawing using transrectal guided placement of probes and injection of freezing/thawing gases.	May eliminate cancer; generally well tolerated; avoids operative risk; single outpatient session	Does not remove prostate gland and may not eradicate cancer; impotence, incontinence, scrotal edema, pelvic pain; sloughed urethral tissue; prostatic abscess; urethrorectal fistula. No long-term outcomes from national sample.

Table 1. Treatment options for clinically localized prostate cancer (continued)

Treatment Option	Treatment Description	Potential Benefits	Potential Risks
Androgen deprivation therapy	Oral or injection medications or surgical removal of testicles to lower or block circulating androgens.	Avoids risks of RP and EBRT. Usually lowers PSA levels and may slow cancer progression.	Gynecomastia, impotence, diarrhea, osteoporosis, lost libido, hot flashes, "androgen deprivation syndrome" (i.e., depression, memory difficulties, fatigue)
Watchful waiting (active surveillance)	Active plan to postpone intervention. May involve monitoring with DRE/PSA and repeat prostate biopsy with further therapy (either "curative or palliative") based on patient preference, symptoms and/or clinical findings.	No immediate side effects or complications; low initial cost; most men do not need therapy and survive at least 10 years.	Cancer could advance, become incurable, and cause death; patient's quality of life could be painfully restricted before he dies; additional treatments may be necessary, not effective, and have side effects. Patients may be too anxious or worried to monitor cancer without treatment.
Laparoscopic (LRP) and Robotic Assisted Radical Prostatectomy (RLRP)	Video-assisted, minimally invasive surgical method to remove the prostate.	May result in fewer complications, especially intraoperative blood loss, and quicker recovery time than conventional open radical prostatectomy.	Same complications associated with RP. LRP and RLRP may not be applicable to all patients (e.g., those with large prostate glands), and requires a learning curve for proficiency as well as purchase of laparoscopic and robotic surgical systems. Long-term effectiveness to prevent disease progression and/or death is not known.
High-intensity focused ultrasound therapy (HIFU)	High-intensity focused ultrasound therapy has been used for a primary therapy in patients with localized prostate cancer not suitable for radical prostatectomy. Tissue ablation of the prostate is achieved by intense heat focusing on the identified cancerous area.	May result in fewer complications, especially intraoperative blood loss, and quicker recovery time than other interventions. Only the targeted area is exposed to the lethal heat.	Does not remove prostate gland and may not eradicate cancer. Common complications include urinary obstruction and sloughing of prostate tissue out through the urine. Risk of infection. No long term comparative data regarding disease specific outcomes including disease progression and mortality.

Methods

Topic Development

The topic of this report and preliminary key questions were developed through a public process involving the public, the Scientific Resource Center (www.effectivehealthcare.ahrq.gov/aboutUS/contract.cfm) for the Effective Health Care program of AHRQ, and various stakeholder groups. Additional study, patient, intervention, and eligibility criteria, as well as outcomes, were refined and agreed upon through discussions between the Minnesota EPC, the Technical Expert Panel (TEP) members, our AHRQ Task Order Officer, and comments received by the public.

Literature Search and Review Strategy

To address questions 1, 2, and 4 we relied on several sources of data. First randomized controlled trials published through mid-September 2007 were identified using the Cochrane Library and the Cochrane Review Group in Prostate Diseases specialized registry. For health status and quality of life studies, a literature search was conducted on Ovid MEDLINE, using the search terms *prostatic neoplasms*, *quality of life*, *QOL*, *HRQOL*, and *health status*. The search was limited to English language randomized trials or large prospective U.S. observational studies published from 2000 to September 2007.

Because our search of RCTs yielded very few trials directly comparing the major treatment options, especially for PSA-detected prostate cancer, we reanalyzed results from a database primarily comprised of nonrandomized studies and previously extracted by our group (TJ Wilt principal contract recipient) under a separate prior contract with AUA for the American Urological Association Treatment Guidelines Panel for Clinically Localized Prostate Cancer. These data were used for development of the "Guidelines for the Management of Clinically Localized Prostate Cancer: 2007 update"[29] and subsequently provided to us as a raw database under a separate contract for additional analysis for this comparative effectiveness review. Studies were identified by the AUA by a series of four PubMed searches conducted by the AUA Guideline Panel between May 2001 and April 2004. This search captured articles published from 1991 through April 2004. Articles identified by the AUA search team and deemed eligible for the AUA Prostate Cancer Guideline were sent to the Minnesota EPC research team for additional evaluation, determination of eligibility, and study extraction. Articles were rejected if patients with higher stage disease were included in the study and the outcomes were not stratified by stage. The 592 articles meeting these inclusion criteria were retrieved for data extraction. An extraction form was developed that included patient characteristics, treatments, and outcomes data, such as the definition of biochemical progression used in the study, survival, disease-free survival, and progression to invasive disease. During the extraction process, articles again were scanned for relevance and were rejected if outcomes were not reported or stratified for clinically localized disease or if outcomes in fewer than 50 patients were reported. Upon completion, which included several quality assurance checks, data from 592 articles were extracted and entered into a Microsoft. Access© (Microsoft, Redmond, WA) database. Articles of cryotherapy, laparoscopic or robotic assisted prostatectomy, HIFU, proton beam radiation, and IMRT with or without imaging guidance, identified through Medline, contact with Endocare (a manufacturer of

cryotherapy devices) and published between April 2004 and September 2007 were included because little published literature on these technologies was available for the AUA Guideline.

Questions 2 and 4 were addressed by reviewing RCTs for comparative effectiveness according to patient (age, race, comorbidities) or tumor characteristics (PSA, tumor stage, histologic grade, tumor risk strata). Any study from the AUA database or U.S. population-based studies that had outcomes stratified according to age or race was extracted, looking for comparative effectiveness between treatments according to these factors (rather than absolute effectiveness of an individual treatment). Due to the initial findings by the AUA Treatment Guideline Panel indicating poor methodologic design quality and reporting of outcomes from nonrandomized trials, our TEP members determined that an updated search for additional high quality evidence or inclusion of nonrandomized studies published after April 2004, was not indicated and would be biased in evaluating comparative effectiveness. They unanimously recommended against such an update. An updated case series assessing long-term outcomes of men in the United States managed with expectant management was included because little is known about the natural history of prostate cancer, especially stratified by patient's age and Gleason score.

Several strategies were used to assess the comparative effectiveness of treatments according to provider characteristics. The ideal method would be to analyze RCT evidence that examined how provider characteristics modified the effectiveness of different treatments. Because no randomized trials were found, we reviewed the evidence of heterogeneity in outcomes in multi center studies and possible subgroup analysis by provider characteristics. The third possible strategy was to review absolute risks of outcomes in different studies in relation to self-reported provider characteristics for possible comparisons across the studies. We excluded reports that only assessed self-reported provider volumes, training, the affiliation with medical schools, experience, and other characteristics. Search terms included MESH major headings of prostate cancer and prostatic neoplasm and were limited to human subjects and English language.

For question 3, the following databases were searched to identify reports of human studies published in English from 1992 to August 2006 (for volume outcome relationships we searched through September 2007): The National Library of Medicine via PubMed®; Cochrane Library; CDC Website; Catalog of U.S. Government Publications (U.S. GPO); LexisNexis™ Government Periodicals Index; and Digital Dissertations. The MeSH terms, key words, and its combinations are presented in Appendix A. The Analytic Framework (Figure 1) outlines the hypothesized relationships between the **exposures (bold)**, ***outcomes (italic bold)***, and <u>effect modifiers (underlined)</u> variables.

Study Selection

Criteria for Selecting Studies for This Review (Table 2)

Types of studies. For questions 1, 2, and 4 randomized trials were included if the randomized treatment allocation was based on men with clinically localized disease and reported clinical outcomes separately for T1 and T2 disease. Since no randomized trials investigated the role of patient race or ethnicity on the efficacy and AEs associated with localized prostate cancer and its treatment, we were left with only observational studies. Studies from the AUA database that had

outcomes stratified according to age, race, PSA, stage, or histology were extracted looking for comparative effectiveness between treatments according to these factors, (rather then absolute effectiveness of an individual treatment). We also included population based studies published through March 2007 evaluating watchful waiting for T1-T2 disease and containing at least 100 men because little is known about the natural history of prostate cancer. We included studies of treatment effectiveness, harms, and patient satisifaction from the Prostate Cancer Outcomes Study (PCOS) cohort study or the National Cancer Institutes Surveillance, Epidemiology, and End Results (SEER) program published through September 2007 because these were large, nationally representative studies that enrolled a high percentage of Medicare eligible men. Confounding from observational studies is a concern since observed differences in health status across and within racial or ethnic groups is likely due to a complex interaction of numerous factors, most of which are unmeasured and therefore impossible to control for statistically. For question 3 we included studies that examined the effect of provider characteristics on probability to be diagnosed and treated with different procedures. We also examined differences in outcomes after RP, the most common treatment for localized prostate cancer (and one in which volume was most likely to have an impact), in association with provider location, volume, and affiliations with academic centers. Eligible studies were administrative reports that measured outcomes in different locations, administrative surveys that measured physician distribution in regions of the United States, and epidemiologic studies that evaluated the association between provider characteristics and patient outcomes and had a control group. Inclusion criteria for the meta-analysis were as follows: studies reporting outcome rates by surgeon and hospital volume categories or relative risk of outcomes between groups with different surgeon and hospital volumes and studies with reported outcomes rates in different locations in the United States.

Articles were excluded if men with disease stage higher than clinical T1 or T2 were enrolled and outcomes were not stratified by stage. Studies were excluded if they were not published in English. We included nonrandomized studies of cryotherapy, IMRT, laparoscopic, or robotic prostatectomy, and HIFU that described men with T3/T4 disease because there is little known about outcomes associated with these treatments, commonly used for T1/T2 patients. Because of their recent introduction into clinical research and practice, these technologies are not addressed in the recent AUA clinical guideline.[29] For question 3 we excluded studies if the target population was outpatients or patients in long-term care facilities, there was no information regarding provider characteristics, or if there were administrative reports and single hospital studies with no control comparisons that did not test an associative hypothesis.

Types of participants. Men considered to have clinically localized prostate cancer (T1-T2, N0-X, M0-X) regardless of age, histologic grade or PSA level.

Types of interventions. For questions 1, 2, and 4 we included treatment options frequently utilized for men with clinically localized prostate cancer: RP (including laparoscopic or robotic assisted); WW, EBRT (including intensity modulated radiation, conformal radiation, photon beam), brachytherapy; ADT; HIFU, and cryotherapy.

From the AUA database, seven treatment categories, with 19 predefined treatments and the option of describing others that fit into each category, were identified. Four main categories were selected: prostatectomy (P), external beam radiotherapy, brachytherapy, and watchful waiting.

Prostatectomy was broken down into radical prostatectomy and nerve-sparing prostatectomy (NSP); and EBRT was divided into EBRT and conformal EBRT. If a second treatment, such as hormone therapy, was used, that group was excluded. Data from randomized trials were also broadly categorized into these treatment options. Within category comparisons (e.g., different doses or methods of EBRT) are described in the broader categories. Emerging technologies were also evaluated based on discussion with TEP members, or internal content experts and feedback from peer reviewers (Appendix B). These included: IMRT, proton beam radiation, cryotherapy, HIFU, and laparoscopic or robot assisted RP.

Types of outcomes measures. The primary outcome for questions 1, 2 and 4 was overall survival. Additional outcomes include prostate cancer-specific survival, biochemical (PSA) metastatic and/or clinical progression free survival, health status, and quality of life. Adverse effects focused on common and severe AEs including bowel, bladder, and sexual dysfunction.

Assessment of the methodological quality of the studies. For question 3, assessment of study quality was based on the "Systems to Rate the Strength of Scientific Evidence scored from 0 (poorest) to 5 (highest).[30] Summated scores were used to establish study quality. The quality of evidence was estimated using U.S. Preventive Services Task Force criteria [31] and the AHRQ scale.

Data Extraction

Study, patient, tumor, and intervention characteristics as well as predefined outcomes were extracted by two researchers onto standardized forms. Standard errors, regression coefficients, and 95 percent CI were calculated from reported means, standard deviations, and sample size when provided/appropriate.[32] Decisions of study eligibility were made with no relation to authors and institutions.[33]

Assessment of Risk of Bias

For Questions 1, 2, and 4 we assessed the risk of bias for the RCTs by evaluating several variables: 1) was there adequate allocation concealment during randomization, 2) were data analyzed based on the intention-to-treat-principle, and 3) did the trials have adequate length of followup and number of dropouts or lost to followup. The findings from RCTs were supplemented by the AUA Clinical Guideline Panel for Treatment of Clinically Localized Prostate Cancer database. This work is based on data extracted from 436 articles, primarily case series (over 80 percent), published between 1991 and April 2004. The potential for bias is considerable. The variability in reporting of results, lack of controls, and likelihood that the database contains results from multiple publications using identical or nearly identical populations limits data interpretation. For Question 3 we assessed the risk of bias by evaluating the adjustment for confounding patient and provider characteristics in observational studies. We conducted sensitivity analysis to estimate the differences in provider volume effect in studies with different adjustment strategies.

Applicability Assessment

Applicability of the population was estimated by evaluating the selection of the subjects in observational studies and clinical trials. Large observational cohorts based on the national registries and nationally representative administrative and clinical databases had high applicability. We conducted sensitivity analysis to examine the differences in provider volume effects in the studies that selected subjects from administrative and clinical databases and that reported random and convenience sampling of participants. Applicability of the intervention duration was high for the studies with followup more than 1 year and low for the studies with followup 6-12 months. No formal applicability assessment was conducted. To assess patients, treatments and outcomes most relevant to patients currently diagnosed with prostate cancer in the U.S. during the PSA era, we evaluated whether enrolled subjects were primarily detected by PSA testing. Health status and quality of life studies from nonrandomized studies were included if they were population based and in particular focused on Medicare eligible men. Based on knowledge from members of our Minnesota EPC, TEP members, and outside peer commentary, we focused on treatments most commonly used for early stage prostate cancer or emerging technologies. Outcomes of interest were selected based on similar feedback so as to be most relevant to clinicians and patients.

Data Synthesis

Due to differences in study designs, treatments tested, patient and tumor characteristics, and reporting of outcomes, we did not conduct pooled analysis for questions 1, 2, and 4. Summaries of effectiveness and AE outcomes with ranges according to treatment option, tumor characteristics, and group sample size are provided. Results are provided separately for randomized trials and nonrandomized studies.

For the AUA database, Minnesota EPC reviewers subsequently divided patients into groups for which the article provided data. For example, disease stage, PSA and Gleason scores, risk categories, and race were used to define groups. Within each group there were sometimes multiple subgroups. It was possible for subgroups to overlap. For the included graphs, each point represents an article/group combination. Some articles may have multiple points for any given time period or treatment. Due to the overlap between subgroups, the most inclusive groups available for each article were selected. When multiple subgroups overlapped, the total patients in the parent group along with subgroup definitions were used to select which subgroups would be used in the graphs. Gleason score was used for some of the graphs, so when a more inclusive definition was not available and Gleason score was used to define subgroups for an article, we tried to use those subgroups rather than subgroups defined by tumor characteristic or PSA, for example. Our primary goal was to assess the comparative effectiveness and adverse effects of the major treatment options for men with clinically localized prostate cancer overall and according to clinically relevant patient and tumor characteristics including: age (< vs. ≥65 years), race (White, Black, Hispanic, other), tumor stage (T1c [PSA detected] vs. other), PSA levels (≤4.0; 4.1-9.9; 10-19.9; ≥20.0 ng/ml), and Gleason histologic scores (2-4, 5-6, 7, and 8-10).

For question 3 the impact of the provider/hospital characteristics on clinical outcomes was estimated analyzing published evidence of the associations. Since no randomized trials were

identified, observational studies were used to calculate the associations between outcomes and provider/hospital characteristics; both crude estimates and estimates adjusted for confounding factors. Relative risks of the outcomes among different providers/hospitals were analyzed.

The results of individual studies were summarized with relation to sample size and 95 percent CI. Weighted by the sample size (number of patients and hospitals) odds ratios and 95 percent CI were calculated with fixed and random effects models.[34] The results from random effects models are included in the report. The likelihood-based approach to general linear mixed models was used to analyze the association between independent variables and outcomes with the basic assumption that the data are linearly related to unobserved multivariate normal random variables.[35] Meta-regression models analyzed possible interactions with the year of data collection, databases to measure outcomes, and adjustment for confounding factors.[36,37] The calculations were performed using STATA[38] and SAS 9.2 packages, Proc Mixed.[35]

Consistency in the results was tested comparing the direction and strength of association in models with provider variables as continuous (overall trend) and categorical, in studies reporting outcome rates and adjusted relative risk, and with goodness of fit analysis. Chi squared tests were obtained to assess heterogeneity in study results.[36]

Rating the Strength of the Body of Evidence

We rated the strength of the available evidence via a three-point scale (High, Medium, Low). High indicated consistent results from at least two high-quality studies with long-term followup. Medium included data from fewer then two high quality studies or studies that did not have long-term followup. Low confidence was from inconsistent results or studies of low quality or from populations with little relevance to current patients/practice.

Figure 1. Analytic framework for Key Question 3

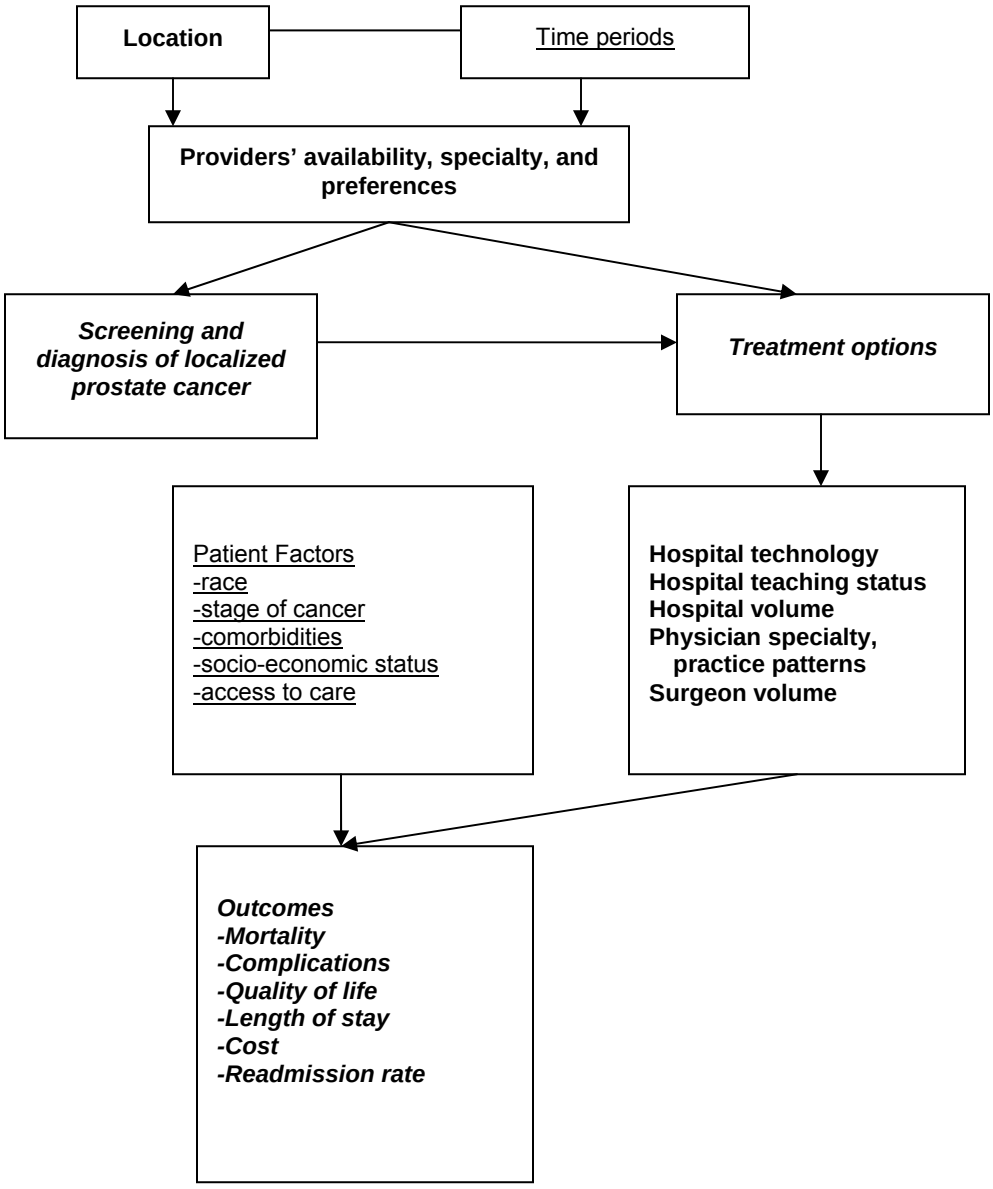


Table 2. Study inclusion criteria* for the key questions

Question components	Inclusion criteria
Key Question 1. What are the comparative risks, benefits, short- and long-term outcomes of therapies for clinically localized prostate cancer?	
Major treatment options (radical prostatectomy; external beam radiotherapy, watchful waiting, brachytherapy, primary androgen deprivation)	RCTs that enrolled patients with clinically localized disease and reported clinical outcomes. Trials enrolling subjects with T3/T4 PCA had to provide separate analyses for subjects with localized disease only. Randomized trials were excluded if treatment assignments were based on pathologic staging, even though patients had clinically localized disease.
Emerging technologies (cryotherapy, high-intensity focused ultrasound therapy, intensity modulated radiation therapy, laparoscopic and robot assisted radical prostatectomy)	Systematic reviews, nonrandomized studies (case series) that included more than 50 patients with localized prostate cancer and reported clinical outcomes and contact with manufacturers (Endocare, a manufacturer of cryotherapy devices).
Adverse effects	Randomized controlled trials, epidemiologic surveys (e.g., Prostate Cancer Outcomes Study), and nonrandomized study data from the AUA Guideline report.
Quality of life	RCTs or prospective, longitudinal survey studies with 100 or more patients per treatment arm with localized prostate cancer, QOL outcomes measured by a standardized survey instrument, and study duration of at least 1 year. CaPSURE (a national disease registry of more than 10,000 men with prostate cancer accrued at 31 sites across the United States) was excluded because the authors noted the sites were not chosen at random and were thus assumed to *not* represent a statistically valid sample of U.S. practice patterns.
Key Question 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?	
Question components	Inclusion criteria
Effectiveness results according to patient (age, race, comorbidities) or tumor characteristics (PSA, tumor stage, histologic grade, tumor risk strata).	Randomized controlled trials, systematic reviews, or observational studies published in English from the AUA database or population-based studies (PCOS) that had outcomes stratified according to age, race or comorbidities were extracted looking for comparative effectiveness between treatments according to these factors.
Key Question 3. How do provider/hospital characteristics affect outcomes overall and differentially (e.g., geographic region and volume)?	
Question components	Inclusion criteria
Association between provider specialty and: 1) prostate cancer screening and diagnosis; 2) prostate cancer management Association between physician characteristics and patient outcomes How does geographic region affect outcomes? How does hospital and provider volume affect outcomes?	Administrative reports that measured outcomes in different locations, administrative surveys that measured physician distribution in regions of the United States, and epidemiologic studies that evaluated the association between provider characteristics and patient outcomes and had a control group. Inclusion criteria for the meta-analysis were as follows: studies reporting outcome rates by surgeon and hospital volume categories or relative risk of outcomes between groups with different surgeon and hospital volumes, and studies with reported outcomes rates in different locations in the United States. Studies were excluded if the population was outpatients or patients in long-term care facilities, there was no information regarding provider characteristics, or were administrative reports and single hospital studies with no control comparisons that did not test an associative hypothesis.

Table 2. Study inclusion criteria* for the key questions (continued)

Key Question 4. How do tumor characteristics, e.g., Gleason score, tumor volume, screen vs. clinically detected tumors, PSA levels, affect the outcomes of these therapies, overall and differentially?	
Question components	Inclusion criteria
Effectiveness results according to tumor characteristics (PSA, tumor stage, histologic grade, tumor risk strata)	Randomized trials for any comparative and any study from the AUA database or population based studies (PCOS) that had outcomes stratified according to tumor characteristics was extracted that examined comparative effectiveness between treatments according to these factors.

* Studies published in English only

Results

Key Question 1: What are the comparative risks, benefits, short- and long-term outcomes of therapies for clinically localized prostate cancer?

The main treatment options for clinically localized prostate cancer are identified in the full version of the key question and briefly described in Table 1.

The literature search identified 13,888 citations that were retrieved and reviewed. Of these, 1,764 (13 percent) met initial inclusion criteria for extraction. Further review yielded 592 articles that were extracted with 436 meeting full inclusion criteria and fully extracted. Among the 436 extracted articles, 352 (81 percent) were case series. Only 28 (6 percent) were controlled trials.

Two randomized trials were excluded because the treatment assignments were based on pathologic staging, even though patients had clinically localized disease.[39,40] The trial by Thompson and colleagues evaluated radiotherapy adjuvant to radical prostatectomy for pathologically advanced prostate cancer (pT3N0M0) while the Messing trial assessed immediate ADT compared to observation after radical prostatectomy and pelvic lymphadenectomy in men with node-positive prostate cancer (pT1-2,N+, M0). An additional RCT by Fransson[41] comparing EBRT vs. deferred therapy was only included in the quality of life data because no further description of deferred therapy or study protocol were available, despite contacting the senior author.

For health status and quality of life studies, 494 references were screened to exclude articles that did not meet the following inclusion criteria: localized prostate cancer; quality of life (QOL) outcomes measured by a standardized survey instrument; study duration of at least 1 year; and randomized controlled trials, or prospective, longitudinal survey studies with 100 or more patients per treatment arm. This screening resulted in the inclusion for data extraction of 11 references describing eight studies (Appendix C, Figure C1). The Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) (a national disease registry of more than 10,000 men with prostate cancer accrued at 31 sites across the United States) was excluded because the authors noted: "the sites were not chosen at random and thus they cannot be assumed to represent a statistically valid sample of U.S. practice patterns…only diagnostic and therapeutic interventions ordered or coordinated by participating urologists are recorded…"[42] (The list of excluded studies is presented in Appendix D, sample abstraction forms are in Appendix E, and Appendix F lists definitions of outcomes.)

Overview of Studies

No one therapy can be considered the most effective treatment for localized prostate cancer due to limitations in the body of evidence. Even if differences in therapeutic effectiveness exist, differences in AEs, convenience, and costs are likely to be important factors in individual patient decisionmaking. All treatment options result in AEs (primarily urinary, bowel, and sexual)

though the severity and frequency may vary between treatments. 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 AEs.

Limitations in the existing evidence include: 1) few randomized trials directly compared the relative effectiveness between (rather than within) major treatment categories; 2) many randomized trials are inadequately powered to provide long-term survival outcomes with the majority reporting biochemical progression or recurrence as the main outcomes; 3) some randomized trials were old, conducted prior to prostate cancer detection with PSA testing, and used technical aspects of treatment that may not reflect current practice so their results may not be generalizable to modern practice settings; 4) wide variation existed in reporting and definitions of outcomes; 5) there was little reporting of outcomes according to major patient and tumor characteristics; and 6) emerging technologies have not been evaluated in randomized trials.

We first summarize findings from RCTs and then describe additional data from nonrandomized reports. Table 3 compares major primary treatment options and reports clinical outcomes for RCTs. Table 4 summarizes RCT treatment options and reported outcomes.

Results by Comparison

Randomized Controlled Trials

Demographic and baseline characteristics (Table 4). The search strategy identified 19 randomized studies[43-62] and one pooled analysis of three trials.[63] Descriptions of these studies are summarized in Table 4. Only three studies directly compared the primary treatment options (i.e., RP vs. EBRT vs. WW) and none were conducted in patients primarily detected by PSA testing. Instead, most randomized trials evaluated variations of a particular treatment approach (e.g., different doses, isotopes, or duration of radiation therapy or addition of ADT to RP or EBRT).

A total of 14,730 patients were enrolled to date (some trials had not yet completed randomization). Thirteen trials were conducted in North America (United States or Canada),[43,45,46,48,50-53,56-60] three in Europe,[44,49,62] one in Japan,[47] and two in Australia and/or New Zealand.[55,61] The three trials of a pooled analysis were conducted in North America, Europe, Israel, Australia, and Mexico.[63] Six studies enrolled subjects with advanced prostate cancer (tumor stage T3 or T4), comprising 24 percent of all subjects.[47,49,53,57,61-63] These subjects were excluded from the baseline demographic, Gleason, efficacy, and adverse effects/toxicity analyses. Mean age of the subjects for eight studies reporting was 65.4 years (n=2,945)[43-45,50-52,59,60] In studies reporting median age, the median ages ranged from 63.6 to 72.5 years.[48,54-56,58] Two trials reported on ethnicity, and over 90 percent of subjects in both studies were White.[51,56] The majority of subjects were classified as having T2 tumor stage (75.5 percent vs. 23.5 percent T1).[44,47-52,56,58] Only one trial enrolled more T1 subjects than T2.[56] Among the nine studies reporting on Gleason score based on the combined score at randomization, 66 percent had a score of 6 or less, 24.1 percent had a score of 7, 6.3 percent had a score of 8 to10, and the score was unknown in 2.6 percent.[43-45,48,51,52,55,56,58] One trial enrolled only subjects with a Gleason score no greater than 6.[51] Six studies reported study eligibility based on level of serum prostate-

specific antigen ranging from <15 ng/ml[56] to <40 or 50 ng/ml,[44,48,50,52,58] and most began enrollment prior to widespread use of PSA testing.

Approximately 45 percent were randomized to RP (n=6,550),[44-51,63] 35 percent to EBRT (n=5,118),[52-58,61-63] 19 percent to WW (n=2,729),[44,45,63] nearly 2 percent to brachytherapy (n=115)[59] and brachytherapy with adjuvant radiation treatment (n=165),[43] and less than 1 percent to either vaccine or nilutamide (n=21 each).[60] Almost 17 percent of subjects assigned RP and 13 percent of subjects assigned radiation treatment received adjuvant or neoadjuvant androgen deprivation therapy. In the pooled three trial analysis, subjects were randomized to either adjuvant bicalutamide (n=4,052) or placebo (4,052) combined with standard care including RP (estimated n=4,445), EBRT (estimated n=1,379), or WW (estimated n=2,313).[63]

Efficacy and Adverse Events Outcomes

Survival outcomes, biochemical progression or recurrence, distance metastases and AEs are summarized in the following tables: (overall mortality/survival—Tables 5-7; disease-specific survival—Table 7 and Appendix C, Table C1; biochemical progression or reoccurrence—Table 8 and Appendix C, Tables C2 and C3; incidence of distant metastases—Table 9 and Appendix C, Table C4; adverse effects and toxicity—Table 10 and Appendix C, Table C5.) The definitions of biochemical progression and reoccurrence differ in the published reports. This high variability in definitions limited analysis of comparative effectiveness of different treatments across studies.

Eight trials reported overall mortality/survival or provided actuarial estimates of overall survival,[44,45,48,52,56,58,60,63] and disease-specific PC deaths.[44,48,52,54,56,58,60,61] The majority (n=16) of the RCTs reported biochemical progression or recurrence as an outcome.[46-50,52-63] Seven RCTs reported incidence of distant metastases[44,46,48-50,52,60] and seven reported on adverse effects or toxicity.[51,52,54,56,58,60,64]

1. Randomized comparisons across primary treatment categories

A. Radical prostatectomy compared to watchful waiting (2 RCTs).

- Compared to WW, men with clinically localized prostate cancer detected by methods other then PSA testing and treated with RP experienced fewer deaths from prostate cancer, fewer deaths from any cause, and fewer distant metastases. The greater benefit of RP on cancer-specific mortality may be limited to men under 65 years of age. Two RCTs compared RP to WW.[44,45] The SPCG trial found lower incidences of all-cause deaths, disease-specific deaths, and distant metastases for subjects treated with RP compared to subjects assigned WW after a median followup of 8.2 years. Surgery was associated with greater urinary and sexual dysfunction compared to 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, though small sample size limited study power.
- Few men had tumors detected by PSA testing. The most recent trial, the Scandinavian Prostate Cancer Group No.4 (SPCG-4), randomized 695 subjects with T1 or T2 localized PC who had a life expectancy of more than 10 years (Table 7).[44] Only 5 percent of enrollees had prostate cancer detected by PSA testing. After a median

followup of 8.2 years, all-cause mortality was higher in the WW group compared with the RP group, 106 (30 percent) vs. 83 (24 percent), with a relative risk (RR) of 0.74 [95 percent CI 0.56; 0.99; p=0.04]. After 5 and 10 years, the absolute risk reductions (ARR) in mortality were 2 percent [95 percent CI -2.2; 6.2] and 5 percent [95 percent CI -2.8; 13.0], respectively. There was a lower risk of disease-specific death for subjects treated with RP compared to subjects assigned WW.[44] There were 30 deaths (9.6 percent) attributable to prostate cancer (PC) in the RP group and 50 deaths (14.9 percent) in the WW group. The RR at 10 years was 0.56 [95 percent CI 0.36; 0.88, p=0.01] with an ARR of 5.3 percent [95 percent CI -0.3; 11.0]. Incidence of distant metastases was lower in the RP group compared to WW (14.4 percent vs. 22.7 percent, p=0.004).[44] The cumulative incidences at 5 and 10 years were 8.1 percent and 15.2 percent for the RP group and 9.8 percent and 25.4 percent for the WW group. At 10 years the ARR was 10.2 percent [95 percent CI 3.1; 17.2] and the RR was 0.60 [95 percent CI 0.42; 0.86].

- The VACURG study randomized 142 subjects with stage I or II localized PC recruited from Veterans Administration hospitals between 1967 and 1975. After a median followup of 23 years the median overall survival was 10.6 years for the RP group and 8 years for the WW group. Results were not statistically significantly different, but this study was underpowered to detect differences between treatments due to the small sample sizes. In addition, the results may not be applicable to contemporary patients due to the evolving techniques in both stage and grade classification subsequent to the introduction of PSA screening for prostate cancer.
- Three ongoing trials are evaluating primary treatment options in men with primarily PSA detected clinically localized prostate cancer. The U.S. based VA/NCI/AHRQ funded CSP#407: Prostate cancer Intervention Versus Observation Trial (PIVOT) is comparing RP vs. WW in 731 men and completed recruitment.[65] Results are due after 2010. The Prostate Testing and Cancer Treatment study, based in the United Kingdom, is comparing surgery (radical prostatectomy), radiotherapy (radical conformal) and active monitoring (monitoring with regular check ups). A Canadian trial comparing cryotherapy with EBRT is expected to present results soon. A combined U.K., U.S., and Canadian trial in its pilot phase is designed to compare expectant management with intervention based on followup PSA and biopsy measures vs. immediate intervention (patient's choice).

B. Radical prostatectomy vs. external beam radiotherapy (1 RCT). One, small (n=106) older trial indicated that compared to EBRT, RP was more effective in preventing progression, recurrence, or distant metastases in men with clinically localized prostate cancer clinical stage A2 or B (T1/T2) and normal serum prostatic acid phosphastase levels detected by methods other then PSA testing.[46] Treatment failure was defined as acid phosphatase elevation on two consecutive followup visits or appearance of bone or parenchymal disease with or without concomitant acid phosphatase elevation. After 5 years of followup, failure occurred in 39 percent for EBRT compared to 14 percent in RP. Two distant metastatic disease events (positive bone scans for distant metastases) occurred in the RP group compared to 14 (11 positive bone scans, one pulmonary, lymph node, parenchymal metastases each) in the EBRT group.[46]

C. Cryotherapy, laparoscopic or robotic assisted radical prostatectomy, primary androgen deprivation therapy, high intensity focused ultrasound, proton beam

radiation therapy, or intensity modulated radiation therapy (0 RCTs). It is not known whether these therapies are better or worse than other treatments for localized prostate cancer because clinically relevant outcomes for these options have not been evaluated in RCTs.

2. Randomized comparisons within primary treatment categories

A. 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 with 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 to RP alone in any of the four trials. The trial comparing 3 months to 8 months neoadjuvant ADT with RP, reported greater AEs in the 8 month group compared to the 3 month group (4.5 percent vs. 2.9 percent), and higher incidence of hot flashes (87 percent vs. 72 percent).

- Overall and disease-specific survival. One small RCT compared RP alone (n=101) vs. RP combined with neoadjuvant ADT (n=112).[48] ADT consisted of 300 mg of cyproterone acetate daily for 3 months prior to surgery. After a median followup of 6 years, there was no benefit with the addition of neoadjuvant ADT. Overall survival at 5 years was 88.4 percent [95 percent CI 80.6; 96.3] and 93.9 percent [95 percent CI 88.6; 99.1] for the RP + neoadjuvant ADT and RP alone groups, respectively (p=0.38). There were five total deaths in the RP group and eight in the RP + neoadjuvant ADT group. The addition of neoadjuvant ADT did not reduce disease-specific deaths compared to RP alone (1 vs. 0,[48] although this trial may have been underpowered to detect differences in this outcome due to the relatively small numbers in the treatment arms.
- Biochemical progression and metastatic disease. Four RCTs reported biochemical progression outcomes.[47-50] All defined progression based on PSA rises, although two trials included local recurrence, distant metastases,[47] or death due to prostate cancer.[48] RP + neoadjuvant ADT did not prevent biochemical progression or recurrence, distant metastases, or death due to prostate cancer more effectively than RP alone. A Japanese study reported 11 (15.9 percent) clinical relapse events in the RP + neoadjuvant ADT group (n=69) vs. 9 (14.3 percent) in the RP alone group (63) for stage A2 and B subjects.[47] Only one event was reported for stage A2 subjects.[47] Klotz found 34 percent and 38 percent of RP subjects and RP + neoadjuvant ADT subjects had biochemical recurrence at a median followup of 6 years, (HR=0.98 RP + neoadjuvant ADT vs. RP alone, [95 percent CI 0.61; 1.56], p=0.92.98 on page 48).[48] A Gleason score of 8 to 10 at biopsy was a significant predictor of recurrence (HR=2.82 score 8-10 vs. 2-6, [95 percent CI 1.52; 5.22], p=0.001), regardless of type of treatment. One small trial (N=303), defining biochemical recurrence as a PSA value >0.4 ng/ml, found no difference between groups in reoccurrence rates although it is unclear if this study was powered to detect differences.[50] Approximately 65 percent in the RP + neoadjuvant ADT group and 68 percent in the RP group had evidence of bNED (p=0.663). For Gleason score of 8-10, 8/14 of RP subjects had

biochemical failure compared to 13/15 of NHT combined with RP subjects (p=0.173).

Three RCTs found the addition of neoadjuvant ADT did not reduce the risk of developing distant metastases.[48-50]

- Toxicity/adverse effects. A trial comparing 3 months to 8 months of neoadjuvant ADT combined with RP focused on AEs of treatment rather than effectiveness. There were no fatal AEs and no difference between the groups in the causality and severity of AEs.[51] Within the 8 month group there were significantly greater numbers of newly reported AEs compared to the 3 month group (4.5 vs. 2.9, p<0.0001), defined as the first occurrence of an event regardless of the ongoing status, and higher incidences of hot flashes (87 percent vs. 72 percent, p<0.0001).

B. External beam radiotherapy (comparison of EBRT regimens) (4 RCTs). Only one small trial compared EBRT to RP. Despite the findings that RP was superior to EBRT in preventing disease progression, the study was small and was conducted prior to PSA testing and prior to refinements in both surgical and radiation therapy. Therefore, the results may not be applicable to current practice.[46] No RCTs compared EBRT to WW. It is not known if using higher doses of EBRT (either by increasing the total amount or type of radiation (e.g., via high-dose intensity modulated or proton beam radiation therapy or by adding brachytherapy after EBRT) 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.

- The majority of RCTs have evaluated different doses/duration of EBRT or use in combination with adjuvant ADT. None have directly evaluated EBRT with WW. EBRT doses typified as "conventional" varied, ranging from 64 Gy to 70.2 Gy. Hypofractionated EBRT uses fewer larger radiation dose fractions compared to conventional EBRT. Recent modifications to EBRT include high dose conformal EBRT which uses three dimensional radiotherapy planning systems and methods to match radiation treatment to prostate and tumor volumes as well as IMRT that uses multiple beams of EBRT to deliver radiation to a small area while attempting to avoid healthy tissue. These modifications have not been directly compared with other primary options.
- Variations in EBRT regimens have not demonstrated that any provide differences in overall or disease-specific survival. Most RCTs are of insufficient size or duration to adequately assess survival or metastases and focus on AEs or biochemical outcomes. Compared to conventional radiotherapy, high-dose conformal EBRT decreased the rate of PSA failure without increasing acute or late serious urinary or rectal complications.[56,66]
  - Overall and disease-specific survival. None of the three RCTs reporting overall survival found a difference in overall survival between groups.[52,55,56] Estimated overall survival in a multicenter Canadian trial, randomizing 936 men with early-stage PC to either long arm (conventional) EBR (66 Gy in 33 fractions over 45 days) or short arm (hypofractionated EBRT (52.5 Gy in 20 fractions over 28 days) was 85.2 and 87.6 percent for the respective groups at the median followup of 5.7 years.[52] The values in an Australian trial (N=217) were 86.4 percent for hypofractionated EBRT (55 Gy/20 fractions/4 weeks) and 84.1 percent for

conventional EBRT (64 Gy/32 fractions/6.5 weeks).[55] A multicenter American trial estimated survival to 97 percent for the conventional EBRT group (70.2 Gy that included 3D conformal proton 50.4 Gy with a 19.8 Gy proton boost) vs. 96 percent for the high dose EBRT group (79.2 Gy that included 3D conformal proton 50.4 Gy with a 28.8 Gy proton boost) in 393 men with stage T1b through T2p PC.[56]

No EBRT treatment regimens were superior in reducing prostate cancer-specific deaths in the three trials reporting.[52,54-56] Incidences of reported disease-specific deaths were low, ranging from 0 to 2 percent. In the study comparing long arm EBRT to short arm, there were three (<1 percent) prostate cancer deaths in the long arm group and none in the short arm group.[52] Three (3 percent) prostate cancer deaths were reported in the conventional arm compared to one in the hypofractionated arm.[55] The conventional dose group had two deaths due to prostate cancer vs. none in the high dose group.[56]

- Biochemical progression. All included RCTs reported biochemical progression.[52-56] Three trials used a composite definition of progression, including death due to prostate cancer and clinical failure[52,53,62] and all used increases in serum PSA. In the Lukka trial, the probability of biochemical or clinical progression at 5 years favored the long arm, 53 percent vs. 60 percent for the short arm, yielding an ARR of -7 percent [95 percent -12.6; -1.4].[52] Because the lower bound of the confidence interval was less than the predefined tolerance of -7.5 percent indicating noninferiority, the authors could not exclude the possibility of the short arm being inferior. The estimated hazard ratio (HR) was 1.18 [95 percent CI 0.99; 1.41], favoring the long arm. There were 263 (56.4 percent) and 236 (50.2 percent) events for the short and long arm groups, respectively.

