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Treatments for Localized Prostate Cancer: Systematic Review to Update the 2002 U.S. Preventive Services Task Force Recommendation

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Structured Abstract

Background: Screening with prostate-specific antigen testing can detect prostate cancer in earlier, asymptomatic stages, when treatments might be more effective. However, treatments for prostate cancer are also associated with potential harms.

Purpose: To systematically review benefits and harms associated with treatments for screen-detected or localized prostate cancer.

Data Sources: We searched the Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews (through the second quarter of 2011), and Ovid MEDLINE (2002 to July 2011) for relevant studies and systematic reviews published in English. Electronic database searches were supplemented by reviews of reference lists of relevant articles.

Study Selection: We selected randomized trials and cohort studies that reported all-cause mortality, prostate cancer-specific mortality, or harms associated with prostatectomy, radiation therapy, hormonal therapy, cryotherapy, and high-intensity focused ultrasonography versus watchful waiting or active surveillance in men with localized prostate cancer. We also included large (n>1,000) uncontrolled observational studies that reported perioperative harms. If no randomized trials, cohort studies, or large uncontrolled studies were available, we included smaller uncontrolled studies.

Data Extraction: One investigator abstracted data and a second investigator checked data abstraction for accuracy. Two investigators independently assessed study quality using methods developed by the U.S. Preventive Services Task Force.

Data Synthesis (Results): Two randomized trials and nine cohort studies on benefits of prostate cancer treatments and two randomized trials, 14 cohort studies, and 11 intervention series of harms were included in the review. One good-quality randomized trial found that prostatectomy for localized (primarily stage T2) prostate cancer was associated with decreased risk of prostate cancer-specific mortality compared with watchful waiting through 13 years of followup (relative risk, 0.62 [95% CI, 0.44–0.87]; absolute risk reduction, 6.1 percentage points); subgroup analyses suggested that benefits were limited to men younger than age 65 years. Cohort studies consistently found that prostatectomy and radiation therapy were associated with decreased risk of all-cause mortality and prostate cancer-specific mortality compared with watchful waiting, but estimates were susceptible to residual confounding. Based primarily on cohort studies, treating approximately three men with prostatectomy, seven men with radiation therapy, or two to three men with androgen deprivation therapy instead of watchful waiting would each result in one additional case of erectile dysfunction, and treating approximately five men with prostatectomy would result in one additional case of urinary incontinence. Prostatectomy was associated with perioperative (30-day) mortality (about 0.5%) and cardiovascular events (0.6% to 3%), radiation therapy with bowel dysfunction, and androgen deprivation therapy with gynecomastia and hot flashes. Evidence did not suggest adverse effects related to general health-related quality of life with either prostatectomy or radiation therapy compared with watchful waiting. Evidence on cryotherapy and high-intensity focused ultrasonography was too limited to reliably estimate benefits or harms.

Limitations: Only English-language articles were included, few randomized trials met inclusion criteria, the lone randomized trial of treatment did not specifically enroll men with screen-detected prostate cancer, and few studies evaluated newer therapies and techniques.

Conclusions: Additional research is needed to understand benefits of treatments for screen-detected, localized prostate cancer. Commonly selected therapies for localized prostate cancer are associated with an increased risk of important harms. More research is needed to understand whether newer therapies and techniques for treating localized prostate cancer are associated with fewer harms.

Table of Contents

Figures

Summary Tables

Appendixes

Chapter 1. Introduction

Purpose of Review and Prior USPSTF Recommendation

Screening with prostate-specific antigen (PSA) testing can detect prostate cancer in earlier, asymptomatic stages, when treatments might be more effective. In 2008, based on an earlier systematic review that focused on studies of PSA-based screening versus no screening,[1] the U.S. Preventive Services Task Force (USPSTF) found insufficient evidence to determine the balance of benefits and harms associated with prostate cancer screening in men younger than age 75 years (I statement), and recommended against screening in men ages 75 years or older (grade D recommendation).[2] See **Appendix A** for a list of all abbreviations included in this report.

Once prostate cancer has been detected by screening, treatments are frequently initiated. Understanding the benefits and harms associated with such treatments is therefore critical for informing screening decisions. Evidence on benefits and harms of treatments for localized prostate cancer was last reviewed by the USPSTF in 2002.[3] This report summarizes the evidence on benefits and harms of treatment for screen-detected or early-stage prostate cancer, with an emphasis on studies published since 2002.

Condition Definition

Prostate cancer is the most commonly diagnosed cancer in American men.[4-6] Adenocarcinoma accounts for over 95% of all prostate cancer cases. Prostate cancer is typically staged according to the American Joint Committee on Cancer's tumor, node, metastasis (TNM) system, in which the tumor stage (T) is based on the extent of penetration or invasion beyond the prostatic capsule into adjacent structures (**Table 1**). Localized prostate cancer is classified as stages T1 (non-palpable) and T2 (palpable) and is confined within the prostatic capsule. The likelihood of progression to invasive cancer is associated with the presence of more poorly differentiated cells and other histopathologic features.

This review focuses on the benefits and harms of treatments for screen-detected prostate cancer. However, many studies do not report how prostate cancer was initially detected. Therefore, we also included studies of treatments for localized (stages T1 and T2) prostate cancer, which is far more frequently detected by screening than more advanced cancer. Among newly diagnosed patients in 2004–2005, 94% had clinically localized prostate cancer.[7]

Prevalence and Burden of Disease

Within the era of PSA testing, an estimated 16% of men will receive a diagnosis of prostate cancer sometime during their lifetime,[5] and about 2.2 million American men are estimated to be living with prostate cancer.[8] In 2010, approximately 217,000 prostate cancer diagnoses and 32,000 prostate cancer deaths were expected in U.S. men.[4] The likelihood of prostate cancer increases with age, particularly starting at around age 45 years.

Prostate cancer is the second leading cause of cancer-related death in American men.[6] Despite an increase in prostate cancer diagnoses since the start of the prostate cancer screening era, the risk of dying from prostate cancer has remained relatively stable at around 3%.[9] Since the adoption of PSA-based screening in the early 1990s, prostate cancer is being detected and treated earlier. Approximately 80% to 90% of men with prostate cancer have clinically localized disease.[10] Survival following a diagnosis of localized prostate cancer has improved in the prostate cancer screening era.[9] This may be due to advances in medical care or earlier detection, but could also be spurious due to additional lead time, overdiagnosis related to PSA testing, grade migration, or other factors.[11]

Etiology and Natural History

The natural history of clinically localized disease varies. The tumor grade, often assessed using the Gleason score, is an important marker of tumor aggressiveness. Tumors that remain localized to the prostate are often asymptomatic, but may cause symptoms of bladder outlet obstruction. Such types of cancer generally do not affect survival. On the other hand, tumors that spread beyond the prostate to invade local structures or metastasize can have severe negative impacts on quality of life and mortality.[12]

The etiology of prostate cancer is not completely understood. Men with 5-alpha-reductase deficiency do not develop prostate cancer, suggesting that androgenic hormones play some role in pathogenesis.[13]

Risk Factors

Age, race, and family history are well-established risk factors for prostate cancer. Age is the strongest risk factor, with over 80% of prostate cancer diagnoses occurring in men older than age 65 years.[14] The degree to which the incidence of prostate cancer increases exponentially with age is greater than with any other cancer.[14] Autopsy studies found that as many as 75% of men older than age 85 years have prostate cancer at the time of death.[15]

Among U.S. men, black men have the highest incidence rates of prostate cancer, at 226 cases per 100,000 person-years.[6] White men have an incidence of 145 per 100,000, Hispanic men have an incidence of 122 per 100,000, and Asian/Pacific Islander and Native American men have incidence rates of 78 and 72 per 100,000, respectively.

Family history is another risk factor for prostate cancer. Having a first-degree relative with a history of prostate cancer increases the risk two- to three-fold.[14,15] Data from studies of twins suggest that 42% of the risk of prostate cancer may be accounted for by genetic factors.[14] However, the exact genes responsible for the development of prostate cancer are not known.[14]

Other potential risk factors such as endogenous levels of androgens and other hormones (vitamin D levels, insulin-like growth factors), differences in diet and use of vitamin supplements, obesity, inflammation, and vasectomy status may also be associated with prostate cancer risk, but evidence is less consistent, or associations are less strong.[14]

Rationale for Screening

The primary rationale for screening with PSA testing is to identify high-grade, localized prostate cancer at earlier, asymptomatic stages, in order to enhance the chances of a cure. Screening also identifies lower-grade, localized prostate cancer, for which benefits of earlier treatment are less clear.

Interventions/Treatment

This systematic evidence review evaluates common treatment options for men with localized prostate cancer, including radical prostatectomy (retropubic, perineal, and laparoscopic [with or without robotic assistance]), radiation therapy (external beam radiation therapy [EBRT] and brachytherapy), and, less commonly, androgen deprivation therapy (ADT), cryoablation, and high-intensity focused ultrasonography (HIFU) (**Table 2**). Other treatments for localized prostate cancer are watchful waiting and active surveillance. Although these terms are not well defined in the published literature and have sometimes been used interchangeably, active surveillance implies a higher degree of monitoring (including PSA levels and prostatic biopsies) in order to guide the decision of when to intervene, whereas watchful waiting implies a more passive approach focused on treatment of symptoms associated with disease progression.[16] The choice of therapy depends on a number of factors, including cancer stage, histologic grade, presence of comorbidities, and patient preferences.

Recommendations of Other Groups

Prostate cancer screening recommendations from other groups are summarized in **Table 3**. The American Urological Association,[17] National Comprehensive Cancer Network,[18] and Prostate Cancer Canada[19] recommend that clinicians consider screening (or offering screening) for prostate cancer with PSA testing beginning at age 40 years. Other groups, such as the American Cancer Society,[20] European Association of Urologists,[21] American Academy of Preventive Medicine,[22] American Academy of Family Physicians,[23] United Kingdom National Health Service,[24] National Health Committee of New Zealand,[25] and Cancer Council of Australia[26] do not recommend prostate cancer screening, though many suggest that clinicians provide information about the potential benefits and harms of screening in order to help patients make an informed screening decision.

Chapter 2. Methods

Key Questions and Analytic Framework

Using the methods developed by the USPSTF,[27] the USPSTF and Agency for Healthcare Research and Quality (AHRQ) determined the scope and key questions for this review. Investigators created an analytic framework with the key questions and the patient populations, interventions, and outcomes reviewed (**Figure 1**). The target population for this review was men treated for screen-detected prostate cancer. Since most studies do not describe whether prostate cancer was identified through screening or some other method, we also included studies of localized (T1 or T2) prostate cancer, as most screen-detected prostate cancer is localized. A contextual question was also requested by the USPSTF to help inform the report. (Contextual questions are not reviewed using systematic review methodology.)

Key Questions

1. What are the benefits of treatment of early-stage or screen-detected prostate cancer?
2. What are the harms of treatment of early-stage or screen-detected prostate cancer?

Contextual Question

1. How often is each treatment currently performed in U.S. men with PSA-detected cancer (i.e., what percentage of men initially choose watchful waiting versus surgery, radiation therapy, cryotherapy, etc.)?

Search Strategy

We searched the Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews (through the second quarter of 2011), and Ovid MEDLINE (2002 to July 2011) for relevant studies and systematic reviews. Search strategies and additional details are described in **Appendix B1**. We also reviewed reference lists of relevant articles.

Study Selection

At least two reviewers independently evaluated each study to determine inclusion eligibility. We restricted inclusion to published studies. We selected studies on the basis of inclusion and exclusion criteria developed for each key question (**Appendix B2**). **Appendix B3** shows the results of our literature search and selection process.

We excluded studies that did not adequately report baseline tumor stage or that enrolled more than 10% of patients with stage T3 tumors or higher unless results related to harms were stratified according to tumor stage at baseline. We also excluded studies that evaluated patients with recurrent or refractory prostate cancer. Studies that described the population as having localized prostate

cancer were included even if they did not report specific tumor stage information, as this term typically refers to T1 and T2 cancer.[28] **Appendix B4** lists studies that were excluded after full-text review.

We included randomized, controlled trials (RCTs) and cohort studies that reported all-cause mortality, prostate cancer-specific mortality, or prespecified harms and compared radical prostatectomy, radiation therapy (EBRT or brachytherapy), ADT, cryoablation, or HIFU with watchful waiting or active surveillance. For assessment of all-cause and prostate cancer-specific mortality, we only included studies that reported risk estimates adjusted at a minimum for age at diagnosis and tumor grade (no study reported adjusted risk estimates for treatment harms). We also included large (n>1,000) uncontrolled observational studies of harms if RCTs and cohort studies were not available. If no RCTs, cohort studies, or large uncontrolled studies of harms were available for a specific intervention, we included smaller uncontrolled studies. We excluded head-to-head studies of active treatments unless there was also a watchful waiting or active surveillance group. Prespecified harms were mortality related to treatment (i.e., not mortality related to prostate cancer itself) and included quality of life and functional status, urinary incontinence, bowel dysfunction, erectile dysfunction, harms related to endocrinological effects, psychological effects, and surgical complications.

We classified "no treatment," "observation," or "deferred treatment" as watchful waiting, since patients probably received at least watchful waiting. We also grouped watchful waiting with active surveillance unless studies of active surveillance provided sufficient information to determine that more active followup actually occurred,[29] as older studies used these terms interchangeably.

Data Abstraction and Quality Rating

One investigator abstracted details about the patient population, study design, analysis, followup, and results. A second investigator reviewed data abstraction for accuracy. Two investigators independently applied criteria developed by the USPSTF[27] to rate the quality of each study as good, fair, or poor (**Appendix B5**). Discrepancies were resolved through a consensus process.

Data Synthesis

We assessed the aggregate internal validity (quality) of the body of evidence for each key question ("good," "fair," or "poor") using methods developed by the USPSTF, based on the number, quality, and size of studies, consistency of results between studies, and directness of evidence.[27] For all outcomes, we synthesized results descriptively, using medians and ranges, since few RCTs were available and studies varied in the populations and interventions evaluated, methodological quality, duration of followup, and other factors. We stratified results according to study type, and qualitatively assessed effects of study quality, duration of followup, year of publication, and mean age on results.

We also conducted meta-analyses on urinary incontinence and erectile dysfunction, the most commonly reported harms, using studies that reported dichotomous measures. We pooled results separately for prostatectomy and radiation therapy versus watchful waiting. There were too few

studies to pool trials of ADT (two studies) or cryotherapy (one study), and no studies of HIFU versus watchful waiting. Data were pooled using the DerSimonian-Laird random effects model with Stata Version 11.1 software (StataCorp, College Station, TX). We calculated pooled relative risks as well as pooled risk differences. Statistical heterogeneity was assessed using the I^2 statistic.[30] Because few RCTs were available for any of the analyses, we pooled both RCTs and cohort studies. As none of the cohort studies reported adjusted risk estimates, we used raw event rates. We stratified analyses by study type in order to assess effects of including cohort studies. If four or more studies were available for pooling, we performed additional analyses based on study quality, duration of followup, and age to evaluate effects on results. For one study that reported results separately for patients followed for varying durations, we combined the data into a single estimate, since an analysis showed no effect related to followup duration.[31] For one study that reported results from the same cohort at 30 to 41 months' followup[32] and 10 years' followup,[33] we used the earlier data, since it was more complete (n=108 vs. n=54) and pooled estimates using either results were similar in sensitivity analyses.

External Review

The draft report was reviewed by content experts, USPSTF members, AHRQ Project Officers, and collaborative partners (**Appendix B6**), and then revised for the final version.

Chapter 3. Results

We identified 11 studies (two RCTs[34-41] and nine cohort studies[10,42-49]) on benefits of prostate cancer treatments and 16 studies (two RCTs[31-33,50] and 14 cohort studies[51-66]) on harms (**Table 4**, **Appendix C1**, and **Appendix C2**). Sample sizes ranged from 72 to 44,630 and duration of followup from 1 to 23 years. Four studies were rated as good quality,[35,50,60,64,66] one as poor quality,[41] and the remainder as fair quality (**Appendix C3** and **Appendix C4**). Frequent methodological shortcomings were failure to describe loss to followup (six cohort studies and all three RCTs met this criterion) and inadequate blinding of outcome assessors (no cohort studies and one RCT met this criterion). Only two studies[33,45] clearly described the control group intervention (**Table 4**). Baseline characteristics differed for patients who received active treatments compared with watchful waiting. For example, men who received ADT had higher baseline PSA levels compared with those who underwent watchful waiting.[51,55,60,63,64]

We also included six observational studies[67-72] of surgical complications following prostatectomy, and five uncontrolled studies of harms associated with HIFU (**Appendix C5**).[73-77]

Studies generally provided limited information about the interventions studied. For example, one study reported harms stratified by type of prostatectomy (nerve sparing vs. non-nerve sparing),[64] while other studies reporting harms provided few details on the type of prostatectomy evaluated. For studies of harms associated with radiation therapy, four reported harms results separately for EBRT and brachytherapy.[51,52,64,65] Of the remaining 10 studies, study participants received EBRT in three studies,[58,62,66] a mixture of EBRT and brachytherapy in one study,[63] and six studies did not describe what type of radiation therapy was given (presumably EBRT for most studies, which covered earlier time periods). One study stratified results by use of conventional radiation, proton-beam radiation, or mixed-beam radiation.[54]

Methods for reporting harms varied among included studies. Studies reported dichotomous outcomes, continuous scales, or both. The studies used a variety of continuous scales (**Table 5**) to assess generic quality of life changes following prostate cancer treatments, most commonly the Short-Form 36-Item Health Survey (SF-36). SF-36 scores range from 0–100, with higher scores representing better functioning or quality of life in eight areas (subscales): physical function, social function, bodily pain, emotional well-being, energy, general health perceptions, role limitations due to physical problems, and role limitations due to emotional problems. Mental and physical component summary scores are derived from combining subscale scores relevant to these broader domains. The most commonly used continuous scale for measuring disease-specific quality of life was the University of California, Los Angeles Prostate Cancer Index (PCI). Like the SF-36, PCI scores also range from 0 to 100, in five areas: urinary bother, urinary function, sexual bother, sexual function, and bowel bother; higher scores indicate less bother or better function.[57] For both the SF-36 and the PCI, differences of 5 to 10 points are generally thought to indicate clinically meaningful changes.[78] Methods for categorizing patients as having or not having urinary incontinence and erectile dysfunction varied. Definitions for urinary incontinence included “at least daily urinary leakage,” “no urinary control or frequent dribbling,” “incontinence,” “use of a pad for urinary leakage,” and “regular reliance on diaper.” Definitions for erectile dysfunction included “no erections at all,” “impotence,” “erectile dysfunction,” “poor or very poor sexual function,” “erection

insufficient for intercourse," and "problems getting an erection nearly all the time." Gastrointestinal effects (e.g., diarrhea, leakage, urgency) were primarily reported in studies of radiation therapy, and hormonal side effects (e.g., hot flashes, gynecomastia) were reported in studies of ADT. Uncommonly reported harms included anxiety or depression and weight gain.

Key Question 1. What Are the Benefits of Treatment of Early-Stage or Screen-Detected Prostate Cancer?

Summary

One good-quality RCT compared treatment for localized prostate cancer with watchful waiting in men with localized prostate cancer. It found that prostatectomy was associated with decreased risk of prostate cancer-specific mortality (15% vs. 21%; relative risk [RR], 0.62 [95% CI, 0.44 to 0.87]; absolute difference, 6.1 percentage points [95% CI, 0.2 to 12]) and all-cause mortality (RR, 0.75 [95% CI, 0.61 to 0.92]; absolute difference, 6.6 percentage points [95% CI, -1.3 to 14]), though benefits appeared to be restricted to men younger than age 65 years, based on subgroup analyses. Applicability of the trial to men with screen-detected prostate cancer is uncertain, as it did not enroll men specifically with screen-detected prostate cancer, and the proportion of men with stage T2 tumors (75%) was substantially higher than observed in recent screening trials. Cohort studies consistently found that prostatectomy and radiation therapy were associated with decreased risk for all-cause mortality (6 studies; median adjusted hazard ratio [HR], 0.46 [range, 0.32 to 0.67] and 5 studies; median adjusted HR, 0.68 [range, 0.62 to 0.81], respectively) and prostate cancer-specific mortality (5 studies; median adjusted HR, 0.32 [range, 0.25 to 0.50] and 5 studies; median adjusted HR, 0.66 [range, 0.63 to 0.70], respectively), but estimates are susceptible to confounding by indication. Two cohort studies found that ADT for localized prostate cancer was associated with increased risk of prostate cancer-specific mortality compared with watchful waiting. No studies evaluated effects of cryotherapy or HIFU compared with watchful waiting on all-cause or prostate cancer-specific mortality.

Evidence

Prostatectomy. Prostatectomy was compared with watchful waiting in one good-quality RCT (n=695) of men with localized (stages T1b, T1c, or T2) prostate cancer (**Table 6**, **Appendix C1**).[34-36,40] It did not specifically enroll men with screen-detected prostate cancer, and about 75% of cases were palpable (stage T2). The 2002 USPSTF review included results from this trial through 6 years of followup.[40] Data now available through 15 years show a sustained decrease in risk for prostate cancer-specific mortality (15% vs. 21%; RR, 0.62 [95% CI, 0.44 to 0.87]; absolute difference, 6.1 percentage points [95% CI, 0.2 to 12]) and all-cause mortality (RR, 0.75 [95% CI, 0.61 to 0.92]; absolute difference, 6.6 percentage points [95% CI, -1.3 to 14]).[35] In subgroup analyses, benefits were restricted to men younger than age 65 years (RR, 0.49 [95% CI, 0.31 to 0.79] for prostate cancer-specific mortality; RR, 0.52 [95% CI, 0.37 to 0.73] for all-cause mortality). One other small (n=142), poor-quality RCT found no difference between prostatectomy for localized prostate cancer and no prostatectomy on overall survival through 23 years.[41] It did not report prostate cancer-specific mortality.

Eight cohort studies (median n=2,264 [range, 316 to 25,900]) with duration of followup ranging from 4 to 13 years consistently found prostatectomy for localized prostate cancer to be associated with decreased risk for all-cause mortality (6 studies; median adjusted HR, 0.46 [range, 0.32 to 0.67])[10,43,45-48] and prostate cancer-specific mortality (5 studies; median adjusted HR, 0.32 [range, 0.25 to 0.50])[10,42,45,47,49] compared with watchful waiting (**Table 6**, **Appendix C1**). The largest was a fair-quality, propensity-adjusted analysis of data from the U.S. Surveillance, Epidemiology, and End Results (SEER) program (n=25,900) of men ages 65 to 80 years that found decreased risk for all-cause mortality after 12 years (adjusted HR, 0.50 [95% CI, 0.66 to 0.72]).[48] Another large (n=22,385), fair-quality Swedish cohort study also found prostatectomy to be associated with decreased risk for all-cause mortality after 4 years of followup, after adjustment for age, Gleason score, and PSA level (adjusted HR, 0.41 [95% CI, 0.36 to 0.48]).[43]

Radiation therapy. No RCTs compared radiation therapy with watchful waiting. Five cohort studies (median n=3,441 [range, 334 to 30,857]) with followup ranging from 4 to 13 years consistently found that radiation therapy (EBRT or unspecified modality) for localized prostate cancer was associated with decreased risk for all-cause mortality (5 studies; median adjusted HR, 0.68 [range, 0.62 to 0.81])[10,43,47-49] and prostate cancer-specific mortality (5 studies; median adjusted HR, 0.66 [range, 0.63 to 0.70])[10,42,47-49] compared with watchful waiting (**Table 6**, **Appendix C1**). The largest study, a previously described analysis of SEER data, found radiation therapy to be associated with decreased propensity-adjusted risk for all-cause mortality (adjusted HR, 0.81 [95% CI, 0.78 to 0.85]).[48] A large Swedish cohort study (also described earlier) found radiation therapy to be associated with decreased risk for all-cause mortality (adjusted HR, 0.62 [95% CI, 0.54 to 0.71]).[43]

Androgen deprivation therapy. No RCTs compared ADT with watchful waiting. Two fair-quality cohort studies evaluated risk of all-cause and prostate cancer-specific mortality following ADT versus watchful waiting after 7 years (**Table 6**, **Appendix C1**).[44,49] One study (n=19,271) found that ADT was associated with increased risk of all-cause mortality (adjusted HR, 1.2 [95% CI, 1.1 to 1.2]) and prostate cancer-specific mortality (adjusted HR, 1.8 [95% CI, 1.6 to 2.0]).[44] Stratification of men into groups with moderately or poorly differentiated tumors did not affect conclusions. A smaller cohort study (n=3,765) also found that ADT was associated with increased risk of prostate cancer-specific mortality (adjusted HR, 1.3 [95% CI, 1.0 to 1.7]), but slightly decreased risk of all-cause mortality (HR, 0.89 [95% CI, 0.80 to 0.98]) after 7 years of followup.[49]

Cryotherapy and high-intensity focused ultrasonography. No RCTs or cohort studies evaluated risk of all-cause or prostate cancer-specific mortality following cryotherapy or HIFU.

Key Question 2. What Are the Harms of Treatment of Early-Stage or Screen-Detected Prostate Cancer?

Summary

Prostatectomy is associated with an increased risk of urinary incontinence (5 studies; RR, 3.1 [95% CI, 2.0 to 4.8]; I^2=55%; risk difference, 20 percentage points [95% CI, 10 to 30]) and erectile dysfunction (6 studies; RR, 1.6 [95% CI, 1.4 to 1.8]; I^2=58%; risk difference, 28 percentage points

[95% CI, 24 to 32]) compared with watchful waiting. Based on large databases and surgical series, prostatectomy is also associated with a risk of perioperative (30-day) mortality (about 0.5%) and cardiovascular events (0.6% to 3%).

Radiation therapy is also associated with an increased risk of erectile dysfunction compared with watchful waiting (6 studies; RR, 1.3 [95% CI, 1.2 to 1.5]; I^2=0%; risk difference, 15 percentage points [95% CI, 10 to 20]), but the difference in risk of urinary incontinence did not reach statistical significance (5 studies; RR, 1.4 [95% CI, 0.78 to 2.4]; I^2=20%). Radiation therapy is also associated with an increased risk of bowel dysfunction, which may improve over time. Data from one study suggest that low-dose brachytherapy may be associated with fewer harms compared with high-dose brachytherapy or EBRT.

There were no clear adverse effects related to general health-related quality of life following either prostatectomy or radiation therapy compared with watchful waiting.

Evidence on harms associated with ADT for localized prostate cancer is relatively limited, but suggests increased risk of erectile dysfunction (3 studies; RR, 2.3 [95% CI, 1.5 to 3.6]; I^2=90%; risk difference, 43% [95% CI, 30 to 56]), as well as other systemic effects related to androgen deprivation, such as gynecomastia and hot flashes. Evidence on harms associated with cryotherapy and HIFU is very limited and consists primarily of uncontrolled studies.

Evidence

Prostatectomy.

Urinary incontinence and erectile dysfunction. Prostatectomy was associated with increased risk of urinary incontinence compared with watchful waiting in one RCT (RR, 2.3 [95% CI, 1.6 to 3.2])[31] and four cohort studies (median RR, 4.0 [range, 2.0 to 11]) (**Table 7**, **Appendix C2**).[55,57,61,64] In the RCT, the absolute increase in risk of urinary incontinence with surgery was 28% (49% vs. 21%).[31] In the cohort studies, the median rate of urinary incontinence with watchful waiting was 6% (range, 3% to 10%), with prostatectomy associated with a median increase in absolute risk of 18 percentage points (range, 8 to 40).[55,57,61,64] In pooled analyses, prostatectomy was associated with a relative risk for urinary incontinence of 3.1 (95% CI, 2.0 to 4.8) (**Figure 2**) and risk difference of 22 percentage points (95% CI, 8.9 to 34) compared with watchful waiting.[31,55,57,61,64] Although statistical heterogeneity was present (I^2=55%), all studies found that prostatectomy was associated with increased risk. Stratification by study type reduced statistical heterogeneity among the cohort studies (I^2=22%), but the confidence intervals for the estimates overlapped.

Prostatectomy was also associated with an increased risk of erectile dysfunction compared with watchful waiting in one RCT (RR, 1.8 [95% CI, 1.5 to 2.2])[31] and five cohort studies (median RR, 1.5 [range, 1.3 to 2.1]) (**Table 7**, **Appendix C2**).[55,57,61,62,64] In the RCT, the absolute increase in risk of erectile dysfunction with surgery was 36% (81% vs. 45%).[31] In the cohort studies, the median rate of erectile dysfunction with watchful waiting was 52% (range, 26% to 68%), with prostatectomy associated with a median increase in absolute risk of 26 percentage points (range, 21 to 29).[55,57,61,62,64] In pooled analyses, prostatectomy was associated with a relative risk for erectile dysfunction of 1.6 (95% CI, 1.4 to 1.8; I^2=58%) (**Figure 3**) and pooled risk difference of 28

percentage points (95% CI, 24 to 32) compared with watchful waiting.[31,55,57,61,62,64] Stratification by study type resulted in similar estimates from the one RCT (RR, 1.8 [95% CI, 1.5 to 2.2])[31] and the cohort studies (RR, 1.6 [95% CI, 1.3 to 1.8]; I^2=63%).

