AHRQ Comparative Effectiveness Review Surveillance Program

CER #13:
Comparative Effectiveness of Therapies for Clinically Localized Prostate Cancer

Original release date:
February 2008

Surveillance Report:
May 2012

Key Findings:

- The PIVOT trial was identified, making many of the existing key conclusions out of date.
- Key questions 1, 2, and 4 were found to be out of date.
- No significant safety concerns were identified.

Summary Decision

This CER's priority for updating is **High**

Authors:
Jennifer Schneider Chafen, MS, MD
Sydne Newberry, PhD
Margaret Maglione, MPP
Aneesa Motala, BA
Roberta Shanman, MLS
Paul Shekelle, MD, PhD

None of the investigators has any affiliations or financial involvement that conflicts with the material presented in this report.

Acknowledgments

The authors gratefully acknowledge the following individuals for their contributions to this project:

Subject Matter Experts

Michael Barry, MD
Massachusetts General Hospital
Boston, Massachusetts

Andrew Loblaw, MD
Toronto Sunnybrook Regional Centre
Toronto, Ontario, Canada

Richard M. Hoffman, MD
University of New Mexico Health Sciences Center
Albuquerque, New Mexico

Contents

Comparative Effectiveness of Therapies for Clinically Localized Prostate Cancer

1. Introduction

Comparative Effectiveness Review (CER) #13, Comparative Effectiveness of Therapies for Clinically Localized Prostate Cancer, was released in February 2008.[1] It was therefore due for a surveillance assessment in August, 2008 but the Surveillance program did not exist at that time. Therefore, it is now undergoing its first assessment.

2. Methods

2.1 Literature Searches

Using the search strategy employed for the original report, we conducted a limited literature search of Pubmed® for the years 2007-March 5, 2012. The search included five high-profile general medical interest journals (Annals of Internal Medicine, British Medical Journal, Journal of the American Medical Association, Lancet, and the New England Journal of Medicine) and five specialty journals (Cancer, Journal of Urology, Journal of the National Cancer Institute, Journal of Clinical Urology, and European Urology). The specialty journals were those most highly represented among the references for the original report. Appendix A includes the search methodology for this topic.

2.2 Study selection

In general we used the same inclusion and exclusion criteria as the original CER.

2.3 Expert Opinion

We shared the conclusions of the original report with 6 experts in the field (including the original project leader, suggested field experts, original technical expert panel (TEP) members, and peer reviewers) for their assessment of the need to update the report and their recommendations of any relevant new studies; the project lead and five subject matter experts responded. Appendix C shows the questionnaire matrix that was sent to the experts.

2.4 Check for qualitative and quantitative signals

After abstracting the study conditions and findings for each new included study into an evidence table (Appendix B), we assessed whether the new findings provided a signal according to the Ottawa Method or the RAND Method, suggesting the need for an update. The criteria are listed in the table below.[2, 3]

	Ottawa Method
	Ottawa Qualitative Criteria for Signals of Potentially Invalidating Changes in Evidence
A1	Opposing findings: A pivotal trial or systematic review (or guidelines) including at least one new trial that characterized the treatment in terms opposite to those used earlier.
A2	Substantial harm: A pivotal trial or systematic review (or guidelines) whose results called into question the use of the treatment based on evidence of harm or that did not proscribe use entirely but did potentially affect clinical decision making.
A3	A superior new treatment: A pivotal trial or systematic review (or guidelines) whose results identified another treatment as significantly superior to the one evaluated in the original review, based on efficacy or harm.
	Criteria for Signals of Major Changes in Evidence
A4	Important changes in effectiveness short of "opposing findings"
A5	Clinically important expansion of treatment
A6	Clinically important caveat
A7	Opposing findings from discordant meta-analysis or nonpivotal trial
	Quantitative Criteria for Signals of Potentially Invalidating Changes in Evidence
B1	A change in statistical significance (from nonsignificant to significant)
B2	A change in relative effect size of at least 50 percent
	RAND Method Indications for the Need for an Update
1	Original conclusion is still valid and this portion of the original report does not need updating
2	Original conclusion is possibly out of date and this portion of the original report may need updating
3	Original conclusion is probably out of date and this portion of the original report may need updating
4	Original conclusion is out of date

2.5 Compilation of Findings and Conclusions

For this assessment we constructed a summary table that included the key questions, the original conclusions, and the findings of the new literature search, the expert assessments, and any FDA reports that pertained to each key question. To assess the conclusions in terms of the evidence that they might need updating, we used the 4-category scheme described in the table above for the RAND Method.

In making the decision to classify a CER conclusion into one category or another, we used the following factors when making our assessments:

- If we found no new evidence or only confirmatory evidence and all responding experts assessed the CER conclusion as still valid, we classified the CER conclusion as still valid.
- If we found some new evidence that might change the CER conclusion, and /or a minority of responding experts assessed the CER conclusion as having new evidence that might change the conclusion, then we classified the CER conclusion as possibly out of date.
- If we found substantial new evidence that might change the CER conclusion, and/or a majority of responding experts assessed the CER conclusion as having new evidence that

might change the conclusion, then we classified the CER conclusion as probably out of date.
- If we found new evidence that rendered the CER conclusion out of date or no longer applicable, we classified the CER conclusion as out of date. Recognizing that our literature searches were limited, we reserved this category only for situations where a limited search would produce prima facie evidence that a conclusion was out of date, such as the withdrawal of a drug or surgical device from the market, a black box warning from FDA, etc.