  There was no difference in PSA relapse events between conventional EBRT and hypofractionated EBRT after 5 years.[54,55] Brachytherapy (Iridium implant) combined with EBRT was superior to EBRT alone in reducing biochemical or clinical progression over a median followup of 8.2 years.[53] For clinical stage T2 patients (n=63), biochemical or clinical failure events occurred in 25.8 percent in the combined brachytherapy/EBRT group compared to 56.3 percent for the EBRT alone group (HR=0.37 [95 percent CI 0.16; 0.85]).

  High dose EBRT was more effective in preventing "biochemical failure" than conventional dose.[56] The proportion of men free from failure at 5 years was 80.4 percent [95 percent CI 74.7; 86.1] in the high dose group and 61.4 percent [95 percent CI 54.6; 68.3] in the conventional dose group ($p<0.001$). Superior effectiveness was reported in both low risk disease (n=227, PSA <10 ng/ml; stage ≤T2a tumors; or Gleason ≤6) and high risk disease (80.5 percent vs. 60.1 percent, $p<0.001$). For the high risk subjects, the percentages were 79.5 percent and 63.4 percent ($p=0.03$) for the respective groups. However, when the higher risk subjects were further divided into intermediate risk (n=129) and high risk groups (n=33), the benefit of high dose therapy remained for the intermediate risk (81 percent vs. 62.7 percent, $p=0.02$) but not for the high risk patients ($p=0.80$). The trial by Peeters (N=664), which included subjects with stage T3/T4 disease (37 percent), found no benefit with high dose EBRT (78 Gy) compared to low dose

(68 Gy) when the analysis was limited to subjects considered "low risk" (n=120), defined as having stage T1/T2 with a Gleason score ≤6, and PSA ≤10 ng/ml.[62] One trial found slightly more distant failure events in the short arm (ten events, 2 percent) compared to the long arm (four events, 1 percent) at the median followup of 5.4 years.[52]

- Toxicity/adverse events. Three RCTs reported on toxicity/adverse effects associated with EBRT.[52,54,56] The trial by Lukka found acute (≤5 months) combined GI and GU toxicity lower in the long arm (7.0 percent) compared to the short arm (11.4 percent), a difference of -4.4 percent [95 percent CI -8.1; -0.6].[52] Late toxicity was similar in both arms (3.2 percent each). Both conventional and hypofractionated EBRT resulted in increases from baseline for all GI symptoms and for five symptoms characterizing GU symptoms 1 month after completion of therapy.[54] For GI symptoms, increases in four of the six symptoms (rectal pain, mucus discharge, urgency of defecation, and rectal bleeding) remained 2 years after EBRT compared to baseline. There were no differences between treatment groups with the exception of rectal bleeding at 2 years after therapy, which had a higher prevalence in the hypofractionated group (42 percent vs. 27 percent for conventional group, $p<0.05$). GI and GU toxicity remained 5 years after EBRT but did not differ between treatment groups with the exception of urgency to defecate, which worsened in subjects treated with hypofractionated EBRT ($p<0.05$).[55] Fewer subjects had urinary frequency equal to or more than every 3 or 4 hours compared to baseline (70 percent vs. 81 percent, $p<0.05$). Only 25 of the 120 subjects completed the sexual function questionnaire (European Organization for Research and Treatment of Cancer). Nine (36 percent) were impotent at baseline. One month after treatment the number of subjects reporting ED increased to 13 (52 percent). Two years after EBRT treatment ED was reported by 9 of 17 subjects.[54]

  The proportion of subjects with acute severe GI or GU symptoms (RTOG ≥3) was similar in the high dose (79.2 Gy) and conventional dose regimens (70 Gy), 2 percent vs. 1 percent.[56] For late severe GI or GU symptoms (RTOG ≥3), the percents were 1 percent and 2 percent for high dose (79.2 Gy) and conventional dose (70 Gy) groups. For acute GI symptoms, 57 percent of high dose subjects experienced grade 2 GI morbidity compared to 41 percent of conventional dose subjects ($p=0.004$). The difference remained significant for late grade 2 GI morbidity, although proportions decreased (17 percent high dose vs. 8 percent conventional dose, $p=0.005$).

C. External beam radiotherapy combined with ADT compared to EBRT alone (2 RCTs) and External beam radiotherapy combined with ADT, comparison of two regimens (1 RCT). ADT combined with EBRT (ADT + EBRT) may decrease overall and disease-specific mortality but increased AE 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=206) found 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 compared to EBRT alone. One RCT (N=818, including T3/T4 subjects) found 6 months of ADT + EBRT did not significantly

reduce disease-specific mortality compared with conformal EBRT alone in 326 T2b and T2c subjects after a median followup of 5.9 years. Six months combination therapy reduced clinical failure, biochemical failure, or death from any cause compared to EBRT alone in subjects with T2c disease but not T2b subjects.

- Overall and disease-specific survival. Conformal EBRT (70 Gy) combined with 6 months of ADT (2 months each of neoadjuvant, concurrent, and adjuvant) was compared with EBRT alone in subjects with localized prostate cancer with PSA levels of <10 ng/ml in one RCT (n=206).[58] ADT consisted of a LHRH agonist (leuprolide acetate) or goserelin and a nonsteroidal anti-androgen (flutamide). EBRT + ADT reduced all-cause mortality vs. EBRT alone: 12 deaths vs. 23 deaths for EBRT alone. The hazard ratio (HR, EBRT alone vs. ADT + EBRT) was 2.07 [95 percent CI 1.02; 4.20, p=0.04]. Overall survival at 5 years was 88 percent [95 percent CI 80; 95] for the combined group compared to 78 percent [95 percent CI 68; 88] for EBRT alone. The addition of ADT also reduced disease-specific mortality compared to EBRT alone (zero vs. six deaths (5.8 percent), p=0.02).[58] An RCT randomizing men with T2 through T4 disease reported fewer prostate cancer deaths with 6 months of ADT added to EBRT vs. EBRT (8 deaths vs. 17 deaths, respectively), though the confidence intervals were wide and the results not statistically different in men with T2 disease after a median followup of 5.9 years.[61] The HR for T2b subjects was 0.22 [95 percent CI 0.03; 1.88] and 0.57 [95 percent CI 0.22; 1.44] for T2C subjects. With the inclusion of T3/T4 subjects, the addition of 6 months of ADT significantly reduced disease-specific mortality compared to EBRT alone (19 deaths vs. 36 deaths, respectively; HR = 0.56 [95 percent CI 0.32; 0.98].
- Biochemical progression. Two RCTs reported biochemical progression outcomes based on rising PSA levels.[57,58] One evaluated different durations of ADT (3 months vs. 8 months) combined EBRT.[57] The overall median followup, which included subjects with stage T3 disease, was 3.7 years. For the low risk subjects (n=92, PSA <10 ng/ml; stage T1c to T2a tumors; Gleason ≤6), the actuarial estimate of freedom from biochemical failure was 61 percent for the 3 month group compared to 72 percent for the 8 month group. In the D'Amico trial, subjects randomized to combined therapy had lower PSA failure events compared to subjects randomized to EBRT alone (21 vs. 46 events, HR=2.86 [95 percent CI 1.69; 4.86], p<0.001) after a median followup of 4.5 years.[58] Survival without salvage ADT was also higher in the combination group vs. the EBRT alone group (p=0.002). Denham found combination therapy reduced clinical failure at any site, biochemical failure, or death from any cause, in subjects with T2c disease but not for T2b subjects.[61] There were 66 events in the EBRT alone group compared to 40 in the EBRT + ADT group in T2c subgroup, with an HR of 0.47 [95 percent CI 0.32; 0.69] favoring the EBRT + ADT group. In the T2b subgroup, there were 48 and 34 events with an HR of 0.68 [95 percent CI 0.44; 1.06].
- Toxicity/adverse effects. In the D'Amico trial incidences of grade 1 and 2 gynecomastia were increased in the EBRT + ADT group (n=18, 18.4 percent) compared to the EBRT alone group (n=3, 2.9 percent, p=0.002).[58] In addition, more men in the EBRT + ADT group who were potent at baseline became impotent after treatment compared to men treated with EBRT alone, 26 vs. 21 (p=0.02). There were no other significant differences in toxicity between the treatment groups.

D. Different doses of adjuvant EBRT combined with brachytherapy (1 RCT). One trial compared different doses of supplemental EBRT, 20 Gy (n=83) vs. 44 Gy (n=76), combined with brachytherapy (^{103}Pd).[43] There were no significant differences between EBRT groups in the number of biochemical failure events and the actuarial estimates of freedom from biochemical progression at 3 years. The estimated freedom from biochemical failure was 83 percent in the 20 Gy group vs. 88 percent in the 44 Gy group (p=0.64). The estimated percents of freedom from biochemical failure in patients with a pre-treatment PSA <10 ng/ml (n=112) were 84 percent and 94 percent for the 20 and 44 Gy groups, respectively (p=0.16). For the 47 subjects with a pretreatment PSA >10 ng/ml, the percents were 82 percent for the 20 Gy group and 72 percent for the 44 Gy group (p=0.38).

E. Brachytherapy compared to brachytherapy (1 RCT). Brachytherapy delivers radiation with small radioactive pellets implanted into the prostate gland under general or spinal anesthesia. These needles deliver the pellets, which can be left either permanently (high dose) or temporarily, and give off radiation at a low dose over several weeks or months. Brachytherapy is increasingly used for selected men with low to moderate risk prostate cancers despite no survival data from randomized trials. No RCTs evaluated brachytherapy alone with other major treatment options.

Preliminary results of RCT comparing different isotopes or adjuvant therapies[59,64] and other underpowered studies have been published[53,67] but preclude conclusions regarding the relative efficacy vs. other treatments, as well as conclusion regarding optimal forms of brachytherapy. Wallner (n=115), compared ^{125}I (144 Gy) to ^{103}Pd (125 Gy). They found similar biochemical control for both treatments at 3 years.[59] Actuarial estimate of freedom from biochemical progression, defined as PSA ≤0.5 ng/ml at last followup, was 89 percent for the ^{125}I group vs. 91 percent for ^{103}Pd group (p=0.76). A trend toward more radiation proctitis, defined as persistent bleeding, was found in the ^{125}I subjects (p=0.21). Actuarial estimates were 13 percent for the ^{125}I group and 8 percent for the ^{103}Pd group.

F. Adjuvant androgen deprivation therapy with bicalutamide combined with standard care (RP, EBRT, or WW) (3 RCT). 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 to placebo. The addition of bicalutamide to standard care did not reduce progression.

The bicalutamide Early Prostate Cancer Program was a pooled analysis of three international RCTs assessing the effectiveness of adjuvant bicalutamide combined with standard care (RP, EBRT, or WW) compared to placebo and standard care.[63] The trials enrolled subjects with both clinically localized (two-thirds of all subjects, n=5,426) and locally advanced prostate cancer. The majority of the subjects received RP (55 percent) followed by WW (28.5 percent) and EBRT (17 percent). 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 subjects receiving RP or radiation therapy (3,799). There were 187 (9.8 percent) and 182 (9.6 percent) deaths for the respective groups with an HR of 1.01 [95 percent CI 0.82; 1.23, p=0.97]. Among the WW subjects with clinically localized disease (n=1,627), there were significantly more deaths in the bicalutamide group (196, 25.2

percent) vs. placebo (174, 20.5 percent) with an HR of 1.23 [95 percent CI 1.00; 1.50, p=0.05].

Progression was defined as death from any cause or objective progression confirmed by bone scan, computerized tomography/ultrasound/MRI, or histological evidence of distant metastases.[63] Among subjects with localized disease (stage T1/T2), the addition of bicalutamide to standard care did not significantly reduce objective progression at the median followup period of 5.4 years. Among subjects who received RP (n=2,734), progression events in the bicalutamide group was 8.4 percent vs. 8.8 percent for placebo (HR=0.93 [95 percent CI 0.72; 1.20], p=0.57). Progression events for radiation therapy subjects (n=1,065) were 21.2 percent and 24.3 percent for the bicalutamide and placebo groups respectively (HR=0.80 [95 percent CI 0.62; 1.03], p=0.09).

Vaccine vs. nilutamide. One small RCT (N=42) compared a vaccine designed to enhance T-cell responses and anti-tumor activity to the antiandrogen, nilutamide, in men with nonmetastatic hormone refractory PC.[60] Overall followup times were not reported. There were three deaths in vaccine group compared to seven in the nilutamide group. There were four reported prostate cancer deaths in the nilutamide group, including two deaths among subjects who had vaccine added.[60] Among the vaccine subjects, there was one prostate cancer death.

Treatment failure was a composite outcome, defined as PSA progression, development of secondary malignancies or toxicity, and was either removed from study or crossed over to the other arm as determined by study protocol.[60] Median time to treatment failure was 9.9 months for the vaccine group compared to 7.6 months for the nilutamide arm. There were twice as many progressive disease events (metastases on bone scans) for subjects initially treated with vaccine (14 total, five events after crossover to nilutamide) than the subjects initially treated with nilutamide (seven total, one event after crossover to vaccine).[60]

Three subjects in the nilutamide arm (14.3 percent) were removed from the study due to grade 3 toxicities[60] and 38 percent in the vaccine arm experienced pain at the injection site. Both arms reported grade 2 and 3 toxicities. Dyspnea, fatigue, and hot flashes were reported for nilutamide patients. Toxicities in the vaccine group included arthralgia, fatigue, dyspnea, and cardiac ischemia (3.4 percent). The vaccine regimen also included injections of aldesleukin (IL-2). Grade 2 and 3 toxicities associated with IL-2 included fever, arthralgias, hyperglycemia (20.7 percent grade 2, 6.9 percent grade 3), lymphopenia (13.8 percent grade 2, 6.9 percent grade 3), dehydration/anorexia, and diarrhea.

Primary androgen deprivation therapy (0 RCTs). No randomized trials of primary ADT for men with clinically localized prostate cancer have been published. However, use of continuous or intermittent long-term ADT as primary therapy in these men has increased.

A previous AHRQ evidence report[68] examined randomized trials of different methods of ADT for advanced prostate cancer. Survival after treatment with an LHRH 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. There was a trend toward lower survival with use of a nonsteroidal antiandrogen compared to orchiectomy or LHRH agonists HR=1.13; 95 percent CI 0.92; 1.39). Individual patient level meta-analysis suggested an

improvement in survival of about 2 percent at 5 years (median survival benefit of 2-3 months) of combined androgen blockade compared to monotherapy.[69]

Primary ADT can last for 20 years or more in men with localized disease, but no randomized trials have compared the relative effectiveness of ADT in localized disease. Evidence from a well-characterized observational study, PCOS, of 276 patients with localized prostate cancer who received primary androgen suppression therapy within 1 year of diagnosis provides some evidence of expected survival following treatment (a nomogram for predicting overall 5 year survival), but no evidence on comparative effectiveness.[70] In addition to treatment costs, 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.[71] The administration of gonadotropin-releasing hormone in Medicare beneficiaries with localized prostate cancer was associated with increased risk of diabetes (adjusted HR=1.44; P <.001), coronary heart disease (adjusted HR, 1.16; P <.001), myocardial infarction (adjusted HR, 1.11; P=.03), and sudden cardiac death (adjusted HR, 1.16; P=.004).[72] Costs, sequalae, and/or use of medications to mitigate these adverse effects, such as androgen deprivation syndrome and osteoporosis (e.g., anxiolytics, bisphosphonates for bone loss, etc.) are issues of greater long-term importance compared to shorter duration treatment in advanced disease.

Laparoscopic or robot-assisted radical prostatectomy vs. radical prostatectomy (1 short-term RCT). One RCT[73] compared intra- and early postoperative outcomes for laparascopic radical prostatectomy (LRP) vs. retropubic radical prostatectomy (RRP) (n=120). Total operative time was greater for LRP vs. RRP (235 ± 49.9 vs. 170 ± 34.2 minutes respectively, p <0.001). Blood loss was less after LRP compared to RRP (257.3 ± 177 vs. 853.3 ± 485cc respectively, p <0.001). The rates of intra-operative outcomes and positive margins did not differ in the treatment groups (Appendix C Table C6). However, patients more often required 5-day catheterization after LRP (86.6 percent) than after RRP (66.6 percent). Intra and early postoperative outcomes were similar between the two procedures. Enrollees assigned to laparoscopic or retropubic RP were men younger than 70 years of age diagnosed with clinically localized prostate cancer, total serum PSA <20 ng/dl, and Gleason score <7.

Nonrandomized evidence: **overall survival, disease-specific survival, and bNED.**
Data from the AUA Clinical Guidelines database were used to assess overall and disease-specific survival and bNED at 5, 10, 15, and 20 years according to treatment and size of reported patient group. This was assessed regardless of risk strata and then separately according to Gleason score when available. Findings are limited because studies frequently did not report certain outcomes, may have provided multiple publications of identical or nearly identical cohorts but did not clearly differentiate these reports, used various definitions, used different followup times, and/or did not provide standard classification of patient/tumor risk characteristics.

The vast majority of data comes from case series. For overall, disease-specific survival and bNED, there were very wide variations in outcome estimates resulting in considerable overlap within and between treatments (e.g., at 10 years overall survival for any of the therapies ranged from approximately 15 percent to 70 to 90 percent; disease-specific survival ranged from approximately 40 percent to nearly 100 percent). Variation in outcomes within and between treatments could be related to provider, patient (age, race, comorbidities), and/or tumor (stage,

PSA, histologic grade) factors. Treatment related outcomes according to provider and patient and tumor factors are described in questions 2, 3, and 4.

Given the limitations of the results and the quality of the studies, it is not possible to accurately estimate the relative effectiveness of options beyond that available from the few randomized trials. Figures 2 and 3 and Appendix C, Figure C2 describe the range of outcomes reported. Overall and disease-specific survival at 10 years and beyond was most commonly reported in patients treated with EBRT and rarely reported with brachytherapy. Figure 2 demonstrates the high variability in overall survival between studies within the same treatment modality, which inhibits comparative effectiveness across treatments. For example, estimates of overall survival at 5 years varied widely, as much as 42 percent to 100 percent. bNED was much more commonly reported than overall or disease-specific survival. There were more than 200 definitions of bNED. Our figures included "all definitions of bNED" and likely account for some variability in percent bNED within and between treatments. While bNED has not been clearly demonstrated to correlate with survival, additional treatments are often based on followup PSA levels.

Adverse Events

3**0-day morbidity and mortality following RP.** Adverse effects due to treatments based on the few reported randomized trials have been noted above. Several studies used national data bases to assess 30-day mortality following radical prostatectomy (but not comparatively to other treatments). Based on a 20 percent random sample from 1984-1990 of male Medicare beneficiaries, Lu-Yao and colleagues found that approximately 1 percent of men between the ages of 65-74 died within 30 days of RP. The risk of mortality and morbidity increased for older men and exceeded 4 percent for men ages 80 or greater.[24] A more recent analysis of Medicare recipients ages 65 years or older, indicated that from 1994-1997 the 30-day mortality following RP was approximately 0.5 percent.[74] Major treatment-related morbidity was common in these older men with cardiopulmonary complications occurring in 4 to 10 percent and need for surgical repairs in 0.5 to 1 percent. Thirty-day readmissions per 1,000 operations declined from about 10-15 per 1,000 in the late 1980s to about 5 per 1,000 in the mid 1990s.[74] Similar results were found using a national sample of male veterans receiving RP at VA medical centers.[68] (A more detailed analysis of provider and hospital factors is described in question 3.)

Comparative adverse events from population-based surveys or administrative data. The PCOS[75] was begun in 1994 to prospectively collect individual level data from a population-based cohort of men with newly diagnosed prostate carcinoma. The PCOS is based on an existing tumor registry system, the National Cancer Institute's SEER program that provides information on cancer incidence and survival for the United States. PCOS assessed the effects of cancer treatments, including RP, EBRT, and ADT on health-related quality of life outcomes. PCOS focused on bladder, bowel, and sexual function and was initiated prior to widespread PSA testing. Baseline characteristics and findings may differ from patients currently diagnosed with prostate cancer.

Survey results indicate that sexual dysfunction was commonly associated with all treatments (Table 11). Sexual dysfunction was the most common AEs related to prostate cancer treatments.

Approximately half of men receiving RP or EBRT had no or little interest in, as well as no sexual activity. Three-quarters of men had erections that were insufficient for intercourse. Inability to achieve an erection was also commonly reported by men treated with ADT (86 percent) though one-third of men treated with WW reported inability to achieve any erections.

Urinary incontinence was more common after RP. At 24 month followup, urinary leakage occurring at least daily was three to five times more commonly reported in men treated with RP than with other options; reported in 7, 11, 12, and 35 percent of men who were treated with WW, ADT, EBRT/brachytherapy, and RP respectively. Five years after diagnosis, 14.4 percent of men who underwent RP vs. 4.9 percent who were treated with some form of EBRT reported that they had no control or frequently leaked urine [OR=4.4, 95 percent CI 2.2; 8.6]. Twenty-nine percent vs. 4 percent of subjects reported that they wore pads to stay dry. (Table 12).

Bowel dysfunction was more commonly noted after EBRT compared to RP. At five years significant differences between the RP and EBRT after adjustment for baseline factors and treatment propensity included bowel urgency (33.4 percent vs. 17.7 percent) and painful hemorrhoids (15.7 percent vs. 11.0 percent). Daily bowel urgency was reported by about 3 percent of individuals treated with ADT or radiation therapy but occurred in less than 1 percent of men receiving either WW or RP.

Both types of primary ADT (orchiectomy or LHRH agonist)[76] had a large adverse impact on sexual interest, activity, and ability to maintain an erection, though there were no significant differences between options. About 30 percent of individuals reported that they had no sexual interest before treatment. This increased to 64 percent and 58 percent at 5-year followup of orchiectomy or LHRH agonist. About 69 percent of men who were potent before treatment were impotent after, regardless of treatment. Only 10 and 13 percent of subjects treated with orchiectomy or LHRH respectively were able to maintain an erection sufficient for sexual intercourse. Breast swelling after treatment was reported by 24.9 percent in LHRH patients compared with 9.7 percent in orchiectomy patients. Hot flashes were similar in both treatment groups (56.5 percent vs. 67.9 percent). PCOS results are consistent with findings from the randomized trials evaluating RP, WW, ADT, and EBRT.

Shahinian and colleagues used SEER Medicare data to evaluate the risk of androgen deprivation syndrome in a cohort of 50,613 men receiving ADT for incident prostate cancer.[77] Of men surviving at least 5 years after diagnosis, 31.3 percent of those receiving ADT developed at least one depressive, cognitive, or constitutional diagnosis compared with 23.7 percent who did not receive ADT. Risk differences compared to men not receiving ADT were substantially reduced when adjusting for age, comorbid conditions, and more advanced prostate cancer.

The risk of fracture after ADT appears to be increased. Shahinian used the SEER Medicare linked database to assess fracture risk in 50,163 men who had a diagnosis of prostate cancer from 1992-1997.[78] Of men surviving at least 5 years after diagnosis, 19.4 percent of those who received ADT had a fracture, compared with 12.6 percent of those not receiving ADT. After controlling for patient and tumor characteristics, there was a statistically significant relation between the numbers of doses of gonadotropin-releasing hormone received during the 12 months after diagnosis and the subsequent risk of fracture.

A previous AHRQ report[68] examined randomized trials of different methods of ADT for advanced prostatic cancer. No LHRH agonist was found to be superior to others when adverse effects were considered. Adverse effects leading to withdrawal from therapy and drug costs were greater with combination therapy (LHRH agonist or orchiectomy plus antiandrogen) than with monotherapy.

Comparative adverse events from the AUA database. The AUA Guideline Panel had 24 predefined complications. These included bladder complications (seven), bowel (six), ED (one), deep venous thromboses and others (ten). Authors infrequently used the same definition for a given complication, often did not report outcomes during the same time period, varied in whether they reported on all subjects, only those with or without dysfunction at baseline, and how the outcome was assessed. For example, we identified 112 different definitions of incontinence, ED (79), bladder (203), bowel (87), and 336 definitions of other complications. The vast majority of definitions were only used once. A report for AEs was included if: 1) it provided one of the predefined complications or 2) additional definitions of bowel, bladder, or ED were used in at least three reports, and 3) the percent of subjects with complications was provided (or the ability to calculate this). At "any time point" the number of reports providing definitions and the number of reports indicating percent of subjects with complications were bowel (57 total/5 reporting percent of subjects with complications); bladder (79/19), and ED (44/13) (Appendix C, Table C7).

A series of figures (Figures 4-7) illustrate the major complications according to treatment, time period, and group sample size. Results were not assessed according to baseline patient or tumor characteristics. Based on the AUA database, as well as surveys or administrative datasets of men treated for prostate cancer (PCOS),[75] Medicare, and VA)[24,79] described above, we make the following general conclusions.

All treatments can cause bladder, bowel, and sexual dysfunction. Frequency and severity of these AEs may vary by treatment, length of followup, reporting method, definition of AE, patient baseline characteristics, and provider/facility factors (question 3). Bladder complications including hematuria, incontinence, cystitis, and urethral stricture were more commonly reported in patients treated with surgery and persisted beyond 24 months of treatment. Bladder neck contracture occurred in 5 to 20 percent of subjects treated with RP. Incontinence of any severity was the most frequently assessed bladder complication, though it was rarely reported. Incontinence rates were reported in brachytherapy (2 to 32 percent); RP (5 to 35 percent); and EBRT (2 to 6 percent). Urethral stricture and hematuria were more frequent with EBRT. Bowel complications including diarrhea, fecal incontinence, and rectal bleeding were rarely reported in studies evaluating patients undergoing RP. When reported, they occurred less commonly than in men treated with radiation therapy (15 to 30 percent), either EBRT or conformal EBRT. Except for rectal injury, bowel complications were present beyond 6 months followup. ED/impotence was common with all treatments ranging from 5 to 95 percent. NSP has been utilized in selected patients in attempts to maintain erectile function. Four patient groups treated with nerve sparing RP were assessed. Impotence rates ranged from less than 5 percent to as high as 60 percent.

Outcomes from Emerging Technologies

Cryosurgery. Cryosurgery induces cell death by two main mechanisms: direct cellular toxicity from disruption of the cellular membrane by ice ball crystals and vascular compromise from thrombosis and ischemia. The degree of cell destruction is dependent on rapid freezing, the lowest temperature achieved, and slow thawing. Newer generation cryosurgery uses pressurized gas-driven probes to both freeze and actively thaw. Transrectal ultrasound guidance assists in probe placement and real time monitoring while urethral warmers have reduced urethral sloughing. However, the requirement to both rapidly freeze the prostate while protecting surrounding structures may affect therapeutic efficacy and/or limit the type of patients/cancers that are candidates for this treatment. Use of cryotherapy has not reached levels comparable to other treatment options.

None of the included studies used randomization or included a control group. The majority of the studies included patients with T3-T4 stages of cancer (Appendix C, Table C8). An overview of the studies[80-101] that reported patient outcomes after cryosurgery as a primary treatment option is presented in Appendix C, Table C9. The sample size ranged from 54[80] to 1,467[100] patients followed for 3-68.6 months. Patients with advanced cancer constituted 7.4 percent[83] to 57 percent of the total samples.[96] Mean baseline PSA levels ranged from 6.5[99] to 26 ng/ml.[80] The proportion of subjects with poorly differentiated tumors (Gleason 7 or more) varied from 14 percent[98] to more than half of the total sample.[81,85,87,93,96]

Progression-free survival in men with T1-2 stages was 39 percent[80] to 100 percent.[81] Positive biopsy after cryosurgery was detected in 11 percent[101] to 38 percent.[83] Progression free and positive biopsy rates varied by tumor characteristics and length of followup. Prevalence of urethrorectal fistula, epididymitis, and sepsis was low in the majority of the studies. Tissue sloughing was observed in 4 (3.8) percent[99] to 23 percent,[96] urethral stricture in 1 percent[83] to 11 percent,[80] bladder obstruction in 3 percent[81,82,99] to 29 percent,[84] and perineal pain in 1 percent[83] to 11 percent[84] reporting this event. Urinary tract infection was diagnosed in 2.2 percent[82,99] to 33 percent[80] of patients and incontinence in 2 percent[93] to 27 percent.[84] The majority of patients reported impotence (40 percent[81] to 100 percent).[100]

Quality of life was assessed with FACT-G scale (160 maximum possible scores)[94,95] in men followed for 12-36 months. Physical well-being was estimated as 26.0 ± 2.9, social/family well-being as 23.5 ± 4.6, functional well-being as 24.3 ± 4.0, and emotional well-being as 17.9 ± 2.9 in subscales with 28 maximum possible scores. Forty seven percent of patients were able to have sexual intercourse at 3 years. Scores did not improve over the time of observation.

Authors compared reported outcomes from nonrandomized clinical trials and case series of cryosurgery with published evidence of other treatments[88,97] and concluded that effectiveness and safety are comparable. However, one phase II clinical trial was stopped due to poor outcomes.[80] Improved techniques including direct transperineal cryoneedles and percutaneous approach monitored by real-time transrectal ultrasound may reduce complications.[92,102] There was no direct comparative effectiveness evidence of cryosurgery for localized prostate cancer. Studies have not assessed long-term outcomes, including overall and disease-specific survival. Outcomes may be biased by patient and provider characteristics.

Laparoscopic and robotic assisted radical prostatectomy. LRP and RLRP have risen in popularity since being introduced in 1998 as a minimally invasive surgical method to remove the prostate. Video-assisted endoscopic surgery may result in fewer complications, especially intraoperative blood loss, and quicker recovery time than conventional open RP. LRP and RLRP appear to cost more, may not be applicable to all patients (e.g., those with large prostate glands), and require a learning curve for proficiency as well as purchase of laparoscopic and robotic surgical systems. Because they have only been used since 1998, long-term outcomes, including overall and disease-specific mortality, are not available.

Three reviews,[103-105] one systematic,[104] estimated the effectiveness and adverse effects of LRP and RLRP from 21 nonrandomized clinical trials and case series (Appendix C, Tables C10-C12). These involved 2,301 and 1,757 patients respectively. Most reports originated from centers outside of the United States with followup ranging from immediate postoperative period to almost 6 years (median about 8 months). Findings may not be directly relevant to men treated in the U.S. Important differences in patient and tumor characteristics as well as variable duration of followup make accurate estimates of effectiveness problematic.

The authors compared outcomes after several laparoscopic techniques including transperitoneal prostatectomy with initial retrovesical dissection of the seminal vesicles, transperitoneal ascending prostatectomy, extraperitoneal descending technique, extraperitoneal ascending technique, robotic assisted laparoscopic prostatectomy, as well as standard open retropubic radical prostatectomy. Pooling was not appropriate due to differences in study design.

Laparoscopic vs. open retropubic radical prostatectomy. One randomized controlled clinical trial[73] compared intra- and early postoperative outcomes of LRP vs. RRP (n=120). Results are provided in the section on randomized trials (Appendix C, Table C13). Several case series[106-112] and three non randomized prospective clinical trials[113-116] analyzed evidence of comparative effectiveness between laparoscopic and open RRP. Overall survival was reported in one study (n=657) (Figure 8) with slight improvement favoring patients treated with LRP compared RP, 99 percent vs. 97 percent.[108] PSA relapse was assessed in three studies (n=941).[103,110,113] There were no statistical differences between treatments with risk estimates ranging from 28 percent lower to 90 percent higher risk of PSA relapse with LRP. Six studies compared positive surgical margins after treatments and did not find significant differences. Percentages of patient reported continence (proportion of pad-free patients) were similar after two treatments in three studies[103,113,117] and better after laparoscopic approach in two studies.[110,116] Long-term potency is not known after LRP. Few studies reported erectile function. All ten comparative studies showed longer operative time for laparoscopic (180–330 minutes) compared to open RRP (105–197 minutes). The majority of the studies demonstrated a lower blood loss after laparoscopic vs. open RRP (189–1,100 ml vs. 550–1,550 ml respectively) and transfusion rate with laparoscopy (Appendix C, Figure C3). Bleeding, urine extravasation, wound healing, and thrombo-embolic events were better after laparoscopic surgery. Re-intervention rates were comparable between LRP and RRP. Recurrence free survival of 84 percent and 99 percent was reported in two studies, though results are limited by study duration and number of patients enrolled.[104] A nonrandomized controlled trial with 12 months of followup compared positive surgical margins, urinary incontinence, and quality of life related to incontinence in 239 patients with clinically

localized prostate cancer.[118] Treatment groups did not differ at baseline by age, PSA levels, Gleason scores, and BMI. The outcomes were measured after RRP in 148 patients and after LRP in 56 patients. The effects of a possible learning curve of LRP were analyzed evaluating differences in the outcomes after the first and the second 28 cases of LRP. The rates of positive surgical margins and the rates of urinary incontinence defined as pad weight gain greater than 8g/24-hours were the same among all treatment groups (Figure 9). The scores of the International Prostate Symptom Score questionnaire and the International Consultation of Incontinence quality of life questionnaire did not differ at 12 months of followup (Figure 10). Long term quality of life after LRP was not associated with the initial surgeon experience based on a case-series of 268 men followed for 26 months.[119]

Transperitoneal vs. extraperitoneal laparoscopic radical prostatectomy. Evidence from case series with historical controls[112,120-123] and with matched-paired controls[124] suggests that both techniques have comparable outcomes (Appendix C, Figure C4). Sample sizes were small and confidence intervals wide, thus precluding the detection of clinically important differences. Extraperitoneal LRP had shorter learning curve and operating times, lower risk of bleeding, and permitted the elimination of the initial retrovesical dissection of the seminal vesicles. The majority of studies compared outcomes with historical controls. The transperitoneal approach reduced the risk of lymphocele formation. No differences were found in overall morbidity, complications, continence, and positive surgical margins. The recent case series of 120 men after extraperitoneal LRP reported a 5.8 percent of PSA failure during the first year of followup with no differences among men operated by two surgeons with different procedure experience duration (7 vs. 2 years).[125] The largest case series of 1,000 men after transperitoneal LRP (30 percent had T3-4 cancer) reported an overall PSA-free survival of more than 90 percent among those with localized PC at 28 months of followup with overall survival of 99.7 percent.[126]

Robotic assisted laparoscopic radical prostatectomy. Evidence of comparative effectiveness between robotic assisted laparoscopic radical prostatectomy, retropubic, and transperitoneal laparoscopic radical prostatectomy are primarily limited to short-term outcomes from nonrandomized trials (Appendix C, Table C14).[104] and case series (Appendix C, Table C15).[127-137] Total complications and continence,[104] positive surgical margins, and operative time were comparable to RRP. Blood loss was less (median 153 ml) after robotic assisted RP compared to RRP (median 910 ml). Transfusion rate demonstrated lower median (0) after robotic assisted vs. open approach (median 38 percent). Recurrence-free survival was 92 percent and 95 percent for robot assisted RP vs. 85 percent and 95 percent for RRP, though there were relatively few patients and followup duration was short. Length of stay after robotic assisted RP was less than half that for RRP (median 1.2 and 2.7 days respectively). The length of catheterization was shorter after robotic assisted RP compared with RRP (median 7 vs. 13 days respectively).

Individual case series reported less blood loss after robotic LRP compared to RP[128,132,135]or laparoscopic RP[127,137] or no differences.[127,134,135,137] Catheterization time was lower after robotic RP compared to RP[129,132] and the same compared to laparoscopic RP.[137] The Vattikuti Urology Institute reported shorter length of stay after robotic LRP compared to RP[128,132] not confirmed by other authors.[137] The rates of detectable PSA were the same after robotic LRP and RP.[129,132] The rates of positive surgical margins did not differ after RP and robotic LRP.[128,129] Complication rates were lower after robotic LRP compared to RP[129] but higher compared to LRP.[137] Short-

term potency at 3 months of followup defined as an erection adequate for vaginal penetration was higher after cautery-free technique to preserve the neurovascular bundles during robotic LRP.[138]

Comparative effectiveness of LRP on quality of life vs. other treatments has not been established. Reports from Europe indicated that quality of life scores improved in 7.8 percent and remained the same in 37.4 percent of the first 500 men who underwent LRP. Authors used global scores to analyze outcomes of RP according to biochemical progression (0–4), incontinence (0–2), and impotence (0–1) to compare quality of life after LRP and RRP. Patients who underwent robotic assisted LRP reported return to baseline urinary function (84 percent) and to baseline sexual function at 12 months of followup (80 percent).[139] The small case series of 90 patients reported the median time to recovery of baseline summary scores in the urinary domain at 6.6 months, in the bowel domain at 2.8 months , and in the hormonal domain at 3.0 months.[136] Estimates are reported from uncontrolled case series and did not include morbidity or adjustment for baseline patient functional characteristics.[103]

One systematic review and pooled analysis[140] reported outcomes from centers of excellence in the United States and Europe after open radical retropubic, laparoscopic, and robotic assisted prostatectomy (Appendix C, Table C13). Estimated blood loss and absolute risk of blood transfusion and post-operative complications were less after robotic prostatectomy. Pathological outcomes were comparable after all three procedures. The learning curve of robotic prostatectomy was faster compared to laparoscopic prostatectomy.

One randomized clinical trial compared surgical performance using two different robotic camera holders (EndoAssist and AESOP) in 20 patients with localized prostate cancer.[141] The new robot, EndoAssist, is automated by surgeon's head movements and reportedly provides a better view and complete control over camera movement. The trial reported comparable surgical performance of two robots with a shorter time to complete the vas deferens and seminal vesicle dissection after EndoAssist (Appendix C, Table C16).

Intensity modulated radiation therapy. In addition to three dimensional conformal radiation, intensity modulated radiation (with or without imaging guidance) is believed to provide better precision and adjustment of the radiation dose to normal tissues.[142] IMRT detects the areas of radiation and adjusts the dose weighting and delivery to process the radiation plan. In contrast to three dimensional conformal radiation, accurate within 7-10 millimeters, IMRT restricts the dose and provides accuracy within 1-3 millimeters. A planning computer with a large number of beamlets or "pencil beams" calculates the dose of radiation in the anatomical areas of a 1 mm slice in an MRI scan of the prostate. More recently, fusion of the two scans have been used to increase accuracy of the patient's anatomy. In addition to four clinical trials, we manually searched the references and found five case series with 100 or more subjects (Table C17-19).

Dose of radiation delivered to target organs and healthy tissues. One small study reported comparable dose delivered to target organs with less irradiation of healthy tissues after IMRT compared to 3D conformal radiation therapy (CRT). This may result in similar effectiveness with lower toxicity. Dose-volume histograms were examined in ten randomly selected patients with localized prostate cancer.[143] Patients received 3D CRT and IMRT with 75.6 Gy to the prostate,

50.4 Gy to the pelvic nodes, and 55.8 Gy to the seminal vesicles for three target volumes: prostate + seminal vesicles + pelvic lymph nodes , prostate + seminal vesicles, or prostate only. The mean dose delivered to pelvic nodal treatment did not differ when 3D CRT and IMRT were compared. However, IMRT provided larger mean doses of radiation to prostate planning target volume (p=0.007 in prostate + seminal vesicles + pelvic lymph nodes group, p=0.03 in prostate + seminal vesicles group) and to seminal vesicle planning target volume (p=0.005 in prostate + seminal vesicles group). In contrast, the minimum dose covering 1 ml of nodal volume was 50 Gy in 3D CRT vs. 44 Gy in IMRT (p=0.005). In all patients, the planning target volumes received the full-prescribed dose, with the mean dose at least as high as the prescribed dose. Normal tissues including rectum, femoral heads, and bladder received less irradiation after IMRT compared to 3D CRT. The rectal volume irradiated was 24 percent for 3D CRT but only 12 percent for IMRT (p <0.005). The group with three planning target volumes (prostate + seminal vesicles + pelvic lymph nodes) experienced the greater benefit from IMRT, bladder volume irradiated was 25 percent after 3D CRT vs. 21 percent after IMRT (dose >70 Gy, p=0.037), femoral head volume irradiated was 65 percent after 3D CRT vs. 20 percent after IMRT (dose >40 Gy, p=0.005).

Recently published preliminary results of an RCT showed benefits of hypofractionation using IMRT on delivered doses.[144] Patients with localized prostate cancer and Gleason score >5 (N=100, 14 had T3) were randomly assigned to 76 Gy in 38 fractions or 70.2 Gy in 26 fractions using IMRT to test the hypothesis that 8 Gy escalation in biologic dose would result in a 15 percent increase of freedom of biochemical failure from 70 to 85 percent without increasing late complications. The patients after 76 Gy in 38 fractions received larger dose of planning target volumes and less volumes of irradiated rectum and femoral heads compared to the groups after 70.2 Gy in 26 fractions.

Clinical outcomes. No clinical trials compared the effects of clinical outcomes after IMRT vs. other treatments. Case-series reported tendency of better biochemical-free survival after IMRT compared to conformal radiation (Appendix C, Table C17).[145,146] The odds ratio of survival without relapse was 1.03 (95 percent CI 0.94; 1.14) at 25-32 months followup and 1.09 (95 percent CI 0.96; 1.24) at 66 months followup after IMRT vs. conformal radiation. The rate of distant metastases was 1 to 3 percent after IMRT in a series of 561 patients.[147] A case-series of 133 men (67 percent with localized PC)[148] reported biochemical relapse-free survival at 5 years of followup of 100 percent in low risk groups, 94 percent in intermediate groups, and 74 percent in high risk groups. Prescribed dose of radiation (adjusted hazard ratio 0.34, 95 percent CI 0.11; 0.98) and the use of androgen deprivation therapy (adjusted hazard ratio 0.28, 95 percent CI 0.10; 0.79) was negatively associated with the risk of biochemical relapse (Table C17).[148]

Acute GI and urinary toxicity were reported in one randomized trial[149] and case series (Appendix C, Table C18).[147,150] The percents of grades 1 and 2 acute GI toxicity were 22 percent and 4 percent respectively[150] and rectal bleeding 1.6 to 10 percent. Acute urinary toxicity, grade 1, was detected in 37 to 46 percent of patients after different doses of IMRT. Percentages were 28 to 31 percent for genitourinary toxicity grade 2. The rates of late gastrointestinal and urinary toxicity were reported from case series and are presented in Appendix C, Table C19. Absolute risk of late toxicity was less than 20 percent in all reports. Quality of life measures were comparable or better after IMRT vs. conformal radiation (Appendix C, Figure C5).