For both of the above analyses, differences in study quality or mean age did not explain the observed statistical heterogeneity. Although meta-regression analysis found that studies with longer mean duration of followup tended to report smaller risk estimates for urinary incontinence (p=0.07), and including duration of followup in meta-regression analysis eliminated statistical heterogeneity (I^2=0%), the one study that stratified patients by duration of followup reported no differences in risk estimates.[31] The studies included in the meta-analysis provided few details about the specific surgical procedures evaluated. Based on practice patterns during the time periods covered by the studies, open retropubic radical prostatectomy was likely the dominant procedure. One observational study reported results for prostatectomy stratified by use of nerve sparing (n=494) or non-nerve sparing techniques (n=476); rates of erectile dysfunction were 68% and 87%, respectively, and rates of urinary incontinence were 9.4% and 15%, respectively (the combined data for both techniques were used in the meta-analysis).[64]

Consistent with the studies reporting dichotomous outcomes, eight cohort studies that evaluated urinary and sexual function outcomes using continuous scales found that prostatectomy was associated with worse outcomes compared with watchful waiting (**Table 8**, **Table 9**, and **Appendix C2**).[51,54,56,59,61,63-65] All of the studies except for two[54,65] used the PCI. Results based on the PCI found worse outcomes following prostatectomy compared with watchful waiting for urinary bother (median difference, -8 points [range, -17 to -1]), urinary function (median difference, -18 points [range, -30 to -9]), sexual bother (median difference, -27 points [range, -35 to 22]), and sexual function (median difference, -22 points [range, -34 to -2]) (**Table 9**). An outlier was one study that showed worse sexual bother scores in men following watchful waiting compared with prostatectomy.[59] One RCT reported a greater likelihood of significant distress due to urinary incontinence and erectile dysfunction in prostatectomy compared with watchful waiting patients, but the difference was not statistically significant (unadjusted RR, 1.8 [95% CI, 0.8 to 4.1] and 1.3 [95% CI, 0.8 to 2.2], respectively).[50]

Quality of life. Nine studies reported generic quality of life (**Table 8**, **Table 10**, and **Appendix C2**).[51,54,56,58,59,61,63,64] Two studies reported very similar SF-36 physical and mental component summary scores following prostatectomy and watchful waiting.[51,64] On specific SF-36 subscales, prostatectomy was associated with better physical function (6 studies; median difference, 8 points [range, 2 to 16])[51,54,56,59,61,63] and emotional role function scores (7 studies; median difference, 8 points [range, -5 to 13]),[51,54,56,58,59,61,63] with small or no clear differences on other SF-36 subscales.

Surgical complications. Evidence on short-term (≤30 days) complications following prostatectomy is available from large database studies and case series of patients with localized or more advanced prostate cancer. The largest study (n=101,604 Medicare claimants) reported a 30-day perioperative mortality of 0.5%[68]; three large observational studies reported nearly identical perioperative mortality rates (about 0.5%) (**Appendix C5**).[67,69,70] Studies showed that advanced age and a higher number of more serious comorbidities were associated with higher mortality rates, although absolute rates remained low even in men at higher risk (<1%). Some studies have also shown that low surgical volume is associated with higher postsurgical mortality,[68,70] while others have not

found such an association.[69] In the Medicare database study, the perioperative rate of serious cardiovascular events was 3% and the rate of vascular events (including pulmonary embolism and deep vein thrombosis) was 2%.[68] In two other large studies (n=1,243[71] and n=11,010[67,71]), rates of cardiovascular events were 0.6% and 3%, respectively, while rates of vascular events (including pulmonary embolism and deep vein thrombosis) were 1% and 2%, respectively. Serious rectal or ureteral injury due to surgery ranged from 0.3% to 0.6%.[68,71]

Comparative data on the effects of surgical technique on complication rates are limited. In the largest cohort study (n=4,592), medical complications were more likely to occur with laparoscopic compared with open prostatectomy in men with localized prostate cancer (HR, 1.9 [95% CI, 1.5 to 2.4]).[72] When limited to serious medical complications, rates were about 2% for both open and laparoscopic prostatectomy patients. Corresponding rates of all surgical complications were 5% and 7%. Mortality was not reported.

Other harms. Five studies (reported in six publications) found no clear differences between prostatectomy and watchful waiting in risk of bowel dysfunction (**Appendix C2**).[31,50,54,55,57,64] One RCT found similar rates of constipation (9% for prostatectomy vs. 8% for watchful waiting), blood or mucus in stool (1% in both groups), and diarrhea (6% vs. 5%, respectively).[50] Bowel urgency rates ranged from 7% to 16% in the prostatectomy groups and 6% to 15% in watchful waiting groups in three studies.[31,55,57] There was a nonsignificant trend toward decreased incidence of fecal leakage in the prostatectomy group (RR, 0.3 [95% CI, 0.04 to 3.2]) compared with watchful waiting in one study.[31] One RCT found no difference between prostatectomy and watchful waiting in risk of high levels of anxiety, depression, or worry after 4 years (**Appendix C2**).[50]

Radiation therapy.

Urinary incontinence and erectile dysfunction. Radiation therapy was associated with increased risk of urinary incontinence compared with watchful waiting in one small RCT, but the estimate was very imprecise (RR, 8.3 [95% CI, 1.1 to 63]) due to small numbers of events (one in the watchful waiting group) (**Table 7**, **Appendix C2**).[32] There was no clear increase in risk in four (total n=1,910) cohort studies (median RR, 1.1 [range, 0.71 to 2.0]).[55,57,61,64] Pooled analyses showed no statistically significant difference in risk of urinary incontinence (RR, 1.4 [95% CI, 0.78 to 2.4]; I^2=20%; risk difference, 3.1 percentage points [95% CI, -1.8 to 8.0]) (**Figure 4**). The single RCT[32] reported a substantially larger risk ratio (8.3 [95% CI, 1.1 to 63]) than the cohort studies (1.3 [95% CI, 0.85 to 2.0]; I^2=0%), but excluding the RCT did not change the overall pooled estimate. Differences in study quality, duration of followup, or mean age did not explain the observed statistical heterogeneity.

Radiation therapy was associated with increased risk of erectile dysfunction compared with watchful waiting in six cohort studies, with similar estimates across studies (median RR, 1.3 [range, 1.1 to 1.5]) (**Table 7**, **Appendix Table C2**).[55,57,61,62,64,66] Rates of erectile dysfunction ranged from 26% to 68% (median, 50%) with watchful waiting; radiation therapy was associated with a median increase in pooled absolute risk of 14 percentage points (range, 7 to 22). In pooled analyses, radiation therapy was associated with a relative risk for erectile dysfunction of 1.3 (95% CI, 1.2 to 1.5; I^2=0%) (**Figure 5**) and risk difference of 15 percentage points (95% CI, 10 to 20).

In six studies included in the meta-analyses, details about the type of radiation therapy (e.g., EBRT vs. brachytherapy) or dosing regimen were not provided. The exception was one good-quality cohort study that reported urinary incontinence after 3 years in 7.0% of men following high-dose brachytherapy (n=47), 5.4% following low-dose brachytherapy (n=58), and 2.7% following EBRT (n=123).[64] Rates of erectile dysfunction were 72%, 36%, and 68%, respectively. For the meta-analysis, we used the rates for men who underwent EBRT, which was the presumed focus of the other pooled studies.

Consistent with the studies reporting dichotomous outcomes, 11 studies found that radiation therapy was associated with worse sexual function compared with watchful waiting based on continuous scales, though no clear differences were seen in sexual bother scores and measures of urinary function (**Table 8**, **Table 9**, and **Appendix C2**).[33,51,52,54,56,59,61,63-66] Most studies used the PCI to measure urinary and sexual function and bother (**Table 8** and **Table 9**),[51,56,59,61,63,64,66] though results appeared similar in studies that used other measures.

Quality of life. Ten studies reported generic quality of life (**Table 8**, **Table 10**, and **Appendix C3**).[33,51,54,56,58,59,61,63,64,66] Three studies found no differences between radiation therapy and watchful waiting in SF-36 physical (median difference, 0 [range, -3 to 0]) or mental component summary scores (median difference, 0 [range, -2 to 1]) (**Table 8** and **Table 10**).[51,64,66] Results favored watchful waiting on the physical role function subscale (7 studies; median difference, -9 points [range, -22 to 1]),[51,54,56,59,61,63,66] with no clear differences on other SF-36 subscales. All of the studies except for the one RCT[33] used the SF-36 or a modified version of the SF-36 (SF-12)[64] to measure quality of life. Results from the RCT, which used the Quality of Life Questionnaire for Cancer to measure general quality of life, also found no clear differences between radiation therapy and watchful waiting (**Appendix Table C2**).[33]

Other harms. Six cohort studies consistently found that radiotherapy was associated with worse PCI bowel bother (median difference, -8 points [range, -15 to -3]) and function (median difference, -6 points [range, -10 to -2]) compared with watchful waiting (**Table 9**).[51,56,59,61,64,66] Studies that used measures other than the PCI also reported more bowel dysfunction following radiotherapy compared with watchful waiting (**Appendix Table C2**).[33,54,65,66] In studies that evaluated bowel function serially, effects appeared most pronounced in the first few months after radiation therapy and gradually improved.[33,54,59,65] This might help explain the inconsistent results among studies that reported dichotomous outcomes: although one study found that radiation therapy was associated with substantially increased risk of bowel urgency after 2 years (3.2% vs. 0.4%; RR, 7.5 [95% CI, 1.0 to 56]),[55] two studies with longer duration of followup (5.6[57] and 3 years[64]) found no increased risk.

One cohort study reported comparable effects of EBRT and brachytherapy on PCI bowel function and bother (**Table 9**).[51] One other study found that low-dose brachytherapy was associated with smaller effects on bowel bother (about 3-point change from baseline) compared with high-dose brachytherapy (9-point change) or EBRT (8-point change).[64]

No study reported effects of radiation therapy versus watchful waiting on anxiety or depression.

Androgen deprivation therapy.

Urinary incontinence and erectile dysfunction. There was no difference between ADT and watchful waiting in risk of urinary incontinence in two cohort studies (RR, 1.4 [95% CI, 0.74 to 2.5][55] and RR, 1.1 [95% CI, 0.23 to 5.3])[64] (**Table 7** and **Appendix C2**). ADT was associated with an increased risk of erectile dysfunction in two cohort studies (RR, 2.9 [95% CI, 2.3 to 3.6][55] and RR, 1.6 [95% CI, 1.3 to 1.9])[64] (**Table 7**). Rates of erectile dysfunction with watchful waiting were 26% and 47% in the two studies; ADT was associated with a median increase in pooled absolute risk of 49 and 27 percentage points, respectively. One study did not provide details about the ADT regimen.[64] In the other study, ADT consisted of orchiectomy, luteinizing hormone-releasing hormone agonist injections, or central androgen block, either with or without flutamide or bicalutamide.[55,60]

Three cohort studies (duration of followup, 3 to 6 years) reported urinary and sexual quality of life scores following ADT versus watchful waiting using the PCI (**Table 8**, **Table 9**, and **Appendix C2**).[51,63,64] Mean PCI sexual function scores were lower following ADT compared with watchful waiting (3 studies; median difference, -31 points [range, -36 to -29]) (**Table 8** and **Table 9**). Men treated with ADT had more sexual bother compared with men treated with watchful waiting in two studies (mean differences of -15 and -20 points),[51,63] but the third found no difference.[64] Differences in PCI urinary function ranged from -9 points (favoring watchful waiting) to no difference.[51,63,64] Unlike the other studies, which adjusted for age and other confounders, the latter study reported unadjusted scores. Differences in PCI urinary bother scores ranged from -5 to -17 points.[51,63,64]

Quality of life. General quality of life following ADT compared with watchful waiting was assessed in four cohort studies, all of which reported SF-36 scores (**Table 8**, **Table 10**, and **Appendix C2**).[51,60,63,64] Compared with watchful waiting, ADT was associated with somewhat worse SF-36 physical component summary scores (mean differences of -3 and -8 points)[51,64] and most SF-36 subscales, but there were too few studies to draw strong conclusions.

In two studies with overlapping patient populations, ADT was associated with greater risk of limitations in daily functioning compared with watchful waiting at 1 year (22% vs. 9%)[60] and 2 years (17% vs. 4%).[55]

Other harms. Other harms associated with ADT were infrequently reported. In one cohort study, gynecomastia (20% for ADT vs. 4% for watchful waiting) and hot flashes (58% vs. 11%) were more frequent with ADT than watchful waiting ($p<0.001$ for both outcomes).[60] In two studies, bowel dysfunction was similar in men who received ADT compared with those who underwent watchful waiting at 2[55] or 3 years[64] of followup. There was no difference in the proportion of men who reported some or a lot of worry about their prostate cancer in one study of ADT compared with watchful waiting (26% vs. 27%; $p=0.3$).[60]

Studies that reported other important harms (such as coronary heart disease, myocardial infarction, diabetes, or fractures) associated with ADT for prostate cancer did not meet our inclusion criteria because they did not evaluate patients with localized prostate cancer[79-82] or did not compare ADT with watchful waiting.[83]

Cryotherapy. Evidence on harms associated with cryotherapy for localized prostate cancer is very limited. One fair-quality cohort study followed a small (n=21) group of men who received cryotherapy for a mean duration of 46 months (**Table 7**, **Table 10**, and **Appendix C2**).[63] Among men older than age 70 years at diagnosis, 25% of those who received cryotherapy reported total urinary control and 75% reported occasional urinary dribbling compared with 55% and 39% among men who underwent watchful waiting. Among men younger than age 70 years at diagnosis, 81% of those who received cryotherapy had total urinary control and 19% had occasional dribbling compared with 74% and 21% in those who underwent watchful waiting. In the same study, 0% and 20% of men older and younger than age 70 years at diagnosis, respectively, reported erections firm enough for intercourse after cryotherapy compared with 47% and 81% among those who underwent watchful waiting.

A 2008 Cochrane review of cryotherapy for localized prostate cancer identified no randomized trials.[84] From case series, it reported rates of erectile dysfunction that ranged from 47% to 100% and rates of urinary incontinence from 1% to 19%.

High-intensity focused ultrasonography. We identified no randomized trials or cohort studies on harms associated with HIFU for localized prostate cancer. Five uncontrolled studies reported harms associated with HIFU for localized prostate cancer (**Appendix C5**).[73-77] No study enrolled more than 1,000 patients (sample sizes ranged from 63 to 402 [median, 142]), and methodological shortcomings were present in all of the studies (e.g., incomplete information regarding method of patient selection). Harms were voluntarily reported[76] or actively elicited[73-75,77] using a patient questionnaire. Only one study reported use of a formal, disease-specific measure to assess harms.[75] Duration of followup ranged from 407 days to 34 months. Rates of urinary incontinence ranged from 2% to 11% (four studies)[73,74,76,77] and rates of urinary tract infection ranged from 5% to 14% (three studies).[73,74,76] In two studies, about half of men with potency at baseline (45% and 53%) developed erectile dysfunction following HIFU.[73,74] One study used the PCI and the International Prostate Symptom Score (IPSS) to assess outcomes of whole versus focal HIFU.[75] There were no significant differences between the two types of HIFU in IPSS (8.1 vs. 9.2) or urinary bother (86 vs. 80) or urinary function (97 vs. 86) scores.

Contextual Question. How Often is Each Treatment Currently Performed in U.S. Men With PSA-Detected Cancer?

Data on the proportion of men who receive various prostate cancer treatments in the United States are available from the SEER program and the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) registry.[7,85,86] SEER collects data from population-based cancer registries covering approximately one quarter of the U.S. population. CaPSURE includes data from 37 community urology practices, three academic medical centers, and three Veterans Health Administration hospitals throughout the United States, with 23 active sites.

An analysis of 19 years of SEER data from 1986 (1 year prior to the introduction of PSA testing) to 2005 found that of approximately 1,300,000 men diagnosed with prostate cancer as a result of PSA testing, 44% elected to have surgical treatment and 37% chose radiation therapy. About 80% had either or both treatments. Men ages 20 to 49 years were more likely to undergo surgery, while older

men (ages>70 years) were more likely to choose radiation.[85] Data on the proportion of men who underwent other treatments were not reported.
A separate analysis of SEER data from 2004–2006 focused specifically on men (n=123,934) with low PSA values (≤10 ng/mL) at the time of prostate cancer diagnosis.[7] Among men with PSA values of 0.0 to 4.0 ng/mL (n=17,343), most chose prostatectomy (44%) or radiation (33%; either EBRT [17%], brachytherapy [12%], or a combination of both [4%]) as primary therapy. Conservative management—described as receiving neither prostatectomy nor radiation, and presumably referring to some type of watchful waiting or active surveillance—was chosen by 23% of men. Rates were similar among men with PSA values of up to 10.0 ng/mL (n=71,352). Men with screen-detected cancer were significantly more likely to undergo prostatectomy (odds ratio [OR], 1.49 [95% CI, 1.38 to 1.62]) or radiation therapy (OR, 1.39 [95% CI, 1.30 to 1.49]) compared with men without screen-detected cancer.

CaPSURE stratifies treatment groups by age, race, baseline risk (low, intermediate, or high), geographic location, and several other variables.[86] Baseline PSA level and method of prostate cancer detection are not specifically reported in CaPSURE, although methods for risk stratification are based on the D'Amico classification and the Cancer of the Prostate Risk Assessment (CAPRA) score, both of which incorporate PSA levels. Of 4,314 men classified as low risk, most (57%) chose radical prostatectomy as a primary therapy. Sixteen percent of men chose brachytherapy as a primary treatment, while less than 10% of men elected each of the other treatments (9% watchful waiting/active surveillance, 7% EBRT, 7% ADT, and 3% cryotherapy). Although prostatectomy was the most popular choice of primary treatment among low-risk patients overall, geographic and age variations in treatment choices were observed. For example, 75% of patients at one site (average CAPRA score, 2.4 [indicating low risk]) chose prostatectomy as primary therapy. At another site where patients had a similar risk score (average CAPRA score, 2.5), only 16% chose prostatectomy as primary therapy, with most patients choosing brachytherapy as primary treatment. Regarding age, 74% of men ages 65 years or younger chose prostatectomy. By age 75 years or older, that proportion dropped to 3%; instead, the higher proportion (42%) of men older than age 75 years opted for primary ADT.

Chapter 4. Discussion

Summary of Review Findings

The results of the evidence review are summarized in **Table 11**.

PSA-based screening identifies prostate cancer that is not clinically evident and, in some cases, may never have been diagnosed without screening. Over three quarters of men with localized prostate cancer undergo prostatectomy or radiation therapy.[85,86] Treatment studies can therefore help inform screening decisions by providing information about potential benefits and harms of interventions once prostate cancer is detected.

Only one good-quality randomized trial compared an active treatment for localized prostate cancer with watchful waiting.[35] It found that prostatectomy was associated with decreased risk of all-cause and prostate cancer-specific mortality after 15 years of followup, though based on subgroup analyses, benefits appeared to be limited to younger (ages <65 years) men. Because the RCT did not enroll men specifically with screen-detected prostate cancer, and evaluated populations with a substantially higher rate of T2 relative to T1 cancer compared with recent screening trials, its applicability to screening is uncertain. Although cohort studies consistently found that prostatectomy and radiation therapy were associated with decreased risk of all-cause and prostate cancer-specific mortality compared with watchful waiting, estimates were susceptible to residual confounding by indication, even after statistical adjustment.

Commonly selected therapies for localized prostate cancer are associated with clinically important harms. Treating approximately three men with prostatectomy, seven with radiation therapy, or two to three with ADT instead of watchful waiting would each result in one additional case of erectile dysfunction, and treating approximately five men with prostatectomy instead of watchful waiting would result in one additional case of urinary incontinence. Estimates for urinary incontinence and erectile dysfunction were similar based on pooled analyses and when results were synthesized more qualitatively (using medians and ranges). Prostatectomy and radiation therapy were not associated with worse outcomes on most measures related to general health-related quality of life compared with watchful waiting, suggesting that negative effects related to specific harms may be offset by positive effects, perhaps related to less worry about untreated prostate cancer. Prostatectomy was also associated with perioperative (30-day) mortality (about 0.5%) and cardiovascular events (0.6% to 3%), radiation therapy with bowel dysfunction, and ADT with gynecomastia and hot flashes.

The evidence on treatment-related harms reviewed for this report appears to be most applicable to open retropubic radical prostatectomy and EBRT, though details about specific surgical or radiation therapy techniques and dosing regimens were frequently lacking. We found little evidence with which to evaluate newer techniques for prostatectomy (including nerve sparing approaches that utilize laparoscopy, either robotic-assisted or freehand) compared with watchful waiting, but found no pattern suggesting that more recent studies reported different risk estimates compared with older studies. Limited data suggest that low-dose brachytherapy may be associated with fewer harms compared with high-dose brachytherapy or EBRT.[64] A potential harm of radiation therapy not addressed in this review is secondary posttreatment carcinogenic effects.[87,88]

Although ADT is the next most commonly utilized therapy for localized prostate cancer following prostatectomy and radiation therapy,[86] its use is comparatively infrequent, and it is not recommended as primary therapy[17,18] due to evidence suggesting ineffectiveness,[44] as well as an association with important adverse events such as coronary heart disease, myocardial infarction, diabetes, and fractures when used in the treatment of more advanced prostate cancer.[79-81]

Evidence on benefits and harms associated with cryotherapy and HIFU is very limited, with no studies comparing these therapies with watchful waiting.

Limitations

We excluded nonEnglish-language articles, which could result in language bias, though we identified no nonEnglish-language studies that would have met inclusion criteria. We included cohort studies of treatments, which are more susceptible to bias and confounding than well-conducted randomized trials. However, confounding by indication may be less of an issue in studies that evaluate harms,[89] and analyses stratified by study design did not suggest differential estimates. If patients are selected for a specific prostate cancer treatment in part based on a lower perceived risk for harms, the likely effect in observational studies would be to underestimate risks. For mortality outcomes, which may be more susceptible to confounding by indication, we only included studies that performed statistical adjustment. Finally, studies did not distinguish well between active surveillance and watchful waiting. Active surveillance might be associated with more harms (due to repeat biopsies or subsequent interventions) compared with watchful waiting, and studies with well-described active surveillance interventions that are consistent with current definitions for this therapy are needed.[29]

Emerging Issues

Therapies for localized prostate cancer continue to evolve. Newer techniques for prostatectomy include minimally invasive approaches that utilize laparoscopy, either robotic-assisted or freehand.[90] With regard to EBRT, efforts to define optimal doses and techniques (e.g., short-course, image-guided regimens) continue. In addition, use of brachytherapy for localized prostate cancer has increased markedly. One large survey of radiation oncology centers found that 36% of patients with localized prostate cancer received brachytherapy as a component of care in 1999 compared with 3% in 1994.[91] Cryotherapy, HIFU, and vascular-targeted photodynamic therapy are newer therapies for localized prostate cancer that have not yet come into widespread use.[92]

Future Research

Evidence from well-conducted randomized trials would be helpful for better characterizing the harms associated with treatments for localized prostate cancer. When available, results from the Prostate Cancer Intervention Versus Observation Trial (PIVOT), which compared prostatectomy with watchful waiting for screen-detected cancer, may help clarify which patients will benefit from prostatectomy or other active treatments, potentially reducing harms from unnecessary treatment.[93] Additional research is needed on the harms associated with newer surgical techniques (such as

robotic-assisted laparoscopic surgery) and radiation therapy regimens, as well as new and emerging therapies, in order to better understand comparative harms. Improved standardization of methods for defining whether a patient has urinary incontinence or erectile dysfunction and improved characterization of the specific techniques and interventions evaluated would be very helpful for interpreting results of future studies. For example, more standardized definitions of watchful waiting and active surveillance (and better reporting of the methods used) would help distinguish between these two types of therapies and facilitate analyses to determine whether they are associated with differential risks of harms.

Conclusions

Additional research is needed to understand the benefits of treatments for screen-detected, localized prostate cancer. Commonly selected therapies for localized prostate cancer are associated with an increased risk of important harms. More research is needed to understand whether newer therapies and techniques for treating localized prostate cancer are associated with fewer harms.

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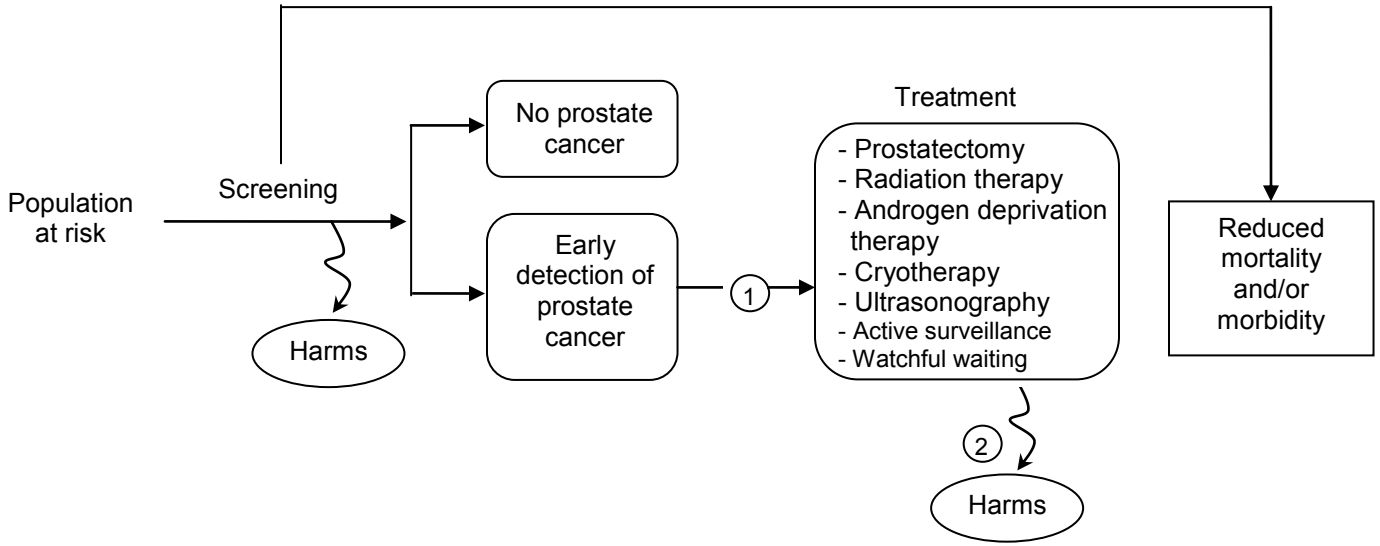
Figure 1. Analytic Framework and Key Questions



Key Questions*

1. What are the benefits of treatment of early-stage or screen-detected prostate cancer?
2. What are the harms of treatment of early-stage or screen-detected prostate cancer?

Contextual Question

1. How often is each treatment currently performed in U.S. men with PSA-detected cancer (i.e., what percentage of men initially choose watchful waiting vs. surgery, radiation, cryotherapy, etc.)?

* This targeted update focuses on the benefits and harms of treatments. The included treatments are listed in the analytic framework. The harms include overall and disease-specific mortality, reduced quality of life or function, and increased risk of urinary incontinence, bowel dysfunction, erectile dysfunction, surgical complications, and psychological or endocrinological effects.