High intensity focused ultrasound. HIFU has been used for the primary treatment of localized disease and salvage therapy for patients in whom radiotherapy has failed.[151] In contrast to diagnostic ultrasound, HIFU can provide prostate tissue ablation from a transducer placed in the rectum.[151,152] Two devices are available, Ablatherm and Sonablate 500.[153] Technical differences of Sonablate 500 include higher frequency (4 MHz vs. 2.25-3 MHz) and use of split-beam technology. Sonablate 500 requires three treatment zones vs. one for Ablatherm, which increases the speed of the treatments and may permit surgeons to ablate the entire gland.[153] We identified four reviews, none reported a systematic literature search or quality of the studies.[151-154]

Randomized controlled clinical trials examined standard ultrasound for cancer detection but not HIFU for treatment.[155-157] Several clinical trials evaluated ultrasound to measure prostate volume and define doses of radiation. We excluded the trial that examined HIFU with recurrent prostate cancer and four case series with less than 50 subjects. We reviewed three nonrandomized not controlled trials and seven case series with more than 50 men to analyze survival, biochemical progression, biopsy negativity, adverse effects, and treatment parameters after HIFU.[158-167]

Available studies included patients with localized prostate cancer (T1-2) not suitable for RP who were older than 66 years of age and followed for 6 months,[164] 23[162] or 27 months.[167] Several studies[158,159,161,162,164,167] included untreated patients and used HIFU as a primary therapy. One study included men with recurrent local cancer after EBRT.[160] Neo-adjuvant hormonal therapy was administered in 8 to 43 percent of patients.[160,163,165,167] Only two studies had a control group. Chaussy et al. compared outcomes after HIFU in combination with transurethral resection of the prostate vs. HIFU alone. One study compared the effects of neo-adjuvant hormonal therapy before HIFU and HIFU alone.[164] Pretreatment PSA averaged 6.99[167] to 7.6[163] to 11.2ng/ml[162] and prostate volume 21.7[161] to 34.9 cm^3 (Appendix C, Table C20).[166]

The majority of studies used the Ablatherm device with 1.04[161] to 1.92[166] HIFU treatments per patient. Biochemical progression-free survival was 66 percent[160] to 87 percent.[163] Negative biopsy at the end of followup was detected in 66 percent[164] to 93 percent.[163] Severe incontinence was observed in less than 5 percent of patients, mild or moderate urinary incontinence occurred in 1.4 percent[158] to 18.6 percent[160] of the subjects. The rate of urethral stenosis differed from 3.6 percent[159] to 27.1 percent.[161] Impotence was reported by 2 percent[166] to 52.7 percent[163] after HIFU. Quality of life assessed by the International Prostate Symptom Scores did not change significantly after the procedure.[158,163,165] Combination of HIFU with TURP was not associated with a better negative biopsy rate compared to HIFU alone.[161] However, catheter time, rates of urinary incontinence, and urinary tract infections were less, and quality of life was better after combined therapy. Neo-adjuvant androgen suppression therapy was not associated with better progression-free survival compared to HIFU alone.[164] One recently published case series of 227 patients with localized PC and no previous radical treatment reported significant increase in disease-free survival among males with baseline PSA <4 ng/ml (90 percent) compared to those with baseline PSA 10.1 to 15 ng/ml (61 percent).[167] The same study showed prognostic value of nadir PSA[167] with negative biopsy rates of 89 percent in the subgroup with nadir PSA <0.5 ng/ml but only 68 percent in those with nadir PSA >1.1 ng/ml.

Proton beam radiation therapy. Radiation therapy with protons may improve dose distribution with higher doses delivered locally to the tumor preserving surrounding healthy tissues.[168]

However, no randomized trials have evaluated the comparative effectiveness of protons vs. photons in men with localized prostate cancer. One randomized trial assessed prostate cancer control of high dose irradiation boosting with conformal protons compared with conventional dose irradiation using photons alone for advanced prostate cancer. At 8 year followup, combination therapy was better than conformal therapy alone (OR 1.88, 95 percent CI 1.04; 3.41).[169]

Overall survival did not differ between groups in an RCT of 393 men with localized prostate cancer and PSA <15 ng/ml treated with a combination of conformal photon and proton beams. The aim was to compare higher dose of radiation (79.2 Gy) with conventional dose (70.2 Gy) during 5 years of followup.[56] A high dose of proton boost (19.8 Gy or 28.8 Gy) was delivered after conformal photon radiation to a fixed dose of 50.4 Gy. Biochemical failure was lower after the higher dose of radiation (OR 0.39, 95 percent CI 0.25; 0.62) without increased risk of AEs. Two non randomized clinical trials, phase II[170,171] and several case series from one center of excellence[171-174] reported clinical outcomes in patients with localized prostate cancer more than years after combined proton and photon radiation therapy (Appendix C, Table C21). The authors noted that 86 to 97 percent[170,172] of subjects were disease free at the end of followup and 73 to 88 percent did not have biochemical failure. Distant metastases were diagnosed in 2.5 to 7.5 percent[170,172] of men. Less than 1 percent had GI and urinary toxicity. Absolute rates of outcomes after proton radiation appear similar to other treatments, but there is no direct evidence that proton radiation is better than treatments.

What Is the Impact of Treatments on Overall and Disease-Specific Quality of Life?

Our review included nationally representative prospective studies of men with clinically localized prostate cancer using standardized QOL instruments. More recently developed therapies such as brachytherapy, cryotherapy, laparoscopic or robotic prostatectomy, and IMRT or proton-beam radiation therapy were not specifically assessed in PCOS but are addressed based on results from other studies. We describe quality of life data as reported in randomized studies.

All men up to age 90 years at the time of diagnosis were eligible for entry into PCOS. We focused on a cohort of over 2,000 men with clinically localized prostate cancer who provided survey responses at least 24 months post diagnosis.[75,175] The study cohort had an average age of 66 years (range 39-88). Fifty-seven percent of men undergoing RP were <65 in contrast to 13 percent, 15 percent, and 23 percent of those receiving no treatment, ADT, or EBRT respectively. Men were primarily of White race (72 percent) with approximately 13 percent Black and 13 percent Hispanic. Treatment received did not vary substantially by race (71 to 77 percent were White across treatment categories). Treatment received varied according to baseline health status. Patients reporting excellent to very good baseline general health were less likely to undergo ADT (35 percent of men receiving) or no treatment (43 percent) compared to RP (52 percent) and radiation (45 percent).

Primary health status domains for prostate cancer treatments include urinary, bowel, and sexual questions. Additional measures include general health status, impact of cancer or its treatment on daily activities or relationships with spouse or friends; belief that one is free of cancer,

satisfaction with treatment selected, and likelihood of making the same treatment decision again. PCOS assessed the prevalence and severity of factors at baseline and followup as well as their overall bother. Questions typically referred to health status/events over the month prior to the completed questionnaire. Treatment decisions, outcomes, and bother may vary by patients' baseline health status. In separate PCOS reports, baseline urinary, bowel, and sexual dysfunction and bother were greater in men who received EBRT than in men who received RP.[176,177]

Urinary dysfunction and bother. The odds of being bothered due to dripping or leaking of urine (13.9 percent vs. 3.0 percent) was more than six times greater in RP treated patients than in EBRT after adjusting for baseline variables including age, race, clinical stage, and comorbidity index (Table 13).[75] Incontinence summary scores (Scale 0-100) varied by treatment received and baseline function. Men with normal baseline function declined from 100 to 60 at 6 months for RP and from 100 to 95 for EBRT but increased to 76 and 96 at 2 years. In comparison, patients with lower baseline urinary function scores had no decline at either 6 months or 5 years when treated with EBRT and a modest decline at 5 years if treated with RP (79 at baseline compared with 72 at 5 years; data not shown). The main reasons patients reported bother included night time urination urgency, slow or difficult urination, and frequent urination, which all were reported by greater than 30 percent of individuals who reported bother. These differences were statistically significant between groups (Appendix C, Table C22).

Bowel dysfunction and bother. Bowel dysfunction was more frequent in men receiving EBRT compared to RP. Five percent vs. 4.3 percent of men undergoing EBRT and RP were bothered by frequent bowel movement, pain, or urgency. Bowel summary scores changed little from baseline during 5 years of followup for either treatment regardless of baseline function.

Sexual dysfunction and bother. Sexual dysfunction and bother related to sexual dysfunction was the most common adverse health status effect related to RP or EBRT. The impact on sexual function at 5 years did not differ by these two treatments. The two most frequent reasons for sexual bother were erectile difficulties and inability to satisfy spouse or partner. Sexual function summary scores decreased markedly within 6 months and remained much lower than baseline throughout 5 years of followup for both RP and EBRT regardless of baseline function. For individuals with normal baseline sexual function, sexual summary scores declined from 91 at baseline for both RP and EBT treated patients to 37 and 67 respectively at 6 months and 47 and 50 at 5 years (data not shown). The percentage of individuals in PCOS treated with ADT who stated that they had a big/moderate overall problem with sexual function increased from 22 to 26 percent (4 percent increase) in the orchiectomy group and from 33 to 38 percent (5 percent increase) in the LHRH group. Nearly one-quarter of men who reported no problems before treatment reported they had some problem with sexual function after treatment.

Other outcomes. Over three-quarters of men treated with RP and one-half of those treated with EBRT or brachytherapy believed that they were free of prostate cancer compared to 16 percent vs. 9 percent of those receiving ADT or no treatment respectively (Table 14). General perceptions of prostate cancer health slightly favored orchiectomy compared to LHRH. For example, the percentage of individuals reporting physical discomfort or worry due to prostate cancer as well as rating their overall health as fair or poor was greater with LHRHa. However, more (47 percent vs. 40 percent) LHRHa patients believed they were free from cancer.

Satisfaction with treatment and willingness to choose the same treatment again was similarly high in both groups (Table 14). Scores on the SF-36 general health status scale or any of its domains did not differ between treatments. As noted earlier, a previous AHRQ EPC report addressed ADT for patients with advanced prostate cancer. In these studies, the mean duration of treatment and patient survival was less than 5 years. Therefore, adverse impact on quality of life or other adverse effects due to prolonged treatment were not adequately addressed.

Satisfaction with treatment, general health status, overall impact of cancer, or treatment on daily activities was reported by Hoffman and colleagues at 24 months of followup (Table 14).[175] Less than 5 percent of patients reported that they were dissatisfied, unhappy, or felt terrible about their treatment, with the highest percent (4.9 percent) occurring in those who underwent radical RP. Patients treated with RP more frequently reported that cancer or treatment affected the relationship with their spouse or friends. Financial problems due to cancer or treatment were highest in patients treated with ADT followed by patients 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 did not limit activity or affect relationships with spouses or friends (Appendix C, Tables C23 and C24). Between 91 percent and 95 percent said they would definitely or probably make the same treatment decision again, with the highest percent reported from patients treated with primary ADT and the lowest with RP (Table 14).

Additional analysis of PCOS data assessed prostate cancer-specific health status and bother among men ages 70 years or older (Table 13).[175] Prevalence, severity, and health impact of urinary, bowel, and sexual dysfunction in these older men was similar to the entire cohort. Separate results for men under the age of 65 vs. those over 65 were not provided. Men who underwent aggressive therapy defined as RP/EBRT or brachytherapy were more bothered by dripping or leaking of urine and bowel or sexual problems than men treated with conservative therapy. When adjusted for treatment propensity score, baseline function, age, race, education, and comorbidity score, the extent of bother due to urine, bowel, or sexual dysfunction was 5.1, 2.4, and 2.8 fold higher respectively for older men treated with aggressive rather than conservative therapy. Despite these findings, men treated with aggressive therapy more frequently reported that they were delighted or very pleased with treatment (68.1 percent vs. 52.8 percent) than those treated conservatively (Table 14).[175] There were no differences in physical discomfort, health worry, limitation in daily activities, overall bother, or decisions on whether they would undergo the same treatment again if given the chance.

Other longitudinal cohort studies assessed quality of life in men treated for localized prostate cancer using validated disease-specific health status measures (Appendix C, Table C25).[178-181] Differences between treatment options were few and of small magnitude. Sample sizes ranged from 98-452 subjects and followup lasted 12-18 months.

Lee evaluated patients treated with brachytherapy, EBRT, and RP.[178] Compared to baseline, none of the treatments altered scores on the Functional Assessment of Cancer Therapy-Prostate (FACT-P) overall scores, FACT-General scores, physical well being, or functional well-being scores. International prostate symptom scores (IPSS), a validated symptom scale score typically used to evaluate the presence and severity of benign lower urinary tract symptoms, demonstrated

slight worsening with brachytherapy and improvement with both EBRT and RP. Comparative evaluations between treatments for each of the health related quality of life (HRQOL) scores demonstrated statistically significant differences of small magnitude.

Schapira assessed bother with urinary, sexual, and bowel function using the UCLA Prostate Cancer Instrument (PCI) in 122 patients treated with RP, EBRT, or expectant management.[179] At 12 months there were no significant differences between treatments in any of the domains.

Soderdahl also used the UCLA PCI instruments and determined that patients treated with brachytherapy were significantly less bothered by sexual and urinary problems than those treated with either open or laparoscopic RP.[180] Patients treated with brachytherapy had marginally more bother with bowel function.

Fulmer reported no differences in urinary symptoms between patients treated with RP and those receiving hormonobrachy therapy with or without EBRT.[182] Hormonobrachy therapy patients had less sexual function bother than RP patients.

Galbraith evaluated 185 men treated with WW, RP, and various forms of radiation therapy.[181] After 18 months there were no significant differences in health related quality of life, physical functioning, or general health.

Quality of Life Outcomes in Randomized Controlled Trials

Two RCTs reported on quality of life in patients treated with early intervention compared with deferred treatment or WW. There were no differences in global health status. Fransson and colleagues (Appendix C, Table C26) evaluated conventional or conformal EBRT vs. deferred treatment (not further stated) in 166 enrollees.[41] Questionnaire data were available in 108 subjects with a median time from randomization of 41 months in the radiation therapy group and 30 months in the deferred therapy group. Subjects treated with EBRT therapy were more likely to note limitation in daily activity due to prostate cancer, incontinence, and limitation in daily activity due to intestinal or urinary problems.

Steineck reported on 4-year health status results for 379 surviving subjects enrolled in the SPCG-4 study comparing RP to WW and who completed the survey.[183] Sexual dysfunction, urinary leakage, and distress were greater with RP. Bowel and urinary obstructive symptoms were greater with WW. The relative risk of sexual dysfunction as measured by desire, penile stiffness, intercourse, orgasm, and distress from compromised sexuality was higher in subjects randomized to RP than in those randomized to WW (RR 1.2-18 for specific domains). Urinary tract dysfunction was markedly higher for domains of urinary leakage with 18 percent vs. 2 percent reporting moderate or severe leakage and 29 percent vs. 9 percent saying they had moderate or great distress. Distress from obstructed voiding of moderate to great degree was similar between treatments. Overall distress from all urinary symptoms was reported in 27 percent of those receiving RP and 18 percent in those receiving WW (RR 1.5 [1.0; 2.3]). Bowel function was worse in patients treated with WW with distress from all bowel symptoms occurring in 6 percent of subjects treated with WW compared with 3 percent of those receiving RP. Physical and psychological function did not differ between treatments. Forty to 50 percent reported low or

moderate physical well being and subjective quality of life. Moderate or high worry was reported by 39 and 45 percent of individuals receiving RP and WW respectively.

Table 3. Randomized controlled trials comparing major primary treatment options and reporting any clinical outcome

	Radical Prostatectomy	Watchful Waiting	External Beam Radiotherapy	Adjuvant or Neoadjuvant Therapy	Brachytherapy
Radical Prostatectomy		OS; DSS; DM; AE; QoL	bNED; DM	OS; DSS; bNED; DM; AE	
Watchful Waiting	OS; DSS; DM; AE; QoL				
External Beam Radiotherapy	bNED; DM		OS; DSS; bNED; DM; AE	OS; DSS; bNED; AE	
Adjuvant or Neoadjuvant Androgen Deprivation Therapy	OS; DSS; bNED; DM; AE		OS; DSS; bNED; AE		bNED
Brachytherapy				bNED	bNED; AE

Note: Neither androgen deprivation therapy nor cryotherapy were tested in randomized controlled trials.

OS = Overall survival
DSS = Disease-specific survival
bNED = Biochemical no evidence of disease
DM = Distant metastasis
AE = Adverse effects/toxicity
QoL = Quality of life

Table 4. Description of randomized studies of treatments for localized prostate cancer

Study (reference) Study Characteristics	Interventions	Followup Years	Description of Subjects; Inclusion Criteria
Radical prostatectomy (RP) compared to watchful waiting (WW)			
Bill-Axelson, 2005[44] Method of allocation: Adequate telephone outside clinic Analysis by intention to treat: Yes	1. RP (n=347) 2. WW (n=348)	10 8.2 Median	695 Swedish, Finnish, and Icelandic men, mean age 65 years. Mean PSA (ng/ml): RP 13.5; WW 12.3. Tumor stage: T1b 11.9%; T1c 11.7%; T2 76.1%; unknown 0.3%. Gleason score: 2-4 13.1%; 5-6 47.6%; 7 22.9%; 8-10 5.0%. Percent available to followup/evaluable: 100% Subjects were eligible if <75 years of age; had newly diagnosed untreated localized PC, confirmed with histologic or cytologic exam, with a tumor stage T0 to T2 (tumor had to be well to moderately differentiated – WHO definition); had to be healthy enough to undergo RP; and had a life expectancy >10 years; bone scan had to show no abnormalities; and PSA had to be less than 50 ng/ml.
Iversen,1995[45] / Graversen, 1990[184] Method of allocation: Unclear Analysis by intention to treat: No	1. RP + oral placebo (n=74) 2. WW + oral placebo (n=68)	23 (19-27) Median	142 American men, mean age 64.2, with early carcinoma. Tumor stage: Stage I 53.5%; Stage II 46.5%. Gleason score: ≥4 18.9%; 5-6 67.6%; 7-10 9.9%; unknown 3.6%. Percent available to followup/evaluable: 78.2% (31 excluded from the analyses).
RP with or without androgen deprivation therapy (ADT) compared to RP combined with neoadjuvant ADT			
Homma,2004[47] Method of allocation: Unclear, Blinding: The pathologist was informed of the patient's treatment group (endocrine therapy may interfere with accuracy of judgment of histologic differentiation) Analysis by intention to treat: No	1. RP followed by adjuvant ADT (leuprolide + chlormadinone for 3 months followed by leuprolide alone) (n=86) 2. RP + 3 months neoadjuvant ADT (leuprolide + chlormadinone for 3 months followed by adjuvant ADT (leuprolide alone) (n=90)	5	224 Japanese men. Tumor stage: A_2 12%; B_1 25%; B_1 38%. Age, PSA, and histologic differentiation contaminated with C stage subjects. Percent available to followup/evaluable: 78.6% (48 excluded from interim analyses). Subjects were eligible if they had histologically confirmed untreated clinical stage A_2, B, or C PC; serum testosterone concentration of ≥1.0 ng/ml; age ≤80 years; and absence of any contraindication to RP or the test drugs.

Table 4. Description of randomized studies of treatments for localized prostate cancer (continued)

Study (reference) Study Characteristics	Interventions	Followup Years	Description of Subjects; Inclusion Criteria
Klotz, 2003, 1999 [48,185] Method of allocation: Adequate Analysis by intention to treat: Yes*	1. RP (n=101) 2. RP + 3 months neoadjuvant ADT (cyproterone 100 mg t.i.d.) (n=112)	5.9 Median	213 Canadian men, median age 63.5. PSA (ng/ml): <10 54%, 10-20 27.2%, >20 16.4%. Tumor stage: T1b/c 8.9%; T2a 33.3%; T2b 18.8%, T2c 34.3%. Gleason score sum: 2-6 69.5%, 7 17.1%, 8-10 10.3%. Percent available to followup/evaluable: 93.9% (13 excluded from the analyses). Subjects were eligible if they had histologically confirmed untreated clinically localized PC (stages T1/T2); negative bone scan; enzymatic prostatic acid phosphatase less than twice normal (<1.8 units/L); and PSA <50 ng/ml.
Schulman, 2000 [49] Method of allocation: Unclear Analysis by intention to treat: No	1. RP (n=210) 2. RP + 3 months neoadjuvant ADT (goserelin monthly and flutamide 250 mg t.i.d) (n=192)	4	487 European men locally confined PC. Tumor stage: T2 54.7%. Percent available to followup/evaluable: 82.5% (85 excluded from the analyses). Subjects were eligible if they histologically confirmed T2/T3NxM0 PC with a PSA <100 ng/ml.
Soloway, 2002 [50] Lupron Depot Prostate Cancer Study Group Method of allocation: Unclear Analysis by intention to treat: No	1. RP (n=154) 2. RP + 3 months neoadjuvant ADT (leuprolide acetate 7.5 mg per month and flutamide 250 mg t.i.d.) (n=149)	5	303 American men, mean age 65 years, with tumor stage T2b PC. Mean PSA (ng/ml) 13.4. Mean Gleason score 6. Mean prostate volume 36.1 cc. White race 68%. Percent available to followup/evaluable: 93.1% (21 excluded from the analyses). Subjects were eligible if they were <75 years of age, had a PSA <50 ng/ml, and had a normal bone scan
RP combined with neoadjuvant ADT, comparison of different regimens			
Gleave, 2001;[51] Toxicity only Method of allocation: Unclear Analysis by intention to treat: No	1. RP + 3 months neoadjuvant ADT (leuprolide acetate 7.5 mg per month and flutamide 250 mg t.i.d.) (n=273) 2. RP + 8 months neoadjuvant ADT (leuprolide acetate 7.5 mg per month and flutamide 250 mg t.i.d.) (n=274)	3 and 8 months	547 Canadian men, mean age 62.6 years, with clinically confirmed PC. PSA (ng/ml): ≤10 62.9%; 11-20 27.2%; >20 9.5%. Tumor stage: T1b 2.6%; T1c 29.1%; T2a 28.9%; T2b 32.9%, T2c 6.6%. Gleason score: ≤3 68.2%, 4-5 31.8%. White race 93%. Percent available to followup/evaluable: 92% (44 excluded from the analyses). Subjects were eligible if they required RP for previously untreated, histologically confirmed clinical stage T1b to T2 PC. Exclusion criteria: Prior RT or hormonal therapy, concomitant use of medications with antiandrogen activity, prior history of cancer (except basal cell carcinoma of the skin), or severe renal or hepatic impairment.

Table 4. Description of randomized studies of treatments for localized prostate cancer (continued)

Study (reference) Study Characteristics	Interventions	Followup Years	Description of Subjects; Inclusion Criteria
RP compared to external beam radiotherapy (EBRT)			
Paulson, 1982[46] Method of allocation: Unclear Analysis by intention to treat: No	1. RP (n=47) 2. EBRT, 4,500-5,000 rad. (n=59)	Unclear, analysis up to 5 years	106 American men with clinical stage A2 or B (T1/T2) PC. Percent available to followup/evaluable: 91.5% (9 excluded from the analyses). Exclusion criteria: Subjects with occult focal carcinoma or patients with stage C disease.
EBRT, comparison of different regimens			
Peeters, 2006[62] Method of allocation: Unclear Analysis by intention to treat: Yes	1. Conventional dose (68 Gy) EBRT group (n=332) 2. High dose (78 Gy) EBRT group (n=337)	4.2 Median	669 Dutch men, mean age 68.7 years. Tumor stage: T1 18.7%; T2 44%. Age, PSA, and Gleason score contaminated with T3/4 stage subjects. Percent available to followup/evaluable: 99.3% (5 excluded from the analyses). Subjects were eligible if they had PC (any stage) with PSA <60 mg/ml, except T1a and well differentiated (or Gleason score <5) T1b-c tumors with PSA ≤4 mg/ml; and Karnofsky performance score ≥80. Exclusion criteria: Patients with metastases, with cystologically or histologically proven positive regional lymph nodes, on anticoagulants, with previous pelvic irradiation and with malignancy (except basal cell carcinoma).
Yeoh, 2006[55] Method of allocation: Adequate Analysis by intention to treat: Yes	1. Hypofractionated (55 Gy) EBRT group (n=108) 2. Conventional (64 Gy) EBRT (n=109)	5 4 Median	217 Australian men, median age 69 years (range 44 to 82), with localized, early stage (T1/T2N0M0) PC. Gleason score: 2-6 79.7%; 7 14.3%; 8-10 6%. Percent available to followup/evaluable: 100%
Lukka,2005[52] Method of allocation: Adequate Analysis by intention to treat: Yes	1. Long (conventional) arm (66 Gy in 33 fractions) EBRT (n=470) 2. Short (hypofractionated) arm (52.5 Gy in 20 fractions) EBRT (n=466)	5.7 Median	936 Canadian men with early stage PC (T1 or T2), mean age 70 (range 53-84). Mean PSA (ng/ml): 10.5. Tumor stage: T1a <1%; T1b 2%; T1c 25%; T2a 27%; T2b 27%; T2c 18%. Gleason score: 2-4 8%; 5 14%; 6 38%; 7 31%; 8-9 9%. Percent available to followup/evaluable: 100% Subjects were eligible if they had early stage PC (T1 or T2). Exclusion criteria: PSA >40 ng/ml; previous therapy for PC; previous hormone therapy; prior or active malignancy (except nonmelanoma skin cancer, colon cancer, or thyroid cancer treated ≥5 years before trial and presumed cured); previous pelvic radiotherapy; inflammatory bowel disease; a serious nonmalignant disease that would preclude radiotherapy or surgery biopsy; psychiatric or addictive disorder.

Table 4. Description of randomized studies of treatments for localized prostate cancer (continued)

Study (reference) Study Characteristics	Interventions	Followup Years	Description of Subjects; Inclusion Criteria
Sathya, 2005[53] Method of allocation: Adequate Analysis by intention to treat: Yes	1. EBRT (66 Gy) + Iridium implant (n=51) 2. EBRT (66 Gy) (n=53)	8.2 Median	138 Canadian men, mean age 66 (range 49-74). Tumor stage: T2 61%. Age, PSA, and Gleason score contaminated with T3 stage subjects. Percent available to followup/evaluable: 75.4% (34 excluded from the analyses). Subjects were eligible if they had histologically proven PC with clinical stage T2 or T3, N0, M0 and had to be fit to undergo pelvic lymphadenectomy as a staging procedure. Exclusion criteria: Prior history of pelvic radiotherapy or RP, androgen ablation, or TURP or evidence of metastatic disease using computed tomography (CT) scan and bone scan.
Zietman, 2005[56] Method of allocation: Unclear Analysis by intention to treat: Yes*	1. Conventional dose (70.2 Gy) EBRT group (n=197): EBRT=3D conformal proton 50.4 Gy and proton boost 19.8 Gy) 2. High dose (79.2 Gy) EBRT group (n=196): EBRT = 3D conformal proton 50.4 Gy and proton boost 28.8 Gy	5 5.5 Median	393 American men, median age 67 years (range 45-91). Median PSA (ng/ml): 6.3. Tumor stage (AJC 1992): T1b <1%; T1c 61.2%; T2a 23.7%; T2b 14.8%. Gleason score: 2-6 75.3%; 7 15.3%; 8-10 8.4%. Risk group: Low (PSA <10 ng/ml, ≤T2a stage, Gleason ≤6) 57.9%; Race: White 90.3%; black 4.3%; Hispanic 2.8%; other 2.6%. Percent available to followup/evaluable: 99.7% (1 excluded from the analyses). Subjects were eligible if they had clinically localized PC (stage T1b through T2b, PSA <15 ng/ml and no evidence of metastatic disease as assessed by both whole-body bone scan (with PSA level >10 ng/ml, tumor stage T2b, or Gleason score ≥7) and abdominopelvic computed tomography scan. There was no exclusion from entry based on basis of tumor histology (Gleason score).
EBRT combined with ADT compared to EBRT alone			
Denham, 2005[61] Method of allocation: Adequate Analysis by intention to treat: Yes*	1. EBRT (66 Gy) and no ADT (n=276) 2. EBRT + 2 months neoadjuvant and 1 month adjuvant ADT (goserelin acetate monthly and flutamide 250 mg t.i.d.) (n=270) 3. EBRT + 5 months neoadjuvant and 1 month adjuvant androgen deprivation (goserelin acetate monthly and flutamide 250 mg t.i.d.) (n=272)	5.9 Median	818 Australian and New Zealand men, median age 68 (range 41-87). Tumor stage (TNM 1992): T2b 26%; T2c 34%. Age, PSA, and Gleason score contaminated with T3/4 stage subjects. Percent available to followup/evaluable: 98% (16 excluded from the analyses). Subjects were eligible if they did not have substantial comorbidity (of a severity that would limit survival to ≤5 years in the absence of PC) or previous malignant disease; stage T2b-T4 PC without evidence of lymph-node involvement, bone metastases, or metastases at other sites.

Table 4. Description of randomized studies of treatments for localized prostate cancer (continued)

Study (reference) Study Characteristics	Interventions	Followup Years	Description of Subjects; Inclusion Criteria
D'Amico, 2004[58] Method of allocation: Adequate Analysis by intention to treat: Yes	1. Conformal (70 Gy) EBRT (n=104). 2. Conformal (70 Gy) EBRT + adjuvant ADT (leuprolide 7.5 mg each month or 22.5 mg IM every 3 months (n=88) or goserelin 3.6 each month or 10.8 mg every 3 months SC (n=10) combined with flutamide 250 mg t.i.d.) (n=102).	4.5 Median	206 American men, mean age 72.5 years. Mean PSA (ng/ml): 11. Tumor stage AJC 1992): T1b 1.9%; T1c 46.1%; T2a 22.3%; T2b 22.8%. Gleason score: mean 7; 5 or 6 27.7%; 3+4 35%; 4+3 22.8%; 8-10 14.6%. Prostate volume (ml) 39. Percent available to followup/evaluable: 100% Subjects were eligible if patient had PSA ≥10 ng/ml (40 ng/ml maximum) or a Gleason score ≥7 (range 5-10). Low-risk patients ineligible unless there was radiographic evidence using MRI of extracapsular extension or seminal invasion. Exclusion criteria: Prior history of malignancy (except nonmelanoma skin cancer) or any history of hormone use.
EBRT combined with neoadjuvant ADT, comparison of different regimens			
Crook, 2004[57] Method of allocation: Adequate Analysis by intention to treat: No	1. EBRT + 3 months neoadjuvant ADT (goserelin monthly for a total of 3 or 8 injections and flutamide 250 mg t.i.d.) (n=177) 2. EBRT + 8 months neoadjuvant ADT (n=184)	3.7 Median	378 (17 excluded from analyses) Canadian men, median age 72 (range 50-85) with clinically localized PC. Tumor stage (TNM 1997): T1c/T2a 52.6%; T2b/T2c 34.1%. Age, PSA, and Gleason score contaminated with T3 stage subjects. Percent available to followup/evaluable: 95.5% (17 excluded from the analyses). Subjects were eligible if they had a histologic diagnosis of adenocarcinoma of the prostate with all Gleason scores and PSA levels, and clinical stages from T1c to T4), normal baseline hepatic and renal function, and estimated life expectancy >5 years.
Brachytherapy, ^{125}I compared to ^{103}Pd			
Wallner, 2003[59] / Herstein, 2005[64] Method of allocation: Adequate Analysis by intention to treat: No	1. ^{125}I 144 Gy (n=63) 2. ^{103}Pd 125 Gy (n=63)	3	126 (of 492 of a planned total of 600) American men with 1997 American Joint Commission on Cancer (AJC) clinical stage T1c-T2a, Gleason 2-6 (mean 5.9), PSA 4-10 ng/ml (mean 6.9) PC. 115 subjects included in the analyses. Percent available to followup/evaluable: 91.3% (11 excluded from the analyses). Herstein (2005) assesses long-term radiation related morbidities in 314 men.
Adjuvant EBRT combined with brachytherapy, comparison of different regimens			
Wallner, 2005[43] Method of allocation: Adequate Analysis by intention to treat: No	1. ^{103} Pd 125 Gy + EBRT (20 Gy) (n=85) 2. ^{103} Pd 125 Gy + EBRT (44 Gy) (n=80)	3 2.9 Median	165 (of a planned total of 600) American men with 1997 AJC clinical stage T1c-T2a, Gleason 7-10 (mean 7.0) and/or PSA 10-20 ng/ml (mean 6.9) PC. 159 subjects included in the analyses. Percent available to followup/evaluable: 91.3% (11 excluded from the analyses).

Table 4. Description of randomized studies of treatments for localized prostate cancer (continued)

Study (reference) Study Characteristics	Interventions	Followup Years	Description of Subjects; Inclusion Criteria
Adjuvant bicalutamide compared to placebo; both treatment arms combined with standard care (RP, EBRT, or WW)			
Wirth, 2004[63] Analysis of 3 RCTs Analysis by intention to treat: Unclear (not reported)	1. Bicalutamide 150 mg daily (n=4,052) 2. Placebo (n=4,061) Trial 23: Standard care received: RP 80%; RT 20% Trial 24: Standard care received: RP 46%; RT 18%; WW 36% Trial 25: Standard care received: RP 13%; RT 5%; WW 81%	5.4	8,113 multinational men with localized or locally advanced PC Trial 23: 3,292 North American men, mean age 64 (38-85). Tumor stage: T1/T2 73%. Trial 24: 3,603 European, South African, Israeli, Australian, and Mexican men, mean age 69 (48-93). Tumor stage: T1/T2 65%. Trial 25: 1,218 Scandinavian men, mean age 69 (48-87). Tumor stage: T1/T2 60%. Age, PSA, and Gleason score contaminated with T3 stage subjects. Percent available to followup/evaluable: Unclear Subjects were eligible if patient was ≥18 (75 years of age upper limit for trial 25) with clinically or pathologically diagnosed T1-T4 PC with no distant metastases.
Vaccine compared to nilutamide			
Arlen, 2005[60] Phase II trial conducted at NCI Method of allocation: Unclear Analysis by intention to treat: Yes	1. Vaccine consisting of recombinant vaccinia viruses containing PSA and B7.1 costimulatory genes (prime vaccinations) and avipox PSA (as boosters) (n=21). Patients also received granulocyte-macrophage colony stimulating factor and interleukin-2 as part of their vaccination schedule. 12 subjects received nilutamide at time of PSA progression. 2. Nilutamide 300 mg qd x 1 month, then 150 mg qd (n=21). 8 subjects received vaccine at time of PSA progression.	Unclear	42 American men with hormone refractory PC, mean age 68 years (range 51-87). Mean PSA: vaccine 35.1; nilutamide 19.32. Gleason score: mean 7; score 2-4 4.8%; 5-7 47.6%; 8-10 40.5%; unknown 7.1%. Current testosterone decreasing Rx: goserelin acetate 21.4%; leuprolide acetate 54.8%; orchiectomy 23.8%. Prior antiandrogens: 0 16.7%; 1 54.8%; 2 28.6%. Subjects were eligible if castrate levels of serum testosterone <50 ng/dl. Subjects with failed prior antiandrogen Rx were required to have 2 consecutive increasing serum PSA levels a week apart, measure ≥6 weeks after bicalutamide withdrawal or 4 weeks after flutamide withdrawal. Subjects need Zubrod performance status 0 or 1. Have adequate hematological, hepatic and renal function. No evidence of an immunocompromised condition, no diagnosis of altered immune function, no prior radiotherapy to more than 50% of nodal groups. Exclusion criteria: Egg allergy, skin disorder, history of seizures, serious intercurrent illnesses, close contact with immunocompromised individuals, contact with individuals with skin disorders or children <5 years old, prior nilutamide therapy.

* If subject received treatment. Reasons for exclusion included lost to followup, previous malignant disease, withdrew early from trial, or chose other treatment.

Table 5. Overall mortality or survival for randomized controlled trials

Study Outcomes	Treatment Group	Control Group	Analyses; p-values
RP compared to WW			
Bill-Axelson, 2005[44]	RP (n=347)	WW (n=348)	Absolute Risk Reduction (ARR) [95% CI] Relative Risk (RR) [95% CI]
Total number of deaths	83	106	p=0.04 all deaths
Cumulative incidence of death	7.8% [5.4 to 11.2]* at 5 years 27.0% [21.9 to 33.1] at 10 years	9.8% [7.1 to 13.5] at 5 years 32.0% [26.9 to 38.2] at 10 years	ARR: 2.0 [-2.2 to 6.2] at 5 years ARR: 5.0 [-2.8 to 13.0] at 10 years RR: 0.74 [0.56 to 0.99] at 10 years
Median followup: 8.2 years			
Iversen, 1995[45]	RP plus placebo (n=74)	WW and placebo (n=68)	p value
Total number of deaths	67	63	Not significant
Median survival	10.6 years	8 years	
Median followup: 23 years (19 to 27)			
RP compared to RP combined with neoadjuvant ADT			
Klotz, 2003[48]	RP (n=101)	RP + neoadjuvant ADT (n=112)	p value
Total number of deaths	5	8	0.38
Overall survival at 5 years	88.4% [80.6 to 96.3]	93.9% [88.6 to 99.1]	
Median followup: 6 years (0.6 to 9.8)			
EBRT comparison of different regimens			
Yeoh,2006[55]	Hypofractionated (55 Gy) EBRT group (n=108)	Conventional (64 Gy) EBRT (n=109)	p value
Total number of deaths	35 total (both groups)		
Overall survival at 5 years	86.4%	84.1%	Not significant
Median followup: 4 years (0.5 to 9)			
Lukka, 2005[52]	Long arm (66 Gy) EBRT (n=470)	Short arm (52.5 Gy) EBRT (n=466)	HR [95% CI]
Total number of deaths	89	77	0.85 [0.63 to 1.15]
Overall survival at 5 years	85.2%	87.6%	
Median followup: 5.7 years (4.5 to 8.3)			
Zietman, 2005[56]	Conventional dose (70 Gy) EBRT (n=197)	High dose (79.2 Gy) EBRT (n=196)	p Value
Total number of deaths	10	8	0.80
Overall survival at 5 years	97%	96%	
Median followup: 5.5 years (1.2 to 8.2)			

Table 5. Overall mortality or survival for randomized controlled trials (continued)

Study Outcomes	Treatment Group	Control Group	Analyses; p-values
EBRT combined with ADT compared to EBRT alone			
D'Amico, 2004[58]	Conformal EBRT (70 Gy) Group (n=103)	Conformal EBRT (70 Gy) + adjuvant ADT (n=98)	p value HR [95% CI]
Total number of deaths	23	12	0.04
Overall survival at 5 years	78% [68 to 88]	88% [80 to 95]	2.07 [1.02 to 4.20]
Median followup: 4.5 years			
Adjuvant bicalutamide compared to placebo; both treatment arms combined with standard care (RP, EBRT, or WW)			
Wirth, 2004[63]	Bicalutamide and adjuvant therapy	Placebo and adjuvant therapy	p value
Localized disease population (T1/T2)	*(estimated n=1,908)*	*(estimated n=1,891)*	HR [95% CI]
Total number of deaths	187 (9.8%)	182 (9.6%)	0.97
Median followup: 5.4 years			1.01 [0.82 to 1.23]
	Bicalutamide and WW	Placebo and adjuvant therapy	p value
	(estimated n=777)	*(estimated n=850)*	
Total number of deaths	196 (25.2%)	174 (20.5%)	0.05
Median followup: 5.4 years			1.23 [1.00 to 1.50]
Vaccine compared to nilutamide			
Arlen, 2005[60]	Vaccine Group (n=21)	Nilutamide Group (n=21)	
Total number of deaths	3**	7**	

* 95% Confidence intervals
** Includes crossover deaths

Table 6. Clinical outcomes after different treatments in patients with localized prostate cancer

Design	Quality	Studies Reference	Treatment Group (Sample Size)	Control Group (Sample Size)	Effect Odds Ratio of Death (95% CI)
RCT	Moderate	1 Bill-Axelson, 2005[186]	RP (n=347) at 10 years	WW (n=348) at 10 years	0.74 (0.56; 0.99)
RCT	Moderate	1 Iversen, 1995[45]	RP (n=74)	WW and placebo(n=68)	0.76 (0.23; 2.52)
RCT	Moderate	1 Klotz, 1999[185]	RP (n=101)	Neoadjuvant androgen ablation + RP (n=112)	0.68 (0.21; 2.14)
RCT	Moderate	1 Lukka, 2005[52]	EBRT Long arm (66 Gy in 33 fractions) (n=470)	EBRT Short arm (52.5 Gy in 20 fractions) (n=466)	1.18 (0.84; 1.65)
RCT	Moderate	1 Zietman, 2005[56]	EBRT Conventional dose (70 Gy) (n=197)	EBRT High dose (79.2 Gy) (n=196)	1.26 (0.48; 3.25)
RCT	Moderate	1 D'Amico, 2004*[58]	Conformal radiation therapy (70 Gy) (n=103)	Conformal radiation therapy and androgen suppression therapy (n=98)	2.06 (0.96; 4.41)
RCT	Moderate	1 Wirth, 2004[63]	Bicalutamide and adjuvant therapy *(estimated n=1,908)*	Placebo and adjuvant therapy *(estimated n=1,891)*	1.02 (0.82; 1.26)
RCT	Moderate	1 Wirth, 2004[63]	Bicalutamide and WW *(estimated n=777)*	Placebo and adjuvant therapy *(estimated n=850)*	1.31 (1.04; 1.65)

Table 7. Main results. Scandinavian Prostatic Cancer Group

Main Results SPCG-4	Over the next **10 years**, what percent of men with new, clinically diagnosed prostate cancer will experience each of the following if they undergo:	
Outcomes	**Radical Prostatectomy**	**Watchful Waiting**
Benefits due to treatment		
Dying from prostate cancer	9.6%	14.9%
Developing metastatic disease	15.2%	25.4%
Developing local progression	19.2%	44.3%
Harm due to treatment at 4 years		
Impotence	80%	45%
Incontinence	49%	21%
Weak urinary stream	28%	44%
Overall benefits vs. harm		
Quality of life after 4 years	*No difference*	
Dying for any reason at 10 years	27.0%	32.0%
Number of men needed to treat with RP to prevent 1 death at 10 years		19

Table 8. Biochemical progression/reoccurrence or bNED after different treatments in patients with localized prostate cancer