Figure 2. Urinary Incontinence After Prostatectomy Versus Watchful Waiting for Treatment of Localized Prostate Cancer

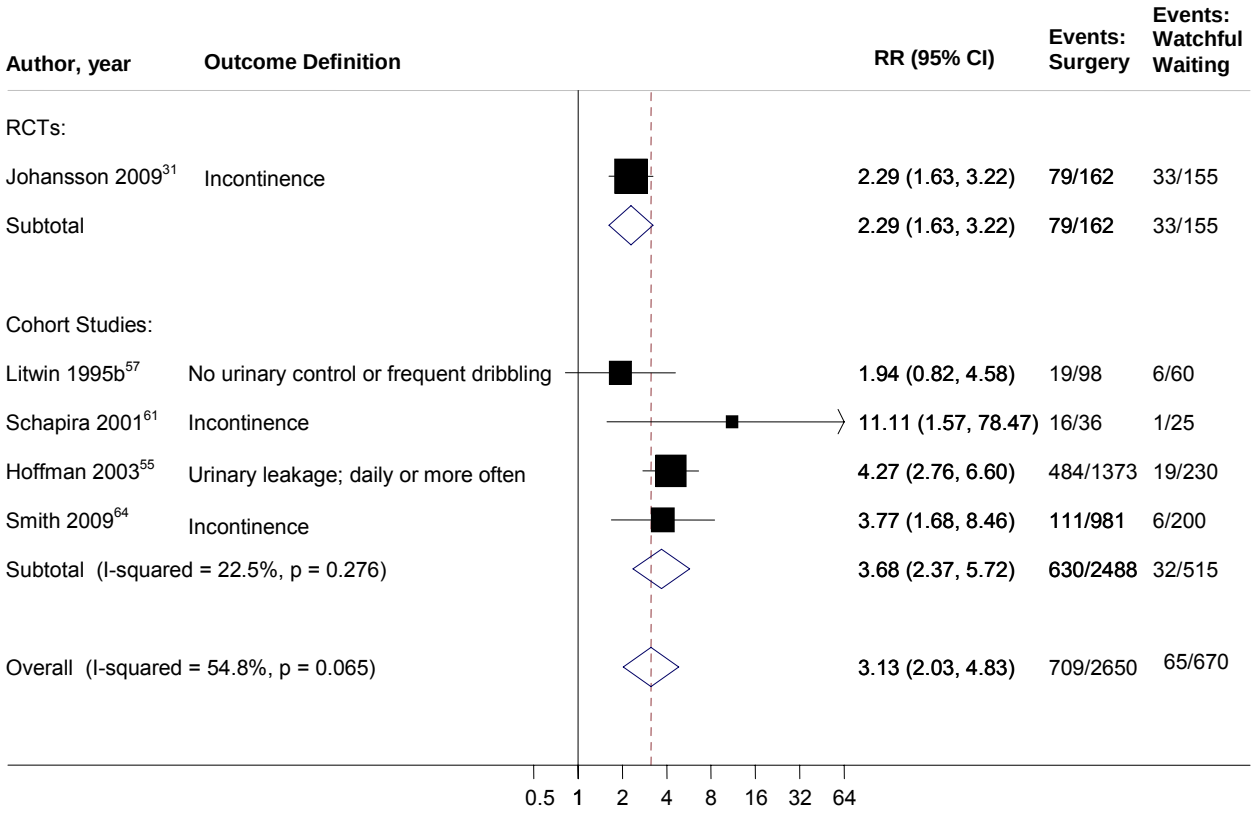


Figure 3. Erectile Dysfunction After Prostatectomy Versus Watchful Waiting for Treatment of Localized Prostate Cancer

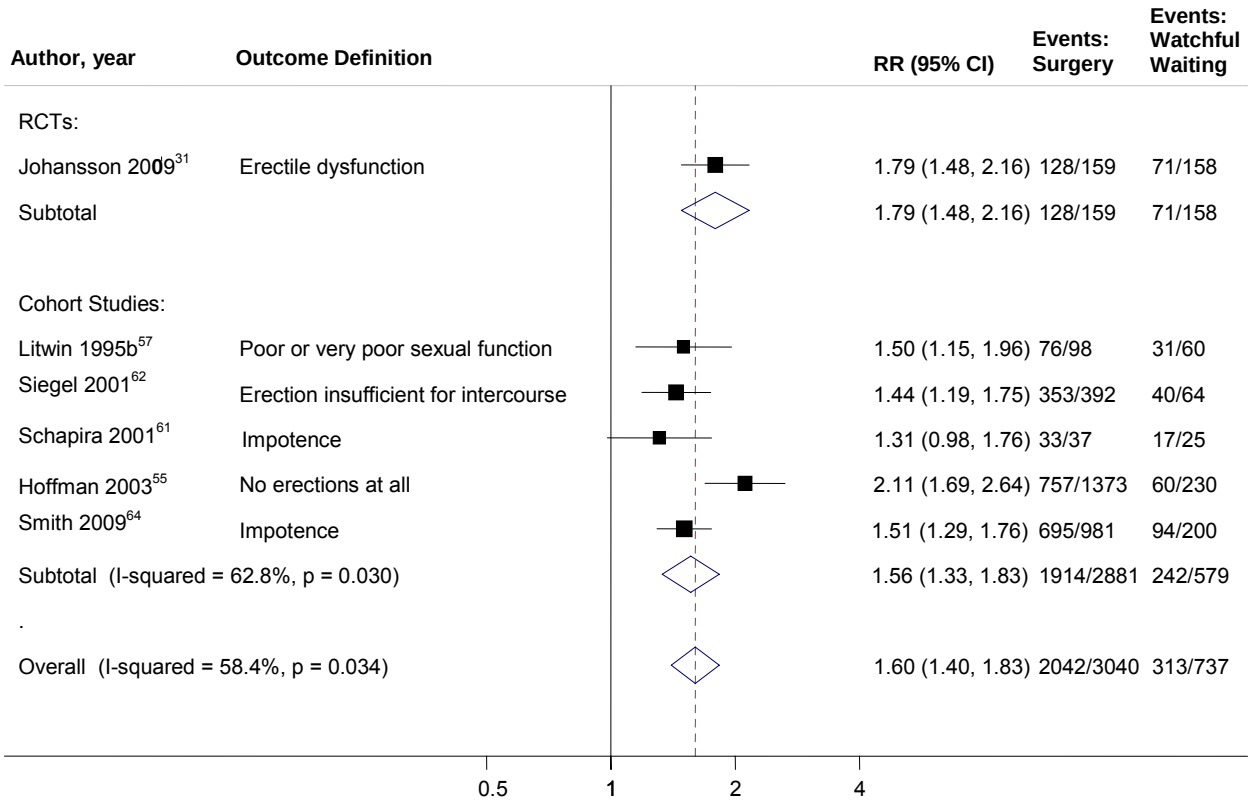


Figure 4. Urinary Incontinence After Radiation Therapy Versus Watchful Waiting for Treatment of Localized Prostate Cancer

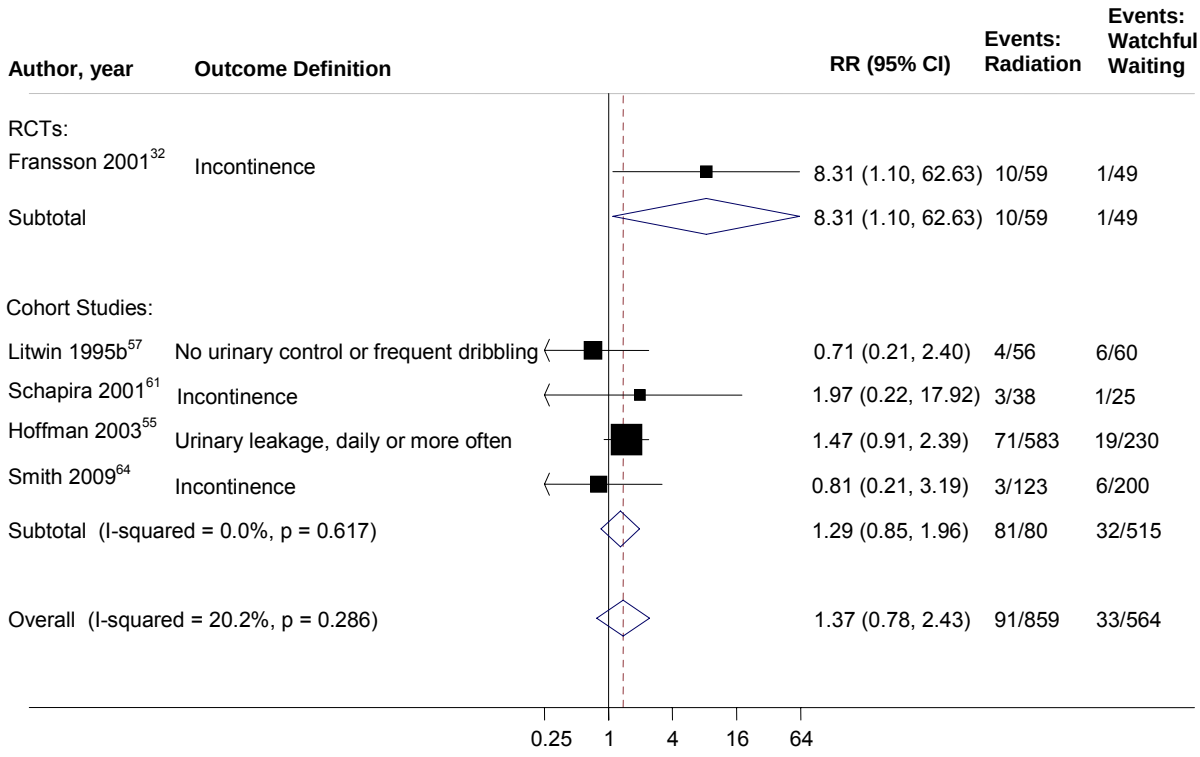


Figure 5. Erectile Dysfunction After Radiation Therapy Versus Watchful Waiting for Treatment of Localized Prostate Cancer

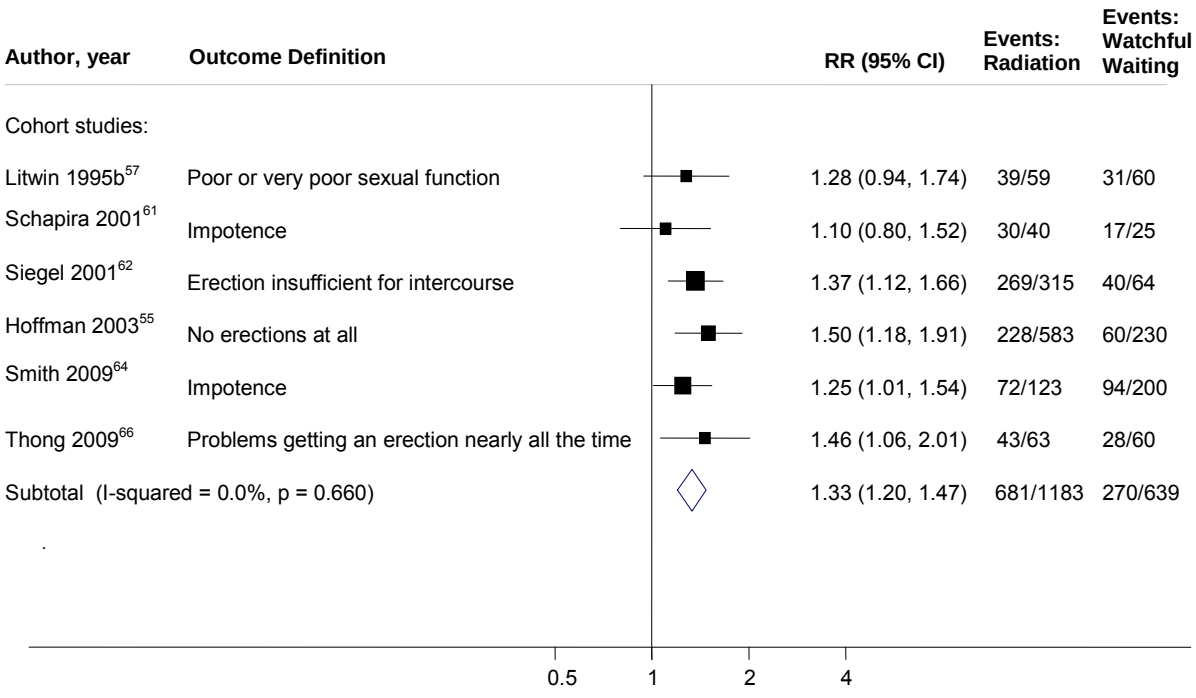


Table 1. Prostate Cancer Tumor Staging*

Tumor Stage	Description
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Clinically unapparent tumor not palpable or 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 (e.g., because of elevated PSA levels)
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

* From the American Joint Committee on Cancer.[94]

Table 2. Treatments for Localized Prostate Cancer

Treatment Option	Treatment Description
Active surveillance*	Active plan to postpone intervention. Decision to proceed with radical treatment based on rate of rise of prostate-specific antigen level and results of repeat biopsies.
Androgen deprivation therapy	Oral or injection medications or surgical removal of testicles to lower or block circulating androgens.
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.
External beam radiotherapy	Multiple doses of radiation from an external source applied over several weeks. Dose and physical characteristics of beam may vary. Conformal radiotherapy uses three-dimensional planning systems to maximize dose to prostate cancer and attempt to spare normal tissue. Intensity modulated radiation therapy 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.
High-intensity focused ultrasonography therapy	High-intensity focused ultrasonography 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.
Laparoscopic radical prostatectomy and robotic assisted radical prostatectomy	Video-assisted, minimally invasive surgical method to remove the prostate.
Radical retropubic or perineal prostatectomy	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.
Watchful waiting*	Active plan to postpone intervention. Palliative treatment given to patients exhibiting symptoms of disease progression.

Adapted with permission from Wilt et al, 2008.[9]
***** From van As, 2007.[95]

Table 3. Recommendations of Other Groups

Organization, year	Population	Recommendation
American Academy of Family Physicians, 2008[23,96]	Asymptomatic men	Adopts the U.S. Preventive Services Task Force 2008 recommendation, which found current evidence insufficient to assess the balance of benefits and harms of prostate cancer screening in men younger than age 75 years.
American Cancer Society, 2006[20]	Asymptomatic men	Recommends that men make an informed decision with their doctor about whether to be tested for prostate cancer. Research has not yet proven that the potential benefits of testing outweigh the harms of testing and treatment. Recommends that men should not be tested without learning about what is known and not known about the risks and possible benefits of testing and treatment. Starting at age 50 years, men should talk to their doctor about the pros and cons of testing so they can decide if testing is the right choice for them. African American men or men with a father or brother who had prostate cancer before age 65 years should have this talk with their doctor starting at age 45 years.
American College of Preventive Medicine, 2008[22]	Asymptomatic men	Insufficient evidence to recommend routine population screening with DRE or PSA. Clinicians caring for men, especially African American men and those with positive family histories, should provide information about potential benefits and risks of prostate cancer screening, and the limitations of current evidence for screening, in order to maximize informed decisionmaking.
American Urologist Association, 2009[17]	Asymptomatic men	Early detection and risk assessment of prostate cancer should be offered to asymptomatic men ages 40 years or older who wish to be screened and have an estimated life expectancy of more than 10 years.
Cancer Council Australia, 2010[26]	Asymptomatic men	The benefits of population screening for prostate cancer are, at this time, unproven. The central concern is that many prostate cancer cases will not progress sufficiently to cause harm in a man's lifetime, while others will progress and be lethal. No current test (including the PSA test) adequately differentiates between these types of cancer. Evidence does not support population-based screening of asymptomatic men for prostate cancer. Recent research confirms that the harms of screening with the PSA test outweigh the benefits.
European Association of Urologists, 2009[21]	Asymptomatic men	Current published data are insufficient to recommend the adoption of population screening for prostate cancer as a public health policy due to the large overtreatment effect.
Japanese Urological Association, 2008[97]	Asymptomatic men	Men ages 50 years or older in general and men ages 40 or 45 years or older with a family history should be screened with the PSA test concomitant with the basic health checkup system in Japan and PSA with or without DRE in human dry-dock (*Ningen* dock). Fact sheets including the merits and demerits of PSA screening should be provided to candidates before carrying out the screening test. The recommended cut-off point of PSA tests for biopsy indication is 4.0 ng/mL. Alternative cut-off points for biopsy indication are age-specific reference ranges of PSA, which are set at 3.0, 3.5, and 4.0 ng/mL in the age ranges of younger than 65, 65 to 69, and 70 years or older, respectively.
National Comprehensive Cancer Network, 2009[18]	Asymptomatic men	Baseline DRE and PSA testing at age 40 years is recommended for men interested in early screening, as well as annual followup for men who have a PSA value ≥1.0 ng/mL. Men with PSA <1.0 ng/mL should be screened again at age 45 years. Regular screening should be offered to all participants starting at age 50 years.
National Health Committee of New Zealand, 2004[25]	Asymptomatic men	Population-based screening for prostate cancer by PSA and/or DRE is not recommended for asymptomatic men in New Zealand.
Prostate Cancer Canada, 2010[19]	Asymptomatic men	Recommends that men older than age 40 years establish a baseline PSA value and men older than age 50 years have annual or semiannual PSA readings.
United Kingdom National Health Service, 2006[24]	Asymptomatic men	Systematic population screening program is not recommended.

Abbreviations: DRE = digital rectal examination; PSA = prostate-specific antigen.

Table 4. Study Characteristics of Randomized, Controlled Trials and Cohort Studies of Treatments for Prostate Cancer

Author, Yr	Interventions	Definition of watchful waiting	Mean duration of followup	Mean age	Stage at diagnosis	Adjusted variables in analysis	Outcomes	Quality rating
Randomized, controlled trials								
Bill-Axelson et al, 2011[35] Other publications: Johansson et al, 2009[31] Bill-Axelson et al, 2008[34] Holmberg et al, 2006[39] Bill-Axelson et al, 2005[36] Steineck et al, 2002[50] Holmberg et al, 2002[40]	Watchful waiting (n=348) Radical prostatectomy (n=347)	No immediate treatment	13 yrs (range, 3 wks to 20.2 yrs); 15-yr estimates reported	65 yrs	12% (83/695) T1b 12% (81/695) T1c 76% (529/695) T2 <1% (2/695) unknown Mean PSA, 12.9 ng/mL	Not applicable (RCT)	Prostate cancer mortality All-cause mortality	Good
Fransson et al, 2001[32] Other publications: Fransson et al, 2009[33]	Watchful waiting (n=27) Radiotherapy (n=27)	Regular monitoring and deferred treatment until time of progression	10 yrs	78 yrs	25% (14/57) T1 75% (43/57) T2	Not applicable (RCT)	Disease-specific quality of life Generic quality of life	Fair
Iversen et al, 1995[41] Other publications: Byar et al, 1981[37] Graversen et al, 1990[38]	Watchful waiting (n=68) Radical prostatectomy (n=74)	Oral placebo, no other treatment	23 yrs (range, 19-27 yrs)	64 yrs	54% (76/142) WHO Stage I 46% (66/142) WHO Stage II	Not applicable (RCT)	All-cause mortality	Poor
Cohort studies								
Albertsen et al, 2007[42]	No initial therapy (n=114) Surgery (n=802) Radiation (n=702)	Observation only (not defined)	Varied according to treatment group (median, 13.1-13.6 yrs)	68 yrs	4% Gleason score 2-4 6% Gleason score 5 47% Gleason score 6 26% Gleason score 7 17% Gleason score 8-10	Gleason score, PSA, clinical stage, age at diagnosis, and Charlson comorbidity score	Prostate cancer mortality	Fair
Bacon et al, 2001[51]	Watchful waiting (n=31) Prostatectomy (n=421) EBRT (n=221) Brachytherapy (n=69) Hormone (n=33) Other* (n=67) **Definition unclear; results not abstracted*	Not defined	5 yrs	71 yrs	3% (23/842) T1 86% (726/842) T2 11% (93/842) other	Age, marital status, waist circumference, metabolic equivalent hours of physical activity per week, smoking status, alcohol intake, comorbidities, Gleason score	Disease-specific quality of life Generic quality of life	Fair
Choo et al, 2010[52]	Watchful waiting (n=9) Radiotherapy (n=52; EBRT=22, brachytherapy=30)	Not defined	2 yrs	64 yrs	4% (3/75) Tx 55% (41/75) T1 37% (28/75) T2 4% (3/75) T3	No adjustment for variables; adjustment made for repeat measures	Disease-specific quality of life	Fair

Table 4. Study Characteristics of Randomized, Controlled Trials and Cohort Studies of Treatments for Prostate Cancer

Galbraith et al, 2001[54]	Watchful waiting (n=30) Surgery (n=59) Conventional radiation (n=25) Proton-beam radiation (n=24) Mixed-beam radiation (n=47)	Not defined	2 yrs	68 yrs	Stage NR (mean PSA values ranged from 9.8 to 17.6 at baseline depending on treatment group)	No adjustment for variables	Disease-specific quality of life Generic quality of life	Fair
Hoffman et al, 2003[55]	No treatment (n=230) Androgen deprivation (n=179) Radiation (n=583) Radical prostatectomy (n=1373)	No active treatment	2 yrs	66 yrs	Stage NR (all were T1 or T2)	Demographic, socioeconomic and clinical variables (not further defined)	Disease-specific quality of life	Fair
Ladjevardi et al, 2010[43]	Conservative management* (watchful waiting [n=9,435] and palliative treatment, including androgen deprivation, [n=3210]) Radical prostatectomy (n=12,950) Radiotherapy (n=6308; EBRT n=4443, brachytherapy n=1865)	Not defined	Median, 4 yrs (range, 0-12 yrs)	65 yrs	<1% T0 49% T1 35% T2 15% T3 <1% TX	Age, Gleason score, PSA	All-cause mortality	Fair
Litwin et al, 1995a[56] Litwin et al, 1995b[57]	Observation (n=60) Prostatectomy (n=98) Radiation (n=56)	Not defined	6 yrs	73 yrs	Tumor stage NR (all were clinically localized)	Age; comorbidities (diabetes, CV disease, respiratory disease, GI disease, renal disease, depression, alcohol or drug problems, smoking)	Disease-specific quality of life Generic quality of life	Fair
Litwin et al, 2002[58]	Watchful waiting (n=66) Radical prostatectomy (n=282) Radiation (n=104)	Not defined	2 yrs	66 yrs	30% (136/452) T1 66% (298/452) T2 4% (18/452) T3/4 or N+ or M+	Comorbidities, PSA, Gleason score, age	Generic quality of life	Fair
Lu-Yao et al, 2008[44]	Conservative management (n=11,404) Primary androgen deprivation therapy (n=7867)	No use of surgery, radiation or androgen deprivation	Median, 7 yrs	78 yrs	58% T1 42% T2	Instrumental variable analysis (covariates in analysis included age, race, comorbidity status, cancer stage, cancer grade, income status, urban resident, marital status, and year of diagnosis)	Prostate cancer mortality All-cause mortality	Fair

Table 4. Study Characteristics of Randomized, Controlled Trials and Cohort Studies of Treatments for Prostate Cancer

Lubeck et al, 1999[59]	Observation (n=87) Prostatectomy (n=351) Radiotherapy (n=75) *Results from the hormone therapy group were not abstracted; 32% (57/179) were stage T3 or higher at baseline*	No surgery, radiation or medical therapy in first year following diagnosis	2 yrs	66 yrs	25% (174/692) T1 62% (427/692) T2 5% (33/179) T3/T4 8% (52/692) other	Time (mixed model used to evaluate rate of quality of life change); age	Disease-specific quality of life Generic quality of life	Fair
Merglen et al, 2007[45]	Watchful waiting (n=378) Prostatectomy (n=158) Any EBRT (n=205; EBRT alone [n=152] or EBRT + ADT [n=53]) ADT (n=72) Other treatment (n=31; not described)	Active followup with treatment for disease progression	7 yrs	71 yrs	29% stage 1 40% stage 2 31% stage 3 22% PSA <10 28% PSA 11-29 23% PSA >30 27% PSA unknown	Age, period of diagnosis, method of detection, lymph node status, clinical tumor stage, differentiation, PSA level	Prostate cancer mortality All-cause mortality	Fair
Potosky et al, 2002[60]	Observation (n=416) ADT (n=245)	No therapy	1 yr	Mean age NR 4% (27/661) 40-59 yrs 22% (145/661) 60-69 yrs 53% (350/661) 70-79 yrs 21% (139/661) 80+ yrs	33% (221/661) T1 51% (338/661) T2 15% (101/661) unknown	Socio-demographic and clinical characteristics, presence of sexual partner, impotence, comorbidities, prostate cancer symptoms	Disease-specific quality of life Generic quality of life	Good
Schapira et al, 2001[61]	Expectant management (n=29) Radical prostatectomy (n=42) Radiation therapy (n=51)	Not defined	1 yr	Median age, 69 yrs	50% (61/122) T1 50% (61/122) T2	Comorbidities, stage, age, yrs of education, race, marital status, employ-ment status	Disease-specific quality of life Generic quality of life	Fair
Schymura et al, 2010[46]	Watchful waiting (n=614) Radical prostatectomy (n=1310) Radiation therapy (EBRT or brachytherapy; n=1037) ADT (n=339)	No therapy within 6 mo of diagnosis	5 yrs	Mean age NR: 18% <60 yrs 17% 60-64 yrs 22% 65-69 yrs 21% 70-74 yrs 14% 75-79 yrs 8% ≥80 yrs	57% PSA <10 26% PSA 10-20 11% PSA >20 13% PSA unknown	Age at diagnosis, race/ethnicity, marital status, state, PSA value, Gleason score, comorbidity score, time since diagnosis	Disease-specific quality of life Generic quality of life	Fair
Siegel et al, 2001[62]	Watchful waiting (n=64) Radical prostatectomy (n=419) EBRT (n=319)	Followup every 3-4 mo for 1 yr, every 6 mo after	4 yrs	66 yrs	7% (58/802) grade A 89% (713/802) grade B 4% (31/802) unknown	No adjustment for variables	Disease-specific quality of life	Fair
Smith et al, 2000[63]	Observation (n=120) Radical prostatectomy (n=1247) Radiotherapy (n=189) Hormonal therapy (n=67) Cryotherapy (n=28)	Not defined	4 yrs	67 yrs	98% (2194/2234) T1/T2 <1% (9/2234) T3 1% (29/2234) T4	Age, current comorbidities, education, time since diagnosis	Disease-specific quality of life Generic quality of life	Fair

Table 4. Study Characteristics of Randomized, Controlled Trials and Cohort Studies of Treatments for Prostate Cancer

Smith et al, 2009[64]	Active surveillance (n=200) Radical prostatectomy (n=981) EBRT (n=123) ADT (n=61) Combined EBRT/ADT (n=166) Low-dose brachytherapy (n=58) High-dose brachytherapy (n=47)	Active surveillance (not further defined)	3 yrs	61 yrs	54% (889/1636) T1 46% (747/1636) T2	Age, insurance status, comorbidity score, stage, Gleason score, PSA	Disease-specific quality of life Generic quality of life	Good
Stattin et al, 2010[10]	Surveillance (n=2021) Radical prostatectomy (n=3399) Radiation (n=1429)	Combined active surveillance and watchful waiting (no further definition)	Median, 8.2 yrs	63 yrs	59% T1 41% T2 Mean PSA, 8.2 ng/mL	Prostate cancer risk category, Charlson co-morbidity index, socioeconomic status	Prostate cancer mortality All-cause mortality	Fair
Talcott et al, 2003[65] Other publications: Clark et al, 2001[53]	Observation (n=19) Radical prostatectomy (n=129) EBRT (n=182) Brachytherapy (n=80)	Not defined	2 yrs	65 yrs	Exact proportion of patients with T1 and T2 unclear due to reporting method; most (>70%) were T1	Age, D'Amico risk category, marital status, education, other variables (not defined)	Disease-specific quality of life	Fair
Tewari et al, 2007[47]	Conservative management (n=197) Radiotherapy (n=137) Radical prostatectomy (n=119)	Not defined	5 yrs	63 yrs	100% stage 3	Propensity analysis (propensity score based on age at diagnosis, race, socioeconomic status, Charlson comorbidity index, and yr of diagnosis)	Prostate cancer mortality All-cause mortality	Fair
Thong et al, 2009[66]	Active surveillance (n=71) EBRT (n=71)	Stage and tumor grade ≤2 at time of diagnosis who received no active treatment	5-10 yrs	76 yrs	80% (114/142) T1 20% (28/142) T2	Demographic and clinical characteristics	Disease-specific quality of life Generic quality of life	Good
Wong et al, 2006[48]	Observation (n=12,608) Active treament (n=32,022; includes radical prostatectomy [n=13,292] and EBRT or brachytherapy [n=18,249], alone or in combination)	No Medicare data for prostatectomy, radiation or hormonal therapy	12 yrs	72 yrs	55% stage ≤T2a 45% stage T2b-T2c	Propensity-adjusted (propensity score based on age at diagnosis, SEER site, yr of diagnosis, tumor size, tumor grade, marital status, residence in urban setting, race, income,	All-cause mortality	Fair

Table 4. Study Characteristics of Randomized, Controlled Trials and Cohort Studies of Treatments for Prostate Cancer

						educational achievement, comorbidities)		
Zhou et al, 2009[49]	No treatment (n=1716) Monotherapy: Radical prostatectomy (n=889) EBRT (n=783) Brachytherapy (n=595) ADT (n=2049) Combination therapy: Radical prostatectomy + EBRT, ADT, or both (n=181) EBRT + ADT (n=1286) Brachytherapy + EBRT or ADT (n=756)	No definitive therapy within 6 mo of diagnosis	7 yrs	Mean age NR; for total cohort (including 1924 patients with distant or unknown stage): 21% 65-69 yrs 32% 70-74 yrs 46% ≥75 yrs	66% Gleason score <7	Age, race, tumor stage, Gleason score, pretreatment comorbidity	Prostate cancer mortality	Fair

*Conservatively managed patients included those who received ADT.

Abbreviations: ADT = androgen deprivation therapy; CV = cardiovascular; EBRT = external beam radiation therapy; GI = gastrointestinal; mo = month; NR = not reported; PSA = prostate-specific antigen; RCT = randomized, controlled trial; SEER = Surveillance, Epidemiology, and End Results; wk = week; WHO = World Health Organization; yr = year.

Table 5. Quality of Life Measures

Abbreviation	Full title	Scales	Scoring	Description
General quality of life measures				
SF-36	Short-form 36-item Health Survey (also known as Medical Outcomes Study General Health Survey; RAND 36-item Health Survey; UCLA 36-item Health Survey)	5-point Likert scales	0-100	36-item self-administered general quality of life measure used to evaluate physical function, social function, bodily pain, emotional well-being, energy/fatigue, general health perceptions, role limitations due to physical problems, and role limitations due to emotional problems.
Cancer-specific quality of life measures (impotence and incontinence)				
CARES-SF	Cancer Rehabilitation Evaluation System–Short Form	5-point Likert scales	0-4	59-item self-administered cancer-specific quality of life measure; one global score and five higher-order factors representing physical, psychosocial, medical interaction, marital, and sexual quality of life.
BSFI	Brief Sexual Function Inventory	5-point Likert scales	0-4	11-item self-administered sexual function measure, divided into five domains: sexual drive (2 questions, pooled scores 0-8); erectile function (3 questions, pooled scores 0-12); ejaculation (2 questions, pooled scores 0-8); problem assessment (3 questions, pooled scores 0-12); and overall satisfaction (1 question, score 0-4).
EPIC	Expanded Prostate Cancer Index Composite	5-point Likert scales	0-100	32-item self-administered prostate cancer treatment-related quality of life measure assessing urinary, bowel, sexual, and hormone function, as well as overall satisfaction.
FACT-G	Functional Assessment of Cancer Therapy–General	5-point Likert scales	0-108	27-item self-administered general quality of life measure with physical, social/family, emotional, and functional well-being subscales.
PCSS	Prostate Cancer Symptom Scale	0- (no problems/very good function) to 10-point linear analogue scale	0-10	18-item self-administered quality of life measure specific to prostate cancer.
PTSS	Southwest Oncology Group Prostate Treatment-Specific Symptoms Measure	5-point Likert scale	1-5	19-item quality of life measure of bowel, bladder, and sexual function specific to prostate cancer.
QLQ-C30	European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire for Cancer	4- and 7-point Likert scales	1-100	30-item self-administered quality of life measure for cancer patients, with disease-specific modules available.
QUF94W	QUF94W	0- (no problems/very good function) to 10-point linear analogue scale	0-10	43-item self-administered quality of life measure for prostate cancer patients, designed to evaluate side effects after pelvic radiotherapy.
UCLA-PCI	University of California, Los Angeles Prostate Cancer Index	Various-point Likert scales	0-100	Self-administered measure of treatment-related sexual (8 items), urinary (5 items), and bowel symptoms (4 items) and bother.

Table 6. Prostate Cancer-Specific and All-Cause Mortality

Author, year, followup	Prostate cancer-specific mortality	All-cause mortality
Prostatectomy vs. watchful waiting		
Randomized, controlled trials		
Bill-Axelson et al, 2011[35] Other publications: Bill-Axelson et al, 2008[34] Holmberg et al, 2006[39] Bill-Axelson et al, 2005[36] Steineck et al, 2002[50] Holmberg et al, 2002[40] Duration: 13 yrs	15% (CI, 11 to 19) vs. 21% (CI, 17 to 26); HR, 0.62 (CI, 0.44 to 0.87) <u>Subgroups: Risk</u> 6.5% (CI, 3.5 to 14) vs. 11% (CI, 6.8 to 18); HR, 0.53 (CI, 0.24 to 1.1) <u>Subgroups: Age</u> Age <65 yrs: 16% (CI, 11 to 24) vs. 26% (CI, 20 to 34); HR, 0.49 (CI, 0.31 to 0.79) Age ≥65 yrs: 13% (CI, 8.9 to 19) vs. 16% (CI, 11 to 23); HR, 0.83 (CI, 0.50 to 1.3) <u>Subgroups: Risk + Age</u> Age <65 yrs and low risk: 7.1% (CI, 2.7 to 19) vs. 12 (CI, 6.0 to 23); HR, 0.41 (CI, 0.14 to 1.2) Age ≥65 yrs and low risk: 6.6% (CI, 2.5 to 17) vs. 10% (CI, 5.1 to 21); HR, 0.76 (CI, 0.35 to 2.3)	46% (CI, 41 to 52) vs. 53% (CI, 47 to 59); HR, 0.75 (CI, 0.61 to 0.92) <u>Subgroups: Risk</u> Low risk: 31% (CI, 24 to 41) vs. 45% (CI, 37 to 54); HR, 0.62 (CI, 0.42 to 0.92) <u>Subgroups: Age</u> Age <65 yrs: 34% (CI, 27 to 43) vs. 47% (CI, 40 to 56); HR, 0.52 (CI, 0.37 to 0.73) Age ≥65 yrs: 57% (CI, 50 to 65) vs. 57% (CI, 50 to 66); HR, 0.98 (CI, 0.75 to 1.3) <u>Subgroups: Risk + Age</u> Age <65 yrs and low risk: 17% (CI, 9.5 to 30) vs. 36% (CI, 26 to 50); HR, 0.36 (CI, 0.18 to 0.7) Age ≥65 yrs and low risk: 47% (CI, 35 to 62) vs. 53% (CI, 41 to 68); HR, 0.92 (CI, 0.57 to 1.5)
Iversen et al, 1995[41] Other publications: Byar et al, 1981[37] Graversen et al, 1990[38] Duration: 23 yrs	NR	Median duration of survival: 8 yrs vs. 11 yrs; p>0.05
Cohort studies		
Albertsen et al, 2007[42] Duration: 13 yrs	14% vs. 4%; RR, 3.4 (CI, 1.9 to 5.9)	NR
Ladjevardi et al, 2009[43] Duration: 4 yrs	NR	HR, 0.41 (CI, 0.36 to 0.48) <u>Subgroups: Risk</u> Gleason score 7: HR, 0.78 (CI, 0.63 to 0.97) Gleason score 8-10: HR, 0.65 (CI, 0.47 to 0.90)
Merglen et al, 2007[45] Duration: 7 yrs	5-yr mortality: 8/158 (5%) vs. 43/378 (11%); HR, 0.56 (CI, 0.24 to 1.3) 10-yr mortality: 15/158 (9%) vs. 70/378 (11%); HR, 0.59 (CI, 0.26 to 0.91) <u>Subgroups: Risk</u> 10-yr mortality, Gleason score <7: 9/112 (8%) vs. 31/225 (14%); HR, 0.5 (CI, 0.22 to 1.1) 10-yr mortality, Gleason score ≥7: 4/31 (13%) vs. 28/76 (37%); HR, 0.23 (CI, 0.06 to 0.91) <u>Subgroups: Age</u> 10-yr mortality, age <70 yrs: 5/118 (4%) vs. 13/104 (13%); HR, 0.12 (CI, 0.04 to 0.42) 10-yr mortality, age ≥70 yrs: 10/40 (25%) vs. 57/274 (21%); HR, 1.25 (CI, 0.59 to 2.5)	5-yr mortality: 21/158 (13%) vs. 147/378 (39%); HR, 0.71 (CI, 0.4 to 1.4) 10-yr mortality: 34/158 (22%) vs. 223/378 (60%); HR, 0.67 (CI, 0.4 to 1.1)
Schymura et al, 2010[46] Duration: 5 yrs	NR	6% vs. 25%; HR, 0.44 (CI, 0.33 to 0.59)

Table 6. Prostate Cancer-Specific and All-Cause Mortality

Author, year, followup	Prostate cancer-specific mortality	All-cause mortality
Stattin et al, 2010[10] Duration: 8 yrs	2.4% (CI, 1.8 to 3.3) vs. 3.6% (CI, 2.7 to 4.8); HR, 0.49 (CI, 0.34 to 0.71) Subgroups: Risk Low risk: 0.4% (CI, 0.13 to 0.97) vs. 2.4% (CI, 1.2 to 4.1); HR, 0.29 (CI, 0.09 to 0.87) Intermediate risk: 3.4% (CI, 2.5 to 4.7) vs. 5.2% (CI, 3.7 to 6.9); HR, 0.53 (CI, 0.35 to 0.80)	11% (CI, 10 to 13) vs. 23% (CI, 21 to 26); HR, 0.49 (CI, 0.41 to 0.57)
Tewari et al, 2007[47] Duration: 4-6 yrs*	18/119 (15%) vs. 85/197 (43%); HR, 0.31 (CI, 0.17 to 1.2)	27/119 (23%) vs. 139/197 (71%); HR, 0.32 (CI, 0.20 to 0.51)
Wong et al, 2006[48] Duration: 12 yrs	NR	HR, 0.50 (CI, 0.47 to 0.53)
Zhou et al, 2008[49] Duration: 7 yrs	HR, 0.25 (CI, 0.13 to 0.48)	NR
Radiation therapy vs. watchful waiting		
Cohort studies		
Albertsen et al, 2007[42] Duration: 13 yrs	9% vs. 14%; rate ratio, 1.5 (CI, 0.9 to 2.6)	NR
Ladjevardi et al, 2009[43] Duration: 4 yrs	NR	HR, 0.62 (CI, 0.54 to 0.71) Subgroups: Risk Gleason score 7: HR, 0.81 (CI, 0.66 to 0.99) Gleason score 8-10: HR, 0.71 (CI, 0.55 to 0.92)
Stattin et al, 2010[10] Duration: 8 yrs	3.3% (CI, 2.5 to 5.7) vs. 3.6% (CI, 2.7 to 4.8); HR, 0.70 (CI, 0.45 to 1.1) Subgroups: Risk Low risk: 1.8% (CI, 0.65 to 4.0) vs. 2.4% (CI, 1.2 to 4.1); HR, 0.94 (CI, 0.31 to 2.85) Intermediate risk: 3.8% (CI, 2.6 to 5.4) vs. 5.2% (CI, 3.7 to 6.9); HR, 0.66 (CI, 0.42 to 1.1)	18% (CI, 16 to 21) vs. 23% (CI, 21 to 26); HR, 0.68 (CI, 0.57 to 0.82)
Tewari et al, 2007[47] Duration: 4-6 yrs*	23/137 (17%) vs. 85/197 (43%); HR, 0.63 (CI, 0.38 to 1.1)	58/137 (42%) vs. 139/197 (71%); HR, 0.70 (CI, 0.50 to 0.99)
Wong et al, 2006[48] Duration: 12 yrs	NR	HR, 0.81 (CI, 0.78 to 0.85)
Zhou et al, 2008[49] Duration: 7 yrs	EBRT: HR, 0.66 (CI, 0.41 to 1.0) Brachytherapy: HR, 0.45 (CI, 0.23 to 0.87) EBRT + ADT: HR, 0.97 (CI, 0.70 to 1.33) Brachytherapy + EBRT or ADT: HR, 0.46 (CI, 0.27 to 0.8)	EBRT: HR, 0.63 (CI, 0.53 to 0.75) Brachytherapy: HR, 0.4 (CI, 0.32 to 0.52) EBRT + ADT: HR, 0.57 (CI, 0.49 to 0.66) Brachytherapy + EBRT or ADT: HR, 0.32 (CI, 0.26 to 0.41)
Androgen deprivation therapy vs. watchful waiting		
Cohort studies		
Lu-Yao et al, 2008[44] Duration: 7 yrs	867/32,744 events per person-yr (rate 2.6/100) vs. 693/55,424 events per person-yr (rate 1.3/100); HR, 1.8 (CI, 1.6 to 1.9) Subgroups: Risk Moderately differentiated tumors: HR, 1.8 (CI, 1.6 to 2.1) Poorly differentiated tumors: HR, 1.1 (CI, 1.0 to 1.3)	4729/39,767 events per person-yr (rate 11.9/100) vs. 6316/66,567 events per person-yr (rate 9.5/100); HR, 1.2 (CI, 1.1 to 1.2) Subgroups: Risk Moderately differentiated tumors: HR, 1.2 (CI, 1.1 to 1.2) Poorly differentiated tumors: HR, 1.0 (CI, 1.0 to 1.1)
Zhou et al, 2008[49] Duration: 7 yrs	HR, 1.3 (CI, 1.0 to 1.7)	HR, 0.91 (CI, 0.83 to 1.0)

* Duration of followup varied by treatment group.

Abbreviations: ADT = androgen deprivation therapy; CI = confidence interval; EBRT = external beam radiotherapy; HR = hazard ratio; NR = not reported; RR = relative risk.

Table 7. Urinary Incontinence and Erectile Dysfunction

Author, year, followup	Urinary incontinence	Erectile dysfunction
Prostatectomy vs. watchful waiting		
Randomized, controlled trials		
Johansson et al, 2009[31] Steineck et al, 2002[50] 2-8 years	Urinary incontinence 49% (79/162) vs. 21% (33/155); RR, 2.3 (CI, 1.6 to 3.2)	Erectile dysfunction 81% (128/159) vs. 45% (71/158); RR, 1.8 (CI, 1.5 to 2.2)
Cohort studies		
Hoffman et al, 2003[55] 2 years	Urinary leakage, daily or more often 35% (484/1373) vs. 8% (19/230); RR, 4.3 (CI, 2.8 to 6.6)	No erections 55% (757/1373) vs. 26% (60/230); RR, 2.1 (CI, 1.7 to 2.6)
Litwin et al, 1995b[57] 6 years	No urinary control or frequent dribbling 19% (19/98) vs. 10% (6/60); RR, 1.9 (CI, 0.82 to 4.6)	Poor or very poor sexual function 78% (76/98) vs. 52% (31/60); RR, 1.5 (CI, 1.2 to 2.0)
Schapira et al, 2001[61] 1 year	Urinary incontinence 44% (16/36) vs. 4% (1/25); RR, 11 (CI, 1.6 to 78)	Impotence 89% (33/37) vs. 68% (17/25); RR, 1.3 (CI, 0.98 to 1.8)
Siegel et al, 2001[62] 4 years	NR	Erection insufficient for intercourse 90% (353/392) vs. 63% (40/64); RR, 1.4 (CI, 1.2 to 1.8)
Smith et al, 2009[64] 3 years	Urinary incontinence 12% (111/981) vs. 3% (6/200); RR, 3.7 (CI, 2.4 to 5.7)	Impotence 71% (695/981) vs. 47% (94/200); RR, 1.5 (CI, 1.3 to 1.8)
Radiation therapy vs. watchful waiting		
Randomized, controlled trials		
Fransson et al, 2001[32] 3 years	Urinary incontinence, proportion of patients using pads 17% (10/59) vs. 2% (1/49); RR, 8.3 (CI, 1.1 to 63)	NR
Cohort studies		
Hoffman et al, 2003[55] 2 years	Urinary leakage, daily or more often 12% (71/583) vs. 8% (19/230); RR, 1.5 (CI, 0.91 to 2.39)	No erections at all 39% (228/583) vs. 26% (60/230); RR, 1.5 (CI, 1.2 to 1.9)
Litwin et al, 1995b[57] 6 years	No urinary control or frequent dribbling 7% (4/56) vs. 10% (6/60); RR, 0.71 (CI, 0.21 to 2.4)	Poor or very poor sexual function 66% (39/59) vs. 52% (31/60); RR, 1.28 (CI, 0.94 to 1.7)
Schapira et al, 2001[61] 1 year	Urinary incontinence 8% (3/38) vs. 4% (1/25); RR, 2.0 (CI, 0.22 to 18)	Impotence 75% (30/40) vs. 68% (17/25); RR, 1.1 (CI, 0.80 to 1.5)
Siegel et al, 2001[62] 4 years	NR	Erection insufficient for intercourse 85% (269/315) vs. 63% (40/64); RR, 1.4 (CI, 1.1 to 1.7)
Smith et al, 2009[64] 3 years	Urinary incontinence 2% (3/123) vs. 3% (6/200); RR, 0.81 (CI, 0.21 to 3.2)	Impotence 59% (72/123) vs. 47% (94/200); RR, 1.2 (CI, 1.0 to 1.5)
Thong et al, 2009[66] 5-10 years	NR	Problem getting an erection nearly all the time 68% (43/63) vs. 47% (28/60); RR, 1.5 (CI, 1.1 to 2.0)
Androgen deprivation therapy vs. watchful waiting		
Cohort studies		
Hoffman et al, 2003[55] 2 years	Urinary leakage daily or more often 11% (20/179) vs. 8% (19/230); RR, 1.4 (CI, 0.74 to 2.5)	No erections at all 75% (135/179) vs. 26% (60/230); RR, 2.9 (CI, 2.3 to 3.6)
Potosky et al, 2002[60] 1 year	NR	Impotence 77% (68/88) vs. 27% (60/223); RR, 2.9 (CI, 2.2 to 3.7)
Smith et al, 2009[64] 3 years	Urinary incontinence 3% (2/61) vs. 3% (6/200); RR, 1.1 (CI, 0.23 to 5.3)	Impotence 74% (45/61) vs. 47% (94/200); RR, 1.6 (CI, 1.3 to 1.9)
Cryotherapy vs. watchful waiting		
Cohort studies		
Smith et al, 2000[63] 3.8 years	Uninary incontinence *Age <70 years* Total urinary control: 17/21 (81%) vs. 53/71 (74%) Occasional urinary dribbling: 4/21 (19%) vs. 15/71 (21%) *Age >70 years* Total urinary control: 5/21 (25%) vs. 39/71 (55%) Occasional urinary dribbling: 16/61 (75%) vs. 28/71 (39%)	Erectile dysfunction *Age <70 years* Erection firm enough for intercourse: 4/21 (20%) vs. 56/71 (81%) *Age >70 years* Erection firm enough for intercourse: 0/21 (0%) vs. 33/71 (47%)

Abbreviations: CI = confidence interval; NR = not reported; RR = relative risk.

Table 8. Summary Scores for Disease-Specific and Generic Health-Related Quality of Life

Scale	Radical Prostatectomy vs. Watchful Waiting		Radiotherapy vs. Watchful Waiting		Androgen Deprivation Therapy vs. Watchful Waiting	
	Number of studies (References)	Median difference in mean scores (range)	Number of studies (References)	Median difference in mean scores (range)	Number of studies (References)	Median difference in mean scores (range)
UCLA-PCI scores						
Urinary function	6 (51, 56, 59, 61, 63, 64)	-18 (-30 to -9)	7 (51, 56, 59, 61, 63, 64, 66)	-4 (-5 to 1)	3 (51, 63, 64)	-4 (-9 to 1)
Urinary bother	6 (51, 56, 59, 61, 63, 64)	-8 (-17 to -1)	7 (51, 56, 59, 61, 63, 64, 66)	-3 (-19 to 3)	3 (51, 63, 64)	-11 (-17 to -5)
Sexual function	6 (51, 56, 59, 61, 63, 64)	-19 (-34 to -2)	6 (51, 56, 59, 61, 63, 64)	-11 (-20 to -4)	3 (51, 63, 64)	-31 (-36 to -29)
Sexual bother	6 (51, 56, 59, 61, 63, 64)	-27 (-35 to 22)	6 (51, 56, 59, 61, 63, 64)	-5 (-18 to 17)	3 (51, 63, 64)	-15 (-20 to 1)
Bowel function	5 (51, 56, 59, 61, 64)	-1 (-5 to 2)	6 (51, 56, 59, 61, 64, 66)	-6 (-10 to -2)	2 (51, 64)	Not calculated (-10 and -5)
Bowel bother	5 (51, 56, 59, 61, 64)	0 (-5 to 5)	6 (51, 56, 59, 61, 64, 66)	-8 (-15 to -3)	2 (51, 64)	Not calculated (-6 and -1)
SF-36 scores						
Physical component summary score	2 (51, 64)	Not calculated (2 and 3)	3 (51, 64, 66)	0 (-3 to 0)	2 (51, 64)	Not calculated (-8 and -3)
Mental component summary score	2 (51, 64)	Not calculated (0 and 1)	3 (51, 64, 66)	0 (-2 to 1)	2 (51, 64)	Not calculated (-3 and 0)
Physical function	6 (51, 54, 56, 59, 61, 63)	8 (2 to 16)	7 (51, 54, 56, 59, 61, 63, 66)	-5 (-10 to 4)	2 (51, 64)	Not calculated (-7 and 3)
Physical role function	6 (51, 54, 56, 59, 61, 63)	2 (-10 to 9)	7 (51, 54, 56, 59, 61, 63, 66)	-9 (-22 to 1)	3 (51, 60, 64)	-11 (-23 to –11)
Bodily pain	6 (51, 54, 56, 59, 61, 63)	3 (-5 to 10)	7 (51, 54, 56, 59, 61, 63, 66)	-5 (-11 to 0)	3 (51, 60, 64)	-6 (-8 to -1)
General health	6 (51, 54, 56, 59, 61, 63)	4 (2 to 21)	7 (51, 54, 56, 59, 61, 63, 66)	1 (-9 to 3)	2 (51, 64)	Not calculated (-5 and -2)
Vitality	7 (51, 54, 56, 58, 59, 61, 63)	3 (-2 to 14)	8 (51, 54, 56, 58, 59, 61, 63, 66)	-4 (-5 to 1)	3 (51, 60, 64)	-7 (-7 to -7)
Social function	6 (51, 56, 58, 59, 61, 63)	3 (-2 to 11)	7 (51, 54, 56, 59, 61, 63, 66)	-2 (-9 to 1)	2 (51, 64)	Not calculated (-10 and -4)
Emotional role function	7 (51, 54, 56, 58, 59, 61, 63)	8 (-5 to 13)	8 (51, 54, 56, 58, 59, 61, 63, 66)	-4 (-9 to 19)	3 (51, 60, 64)	-15 (-16 to -3)
Mental health	7 (51, 54, 56, 58, 59, 61, 63)	-1 (-4 to 10)	8 (51, 54, 56, 58, 59, 61, 63, 66)	-2 (-6 to 2)	3 (51, 60, 64)	-4 (-6 to 0)

Abbreviations: UCLA-PCI = University of California, Los Angeles Prostate Cancer Index; SF-36 = Short-form 36-item Health Survey.

Table 9. Summary of UCLA Prostate Cancer Index Scores

Author, year	Urinary function			Urinary bother			Sexual function			Sexual bother			Bowel function			Bowel bother		
Duration of followup	RP	WW	MD	RP	WW	MD	RP	WW	MD	RP	WW	MD	RP	WW	MD	RP	WW	MD
Radical prostatectomy vs. watchful waiting																		
Bacon et al, 2001[51] Up to 5 years	76	93	-17	82	89	-7	26	54	-28	43	74	-31	86	91	-5	86	89	-3
Litwin et al, 1995a[56] 6 years	65	86	-21	68	80	-12	19	41	-22	13	37	-24	82	84	-2	80	85	-5
Lubeck et al, 1999[59] 2 years	71	87	-16	81	84	-3	27	29	-2	47	25	22	88	89	-1	90	90	0
Schapira et al, 2001[61] 1 year	62 (-28)	92 (+5)	-30 (-33)	67 (-15)	84 (-2)	-17 (-13)	20 (-38)	36 (-9)	-16 (-29)	29 (-35)	62 (+6)	-33 (-41)	88 (0)	86 (-3)	2 (3)	86 (-5)	81 (-5)	+5 (0)
Smith et al, 2000[63] 4 years	75	94	-19	78	88	-10	26	60	-34	34	69	-35	NR	NR	--	NR	NR	--
Smith et al, 2009[64] (Nerve sparing RP) 3 years	86	92	-6*	85	84	1*	35	44	-9*	52	66	-14*	88	87	1*	90	88	2*
Smith et al, 2009[64] (Non-nerve sparing RP) 3 years	83	92	-9	83	84	-1	22	44	-22	54	66	-12	89	87	2	91	88	3
No. of studies			**6**			**6**			**6**			**6**			**5**			**5**
Median (range)			**-18 (-30 to -9)**			**-8 (-17 to -1)**			**-19 (-34 to -2)**			**-27 (-35 to 22)**			**-1 (-5 to 2)**			**0 (-5 to 5)**
	RT	**WW**	**MD**	**RT**	**WW**	**MD**	**RT**	**WW**	**MD**	**RT**	**WW**	**MD**	**RT**	**WW**	**MD**	**RT**	**WW**	**MD**
Radiotherapy vs. watchful waiting																		
Bacon et al, 2001[51] (EBRT) Up to 5 years	89	93	-4	83	89	-6	34	54	-20	51	54	-3	81	91	-10	78	89	-11
Bacon et al, 2001[51] (Brachytherapy) Up to 5 years	87	93	-6*	75	89	-14*	36	54	-18*	54	74	-20*	80	91	-11*	72	89	-17*
Litwin et al, 1995a[56] 6 years	82	86	-4	77	80	-3	35	41	-6	29	37	-8	81	84	-3	77	85	-8
Lubeck et al, 1999[59] 2 years	85	87	-2	65	84	-19	25	29	-4	32	25	7	83	89	-6	75	90	-15
Schapira et al, 2001[61] 1 year	89 (0)	92 (+5)	-3 (-5)	81 (+1)	84 (-2)	-3 (3)	25 (-14)	36 (-9)	-11 (-5)	60 (+5)	62 (+6)	-2 (+11)	79 (-10)	86 (-3)	-7 (-7)	77 (-9)	81 (-5)	-4 (-4)
Smith et al, 2000[63] 4 years	89	94	-5	81	88	-7	40	60	-20	51	69	-18	NR	NR	--	NR	NR	--
Smith et al, 2009[64] (EBRT) 3 years	93	92	1	81	84	-3	32	44	-12	58	66	-8	85	87	-2	85	88	-3
Smith et al, 2009[64] (LDB) 3 years	94	92	2*	84	84	0*	54	44	10*	67	66	1*	89	87	2*	91	88	3*
Smith et al, 2009[64] (HDB) 3 years	90	92	-2*	77	84	-7*	30	44	-14*	61	66	-5*	88	87	1*	84	88	-4*
Thong et al, 2009[66]† 5-10 years	82	86	-4	75	78	3	NR	NR	--	NR	NR	--	87	93	-6	85	94	-9
No. of studies			**7**			**7**			**6**			**6**			**6**			**6**
Median (range)			**-4 (-5 to 1)**			**-3 (-19 to 3)**			**-11 (-20 to -4)**			**-5 (-18 to 17)**			**-6 (-10 to -2)**			**-8 (-15 to -3)**

Table 9. Summary of UCLA Prostate Cancer Index Scores

Author, year	Urinary function			Urinary bother			Sexual function			Sexual bother			Bowel function			Bowel bother		
Duration of followup	ADT	WW	MD	ADT	WW	MD	ADT	WW	MD	ADT	WW	MD	ADT	WW	MD	ADT	WW	MD
Androgen deprivation therapy vs. watchful waiting																		
Bacon et al, 2001[51] Up to 5 years	84	93	-9	72	89	-17	25	54	-29	59	74	-15	81	91	-10	83	89	-6
Smith et al, 2000[63] 4 years‡	90	94	-4	83	88	-5	29	60	-31	49	69	-20	NR	NR	--	NR	NR	--
Smith et al, 2009[64] 3 years	93	92	1	73	84	-11	8	44	-36	67	66	1	82	87	-5	87	88	-1
No. of studies			**3**			**3**			**3**			**3**			**2**			**2**
Median (range)			**-4 (-9 to 1)**			**-11 (-17 to -5)**			**-31 (-36 to -29)**			**-15 (-20 to 1)**			**NA**			**NA**
	CRYO	**WW**	**MD**	**CRYO**	**WW**	**MD**	**CRYO**	**WW**	**MD**	**CRYO**	**WW**	**MD**	**CRYO**	**WW**	**MD**	**CRYO**	**WW**	**MD**
Cryotherapy vs. watchful waiting																		
Smith et al, 2000[63] 4 years‡	93	94	-1	90	88	2	26	60	-34	43	69	-26	NR	NR	_	NR	NR	_
No. of studies			**1**			**1**			**1**			**1**			**0**			**0**
Median (range)			**NA**			**NA**			**NA**			**NA**			**NA**			**NA**

Note: All scores are mean scores at followup (i.e., mean change from baseline), on a 0-to-100 scale.
*Not included in calculation of median.
†Expanded Prostate Cancer Index Composite scores.
‡For the subset of patients diagnosed after 1994 (806/2334), mean duration of followup was 1 year.

Abbreviations: ADT = androgen deprivation therapy; CRYO = cryotherapy; EBRT = external beam radiation therapy; HDB = high-dose brachytherapy; LDB = low-dose brachytherapy; MD = mean difference; NA = not applicable; RP = radical prostatectomy; RT=radiotherapy; UCLA = University of California, Los Angeles; WW = watchful waiting.