Design	Quality	Studies Reference	Treatment Group	Control Group	Definition	Effect Odds Ratio (95% CI)
RCT	Moderate	1 Klotz, 1999[185]	RP (n=101)	Neoadjuvant androgen ablation + RP (n=112)	2 consecutive detectable PSAs (>2.0 ng/ml) at least 4 weeks apart, re-treatment or death from prostate cancer	0.85 (0.51; 1.41)
RCT	Moderate	1 Lukka, 2005[52]	EBRT long arm (66 Gy in 33 fractions); (n=470)	EBRT short arm (52.5 Gy in 20 fractions); (n=466)	3 consecutive increases in PSA, clinical evidence of failure (local and distant), initiation of hormonal therapy	0.78 (0.6; 1.01)
RCT	Moderate	1 Zietman, 2005[56]	EBRT high dose (79.2 Gy); (n=197)	EBRT conventional dose (70 Gy) (n=196)	3 consecutive increases in PSA level, with the failure backdated to a point halfway between the first increase and the last nonincreasing value	0.39 (0.25; 0.62)
RCT	Moderate	1 D'Amico, 2004[58]	Conformal radiation therapy and androgen suppression therapy (n=103)	Conformal radiation therapy (70 Gy) (n=98)	PSA >1.0 ng/ml and increasing >0.2 ng/ml on 2 consecutive visits	0.34 (0.18; 0.63)
RCT	Moderate	1 Wirth, 2004[63]	Bicalutamide and RP *(estimated n=1365)*	Placebo and radical prostatectomy *(estimated n=1,369)*	The time from randomization to the earliest occurrence of objective progression (confirmed by bone scan, computerized tomography/ ultrasound/MRI or histological evidence of distant metastases)	0.95 (0.73; 1.24)
RCT	Moderate	1 Paulson, 1982[46]	RP (n=47)	Radiation therapy (n=59)	Acid phosphatase elevation on 2 consecutive followups or appearance of bone or parenchymal disease with or without acid phosphatase elevation	0.27 (0.11; 0.71)
RCT	Moderate	1 Homma, 2004[47]	RP (n=63, stage A and B)	RP and neoadjuvant androgen deprivation (n=69, stage A and B)	PSA above the normal level, local reoccurrence, or distant metastases	0.88 (0.4; 1.93)
RCT	Moderate	1 Schulman, 2000[49]	RP (n=115, T2 only)	Neoadjuvant androgen ablation + RP (n=105, T2 only)	Increase in PSA on 2 consecutive occasions of >1.0 ng/ml	1.41 (0.84; 2.38)
RCT	Moderate	1 Soloway, 2002[50]	RP (n=154)	Neoadjuvant androgen ablation + RP (n=149)	PSA >0.4 ng/ml	1.12 (0.7; 1.77)

Table 8. Biochemical progression/reoccurrence or bNED after different treatments in patients with localized prostate cancer (continued)

Design	Quality	Studies Reference	Treatment Group	Control Group	Definition	Effect Odds Ratio (95% CI)
RCT	Moderate	1 Yeoh, 2006[55]	Conventional EBRT (n=61)	Hypo fractionated EBRT (n=59)	3 consecutive increases in PSA after nadir	1.10 (0.4; 3.08)
RCT	Moderate	1 Sathya, 2005[53]	EBRT: (n=32, T2 only)	Iridium implant + EBRT (n=31, T2 only)	PSA failure, clinical failure	3.67 (1.27; 10.7)
RCT	Moderate	1 Crook, 2004[57]	Hormonal therapy combined with radiation therapy 8 months (n=41, low risk T1c-T2a; PSA <10 ng/ml; Gleason ≤6)	Hormonal therapy combined with radiation therapy 3 months (n=51, low risk T1c-T2a; PSA <10 ng/ml; Gleason ≤6)	Freedom from failure was biochemical (PSA) disease-free survival according to ASTRO definition	0.64 (0.27; 1.54)
RCT	Moderate	1 Wallner, 2003[59]	Brachytherapy ^{125}I (n=57)	Brachytherapy ^{103}I (n=58)	PSA ≤0.5 ng/ml at last follow up	1.25 (0.36; 4.34)
RCT	Moderate	1 Wallner, 2005[43]	Adjuvant EBRT combined with brachytherapy: ^{103}Pd + EBRT (44 Gy) (n=76)	Adjuvant EBRT combined with brachytherapy: ^{103}Pd + EBRT (20 Gy); (n=83)	PSA ≤0.5 ng/ml at last follow up	1.97 (0.88; 4.4)
RCT	Moderate	1 Wirth, 2004[63]	Bicalutamide and radiation therapy *(estimated n=538)*	Placebo and radiation therapy *(estimated n=527)*	Time from randomization to the earliest occurrence of objective progression (confirmed by bone scan, computerized tomography/ ultrasound/MRI or histological evidence of distant metastases)	0.84 (0.63; 1.12)

Table 9. Distant failure after different treatments in patients with localized prostate cancer

Design	Quality	Studies Reference	Active	Control	Active, %	Control, %	Odds Ratio (95% CI)	%*	**	***
RCT	Moderate	1 Bill-Axelson, 2005[186]	RP	WW	15.2	25.4	0.60 (0.42; 0.86)	47.4	10	102
RCT	Moderate	1 Paulson, 1982[46]	RP	Radiation therapy	4.3	23.7	0.14 (0.05; 0.42)	85.7	5	195
RCT	Moderate	1 Klotz, 2003[48]	RP	Neoadjuvant androgen ablation + RP	1.0	4.5	0.21 (0.02; 1.92)	78.6	29	35
RCT	Moderate	1 Schulman, 2000[49]	RP	Neoadjuvant androgen ablation + RP	5.0	6.0	0.83 (0.24; 2.80)	17.5	100	10
RCT	Moderate	1 Soloway, 2002[50]	RP	Neoadjuvant androgen ablation + RP	6.0	6.0	1.00 (0.31; 3.21)			
RCT	Moderate	1 Lukka, 2005[52]	Long arm (66 Gy in 33 fractions) EBRT	Short arm (52.5 Gy in 20 fractions)	1.0	2.0	0.50 (0.04; 5.55)	50.5	100	10

* attributable fraction of events among exposed
** number needed to treat to avoid distant failure in one patient
*** number of avoided events per 1,000 treated

Table 10. Adverse events and toxicity for randomized controlled trials

Study Outcomes	Treatment Group	Control Group	Analyses; p-values
RP with or without neoadjuvant therapy			
Gleave, 2001[51]	3 months neoadjuvant androgen ablation + radical prostatectomy (n=273)	8 months neoadjuvant androgen ablation + radical prostatectomy (n=274)	p value
Newly reported adverse effects	2.9	4.5	<0.0001
Hot flashes	72%	87%	<0.0001
Fatal AEs	None	None	
Severity of AEs	Not reported	Not reported	0.287
Causality of AEs	Not reported	Not reported	0.0564
Increased liver enzymes	Not reported	Not reported	0.691
Diarrhea	Not reported	Not reported	0.288
EBRT			
Lukka, 2005[52]	Long arm (66 Gy in 33 fractions) EBRT (n=470)	Short arm (52.5 Gy in 20 fractions) EBRT (n=466)	% Difference [95% CI]*
Number of subjects with Acute NCIC** Grade 3/4 toxicity, ≤5 months			
GI system	12 (2.6%)	19 (4.1%)	-1.5 [-4.0 to 0.8]
GU system	23 (4.9%)	40 (8.6%)	-3.7 [-7.0 to -0.5]
GI or GU	33 (7.0%)	53 (11.4%)	-4.4 [-8.1 to -0.6]
Number of subjects with Late NCIC** Grade 3/4 toxicity, >5 months			
GI	6 (1.3%)	6 (1.3%)	0.0 [-1.7 to 1.6]
GU	9 (1.9%)	9 (1.9%)	0.0 [-1.9 to 1.9]
GI or GU	15 (3.2%)	15 (3.2%)	0.0 [-2.4 to -2.3]
Yeoh, 2003[54]	Conventional (64 Gy) EBRT (n=61)	Hypofractionated (55 Gy) EBRT group (n=59)	p value compared to Series 1
GI Symptoms, patients scoring ≥1 before RT			
Abnormal frequency of bowel movements	27 (44%)	31 (53%)	
Diarrhea	13 (21%)	15 (26%)	
Pain on using bowels	2 (3%)	4 (7%)	
Mucous discharge from bowel	4 (5%)	5 (9%)	
Urgency of defecation	22 (38%)	16 (28%)	
Rectal bleeding	5 (9%)	4 (7%)	
1 month after RT			
Abnormal frequency of bowel movements	43 (69%)	43 (75%)	
Diarrhea	27 (44%)	21 (37%)	
Pain on using bowels	23 (37%)	24 (41%)	
Mucous discharge from bowel	17 (27%)	22 (39%)	
Urgency of defecation	29 (47%)	36 (59%)	
Rectal bleeding	8 (13%)	13 (23%)	

Table 10. Adverse events and toxicity for randomized controlled trials (continued)

Study Outcomes	Treatment Group	Control Group	Analyses; p-values
2 years after RT			
Abnormal frequency of bowel movements	32 (58%)	30 (59%)	
Diarrhea	18 (33%)	18 (35%)	
Pain on using bowels	9 (16%)	6 (12%)	
Mucous discharge from bowel	17 (31%)	10 (20%)	
Urgency of defecation	24 (44%)	26 (51%)	
Rectal bleeding	15 (27%)	21 (42%)	64 Gy <0.05; 55 Gy <0.05
GU Symptoms, patients scoring ≥1 before RT			
Abnormal urinary frequency by day	52 (84%)	45 (80%)	
Abnormal urinary frequency by night	25 (40%)	27 (47%)	
Hematuria	2 (3%)	3 (5%)	
Urgency of urination	23 (37%)	26 (46%)	
Dysuria	8 (13%)	11(19%)	
1 month after RT			
Abnormal urinary frequency by day	56 (92%)	52 (92%)	
Abnormal urinary frequency by night	39 (64%)	41 (72%)	
Hematuria	3 (5%)	3 (6%)	
Urgency of urination	31 (51%)	36 (63%)	
Dysuria	17 (28%)	21 (37%)	
2 years after RT			
Abnormal urinary frequency by day	38 (69%)	36 (71%)	
Abnormal urinary frequency by night	23 (42%)	24 (47%)	
Hematuria	2 (4%)	2 (4%)	
Urgency of urination	20 (36%)	24 (47%)	
Dysuria	5 (9%)	3 (6%)	
Zietman, 2005[56]	Conventional dose (70.2 Gy) group (n=196)	High dose (79.2 Gy) group (n=195)	p value
Acute symptoms, RTOG scale 0-4:			
GU, Grade 1	79 (40%)	69 (35%)	
GU, Grade 2	82 (42%)	95 (49%)	Not significant
GU, Grade 3	2 (1%)	2 (1%)	
GU, Grade 4	0	1 (1%)	
GI, Grade 1	62 (31%)	48 (25%)	
GI, Grade 2	81 (41%)	112 (57%)	0.004
GI, Grade 3	2 (1%)	0	
GI, Grade 4	0	0	
Late symptoms, RTOG scale 0-4:			
GU, Grade 1	85 (43%)	84 (43%)	
GU, Grade 2	35 (18%)	39 (20%)	
GU, Grade 3	3 (2%)	1 (1%)	
GU, Grade 4	0	0	

Table 10. Adverse events and toxicity for randomized controlled trials (continued)

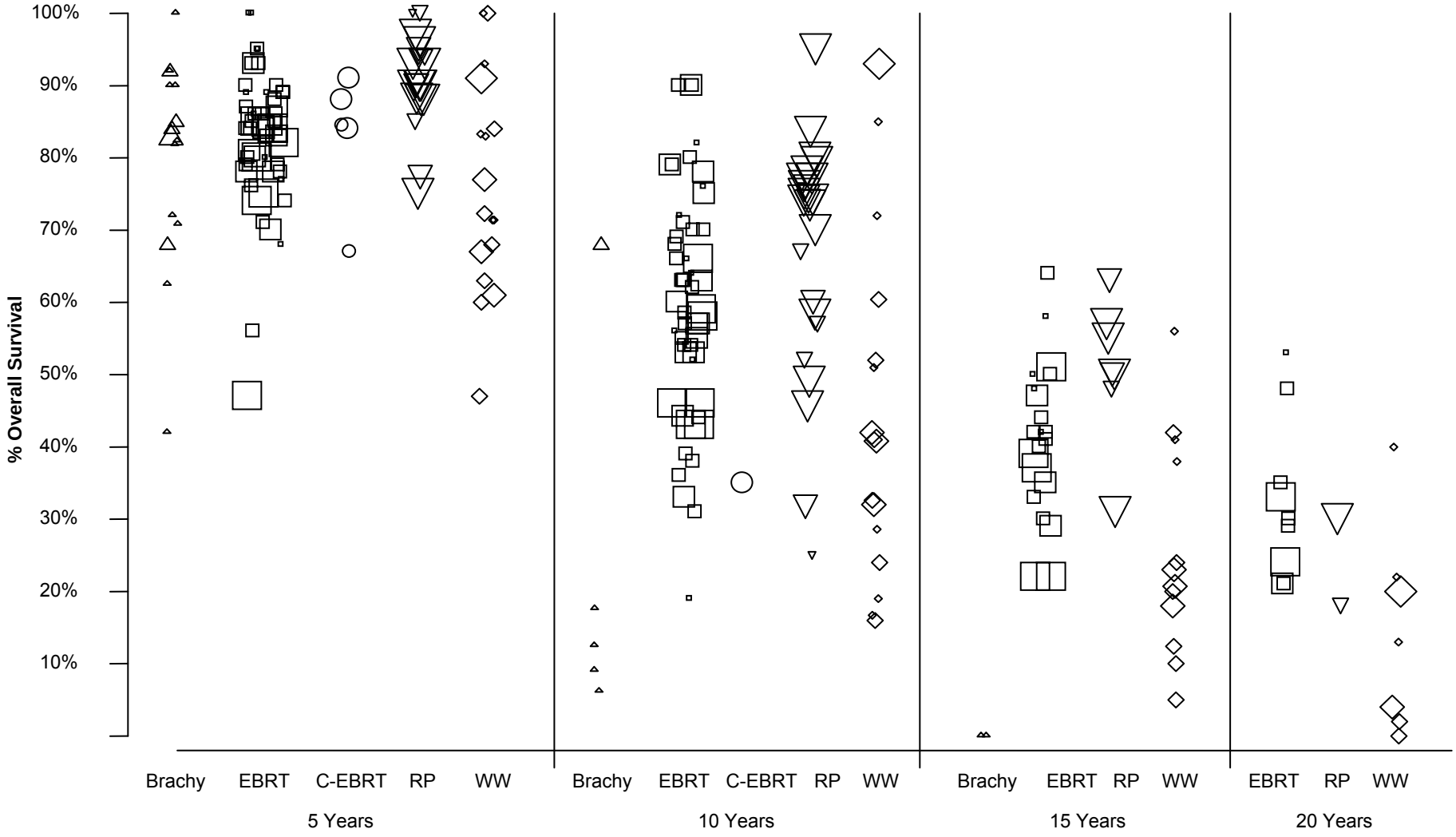
Study Outcomes	Treatment Group	Control Group	Analyses; p-values
GI, Grade 1	71(36%)	84 (43%)	
GI, Grade 2	15 (8%)	33 (17%)	0.005
GI, Grade 3	1 (1%)	1 (1%)	
GI, Grade 4	0	0	
Actuarial risk of a GU event of ≥ Grade 2 at 3 years	15%	13%	
Actuarial risk of a GU event of ≥ Grade 2 at 5 years	19%	18%	
Hormonal therapy combined with radiation therapy			
D'Amico, 2004[58]	Conformal radiation therapy (70 Gy) group (n=103)	Conformal radiation therapy and androgen suppression therapy group (n=98)	p value
Toxicity, number of events:			
Urinary incontinence (UI), complete:			
Grade 1	3	2	Not significant for all events
Grade 2	1	1	unless noted
Grade 3	1	1	
UI, stress:			
Grade 1	20	22	
Grade 2	7	6	
Grade 3	0	0	
Hematuria:			
Grade 1	6	7	
Grade 2	5	6	
Grade 3	3	3	
Diarrhea:			
Grade 1	19	18	
Grade 2	8	9	
Grade 3	3	1	
Rectal bleeding:			
Grade 1	34	26	
Grade 2	18	16	
Grade 3	2	3	
Impotence (men potent at baseline):			
Grade 1	4	1	
Grade 2	7	6	
Grade 3	21	26	0.02
Gynecomastia:			
Grade 1	1	14	0.002 for Grades 1 and 2
Grade 2	2	4	combined
Grade 3	0	0	
Liver dysfunction	2: Grade 3 (1); Grade 4 (1)		

Table 10. Adverse events and toxicity for randomized controlled trials (continued)

Study Outcomes	Treatment Group	Control Group	Analyses; p-values
Brachytherapy			
Herstein, 2005[64] / Wallner, 2003[59]	^{125}I (144 Gy) (n=159)	^{103}Pd (125 Gy) (n=155)	p value
Actuarial risk of radiation proctitis (persistent bleeding) at 5 years	Estimated 13%	Estimated 8%	0.21 29 events total (n=314) for both groups, trending more toward ^{125}I
Vaccine vs. nilutamide			
Arlen, 2005[60]	Vaccine Group (n=21)	Nilutamide Group (n=21)	
Subjects removed from trial due to toxicity	0	3	
Injection site reaction	39.7		
Percent patients with toxicity	Grade 2 toxicity included: arthralgia (13.8%); fatigue (10.3%); dyspnea (6.9%) Grade 3 AEs included: cardiac ischemia (3.4%) Interleukin-2 Grade 2 toxicity included: fatigue (48.3%); fever (13.8%); arthralgias (6.9%); hyperglycemia (20.7%); lymphopenia (13.8%); dehydration/anorexia (10.3%); diarrhea (10.3%) Grade 3 toxicity included: fatigue (10.3%); fever (6.9%); hyperglycemia (6.9%); lymphopenia (6.9%); dehydration/anorexia (3.4%)	Grade 2 toxicity included: dyspnea (15.2%); fatigue (15.2%); hot flashes (15.2%) Grade 3 toxicity included: dyspnea (3%); fatigue (3%)	

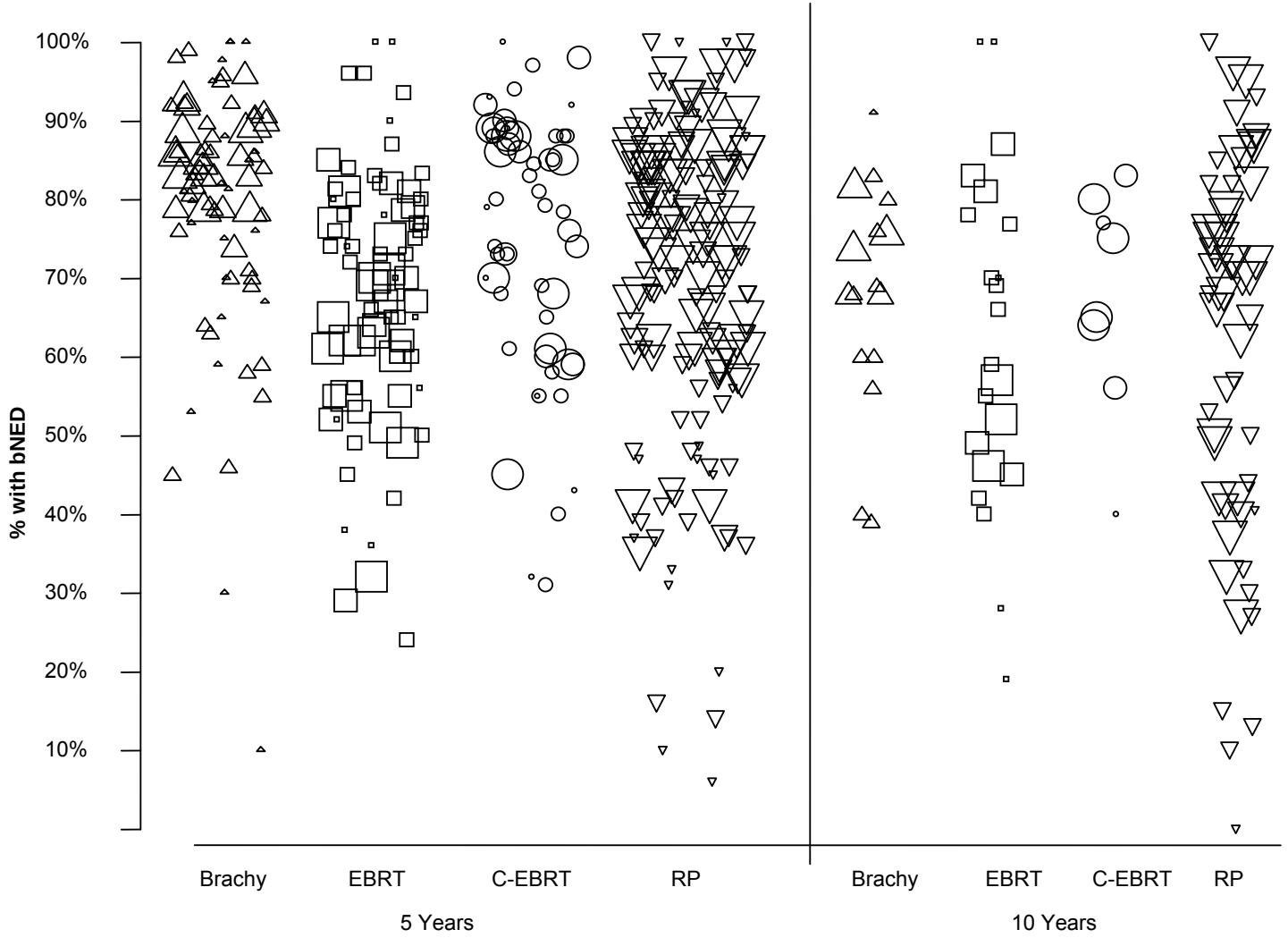
* CI = Confidence intervals
** NCIC = National Cancer Institute of Canada

Figure 2. Overall survival at time points by treatment



Brachy = Brachytherapy; EBRT = External Beam Radiotherapy; C-EBRT = Conformal External Beam Radiotherapy, RP = Radical Prostatectomy; WW = Watchful Waiting
Point size indicates N, <50 (smallest), 50-150 (next smallest) 150-300 (next largest) and >300 (largest)

Figure 3. Biochemical no evidence of disease (bNED) at time points by treatment (all definitions)



Brachy = Brachytherapy; EBRT = External Beam Radiotherapy; C-EBRT = Conformal External Beam Radiotherapy; RP = Radical Prostatectomy

Point size indicates N, <50 (smallest), 50-150 (next smallest) 150-300 (next largest) and >300 (largest)

Table 11. PCOS: Percent comparison of 24-month survey in older responders on urinary, bowel, and sexual items[187]

Domain and Survey Items	*Conservative AD/WW** (n=290)	Aggressive RP/EBRT/ Brachy** (n = 175)	Odds Ratio (95% CI)	p Value
Urinary				
No control or frequent leakage	6.7	12.4	2.0 (0.7-5.7)	0.17
Leaks more than once daily	10.1	22.2	2.9 (1.2-7.0)	0.01
Frequent urination more than half the time	10.3	7.9	0.7 (0.3-1.7)	0.46
Bothered by dripping or leaking urine	4.2	14.4	5.1 (1.3-19.1)	0.02
Bowel				
Frequency some/almost all days	17.7	29.8	2.3 (1.0-5.0)	0.04
Bowel urgency some/almost all days	20.3	27.6	1.7 (0.8-3.5)	0.19
Painful bowel movements some/almost all days	11.7	16.8	1.6 (0.7-3.7)	0.24
Bothered by bowel function problems	4.4	9.4	2.4 (0.8-7.5)	0.12
Sexual				
No/little interest in sexual activity	66.3	64.4	0.9 (0.4-1.8)	0.75
No sexual activity	73.3	68.1	0.7 (0.3-2.3)	0.63
Erections not firm enough for intercourse	88.0	80.1	0.4 (0.1-1.4)	0.16
No erections/a lot of difficulty keeping erections	86.0	83.2	0.4 (0.3-2.3)	0.63
Bothered by sexual function problems	23.5	43.3	2.8 (1.2-6.3)	0.01

Percents and odds ratios adjusted for treatment propensity score, baseline function, age, race, education, and comorbidity score

* Reference group

** AD/WW = androgen deprivation/watchful waiting; RP/EBRT/Brachy = radical prostatectomy/external beam radiotherapy/brachytherapy

Table 12. PCOS: Comparison of 5-year responders to urinary, bowel, and sexual questions according to treatment*[75]

Domain	RP† (n=901)	EBRT† (n=286)	Odds ratio (95% CI)
Urinary			
No control or frequent leaks vs. total control or occasional leaks	14.4 (15.3)	4.9 (4.1)	4.4 (2.2-8.6)
Leaks ≥2 times per day‡	15.6 (16.1)	4.1 (3.6)	5.3 (2.6-10.8)
Wears any pads to stay dry‡	28.6 (28.6)	4.2 (4.2)	9.4 (4.7-18.9)
Frequent urination more than half the time‡	10.6 (10.1)	8.9 (9.3)	1.1 (0.6-1.9)
Bothered by dripping or leaking urine§	13.9 (14.3)	3.0 (2.6)	6.5 (2.7-15.6)
Bowel‖			
Diarrhea‡	23.3 (23.9)	28.8 (26.7)	0.84 (0.55-1.26)
Painful bowel movement‡	10.4 (11.5)	12.2 (9.4)	1.31 (0.73-2.35)
Bowel urgency‡	17.7 (19.3)	33.4 (28.5)	0.56 (0.36-0.87)
Wetness in rectal area‡	13.8 (14.8)	20.6 (18.3)	0.75 (0.47-1.20)
Painful hemorrhoids‡	11.0 (10.2)	15.7 (19.6)	0.43 (0.25-0.74)
Bothered by frequent bowel movement to pain or urgency	4.3 (4.8)	5.0 (4.0)	1.23 (0.52-2.89)
Sexual			
No/little interest in sexual activity	46.5 (48.9)	55.2 (47.4)	1.1 (0.73-1.6)
No sexual activity	48.9 (50.7)	51.3 (43.9)	1.4 (0.93-2.0)
Erection insufficient for intercourse‡	76.9 (79.3)	73.1 (63.5)	2.5 (1.6-3.8)
Bothered by sexual dysfunction§	47.4 (46.7)	42.0 (44.6)	1.1 (0.75-1.6)

* EBRT is the referent group. Adjusted percentages are from separate logistic regression models, each adjusted for treatment propensity score, age, baseline function, race, comorbidity, and educational level. All estimates were weighted to total eligible cases.

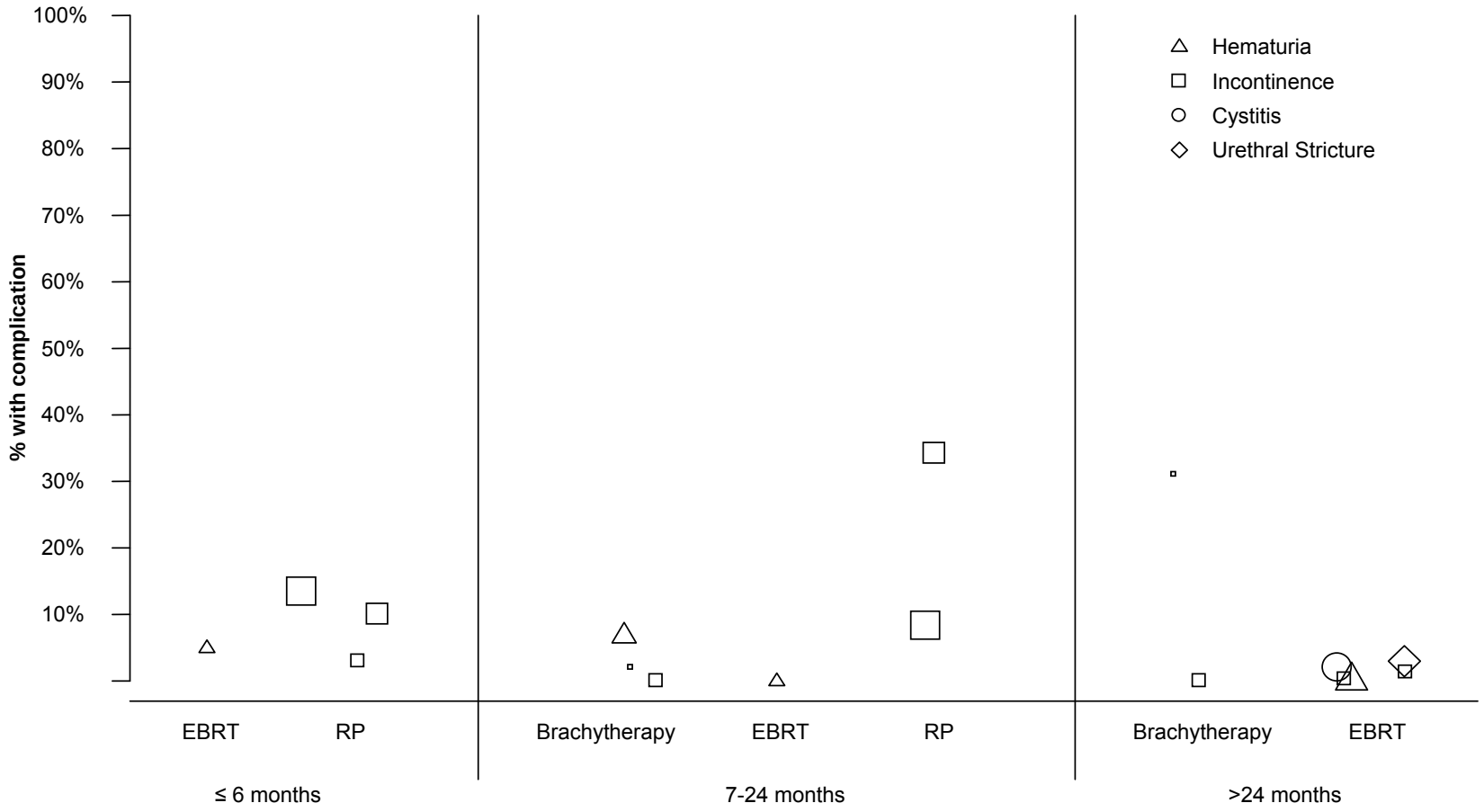
† RP = radical prostatectomy, EBRT = external beam radiotherapy. Values in columns are unadjusted percentages, in parentheses, adjusted percentages.

‡ Percentages and odds ratios for yes vs. no/none.

§ For bother items, percentages refer to patients reporting a large or moderate problem vs. a small or no problem.

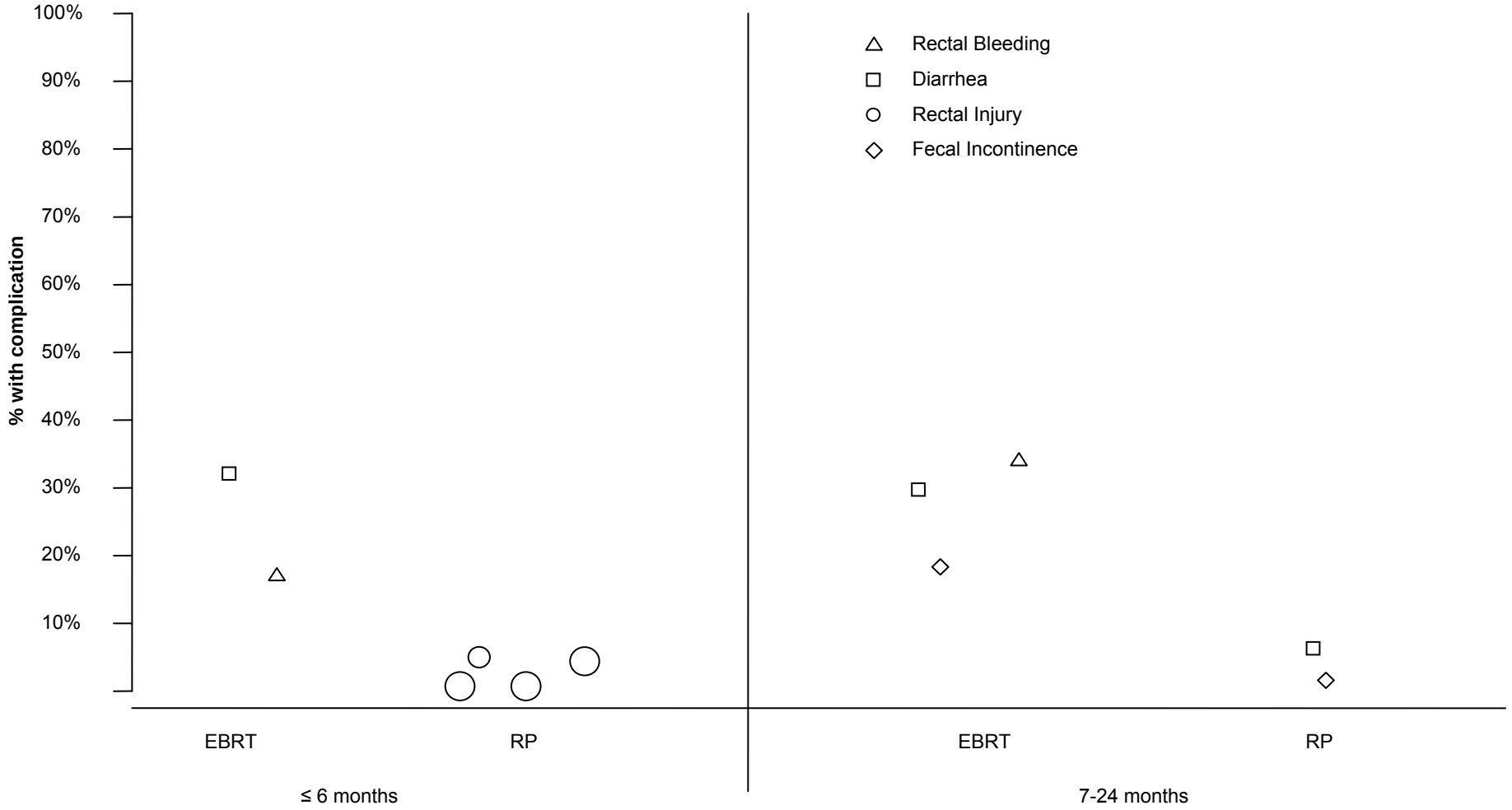
‖ For the 5 bowel functions, percentages refer to patients reporting having the problem every day or some days vs. rarely or never.

Figure 4. Bladder complications at time points by treatment



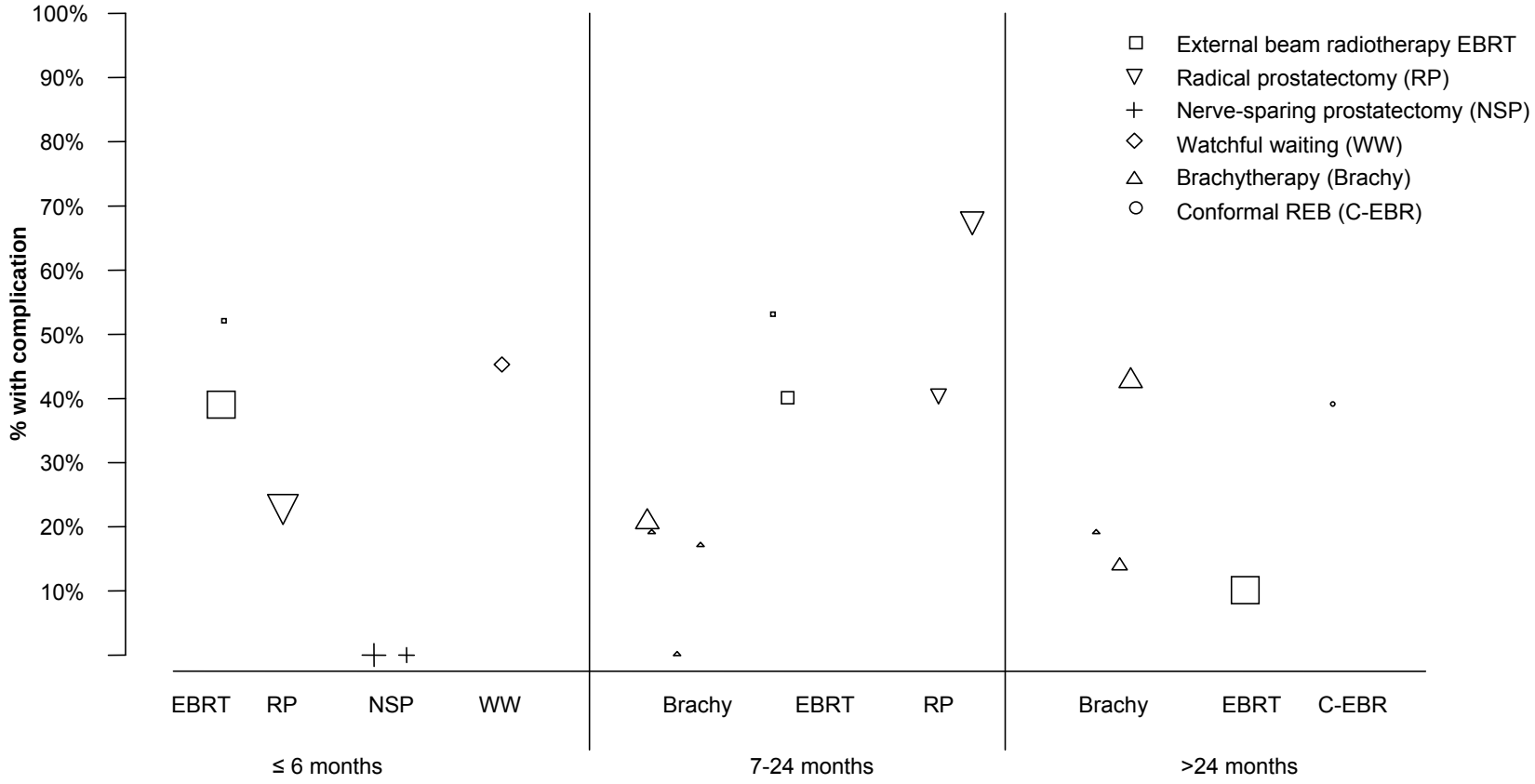
Point size indicates N, <50 (smallest), 50-150 (next smallest) 150-300 (next largest) and >300 (largest)

Figure 5. Bowel complications at time points by treatment



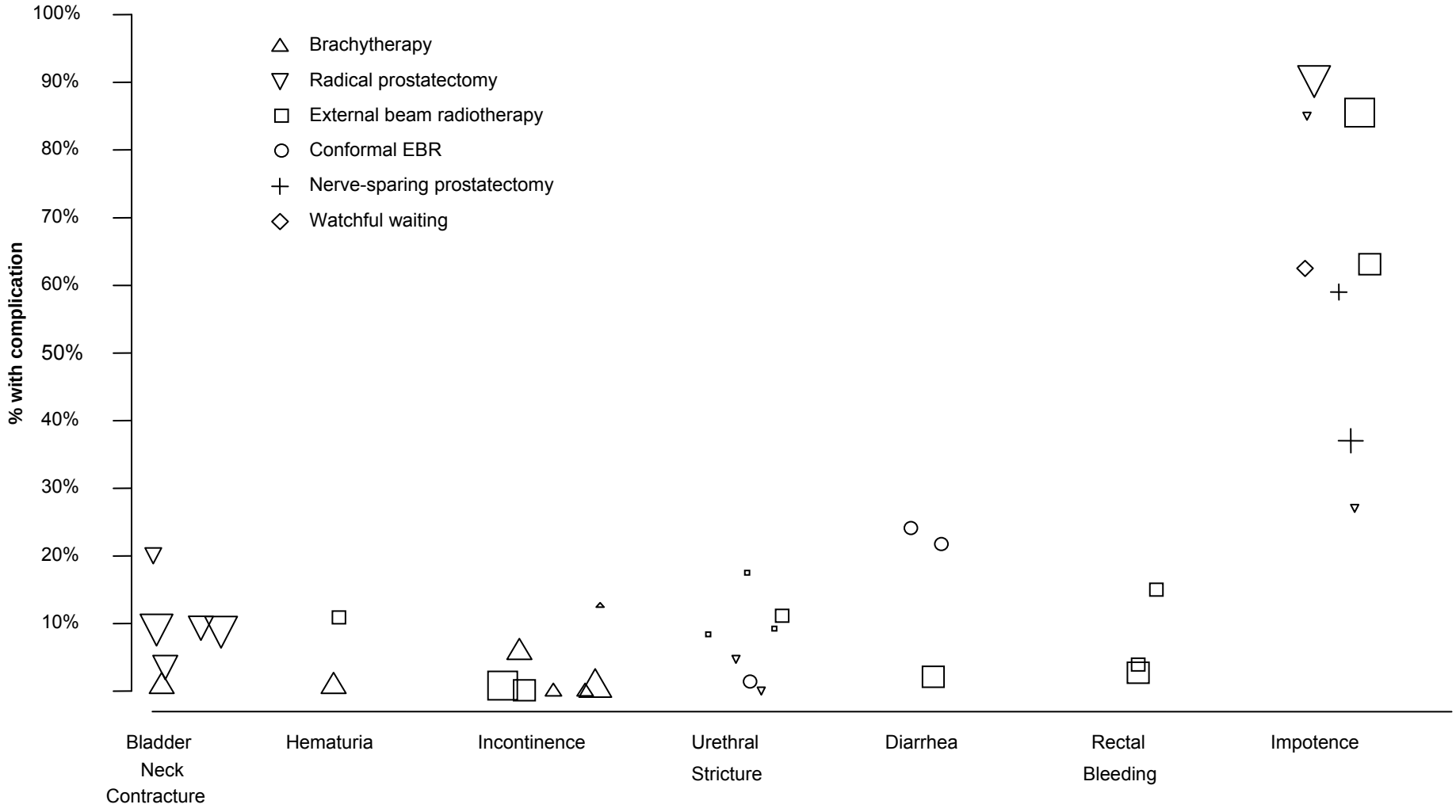
Point size indicates N, <50 (smallest), 50-150 (next smallest) 150-300 (next largest) and >300 (largest)

Figure 6. ED complications at time points by treatment



Point size indicates N, <50 (smallest), 50-150 (next smallest) 150-300 (next largest) and >300 (largest)

Figure 7. Complications by treatment



Point size indicates N, <50 (smallest), 50-150 (next smallest) 150-300 (next largest) and >300 (largest)

Figure 8. Comparative studies of LRP vs. RRP; functional and oncologic data (from the systematic review of nonrandomized clinical trials and case series by Rassweiler et al.)[103]