Table 10. Summary of Short-Form 36-Item Health Survey Scores

Author, year	Physical component summary score			Mental component summary score			Physical function			Physical role function			Bodily pain			General health			Vitality			Social function			Emotional role function			Mental Health		
Duration of followup	RP	WW	MD	RP	WW	MD	RP	WW	MD	RP	WW	MD	RP	WW	MD	RP	WW	MD	RP	WW	MD	RP	WW	MD	RP	WW	MD	RP	WW	MD
Prostatectomy vs. watchful waiting																														
Bacon et al, 2001[51] Up to 5 years	52*	49*	3	55*	55*	0	90	79	11	86	85	1	85	81	4	80	71	9	71	68	3	92	87	5	90	90	0	84	83	1
Galbraith et al, 2001[54] 1.5 years	NR	NR	_	NR	NR	_	81 (1)	75 (0)	6 (1)	55 (-12)	65 (12)	-10 (-24)	85 (-2)	84 (4)	1 (-6)	58 (6)	54 (6)	4 (0)	62 (-1)	64 (2)	2 (1)	NR	NR	_	80 (18)	70 (9)	10 (9)	77 (1)	79 (7)	-2 (-6)
Litwin et al, 1995a[56] 5.6 years	NR	NR	_	NR	NR	_	75	71	4	61	55	6	77	74	3	65	63	2	60	60	0	80	80	0	70	57	13	76	77	-1
Litwin et al, 2002[58] 2 years	NR	NR	_	NR	NR	_	NR	NR	_	NR	NR	_	NR	NR	_	NR	NR	_	73	66	7	100	89	11	94	86	8	85	81	4
Lubeck et al, 1999[59] 2 years	NR	NR	_	NR	NR	_	86	71	15	72	63	9	84	76	8	75	54	21	71	57	14	89	78	11	84	73	11	86	76	10
Schapira et al, 2001[61] 1 year	NR	NR	_	NR	NR	_	84 (-5)	68 (-8)	16 (3)	72 (-11)	64 (-2)	8 (-9)	78 (-10)	68 (-2)	10 (-8)	71 (-3)	68 (4)	3 (-7)	69 (-2)	60 (-4)	9 (2)	88 (0)	86 (-1)	2 (1)	83 (3)	77 (-7)	6 (10)	77 (2)	81 (0)	-4 (2)
Smith et al, 2000[63] 3.8 years	NR	NR	_	NR	NR	_	87	85	2	78	80	-2	82	87	-5	76	71	5	67	69	-2	90	92	-2	86	91	-5	81	82	-1
Smith et al, 2009[64] 3 years (Nerve-sparing)	50*	47*	3	53*	53*	0	NR	NR	_	NR	NR	_	NR	NR	_	NR	NR	_	NR	NR	_	NR	NR	_	NR	NR	_	NR	NR	_
Smith et al, 2009[64] 3 years (Non nerve-sparing)	49*	47*	2	54*	53*	1	NR	NR	_	NR	NR	_	NR	NR	_	NR	NR	_	NR	NR	_	NR	NR	_	NR	NR	_	NR	NR	_
Number of studies			**2**			**2**			**6**			**6**			**6**			**6**			**7**			**6**			**7**			**7**
Median (range)			**NA**			**NA**	**8 (2 to 16)**			**2 (-10 to 9)**			**3 (-5 to 10)**			**4 (2 to 21)**			**3 (-2 to 14)**			**3 (-2 to 11)**			**8 (-5 to 13)**			**-1 (-4 to 10)**		
	RT	**WW**	**MD**	**RT**	**WW**	**MD**	**RT**	**WW**	**MD**	**RT**	**WW**	**MD**	**RT**	**WW**	**MD**	**RT**	**WW**	**MD**	**RT**	**WW**	**MD**	**RT**	**WW**	**MD**	**RT**	**WW**	**MD**	**RT**	**WW**	**MD**
Radiation therapy vs. watchful waiting																														
Bacon et al, 2001[51] Up to 5 years (EBRT)	49*	49*	0	53*	55*	-2	83	79	4	72	85	-13	79	81	-2	74	71	3	64	68	-4	87	87	0	82	90	-4	81	83	-2
Bacon et al, 2001[51] Up to 5 years (Brachytherapy)	51*	49*	2^	54*	55*	-1^	90	79	11^	79	85	-6^	81	81	0^	78	71	7^	66	68	-2^	92	87	5^	86	90	-4^	84	83	1^
Galbraith et al, 2001[54] 1.5 years (Conventional radiation)	NR	NR	_	NR	NR	_	70 (-9)	75 (0)	-5 (-9)	53 (-15)	67 (12)	-14 (-27)	73 (-13)	84 (4)	-11 (-17)	55 (-3)	54 (6)	1 (-9)	59 (-7)	64 (2)	-5 (-9)	NR	NR	_	61 (-17)	70 (9)	-9 (-26)	77 (4)	79 (7)	-2 (-3)
Galbraith et al, 2001[54] 1.5 years (Proton-beam radiation)	NR	NR	_	NR	NR	_	78 (-6)	75 (0)	3^ (-6)	82 (0)	67 (+12)	15^ (+12)	80 (+1)	84 (+4)	-4^ (+5)	59 (+5)	54 (+6)	5^ (+1)	63 (+12)	64 (+2)	-1^ (+10)	NR	NR	_	90 (+8)	70 (+9)	20^ (-1)	82 (+12)	79 (+7)	3^ (+5)
Galbraith et al, 2001[54] 1.5 years (Mixed-beam radiation)	NR	NR	_	NR	NR	_	78 (-6)	75 (0)	3^ (-6)	67 (-6)	67 (+12)	0^ (-18)	82 (0)	84 (+4)	-2^ (-4)	58 (-2)	54 (+6)	4^ (-8)	63 (+2)	64 (+2)	-1^ (0)	NR	NR	_	80 (+8)	70 (+9)	10^ (-1)	80 (+5)	79 (+7)	1^ (-2)
Litwin et al, 1995a[56] 5.6 years	NR	NR	_	NR	NR	_	74	71	3	56	55	1	74	74	0	66	63	3	61	60	1	81	80	1	76	57	19	79	77	2
Litwin et al, 2002[58] 2 years	NR	NR	_	NR	NR	_	NR	NR	_	NR	NR	_	NR	NR	_	NR	NR	_	61	66	-5	86	89	-3	81	86	-5	75	81	-6
Lubeck et al, 1999[59] 2 years	NR	NR	_	NR	NR	_	65	71	-6	55	63	-8	74	76	-2	54	54	0	54	57	-3	77	78	-1	76	73	3	78	76	2

Table 10. Summary of Short-Form 36-Item Health Survey Scores

Author, year	Physical component summary score			Mental component summary score			Physical function			Physical role function			Bodily pain			General health			Vitality			Social function			Emotional role function			Mental Health		
Duration of followup	**RT**	**WW**	**MD**	**RT**	**WW**	**MD**	**RT**	**WW**	**MD**	**RT**	**WW**	**MD**	**RT**	**WW**	**MD**	**RT**	**WW**	**MD**	**RT**	**WW**	**MD**	**RT**	**WW**	**MD**	**RT**	**WW**	**MD**	**RT**	**WW**	**MD**
Schapira et al, 2001[61] 1 year	NR	NR	_	NR	NR	_	58 (-5)	68 (-8)	-10 (3)	42 (-15)	64 (-2)	-22 (-13)	61 (-2)	68 (-4)	-7 (2)	59 (-1)	68 (4)	-9 (-5)	55 (-4)	60 (-4)	-5 (0)	59 (-19)	68 (-1)	-9 (-18)	70 (-1)	77 (-7)	-7 (6)	76 (1)	81 (0)	-5 (1)
Smith et al, 2000[63] 3.8 years	NR	NR	_	NR	NR	_	80	85	-5	71	80	-9	82	87	-5	70	71	-1	65	69	-4	88	92	-4	85	91	-6	82	82	0
Smith et al, 2009[64] 3 years (EBRT)	47*	47*	0	53*	53*	0	NR	NR	_	NR	NR	_	NR	NR	_	NR	NR	_	NR	NR	_	NR	NR	_	NR	NR	_	NR	NR	_
Smith et al, 2009[64] 3 years (LDB)	49*	47*	2†	54*	53*	1†	NR	NR	_	NR	NR	_	NR	NR	_	NR	NR	_	NR	NR	_	NR	NR	_	NR	NR	_	NR	NR	_
Smith et al, 2009[64] 3 years (HDB)	49*	47*	2†	52*	53*	-1†	NR	NR	_	NR	NR	_	NR	NR	_	NR	NR	_	NR	NR	_	NR	NR	_	NR	NR	_	NR	NR	_
Thong et al, 2009[66] 5-10 years	42	45	-3	50	49	1	62	70	-8	56	57	-1	70	77	-7	60	59	1	62	65	-3	81	79	-2	78	71	7	73	77	-4
Number of studies			**3**			**3**			**7**			**7**			**7**			**7**			**8**			**7**			**8**			**8**
Median (range)			**0 (-3 to 0)**			**0 (-2 to 1)**			**-5 (-10 to 4)**			**-9 (-22 to 1)**			**-5 (-11 to 0)**			**1 (-9 to 3)**			**-4 (-5 to 1)**			**-2 (-9 to 1)**			**-4 (-9 to 19)**			**-2 (-6 to 2)**
	ADT	**WW**	**MD**	**ADT**	**WW**	**MD**	**ADT**	**WW**	**MD**	**ADT**	**WW**	**MD**	**ADT**	**WW**	**MD**	**ADT**	**WW**	**MD**	**ADT**	**WW**	**MD**	**ADT**	**WW**	**MD**	**ADT**	**WW**	**MD**	**ADT**	**WW**	**MD**
Androgen deprivation therapy vs. watchful waiting																														
Bacon et al, 2001[51] Up to 5 years	46*	49*	-3	52*	55*	-3	76	79	3	62	85	-23	75	81	-6	66	71	-5	61	68	-7	83	87	-4	74	90	-16	79	83	-4
Potosky et al, 2002[60] 1 year	NR	NR	_	NR	NR	_	NR	NR	_	50	61	-11	73	74	-1	NR	NR	_	53	60	-7	NR	NR	_	74	77	-3	78	78	0
Smith et al, 2000[63] 3.8 years	NR	NR	_	NR	NR	_	72	85	-7	69	80	-11	79	87	-8	69	71	-2	62	69	-7	82	92	-10	76	91	-15	76	82	-6
Smith et al, 2009[64] 3 years	39*	47*	-8	53*	53*	0	NR	NR	_	NR	NR	_	NR	NR	_	NR	NR	_	NR	NR	_	NR	NR	_	NR	NR	_	NR	NR	_
Number of studies			**2**			**2**			**2**			**3**			**3**			**2**			**3**			**2**			**3**			**3**
Median (range)			**NA**			**NA**			**NA**			**-11 (-23 to -11)**			**-6 (-8 to -1)**			**NA**			**-7 (-7 to -7)**			**NA**			**-15 (-16 to -3)**			**-4 (-6 to 0)**
	CRY	**WW**	**MD**	**CRY**	**WW**	**MD**	**CRY**	**WW**	**MD**	**CRY**	**WW**	**MD**	**CRY**	**WW**	**MD**	**CRY**	**WW**	**MD**	**CRY**	**WW**	**MD**	**CRY**	**WW**	**MD**	**CRY**	**WW**	**MD**	**CRY**	**WW**	**MD**
Cryotherapy vs. watchful waiting																														
Smith et al, 2000[63] 3.8 years	NR	NR	_	NR	NR	_	87	85	3	84	80	4	87	87	0	72	71	1	69	69	0	95	92	3	97	91	6	86	82	4
Number of studies			**0**			**0**			**1**			**1**			**1**			**1**			**1**			**1**			**1**			**1**
Median (range)			**NA**			**NA**			**NA**			**NA**			**NA**			**NA**			**NA**			**NA**			**NA**			**NA**

Note: All data are mean scores (i.e., mean change from baseline) on a 0-to-100 scale (higher scores indicate better function), unless indicated otherwise.
*Scores standardized to the U.S. general population, mean of 50 (standard deviation, 10).
†Not included in calculation of median.

Abbreviations: ADT = androgen deprivation therapy; CRY = cryotherapy; EBRT = external beam radiation therapy; HDB = high-dose brachytherapy; LDB = low-dose brachytherapy; RP = radical prostatectomy; RT = radiotherapy; MD=mean difference; NA = not applicable; WW = watchful waiting.

Table 11. Summary of Evidence

Number of studies *Overall quality rating*	Limitations	Consistency	Applicability to screening population	Summary of findings
KQ 1. What are the benefits of treatment of early-stage or screen-detected prostate cancer?				
Prostatectomy				
9 studies 1 RCT; 8 cohort studies *Overall quality: fair*	Only 1 RCT	High	Prostate cancer in the RCT were primarily clinically rather than screen-detected and there was a high proportion of stage T2 cancer; limited information provided on specific surgical techniques evaluated	Prostatectomy was associated with decreased risk of prostate cancer-specific (RR, 0.62 [CI, 0.44-0.87]; absolute difference, 6.1 percentage points [CI, 0.2 to 12]) and all-cause mortality (RR, 0.75 [CI, 0.61-0.92]; absolute difference, 6.6 percentage points [CI, -1.3 to 14]) compared with watchful waiting after 15 years of followup in 1 good-quality RCT. Subgroup analysis suggests benefits are limited to men ages <65 years. Observational studies also found prostatectomy to be associated with decreased risk of prostate cancer (6 studies; median adjusted HR, 0.46 [range, 0.32 to 0.67]) and all-cause (5 studies; median adjusted HR, 0.32 [range, 0.25 to 0.50]) mortality after 4 to 13 years of followup compared with watchful waiting.
Radiation therapy				
5 cohort studies *Overall quality: fair*	No RCTs	High	Limited information provided on specific radiation therapy techniques and regimens evaluated	Radiation therapy was associated with decreased risk of prostate cancer-specific (5 studies; median adjusted HR, 0.66 [range, 0.63 to 0.70]) and all-cause (5 studies; median adjusted HR, 0.68 [range, 0.62 to 0.81]) mortality after 4 to 13 years of followup compared with watchful waiting.
Androgen deprivation therapy				
2 cohort studies *Overall quality: poor*	No RCTs	Moderate	Limited information provided on specific androgen deprivation therapy regimens evaluated	Two cohort studies found that androgen deprivation therapy for localized prostate cancer was associated with increased risk of prostate cancer-specific mortality compared with watchful waiting (adjusted HR, 1.8 [95% CI, 1.6 to 2.0] and 1.3 [95% CI, 1.0 to 1.7]).
Cryotherapy and high-intensity focused ultrasonography				
No studies	No studies	Not applicable	No studies	No studies
KQ 2. What are the harms of treatment of early-stage or screen-detected prostate cancer?				
Prostatectomy				
18 studies 1 RCT; 11 cohort studies; 6 uncontrolled observational studies *Overall quality: fair*	Only 1 RCT of fair quality, unadjusted risk estimates for presence of urinary incontinence or erectile dysfunction from cohort studies	Moderate	Limited information provided on specific surgical techniques evaluated	Prostatectomy was associated with increased risk of urinary incontinence compared with watchful waiting in 1 RCT (RR, 2.3 [CI, 1.6 to 3.2]; RD, 28%) and 4 cohort studies (median RR, 4.0 [range, 2.0 to 11]; median RD, 18% [range, 8 to 40%]). Based on large databases and surgical series, prostatectomy was associated with risk of perioperative mortality (about 0.5%) and cardiovascular events (0.6% to 3%). Prostatectomy was not associated with worse outcomes on SF-36 summary component scores and most SF-36 subscales.
Radiation therapy				
14 studies 1 RCT; 13 cohort studies *Overall quality: fair*	Only 2 RCTs, unadjusted risk estimates for presence of urinary incontinence or erectile dysfunction from cohort studies	Moderate	Limited information provided on specific radiation therapy techniques and regimens evaluated	Radiation therapy was associated with an increased risk of erectile dysfunction compared with watchful waiting in 6 cohort studies (median RR, 1.3 [range, 1.1 to 1.5]). Risk of urinary incontinence was increased in 1 RCT with a very imprecise estimate (RR, 8.3 [CI, 1.1 to 63]), but not in 4 cohort studies (median RR, 1.1 [range, 0.71 to 2.0]). Radiation therapy was also associated with an increased risk of bowel dysfunction, which appeared to improve over time. Radiation therapy was not associated with worse outcomes on SF-36 summary component scores and most SF-36 subscales.

Table 11. Summary of Evidence

Number of studies *Overall quality rating*	Limitations	Consistency	Applicability to screening population	Summary of findings
Androgen-deprivation therapy				
5 cohort studies *Overall quality: fair*	No RCTs; small sample sizes in the ADT arms of included studies; unadjusted risk estimates for presence of urinary incontinence or erectile dysfunction from cohort studies	High	Moderate (limited information on specific ADT regimens evaluated)	Androgen deprivation therapy was associated with an increased risk of erectile dysfunction (3 studies; RR, 2.3 [95% CI, 1.5 to 3.6]; I^2=90%; RD, 43% [95% CI, 30 to 56]), as well as other systemic effects related to androgen deprivation, such as gynecomastia and hot flashes. Most studies show no clear differences between androgen deprivation studies and watchful waiting in measures related to general health-related quality of life.
Cryotherapy				
1 cohort study *Overall quality: poor*	Only 1 cohort study with a small cryotherapy sample	NA (1 study)	Low	In 1 cohort study, rates of urinary incontinence were similar with cryotherapy and watchful waiting in patients younger than age 70 years, but men older than age 70 years who were treated with cryotherapy were more likely to have urinary dysfunction. Men in the cryotherapy arm were more likely to report erectile dysfunction than men in the watchful waiting arm, regardless of age.
High-intensity focused ultrasonography				
5 uncontrolled observational studies *Overall quality: poor*	No evidence from RCTs or cohort studies	Fair	Low	No study compared high-intensity focused ultrasonography with watchful waiting or no treatment, and all studies had methodological shortcomings. Erectile dysfunction occurred in about half of men who were potent at baseline in 2 uncontrolled studies, and urinary incontinence rates ranged from 2%–11%.

Abbreviations: ADT = androgen deprivation therapy; CI = confidence interval; HR = hazard ratio; KQ = key question; NA = not applicable; RCT = randomized, controlled trial; RD = risk difference; RR = relative risk; SF-36 = Short-form 36-item Health Survey.

Appendix A. Abbreviations

Abbreviation	Meaning
ADT	Androgen deprivation therapy
AHRQ	Agency for Healthcare Research and Quality
AJCC	American Joint Committee on Cancer
AS	Active surveillance
BSFI	Brief Sexual Function Inventory
CAPRA	Cancer of the Prostate Risk Assessment
CaPSURE	Cancer of the Prostate Strategic Urologic Research Endeavor
CARES-SF	Cancer Rehabilitation Evaluation System–Short Form
CI	Confidence interval
DRE	Digital rectal examination
EBRT	External beam radiotherapy
EPIC	Expanded Prostate Cancer Index Composite
FACT-G	Functional Assessment of Cancer Therapy–General
HDR	High-dose radiotherapy (brachytherapy)
HIFU	High-intensity focused ultrasonography
IPCSS	International Prostate Cancer Symptom Scale
KQ	Key question
LDR	Low-dose radiotherapy (brachytherapy)
LHRH	Luteinizing hormone-releasing hormone
MCS	Mental component score
NA	Not applicable
NR	Not reported
PCS	Physical component score
PCSS	Prostate Cancer Symptom Scale
PSA	Prostate-specific antigen
QLQ-C30	Quality of Life Questionnaire for Cancer
QOL	Quality of life
RCT	Randomized, control trial
RD	Risk difference
RP	Radical prostatectomy
RR	Relative risk
RT	Radiotherapy
SD	Standard deviation
SE	Standard error
SEER	Surveillance, Epidemiology, and End Results
SF-36	Short-Form 36-Item Health Survey
T	Tumor stage
TNM	Tumor, node, metastasis
UCLA-PCI	University of California, Los Angeles Prostate Cancer Index
USPSTF	U.S. Preventive Services Task Force
WW	Watchful waiting

Database: Ovid MEDLINE and Cochrane Central Register of Controlled Trials

1 Prostatic Neoplasms/dh, dt, rt, su, th, us
2 prostate cancer.mp. or Prostatic Neoplasms/
3 Treatment Outcome/
4 2 and 3
5 1 or 4
6 (ae or co or de or mo).fs.
7 (adverse and (effect$ or event$)).mp.
8 (safe$ or harm$ or side effect$).mp.
9 or/6-8
10 "Quality of Life"/
11 Anxiety/
12 Depression/
13 px.fs.
14 or/10-13
15 5 and (9 or 14)
16 15 and (20021$ or 2003$ or 2004$ or 2005$ or 2006$ or 2007$ or 2008$ or 2009$ or 2010$ or 2011$).ed.
17 16 not (case reports or comment or editorial or letter).pt*
18 limit 17 to (English language and humans)

Database: EBM Reviews - Cochrane Database of Systematic Reviews

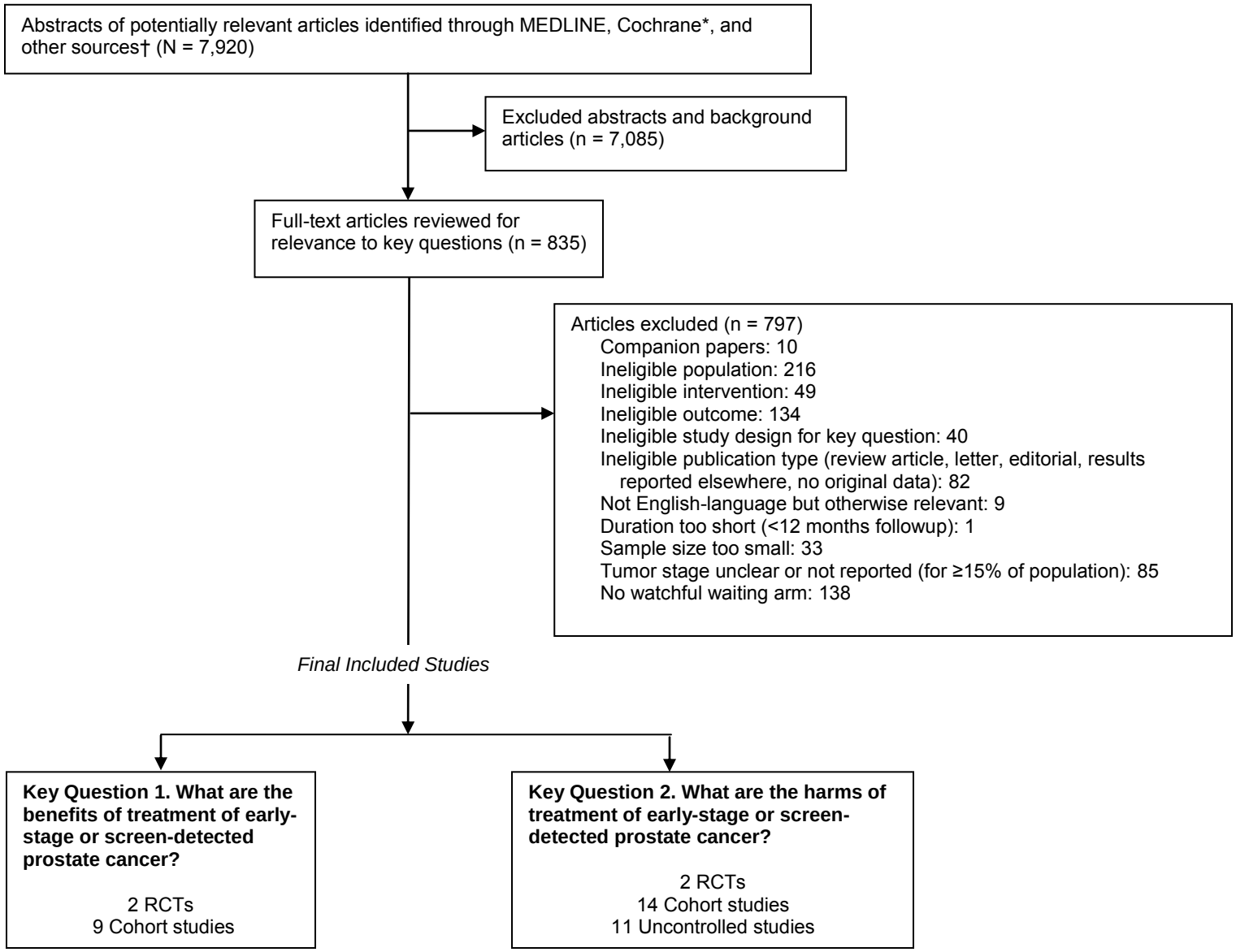
1 prostate cancer.mp.
2 (harm$ or safe$ or adverse$).mp.
3 1 and 2
4 limit 3 to full systematic review

**Search phrase not used in CCRCT search.*

Appendix B2. Inclusion and Exclusion Criteria

	Include	Exclude
Population	Men with screen-detected or early-stage prostate cancer (defined as stage I or II)	Men with later-stage prostate cancer Men with refractory, hormone refractory, or recurrent prostate cancer
Interventions	Surgery (radical prostatectomy, including different surgical techniques, such as nerve sparing, robotic) Androgen deprivation therapy (androgen deprivation therapy via luteinizing hormone-releasing hormone agonists, antiandrogen therapy, and/or orchiectomy) Radiation therapy (external-beam radiation therapy, brachytherapy, and combination therapies) Cryotherapy Ultrasonography (high-intensity focused ultrasonography)	Chemotherapy (this treatment is typically used for later-stage cancer)
Outcomes (unintended effects of therapies)	Mortality (overall and disease-specific) Quality of life (overall and disease-specific) Function (overall and disease-specific) Bowel, urinary, and sexual dysfunction Psychological effects (e.g., mental status, depression, cognitive dysfunction) Endocrinological effects (e.g., bone health, hot flashes, gynecomastia) Surgical complications	
Study types and designs	Randomized, controlled trials of included treatments versus watchful waiting/active surveillance or no treatment Cohort studies of included treatments versus watchful waiting/active surveillance or no treatment Uncontrolled observational studies of harms (sample size of at least 1,000), if randomized, controlled trials and cohort studies not available Smaller, uncontrolled observational studies of harms, if randomized, controlled trials, cohort studies, and larger uncontrolled studies not available	
Duration	30 days for perioperative complications >12 months for other harms	

Appendix B3. Literature Flow Diagram for Treatment Effectiveness and Harms



*Cochrane databases include the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews.
†Identified from reference lists, suggested by experts, etc.

Ineligible Population

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Appendix B4. Excluded Studies

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Appendix B4. Excluded Studies

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Appendix B4. Excluded Studies

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Note: Companion papers are not listed in this appendix, as indicated on the literature tree.

Randomized Controlled Trials (RCTs) and Cohort Studies

Criteria

- Initial assembly of comparable groups:
  - RCTs: adequate randomization, including concealment and whether potential confounders were distributed equally among groups
  - Cohort studies: consideration of potential confounders with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts
- Maintenance of comparable groups (includes attrition, cross-overs, adherence, contamination)
- Important differential loss to followup or overall high loss to followup
- Measurements: equal, reliable, and valid (includes masking of outcome assessment)
- Clear definition of interventions
- Important outcomes considered
- Analysis: adjustment for potential confounders for cohort studies, or intention-to-treat analysis for RCTs; for cluster RCTs, correction for correlation coefficient

Definition of ratings based on above criteria

Good: Meets all criteria: comparable groups are assembled initially and maintained throughout the study (followup at least 80%); reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; important outcomes are considered; and appropriate attention to confounders in analysis.

Fair: Studies will be graded "fair" if any or all of the following problems occur, without the important limitations noted in the "poor" category below: generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred in followup; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for.

Poor: Studies will be graded "poor" if any of the following major limitations exists: groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied at all equally among groups (including not masking outcome assessment); and key confounders are given little or no attention.

Source: Harris et al, 2001[27]

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Philipp Dahm, MD
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Bruce L. Dalkin, MD, FACS
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Richard M. Hoffman, MD, MPH
Professor, Internal Medicine, Division of Epidemiology, University of New Mexico Cancer Center.

Barnett S. Kramer, MD, MPH
Director, National Institutes of Health Office of Medical Applications of Research.

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Professor, Chairman, Department of Urology, University of Texas San Antonio.

Appendix C1. Randomized, Controlled Trials and Cohort Studies of Treatment Benefits

Author, Year *Title*	Study name	Inclusion criteria	Exclusion criteria	Number screened/eligible /enrolled	Subject age and race Stage at diagnosis Screen detected	Country and setting	Sponsor	Variables adjusted for in analysis
Randomized, Controlled Trials								
Bill-Axelson et al, 2011[35] Other publications: Bill-Axelson et al, 2008[34] Holmberg et al, 2006[39] Bill-Axelson et al, 2005[36] Steineck et al, 2002[50] Holmberg et al, 2002[40]	Scandinavian Prostate Cancer Center Group Study 4 (SPCG-4)	Include: ages <75 yrs with newly diagnosed moderately or well-differentiated T0d, T1, or T2 tumors; PSA <50 ng/mL; negative bone scan; free of other cancer; healthy enough to allow prostatectomy; life expectancy >10 yrs	Poorly differentiated tumor	NR/NR/695	Mean age: 65 yrs Race: NR Mean PSA: 12.9 ng/mL T1b: 12% (83/695) T1c: 12% (81/695) T2: 76% (529/695) Unknown: <1% (2/695) Screen detected: no	Sweden, Finland, Iceland 14 cancer centers	National Institutes of Health; Swedish Cancer Society	Not applicable (RCT)
	Subgroup analyses	**Intervention type**	**Outcomes method of ascertainment**	**Results**			**Mean duration and loss to followup**	**Quality rating**
	Risk Low risk (PSA <10 ng/mL and Gleason score <7 or WHO grade 1) Age <65 yrs ≥65 yrs	Radical prostatectomy (n=347) Watchful waiting (n=348)	All-cause mortality Prostate cancer mortality Distant metastases	All-cause mortality, radical prostatectomy vs. watchful waiting All patients: cumulative incidence, 46.1% (CI, 40.8 to 52.0) vs. 52.7% (CI, 47.4 to 58.6); HR, 0.75 (CI, 0.61 to 0.92); ARR, 6.6 (CI, -1.3 to 14.5) Low risk: cumulative incidence, 31.4% (CI, 23.9 to 41.3) vs. 44.6% (CI, 36.6 to 54.4); HR, 0.62 (CI, 0.42 to 0.92); ARR, 13.2 (CI, 0.9 to 25.5) Age <65 yrs: cumulative incidence, 33.9% (CI, 26.9 to 42.6) vs. 47.4% (CI, 40.4 to 56.1); HR, 0.52 (CI, 0.37 to 0.73); ARR, 13.5 (CI, 2.4 to 24.7) Age <65 yrs and low risk: cumulative incidence, 16.9% (CI, 9.5 to 30.1) vs. 36.2% (CI, 26.1 to 50.2); HR, 0.36 (CI, 0.18 to 0.70); ARR, 19.3 (CI, 4.0 to 34.7) Age ≥65 yrs: cumulative incidence, 56.7% (CI, 49.5 to 65.0) vs. 57.4% (CI, 50.2 to 65.8); HR, 0.98 (CI, 0.75 to 1.28); ARR, 0.7 (CI, -10.3 to 11.7) Age ≥65 yrs and low risk: cumulative incidence, 46.8% (CI, 35.1 to 62.3) vs. 52.9% (CI, 41.3 to 67.6); HR, 0.92 (CI, 0.57 to 1.49); ARR, 6.1 (CI, -12.6 to 24.8) Prostate cancer mortality, radical prostatectomy vs. watchful waiting All patients: cumulative incidence, 14.6% (CI, 11.2 to 19.1) vs. 20.7% (CI, 16.7 to 25.6); HR, 0.62 (CI, 0.44 to 0.87); ARR, 6.1 (CI, 0.2 to 12.0) Low risk: cumulative incidence, 6.8% (CI, 3.5 to 13.5) vs. 11.0 (CI, 6.8 to 17.8); HR, 0.53 (CI, 0.24 to 1.14); ARR, 4.2 (CI, -2.9 to 11.2) Age <65 yrs and low risk: cumulative incidence, 7.1% (CI, 2.7 to 18.6) vs. 11.6 (CI, 6.0 to 22.6); HR, 0.41 (CI, 0.14 to 1.17); ARR, 4.5 (CI, -5.7 to 14.8) Age <65 yrs: Cumulative incidence, 16.4% (CI, 11.3 to 23.8) vs. 25.8% (CI, 19.7 to 33.7); HR, 0.49 (CI, 0.31 to 0.79); ARR, 4.5 (CI, -5.7 to 14.8) Age ≥65 yrs: cumulative incidence, 13.0% (CI, 8.9 to 18.9) vs. 16.0% (CI, 11.4 to 22.6); HR, 0.83 (CI, 0.50 to 1.30); ARR, 3.8 (CI, -5.9 to 13.4) Age ≥65 yrs and low risk: cumulative incidence, 6.6% (CI, 2.5 to 17.1) vs. 10.3% (CI, 5.1 to 21.0); HR, 0.76 (CI, 0.35 to 2.32); ARR, 3.8 (CI, -5.9 to 13.4)		Duration: 12.8 yrs (range, 3 wks to 20.2 yrs) Loss to followup: none	Good

Appendix C1. Randomized, Controlled Trials and Cohort Studies of Treatment Benefits

				Distant metastases, radical prostatectomy vs. watchful waiting All patients: cumulative incidence, 21.7% (CI, 17.6 to 26.7) vs. 33.4 (CI, 28.6 to 39.0); HR, 0.59 (CI, 0.45 to 0.79); ARR, 11.7 (CI, 4.8 to 18.6) Low risk: cumulative incidence, 9.9% (CI, 5.8 to 17.1) vs. 21.4% (CI, 15.4 to 29.6); HR, 0.43 (CI, 0.23 to 0.79); ARR, 11.4 (CI, 2.6 to 20.2) Age <65 yrs: cumulative incidence, 21.5% (CI, 15.9 to 29.2) vs. 39.8% (CI, 32.6 to 48.5); HR, 0.47 (CI, 0.32 to 0.70); ARR, 18.3 (CI, 8.0 to 28.5) Age <65 yrs and low risk: cumulative incidence, 9.5% (CI, 4.4 to 20.4) vs. 20.6% (CI, 12.8 to 33.0); HR, 0.41 (CI, 0.18 to 0.95); ARR, 11.1 (CI, -1.0 to 23.2) Age >65 yrs: cumulative incidence, 22.1% (CI, 16.6 to 29.4) vs. 27.5% (CI, 21.5 to 35.1); HR, 0.77 (CI, 0.51 to 1.15); ARR, 5.4 (CI, -3.9 to 14.6) Age >65 yrs and low risk: cumulative incidence, 10.5% (CI, 4.8 to 23.0) vs. 21.8% (CI, 13.9 to 34.3); HR, 0.46 (CI, 0.19 to 1.11); ARR, 11.3 (CI, -1.6 to 24.1)			

Author, Year ***Title***	**Study name**	**Inclusion criteria**	**Exclusion criteria**	**Number screened/eligible/ enrolled**	**Subject age & race Stage at diagnosis Screen detected**	**Country and setting**	**Sponsor**	**Variables adjusted for in analysis**
Iversen et al, 1995[41] Other publications: Byar et al, 1981[37] Graversen et al, 1990[38]	Veterans Administration Cooperative Urological Research Group (VACURG)	Newly diagnosed and untreated stage I (no palpable tumor on digital rectal exam) or II (palpable tumor believed to be confined within prostatic capsule) prostate cancer with no metastases and normal prostatic acid phosphatase level	None reported	NR/NR/142	Mean age: 64 yrs Race: NR Stage I: n=76 Stage II: n=66 Screen detected: no	United States 15 Veterans Health Administration hospitals	Veterans Health Administration	Not applicable (RCT)
	Subgroup analyses	**Intervention type**	**Outcomes method of ascertainment**	**Results**			**Mean duration and loss to followup**	**Quality rating**
	None	Radical prostatectomy (n=74) Watchful waiting (n=68)	All-cause mortality Prostate cancer mortality Distant metastases	All-cause mortality, radical prostatectomy vs. watchful waiting Median duration of survival: 10.6 yrs vs. 8 yrs; p=NS			Duration: 23 yrs (range, 19-27) Loss to followup: 22% (31/142)	Poor

Author, Year ***Title***	**Study name**	**Inclusion criteria**	**Exclusion criteria**	**Number screened/eligible/ enrolled**	**Subject age & race Stage at diagnosis Screen detected**	**Country and setting or data source**	**Sponsor**	**Variables adjusted for in analysis**
Observational Studies								

Appendix C1. Randomized, Controlled Trials and Cohort Studies of Treatment Benefits

Albertsen et al, 2007[42]	Study not named	Age ≤75 yrs diagnosed with prostate cancer between January 1, 1990 and December 31, 1992	Advanced prostate cancer or initial PSA of ≥50 ng/mL	3739/1862/1618	Median age: 68 yrs Race: NR 4% Gleason score 2-4 6% Gleason score 5 47% Gleason score 6 26% Gleason score 7 17% Gleason score 8-10 Screen detected: unclear	United States Connecticut Tumor Registry	AHRQ; Catherine Weldon Donaghue Foundation Grant; Veterans Affairs Health Services Research and Development Service	Gleason score, PSA, clinical stage, age at diagnosis, Charlson comorbidity score
	Subgroup analyses	**Intervention type**	**Outcomes method of ascertainment**	**Results**			**Mean duration and loss to followup**	**Quality rating**
	None	No initial therapy (n=114) Surgery (n=802) Radiation (n=702)	Prostate cancer mortality Connecticut Department of Public Health Records	Prostate cancer mortality Surgery vs. radiation: rate ratio, 2.2 (CI, 1.6 to 3.1) Surgery vs. observation: rate ratio, 3.4 (CI, 1.9 to 5.9) No initial therapy vs. radiation: rate ratio, 1.5 (CI, 0.9 to 2.6) Estimated 10-yr absolute rate of prostate cancer mortality: surgery, 4% vs. radiation, 9% vs. observation, 14%			Duration: varied according to treatment group; median, 13.1 to 13.6 yrs Loss to followup: none reported	Fair
Author, Year ***Title***	**Study name**	**Inclusion criteria**	**Exclusion criteria**	**Number screened/eligible/ enrolled**	**Subject age & race Stage at diagnosis Screen detected**	**Country and setting or data source**	**Sponsor**	**Variables adjusted for in analysis**
Ladjevardi et al, 2009[43]	Study not named	Age <75 yrs; stage T1-T3, NO/NX, MO/MX; PSA <20 ng/mL	None reported	81,195/34,902/31,903	Mean age: 65 yrs Race: NR <1% T0 49% T1 35% T2 15% T3 <1% TX Screen detected: 33%; others were symptomatic or detected for other reasons	Sweden National Prostate Cancer Registry	No sponsor	Age, Gleason score, PSA
	Subgroup analyses	**Intervention type**	**Outcomes method of ascertainment**	**Results**			**Mean duration and loss to followup**	**Quality rating**
	Risk Gleason score 7 Gleason score 8-10	Conservative management (watchful waiting [n=9435] and palliative treatment, including androgen deprivation [n=3210]) Radical prostatectomy (n=12,950) Radiotherapy (n=6308; EBRT n=4443; brachytherapy n=1865)	All-cause mortality Registered deaths	All-cause mortality vs. conservative management (reference standard) *Radical prostectomy* Gleason score 2-10: HR, 0.41 (CI, 0.36 to 0.48) Gleason score 7: HR, 0.78 (CI, 0.63 to 0.97) Gleason score 8-10: HR, 0.65 (CI, 0.47 to 0.90) *Radiotherapy* Gleason score 2-10: HR, 0.62 (CI, 0.54 to 0.71) Gleason score 7: HR, 0.81 (CI, 0.66 to 0.99) Gleason score 8-10: HR, 0.71 (CI, 0.55 to 0.92)			Duration: median, 4 yrs (range, 0-12) Loss to followup: none reported	Fair

Appendix C1. Randomized, Controlled Trials and Cohort Studies of Treatment Benefits

Author, Year *Title*	Study name	Inclusion criteria	Exclusion criteria	Number screened/eligible/ enrolled	Subject age & race Stage at diagnosis Screen detected	Country and setting or data source	Sponsor	Variables adjusted for in analysis
Lu-Yao et al, 2008[44]	Study not named	Age >66 yrs diagnosed with T1-T2 prostate cancer between 1992 and 2002	Death within 180 days of diagnosis; use of radiation or prostatectomy within 180 days of diagnosis; no Medicare Part A or B coverage; missing data; unknown cancer grade; initiation of ADT before cancer diagnosis	89,877/22,266/19,271	Mean age; 78 yrs 11% black (other races NR) 58% T1 42% T2 Screen detected: unclear	United States SEER data	US Army Medical Research Acquisition Activity; Cancer Institute of New Jersey; US Department of Defense; Ohl Foundation; National Cancer Institute	Instrumental variable analysis (covariates in analysis included age, race, comorb-idity status, cancer stage, cancer grade, income status, urban resident, marital status, and year of diagnosis)
	Subgroup analyses	**Intervention type**	**Outcomes method of ascertainment**	**Results**			**Mean duration and loss to followup**	**Quality rating**
	Risk Moderately differentiated tumors Poorly differentiated tumors	Conservative management (no use of surgery, radiation, or androgen deprivation; n=11,404) Primary androgen deprivation therapy (PADT; n=7867)	Prostate cancer mortality All-cause mortality SEER data (confirmed in medical records for 87%-88% of cases)	All-cause mortality Conservative management, 6316/66,567 events per person-yr (rate, 9.5/100) vs. PADT, 4729/39,767 events per person-yr (rate, 11.9/100); HR, 1.17 (CI, 1.12 to 1.21) Moderately differentiated tumors: HR, 1.15 (CI, 1.10 to 1.21) Poorly differentiated tumors: HR, 1.04 (CI, 0.97 to 1.13) Prostate cancer mortality Conservative management, 693/55,424 events per person-yr (rate, 1.3/100) vs. PADT, 867/32,744 events per person-yr (rate 2.6/100); HR, 1.76 (CI, 1.59 to 1.95) Moderately differentiated tumors: HR, 1.83 (CI, 1.58 to 2.12) Poorly differentiated tumors: HR, 1.12 (CI, 0.96 to 1.29)			Duration: median, 7 yrs Loss to followup: none reported	Fair
Author, Year ***Title***	**Study name**	**Inclusion criteria**	**Exclusion criteria**	**Number screened/eligible/ enrolled**	**Subject age & race Stage at diagnosis Screen detected**	**Country and setting or data source**	**Sponsor**	**Variables adjusted for in analysis**
Merglen et al, 2007[45]	Study not named	Patients in Geneva Cancer Registry between 1989-1998	Diagnosis of prostate cancer at time of death; previous; previous invasive cancer except non-melanoma skin cancer	1,740/ 1,495 844	Mean age 71 years (range 44-97 years) Race not reported 29% Stage 1 40% Stage 2 31% Stage 3 PSA <10 22% PSA 11-29 28% PSA >30 23% PSA unknown 27% Screen detected: unclear	Switzerland Geneva Cancer Registry data	Swiss National Science Foundation	Age, period of diagnosis, method of detection, lymph node status, clinical tumor stage, differentiation, and PSA level

Appendix C1. Randomized, Controlled Trials and Cohort Studies of Treatment Benefits

Author, Year *Title*	Subgroup analyses	Intervention type	Outcomes method of ascertainment	Results	Mean duration and loss to followup	Quality rating
Merglen et al, 2007[45]	Risk Gleason score <7 Gleason score ≥7 Age <70 yrs ≥70 yrs	Watchful waiting (n=378) Prostatectomy (n=158) Any EBRT (n=205; EBRT alone [n=152] or EBRT + ADT [n=53]) ADT (n=72) Other treatment (n=31; not described)	Prostate cancer mortality All-cause mortality Registry data	Prostate cancer mortality, 5 yrs Prostatectomy (reference standard): 8/158 (5%) vs.: All EBRT: 13/205 (6%); HR, 1.3 (CI, 0.6 to 3.5) EBRT alone: 10/152 (7%); HR, 1.3 (CI, 0.5 to 3.4) EBRT + ADT: 3/53 (6%); HR, 1.5 (CI, 0.4 to 6.1) Watchful waiting: 43/378 (11%); HR, 1.8 (CI, 0.8 to 4.1) ADT: 18/72 (25%); HR, 3.5 (CI, 1.6 to 9.6) Other treatment: 8/31 (26%); HR, 5.8 (CI, 2.2 to15.3) Prostate cancer mortality, 10 yrs (all ages) Prostatectomy (reference standard): 15/158 (9%) vs.: All EBRT: 36/205 (18%); HR, 2.3 (CI, 1.2 to 4.3) EBRT alone: 30/152 (20%); HR, 2.4 (CI, 1.2 to 4.6) EBRT + ADT: 6/53 (11%); HR, 1.9 (CI, 0.7 to 5.1) Watchful waiting: 70/378 (11%); HR, 2.0 (CI, 1.1 to 3.8) ADT: 28/72 (25%); HR, 4.4 (CI, 2.2 to 8.8) Other treatment: 8/31 (26%); HR, 3.1 (CI, 1.3 to 7.5) Prostate cancer mortality, 10 yrs (ages <70 yrs) Prostatectomy (reference standard): 5/118 (4%) vs.: All EBRT: 19/125 (15%); HR, 6.7 (CI, 2.2 to 20.7) EBRT alone: 15/89 (17%); HR, 6.9 (CI, 2.2 to 21.5) EBRT + ADT: 4/36 (11%); HR, 4.2 (CI, 1.0 to 10.3) Watchful waiting: 13/104 (13%); HR, 8.4 (CI, 2.4 to 28.5) ADT: 8/18 (44%); HR, 10.7 (CI, 3.2 to 36.2) Other treatment: 5/17 (29%); HR, 7.0 (CI, 1.9 to 25.9) Prostate cancer mortality, 10 yrs (ages ≥70 yrs) Prostatectomy (reference standard): 10/40 (25%) vs.: All EBRT: 17/80 (22%); HR, 1.0 (CI, 0.4 to 2.4) EBRT alone: 15/63 (24%); HR, 1.1 (CI, 0.5 to 2.6) EBRT + ADT: 2/17 (12%); HR, 1.4 (CI, 0.3 to 6.9) Watchful waiting: 57/274 (21%); HR, 0.8 (CI, 0.4 to 1.7) ADT: 20/54 (37%); HR, 1.7 (CI, 0.7 to 3.8) Other treatment: 3/14 (21%); HR, 1.8 (CI, 0.5 to 7.3) Prostate cancer mortality, 10 yrs (Gleason score <7) Prostatectomy (reference standard): 9/112 (8%) vs.: All EBRT: 17/143 (12%); HR, 1.7 (CI, 0.7 to 3.9) EBRT alone: 15/110 (14%); HR, 1.8 (CI, 0.7 to 4.2) EBRT + ADT: 2/33 (6%); HR, 1.2 (CI, 0.2 to 5.7) Watchful waiting: 31/225 (14%); HR, 2.0 (CI, 0.9 to 4.5) ADT: 12/31 (39%); HR, 3.9 (CI, 1.5 to 10.5) Other treatment: 2/13 (15%); HR, 1.0 (CI, 0.2 to 4.7) Prostate cancer mortality, 10 yrs (Gleason score ≥7) Prostatectomy (reference standard): 4/31 (13%) vs.: All EBRT: 10/32 (31%); HR, 7.1 (CI, 1.7 to 29.9) EBRT alone: 6/14 (43%); HR, 6.9 (CI, 1.5 to 32.9) EBRT + ADT: 4/18 (22%); HR, 7.3 (CI, 1.4 to 38.1) Watchful waiting: 28/76 (37%); HR, 4.3 (CI, 1.1 to 17.0) ADT: 13/25 (52%); HR, 10.6 (CI, 2.5 to 45.5) Other treatment: 6/14 (43%); HR, 26.7 (CI, 5.7 to 126.0) All-cause mortality, 5 yrs Prostatectomy (reference standard): 21/158 (13%) vs.:	Duration: mean, 7 yrs (range, 0-16) Loss to followup: 6% (47/844)	Fair

Appendix C1. Randomized, Controlled Trials and Cohort Studies of Treatment Benefits

				All EBRT: 26/205 (13%); HR, 0.7 (CI, 0.3 to 1.5) EBRT alone: 22/152 (14%); HR, 0.7 (CI, 0.3 to 1.6) EBRT + ADT: 4/53 (8%); HR, 0.4 (CI, 0.1 to 2.8) Watchful waiting: 147/378 (39%); HR, 1.4 (CI, 0.7 to 2.5) ADT: 36/72 (50%); HR, 1.4 (CI, 0.7 to 3.0) Other treatment: 11/31 (35%); HR, 1.5 (CI, 0.4 to 5.3) All-cause mortality, 10 yrs Prostatectomy (reference standard): 34/158 (22%) vs.: All EBRT: 71/205 (35%); HR, 1.1 (CI, 0.6 to 2.0) EBRT alone: 62/152 (41%); HR, 1.2 (CI, 0.7 to 2.2) EBRT + ADT: 9/53 (17%); HR, 0.7 (CI, 0.2 to 2.4) Watchful waiting: 223/378 (60%); HR, 1.5 (CI, 0.9 to 2.5) ADT: 54/72 (75%); HR, 1.6 (CI, 0.8 to 2.9) Other treatment: 11/31 (35%); HR, 0.9 (CI, 0.3 to 2.9)			
Author, Year ***Title***	**Study name**	**Inclusion criteria**	**Exclusion criteria**	**Number screened/eligible/ enrolled**	**Subject age & race Stage at diagnosis Screen detected**	**Country and setting or data source**	**Sponsor**	**Variables adjusted for in analysis**
Schymura et al, 2010[46]	CDC-NPCR Breast, Colon and Prostate Cancer Data Quality and Patterns of Care Study (PoC1)	Diagnosis in 1997 with first primary prostate cancer; clinically localized (clinically inapparent or T1c or T2); no evidence of metastasis; alive 6 months following diagnosis	None reported	3504/3504/3328 (for mortality outcome, n=3297)	Mean age: NR 18% <60 yrs 17% 60-64 yrs 22% 65-69 yrs 21% 70-74 years 14% 75-79 yrs 8% ≥80 yrs 80% white 14% black 3% Hispanic 2% other 1% unknown 57% PSA <10 ng/mL 26% PSA 10-20 ng/mL 11% PSA >20 ng/mL 13% PSA unknown Screen detected: 63% (26% not screen detected, 11% unknown method of detection)	United States Database registries from California, Colorado, Illinois, Louisiana, New York, Rhode Island, and South Carolina	CDC; States of California, Colorado, Illinois, Louisiana, New York, Rhode Island, and South Carolina	Age at diagnosis, race/ethnicity, marital status, State, PSA value, Gleason score, comorbidity score, time since diagnosis
	Subgroup analyses	**Intervention type**	**Outcomes method of ascertainment**	**Results**			**Mean duration and loss to followup**	**Quality rating**
	None	Watchful waiting (n=614) Radical prostatectomy (n=1310) Radiation therapy (EBRT or brachy-therapy; n=1037) ADT (n=339)	All-cause mortality Registry data	All-cause mortality, 5 yrs Radical prostatectomy (reference standard): 6% vs.: Watchful waiting: 25%; HR, 2.3 (CI, 1.7 to 3.12) Radiation: 14%; HR, 1.66 (CI, 1.24 to 2.21) Hormone therapy: 35%; HR, 2.83 (CI, 2.06 to 3.9)			Duration: 5 yrs Loss to followup: 3/3328 (0.9%)	Fair

Appendix C1. Randomized, Controlled Trials and Cohort Studies of Treatment Benefits

Author, Year *Title*	Study name	Inclusion criteria	Exclusion criteria	Number screened/eligible/ enrolled	Subject age & race Stage at diagnosis Screen detected	Country and setting or data source	Sponsor	Variables adjusted for in analysis
Stattin et al, 2010[10]	National Prostate Cancer Register (NPCR) of Sweden Follow-up Study	Age ≤70 yrs; registration in NPCR between January 1, 1997 and December 31, 2002; stage T1-T2; no lymph node involvement or metastases; PSA <20 ng/mL	Primary hormone treatment; poorly differentiated tumors	8304/7960/6849	Mean age: 63 yrs Race: NR 59% T1 41% T2 Mean PSA: 8.2 ng/mL Screen detected: unclear	Sweden National Prostate Cancer Registry	Swedish Research Council; Swedish Cancer Foundation; Vasterbotten County Council	Prostate cancer risk category, Charlson comorbidity index, socioeconomic status
	Subgroup analyses	**Intervention type**	**Outcomes method of ascertainment**	**Results**			**Mean duration and loss to followup**	**Quality rating**
	Risk Low risk (T1a, b, or c; Gleason score 2-6 or WHO grade I or II; and PSA <10 ng/mL) Intermediate risk (Gleason score 7, stage T2, or PSA ≥10 ng/mL)	Surveillance (n=2021) Radical prostatectomy (n=3399) Radiation (n=1429)	Prostate cancer mortality All-cause mortality	Prostate cancer mortality Surveillance (reference standard): 3.6% (CI, 2.7 to 4.8) vs.: Radical prostatectomy: 2.4% (CI, 1.8 to 3.3); HR, 0.49 (CI, 0.34 to 0.71) Radiation: 3.3% (CI, 2.5 to 5.7); HR, 0.70 (CI, 0.45 to 1.09) Prostate cancer mortality, low-risk patients Surveillance (reference standard): 2.4% (CI, 1.2 to 4.1) vs.: Radical prostatectomy: 0.4% (CI, 0.13 to 0.97); HR, 0.29 (CI, 0.09 to 0.87) Radiotherapy: 1.8% (CI, 0.65 to 4.0); HR, 0.94 (CI, 0.31 to 2.85) Prostate cancer mortality, intermediate-risk patients Surveillance (reference standard): 5.2% (CI, 3.7 to 6.9) vs.: Radical prostatectomy: 3.4% (CI, 2.5 to 4.7); HR, 0.53 (CI, 0.35 to 0.80) Radiation: 3.8% (CI, 2.6 to 5.4); HR, 0.66 (CI, 0.42 to 1.06) All-cause mortality Surveillance (reference standard): 23.4% (CI, 21.3 to 25.8) vs.: Radical prostatectomy: 11.3% (CI, 10.0 to 12.9); HR, 0.49 (CI, 0.41 to 0.57) Radiation: 18.3% (CI, 15.7 to 21.3); HR, 0.68 (CI, 0.57 to 0.82)		Duration: median, 8.2 yrs Loss to followup: none reported	Fair
Author, Year ***Title***	**Study name**	**Inclusion criteria**	**Exclusion criteria**	**Number screened/eligible/ enrolled**	**Subject age & race Stage at diagnosis Screen detected**	**Country and setting or data source**	**Sponsor**	**Variables adjusted for in analysis**
Tewari et al, 2007[47]	Study not named	Registered in the Henry Ford Health System with ICD code 185 (diagnosis of prostate cancer) between January 1, 1980 and December 31, 1997 with tumor grade and Gleason score; localized, grade 3 or Gleason score 8-10	Age >75 yrs; grade 1 or 2 or Gleason score <8; in-complete followup; bone metastases within 1 year of diagnosis	4387/3371/453	Mean age: 63 yrs 100% stage 3 28% adjuvant hormone therapy (40% watchful waiting; 26% radiotherapy; 22% prostatectomy patients) Screen detected: unclear	United States Henry Ford Health System data	Not reported	Propensity analysis (propensity score based on age at diagnosis, race, socioecononomic status, Charlson comorbidity index, and year of diagnosis)

Appendix C1. Randomized, Controlled Trials and Cohort Studies of Treatment Benefits

Author, Year *Title*	Subgroup analyses	Intervention type	Outcomes method of ascertainment	Results	Mean duration and loss to followup	Quality rating
Tewari et al, 2007[47]	None	Conservative management (n=197) Radiotherapy (n=137) Radical prostatectomy (n=119)	Prostate cancer mortality All-cause mortality Registry data	Prostate cancer mortality Conservative management (reference standard): 85/197 (43%) vs.: Radical prostatectomy: 18/119 (15%); HR, 0.32 (CI, 0.17 to 1.22; p=0.16) Radiotherapy: 23/137 (17%); HR, 0.63 (CI, 0.38 to 1.06; p=0.81) Radical prostatectomy vs. radiotherapy: HR, 0.51 (CI, 0.26 to 1.01; p=0.05) All-cause mortality Conservative management (reference standard): 139/197 (71%) vs.: Radical prostatectomy: 27/119 (23%); HR, 0.32 (CI, 0.20 to 0.51; p=0.001) Radiotherapy: 58/137 (42%); HR, 0.70 (CI, 0.50 to 0.99; p=0.04) Radical prostatectomy vs. radiotherapy: HR, 0.46 (CI, 0.28 to 0.75; p=0.002)	Duration: varied by group - median 4 years conservative management, 6 years radical prostatectomy, 5 years radiotherapy Loss to follow-up: none reported	Fair