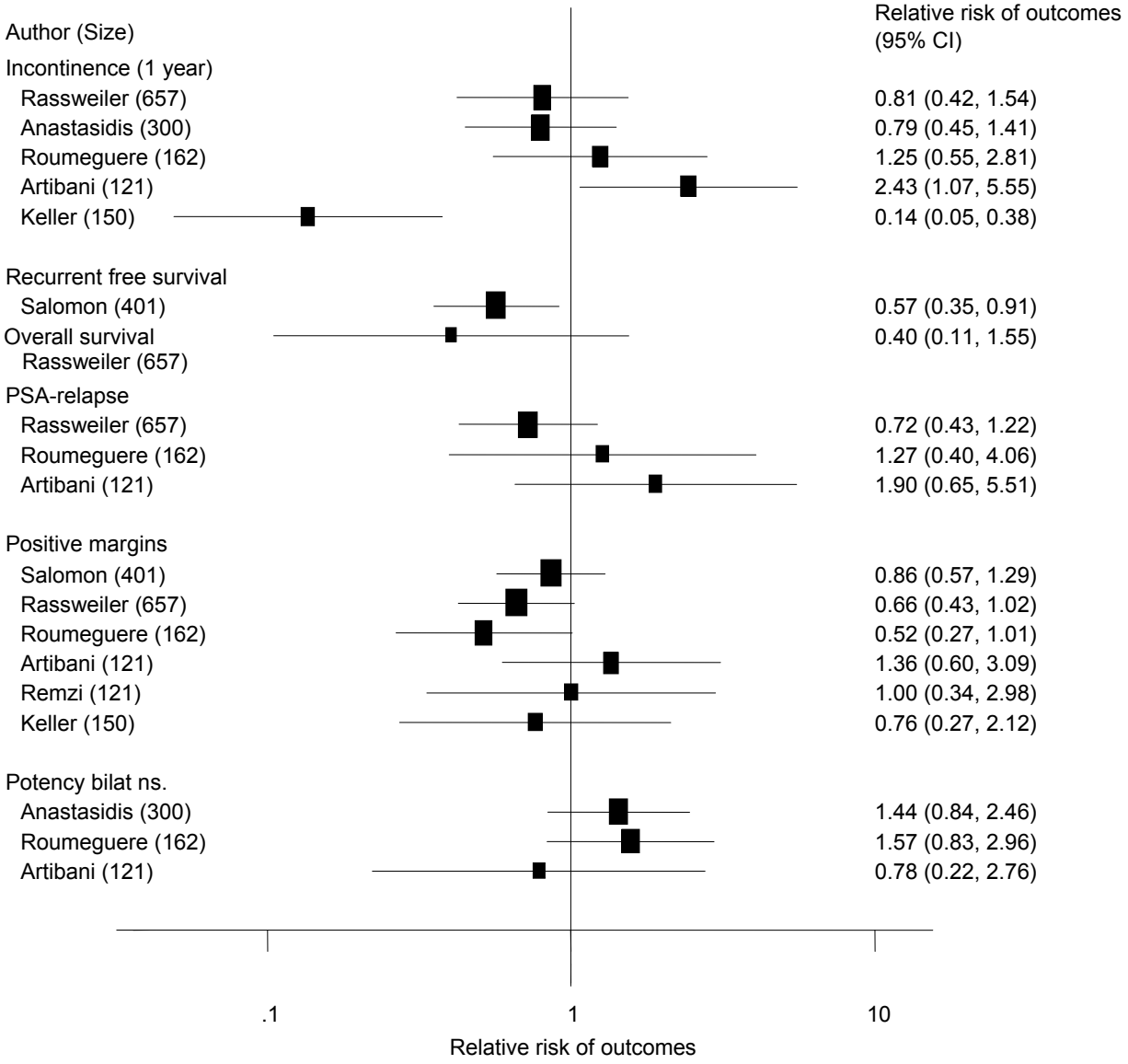


Figure 9. Risk of positive surgical margins and urinary incontinence after RP vs. the second 28 cases of LRP

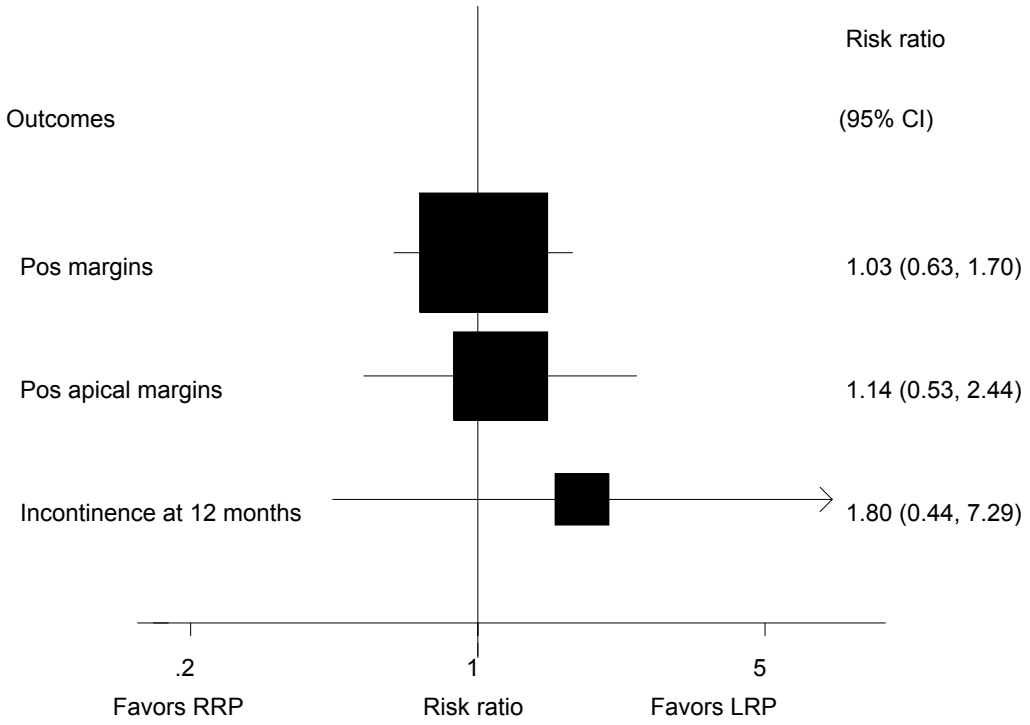


Figure 10. Scores of the International Prostate Symptom Score questionnaire and the International Consultation of Incontinence Quality of Life questionnaire after RP and the second 28 cases of LRP at baseline and during followup (standardized mean difference)

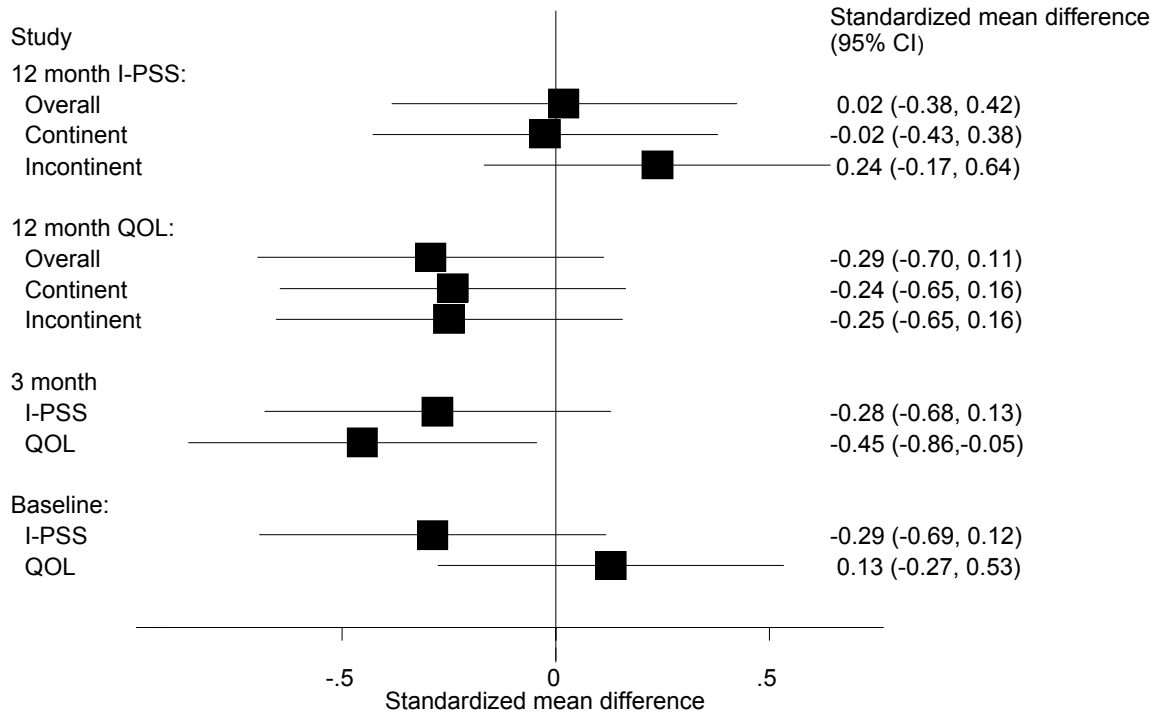


Table 13. PCOS: Percentage overall effects of prostate cancer and treatment[187]

Outcome	*Conservative AD/WW** (n = 290)	Aggressive RP/EBRT/ Brachy** (n = 175)	Odds Ratio (95% CI)
Treatment satisfaction			
Delighted/very pleased	52.8	68.1	2.1 (1.0-4.4)
Make same treatment decision again if given chance			
Definitely yes	56.5	53.3	0.9 (0.4-1.7)
Physical discomfort related to cancer/treatment			
A lot/some	13.9	20.6	1.8 (0.8-4.4)
Health worries related to cancer/treatment			
A lot/some	19.7	18.0	0.9 (0.4-1.9)
Limited daily activities related to cancer/treatment			
A lot/some	12.1	13.8	1.2 (0.4-3.8)
Overall bother related to cancer/treatment			
A lot/some	19.3	16.5	0.8 (0.3-1.9)

Percents and odds ratios adjusted for treatment propensity score, age, race, education, and comorbidity score

* Reference group

** AD/WW = androgen deprivation/watchful waiting; RP/EBRT/Brachy = radical prostatectomy/external beam radiotherapy/brachytherapy

Table 14. PCOS: Distribution of patient responses at 24 month followup by treatment*[175]

Characteristic	WW** (n = 230) %	AD** (n = 179) %	EBRT/Brachy** (n = 583) %	RP** (n = 1373) %	p value
Satisfied with treatment					0.00
Delighted	17.6	22.9	32.1	22.5	
Pleased	30.8	40.3	37.8	36.1	
Mostly satisfied	37.9	27.7	21.0	24.5	
Mixed	10.9	7.0	8.0	12.2	
Dissatisfied/unhappy/feel terrible	2.8	2.1	1.1	4.9	
Would make same decision again					0.02
Definitely yes	51.2	64.4	62.4	56.2	
Probably yes	40.8	30.6	31.4	34.5	
Definitely/probably not	8.0	5.0	6.2	9.3	
Free of PC					0.00
No	63.0	52.2	7.9	5.3	
Don't know	27.8	31.6	40.5	18.3	
Yes	9.3	16.2	51.7	76.4	
Bowel urgency					0.00
Rarely or not at all	83.8	80.9	68.2	85.0	
Some days	15.9	15.8	28.6	14.1	
Almost everyday	0.2	3.3	3.2	0.9	
Urinary leakage					0.00
Not at all	78.0	60.0	66.1	38.0	
Once per week or less	14.9	29.2	22.2	27.2	
Daily or more often	7.0	10.8	11.8	34.8	
Erectile dysfunction					0.00
None or only a little	33.2	6.1	23.0	15.6	
Some or a lot	34.2	8.1	34.3	26.0	
No erections at all	32.5	85.8	42.7	58.4	
Cancer or treatment limits activities					0.00
None	87.9	69.1	71.2	67.1	
A little	7.7	14.2	17.9	18.5	
Some/a lot	4.4	16.6	10.9	14.2	
Cancer or treatment caused financial problems					0.00
None	82.9	65.9	76.9	70.9	
A little	11.5	20.7	14.6	18.0	
Some/a lot	5.6	13.5	8.6	11.0	
Cancer or treatment affects relationships with spouse/friends					0.00
None	73.4	64.6	68.9	53.4	
A little	16.1	19.0	18.3	24.1	
Some/a lot	10.5	16.4	12.8	22.5	
General health					0.00
Excellent	14.1	5.4	10.6	17.8	
Very good	25.7	32.9	35.4	39.1	
Good	37.1	29.8	31.8	31.5	
Fair or poor	23.1	31.9	22.1	11.6	

* Weighted to reflect all patients in the study.

** WW = watchful waiting; AD = androgen deprivation; EBRT/Brachy = external beam radiotherapy/brachytherapy; RP = radical prostatectomy

Key Question 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?

Treatment Decisions According to Patient Factors

Factors that influence patient treatment preferences are poorly understood. A systematic review of patient decisionmaking for localized prostate cancer treatment indicated that many factors are incorporated into the decision process, including cancer eradication, AEs, physician recommendations, convenience, and costs.[3] The various weights that patients attributed to these factors in decisionmaking and/or satisfaction with treatment outcomes is difficult to determine. Based on indepth semistructured interviews of 20 men with newly-diagnosed clinically localized prostate cancer, one study concluded that treatment preferences were not based on careful assessment of numerical risks for various clinical outcomes. Instead, feelings of fear and uncertainty contributed to a desire for rapid treatment; preferences were influenced by misconceptions, especially about RP, and anecdotes about the experiences of others with cancer.[28] Few patients sought second opinions. At 6-8 months of post treatment followup justification for treatment choices was based on similar anecdotal influences and misconceptions that were present during their initial treatment deliberations.

Results described in question 1 (Quality of Life) indicate that frequency, severity, and bother associated with adverse effects varied by baseline general and condition-specific functional status and whether the "adverse condition" existed at baseline. Despite patients having more AEs and condition-specific bother with early intervention, they generally were as satisfied with treatment and likely to choose this therapy again if they had another chance. In question 3 we describe that treatment recommendations vary according to physician specialty.

Treatments for Localized Prostate Cancer by Race or Ethnicity

Currently, little to no evidence exists to suggest that a patient's racial or ethnic characteristics significantly impact the comparative effectiveness of any treatment for localized prostate cancer independent of other patient characteristics such as age, tumor stage, tumor grade, or treatment preferences. National data show that a higher percent of Black men are diagnosed with metastasic disease and poorly differentiated tumors. However staging evaluation for prostate cancer is similar between White and Black men.[188] Additionally, while some studies identified differences in the rate of localized prostate cancer outcomes by racial or ethnic groups, the purpose of this section is to highlight the evidence that race or ethnicity of a patient might modify the effect of treatments on outcomes. Since no randomized trials investigated the role of patient race or ethnicity on the efficacy and adverse effects associated with localized prostate cancer and its treatment, we are left with only observational studies. Confounding from observational studies is a concern since observed differences in health status across and within

racial or ethnic groups is likely due to a complex interaction of numerous factors, most of which are unmeasured and therefore impossible to control for statistically.

Results from observational studies. There is no evidence that patient race or ethnicity make one type of treatment significantly better than another type of treatment. There have, however, been some reports that patient race or ethnicity, might be associated with differences in treatment selection[189] and treatment satisfaction.[190]

Furthermore, while there have been several observational studies that have reported treatment outcomes by racial or ethnic groups,[175,190-199] most of these studies were limited by the small numbers of non-White participants, and few reported results that were adjusted for known confounders, such as age and tumor severity. Also several of the larger studies included participants who received one of several types of treatments; therefore, the number of participants receiving any one type of treatment was sometimes small even before stratifying by race and ethnicity. Since this report relates to comparative effectiveness, we focused on reports related to outcomes from treatment. The studies identified in this report present results on whether or not outcomes differed for a specific treatment according to race or ethnicity and not whether one treatment was superior in some racial or ethnic groups and not others.

Radical prostatectomy. There is little to no evidence of a substantial difference in outcomes following RP attributable to patient race or ethnicity. There is some weak evidence that cancer recurrence outcomes might be slightly better in White patients as compared to other groups of patients following RP; however, these findings have not been consistently reported and require large numbers of patients to reach statistical significance.

Several studies have failed to find evidence that race or ethnicity has an impact on treatment efficacy[195,197] or adverse effects[198] related to RP. Powell et al. found no evidence of a difference in biochemical recurrence following a RP between Black and White men with organ-confined prostate cancer.[197] In a study of 693 men (44 percent Blacks and the rest Whites) treated at the same cancer institute of whom 391 were treated with RP, there was no significant evidence that Black men had a differential biochemical disease-free survival compared to White men.[195] In multivariate analyses of disease-free survival that included stage, PSA, Gleason score, and procedure (combined EBRT and RP) the Cox's proportional hazards ratio for race (Black/White) was not significant (1.22, 95 percent CI 0.87; 1.72). In multivariable analyses of 278 men (Black=100 and White=178) with organ-confined disease, after adjusting for Gleason score and PSA, race was not a statistically significant predictor (p=0.41). Finally, in a cohort study of 802 men of whom 385 received RP (White=285 and Black=92), there was no statistically significant difference in potency between White or Black men.[198]

A few large studies have published treatment efficacy,[191,192] treatment satisfaction,[175,190] and adverse effect[199] differences in subgroup analyses by race or ethnicity, including the PCOS,[175,190,199] a pooled analysis of nine U.S. military medical centers,[192] and the SEER analysis.[191] In a study of 3,162 men (Black = 626 and White = 2,299) with localized prostate cancer who were treated with RP, Black men had a somewhat greater risk of biochemical recurrence than White men HR=1.22 (95 percent CI 1.03; 1.45, p=0.021), even after controlling for stage, Gleason margin status, and seminal vesicle involvement.[192] This magnitude of effect is

similar to that reported in a smaller study.[195] While the smaller study was not statistically significant, it was significant in the larger study.

Recent reports from SEER data have shown that among 27,213 patients between the ages of 65 and 84 who received either surgery or radiation, Black patients had lower disease free survival.[191] At 120 months from the initial treatment 58 percent of Black patients and 65.5 percent of White patients were alive without disease. However, in the same group of men (surgery and radiation combined), disease recurrence hazard rates were similar regardless of race/ethnicity after accounting for age, comorbidity score, SEER site, census tract income and educational level, marital status, tumor grade and stage and PSA testing era (Black men vs. White men HR 1.12 (95 percent CI; 0.99; 1.28). Among RP patients only, Black patients had a slightly elevated rate of disease recurrent HR 1.18 (95 percent CI; 1.01; 1.39) compared to White patients, but rates for Hispanic and Asian men were nearly identical to White men (HRs 0.97 and 0.98, respectively).

Within the PCOS study, Stanford et al. found that sexual function following RP varied by race with 38 percent of Black men reporting firm erections at >18 months vs. 26 percent of Hispanic and 21 percent of White men (p=0.001).[199] At 60 months after diagnosis, Black men reported better recovery of sexual and urinary function following RP, despite reporting feeling higher level problems.[190] Also, from the PCOS, Hispanic men were somewhat less satisfied with RP than either Black or White men (p=0.05).[175] These divergent findings between level of functional loss and perceived problem suggest that racial/ethnic differences in the perception and reporting of functional problems may exist.

Electron beam radiotherapy. There is little to no evidence of a substantial difference in outcomes following EBRT attributable to patient race or ethnicity.

In a cohort study of 467 men with localized prostate cancer between the ages of 46 and 82 (of whom a quarter were Black and three-quarters were White) who were treated with definite radiotherapy, race was not a significant factor in biochemical relapse-free survival.[196] In another study of 893 men treated with conformal radiotherapy within one large department, while Black men presented with more advanced disease, within similar risk strata Black men had statistically similar five-year bNED.[194] In a third study of 693 men (44 percent Black and the rest White) of whom 302 men were treated with conformal radiation, Black men did not have a differential biochemical disease-free survival compared to White men.[195] As noted above in the section on RP, while the effect of race in this study in multivariate analyses was not statistically significant when EBRT and RP participants were combined, it was similar in magnitude (HR=1.22) to the statistically significant finding from another study.[192] In the same SEER data report mentioned in the RP section above, the results on disease recurrence among radiation patients found no evidence of a difference by race or ethnic group.[191] Black patients had a nearly identical rates of disease recurrence (HR 1.03 95 percent CI; 0.83; 1.28) compared to White patients, and rates for Hispanic and Asian men were also not significantly different than White men (HR= 0.82 95 percent CI; 0.26; 2.56 and HR 0.98 95 percent CI; 0.64; 1.49, respectively). In a cohort study of 802 men, of whom 305 received EBRT, there was some statistically significant evidence (p=0.035) that White men had a greater decrease in potency following EBRT.[198] The reasons for this difference were not clear, and since followup for potency was 12-24 months, it is not

possible to know if this difference would persist with longer followup. The PCOS did have followup reported up to 60 months post diagnosis and found no statistically significant evidence of a difference in treatment satisfaction[175] or functional outcomes[190] by race or ethnicity for men who received EBRT. The only exception was borderline (p=0.05) better bowel function in Black men.

Watchful waiting. There is little to no evidence of a substantial difference in outcomes following WW attributable to patient race or ethnicity.

Only three studies stratified results by race and included participants who were either enrolled in WW or had no treatment (a combined total of 607 participants).[175,193,198] None of these studies found statistically significant differences between racial groups. With such a small number of participants over three studies focused on different outcomes, there is not adequate information to tell whether there are meaningful racial differences with WW. In the first study of 313 men who chose WW (White=209, Black=76, and Asian or Hispanic=19), there was no significant race effect on the likelihood to have a secondary treatment. In Cox proportional hazards models adjusted for clinical stage, PSA doubling time, age, PSA at diagnosis, Gleason score, number of comorbidities, and family history of disease, White men had a 1.13 times greater rate of secondary treatments (95 percent CI of 0.73; 1.76, p=0.586) compared to Black men.[193] In a second cohort study of 802 men who received either RP, EBRT, or WW (n=64), with a reported outcome of erectile function, there was no statistically significant difference in potency between White or Black men treated with WW.[198] Finally, a report from the PCOS study of 230 men who reported receiving no treatment for their prostate cancer found no statistically significant evidence that treatment satisfaction varied by race at 24 months post diagnosis.[175]

Androgen deprivation. There is little to no evidence of a substantial difference in outcomes following ADT attributable to patient race or ethnicity. Only the PCOS included participants treated with ADT and stratified by racial or ethnic groups.[175] Among the 179 men treated with ADT, Hispanic men reported lower treatment satisfaction at 24 months post diagnosis (30 percent) than either White (72 percent) or Black (57 percent) men (p=0.0014).

Summary. 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 groups. Modest treatment differences in some studies have not been consistently reported in well-powered studies. Future research is needed to better explore potential racial/ethnic differences in the perception and reporting of sexual function and incontinence. There are no RCTs of such effects.

Treatments for Localized Prostate Cancer by Age

U.S. population based trends in RP, brachytherapy, and EBRT for older men were assessed using Medicare data from 1984-1997.[74] RP was less frequently used in men older than 70 years than in the past. However, because brachytherapy increased, the total population-based treatment rates changed little over time. Use of any of these interventions increased 15 percent for men ages 65 to 69 but decreased for older men. From 1993-1997 RP remained the most common intervention for men 65-69 years and 70-74 years of age but decreased by 6 percent and 34 percent

respectively during this time period. Among men 75 years and older EBRT was the most common intervention. Brachytherapy was used twice as often as RP, which declined 50 percent during this period. Differences in age have also been reported in the Medicare data to be associated with differential use of additional treatment for prostate cancer after prior treatment with RP, RT, ADT, or WW.[200] Older men were more likely to receive ADT as a followup therapy to RP, RT, or WW, while older men were less likely to receive RT as a follow-up to RP, ADT, or WW.

The focus of this section is whether the effects of treatment depend on the patients' ages. More specifically, we assessed whether age modifies effect of treatments on outcomes. Therefore, the important question is whether there is evidence that either Treatment A's benefit (reduced death) or Treatment A's side effect (increased impotence) is different relative to Treatment B, depending on the age of the patient. RCTs including multiple treatments and a large number of patients with diverse range of ages would be the ideal situations to address this issue. However, this type of evidence is lacking; therefore, we summarize the information that is available and highlight some of the gaps in knowledge.

Life expectancy may be a more relevant characteristic to use when deciding on treatment options than age. However, age will be used primarily as a proxy for life expectancy in this review. While individual treatment consideration should include attention to patient life expectancy, which includes the consideration of competing comorbid conditions, life expectancy is not easily obtained and is rarely a characteristic reported in journal articles.

Many articles regarding treatments for localized prostate cancer have reported results by age;[44,176,194,196,198,199,201-225] however, few studies have included multiple treatments and reported whether age was an effect modifier for the treatment effects.[44,199,203,212,213,218,223,224] Fewer still reported differences in survival or biochemical disease-free survival.[44,203,213,223,224] One study reported on long-term overall and disease-specific survival by different age and Gleason histologic strata in men treated with WW who were diagnosed prior to the PSA error.[226] Regardless of age, prostate cancer-specific mortality after 20 years of followup was low in men with well differentiated tumors (Gleason 2-4). However, for men with poorly differentiated prostate cancer (Gleason 8-10), death from prostate cancer comprised the majority of deaths within 5-10 years, even those >75 years at the time of diagnosis.

As noted in question 1, the prevalence, severity, and bother related to bladder, bowel, and sexual dysfunction did not appear to differ in men >70 years compared to the entire cohort of PCOS participants.

Results from RCTs. There are very limited data from RCTs regarding the role of patient age on the efficacy of treatments for localized prostate cancer. We identified only one study that reported whether or not they found evidence their intervention groups differed based on the age of the participant.[44] In the long-term SPCR Study Number 4 comparing RP (n=347) to WW (n=348), men ranged in age from 48-74 with some sites only including men <70 years and the remaining sites including men 70-74 years if they were considered otherwise healthy. In the overall cohort, the WW group was more likely to die from any cause or from prostate cancer. However, the WW group was less likely to experience urinary leakage or erectile dysfunction.[183]

In a subgroup analysis of men <65 years compared to men ≥65 years, the difference in prostate cancer mortality between RP and WW appeared to be primarily in younger men (Figure 11). Differences in adverse effects were not reported by age strata. These results support the idea that the potential comparative effectiveness of RP vs. WW regarding overall and disease-specific mortality and prevention of metastatic disease may be limited to men under age 65. However, the clinical decision is clouded somewhat by the fact that fewer than 5 percent of prostate cancers in this study were detected by PSA testing, as is currently the case in the United States. Because of lead and length bias associated with PSA testing it is not known how these findings might apply to men with PSA-detected prostate cancer.

Results from observational studies. Only a few studies have included multiple treatments and reported whether the effects of the different treatment options differed according to the age of the patient. Most of these studies have been small, so the power to detect statistically significant differences is limited. Additionally, since there is evidence that older men (over 75) who are treated more aggressively tend to be healthier at baseline,[187] it is important to make sure that analyses comparing treatments, especially aggressive to conservative treatments, adequately control for selection bias. Since most, if not all, of the currently available observational studies with adequate numbers of patients to address age by treatment interactions (primarily SEER-based analyses), lack important information regarding factors related to patient treatment selection, the quality of evidence drawn from observational studies regarding the impact of patient age is weak.

Evidence of treatment effect modification by age for survival. Two recent SEER publications have used this large cancer registry of tens of thousands of U.S. men to show that survival is on average somewhat greater for men with localized prostate cancer who have RP or radiation therapy compared to other men.[223,224] The comparison group has varied between men who delayed treatment for at least 6 months following their initial diagnosis[224] and men who had a "non-definitive treatment" (something other than RP or radiation therapy).[223] Both these nonRCT reports found evidence that the survival effect was significant in men over 65, which was unlike the only RCT on this topic that looked at only RP vs. WW and found a survival benefit only in men younger than 65 years of age.[186] The magnitude of the survival effect seemed to plateau in the first 5 years.[224] This plateau in the effect is counter-intuitive, since prostate cancer is typically slow growing, so the impact of active treatment on survival would be expected to be minimal initially and increase with time, as seen in the RCT.[44] Early differences appear to be more consistent with a bias resulting from an uncontrolled case-mix between the more aggressively treated patients and the conservatively treated patients. Both the SEER based reports employed statistical measures to account for covariates available in either the SEER[223] or both SEER and Medicare databases;[224] however, patient and provider reasons for treatment were not available.

The strength of the SEER database rests in the large number of men included in the registry and the geographical diversity that makes estimates more generalizable to the entire U.S. The limitations involved with using SEER are similar to other databases derived largely from administrative data in that it is difficult to obtain enough information about the individual men to sufficiently eliminate selection bias. Newer statistical methods, including using propensity scores to control for differences in measured covariates between treated and untreated individuals, are helping to decrease some of the bias that has discouraged analyses of treatment effects from

observational databases. However, no amount of statistical manipulation can correct for incomplete control of unmeasured confounders. Therefore, while there have been significant improvements in the methods used to glean clinically useful information from observational data, there remains significant concern that selection bias is likely to be a substantial factor in these types of analyses, and it is widely recognized that randomized controlled trials would be less prone to this bias.[227] As such, conclusions about the comparative effectiveness of various treatments for localized prostate cancer should rest primarily on data available from randomized clinical trials whenever possible, and differences in effectiveness found in observational studies should be interpreted with caution.

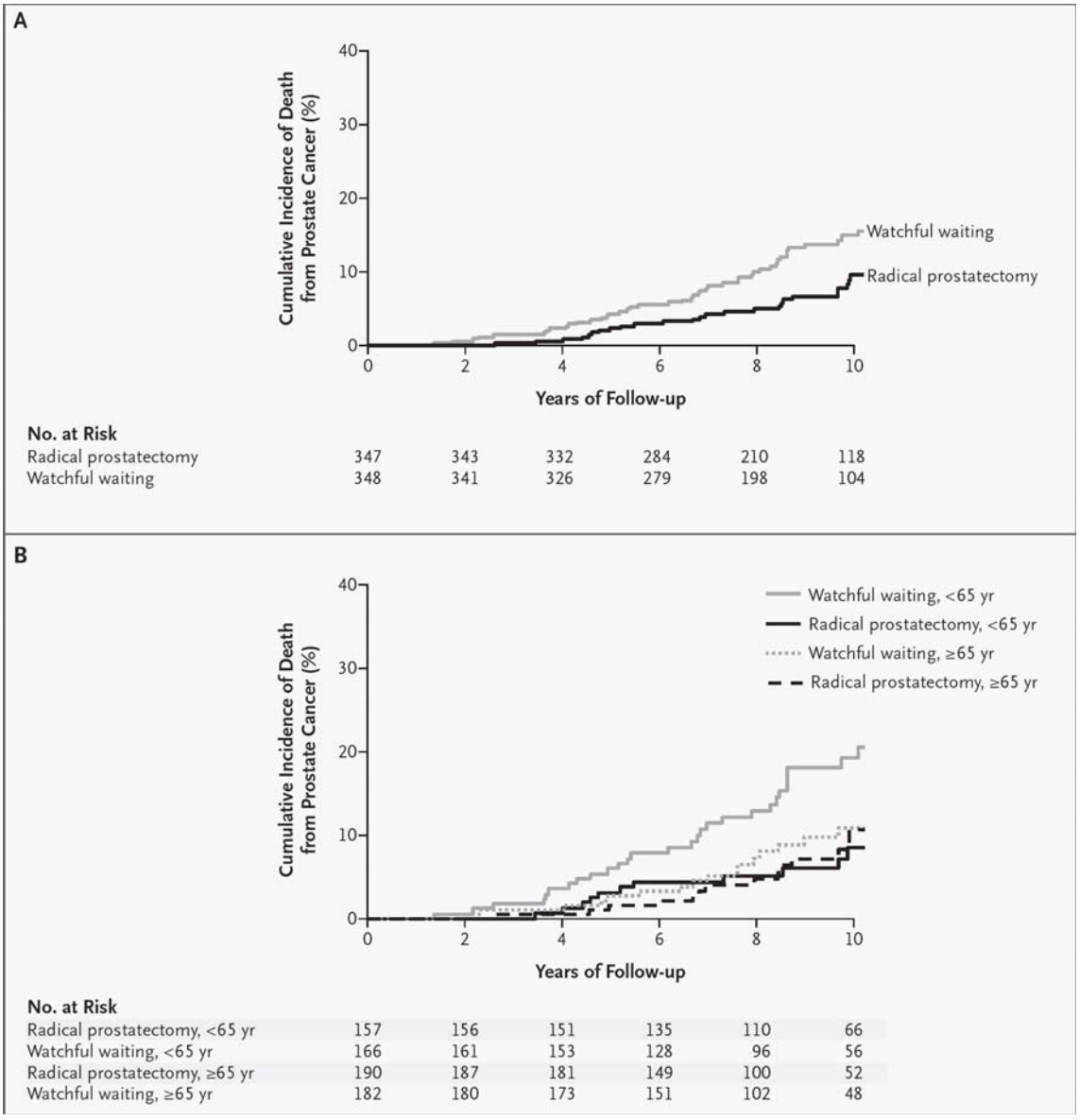
Two additional studies reported age stratified results comparing the survival or biochemical relapse-free survival of patients treated with either surgery or radiation therapy.[203,213] In a combined study of 354 men treated with RP and 253 men treated with EBRT, there was no evidence that biochemical relapse-free survival was different for the two treatments.[213] This study tested whether age (<65 vs. 65-69 vs. ≥70) was an effect modifier of treatment effect for biochemical relapse-free survival and found no statistically significant evidence that the treatment effects differed in the three age strata (univariate adjusted p=0.77 and multivariable adjusted p=0.59). In a second larger study including 44 institutions and 7,316 men, patients treated with RP were much more likely (p=<0.0001) to be <70 years old (86 percent) compared to men treated with radiation therapy (42 percent).[203] This study found evidence, consistent they claimed, with practice patterns during the time period, that men who were <70 and treated with radiation therapy tended to be less healthy than men <70 who were treated with RP. Following PSA failure, men initially treated with radiation therapy had a significantly higher rate of non-prostate cancer related death compared to men who were treated with radiation therapy (p=0.03); however, this effect was only seen in men <70 years old (p=0.007) and not in men ≥70 (p=0.58).

Evidence of treatment effect modification by age for sexual function. Three observational studies have reported results for multiple treatments on sexual function stratified by age group. The largest study included 802 men with 52 percent receiving RP, 40 percent receiving EBRT, and 8 percent in the WW group.[198] Across all three groups, baseline pre-treatment potency was lower in the older men (60-70 and >70) compared to the younger men (<60). In general, the EBRT group had somewhat lower baseline potency. Following treatment, the post-treatment potency was substantially reduced in both active treatment groups, and the post-treatment potency levels were similar between RP and EBRT groups. There was no evidence that the effects of the treatments on potency varied by age. The other two studies compared patients with nerve sparing vs. patients with partial or non-nerve sparing RP.[212,218] Due to small numbers in the treatment by age strata and a lack of adjustment for baseline differences between the groups, it is not possible to draw robust conclusions from either of these two studies.

Summary. In general there is little high-quality evidence available to answer whether age substantially impacts the comparative effectiveness of various treatments for localized prostate cancer. In spite of the overall lack of evidence for an interaction between age and treatment effects, treatment options have different risks and benefits and these differences may be more or less desirable, depending on a patient's current age, life expectancy, and lifestyle. While there are definitely 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, there are few

studies that directly compare the treatment effects of different therapies across age groups. Evidence from a subgroup analysis of one randomized trial suggests that survival benefits of RP when compared with WW may be limited to men <65 years of age. 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. These differences in practice patterns appear to be based more on preferences of the patients and providers that are related to age via lifestyle and life expectancy than particular age independent treatment benefits and side effects.

Figure 11. Cumulative incidence of death from prostate cancer in the two study groups overall (Panel A) and according to age (Panel B). (Source: New England Journal of Medicine, used with permission [Bill-Axelson A, Holmberg A, Ruutu M, et al. Radical prostatectomy vs. watchful waiting in early prostate cancer. N Engl J Med 2005 352(19):1977-1984][44] Copyright © 2005 Massachusetts Medical Society



Key Question 3: How do provider/hospital characteristics affect outcomes overall and differentially (e.g., geographic region and volume)?

Of the 850 potentially relevant references identified (literature search strategy is presented in Appendix B; excluded studies are listed in Appendix D), 91 percent were excluded (Appendix C, Figure C6). We could not identify randomized controlled clinical trials that examined how provider characteristics can modify the effectiveness of different treatments. No multicenter studies provided evidence of heterogeneity in and subgroup analysis by provider characteristics. We identified 75 eligible original studies; five reports presented a geographic distribution of physicians in the United States, 23 investigated regional variations of screening and treatment of prostate cancer, 18 articles analyzed the differences of physician characteristics on the diagnosis and management of prostate cancer, 15 analyzed the impact of physician experience on learning curves of treatment procedures, six tested the association between hospital volume and patient outcomes, and eight evaluated the role of surgeon volume and patient outcomes.

All eligible studies were original epidemiologic investigations to test associative hypotheses between provider characteristics and patient outcomes with IIA-III levels of evidence.[30] Study quality varied from 70 to 85 percent of the maximum score possible in the studies that analyzed the difference in outcomes in regions of the United States[30,228,229] and from 55 to 60 percent of maximum possible in surveys of clinicians to estimated differences in practice patterns, individual preferences, and opinions. The quality scores of studies that examined differences in outcomes in regions of the United States averaged 82.2 percent, with 77 percent for sampling of subjects and 44 percent for adjustment for confounding factors. Retrospective cohorts that investigated association between provider volumes on patient outcomes averaged 65 percent of the maximum possible quality score (Appendix C, Table C27), with the highest quality in studies that measured morbidity and urinary complications after RP. Quality of the studies that assessed provider volumes was not associated with sponsorship, country, or data sources (Appendix C, Table C28).

The average applicability of the studies was 70 percent, compared with criteria of external validity of nationally representative cohorts.[228] Few authors analyzed the differences between selected patients and target population; as a result the mean quality score for adequacy of sampling was 58 percent. The majority of the authors selected patients from existing databases (Appendix C, Tables C29 and C30), including the National Center for Health Statistics, Cancer Surveillance System,[230,231] the North American Association of Central Cancer Registries (SEER),[232-239] CaPSURE,[240,241] and the Medicare health claims national database.[17-19,74,242-246] Several single hospital[247-251] and multi hospital studies[252-254] selected patients in clinics to analyze medical records (Appendix C, Tables C31-C39). One study obtained the Quebec Healthcare Plan database to identify eligible subjects,[254] one selected participants within the State Cancer control map,[255] and one was conducted in the Veteran's Affairs Medical system.[79] Few authors reported random sampling of subjects.[18,237,238] We compared time periods when patient events occurred and databases the authors obtained to select participants (Appendix C, Tables C40-C42) to avoid including the same patients more than once in the analysis.

Studies of geographical variations adjusted for patient age,[18,24,74,79,231-234,240,241,244,246,256] race or ethnicity,[18,24,231,233,234,241,244,246] comorbidity,[18,74,243,246] and cancer stage and grade[18,231,232,236] (Appendix C, Tables C29 and C30). Studies that investigated provider volumes of RP adjusted for patient age and comorbidity,[17-19,236,237,239,242,250] race,[18,19,239,242,248] cancer stage and grade,[238,239,248] provider location and teaching status,[17,18,236,242,252,254] and clustering of patients and providers.[239,257-259] Authors stated that the target population included patients with localized prostate cancer,[234] reported the number of participants with localized cancer,[237-239] adjusted for cancer stage and grade,[18,231,233,234,238,239,248] or assumed that all patients treated primarily with RP would have localized disease.[254] Pooled adjusted rates and relative risk of patient outcomes estimated the association with provider location and volumes independent of cancer stage. Interaction models examined the effect modification by adjustment for cancer stage.

Association Between Provider Specialty and Prostate Cancer Screening and Diagnosis

Different screening practices can result in variation in the incidence and stages of detected prostate cancer across various patient characteristic categories and consequently affect treatment selection and outcomes. Therefore, we assessed the association between provider specialty and the prostate cancer screening beliefs and practices. Several physician surveys found differences in prostate cancer screening and referral[25,26,260-263] (Appendix C, Table C43) according to provider characteristics. Members of the Academy of Family Physicians (113 family physicians and 238 general internists) were asked which test they would recommend for prostate cancer screening for patients 50 years old and older.[260] Physician preferences were different for all screening practices (Appendix C, Figure C7): family physicians more often recommended digital rectal examination (87 percent vs. 69 percent of positive responses, $p<0.001$)) and PSA testing (67 percent vs. 40 percent of positive responses, $p <0.001$) and would screen patients in all ages. General internists prefer to refer men with elevated PSA to urologists rather than repeat PSA tests at 4-6 weeks. Board certified physicians in three states (231 urologists and 205 family physicians) responded on their screening preferences in older and asymptomatic patients (Appendix C, Figure C8).[261] Urologists believe that PSA is the best screening test to detect prostate cancer but would generally not screen males 70 years and older and asymptomatic patients less than age 50. Another survey conducted in a random sample of the American Medical Association Registry of Physicians (444 primary care physicians and 394 urologists)[25] showed that more than half of clinicians perform PSA testing as a part of routine health care in patients 50-74 years of age with higher prevalence of using PSA among urologists compared with primary care physicians. The difference was significant ($p<0.05$) in patients 50-59 yeas old: 97 percent of urologists, but only 55 percent if primary care physicians, almost always recommend PSA for patients at this age.

Radiation oncologists more often than urologists recommended that primary care physicians include PSA testing as a part of the routine examination in patients 70 years and older, as reported in a survey of 504 urologists and 559 radiation oncologists randomly selected from the American Medical Association Registry of Physicians.[26] Radiation oncologists recommended that primary care clinicians include PSA for males 75-79 years of age (77 percent of positive responses vs. 51 percent among urologists, $p<0.001$) and older than 80 years (43 percent of positive responses vs. 16 percent among urologists, $p<0.001$) (Appendix C, Figure C9).