Author, Year *Title*	Study name	Inclusion criteria	Exclusion criteria	Number screened/eligible/ enrolled	Subject age & race Stage at diagnosis Screen detected	Country and setting or data source	Sponsor	Variables adjusted for in analysis
Wong et al, 2006[48]	Study not named	Age 65-80 yrs; prostate cancer diagnosis between 1991 and 1999; well or moderately differentiated T1 or T2 tumors	Diagnosis of prostate cancer at autopsy or time of death; end-stage renal disease (per Medicare); initial enrollment in managed care 3 mo prior to 6 mo after diagnosis; T3, T4, poorly differentiat-ed, or anaplastic tumors; metastatic disease; unknown tumor size or grade; disability; age >80 yrs; use of hormone therapy; history of cancer; missing data; death within 1 year of diagnosis	111,640/44,603/44,630	Mean age: 72 yrs (73 yrs in observation group; 71 yrs in active treatment group; p≤0.01) 80% white 10% black 10% other 55% stage ≤T2a 45% stage T2b-T2c Screen detected: unclear	United States SEER/Medicare data	NIH; Center for Population Health and Health Disparities (University of Pennsylvania)	Propensity-adjusted (propensity score based on age at diagnosis, SEER site, year of diagnosis, tumor size, tumor grade, marital status, residence in urban setting, race, income, educational achievement, and comorbidities)

Subgroup analyses	Intervention type	Outcomes method of ascertainment	Results	Mean duration and loss to followup	Quality rating
Age 65-67 yrs 68-70 yrs 71-73 yrs 74-77 yrs 78-80 yrs	Observation (n=12,608) Active treament (n=32,022; includes radical prostatectomy [n=13,292] and EBRT or brachytherapy [n=18,249], alone or in combination)	Prostate cancer mortality All-cause mortality Registry data	Prostate cancer mortality Active treatment, 612/32,022 (2%) vs. observation, 314/12,608 (3%); HR, 0.67 (CI, 0.58 to 0.77; adjusted for propensity score only) All-cause mortality Active treatment, 7639/32,022 (24%) vs. observation, 4663/12,608 (37%); HR, 0.69 (CI, 0.66 to 0.72) Radical prostatectomy vs. observation: HR, 0.50 (CI, 0.47 to 0.53) Radiation vs. observation: HR, 0.81 (CI, 0.78 to 0.85)	Duration: 12 yrs Loss to followup: none reported	Fair

Appendix C1. Randomized, Controlled Trials and Cohort Studies of Treatment Benefits

				All-cause mortality, active treament vs. observation, stratified by age Age 65-67: HR, 0.67 Age 68-70: HR, 0.61 Age 71-73: HR, 0.70 Age 74-77: HR, 0.71 Age 78-80: HR, 0.74 Median survival Observation, 47 months vs. active treatment, 55 months; p<0.001				
Author, Year ***Title***	**Study name**	**Inclusion criteria**	**Exclusion criteria**	**Number screened/eligible/ enrolled**	**Subject age & race Stage at diagnosis Screen detected**	**Country and setting or data source**	**Sponsor**	**Variables adjusted for in analysis**
Zhou et al, 2008[49]	Study not named	Age ≥65 yrs residing in Ohio; prostate cancer diagnosis between January 1, 1999 and December 31, 2001; continuous Medicare coverage for at least 6 months prior to diagnosis	Initial enrollment in Medicare-managed care program 6 mo prior or 1 mo after prostate cancer diagnosis; diagnosis at time of death	10,632/10,179/10,179 (8255 local-regional prostate cancer)	Mean age: NR; for total cohort (including 1924 patients with distant or unknown stage): 21% 65-69 yrs 32% 70-74 yrs 46% ≥75 yrs 9% black 91% other (primarily white) 66% Gleason score <7 Screen detected: unclear	United States Ohio Cancer Incidence Surveillance System/Medicare data	National Cancer Institute; National Institutes of Health Cancer-Aging Research Development Grant	Age, race, tumor stage, Gleason score, pretreatment comorbidity
	Subgroup analyses	**Intervention type**	**Outcomes method of ascertainment**	**Results**			**Mean duration and loss to followup**	**Quality rating**
	None	No treatment (no definitive therapy within 6 mo of diagnosis, n=1716) Monotherapy Radical prostatectomy (n=889) EBRT (n=783) Brachytherapy (n=595) ADT (n=2049) Combination therapy Radical prostatectomy + EBRT, ADT, or both (n=181) EBRT + ADT (n=1286) Brachytherapy + EBRT or ADT (n=756)	Prostate cancer mortality All-cause mortality Registry data	Prostate cancer mortality vs. no treatment (localized disease only) *Monotherapy* Radical prostatectomy: HR, 0.25 (CI, 0.13 to 0.48; p<0.0001) EBRT: HR, 0.66 (CI, 0.41 to 1.04; p=0.07) Brachytherapy: HR, 0.45 (CI, 0.23 to 0.87; p=0.02) ADT: HR, 1.32 (CI, 1.01 to 1.73; p=0.05) All-cause mortality vs. no treatment (localized disease only) *Monotherapy* Radical prostatectomy: HR, 0.32 (CI, 0.24 to 0.41; p<0.0001) EBRT: HR, 0.63 (CI, 0.53 to 0.75; p<0.0001) Brachytherapy: HR, 0.40 (CI, 0.32 to 0.52; p<0.0001) ADT: HR, 0.89 (CI, 0.80 to 0.98; p=0.02)			Duration: 7 yrs Loss to followup: none reported	Fair

Abbreviations: ADT = androgen deprivation therapy; ARR = adjusted relative risk; CI = confidence interval; EBRT = external beam radiation therapy; HR = hazard ratio; NR = not reported; NS = not signficant; PSA = prostate-specific antigen; RCT = randomized, controlled trial; SEER = Surveillance, Epidemiology, and End Results; WHO = World Health Organization.

Appendix C2. Harms of Radical Prostatectomy, Radiation, Androgen Deprivation Therapy, and Cryotherapy Versus Watchful Waiting

Author, year Followup	General QOL scores	Disease-specific QOL scores	Urinary incontinence	Erectile dysfunction	Other outcomes
Radical prostatectomy vs. watchful waiting					
Randomized, controlled trials					
Johansson et al, 2009*[31] and Steineck et al, 2002*[50] 8 years	NR	NR	2–3 yr followup Weak urinary stream: 12/51 (24%) vs. 19/52 (37%); RR, 0.6 (CI, 0.4 to 1.2) Urinary incontinence: 22/52 (42%) vs. 6/53 (11%); RR, 3.7 (CI, 1.6 to 8.5) 4–5 yr followup Weak urinary stream: 17/55 (31%) vs. 23/52 (44%); RR, 0.7 (CI, 0.4 to 1.2) Urinary incontinence: 26/55 (47%) vs. 15/54 (28%); RR, 1.7 (CI, 1.0 to 2.8) 6–8 yr followup Weak urinary stream: 16/56 (29%) vs. 26/49 (53%); RR, 0.5 (CI, 0.3 to 0.9) Urinary incontinence: 31/55 (56%) vs. 12/48 (25%); RR, 2.3 (CI, 1.3 to 3.9) Other outcomes (4 yr followup) Moderate or severe symptoms: 55/159 (35%) vs. 74/150 (49%); RR, 0.7 (CI, 0.5 to 0.9) Leakage, once a week or more: 80/164 (49%) vs. 33/155 (21%); RR, 2.3 (CI, 1.6 to 3.2) Regular dependence on protective aids: 71/165 (43%) vs. 16/154 (10%); RR, 4.1 (CI, 2.5 to 6.8) Regular dependence on diaper or urine bag: 23/165 (14%) vs. 1/154 (1%); RR, 21.5 (CI, 2.9 to 157.0) Urinary problems moderately or severely affecting sex life: 15/159 (9%) vs. 5/158 (3%); RR, 3.0 (CI, 1.1 to 8.0)	2–3 yr followup Erectile dysfunction: 41/51 (80%) vs. 19/51 (37%); RR, 2.2 (CI, 1.5 to 3.2) 4–5 yr followup Erectile dysfunction: 42/54 (78%) vs. 23/54 (43%); RR, 1.8 (CI, 1.3 to 2.6) 6–8 yr followup Erectile dysfunction: 45/54 (83%) vs. 29/53 (55%); RR, 1.5 (CI, 1.2 to 2.0) Other outcomes (4 yr followup) Voluntary penile stiffness seldom or never sufficient: 135/158 (85%) vs. 79/158 (50%); RR, 1.7 (CI, 1.4 to 2.0) Penile stiffness at awakening seldom or never sufficient: 131/158 (83%) vs. 93/157 (59%); RR, 1.4 (CI, 1.2 to 1.6) Spontaneous penile stiffness seldom or never sufficient: 141/157 (90%) vs. 93/152 (61%); RR, 1.5 (CI, 1.3 to 1.7) Erectile function seldom or never sufficient: 129/161 (80%) vs. 71/158 (45%); RR, 1.8 (CI, 1.5 to 2.2) Great distress from erectile dysfunction: 45/160 (28%) vs. 25/153 (16%); RR, 1.7 (CI, 1.1 to 2.7) Insufficient maintenance of erection: 24/44 (55%) vs. 29/98 (30%); RR, 1.8 (CI, 1.2 to 2.8) Intercourse less than once a month: 130/162 (80%) vs. 91/154 (59%); RR, 1.4 (CI, 1.2 to 1.6) No orgasm in past 6 months: 101/162 (62%) vs. 48/153 (31%); RR, 2.0 (CI, 1.5 to 2.6)	2–3 yr followup Fecal leakage: 1/52 (2%) vs. 3/53 (6%); RR, 0.3 (CI, 0.04 to 3.2) Moderate or high anxiety: 8/51 (16%) vs. 17/52 (33%); RR, 0.5 (CI, 0.2 to 1.0) Moderate or high level of depression: 13/51 (26%) vs. 23/52 (44%); RR, 0.6 (CI, 0.3 to 1.0) Low or moderate self-assessed QOL: 18/51 (35%) vs. 19/52 (36%); RR, 1.0 (CI, 0.6 to 1.6) 4–5 yr followup Fecal leakage: 0/53 (0%) vs. 4/53 (8%); RR, not calculable Moderate or high anxiety: 15/54 (28%) vs. 12/53 (23%); RR, 1.2 (CI, 0.6 to 2.4) Moderate or high level of depression: 26/54 (48%) vs. 16/53 (30%); RR, 1.6 (CI, 1.0 to 2.6) Low or moderate self-assessed QOL: 24/54 (44%) vs. 22/51 (43%); RR, 1.0 (CI, 0.7 to 1.6) 6–8 yr followup Fecal leakage: 0/57 (0%) vs. 2/51 (3.9%); RR, not calculable Moderate or high anxiety: 13/57 (23%) vs. 19/52 (36%); RR, 0.6 (CI, 0.3 to 1.1) Moderate or high level of depression: 18/57 (32%) vs. 21/52 (40%); RR, 0.8 (CI, 0.5 to 1.3) Low or moderate self-assessed QOL: 22/54 (42%) vs. 27/48 (56%); RR, 0.8 (CI, 0.5 to 1.1) Other outcomes (4 yr followup) Decreased physical capacity: 89/164 (54%) vs. 89/157 (57%); RR, 1.0 (CI, 0.8 to 1.2) Low or moderate physical well-being: 68/164 (41%) vs. 78/157 (50%); RR, 0.8 (CI, 0.7 to 1.1) Distress from bowel symptoms: 5/159 (3%) vs. 10/156 (6%); RR, 0.49 (CI, 0.17 to 1.40) High level of anxiety (score >90th percentile on State-Trait Anxiety Inventory): 15/159 (9%) vs. 16/157 (10%); RR, 0.9 (CI, 0.5 to 1.8) High level of depression (score >90th percentile, Center for Epidemiological Studies Measure of Depression): 10/153 (7%) vs. 16/151 (11%); RR, 0.6 (CI, 0.3 to 1.3) Low or moderate psychological well-being: 57/164 (35%) vs. 57/158 (36%); RR, 1.0 (CI, 0.7 to 1.3) Low or moderate subjective QOL: 64/159 (40%) vs. 68/151 (45%); RR, 0.9 (CI, 0.7 to 1.2)

Appendix C2. Harms of Radical Prostatectomy, Radiation, Androgen Deprivation Therapy, and Cryotherapy Versus Watchful Waiting

Author, year Followup	General QOL scores	Disease-specific QOL scores	Urinary incontinence	Erectile dysfunction	Other outcomes
Cohort studies					
Bacon et al, 2001[51] Up to 5 years	SF-36 mean scores PCS: 52 vs. 49 MCS: 55 vs. 55 Physical function: 90 vs. 79 Physical role function: 86 vs. 85 Bodily pain: 85 vs. 81 General health: 80 vs. 71 Vitality: 71 vs. 68 Social function: 92 vs. 87 Emotional role function: 90 vs. 90 Mental health: 84 vs. 83 CARES-SF mean scores† Physical: 0.20 vs. 0.16 Sexual problems: 1.04 vs. 0.70 Global summary: 0.26 vs. 0.19	UCLA PCI mean scores Urinary function: 76 vs. 93 Urinary bother: 82 vs. 89 Sexual function: 26 vs. 54 Sexual bother: 43 vs. 74 Bowel function: 86 vs. 91 Bowel bother: 86 vs. 89	NR	NR	NR
Galbraith et al, 2001[54] 1.5 years	SF-36 mean scores Physical function: 81 vs. 75 Physical role function: 55 vs. 65 Bodily pain: 85 vs. 84 General health: 58 vs. 54 Vitality: 62 vs. 64 Emotional role function: 80 vs. 70 Mental health: 77 vs. 79 Quality of Life Index mean scores Overall QOL: 57 vs. 59	PTSS mean scores Sexual symptoms: 4.0 vs. 3.6 Urinary symptoms: 1.7 vs. 2.0 Gastrointestinal symptoms: 1.3 vs. 1.3	NR	NR	NR
Hoffman et al, 2003[55] 2 years	NR	NR	Urinary leakage, daily or more often: 35% (484/1373) vs. 8% (19/230)	Erectile dysfunction, no erections at all: 55% (757/1373) vs. 26% (60/230)	Cancer treatment limits activities some or a lot: 14% (196/1373) vs. 4% (10/230) Bowel urgency, almost every day: 0.8% (11/1373) vs. 0.4% (1/230)
Litwin et al, 1995a[56] 5.6 years	SF-36 mean scores Physical function: 75 vs. 71 Physical role function: 61 vs. 55 Bodily pain: 77 vs. 74 General health: 65 vs. 63 Vitality: 60 vs. 60 Social function: 80 vs. 80 Emotional role function: 70 vs. 57 Mental health: 76 vs. 77 CARES-SF mean scores† Physical: 0.64 vs. 0.79 Psychosocial: 0.71 vs. 0.73 Marital: 0.56 vs. 0.70 Sexual: 1.32 vs. 1.12	UCLA-PCI Urinary function: 65 vs. 86 Urinary bother: 68 vs. 80 Sexual function: 19 vs. 41 Sexual bother: 13 vs. 37 Bowel function: 82 vs. 84 Bowel bother: 80 vs. 85	NR	NR	NR

Appendix C2. Harms of Radical Prostatectomy, Radiation, Androgen Deprivation Therapy, and Cryotherapy Versus Watchful Waiting

Author, year Followup	General QOL scores	Disease-specific QOL scores	Urinary incontinence	Erectile dysfunction	Other outcomes
Litwin et al, 1995b[57] 5.6 years	NR	NR	Urinary control Total control: 33/94 (35%) vs. 39/63 (62%) Occasional dribbling: 42/94 (45%) vs. 18/63 (29%) Frequent dribbling: 10/94 (11%) vs. 4/63 (6%) No control: 9/94 (10%) vs. 2/63 (3%)	Sexual function Very good: 5/96 (5%) vs. 4/63 (6%) Good: 6/96 (6%) vs. 9/63 (14%) Fair: 9/96 (9%) vs. 19/63 (30%) Poor: 12/96 (12%) vs. 7/63 (11%) Very poor: 64/96 (67%) vs. 24/63 (38%)	Rectal urgency Rarely or never: 62/97 (64%) vs. 43/63 (68%) About once/week: 15/97 (15%) vs. 6/63 (10%) More than once/week: 7/97 (7%) vs. 3/63 (5%) About once/day: 9/97 (9%) vs. 8/63 (13%) More than once/day: 4/97 (4%) vs. 3/63 (5%)
Litwin et al, 2002[58] 2 years	SF-36 mean scores Vitality: 73 vs. 66 Social function: 100 vs. 89 Emotional role function: 94 vs. 86 Mental health: 85 vs. 81	NR	NR	NR	NR
Lubeck et al, 1999[59] 2 years	SF-36 mean scores Physical function: 86 vs. 71 Physical role function: 72 vs. 63 Bodily pain: 84 vs. 76 General health: 75 vs. 54 Vitality: 71 vs. 57 Social function: 89 vs. 78 Emotional role function: 84 vs. 73 Mental health: 86 vs. 76	UCLA PCI Urinary function: 71 vs. 87 Urinary bother: 81 vs. 84 Sexual function: 27 vs. 29 Sexual bother: 47 vs. 25 Bowel function: 88 vs. 89 Bowel bother: 90 vs. 90	NR	NR	NR
Schapira et al, 2001[61] 1 year	SF-36 mean scores Physical function: 84 vs. 68 Physical role function: 72 vs. 64 Bodily pain: 78 vs. 68 General health: 71 vs. 68 Vitality: 69 vs. 60 Social function: 88 vs. 86 Emotional role function: 83 vs. 77 Mental health: 77 vs. 81	UCLA PCI mean scores Urinary function: 62 vs. 92 Urinary bother: 67 vs. 84 Sexual function: 20 vs. 36 Sexual bother: 29 vs. 62 Bowel function: 88 vs. 86 Bowel bother: 86 vs. 81	Urinary incontinence 16/36 (44%) vs. 1/25 (4%)	Erectile dysfunction 33/37 (89%) vs. 17/25 (68%)	NR
Siegel et al, 2001[62] 4.4 years	NR	NR	NR	Erectile dysfunction 353/392 (90%) vs. 40/64 (63%)	NR
Smith et al, 2000[63] 3.8 years	SF-36 mean scores Physical function: 87 vs. 85 Physical role function: 78 vs. 80 Bodily pain: 82 vs. 87 General health: 76 vs. 71 Vitality: 67 vs. 69 Social function: 90 vs. 92 Emotional role function: 86 vs. 91 Mental health: 81 vs. 82	UCLA PCI mean scores Urinary function: 75 vs. 94 Urinary bother: 78 vs. 88 Sexual function: 26 vs. 60 Sexual bother: 34 vs. 69	NR	NR	NR

Appendix C2. Harms of Radical Prostatectomy, Radiation, Androgen Deprivation Therapy, and Cryotherapy Versus Watchful Waiting

Author, year Followup	General QOL scores	Disease-specific QOL scores	Urinary incontinence	Erectile dysfunction	Other outcomes
Smith et al, 2009[64] 3 years	SF-36 mean scores *Nerve sparing vs. non-nerve sparing radical prostatectomy vs. watchful waiting* PCS: 50 vs. 49 vs. 47 MCS: 53 vs. 54 vs. 53	UCLA PCI mean scores *Nerve sparing vs. non-nerve sparing radical prostatectomy vs. watchful waiting* Urinary function: 86 vs. 83 vs. 92 Urinary bother: 85 vs. 83 vs. 84 Sexual function: 35 vs. 22 vs. 44 Sexual bother: 52 vs. 54 vs. 66 Bowel function: 88 vs. 89 vs. 87 Bowel bother: 90 vs. 91 vs. 88	Urinary incontinence 111/981 (12%) vs. 6/200 (3%)	Erectile dysfunction 695/981 (71%) vs. 94/200 (47%)	Moderate or severe bowel problems 32/981 (3%) vs. 11/200 (6%)
Talcott et al, 2003[65] 2 years	NR	Urinary incontinence mean scores 23 vs. 18 Sexual function mean scores 69 vs. 51 Bowel problems mean scores 5 vs. 7	NR	NR	NR
Radiotherapy vs. watchful waiting					
Randomized, controlled trials					
Fransson et al, 2001[32] and Fransson et al, 2009[33] 10 years	QLQ-C30 mean scores *3-yr followup* Physical functioning: 83 vs. 85 Role functioning: 80 vs. 87 Emotional functioning: 85 vs. 86 Cognitive functioning: 85 vs. 86 Social functioning: 80 vs. 93 Global health: 68 vs. 71	QUFW94‡ mean scores *3-yr followup* Urinary incontinence: 1.5 (CI, 0.55 to 2.18) vs. 0.6 (CI, 0.13 to 1.0); p=0.008 Urinary problems in general: 1.8 (CI, 1.15 to 2.42) vs. 1.2 (CI, 0.60 to 1.86); p=0.23 Limitation in daily activity due to urinary problems: 1.1 (CI, 0.63 to 1.62) vs. 0.9 (CI, 0.27 to 1.47); p=0.06	Urinary incontinence, proportion of patients using pads *3-yr followup* 10/59 (17%) vs. 1/49 (2%)	NR	NR
Fransson et al, 2001[32] and Fransson et al, 2009[33] 10 years	QLQ-C30 mean scores *10-yr followup* Physical functioning: 82 vs. 76 Role functioning: 77 vs. 82 Emotional functioning: 84 vs. 82 Cognitive functioning: 78 vs. 83 Social functioning: 83 vs. 85 Global health: 63 vs. 75	PCSS‡ mean scores *10-yr followup* Urinary function: 2 vs. 1 Urinary bother: 3 vs. 2 Urinary interference with daily activity: 1 vs. 2 Sexual function: 8 vs. 7 Sexual bother: 7 vs. 4	Urinary incontinence, proportion of patients regularly using pads *10-yr followup* 5/27 (19%) vs. 2/27 (7%)	NR	NR
Cohort studies					
Bacon et al, 2001[51] Up to 5 years	SF-36 mean scores *EBRT vs. brachytherapy vs. watchful waiting* PCS: 49 vs. 51 vs. 49 MCS: 53 vs. 54 vs. 55 Physical function: 83 vs. 90 vs. 79 Physical role function: 72 vs. 79 vs. 85 Bodily pain: 79 vs. 81 vs. 81 General health: 74 vs. 78 vs. 71 Vitality: 64 vs. 66 vs. 68 Social function: 87 vs. 92 vs. 87 Emotional role function: 82 vs. 86 vs. 90 Mental health: 81 vs. 84 vs. 83	UCLA-PCI mean scores *EBRT vs. brachytherapy vs. watchful waiting* Urinary function: 89 vs. 87 vs. 93 Urinary bother: 83 vs. 75 vs. 89 Sexual function: 34 vs. 36 vs. 54 Sexual bother: 51 vs. 54 vs. 74 Bowel function: 81 vs. 80 vs. 91 Bowel bother: 78 vs. 72 vs. 89	NR	NR	NR

Appendix C2. Harms of Radical Prostatectomy, Radiation, Androgen Deprivation Therapy, and Cryotherapy Versus Watchful Waiting

Author, year Followup	General QOL scores	Disease-specific QOL scores	Urinary incontinence	Erectile dysfunction	Other outcomes
Choo et al, 2010[52] 2 years	NR	BSFI mean scores Sexual drive: 3.3 (EBRT, 3.3; brachytherapy, 3.3) vs. 3.4 Erectile function: 5.3 (EBRT, 4.3; brachytherapy, 6.3) vs. 6.5 Ejaculation: 4.0 (EBRT, 3.5; brachytherapy, 4.5) vs. 6.3 Sexual problem assessment: 7.7 (EBRT, 6.4; brachytherapy, 8.8) vs. 7.7 Overall satisfaction with sexual function: 2.0 (EBRT, 1.9; brachytherapy, 2.1) vs. 2.7	NR	NR	NR
Galbraith et al, 2001[54] 1.5 years	SF-36 mean scores *Conventional radiation vs. proton-beam radiation vs. mixed-beam radiation vs. watchful waiting* Physical function: 70 vs. 78 vs. 78 vs. 75 Physical role function: 53 vs. 82 vs. 67 vs. 67 Bodily pain: 73 vs. 80 vs. 82 vs. 84 General health: 56 vs. 59 vs. 58 vs. 54 Vitality: 59 vs. 63 vs. 63 vs. 64 Emotional role function: 61 vs. 90 vs. 80 vs. 70 Mental health: 77 vs. 82 vs. 80 vs. 79 Quality of Life Index mean scores Overall QOL: 57 vs. 61 vs. 61 vs. 59	PTSS mean scores *Conventional radiation vs. proton-beam radiation vs. mixed-beam radiation vs. watchful waiting* Sexual symptoms: 3.5 vs. 3.8 vs. 3.5 vs. 3.6 Urinary symptoms: 1.7 vs. 1.7 vs. 1.6 vs. 2.0 Gastrointestinal symptoms: 1.8 vs. 1.6 vs. 1.6 vs. 1.3	NR	NR	NR
Hoffman et al, 2003[55] 2 years	NR	NR	Urinary incontinence (leakage) Daily or more often: 12% (71/583) vs. 8% (19/230)	Erectile dysfunction No erections at all: 39% (228/583) vs. 26% (60/230)	Bowel urgency Almost every day: 3% (19/583) vs. 0.4% (1/230), RR, 7.5 (CI, 1.0 to 56)
Litwin et al, 1995a[56] 5.6 years	SF-36 mean scores Physical function: 74 vs. 71 Physical role function: 56 vs. 55 Bodily pain: 74 vs. 74 General health: 66 vs. 63 Vitality: 61 vs. 60 Social function: 81 vs. 80 Emotional role function: 76 vs. 57 Mental health: 79 vs. 77	UCLA-PCI mean scores Urinary function: 82 vs. 86 Urinary bother: 77 vs. 80 Sexual function: 35 vs. 41 Sexual bother: 29 vs. 37 Bowel function: 81 vs. 84 Bowel bother: 77 vs. 85	NR	NR	NR
Litwin et al, 1995b[57] 5.6 years	NR	NR	Urinary incontinence Total urinary control: 28/54 (52%) vs. 39/63 (62%) Occasional urinary dribbling: 22/54 (41%) vs. 18/63 (29%) Frequent urinary dribbling: 3/54 (6%) vs. 4/63 (6%) No control: 1/54 (2%) vs. 2/63 (3%)	Sexual function Very good: 1/55 (2%) vs. 4/63 (6%) Good: 7/55 (13%) vs. 9/63 (14%) Fair: 8/55 (15%) vs. 19/63 (30%) Poor: 5/55 (9%) vs. 7/63 (11%) Very poor: 34/55 (62%) vs. 24/63 (38%)	Bowel urgency Rarely or never: 36/54 (67%) vs. 43/63 (68%) About once/week: 2/54 (4%) vs. 6/63 (10%) More than once/week: 4/54 (7%) vs. 3/63 (5%) About once/day: 3/54 (6%) vs. 8/63 (13%) More than once/day: 9/54 (17%) vs. 3/63 (5%)

Appendix C2. Harms of Radical Prostatectomy, Radiation, Androgen Deprivation Therapy, and Cryotherapy Versus Watchful Waiting