Association Between Provider Specialty and Prostate Cancer Management

Treatment recommendations and beliefs in effectiveness were associated with clinician specialty, training, experience, and gender. Nearly all urologists responded that RP provided a survival benefit for patients with localized prostate cancer and life expectancy of more than 10 years (Appendix C, Figure C10).[25] Primary care physicians believed EBRT offered a survival benefit for patients independent of life expectancy. Radiation oncologists responded that radiation therapy offers better survival for patients with localized disease and baseline life expectancy of more than 10 years (Appendix C, Figure C11). In contrast, urologists responded that RP is better than radiation (17 percent of positive responses among urologists compared with 2 percent among radiation oncologists, $p<0.001$).[26] Urologists and radiation oncologists differed regarding survival benefit of treatment options for patients with localized prostate cancer. For instance, 93 percent of urologists believe that RP is preferred compared with EBRT (vs. 20 percent of radiation oncologists, $p<0.001$). Moreover, 82 percent of radiation oncologists reported that RP is overused as a potentially curative treatment, while brachytherapy and EBRT are underused (44 and 50 percent responses respectively) (Appendix C, Figure C12). Urologists who performed more than ten RPs in residency used this treatment more often (53 percent vs. 21 percent) compared to urologists who performed less than ten RPs in residency.[263] Older physicians recommend noncurative approaches, including WW and hormone therapy, more often than younger colleagues (adjusted OR 1.10; 95 percent CI 1.02; 1.10).[264] Female general practitioners referred elderly patients more often than male general practitioners (OR 2.3, $p=0.03$) after adjustment for patient and physician characteristics.[264]

Several surveys found little consensus about which treatment provides the best benefits for patients with localized prostate cancer (Appendix C, Table C44).[262,264-266] Clinical oncologists favored radical radiotherapy for prostate cancer (52 percent of positive responses) and for poorly differentiated local tumor (77 percent of positive responses).[264] Urologists and radiation oncologists in the South (Florida) recommended EBRT and early androgen deprivation for patients with <10 years of life expectancy more often compared to their colleagues in the Northeast, Midwest, and Western regions of the United States[262]

Recommended diagnostic and treatment procedures differed from evidence-based guidelines and suggested overuse of computerized tomography, pelvic MRI, radionuclide bone imaging, and high prevalence of hormone therapy in young patients.[265,266] One large retrospective cohort[71] reported that the proportion of variation in use of ADT attributable to urologists (22.6 percent) was more than tumor (9.7 percent) or patient characteristics (4.3 percent). The significant influence of urologists' personal opinions on use of ADT increased over time from 16 percent in 1992 to 22.56 percent in 1999. For patients receiving EBRT who had T3 tumors or who had T2 tumors with high grade histology, approximately 12 percent of urologists had significantly lower prescribing rates and 5 percent had higher prescribing rates than the mean rate of 71 percent of patients receiving ADT (range = 15-95 percent). For patients not in this group ("uncertain-benefit group") the mean prescribing rate was 36 percent with a range from 5 percent to 92 percent. One-quarter of urologists had a rate of ADT use that was significantly different from the mean.

Association Between Physician Characteristics and Patient Outcomes

Several studies (two non randomized interventions,[267,268] three prospective cohorts,[269-271] and two surveys,[272,273]) examined the association between physician characteristics with patient outcomes (Appendix C, Table C45). Implementation of evidence-based physician education programs reduced lengths of stay and total hospital charges in patients undergoing RP.[267,268] Patients receiving care in an HMO were treated more often with radiation therapy (OR 2.99, 95 percent CI 1.26; 7.09) and had lower mortality (OR 0.30, 95 percent CI 0.20; 0.70) compared with those treated in fee-for-service settings independent of patient characteristics.[274] HMO members were treated with RP less often compared with Medicare beneficiaries and had higher mortality (OR 1.25, 95 percent CI 1.12; 1.39).[271]

Studies that examined the learning curves of treatment procedures in patients with prostate cancer included a single surgeon experience[275-280] and did not test the association with provider characteristics; rather they reported the improvement in outcomes in early experience (Appendix C Table C46). Some evidence suggests that the operative time for laparoscopic RPs was less among senior compared with junior surgeons.[281,282] Experienced surgeons had less crude, but not adjusted rates, of positive margins after laparoscopic RP.[282] Rate of postoperative catheterization less than two weeks after 101-150 performed procedures reduced from 70 to 68 percent in one surgeon (150 previous RPs) but increased from 66 to 88 percent in another (600 previous RPs).[278] Relative risk of acute and prolonged acute urinary retention was less after 400 brachytherapy procedures by 50 to 60 percent.[283]

In summary, evidence from observational studies suggests substantial differences in physicians' screening and treatment recommendations; that is partly related to clinician specialty, age and experience, gender, and clinical settings.

How Does Geographic Region Affect Outcomes?

Provider availability in geographic regions of the U.S. Distribution of urologists and radiation oncologists at a state level was obtained from surveys conducted by the American Medical Association from 1999-2005 (Appendix C, Tables C47-C49 and Figures C13 and C14).[284-288] The ratio of physicians per 100,000 adult citizens in each U.S. Census region in 2002[289] was largest in the Middle Atlantic and lowest in the West North and East South (Appendix C, Figures C15 and C16).

Screening and diagnosis of prostate cancer in U.S. regions. Differences in PSA testing were derived from the Behavioral Risk Factor Surveillance System Survey Data in U.S. regions from 2002-2004 (Appendix C, Figure C17 and Appendix C, Tables C50 and C51).[290] Participants were asked whether they ever or within the past 2 years had PSA testing. Prevalence of PSA testing was higher in the South and lower in North East regions (Appendix C Figure C18). PSA testing prevalence did not correlate with a distribution of urologists and radiation oncologists ($p = 0.17$ and 0.36 respectively).

Incidence of prostate cancer in U.S. regions varied by data source. Three large nationally representative cohorts (Appendix C, Table C29) examined the incidence of prostate cancer in

U.S. regions[232,256,291] as well as the U.S. Cancer Statistics data from 1999-2004.[292] Results from the U.S. Cancer Statistics (Appendix C, Figure C19) and from individual studies compared with the CDC data are presented in Appendix C, Table C52**.** Incidence differed among regions with the highest in the Middle Atlantic and the lowest in the Mountain regions (Appendix C, Figure C20). Incidence of prostate cancer in the Middle Atlantic was significantly higher (24.34 ± 12.22 per 100,000 males) compared with the national average (Appendix C, Table C53)**.** Increased incidence was greater among Hispanics (36.08 ± 13.87 per 100,000 males (Appendix C, Table C54). The incidence was significantly lower in African-American males and residents of the Mountain and West North regions, compared with the national average among Blacks by 43.42 ± 13.06 and by 33.09 ± 12.97 per 100,000 males, respectively. The year when cancer was diagnosed did not modify the associations between incidence and location. Two cohorts[232,291] examined incidence of localized prostate cancer in U.S. regions (Appendix C, Table C55), one included Black men only.[232] Incidence of localized disease was the highest in the Middle Atlantic and East North regions and lowest in the East South (heterogeneity not significant), but the differences were not statistically significant. Patient race and the time when the cancer was diagnosed did not modify the association between incidence and location.

Incidence of prostate cancer was not correlated with the number of urologists or radiation oncologists in U.S. regions (Figure 12) with or without stratification for race. Regional variation in incidence of prostate cancer was not correlated with regional differences in the prevalence of PSA testing (Appendix C Tables C56-C59); however, there was little variation in testing between regions. In contrast with ecologic analysis, individual studies reported that prostate cancer incidence reflected screening prevalence, even though difference in incidence diminished over time.[245]

Treatment options for localized prostate cancer in U.S. regions. The prevalence of treatment options for patients with localized prostate cancer varied substantially among U.S. regions (Figure 13 and Appendix C, Table C59). The prevalence of therapies was not associated with the number of urologists and radiation oncologists, despite a borderline significant negative tendency for lower use of RP in regions with higher numbers of radiation oncologists (correlation coefficient -0.66, p=0.052) (Appendix C, Table C60).

External beam radiotherapy. Four studies examined the percentage of patients with prostate cancer treated with EBRT as the first treatment option (Appendix C, Table C30).[74,230,239,240] The probability of receiving EBRT as a primary treatment was lowest in the Mountain region and highest in New England (Appendix C, Figure C21) (p for heterogeneity <0.05). Large differences in prevalence of EBRT were observed between the North East and West (11 percent, 95 percent CI 10; 12 percent) and the Midwest (-7.8 percent, 95 percent CI -6; -9 percent) (Appendix C, Table C61).

Two studies[232,256] examined the prevalence of EBRT as a primary treatment (Appendix C, Figure C22) (p for heterogeneity not significant) with small insignificant differences in U.S. regions. Three studies evaluated the prevalence of WW[232,240,241] (Appendix C, Figure C23) reporting the higher prevalence in the West, Mountain, and Pacific regions (Appendix C Table C62), heterogeneity not significant.

Brachytherapy. Three studies examined the prevalence of brachytherapy in U.S. regions (Appendix C, Figure C24).[240,241,243] The prevalence of brachytherapy was less than 11 percent in all regions with the lowest 4 percent in the Middle Atlantic (p for heterogeneity <0.05) and the highest in the West South (mean difference 6.6 percent, 95 percent CI 4.7; 8.5 percent) (Appendix C, Tables C44-C63).

Androgen deprivation therapy. Three studies examined the prevalence of primary androgen deprivation in U.S. regions.[235,240,241] The Middle Atlantic had the lowest prevalence of ADT, while the West South and East South regions had the highest (Appendix C, Figure C25) (p for heterogeneity <0.05) by 10.2 percent (95 percent CI 2.7; 17.6 percent) (Appendix C, Table C64). One study[240] reported the relative risk of utilization of primary ADT in U.S. regions compared with the West (Appendix C, Figure C26). The RR was highest in the Pacific and in Mountain regions (relative risk 1.25, 95 percent CI 1.20; 1.30) and lowest in the North East (relative risk 0.40, 95 percent CI 0.39; 0.41).

Radical prostatectomy. The majority of studies evaluated the probability of receiving RP.[231-233,240,241,243,256] Results differed substantially. Prevalence was highest in the Mountain region (36 percent) and lowest in the Middle Atlantic (22.7 percent) (Appendix C, Figure C27). The probability of RP was also 12.7 percent greater in the Mountain region compared with New England (95 percent CI 9.5; 15.8 percent) (Table C65).

Four studies reported age adjusted rates of RP in U.S. regions (Appendix C, Table C66).[24,78,244,256] Rates were lower than the national average in the North East by 55.98 per 100,000 males (95 percent CI -36.61; 75.36) and in New England by -58.16 per 100,000 males (95 percent CI -38.52; 77.80) (Appendix C, Table C67). Mountain and West regions had higher rates of RP by 37.78 (95 percent CI 19.38; 56.17) and 33.45 (95 percent CI 16.50; 50.40) per 100,000 males respectively.

Three large studies evaluated the utilization rate of RPs in U.S. regions,[24,74,79] (Appendix C, Figure C28, and Appendix C, Table C68), two in nationally representative Medicare samples,[24,246] and one in the Department of Veterans Affairs Patient Treatment File and Outpatient Clinic File.[286] All studies reported a consistent (heterogeneity not significant) decrease in utilization of RP by 35 percent (95 percent CI 0.56; 0.75) in the North East and increase by 38 percent (RR 1.38, 95 percent CI 1.19; 1.6) in the West compared with the U.S. average (Figure 14). Despite the difference in treatment utilization, all-cause and cancer-specific mortality[79,233] were the same across regions (Figure 14). Limited evidence[18] suggests that hospital complications after RP varied in U.S. regions with a 42 percent reduction in the West compared to the North East (RR 0.58, 95 percent CI 0.38; 0.88) independent of patient age, race, comorbidities, and hospital type. The rates of anastomatic stricture after RP did not differ in the studied locations (Appendix C, Table C30).

Few studies examined length of hospital stay after RP in U.S. regions (Appendix C, Table C69).[18,293] Length of hospital stay did not differ in the regions compared to the national average (Appendix C, Figure C29). However, it varied from lowest in the West (3.8 days, 95 percent CI 1.6; 5.8 to highest in the Northeast (5.2 days, 95 percent CI 3.1; 7.3). The cost of RP in various regions did not differ from the U.S. average (Appendix C, Tables C70 and C71) with the lowest

($14,103, 95 percent CI $4,707-$23,498) in the East South and the highest in the Middle Atlantic ($20,915, 95 percent CI $11,519-$30,311). Substantial differences in cost of $6,075 (95 percent CI $1,429-$10,721) were also observed between Middle Atlantic and Mountain regions (Appendix C, Figure C30). The published studies analyzed the data before 2001 (Kafadar et al 1953-1997 and Jemal et al 1995-2000)[230,255] and may not reflect the recent decrease in length of stay in U.S. hospitals.

Mortality from prostate cancer in U.S. regions. Four large cohort studies[230,232,255,291] examined age-adjusted mortality in the U.S. in addition to the U.S. Cancer Statistics data from 1999-2002[292] with substantial differences in estimates. Results from the individual studies are presented in Appendix C, Table C72. Mortality was highest in the East South and lowest in the Pacific region (Figure 15). Age adjusted mortality in U.S. regions did not differ compared with the national average (Appendix C, Table C73). The highest age adjusted mortality was observed among Black males in the South Atlantic region (5.55 ± 2.67 per 100,000 males above the U.S. average, p=0.04) and in the East South region (6.39 ± 2.79 per 100,000 males above the U.S. average, p=0.02) and the lowest among Hispanic males in the East North and Pacific regions (Appendix C, Table C74 and Figure C31). Black males in New England had lower age-adjusted mortality by 12.1 ± 2.9 per 100,000 males compared with the national average among Blacks (Figure 16). The year of death did not modify the association between mortality and location.

Adjustment for years of schooling and for the proportion employed in agriculture did not change geographical differences in mortality in either Whites or Blacks (Appendix C, Table C29).[230] Prostate cancer death rates were higher in non metro than metro areas by 12 percent in Blacks and 4 percent in Whites.[291] Mortality in Blacks increased over time from 1973 to 1998 in Connecticut and Iowa and decreased in New Mexico (Appendix C, Table C29).[232]

The observed trend in mortality among Blacks was not attributable to regional differences in PSA testing and treatment utilization. Another study reported that more intensive screening for prostate cancer was not associated with lower mortality.[245] The PSA testing rate was five times higher (RR 5.39, 95 percent CI 4.76; 6.11) in Seattle than Connecticut with no difference in mortality. However, in ecological analysis, regional variation in age-adjusted mortality was positively correlated with the prevalence of PSA testing within the last 2 years in males older than 40 years (correlation coefficient 0.43, p=0.002) and with the prevalence of ever having a PSA test (correlation coefficient 0.44, p=0.001) (Figure 17 and Appendix C, Tables C56-C58). The states with higher PSA testing (ranges 38 to 61 percent) had higher age-adjusted mortality (26-54 per 100,000 males) (Appendix C Figure C32). Ecologic correlations ignored the regional differences in patient baseline risk including PSA levels, Gleason score, and tumor stage as possible explanatory factors for mortality variations.

Age-adjusted mortality was not correlated with numbers of urologists and radiation oncologists (Figure 18) when patients of all races were combined and among Black males, but mortality rates were lower among Whites in regions with higher numbers of urologists (correlation coefficient -0.16, p=0.01) and radiation oncologists (correlation coefficient -0.15, p=0.02) (Appendix C, Table C56).

Increased PSA screening and cancer detection may result in attribution bias when patients diagnosed with prostate cancer died from other diseases but had cancer as the underlying cause of death.[294] No studies examined regional difference in misclassification of prostate cancer mortality, so we were unable to determine the extent that increased cancer screening or diagnoses contributed to increased differences in cancer-specific mortality.

Summary for regional variation. Differences in structure (number of physicians involved in prostate cancer care) and process variables (screening and treatment practices) in U.S. regions were not correlated in ecologic analysis. Incidence and mortality varied in regions but with no significant differences compared with the national average. Significant geographic differences in incidence and mortality vs. the U.S. average were observed in Black males with the highest mortality in the East South and South Atlantic regions. Physician availability negatively correlated with mortality in Whites but not in Blacks. Limited evidence suggests variations in morbidity related to RP and in cost of this procedure. Pooling analysis at state and regional levels may diminish differences in access to and quality of care in smaller urban/rural areas.[24,256] Patient characteristics, including ethnicity and socioeconomic status, were not associated with treatment choices in the study conducted in the SEER database.[234] However, the Cancer of the Prostate Strategic Urologic Research Endeavor database reported that patients with higher annual incomes and fee-for-service patients more likely received RP than other treatments.[241] Managed care was not associated with mortality of Medicare beneficiaries with prostate cancer.[271] In one region, Black patients had a 168 percent higher mortality rate compared with Whites in the private sector but not in the Veteran Affairs sector.[295] Uncertain effectiveness of treatment options may contribute to differences in patient outcomes.[79] Future research should address geographic differences in process variables (distribution of hospital technology and quality of care) and in patient characteristics (distribution of socioeconomic status and access to care).

How Does Hospital and Provider Volume Affect Outcomes?

Association between hospital volume and patient outcomes. Several epidemiologic investigations examined associations between hospital volume of RP and patient outcomes.[17,18,237-239,242,296] We evaluated studies that examined hospital volumes of perineal and retropubic RP. Authors defined volume as an annual average of procedures[237,239] or the total number of procedures during the time the study was performed in each hospital.[17,18,242] Volumes were measured from linked SEER and the Medicare hospital claims database (Appendix C, Tables C31-C34). Authors compared volume measurements from different databases (State Discharge Registry and Medicare database) and concluded that both approaches yield the same results.[239] The distribution of hospital volume is presented in Appendix C, Table C75.

Surgery related mortality. Four retrospective cohorts examined the association between hospital volumes of RP and surgery-related mortality (Appendix C, Table C31).[17,237,239,242] Authors defined mortality related to RP as in-hospital death[237] or postoperative death within 30-90 days after surgery.[17,239,242] We combined these two measurements. Authors reported death rates in different categories of hospital volume. We computed death rate corresponding to an increase by ten procedures performed annually in hospitals for a pooling analysis (Appendix C, Figure C33). One study,[242] of three[237,239,242] that reported random changes in mortality, showed a significant reduction in death rate that resulted in a random pooled estimate (p for heterogeneity = 0.017). One study[238]

did not find a significant association between hospital volume and all-cause and cancer-specific mortality 10 years after surgery.

Three studies reported adjusted relative risk of surgery related mortality (Appendix C, Figure C34).[17,237,239] The relative risk of death in hospitals that performed 25-54 vs. 55 or more RPs per year was 1.71 (95 percent CI 1.20; 2.60) with absolute increase in risk from 0.17 percent to 0.28 percent.[237] Considering that approximately 70 percent of patients were treated in hospitals with a volume of less than 50 procedures per year,[237,239] more than 41 percent of deaths in such hospitals might be attributable to low volume independent of patient characteristics (Table 15). Among all patients treated with RP, 33 to 35 percent of deaths might have been avoided if patients had been treated in hospitals with higher volume. Another large study[242] showed a 42 percent higher relative increase (RR 1.42, 95 percent CI 1.16; 1.68) of surgery-related mortality in hospitals that performed less than 27 vs. more than 36 procedures per year with an increase in absolute risk from 0.39 to 0.56 percent. In terms of attributable events, 5.3 deaths per 1,000 RP patients might be avoided if patients had been treated in hospitals that performed more than 36 procedures per year. One earlier study[17] did not find an association with mortality. Our pooled analysis showed a relative reduction of 13 percent (RR 0.87, 95 percent CI 0.81; 0.94) corresponding to ten additional RPs performed annually in hospitals (p for heterogeneity 0.11) (Table 16). The time when events occurred, the database, and the sampling strategy did not modify the association between hospital volume and surgery related mortality.

The relative risk of surgery related mortality in categories of quartiles of hospital volume was estimated (Appendix C, Figure C35). Relative risk of death was almost twice that in hospitals performing less than 22 (1st quartile) (RR 1.97, 95 percent CI 1.4; 2.76) and 64 percent higher in hospitals with 23-39 operations per year (2nd quartile) (RR 1.64, 95 percent CI 1.28; 2.1) compared with hospitals that had done more than 85 surgeries per year (4th quartile) (p for heterogeneity = 0.08). The mean hospital volume appears to be a reasonable cut point to identify a threshold in volume effect (p for heterogeneity = 0.24). The relative risk of death related to surgery was 0.62 times less in hospitals that performed more than 43 RPs per year (RR 0.62, 95 percent CI 0.47; 0.81). Appendix C, Figure C36, presents the number of avoided deaths per 1,000 hospitalized patients in hospitals with volume above an average mean level and number of excessive deaths in hospitals with lower volumes.

Surgery related morbidity. Four cohorts[18,239,242,248] examined the association between hospital volume and surgery related morbidity including cardiac, respiratory, and vascular complications, bleeding, renal failure, shock, and need for re-operation (Appendix C, Table C32). Three of four studies reported a significant reduction in complication rates among higher categories of hospital volume. We calculated pooled rates corresponding to ten additional procedures in three studies (Appendix C, Figure C37). Overall, every ten RPs performed annually in hospitals was associated with absolute reduction in complications by 1.1 percent (95 percent CI 0.71; 1.7). The association was significant with a reduction in complication rate by 7.3 percent per natural logarithm of ten surgeries per year (95 percent CI 4; 10, p <0.001). At the time when events occurred, the database, and the sampling strategy did not modify the association between hospital volume and surgery related morbidity.

We found an absolute reduction in complication rates of 2.8 percent among hospitals that performed 23-39 surgeries per year (2nd quartile) vs. fewer than 22 (1st quartile) (95 percent CI 1.1; 4.6 percent). Hospitals with more than 85 procedures per year (4th quartile) vs. fewer than 22 (1st quartile) had a 7.3 percent reduction in complication rates (95 percent CI 2.1; 12.5) (p for heterogeneity = 0.07). The absolute differences in complication rates of 9.7 percent (95 percent CI 3.6; 15.8) were observed among hospitals above vs. below the mean volume (43 procedures per year) (p for heterogeneity = 0.23) (Table 16).

Three studies evaluated relative risk of morbidity after RP.[18,242,248] Hu et al[18] compared complication rates in hospitals with greater vs. less than 60 procedures per year: 85 percent of procedures were performed in hospitals with lower volume. The authors reported an insignificant 16 percent reduction in complications (RR 0.84, 95 percent CI 0.59; 1.19) in hospitals with higher volume. Yao et al[242] defined low volume as less than nine procedures per year and reported a 1.43 fold increase in the adjusted complication risk (RR 1.43, 95 percent CI 1.37; 1.48). The reduction in relative risk was consistent across the categories of hospital volume in this study, with an 8 percent relative reduction corresponding to an additional ten procedures per year in hospital (RR 0.92, 95 percent CI 0.89; 0.96). However, pooled analysis of all studies did not detect a significant association between hospital volume and relative risk of complications.

Surgery related quality measures (cancer control, urinary complications, and operative quality). One cohort study[238] included 5,837 patients with prostate cancer followed for 10 years after RP performed in 348 hospitals. The authors examined the association between hospital volume and use of adjuvant therapy started more than 6 months after surgery adjusted for tumor stage and grade and patient comorbidity. Patients whose operations were in hospitals with low volume (<16 procedures per year) were treated 1.25 times more often with adjuvant therapy (95 percent CI 1.14; 1.38) compared with those operated in hospitals that performed more than 85 surgeries per year. The association was consistent across volume categories with a significant reduction in risk of adjuvant therapy by 2 percent (RR 0.98, 95 percent CI 0.97; 0.99) per ten additional surgeries per year (Appendix C, Figure C38). Patients operated in hospitals with less than 22 procedures per year had a 12 to 13 percent increase in use of adjuvant therapy compared with those treated in hospitals that performed 23-40 and more than 85 RPs per year, respectively (Appendix C, Figure C38).

Two cohort studies[18,239] examined the association between urinary and incontinence complications and hospital volume with different definitions of low and high volumes. We calculated changes in frequency of diagnosed events (in hospitals claims) and symptoms (in medical charts) corresponding to ten additional RPs performed annually in hospitals (Appendix C, Figure C39). Rates of any urinary complications but not incontinence were lower by -0.74 percent (95 percent CI -1.12; -0.36) in patients sampled from the SEER database[239] and by -1.83 (95 percent CI -3.57; -0.09) in Medicare beneficiaries.[18]

A pooled analysis conducted to estimate the association between hospital volume as a continuous variable and rates of surgery-related complications detected a decrease by 0.85 percent (-1.53, -0.17) in diagnosed events of late urinary complications (Figure 19) (p for heterogeneity = 0.02). A small but significant increase of 0.16 percent (95 percent CI 0.01; 0.30) in the rates of long-term incontinence corresponded to an additional ten RPs per year. Patients treated in hospitals

with volume above vs. below the mean (43 procedures) (Figure 20) had lower rates of urinary complications by 5.3 percent (95 percent CI -9.3; -1.3). A further increase in hospital volume (4th quartile, more than 85 procedures per year) was not associated with the larger benefit reduction of 5.3 percent (95 percent CI 0.6; 10) in rate of late urinary complications compared with hospitals that performed 23-39 procedures (2nd quartile) annually.

One study examined operative quality indicators in 133 hospitals from New York state and reported an increase in quality scores of 2.7 (95 percent CI 0.9; 4) for every additional RP performed annually.[296] Hospitals that performed 23-39 procedures per year vs. less than 23 had higher operative quality by a score of 62 (95 percent CI 24; 99. p=0.002). We could not find studies that examined positive surgical margins in relation to hospital volume.

Length of stay and readmission to hospital. Hospital volume was associated with reduced length of stay and readmission. Four studies[18,237,242,250] reported length of stay and readmission rate in relation to hospital volume; three[18,237,242] tested the associative hypothesis (Appendix C, Table C34). The authors obtained the Nationwide Inpatient Sample[237] and the Medicare claims databases[18,242] to analyze hospital volume, length of stay, and readmission rate and adjusted for patient[18,237,242] and hospital[18,242] characteristics to estimate the effect of volume. We calculated the differences in outcomes corresponding to an increase by ten procedures in annual hospital volume (Appendix C, Figure C40). All studies reported a small reduction in length of stay by an increase in volume. Pooled analysis with four studies detected a decrease in length of stay by 0.32 days (95 percent CI 0.2; 0.44) corresponding to ten additional procedures and by 1.7 days (95 percent CI 0.97; 2.4) corresponding to an increase in natural logarithm of ten RPs performed annually in hospitals (Appendix C, Figure C41).

Hospital volume was categorized to find a threshold in volume effects (Appendix C. Figure C42). Hospitals in the highest volume quartile (more than 85 procedure per year) had lower lengths of stay by 0.9 days (95 percent CI 0.3; 1.5) compared with those that performed 23-39 RPs annually and by 1.5 days (95 percent CI 0.8; 2.2) compared with those in the lowest quartile (<22 surgeries per year). The decrease in length of stay was 0.9 days (95 percent CI 0.3; 1.6) in hospitals above vs. below the mean (43 procedures per year).

Crude readmission rates did not differ in relation to hospital volume (Appendix C, Figures C41 and C42). However, adjusted for patient age, race, and comorbidity, surgeon specialty, and hospital teaching status, relative risk of readmission was 1.3 times higher among patients operated in hospitals that performed an average of nine surgeries per year compared with patients operated in high (more than 36 procedures per year) volume clinics.[242] The relative risk was 1.16 times higher in patients operated in hospitals with an average of 14 RPs per year. We estimated that an increase in hospital volume by ten surgeries per year was associated with a decrease in relative risk of readmission by 10 percent (RR 0.90, 95 percent CI 0.85; 0.99).

Association between hospital status and patient outcomes. Teaching status was defined by an affiliation with an academic center[254] or membership in the Council of Teaching hospitals[19] (Appendix C, Table C35). The ownership of the hospitals was defined as for-profit or not for profit institutions, government, or public hospitals.[18,19,253] Higher rates of surgery-related mortality[254] and increased relative risk of death were reported in nonteaching hospitals.[19] A

relative increase in surgery-related mortality by 18 percent was shown in for-profit institutions compared with teaching not-for-profit institutions (RR 1.18, 95 percent CI 1.10; 1.22). The majority of the authors combined hospitals with different status in the investigations. We included all studies that reported rates[17,19,237,239,242,246,253] and relative risk[17,19,237,242] of surgery-related mortality in pooled analysis and did not find significant associations with hospital status. However, teaching hospitals had lower rates of surgery-related complications (p for heterogeneity not significant) by 17.6 percent (95 percent CI 9; 25.8)[239,242,248,253] and higher scores of operative quality (mean 141 scores, 95 percent CI 75; 210).[296] Length of stay was higher in private institutions compared with academic centers.[249] Public nonteaching hospitals had lower length of stay by 1.5 days (95 percent CI 0.3; 2.6) compared with academic centers[18,19,237,242,249,250,253] (p for heterogeneity <0.01). Hospital charges[237,253] were not associated with teaching status being higher in for-profit clinics.[253]

Association between surgeon volume and patient outcomes. Authors defined surgeon volume as an average of RPs performed annually by a surgeon[239,248] or the total number of procedures during the time of the study.[236,247,250,252,254] Two studies[239,254] examined the association with surgery-related mortality and did not find differences in death rates in relation to surgeon volumes (Appendix C, Table C36).

Five studies examined the association between surgeon volumes and complications,[18,236,239,248,250] including cardiac, respiratory, or vascular events, the need for reoperation bleeding, renal failure, and shock in different volume categories (Appendix C, Table C37). We calculated the difference in complication rates corresponding to an increase by one surgery per year in individual studies (Appendix C, Figure C43), when possible, and pooled estimates including all studies (Figure 21 and Table 17). Patients that were operated by surgeons with higher volume experienced lower rates of complications (-0.19; 95 percent CI -0.07; -0.3 per one RP per year) (p for heterogeneity = 0.01). This decrease was larger by 2.8 percent (95 percent CI 0.5; 5) per natural logarithm of surgeon volume. The relative risk of surgery-related complications adjusted for patient age, race, and comorbidity and hospital type and location was 0.53 times lower in men treated by higher volume surgeons (>40 vs. ≤40 surgeries per year).[18] Patients needed blood transfusions 8.6 times more often when the operating surgeon performed fewer than 15 RPs per year.[248]

Cohort studies that examined the association between surgeon volume and quality measures[18,236,239,247,252] reported rates of late urinary complications and long-term incontinence (events and symptoms), and positive surgical margins among different categories of surgeon volumes (Appendix C, Table C38). We calculated the difference in outcome rates corresponding to an increase of one procedure in surgeon annual volume (Appendix C, Figure C43) and found a reduction in urinary complications and symptoms of long-term incontinence. In pooled analysis (Table 17) the rate of late urinary complications was lower by 0.24 percent (95 percent CI 0.001; 0.5 percent) and the rate of long-term incontinence was lower by 0.12 percent (95 percent CI 0.001; 0.25) corresponding to an increase of one RP per year in surgeon experience. The rate of long-term incontinence was less by 0.6 percent (95 percent CI 0.34; 0.84) in men operated by surgeons that performed more than ten RPs per year. Surgeon volume was not associated with positive surgical margins.

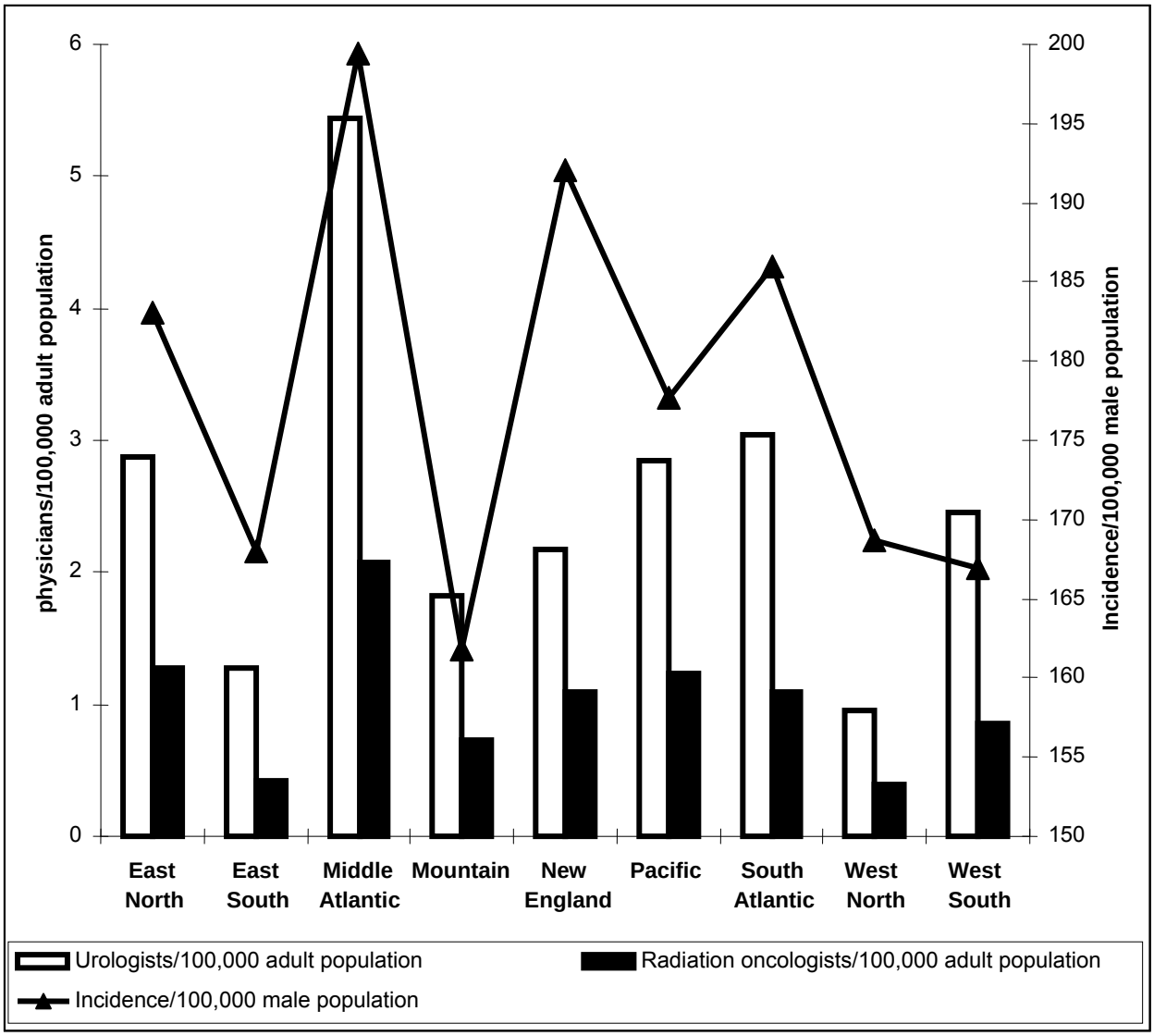
Length of stay in hospitals after RP was assessed in four studies (Appendix C Table C39).[18,249-251] Pooled analysis showed reduction in length of stay by 0.97 days (95 percent CI -1.45; -0.48) corresponding to an increase in surgeon volume logarithm (p for heterogeneity = 0.13). The hospital stay for patients operated by higher volume surgeons (4-9 RPs per year, 2nd quartile) decreased by -2.18 days (95 percent CI -4.43; 0.06 day) compared with surgeons who performed less than three surgeries per year (1st quartile) (Figure 22). Length of stay was shorter by 3.3 days (95 percent CI 0.5; 6) in men operated by surgeons who performed more than 15 (4th quartile) vs. fewer than three surgeries (1st quartile) per year (p for heterogeneity = 0.5). Cost was not associated with surgeon volume.

Association between surgeon volume of robotic prostatectomy and surgical margins. Positive surgical margins of 193 consecutive robotic prostatectomy patients (192 with T1-2 and one with T3 tumor) were analyzed in association with surgeon volume in one study.[297] Baseline patient and tumor characteristics were the same across surgeon volume levels. A significant decrease in adjusted odds of extensive positive margins was found when surgeons performed more than 80 procedures compared to those performing 15 or less robotic prostatectomies (Figure 23).

Summary of the association between hospital and provider volume with patient outcomes. Observational studies suggest that hospital volume of RP was associated with a decrease in surgery-related mortality independent of measured confounding factors. Limited evidence suggests a reduction in relative risk of readmission and rate of adjuvant therapy in association with increased hospital volume. The decrease in length of stay was significant in most reports, but the pooled estimate may not be valid due to heterogeneity in the results from individual studies. Hospital volume was associated with decreased rates of surgery-related morbidity and complications. Patient referral patterns and clustering patients among hospitals can affect the association and cannot be estimated from the reports. Despite different definitions of "high" and "low" hospital volumes in individual studies, pooled analysis showed that facilities with above average numbers of RPs per year had better patient outcomes, including lower surgery-related mortality, late urinary complications, and length of stay. Surgeon volume was also inversely associated with surgery-related late urinary complications, long-term incontinence, and length of stay.

Whether patients who attended lower volume facilities would, in fact, on average have had better outcomes had they attended higher volume facilities cannot be absolutely confirmed from these observational studies, but the consistency of the results implies that further research into this issue, including possible randomized assignment of some patients to higher volume facilities, is warranted.

Figure 12. Regional variations in incidence of prostate cancer (CDC 1999-2004) and distribution of urologists and radiation oncologists* in U.S. regions



* an average of absolute number of physicians who identified themselves as radiation oncologists in the U.S. obtained from surveys conducted by the American Medical Association from 1999-2005[284-288] the ratio per 100,000 adult population was calculated with U.S. Census data[289]

Figure 13. Proportion of patients with localized prostate cancer treated with external beam radiotherapy, brachytherapy, primary androgen deprivation therapy, radiation, and watchful waiting (%) in U.S. regions (pooled analysis)

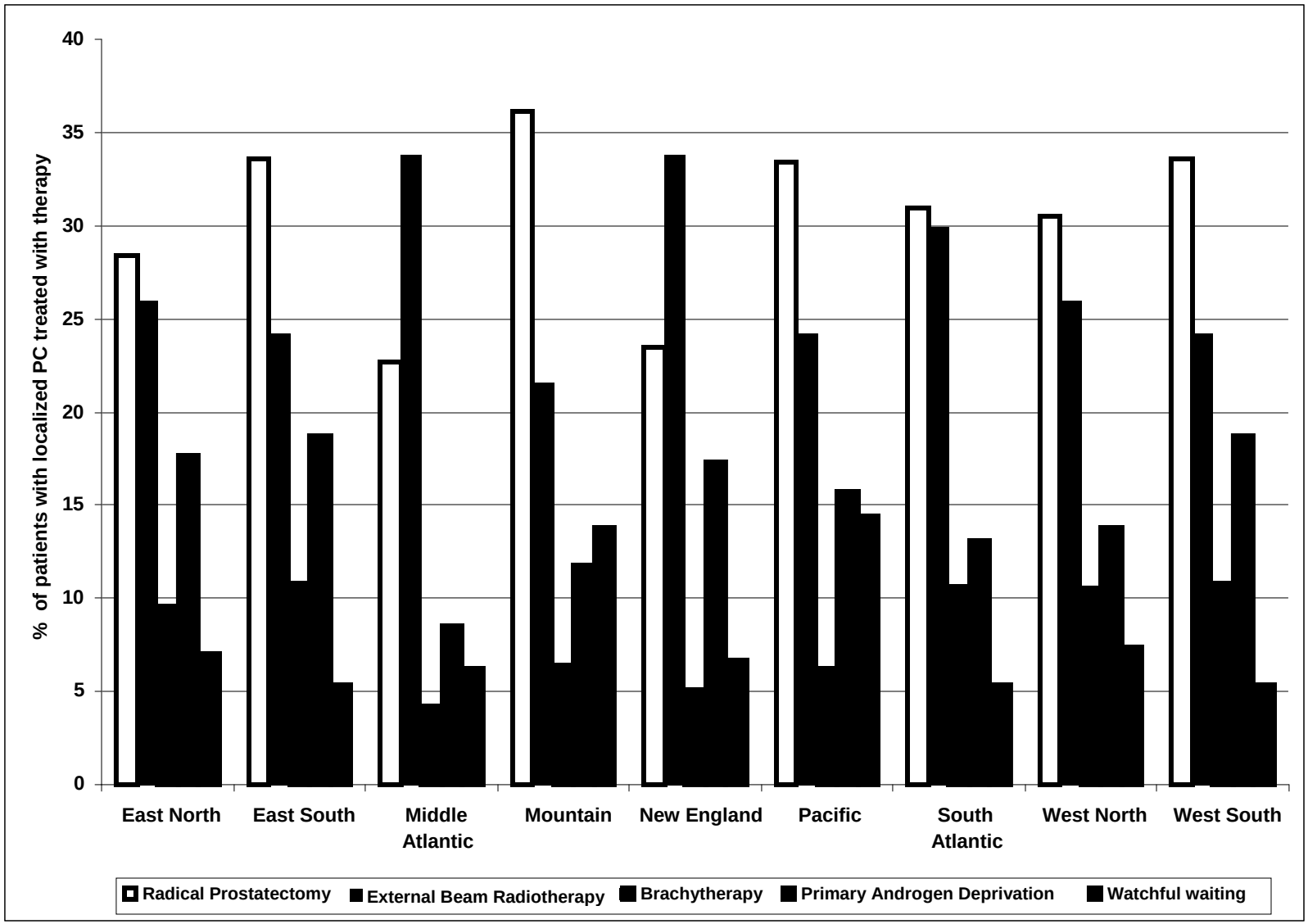


Figure 14. Utilization of radical prostatectomy, all cause and prostate cancer mortality in patients with prostate cancer treated with radical prostatectomy in U.S. regions (pooled analysis)

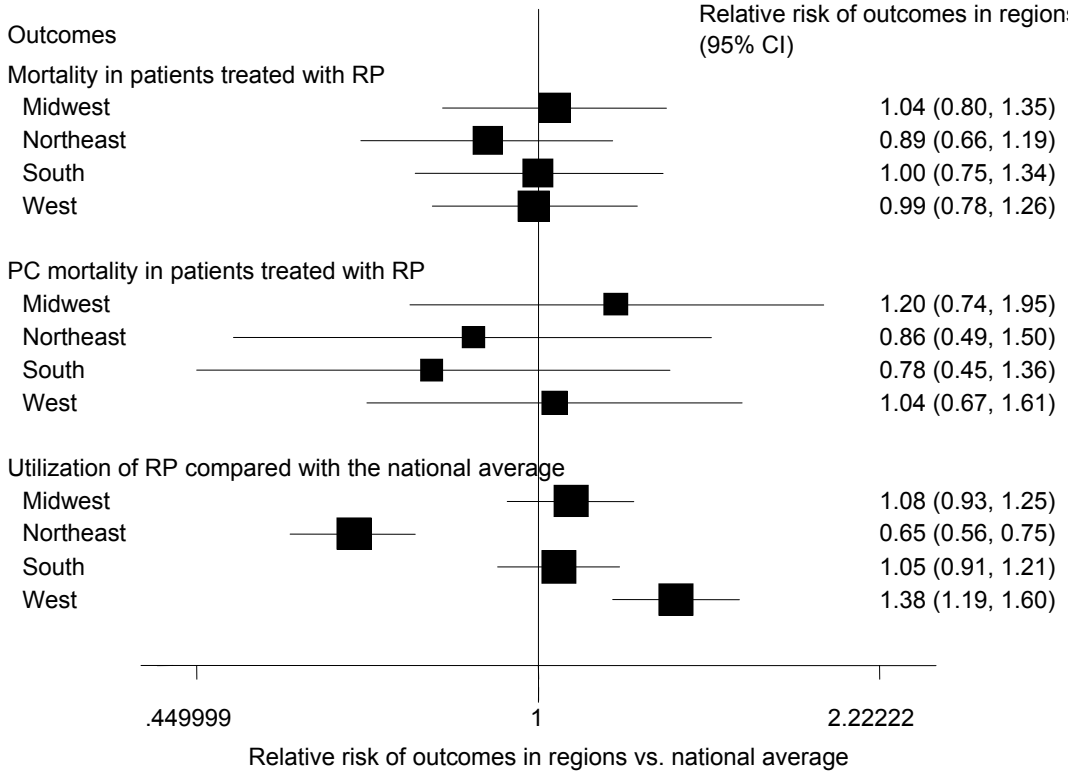


Figure 15. Mortality from prostate cancer (per 100,000 male population) in U.S. regions (CDC data 1999-2004)

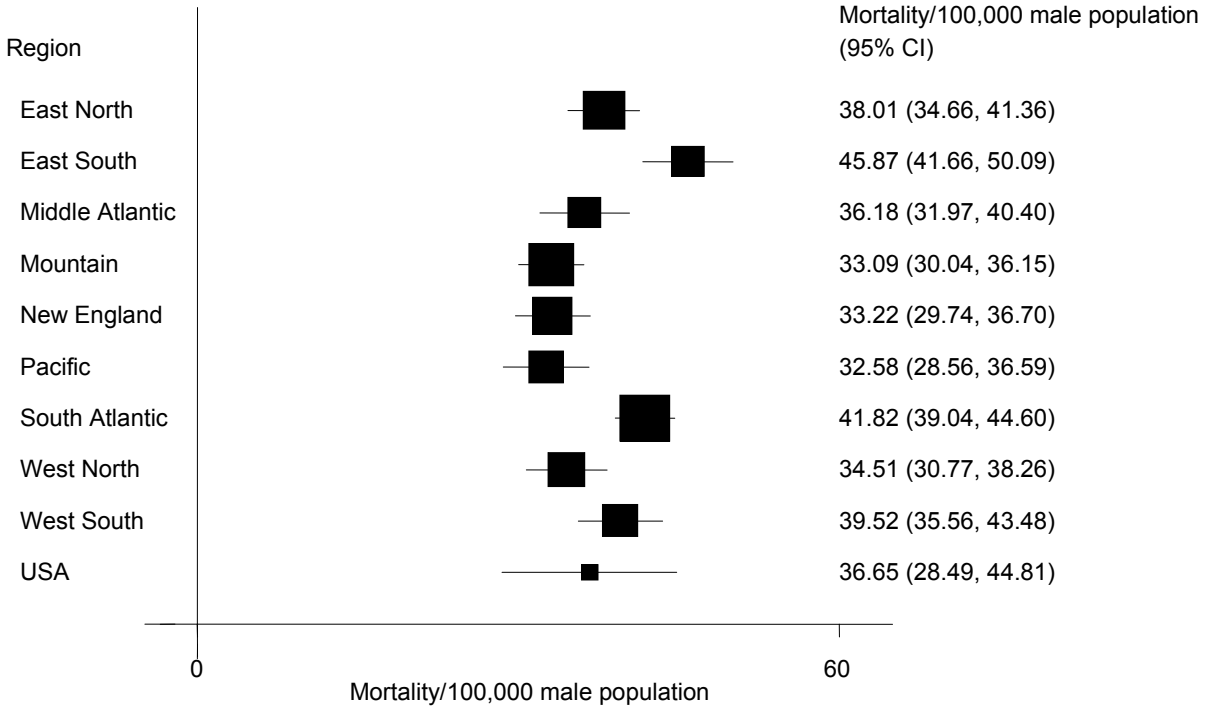


Figure 16. Mortality from prostate cancer (per 100,000 male population) among different races in U.S. regions (CDC data, 1999-2004)

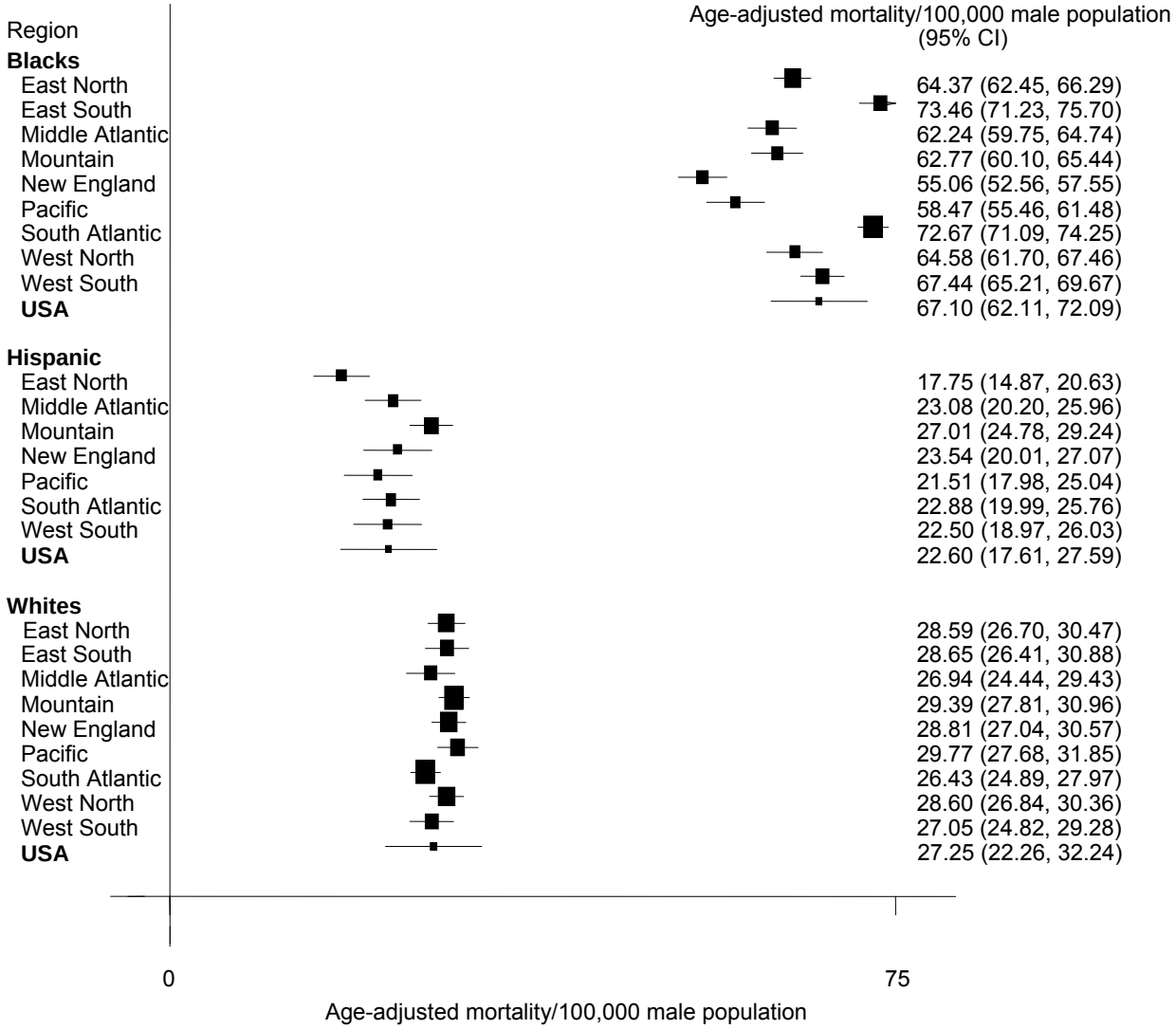
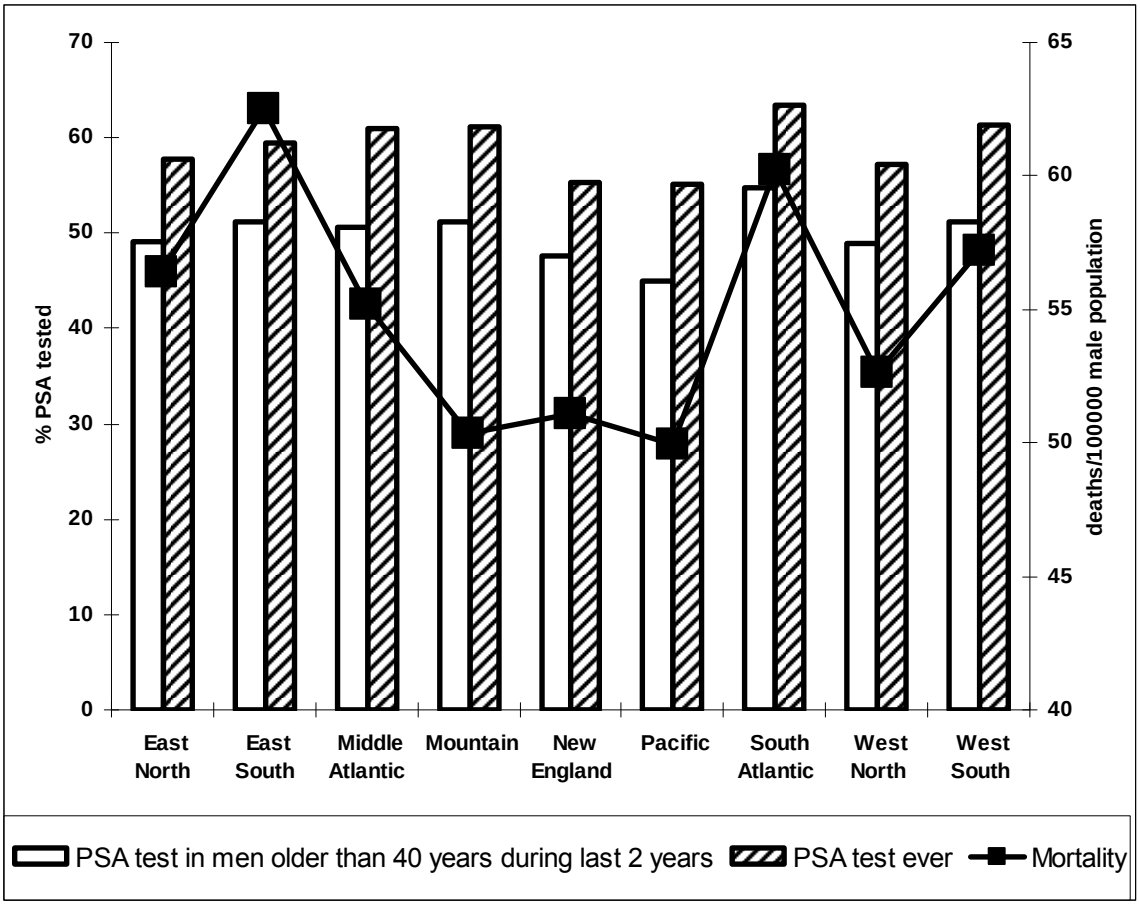


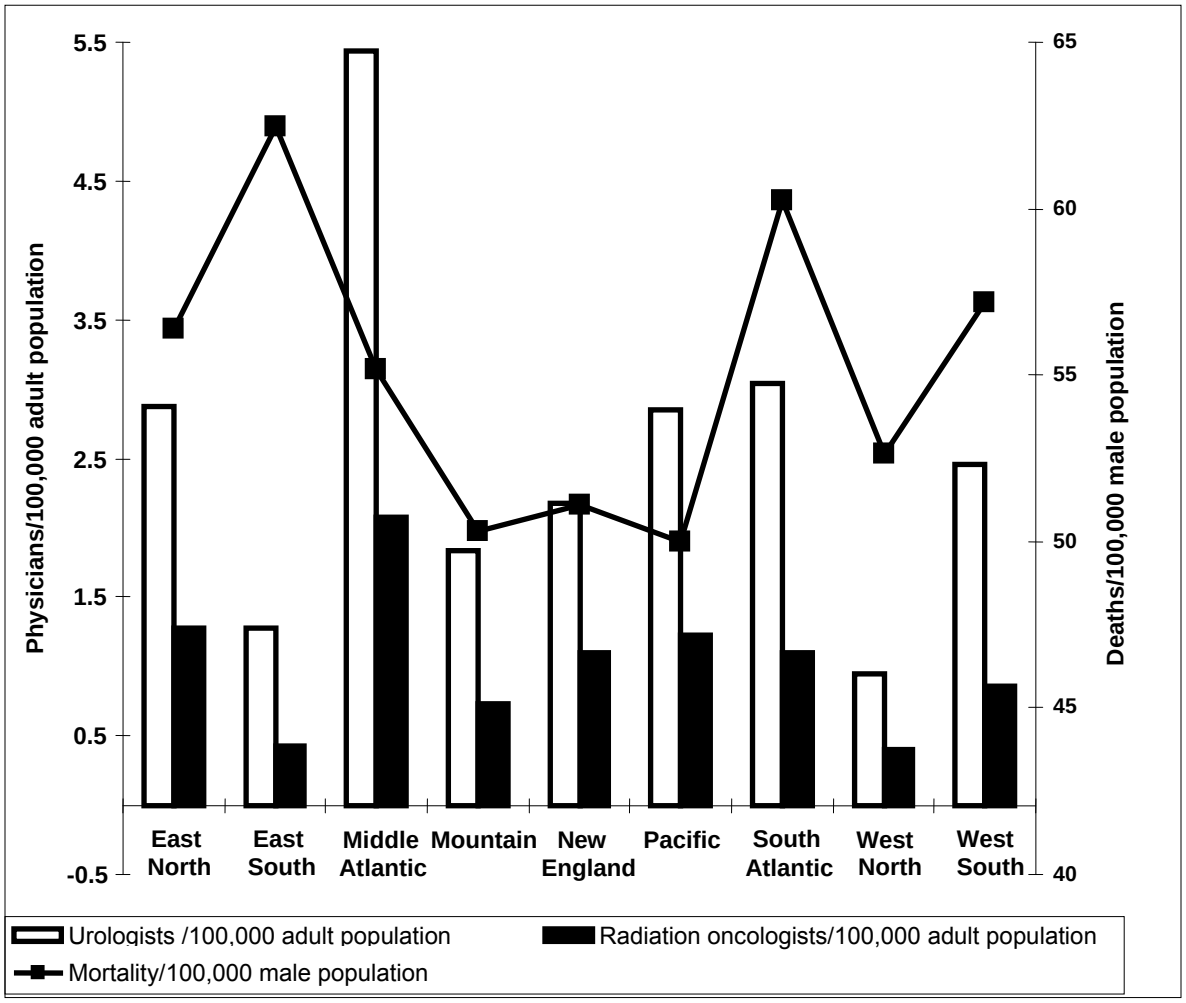
Figure 17. Regional variations in PSA testing* and prostate cancer age-adjusted mortality in the U.S.**



* average responses in U.S. regions to the BRFSS questionnaire[290] having ever had PSA test and during last 2 years in males older than 40 years

** 1999-2004 average of age-adjusted prostate cancer mortality (U.S. Cancer statistic)[292]

Figure 18. Regional variations in prostate cancer age-adjusted mortality* and distribution of urologists and radiation oncologists in the United States (pooled analysis)**



* 1999-2004 average of age adjusted prostate cancer mortality (the U.S. Cancer statistic)[292]
** average of absolute numbers of physicians who identified themselves as radiation oncologists in the U.S. obtained from surveys conducted by the American Medical Association from 1999-2005[284-288]

Table 15. Association between hospital volume and mortality—results from individual studies

Reference	Volume Categories *(% Hospitals)*	Crude Rate, %	Adjusted Volume Effect	Number Needed to Treat	Number of Excess or Avoided Deaths/1,000	Attributable Fraction of Events in Patients Operated in Low Volume Hospitals (95% CI)	Attributable Fraction of Events in Population with PC (95% CI)
Ellison, 2000[237]	<25 (76)	0.3	1.78 (1.2; 2.7)	756	1.3	43.8 (16.7; 63.0)	35.3 (12.3; 54.3)
	25-54 (17)	0.3	1.71 (1.2; 2.6)	831	1.2	41.5 (16.7; 61.5)	33.2 (12.3; 52.8)
	>54 (7)	0.2	1 (reference)				
	Increase by 10 procedures per year		0.83 (0.76; 0.91)		0.5		
Yao, 1999[242]	Hospital Volume						
	<38 (9/year)	0.6	1.51 (1.25; 1.77)	506	2	33.8 (20.0; 43.5)	26.3 (14.9; 35.0)
	39-74 (14/year)	0.6	1.43 (1.17; 1.69)	600	1.7	30.1 (14.5; 40.8)	23.1 (10.6; 32.6)
	75-140 (27/year)	0.6	1.42 (1.16; 1.68)	614	1.6	29.6 (13.8; 40.5)	22.7 (10.1; 32.2)
	>141 (36/year)	0.4	1 (reference)				

Table 16. Pooled analysis† of association between annual volume of radical prostatectomy and patient outcomes: hospital volume

Measure	Hospital Volume	Effect of Volume
Surgery related mortality (3 studies)		Relative Risk (95% CI)
Dose response	10 procedures	0.87 (0.81; 0.94)
Mean	>43 vs. <43	0.62 (0.47; 0.81)
Quartiles	>85 vs. <22	0.51 (0.36; 0.71)
Quartiles	>85 vs. 23-39	0.61 (0.48; 0.78)
Difference in rate of complications (3 studies)		% (95% CI)
Dose response	10 procedures	-1.21 (-0.71; -1.70)
Mean	>43 vs. <43	-9.70 (-3.60; -15.80)
Quartiles	>85 vs. <22	-7.30 (-2.10; -12.50)
Quartiles	23-39 vs. <22	-2.85 (-1.10; -4.60)
Difference in lengths of stay (3 studies)		Days (95% CI)
Dose response	10 procedures	-0.32 (-0.44; -0.02)*
Quartiles	>85 vs. <22	-1.49 (-2.2; -0.82)*
Quartiles	>85 vs. 23-39	-0.9 (-1.46; -0.34)*
Difference in rate of events of late urinary complications (2 studies)		% (95% CI)
Dose response	10 procedures	-0.85 (-1.53;-0.17)*
Difference in rate of long term incontinence (2 studies)		% (95% CI)
Dose response	10 procedures	0.16 (0.01; 0.3)*
Difference in rate (%) of symptoms of late urinary complications (2 studies)		
Dose response	10 procedures	-1.16 (-2.7; 0.38)
Difference in rate (%) of symptoms of long-term incontinence (2 studies)		
Dose response	10 procedures	-0.14 (-0.44; 0.17)

† pooled analysis using random effects model
* significant between studies heterogeneity

Figure 19. Difference in surgery-related complications rate corresponding to an increase by 10 radical prostatectomies performed in hospital (pooled analysis)

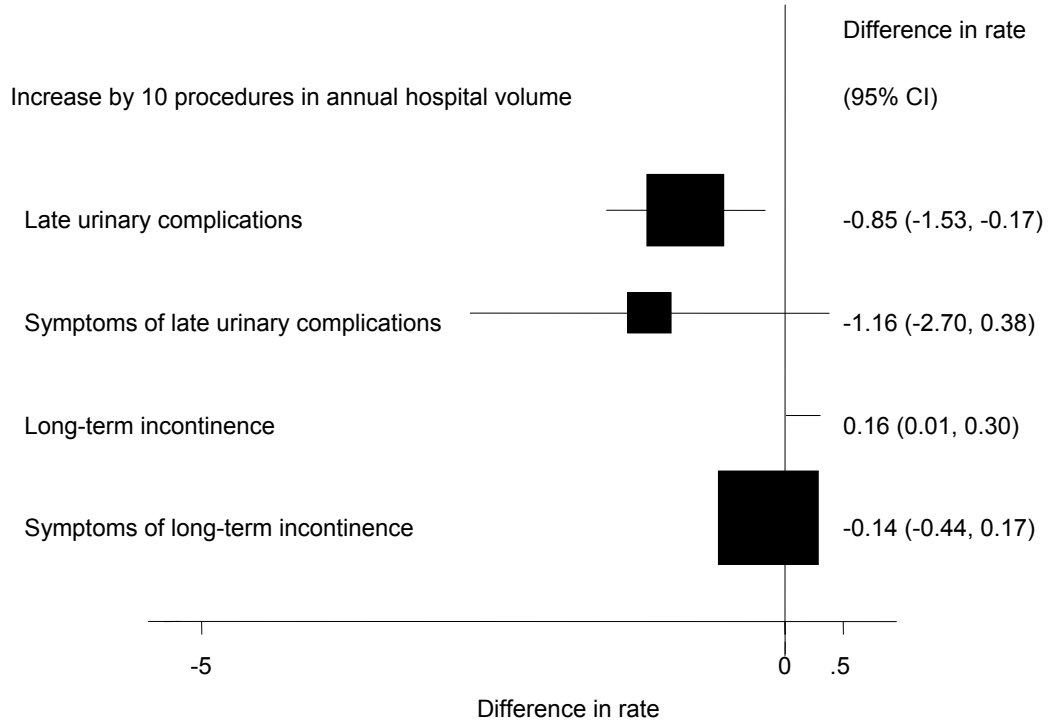


Figure 20. Difference in surgery-related complications in categories of hospital volume (pooled analysis)

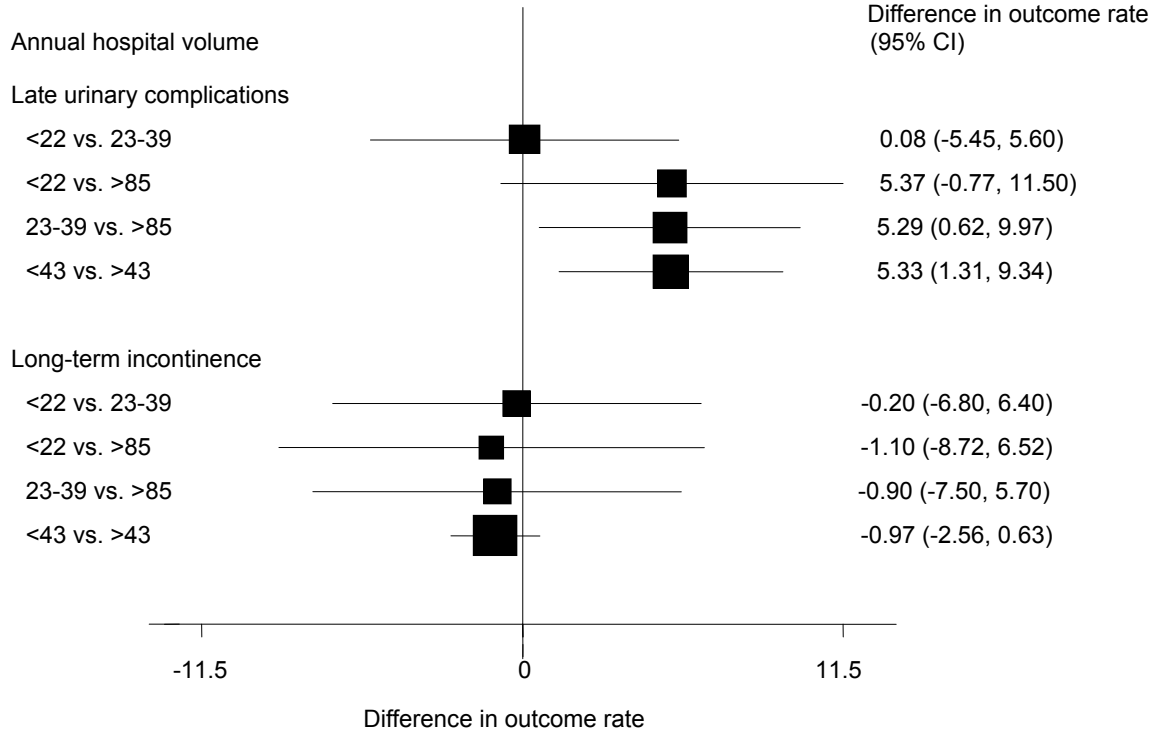


Figure 21. Difference in rates of surgery-related urinary complications and long-term incontinence corresponding to an increase by one radical prostatectomy performed by a surgeon and in categories of surgeon volumes above and below the median (results from individual studies)

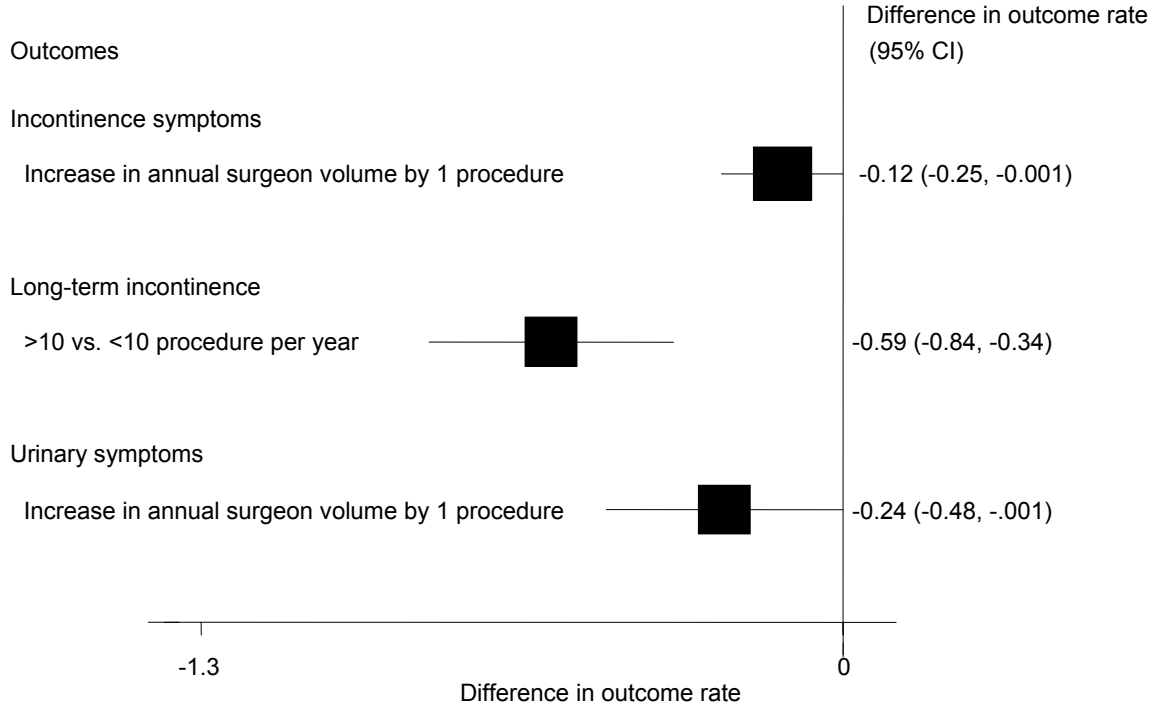
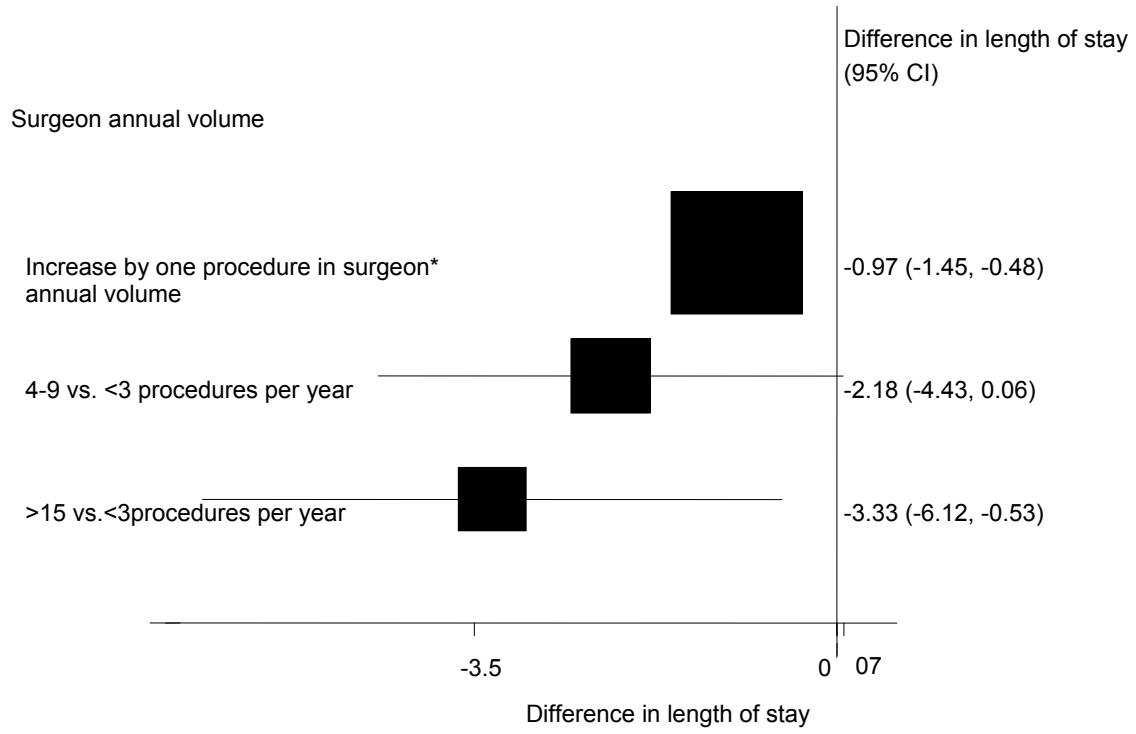


Table 17. Pooled analysis† of association between annual volume of radical prostatectomy and patient outcomes: surgeon annual volume

Measure	Surgeon volume	Effect, 95% CI
Difference in rate of surgery-related mortality (2 studies)		
Dose response	10 procedures	0.02 (-0.01; 0.4)
Difference in rate (%) of surgery-related complications (4 studies)		
Dose response	10 procedures	-1.92 (-3.13; -0.70)*
Difference in lengths of stay (4 studies)		
Dose response	1 procedure in logarithmic scale	-0.9 7(-0.48; -1.45)
Quartiles	<3 vs. >15	-3.30 (-0.50; 6.10)
Difference in rate (%) of events of long-term incontinence (2 studies)		
Median	>10 vs. <10	-0.60 (-0.34; -0.84)
Difference in rate (%) of symptoms of long-term incontinence (2 studies)		
Dose response	10 procedures	-1.2 (-2.5; -0.1)
Difference in rate (%) of symptoms of late urinary complications (2 studies)		
Dose response	10 procedures	-2.4 (-5; -0.1)

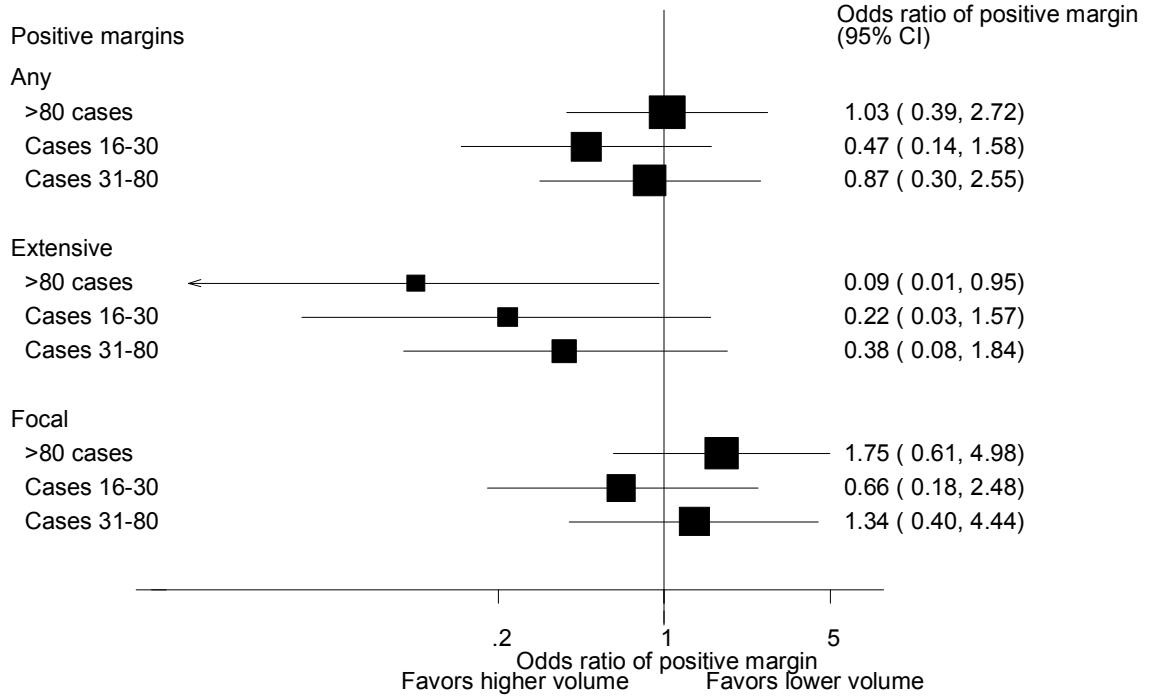
† pooled analysis using random effects model
*significant between studies' heterogeneity

Figure 22. Difference in length of stay after radical prostatectomy by increase in surgeon annual volume (pooled analysis)



* in logarithmic scale

Figure 23. Odds ratio of margin compared with initial 15 cases (model adjusted for above and maximal tumor diameter, extraprostatic extension, blood loss, and nerve sparing)



Key Question 4: How do tumor characteristics, e.g., Gleason score, tumor volume, screen vs. clinically detected tumors, and PSA levels, affect the outcomes of these therapies, overall and differentially?

Tumor characteristics are often utilized by patients and providers when choosing or recommending treatments because they are believed to affect outcomes. The primary measure of aggressiveness is the Gleason histologic score, which ranges from 2-10. Gleason 8-10 tumors are considered the most aggressive, Gleason 7 tumors somewhat less, and Gleason ≤6 tumors potentially indolent. Pretreatment Gleason scores are determined based on a pathologist's examination of several small cores of prostate tissue. Typically, six cores are obtained during a prostate biopsy (sextant biopsy that includes both lobes of the prostate). However, the number has increased over time to 12, 24, and even "saturation techniques." Compared to fewer cores, a greater number of biopsy cores increases the amount of the prostate gland sampled and enhances the likelihood of detecting even small volume disease. In addition to the histologic score, the number of biopsy cores that contain prostate cancer and the percent within each core containing tumor is recorded. Because the Gleason score and tumor volume are not ideal or complete indicators of an individual tumor risk characteristic, additional efforts are underway to identify more reliable prognostic factors for individual tumors.[298] Risk stratification strategies have incorporated PSA level, biopsy Gleason score, and clinical tumor category because these appear to be associated with risk of PSA failure and prostate cancer specific mortality[13] A risk classification currently recommended is:

Low Risk: PSA ≤10 ng/ml, Gleason score ≤6 and clinical stage T1c or T2a
Intermediate Risk: 10 <PSA ≤20 ng/ml, or Gleason score 7, or clinical stage T2b
High Risk: PSA >20 ng/ml or Gleason score 8-10 or clinical stage T2c

Little information exists on the comparative effectiveness of treatments based on low, intermediate, or high risk classifications. Our analysis was confined to baseline PSA levels and Gleason histologic grade.

The true natural history of prostate cancer is not well known because patients rarely remain untreated for the full duration of their disease. A recent report assessed 20-year outcomes among 767 men diagnosed in the United States with clinically localized prostate cancer between 1971 and 1984 (pre PSA era) and followed with WW and delayed palliative interventions. Sixty percent were diagnosed by transurethral resection of the prostate, 58 percent had no treatment within 6 months of diagnosis, and the remainder had some form of ADT. The median age at diagnosis was 69 years, and all but 6 percent have died. Overall, 29 percent died of prostate cancer. Both overall survival and cumulative mortality from prostate cancer and other causes varied according to age at diagnosis and comorbidities as measured by Charlson Comorbidity score and Gleason score (Figure 24). Among men with no or only minor comorbidities, 26 percent, 15 percent, and 8 percent survived at least 15, 20, and 25 years respectively. In comparison, in men with significant comorbidities, only 11 percent, 6 percent, and 3 percent, respectively, survived at least 15, 20, and 25 years).[226]

Gleason histologic score was associated with mortality. Men with palpable low grade prostate cancers managed with WW had a minimal risk of dying from prostate cancer during 20 years of followup (Gleason score of 2-4, six deaths per 1,000 person years; 7 percent died due to prostate cancer).[226] Men with high grade prostate cancers had a high probability of dying from prostate cancer within 10 years of diagnosis regardless of their age at diagnosis (Gleason score of 8-10, 121 deaths per 1,000 person years; 53 percent died due to prostate cancer). Death due to prostate cancer over this time period was 20 percent in men ages 55-59; 27 percent in men ages 65-69, and 30 percent in men ages 70-74, though the percent of high grade tumors was greater in older patients. Annual prostate cancer-specific mortality rates were similar when assessed before and after 15 years of followup. Because PSA testing increases the time of detection by 5-15 years, it is likely that men with PSA-detected tumors treated with WW will have a better 20 year disease-specific survival than this cohort

AUA database results were infrequently stratified by PSA or Gleason score, making comparative effectiveness of treatments according to these tumor characteristics difficult. When results were stratified, studies often used varying followup times, making comparative effectiveness difficult. Results were not controlled for confounding variables including age, comorbid conditions, or histologic score. No studies assessed survival or bNED in patients with baseline PSA levels ≤4.0. Outcomes were stratified according to baseline PSA <10 vs. ≥10 ng/ml and reported for two time periods: 26-60 months (short term) and 61-120 months (mid to long term).

Based on very limited nonrandomized trial data, mid term disease-specific survival appeared similar for subjects treated with EBRT compared to RP in men with baseline PSA >10 ng/ml. Men with Gleason scores 8-10 appeared more likely to have biochemical reoccurrence than men with Gleason scores 2-6, regardless of type of treatment. It was not possible to clearly determine whether comparative effectiveness between treatments varies by Gleason scores (Figure 25 and Appendix C, Figure C44).

In contrast to the survival data, many patient groups treated with brachytherapy, EBRT, or RP reported bNED (Figure 26). While there was a wide range in outcomes within and across treatment modalities, there appears to be an inverse association of mid and longer term bNED with baseline PSA categories across these three treatments. However, data were too variable to make conclusive statements, and it is not possible to determine if the relative effectiveness between brachytherapy, EBRT, and RP varies according to these PSA categories.

Overall and disease-specific survival were infrequently stratified by Gleason scores (Figures 27 and 28).When provided, the full spectrum of Gleason scores for each treatment modality was rarely available. Within and between treatment comparisons were limited for reasons noted above. For long-term outcomes, limited data from nonrandomized trials suggest that both overall and disease-specific survival are associated with Gleason score regardless of treatment. Because of the paucity of information, wide variation in outcomes, and the lack of controlling for potentially prognostic factors, it is not possible to determine if survival outcomes varied between treatments according to Gleason score. Results suggest that both mid- and long-term bNED were inversely associated with Gleason score (Figure 29). The wide range of outcomes and the lack of controlling for confounding variables preclude determining whether one treatment provides superior outcomes based on baseline Gleason score.

Some randomized trials reported outcomes according to baseline PSA levels, Gleason scores, or risk strata (question 1). Most reported biochemical progression rather than overall or disease-specific mortality or development of metastatic disease. In preplanned multivariate analyses from the SPCG-4, randomized study reduction in disease-specific mortality at 10 years due to RP compared to WW differed according to age but not baseline PSA level or Gleason score. Only 5 percent of men enrolled in SPCG-4 had PSA-detected disease and therefore findings may not be relevant to men currently detected. The number needed to treat and the duration of time needed to achieve a benefit is likely greater in PSA detected compared to nonPSA detected disease.[299] In another randomized trial, men with Gleason scores 8-10 were more likely to have evidence of biochemical reoccurrence than men with Gleason scores 2-6, and the results did not differ whether treatment was RP alone or combined with NHT. High dose EBRT was more effective in controlling biochemical failure (three successive increases in PSA level) than conventional dose[56] in both low-risk disease (n=227, PSA <10 ng/ml; stage ≤T2a tumors; or Gleason ≤6) and high-risk disease. In the low-risk subgroup, the percentages were 80.5 percent for the high-dose group and 60.1 percent in the conventional dose ($p < 0.001$), a 51 percent risk reduction. For the high-risk subjects, the percentages were 79.5 percent and 63.4 percent (44 percent risk reduction; $p=0.03$) for the respective groups. However, when the high-risk subjects were further divided into intermediate risk and high-risk groups, the benefit of high-dose therapy remained for the intermediate risk (81 percent vs. 62.7 percent, $p=0.02$) but not for the 33 high-risk patients ($p=0.80$).

In summary, tumor characteristics such as Gleason score, tumor volume, screen detected tumors, and PSA levels (and rates of PSA change) affect the overall outcomes of therapies. However, the affect on relative effectiveness of therapies is not well established. In a single randomized trial comparing RP with WW, disease-specific mortality at 10 years due to RP compared to WW differed according to age but not baseline PSA level or Gleason score. Only 5 percent of subjects enrolled in this trial had PSA-detected disease. The relative effect of these and other tumor prognostic characteristics require evaluation through the conduct of adequately powered RCTs..