Author, year Followup	General QOL scores	Disease-specific QOL scores	Urinary incontinence	Erectile dysfunction	Other outcomes
Litwin et al, 2002[58] 1.6 years	SF-36 mean scores Vitality: 61 vs. 66 Social function: 86 vs. 89 Emotional role function: 81 vs. 86 Mental health: 75 vs. 81	NR	NR	NR	NR
Lubeck et al, 1999[59] 2 years	SF-36 mean scores Physical function: 65 vs. 71 Physical role function: 55 vs. 63 Bodily pain: 74 vs. 76 General health: 54 vs. 54 Vitality: 54 vs. 57 Social function: 77 vs. 78 Emotional role function: 76 vs. 73 Mental health: 78 vs. 76	UCLA-PCI mean scores Urinary function: 85 vs. 87 Urinary bother: 65 vs. 84 Sexual function: 25 vs. 29 Sexual bother: 32 vs. 25 Bowel function: 83 vs. 89 Bowel bother: 75 vs. 90	NR	NR	NR
Schapira et al, 2001[61] 1 year	SF-36 mean scores Physical function: 58 vs. 68 Physical role function: 42 vs. 64 Bodily pain: 61 vs. 68 General health: 59 vs. 68 Vitality: 55 vs. 60 Social function: 59 vs. 86 Emotional role function: 70 vs. 77 Mental health: 76 vs. 81	UCLA-PCI mean scores Urinary function: 89 vs. 92 Urinary bother: 81 vs. 84 Sexual function: 25 vs. 36 Sexual bother: 60 vs. 62 Bowel function: 79 vs. 86 Bowel bother: 77 vs. 81	Urinary incontinence 3/38 (8%) vs. 1/25 (4%)	Erectile dysfunction 30/40 (75%) vs. 17/25 (68%)	NR
Siegel et al, 2001[62] 4.4 years	NR	NR	NR	Erectile dysfunction 269/315 (85%) vs. 40/64 (63%)	NR
Smith et al, 2000[63] 3.8 years	SF-36 mean scores Physical function: 80 vs. 85 Physical role function: 71 vs. 80 Bodily pain: 82 vs. 87 General health: 70 vs. 71 Vitality: 65 vs. 69 Social function: 88 vs. 92 Emotional role function: 85 vs. 91 Mental health: 82 vs. 82	UCLA-PCI mean scores Urinary function: 89 vs. 94 Urinary bother: 81 vs. 88 Sexual function: 40 vs. 60 Sexual bother: 51 vs. 69	NR	NR	NR
Smith et al, 2009[64] 3 years	SF-36 mean scores PCS: EBRT, 47 vs. LDB, 49 vs. HDB, 49 vs. watchful waiting, 47 MCS: EBRT, 53 vs. low-dose brachytherapy, 54 vs. high-dose brachytherapy, 52 vs. watchful waiting, 53	UCLA-PCI mean scores Urinary function: EBRT, 93 vs. LDB, 94 vs. HDB, 90 vs. watchful waiting, 92 Urinary bother: EBRT, 81 vs. LDB, 84 vs. HDB, 77 vs. watchful waiting, 84 Sexual function: EBRT, 32 vs. LDB, 54 vs. HDB, 30 vs. watchful waiting, 44 Sexual bother: EBRT, 58 vs. LDB, 67 vs. HDB, 61 vs. watchful waiting, 66 Bowel function: EBRT, 85 vs. LDB, 89 vs. HDB, 88 vs. watchful waiting, 87 Bowel bother: EBRT, 85 vs. LDB, 91 vs. HDB, 84 vs. watchful waiting, 88	Urinary incontinence EBRT, 3/123 (2%) vs. LDB, 3/58 (5%) vs. HDB, 3/47 (6%) vs. watchful waiting 6/200 (3%)	Erectile dysfunction EBRT, 72/123 (59%) vs. LDB, 20/58 (34%) vs. HDB, 31/47 (66%) vs. watchful waiting, 94/200 (47%)	Moderate or severe bowel problems EBRT, 6/123 (13%) vs. LDB, 0/58 (0%) vs. HDB, 4/47 (9%) vs. watchful waiting, 11/200 (6%)

Appendix C2. Harms of Radical Prostatectomy, Radiation, Androgen Deprivation Therapy, and Cryotherapy Versus Watchful Waiting

Author, year Followup	General QOL scores	Disease-specific QOL scores	Urinary incontinence	Erectile dysfunction	Other outcomes
Talcott et al, 2003[65] 2 years	NR	Talcott Scale mean scores Urinary incontinence: EBRT, 9 (SD, 16) vs. brachytherapy, 8 (SD, 15) vs. watchful waiting, 18 (SD, 19) Sexual function: EBRT, 69 (32) vs. brachytherapy, 45 (SD, 33) vs. watchful waiting, 51 (SD, 34) Bowel problems: EBRT, 9 (SD, 9) vs. brachytherapy, 7 (SD, 9) vs. watchful waiting, 7 (SD, 11)	NR	NR	NR
Thong et al, 2009[66] 5-10 years following diagnosis	SF-36 mean scores PCS: 42 vs. 45 MCS: 50 vs. 49 Physical function: 62 vs. 70 Physical role function: 56 vs. 57 Bodily pain: 70 vs. 77 General health: 60 vs. 59 Vitality: 62 vs. 65 Social function: 81 vs. 79 Emotional role function: 78 vs. 71 Mental health: 73 vs. 77	EPIC mean scores – physical symptoms Urinary function: 82 vs. 86 Urinary bother: 75 vs. 78 Bowel function: 87 vs. 93 Bowel bother: 85 vs. 94	NR	Erectile dysfunction, proportion of patients *Problem getting an erection* Nearly always: 68% (43/63) vs. 47% (28/60) Occasionally: 16% (10/63) vs. 8% (5/60) Never: 16% (10/63) vs. 45% (27/60) *Problem maintaining an erection* Nearly always: 71% (43/63) vs. 48% (28/60) Occasionally: 6% (4/63) vs. 5% (3/60) Never: 23% (14/63) vs. 47% (28/60)	NR
Androgen deprivation therapy vs. watchful waiting					
Cohort studies					
Bacon et al, 2001[51] Up to 5 years	SF-36 mean scores PCS: 46 vs. 49 MCS: 52 vs. 55 Physical function: 76 vs. 79 Physical role function: 62 vs. 85 Bodily pain: 75 vs. 81 General health: 66 vs. 71 Vitality: 61 vs. 68 Social function: 83 vs. 87 Emotional role function: 74 vs. 90 Mental health: 79 vs. 83	UCLA-PCI mean scores Urinary function: 84 vs. 93 Urinary bother: 72 vs. 89 Sexual function: 25 vs. 54 Sexual bother: 59 vs. 74 Bowel function: 81 vs. 91 Bowel bother: 83 vs. 89	NR	NR	NR
Hoffman et al, 2003[55] 2 years	NR	NR	Urinary incontinence Leakage daily or more often: 11% (20/179) vs. 8% (19/230)	Erectile dysfunction No erections at all: 75% (135/179) vs. 26% (60/230)	Bowel urgency, almost every day: 4% (7/179) vs. 0.4% (1/230) Cancer treatment limits activities some or a lot: 16% (29/179) vs. 4% (10/230)
Potosky et al, 2002[60] 1 year	SF-36 mean scores Physical role function: 50 vs. 61 Bodily pain: 73 vs. 74 Vitality: 53 vs. 60 Emotional role function: 74 vs. 77 Mental health: 78 vs. 78	NR	NR	Erectile dysfunction Mean change from baseline: 68/88 (80% [CI, 70 to 89]) vs. 60/223 (30% [CI, 22 to 36]); p<0.001 Loss of libido, mean change from baseline: 79/149 (54% [CI, 45 to 64]) vs. 35/295 (12% [CI, 8 to 17]); p<0.001 Sexually inactive, mean change from baseline: 104/139 (75% [CI, 65 to 85]) vs. 52/248 (21% [CI, 15 to 27]); p<0.001	Gynecomastia: 49/245 (20%) vs. 16/416 (4%); p<0.001 Hot flashes, any occurrence: 142/245 (58%) vs. 46/416 (11%); p<0.001

Appendix C2. Harms of Radical Prostatectomy, Radiation, Androgen Deprivation Therapy, and Cryotherapy Versus Watchful Waiting

Author, year Followup	General QOL scores	Disease-specific QOL scores	Urinary incontinence	Erectile dysfunction	Other outcomes
Smith et al, 2000[63] 3.8 years**	SF-36 mean scores Physical function: 72 vs. 85 Physical role function: 69 vs. 80 Bodily pain: 79 vs. 87 General health: 69 vs. 71 Vitality: 62 vs. 69 Social function: 82 vs. 92 Emotional role function: 76 vs. 91 Mental health: 76 vs. 82	UCLA-PCI mean scores Urinary function: 90 vs. 94 Urinary bother: 83 vs. 88 Sexual function: 29 vs. 60 Sexual bother: 49 vs. 69	NR	NR	NR
Smith et al, 2009[64] 3 years	SF-36 mean scores PCS: 39 vs. 47 MCS: 53 vs. 53	UCLA-PCI mean scores Urinary function: 93 vs. 92 Urinary bother: 73 vs. 84 Sexual function: 8 vs. 44 Sexual bother: 67 vs. 66 Bowel function: 82 vs. 87 Bowel bother: 87 vs. 88	Urinary incontinence 2/61 (3%) vs. 6/200 (3%)	Erectile dysfunction 45/61 (74%) vs. 94/200 (47%)	Moderate or severe bowel problems 3/61 (5%) vs. 11/200 (6%)
Cryotherapy vs. watchful waiting					
Cohort studies					
Smith et al, 2000[63] 3.8 years	SF-36 mean scores Physical function: 87 vs. 85 Physical role function: 84 vs. 80 Bodily pain: 87 vs. 87 General health: 72 vs. 71 Vitality: 69 vs. 69 Social function: 95 vs. 92 Emotional role function: 97 vs. 91 Mental health: 86 vs. 82	UCLA-PCI mean scores Urinary function: 93 vs. 94 Urinary bother: 90 vs. 88 Sexual function: 26 vs. 60 Sexual bother: 43 vs. 69	Uninary incontinence *Age <70 years* Total urinary control: 17/21 (81%) vs. 53/71 (74%) Occasional urinary dribbling: 4/21 (19%) vs. 15/71 (21%) *Age >70 years* Total urinary control: 5/21 (25%) vs. 39/71 (55%) Occasional urinary dribbling: 16/61 (75%) vs. 28/71 (39%)	Erectile dysfunction *Age <70 years* Erection firm enough for intercourse: 4/21 (20%) vs. 56/71 (81%) *Age >70 years* Erection firm enough for intercourse: 0/21 (0%) vs. 33/71 (47%)	NR

* Number of respondents varied according to question.
** For the subset of patients diagnosed after 1994 (806/2234), mean followup was 1 year.
† Cancer Rehabilitation Evaluation System-Short Form scores range from 0–4.
‡ Scored 0–10, higher scores indicate worse function.

Abbreviations: ADT = androgen deprivation therapy; BSFI = Brief Sexual Function Inventory; CI = confidence interval; CARES-SF = Cancer Rehabilitation Evaluation System-Short Form; EBRT = external beam radiotherapy; EPIC = Expanded Prostate Cancer Index Composite; HDB = high-dose brachytherapy; LDB = low-dose brachytherapy; MCS = mental component score; NR = not reported; PCS = physical component score; PCSS = Prostate Cancer Symptom Scale; PTSS = Southwest Oncology Group Prostate Treatment-Specific Symptoms Measure; QOL = quality of life; QLQ-C30 = Quality of Life Questionnaire for Cancer; ; RR = relative risk; SD = standard deviation; SE = standard error; SF-36 = Short-form 36-item Health Survey; UCLA-PCI = University of California, Los Angeles Prostate Cancer Index.

Appendix C3. Quality Assessment of Randomized, Controlled Trials

Trial Author, Year	Adequate randomization	Adequate allocation concealment	Similar groups at baseline	Comparable groups maintained	Eligibility criteria specified	Outcome assessors masked	Care provider masked	Patient masked	Reporting of attrition, crossovers, adherence, and contamination	Loss to followup differential or high	Intention-to-treat analysis	Post-randomization exclusions	Outcomes prespecified	Quality rating
Bill-Axelson et al, 2011[35]	Unclear	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Differential: no High overall: no	Yes	Unclear	Yes	Good
Fransson et al, 2001[32]	Unclear	Unclear	Yes	Yes	Yes	Unclear	No	No	No	Differential: no High overall: yes	No	Yes	Yes	Fair
Iversen et al, 1995[41]	Unclear	Unclear	Unclear	Unclear	Yes	Unclear	No	No	Yes	Differential: no High overall: yes	No	Yes	Yes	Poor

Appendix C4. Quality Assessment of Cohort Studies

Author, Year	Study attempted to enroll a random sample or consecutive patients meeting inclusion criteria (inception cohort)	Groups comparable at baseline	Study used accurate methods for ascertaining exposures, potential confounders, and outcomes	Outcome assessors and/or data analysts blinded to treatment	Article reported attrition	Study performed appropriate statistical analyses on potential confounders	Important differential or overall high loss to followup	Outcomes prespecified, defined, and ascertained using accurate methods	Quality rating
Albertsen et al, 2007[42]	Yes	No	Yes	Unclear	No	Yes	Differential: unclear High overall: unclear	Yes	Fair
Bacon et al, 2001[51]	Yes	No	Yes	Unclear	No	Yes	Differential: unclear High overall: unclear	Yes	Fair
Choo et al, 2010[52]	Yes	Unclear	Yes	Unclear	Yes	No	Differential: unclear High overall: yes	Yes	Fair
Galbraith et al, 2001[54]	Unclear	Yes	Yes	Unclear	Yes	No	Differential: unclear High overall: yes	Yes	Fair
Hoffman et al, 2003[55]	Yes	No	Yes	Unclear	No	No	Differential: unclear High overall: yes	Yes	Fair
Ladjevardi et al, 2010[43]	Yes	No	Yes	Unclear	No	Yes	Differential: unclear High overall: unclear	Yes	Fair
Litwin et al, 1995a[56]	Yes	No	Yes	Unclear	No	Yes	Differential: no High overall: unclear (patients per analysis varied)	Yes	Fair
Litwin et al, 1995b[57] (Methods reported in Litwin et al, 1995a[56])	Yes	No	Yes	Unclear	No	Yes	Differential: no High overall: no	Yes	Fair
Litwin et al, 2002[58]	Yes	Yes	Yes	Unclear	No	Yes	Differential: unclear High overall: unclear	Yes	Fair
Lu-Yao et al, 2008[44]	Yes	No	Yes	Unclear	No	Yes	Differential: unclear High overall: unclear	Yes	Fair
Lubeck et al, 1999[59]	Yes	No	Yes	Unclear	Yes	Yes	Differential: unclear High overall: yes	Yes	Fair
Merglen et al, 2007[45]	Yes	No	Yes	Unclear	Yes	Yes	Differential: unclear High overall: no	Yes	Fair
Potosky et al, 2002[60]	Yes	Yes	Yes	Unclear	Yes	Yes	Differential: no High overall: no	Yes	Good

Appendix C4. Quality Assessment of Cohort Studies

Author, Year	Study attempted to enroll a random sample or consecutive patients meeting inclusion criteria (inception cohort)	Groups comparable at baseline	Study used accurate methods for ascertaining exposures, potential confounders, and outcomes	Outcome assessors and/or data analysts blinded to treatment	Article reported attrition	Study performed appropriate statistical analyses on potential confounders	Important differential or overall high loss to followup	Outcomes prespecified, defined, and ascertained using accurate methods	Quality rating
Schapira et al, 2001[61]	Unclear	Yes	Yes	Unclear	Yes	Yes	Differential: unclear High overall: no	Yes	Fair
Schymura et al, 2010[46]	Yes	No	Yes	Unclear	Yes	Yes	Differential: no High overall: No	Yes	Fair
Siegel et al, 2001[62]	Unclear	Unclear	Yes	Unclear	No	No	Differential: no High overall: no	Yes	Fair
Smith et al, 2000[63]	Yes	No	Yes	Unclear	Yes	Yes	Differential: unclear High overall: yes	Yes	Fair
Smith et al, 2009[64]	Yes	No	Yes	Yes	Yes	Yes	Differential: unclear High overall: no	Yes	Good
Stattin et al, 2010[10]	Yes	No	Yes	Unclear	No	Yes	Differential: unclear High overall: unclear	Yes	Fair
Talcott et al, 2003[65]	Yes	No	Yes	Unclear	Yes	No	Differential: no High overall: no	Yes	Fair
Tewari et al, 2007[47]	Yes	No	Yes	Unclear	No	Yes	Differential: unclear High overall: unclear	Yes	Fair
Thong et al, 2009[66]	Yes	Yes	Yes	Unclear	Yes	Yes	Differential: no High overall: no	Yes	Good
Wong et al, 2006[48]	Yes	No	Yes	Unclear	No	Yes	Differential: unclear High overall: unclear	Yes	Fair
Zhou et al, 2009[49]	Yes	No	Yes	Unclear	No	Yes	Differential: unclear High overall: unclear	Yes	Fair

Appendix C5. Evidence Table of Uncontrolled Observational Studies

Study, Year *Title*	Inclusion & exclusion criteria	Number screened/ eligible/enrolled	Subject age & race Stage at diagnosis Screen detected	Country & data source	Sponsor	Statistical analysis/ adjustment for potential confounders (for cohort studies)	Method of outcome ascertainment	Adverse events	Duration of followup	Loss to followup
Prostatectomy										
Alibhai et al, 2005[67]	All RP patients in Ontario, Canada 1990-1999	NR/NR/11,010	Mean age: 63 yrs Race: NR Stage: NR Screen detected: NR	Canada; database	Canadian Institutes of Health Research; Toronto Rehabilitation Foundation; Mary Trimmer Chair in Geriatric Medicine Research (University of Toronto)	Charlson index; diagnosis count; AIDS; anemia; cardiac disease; COPD; connective tissue disease; dementia; diabetes; hypercholesterolemia; hypertension; liver disease; obesity; other malignancy; peptic ulcer disease; peripheral vascular disease; renal failure; stroke	Database	30-day mortality: 53/11,010 (0.5%) Any complication: 2246/11,000 (20%) Cardiovascular: 309/11,010 (3%) Vascular: 215/11,010 (2%) Wound: 555/11,010 (5%) Genitourinary: 829/11,010 (8%)	30 days	NR
Augustin et al, 2003[71]	Prostatectomy patients between January 1999 and February 2002	NR/NR/1243	Mean age: 62 yrs (SD, 6; range, 40-76) Race: NR T1: 65% (806/1243) T2: 34% (422/1243) T3: 1% (15/1243) Screen detected: NR	Germany; single center	NR	NR	Blinded chart review	Any AE: 20% (247/1243) Major complication: 4% (50/1243) Rehospitalization due to major complication: 0.6% (8/1243) Mortality: 0/1243 (0%) Any intraoperative AE: 0.7% (9/1243) -AV blockage: 0.1% (1/1243) -Orturator nerve injury: 0.1% (1/1243) -Rectal injury: 0.1% (1/1243) -Ureteral injury: 0.1% (4/1243) Any postoperative AE: 4% (51/1243) -Arrythmia: 0.2% (2/1243) -CHF: 0.2% (3/1243) -MI: 0.1% (1/1243) -Myocardial ischemia: 0.1% (1/1243) -Severe hypotension: 0.1% (1/1243) -DVT: 1% (12/1243) -PE: 0.2% (2/1243) -Acute renal insufficency: 0.2% (2/1243) -Sepsis: 0.2% (3/1243) -Wound infection: 0.1% (1/1243) -Postoperative bleeding: 0.2% (3/1243) Minor complications: 16% (197/1243)	30 days	NR

Appendix C5. Evidence Table of Uncontrolled Observational Studies

Study, Year *Title*	Inclusion & exclusion criteria	Number screened/ eligible/enrolled	Subject age & race Stage at diagnosis Screen detected	Country & data source	Sponsor	Statistical analysis/ adjustment for potential confounders (for cohort studies)	Method of outcome ascertainment	Adverse events	Duration of followup	Loss to followup
Begg et al, 2002[69]	Prostate cancer patients age ≥65 yrs in SEER database diagnosed between 1992 and 1996 Exclusion: Treated outside of a SEER state; not enrolled in Medicare Part A and B; did not have prostate-ctomy w/in 6 mo of diagnosis	77,796/11,522/ 10,737	Mean age: 70 yrs 85% white Other races NR 44% stage ≥T3 Screen detected: NR	United States; SEER database	NR	Age, stage, comorbidities using the Romano-Charlson Index	Database	30-day mortality: 0.5% (number of patients NR)	60 days	NR
Rabbani et al, 2010[72]	Consecutive prostatectomy patients between January 1999 and June 2007	NR/NR/4592	Mean age: 60 yrs (range, 55 to 64) 89% (4067/4592) white 7% (317/4592) black 4% (208/4592) other/unknown T1: 62% (2864/4592) T2: 34% (1571/4592) T3: 3% (150/4592) Tx: <1% (7/4592) Screen detected: NR	United States; single center database	Sidney Kimmel Center for Prostate and Urologic Cancers (?)	Age, ethnicity, BMI, stage (clinical and pathological), Gleason (clinical and pathologic) score, PSA, use of neoadjuvant hormone therapy, ASA score, Charlson score, individual comorbidity, surgical approach, nodal status, positive surgical margins, specimen weight, estimated blood loss, need for blood tranfusion, operative time	Incidence reported in prostatectomy and morbidity databases	<u>Early RP complications (<30 days)</u> Hypotension: 0.4% (14/3458) Respiratory distress: 0.2% (7/3458) Acute renal insufficiency: 0.2% (7/3458) Lymphocele: 0.8% (28/3458) Rectal or bowel injury: 0.7% (24/3458) Hematoma: 0.5% (17/3458) <u>Intermediate complications (31-90 days)</u> Sepsis: 0.03% (1/3458) Bladder neck contracture: 2.3% (80/3458) Urethral stricture: 0.6% (21/3458) Urinary retention: 0.4% (14/3458) <u>Late complications (>90 days)</u> Cerebrovascular accident or transient ischemic attack: 0.09% (3/3458) Acute renal insufficiency: 0.03% (1/3458) Bladder neck contracture: 2.8% (97/3458) Inguinal hernia: 1.2% (41/3458) Urethral stricture: 0.4%	37 mos (range, 20-61)	NR

Appendix C5. Evidence Table of Uncontrolled Observational Studies

Study, Year *Title*	Inclusion & exclusion criteria	Number screened/ eligible/enrolled	Subject age & race Stage at diagnosis Screen detected	Country & data source	Sponsor	Statistical analysis/ adjustment for potential confounders (for cohort studies)	Method of outcome ascertainment	Adverse events	Duration of followup	Loss to followup
Rabbani et al, 2010[72] (cont.)	See above	See above	See above	See above	See above	See above	See above	(14/3458) Any complication 27% (950/3458) Early LP complications (<30 days) Hypotension: 0.5% (6/1134) PE: 0.4% (5/1134) MI/ischemia: 0.3% (3/1134) Urinoma/urine leak: 1.3% (15/1134) Lymphocele: 1.1% (12/1134) Abscess: 1.1% (12/1134) Intermediate LP complications (31-90 days) Lymphocele: 0.4% (5/1134) Incisional hernia: 0.2% (2/1134) Urethral stricture: 0.2% (2/1134) Late LP complications (>90 days) Incisional hernia: 1.1% (12/1134) Bladder neck contracture: 0.7% (8/1134) Inguinal hernia: 0.5% (6/1134) Any complication 39% (442/1134) Hazard ratios Risk of any medical complication, RP vs. LP: HR, 1.9 (CI, 1.5 to 2.4; p<0.001) Risk of any surgical complication, RP vs. LP: HR, 1.6 (CI, 1.3 to 1.9; p<0.001) Risk of complication according to race, black vs. white: HR, 1.4 (CI, 1.0 to 2.0; p=0.027) Mortality (results not stratified by surgery type) 0.1% (6/4592)	See above	See above

Appendix C5. Evidence Table of Uncontrolled Observational Studies

Study, Year *Title*	Inclusion & exclusion criteria	Number screened/ eligible/enrolled	Subject age & race Stage at diagnosis Screen detected	Country & data source	Sponsor	Statistical analysis/ adjustment for potential confounders (for cohort studies)	Method of outcome ascertainment	Adverse events	Duration of followup	Loss to followup
Walz et al, 2008[70]	Prostatectomy patients included in Quebec Health Plan database diagnosed between 1989 and 2000	NR/9739/9208	Mean age: 65 yrs (range, 45-89) Race NR Stage NR Screen detected: NR	Canada; database	NR	Age, Charlson index, surgical volume, year of surgery	Billing codes	30-day mortality: 0.5% (48/9208)	30 days	NR
Yao et al, 1999[68]	Prostatectomy patients in Medicare data-base diagnosed between 1991 and 1994 Excluded: Enrollment in HMO or treated at VHA hospital	NR/NR/101,604	Mean age: 69 yrs 90% white 5% black 5% other Stage NR Screen detected: NR	United States; database	NR	Age, race, type of surgeon, surgical volume, teaching status of hospital, year of surgery	Procedure code 60.5 and CPT codes 55810, 55812, 55815, 55840, 55842, and 55845	30-day mortality: 0.5% Serious cardiac event: 3% Serious pulmonary event: 6% -PE: 0.4% -DVT: 0.05% Serious wound: 0.7% Serious surgical complication: 0.8%	30 days	NR
High-intensity focused ultrasonography										
Blana et al, 2004[73]	Stage T1-T2N0 M0; PSA <15 ng/mL; Gleason score ≤7; unsuitable for prostatectomy or unwilling to risk potential morbidity of prostatectomy	NR/NR/146	Mean age: 67 yrs (SD, 7) Race NR Stage NR (all were T1-T2N0M0) Screen detected: NR	Germany; consecutive patients	NR	NR	Physician-elicited and patient self-report (questionnaire)	Symptomatic UTI: 6/137 (5%) Chronic pelvic pain: 2/137 (2%) Stress incontinence (grade 1): 8/137 (6%) Posttreatment erectile dys-function (among pretreat-ment potent patients; n=NR): 53%	Mean, 23 mo (range, 4-62)	n=142 6% (9/142)
Blana et al, 2008[74]	Prostate cancer patients unsuitable for prostatectomy (comorbidity or life expectancy <10 yrs); refusal to undergo surgery or EBRT	NR/NR/163	Mean age: 66 yrs (SD, 7) Race NR Stage T1: 39/163 (24%) Stage T2: 124/163 (76%) Screen detected: NR	Germany; consecutive patients	NR	Age, prostate volume, PSA level, Gleason score, clinical stage, use of neadjuvant hormone therapy and transurethral resection of the prostate	Physician-elicited and patient self-report (questionnaire)	Urinary incontinence, grade 1: 10/163 (6%) Grade 2: 3/163 (2%) Posttreatment erectile dys-function (among 76 pretreat-ment potent patients): 34/76 (45%) UTI: 11/163 (8%) Need for surgical interven-tion: 40/163 (25%)	Mean, 4.8 yrs (SD, 1.2 range, 3-8.6)	NR
Muto et al, 2008[75]	Age >60 yrs; stage T1c-T2N0 M0; biopsy and MRI indicating localized dis-ease; unsuitable for prostatectomy due to comorbid-ity or personal preference	NR/NR/70	Median age: 72 yrs (range, 61-80) Race NR T1: 57/70 (81%) T2: 13/70 (19%) Screen detected: NR	Japan; method of patient selection unclear	NR	NR	Patient self-report using UCLA-PCI and IPSS	IPS score: whole HIFU, 8.13 (SD, 5.5); focal HIFU, 9.25 (SD, 7.3); p=0.37 Urinary function: whole HIFU, 97.2 (SD, 11.4); focal HIFU, 86.0 (SD, 20.8); p=0.68 Urinary bother: whole HIFU, 85.7 (SD, 24.4); focal HIFU, 80.0 (SD, 20.9); p=0.19	Median, 34 mo (range, 8-45)	NR

Appendix C5. Evidence Table of Uncontrolled Observational Studies

Study, Year *Title*	Inclusion & exclusion criteria	Number screened/ eligible/enrolled	Subject age & race Stage at diagnosis Screen detected	Country & data source	Sponsor	Statistical analysis/ adjustment for potential confounders (for cohort studies)	Method of outcome ascertainment	Adverse events	Duration of followup	Loss to followup
Thuroff et al, 2003[76]	Biopsy-proven prostate cancer; not suitable for prostatectomy	NR/NR/402	Mean age: 69 yrs (SD, 7; range, 51-80) Race NR Stage NR (all were T1-T2N0M0) Screen detected: NR	Germany, France and Netherlands; method of patient selection unclear	NR	NR	Unclear	Urethrorectal fistula: 5/402 Urinary incontinence, grade 1: 44/402 (11%) Urinary incontinence, grade 2: 12/402 (3%) Urinary incontinence, grade 3: 6/402 (2%) UTI: 56/402 (14%) Erectile dysfunction: 35/402 (8%; proportion with pretreatment potency NR)	Mean, 407 days (range, 0-1541)	NR
Uchida et al, 2006[77]	Stage T1c-T2N0M0 without anal stricture	NR/NR/63	Mean age: 71 yrs (SD, 1; range, 45-87) Race NR T1: 39/63 (62%) T2: 24/63 (38%) Screen detected: NR	Japan; method of patient selection unclear	NR	Age, clinical stage, Gleason score, prostate volume, PSA level	Physician-elicited and patient self-report (questionnaire)	Urethral stricture: 15/63 (24%) Retrograde ejaculation: 2/63 (3%) Urinary incontinence, grade 1: 1/63 (2%) Erectile dysfunction: 8/34 (24% among patients with pretreatment erectile function)	Mean, 22 mo (range, 3-63)	None

Abbreviations: AE = adverse event; ASA = American Society of Anesthesiologists; AV = atrioventricular; BMI = body mass index; CHF = congestive heart failure; CI = confidence interval; COPD = chronic obstructive pulmonary disease; CPT = Current Procedural Terminology; DVT = deep vein thrombosis; EBRT = external beam radiotherapy; HIFU = high-intensity focused ultrasonography; HMO = health maintenance organization; HR = hazard ratio; IPSS = International Prostate Symptom Score; LP = laparoscopic radical prostatectomy; MI = myocardial infarction; MRI = magnetic resonance imaging; NR = not reported; PE = pulmonary embolism; PSA = prostate-specific antigen; RP = radical prostatectomy; SD = standard deviation; SEER = Surveillance, Epidemiology, and End Results; UCLA-PCI = University of California, Los Angeles Prostate Cancer Index; UTI = urinary tract infection; VHA = Veterans Health Administration.