Figure 24. Survival and cumulative mortality from prostate cancer causes up to 20 years after diagnosis, stratified by age at diagnosis and Gleason score (Source: American Medical Association, 2005, used with permission [Albertsen PC, Hanley JA, Fine J. 20-year outcomes following conservative management of clinically localized prostate cancer. JAMA 2005;293:2095-101][226] Copyright© 2005 American Medical Association

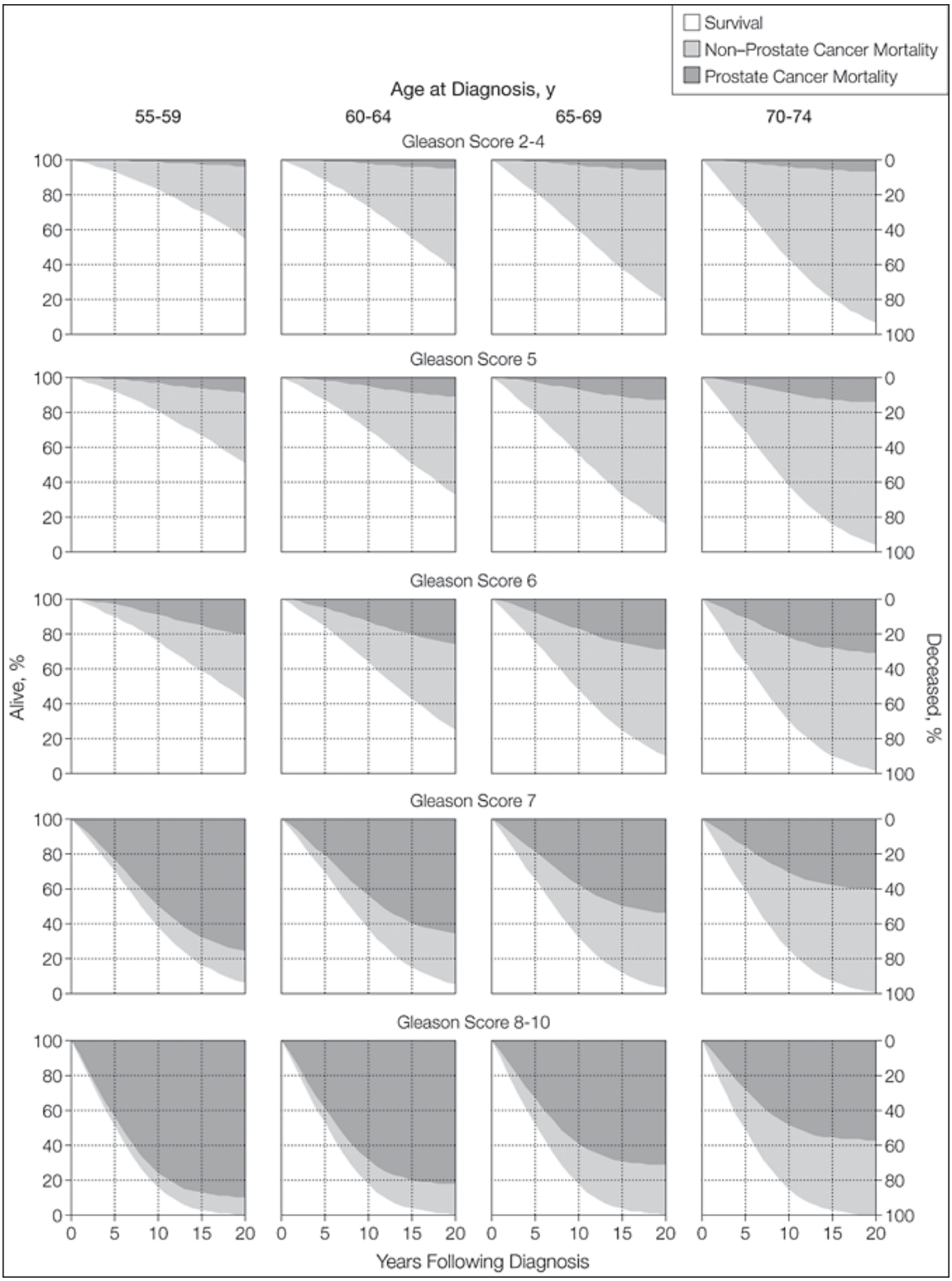
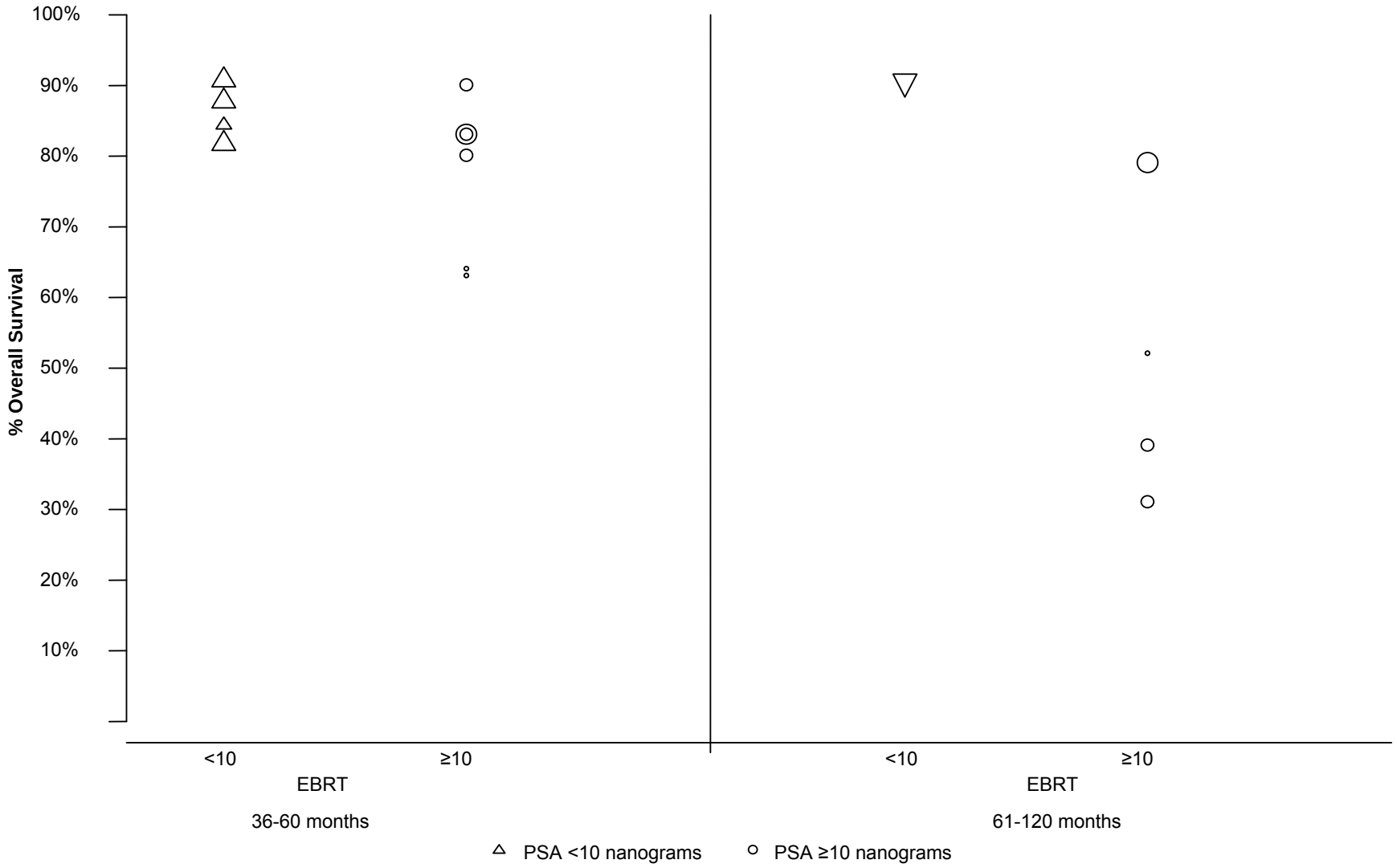
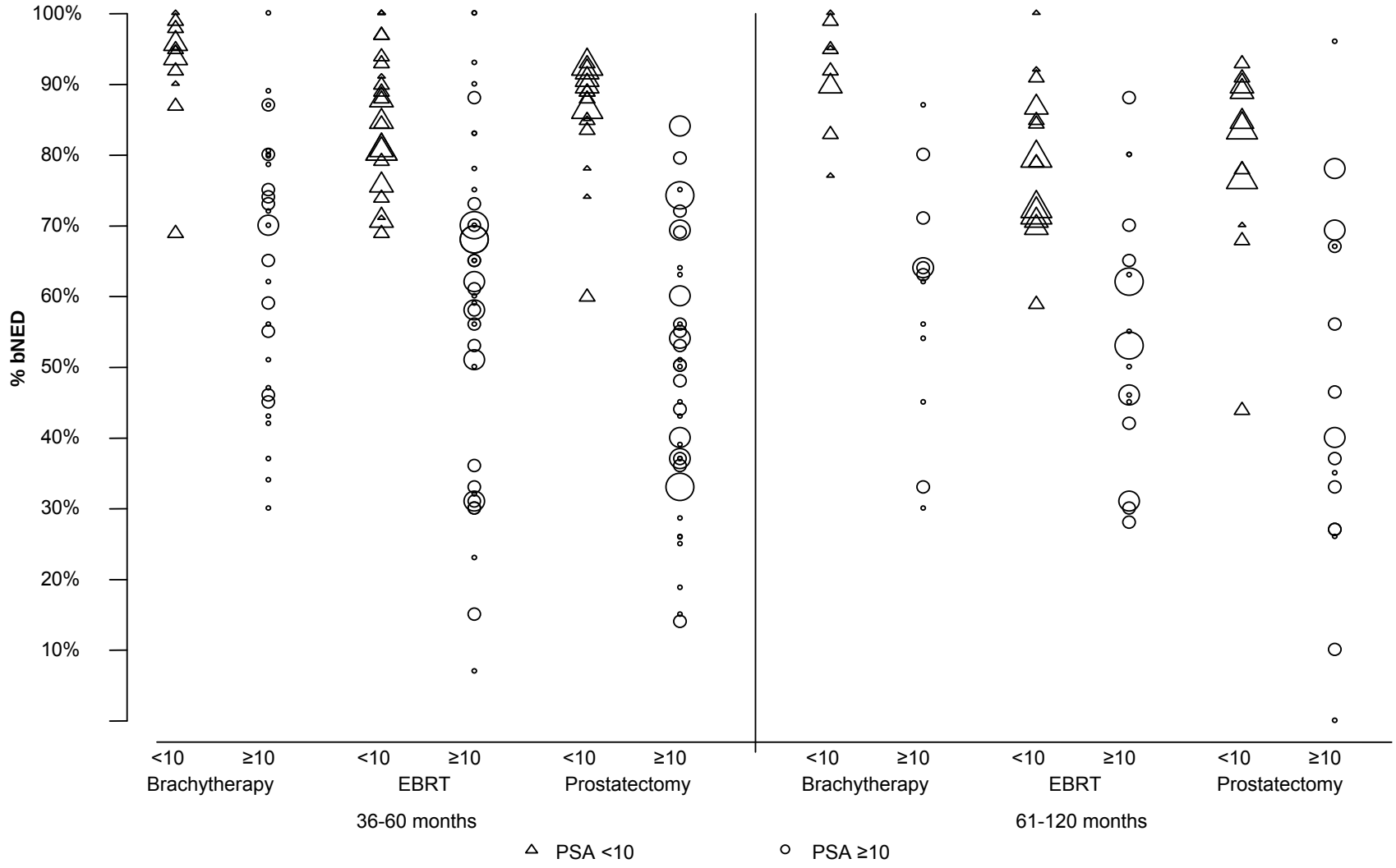


Figure 25. Overall survival at time points by treatment and PSA level (ng/ml)



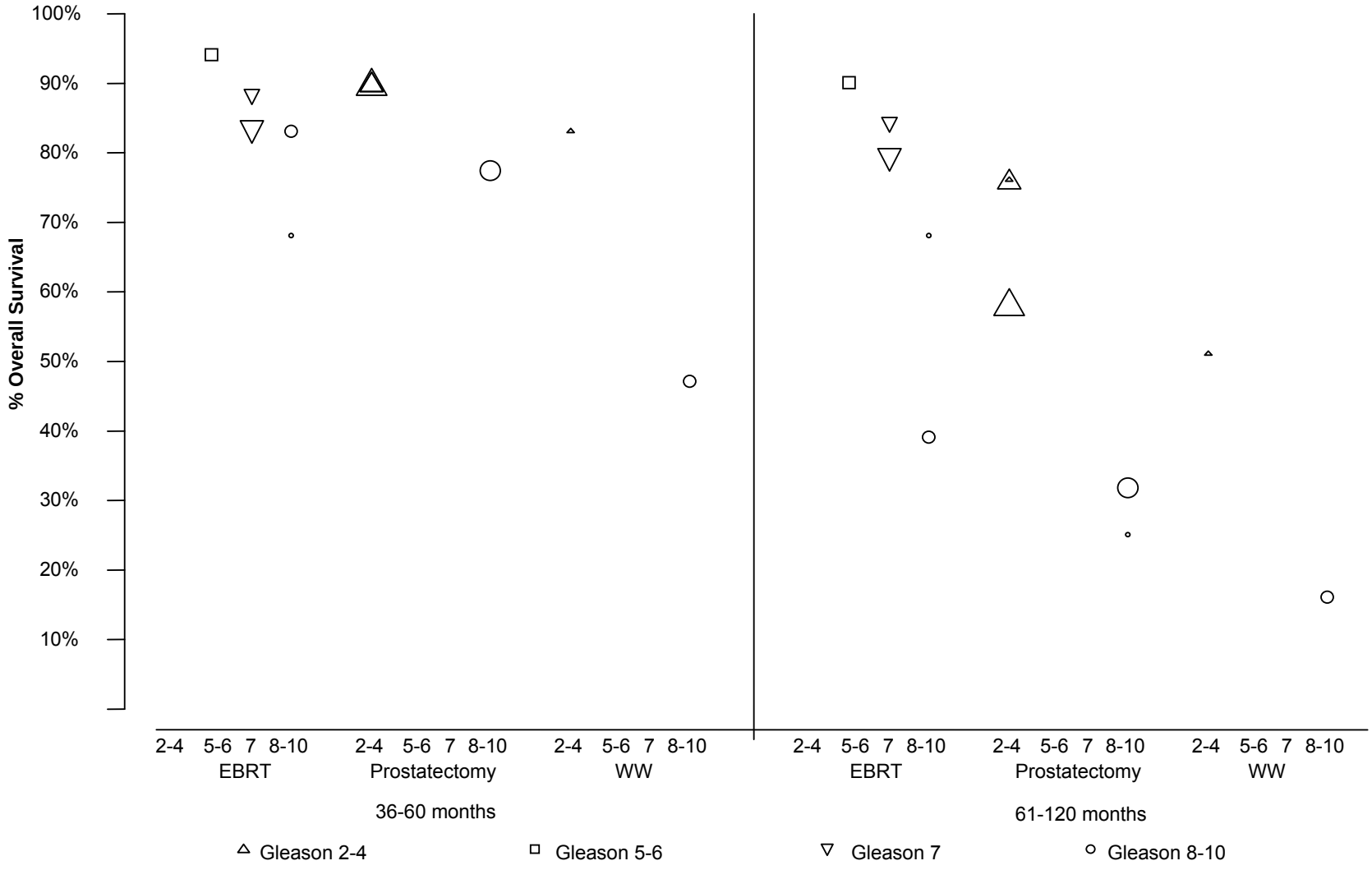
Point size indicates N, <50 (smallest), 50-150 (next smallest) 150-300 (next largest) and >300 (largest)

Figure 26. Biochemical No Evidence of Disease (bNED) at time points by treatment and PSA level (ng/ml)



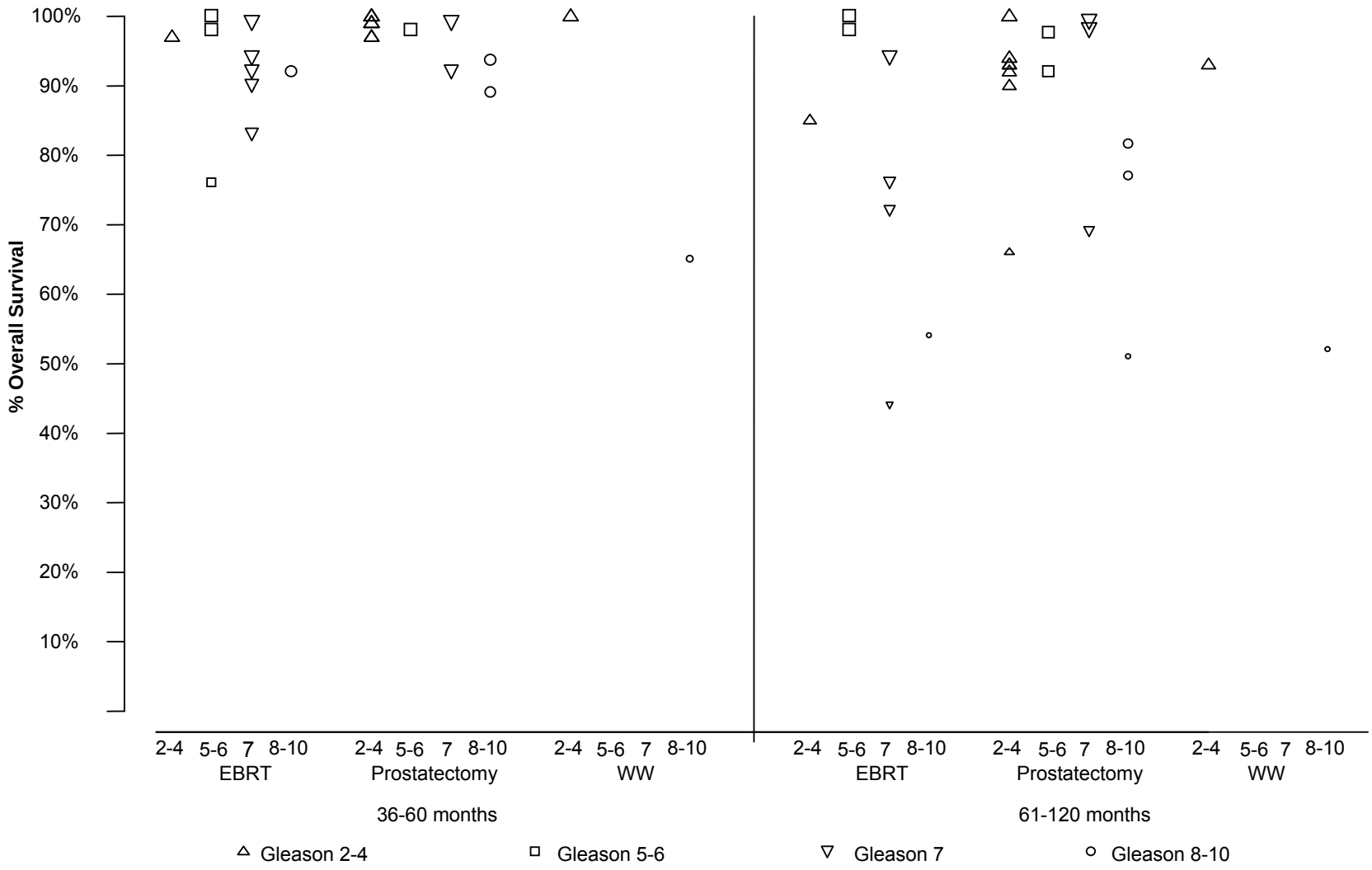
Point size indicates N, <50 (smallest), 50-150 (next smallest) 150-300 (next largest) and >300 (largest)

Figure 27. Overall survival at time points by treatment and Gleason score



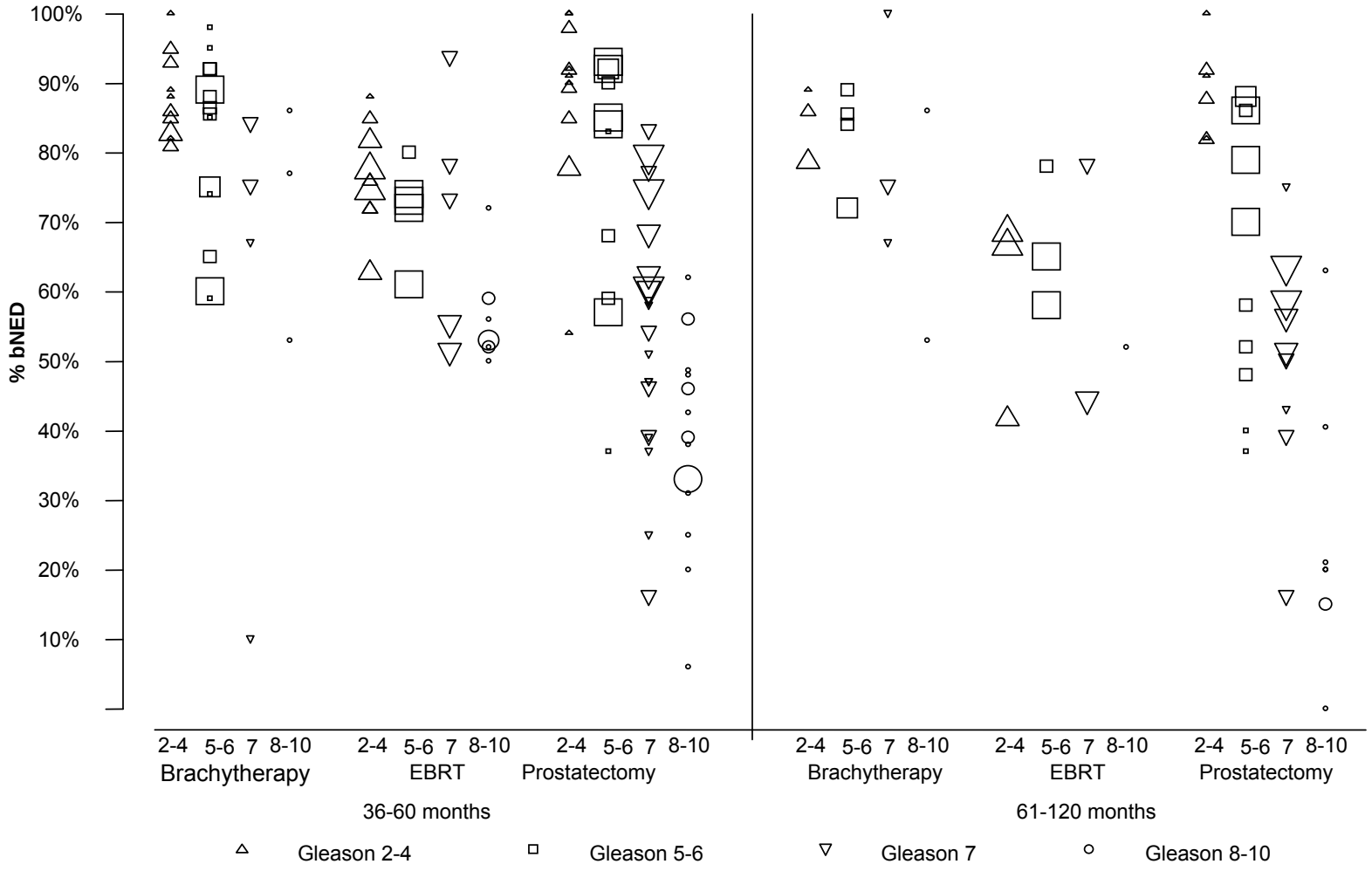
Point size indicates N, <50 (smallest), 50-150 (next smallest) 150-300 (next largest) and >300 (largest)

Figure 28. Disease-specific survival at time points by treatment and Gleason score



Point size indicates N, <50 (smallest), 50-150 (next smallest) 150-300 (next largest) and >300 (largest)

Figure 29. Biochemical No Evidence of Disease (bNED) at time points by treatment and Gleason score



Point size indicates N, <50 (smallest), 50-150 (next smallest) 150-300 (next largest) and >300 (largest)

Summary Table

Table 18. 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 18. 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 18. 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.*
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).

Table 18. Summary of evidence on therapies for localized prostate cancer (continued)

Key question	Quality of evidence	Summary, conclusion, comments
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 18. 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 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.

Table 18. Summary of evidence on therapies for localized prostate cancer (continued)

Key question	Quality of evidence	Summary, conclusion, comments
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. • 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.

Table 18. Summary of evidence on therapies for localized prostate cancer (continued)

Key question	Quality of evidence	Summary, conclusion, comments
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 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.

Table 18. Summary of evidence on therapies for localized prostate cancer (continued)

Key question	Quality of evidence	Summary, conclusion, comments
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. • 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.

Table 18. Summary of evidence on therapies for localized prostate cancer (continued)

Key question	Quality of evidence	Summary, conclusion, comments
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 (4^{th} quartile) vs. fewer than 3 surgeries (1^{st} quartile) per year. • There were no data for volume and other forms of prostate cancer treatment
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.

Table 18. Summary of evidence on therapies for localized prostate cancer (continued)

Key question	Quality of evidence	Summary, conclusion, comments
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.
	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.

Discussion

Conclusions

Published evidence indicates that no one therapy can be considered preferred for localized prostate cancer due to limitations in quality of the body of comparative effectiveness evidence (Appendix C, Tables C76 and C77). All treatment options result in adverse effects (primarily urinary, bowel, and sexual) though the severity and frequency may vary between treatments and according to the provider/hospital. Even if differences in therapeutic efficacy exist, differences in AEs, convenience, and costs are likely to be important factors in individual patient decision making. Despite this uncertainty, patient-reported satisfaction with any individual therapy received is high (Appendix C, Table C78). Satisfaction is associated with adverse treatment effects and perception that the tumor was eradicated. However, data from nonrandomized trials are inadequate to reliably assess comparative effectiveness and adverse effects. Additional RCTs are needed, especially in men with PSA-detected prostate cancer, that compare outcomes between, rather than within, major treatment options.

Limitations in the existing evidence include: 1) few randomized trials directly compared the relative effectiveness between, rather than within, major treatment categories; 2) many randomized trials are inadequately powered to provide long-term survival outcomes with the majority reporting biochemical progression or recurrence as the main outcomes; 3) some randomized trials were old, conducted prior to prostate cancer detection with PSA testing, and used technical treatment aspects that may not reflect current practice so their results may not be generalizable to modern practice settings; 4) wide variation existed in reporting and definitions of outcomes, tumor and patient characteristics; 5) there was little reporting of outcomes according to major patient and tumor characteristics; and 6) emerging technologies while increasingly utilized have not been evaluated in randomized trials or even in long-term prospective controlled studies.

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. Reports of modest treatment differences according to race/ethnicity in some nonrandomized reports have not been consistently reported in well-powered studies. One subgroup analysis of an RCT suggested that the comparative effectiveness of RP vs. WW on overall and disease specific survival may be limited to men less than age 65. However, this study had few men with PSA-detected prostate cancers, and there was little other high-quality 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.

Results from national administrative databases and surveys suggested that provider/hospital characteristics including procedure volume, physician specialty, and geographic region affect outcomes. 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 and 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 there were many different methods 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 hospital type and location was lower in patients treated by higher volume surgeons. Urinary complications and incontinence were lower among surgeons that performed more than 10 RPs per year. The length of hospital stay was shorter in patients operated by surgeons who performed more RPs per year. Cost was not associated with surgeon volume.

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 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.

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. The aforementioned RCT of RP vs. WW noted that the relative benefit of surgery did not vary according to baseline PSA level, tumor volume, or histologic grade. 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 followup 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 (Gleason score 2-4, 7 percent 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 (Gleason score of 8-10, 53 percent 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 due to RP compared to 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 combined with 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 compared to RP in men with baseline PSA >10 ng/ml. Men with Gleason scores 8-10 were more likely to have biochemical reoccurrence than men with Gleason scores 2-6 regardless of type of treatment.

Remaining Issues and Future Research Needs

- Based on the findings from this comparative effectiveness review, the following high priority gaps in knowledge in the diagnosis, prevention, and treatment of localized prostate cancer were identified, along with research suggestions to close those gaps:

- The comparative effectiveness and adverse effects associated with the major treatment options for clinically localized prostate cancer is not well known. This is due to the paucity of high-quality information from large, long-term RCTs, especially in the PSA era. Because the magnitude of relative effectiveness appears fairly small and may be influenced by multiple patient, tumor, and provider confounding factors, data from nonrandomized studies are unable to accurately provide this information. The highest priority for closing this gap is designing, activating, and completing large-scale RCTs that evaluate the long-term relative effectiveness and AEs of the primary treatment modalities in men with PSA-detected prostate cancer. Key outcomes include overall survival, disease-specific survival, metastatic-free survival, standard definitions of biochemical free survival, AEs, quality of life, and costs. Previously initiated RCTs in the United States of brachytherapy vs. RP for men with low-risk prostate cancer, EBRT vs. RP, and cryotherapy were closed due to lack of recruitment. Consumer-based (patient, spouse, partner, family) support groups can play a key role by advocating for initiation of these RCTs, and encouraging patient/provider participation and adequate funding.

- Emerging technologies are becoming popular and include laparoscopic and robotic-assisted prostatectomy, proton-beam and intensity modulated radiation therapy, cryotherapy, and high frequency ultrasound prostatectomy. Despite their increasing use, no randomized trials have been conducted. These technologies need to be studied in large RCTs to assess long-term tumor control, complications, costs, and survival. Studies evaluating learning curves and volume-outcome relationships for new technologies are needed.

- Widespread use of PSA testing for early cancer detection has been associated with an increase in the incidence of prostate cancer. The vast majority of prostate cancers currently detected in the United States are found due to PSA testing, a situation vastly different from 10-15 years previously when prostate cancers were primarily detected based on digital rectal examination or tissue specimens obtained during transurethral resection of the prostate for treatment of benign prostatic obstruction. Furthermore, men are receiving multiple PSA tests, beginning at earlier ages, and continuing well into their 80s. Additionally, the criteria for an abnormal PSA test has become more inclusive (i.e., lower PSA levels, rate of PSA change, nomograms incorporating patient race, family history, digital rectal examination results, etc.) and the number of prostate specimens obtained during prostate biopsy (from six to 12 specimens and then "saturation techniques") has increased. More men are being labeled as abnormal with increasing use of prostate biopsies and serendipitous detection of asymptomatic prostate cancer having prolonged latent phase even without treatment. Patient and tumor characteristics among men with prostate cancer diagnosed in the future are likely to be different than men diagnosed in the past and currently. For example, systematic histologic upgrading of tumor specimens (by approximately one grade) has occurred compared to previous pathologic assessment. Currently it is unusual for men with prostate cancers to receive a Gleason sum less than 6. This leads to individuals with a histologic sum based on current grading having an improved prognosis compared to historical controls, regardless of treatment provided.

- Relatively few men with prostate cancer are treated with WW. However, because the long-term natural history of these tumors is likely to be very good and the risk of disease spread/death lower than currently exists, it is increasingly important to determine the natural history of prostate cancers detected with new PSA testing and biopsy strategies. This is particularly important in men with life expectancies less than about 15 years based on advanced age or comorbidities where results indicate that PSA testing is still routinely conducted in about one-third. Based on information from long-term studies evaluating the natural history of localized prostate cancer and the results from the few RCTs evaluating surgery with WW detected in the era prior to PSA testing, many more men are diagnosed with prostate cancer than will develop clinically related problems, including death, local, or metastatic spread due to the disease, even with no initial treatment. Results from ongoing randomized screening trials are needed to determine if detection and treatment reduce mortality. To reduce treatment-related morbidity and costs, while still providing opportunity for disease eradication in men who may need intervention, discovery and validation of biomarkers are needed that can reliably identify cancers requiring therapy and assist in determining the relative effectiveness of therapies.

- Tumor risk categories incorporating histologic score, stage, and PSA levels are associated with prostate cancer outcomes. They are widely incorporated in treatment decisionmaking. Age, race, and comorbid conditions may influence treatment decisionmaking, effectiveness, and adverse effects. Studies rarely stratified outcomes for individual treatments according to these factors. Few RCTs have been conducted, and even fewer are of sufficient size to determine if outcomes vary overall or differentially according to these factors. Determining the relative effectiveness/adverse effects of treatments likely requires conducting RCTs of sufficient size and use of standardized reporting of outcomes

according to these tumor and patient characteristics. However, the field of research needed is broad and large high-quality prospective cohort studies or cancer registries that identify patients 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. Where large differences in outcomes might exist, high quality observational studies may be useful for estimating comparative effectiveness in high priority patient and tumor subgroups that have not been adequately addressed in randomized trials. However, clinicians, patients, policymakers and researchers need to be aware of the limitations of these lower quality studies in accurately estimating comparative effectiveness. Standardized/validated methods to determine cause-specific survival and biochemical, quality of life outcomes, and treatment-related AEs are needed for all future research designs. The American Society of Therapeutic Radiation Oncologists and the AUA have proposed standard methods for assessing PSA recurrence following therapy.

- There is considerable interest in identifying strategies to prevent or delay the onset/progression of prostate cancer. To date, only the 5 alpha reductase inhibitor, finasteride, has been specifically evaluated in large-scale prevention RCTs. Concern regarding long-term adverse effects and costs of this agent, as well the possibility that it may result in a greater incidence of potentially serious high-grade malignancies, has limited its clinical use. Research is needed to determine if dietary or other pharmacologic interventions prevent prostate cancer. The ongoing Selenium and Vitamin E Chemoprevention Trial (SELECT) is currently addressing these two options alone or in combination vs. placebo. The 5 alpha reductase inhibitor, dutasteride is also being evaluated. Other potential preventive agents include 5 alpha reductase inhibitors, lycopenes in tomato-based foods and soy based products. RCTs are needed that will evaluate whether these agents prevent and/or slow the progression of existing prostate cancer.

- Prostate cancer screening with widespread PSA testing is common even in the elderly or those with comorbid conditions. It is frequently requested by patients and recommended by physicians, despite the lack of evidence that such a strategy reduces overall or disease-specific mortality or morbidity. Widespread PSA testing has been associated with a marked increase in prostate cancer incidence and a shift in the type/stage of cancers detected. Long-term outcomes of PSA-detected cancers are not well known. Two screening trials in progress will help determine if prostate cancer screening reduces overall and disease-specific morbidity and mortality. The Prostate, Lung, Colorectal and Ovarian (PLCO) Screening Trial in the United States[300] and the European Randomized Study of Screening for Prostate Cancer (ERSPC) trial[301] in Europe should provide results around 2009. The PLCO trial is an effectiveness trial of mass screening with PSA testing. Subsequent management of subjects with elevated PSA levels is left to usual care. The ERSPC trial is designed more as an efficacy study with management of elevated PSA levels specified by protocol. These studies should give complementary information. The Prostate Testing for Cancer and Treatment (ProtecT) feasibility study aimed to examine the accuracy of PSA testing compared with histologically confirmed prostate cancer among 8,505 males in 18 primary care centers. The positive predictive value of PSA >3 ng/ml was 0.23 (95 percent CI 0.18; 0.28) in males 50-59 years and 0.33 (95 percent CI 0.29; 0.38) in males 60-69 years.[302]

- A search of www.clinicaltrials.gov for randomized trials of localized prostate cancer identified 30 references to ongoing trials. However, few were directly comparing the primary treatment options and/or were adequately powered to assess survival. Due to the lack of RCTs, the comparative effectiveness and adverse effects of different treatment options for localized prostate cancer (especially those detected by PSA testing) is not known. Basing treatment decisions on comparative effectiveness results from nonrandomized data is problematic due to the poor methodologic quality of nonrandomized reports and the risk of biased outcomes. To provide patients with reliable information, RCTs need to be conducted to determine if outcomes vary according to patient, tumor, and/or provider characteristics. Two ongoing trials are evaluating primary treatment options in men with primarily PSA-detected clinically-localized prostate cancer. The U.S. based VA/NCI/AHRQ funded CSP#407: PIVOT is comparing RP vs. WW in 731 men and completed recruitment.[65] Results are due after 2010. The ProtecT study, based in the United Kingdom is comparing surgery (RP), radiotherapy (radical conformal), and active monitoring (monitoring with regular check ups). Studies in development include cryotherapy vs. EBRT and RP vs. expectant management in men with "low risk" prostate cancer with delayed intervention based on repeat PSA testing and prostate biopsy results.

- Decisions regarding treatment for early stage prostate cancer are limited by little data comparing quality of care according to provider, facility, and other healthcare system factors. Furthermore, there is increasing evidence that factors related to the structure and process of health care are associated with clinically relevant outcomes. However, little information is available for prostate cancer treatment. Structure of care includes the equipment, resources, and provider experience necessary to provide care. Process of care refers to technical and interpersonal elements of care that transpire between doctor and patient. Preliminary work suggests that the indicated variables can be reliably assessed, but their validity in predicting quality of prostate cancer care and outcomes remains to be established. Proposed quality of care indicators for early-stage prostate cancer have been developed using a RAND Global Quality Assessment Tool following the conceptual framework established by Donabedian. Future studies need to identify systemwide structure and process measures associated with improved quality of prostate cancer care, disseminate these results so that they are widely available for patients, health care providers, and policymakers; and implement programs to improve and enhance their application in routine clinical care.

- Patients and family members are faced with a vast array of information related to detection and treatment of prostate cancer. It is increasingly difficult for them (and their physicians) to accurately assess this information and incorporate it into decisionmaking. Systematic reviews of educational materials have found that the majority of these are not evidence based and rather promote a particular treatment approach. In order to assist patients, family members, and health care providers match treatment selection with personal preference, a new generation of education materials and multidisciplinary health care teams are needed. These should describe all standard treatments and provide comprehensive and up-to-date information about the risks and benefits of each treatment. Key features include: 1) accuracy of information; 2) balanced presentation of treatment options; and 3)

comprehensibility to the average reader/viewer. Examining different formats (e.g., print, vs. CD-ROMs vs. websites) length/depth of information, and presentation of risk/benefit communication (words, figures, tables, items of numeracy) is important. It is hoped that this comparative effectiveness review and the accompany patient and clinician guides will serve as a model for development of future decisionmaking guides. These reports aim to identify and evaluate quality and strength of evidence regarding the comparative effectiveness and adverse effects of treatments according to key patient, tumor, and provider factors. The resulting patient/clinician guides are developed by individuals with communication/dissemination skills who are separate from authors of the evidence report.

- Many factors are involved in patient decisionmaking and may differ according to patient and tumor characteristics. A greater understanding of factors related to patient decisionmaking is needed. Interventions to assist patients incorporate numerical risks for various outcomes and minimize undue influence from misconceptions and/or anecdotal evidence are needed.

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(Note that there is a separate set of references at the end of Appendix C whose reference numbers are different from those in the text of the report)

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Abbreviations

ADT	Androgen Deprivation Therapy
AE	Adverse effects
AHRQ	Agency for Healthcare Research and Quality
AJCC stages	American Joint Committee on Cancer
Stage I	T1a,N0,M0,G1
Stage II	T1a,N0,M0,G2-4
	T1b,N0,M0,any G
	T1c,N0,M0,any G
	T1,N0,M0,any G
	T2,N0,M0,any G
Stage III	T3,N0,M0,any G
Stage IV	T4,N0,M0,any G
	Any T,N1,M0,any G
	Any T,anyN,M1,any G
ARR	Absolute Risk Reduction
ASTRO	American Society of Therapeutic Radiation Oncologists
AUA	American Urological Association
bNED	biochemical No Evidence of Disease
Brachy	Brachytherapy
CaPSURE	Cancer of the Prostate Strategic Urologic Research Endeavor
C-EBRT	Conformal External Beam Radiotherapy
CI	Confidence Interval
CRT	Conformed Radiation Therapy
CT	Computerized Tomography
DRE	Digital Rectal Examination
EBRT	External Beam Radiotherapy
ED	Erectile Dysfunction
EPC	Evidence-based Practice Center
ERSPC	European Randomized Study of Screening for Prostate Cancer
FACT-G	Functional Assessment of Cancer Therapy-General
FACT-P	Functional Assessment of Cancer Therapy-Prostate
G	Histopathologic grade of the tumor
G1	Well differentiated (slight anaplasia) (Gleason 2-4)
G2	Moderately differentiated (moderate anaplasia) (Gleason 5,6)
G3,4	Poorly differentiated or undifferentiated (marked anaplasia) (Gleason 7-10)
GX	Grade cannot be assessed
GI	Gastrointestinal
GU	Gentiourinary
HIFU	High Intensity Focused Ultrasound
HMO	Health Maintenance Organization
HR	Hazard Ratio
HRQOL	Health-Related Quality of Life
IMRT	Intensity Modulated Radiation Therapy
^{125}I	Iodine (I)-125

IPSS	International Prostate Symptom Scores
Jewett stages	
Stage A	A clinically undetectable tumor confined to the prostate gland and is an incidental finding at prostatic surgery
Substage A1	Well differentiated with focal involvement, usually left untreated
Substage A2	Moderately or poorly differentiated or involves multiple foci in the gland
Stage B	Tumor is confined to the prostate gland
Substage B0	Nonpalpable, PSA detected
Substage B1	Single nodule in one lobe of the prostate
Substage B2	More extensive involvement of one lobe or involvement of both lobes
Stage C	Tumor clinically localized to the periprostatic area but extending through the prostatic capsule
Substage C1	Clinical Extracapsular extension
Substage C2	Extracapsular tumor producing bladder outlet or ureteral obstruction
Stage D	Metastatic disease
Substage D0	Clinically localized disease (prostate only) but persistently elevated enzymatic serum acid phosphatase titers
Substage D1	Regional lymph nodes only
Substage D2	Distant lymph nodes, metastases to bone or visceral organs
Substage D3	D2 prostate cancer patients who relapsed after adequate endocrine therapy
LHRH	Luteinizing Hormone-Releasing Hormone
LHRHa	Luteinizing Hormone-Releasing Hormone agonist
LRP	Laparoscopic Radical Prostatectomy
MESH	Medical Subheading Subjects
M	Distant metastasis presence
M0	No distant metastasis
M1	Distant metastasis
M1a	Nonregional lymph node(s)
M1b	Bone(s)
M1c	Other site(s) with or without bone disease
MX	Distant metastasis cannot be assessed (not evaluated by any modality)
MRI	Magnetic Resonance Imaging
N	Regional lymph nodes involvement
N0	No regional lymph node metastasis
N1	Metastasis in regional lymph node(s)
NX	Regional lymph nodes were not assessed
NCIC	National Cancer Institute of Canada
NHT	Neoadjuvant Hormonal Therapy
NSP	Nerve-Sparing Prostatectomy
OR	Odds Ratio
^{103}Pd	Palladium (P)-103
P	Prostatectomy
PC	Prostate Cancer
PCI	Prostate Cancer Instrument
PCOS	Prostate Cancer Outcomes Study
PIVOT	Prostate Cancer Intervention Versus Observation Trial

PLCO	Prostate, Lung, Colorectal, and Ovarian
ProtecT	Prostate Testing for Cancer and Treatment
PSA	Prostate Specific Antigen
QOL	Quality of Life
RCT	Randomized Controlled Trial
RLRP	Robotic Assisted Laparoscopic Radical Prostatectomy
RP	Radical Prostatectomy
RR	Relative Risk
RRP	Retropubic Radical Prostatectomy
RTOG	Radiation Therapy Oncology Group
SEER	Surveillance, Epidemiology, and End Results
SELECT	Selenium and Vitamin E Chemoprevention Trial
SPCG	Scandinavian Prostate Cancer Group
TEP	Technical Expert Panel
T	Primary tumor staging
T0	No evidence of primary tumor
T1	Clinically inapparent tumor not palpable nor visible by imaging
T1a	Tumor incidental, histologic finding in ≤5% of tissue resected
T1b	Tumor incidental, histologic finding in >5% of tissue resected
T1c	Tumor identified by needle biopsy
T2	Tumor confined within prostate
T2a	Tumor involves 50% of one lobe or less
T2b	Tumor involves >50% of one lobe but not both lobes
T2c	Tumor involves both lobes
T3	Tumor extends through the prostate capsule
T3a	Extracapsular extension (unilateral or bilateral)
T3b	Tumor invades seminal vesicle(s)
T4	Tumor is fixed or invades adjacent structures other than seminal vesicles: bladder neck, external sphincter, rectum, levator muscles, and/or pelvic wall
TX	Primary tumor cannot be assessed
TURP	Transurethral Resection of the Prostate
UI	Urinary incontinence
VACURG	Veterans Administration Cooperative Urological Research Group
WHO	World Health Organization
WW	Watchful Waiting