2.6 Determining Priority for Updating

We used the following two criteria in making our final conclusion for this CER:

- How much of the CER is possibly, probably, or certainly out of date?
- How out of date is that portion of the CER? For example, would the potential changes to the conclusions involve refinement of original estimates or do the potential changes mean some therapies are no longer favored or may not exist? Is the portion of the CER that is probably or certainly out of date an issue of safety (a drug withdrawn from the market, a black box warning) or the availability of a new drug within class (the latter being less of a signal to update than the former)?

3. Results

3.1 Search

The literature search identified 1,458 titles. After title and abstract review, we further reviewed the full text of 25 journal articles. The remaining 1,433 titles were rejected because they were editorials, letters, or did not include topics of interest. Sixteen additional articles and one conference proceeding were reviewed at the suggestion of the experts.

Thus, through literature searches and expert recommendations, 41 articles and one conference proceeding went on to full text review. Of these, 20 articles were rejected because they did not answer a key question or did not include a comparison of interest. Thus, 21 articles and one conference proceeding were abstracted into an evidence table (Appendix B).[4-25]

3.2 Expert Opinion

Two of the three experts agreed that KQ1 and KQ2 were out of date. All three experts agreed that KQ4 was out of date. Two of the three experts agreed that KQ3 was still valid.

3.3 Identifying qualitative and quantitative signals

Table 1 shows the original key questions, the conclusions of the original report, the results of the literature and drug database searches, the experts' assessments, the recommendations of the Southern California Evidence-based Practice Center (SCEPC) regarding the need for update, and qualitative signals.

Table 1: Summary Table

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
Key Question 1. What are the comparative risks, benefits, and outcomes of therapies?				
No one therapy can be considered the preferred treatment for localized prostate cancer due to limitations in the body of evidence as well as the likely tradeoffs an individual patient must make between estimated treatment effectiveness, necessity, and adverse effects. All treatment options result in adverse effects (primarily urinary, bowel, and sexual), although the severity and frequency may vary between treatments. Even if differences in therapeutic effectiveness exist, differences in adverse effects, convenience, and costs are likely to be important factors in individual patient decision making. Patient satisfaction with therapy is high and associated with several clinically relevant outcome measures. Data from nonrandomized trials are inadequate to reliably assess comparative effectiveness and adverse effects. Additional randomized controlled trials (RCTs) are needed.				
Randomized comparisons across primary treatment categories				
Radical prostatectomy compared with watchful waiting (2 RCTs). Compared with men who used watchful waiting (WW), men with clinically localized prostate cancer detected by methods other than PSA testing and treated with	The Prostate Intervention versus Observation Trial (PIVOT) trial results were presented by Dr. Timothy Wilt at the American Urology Association ~~last May~~May 2011. The study showed no disease-specific survival for surgery vs. watchful	Not reported	2 experts thought this was out of date. 1 expert thought this was still supported by the literature	Original conclusion is out of date.

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
radical prostatectomy (RP) experienced fewer deaths from prostate cancer, marginally fewer deaths from any cause, and fewer distant metastases. The greater benefit of RP on cancer-specific and overall mortality appears to be limited to men under 65 years of age but is not dependent on baseline PSA level or histologic grade. Two RCTs compared WW with RP. The Scandinavian Prostate Cancer Group (SPCG) trial found significantly lower incidences of all-cause deaths (24 vs. 30 percent), disease-specific deaths (10 vs. 15 percent), and distant metastases (14 vs. 23 percent) for subjects treated with RP than for subjects assigned WW after a median follow-up of 8.2 years. Surgery was associated with greater urinary and sexual dysfunction than WW. An older trial of 142 men found no significant differences in overall survival between RP and WW after a median follow-up of 23 years, although small sample size limited study power.	waiting. However, a subgroup analysis suggested that men with high-risk features (PSA > 10, and intermediate risk) might have a survival benefit			
Radical prostatectomy vs. external beam radiotherapy (1 RCT). One small (N=106), older trial indicated that, compared with EBRT, RP was more effective in preventing progression, recurrence, or distant metastases in men with clinically localized prostate cancer detected by methods other then PSA testing.	No new data	Not reported	2 experts thought this was still supported by the literature.	Original conclusion is still valid and this portion of the original report does not need updating.

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
Treatment failure at 5 years of follow-up, defined as acid phosphatase elevation on two consecutive follow-up visits or appearance of bone or parenchymal disease with or without concomitant acid phosphatase elevation, occurred in 39 percent for EBRT compared with 14 percent for RP.				
Cryotherapy, laparoscopic or robotic assisted radical prostatectomy, primary androgen deprivation therapy, high-intensity focused ultrasound (HIFU), proton beam radiation therapy, or intensity modulated radiation therapy (IMRT) (0 RCTs). It is not known whether these therapies are better or worse than other treatments for localized prostate cancer because these options have not been evaluated in RCTs.	1 study (Donnelly) showed no statistical difference between external beam radiotherapy and cryoablation.	Not reported	2 experts thought this was still supported by the literature. 1 expert thought this was out of date.	Original conclusion is still valid and this portion of the original report does not need updating.
Randomized comparisons within primary treatment categories				
Radical prostatectomy combined with neoadjuvant androgen deprivation therapy (5 RCTs). The addition of neoadjuvant hormonal therapy to RP did not improve survival or cancer recurrence rates, defined by PSA recurrence, but increased AEs. One small RCT comparing RP alone and RP combined with neoadjuvant ADT found no overall or disease-specific survival benefit with the addition	No new data	Not reported	3 experts thought this was still supported by the literature.	Original conclusion is still valid and this portion of the original report does not need updating.

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
of neoadjuvant ADT after a median follow-up of 6 years. The addition of neoadjuvant ADT did not prevent biochemical progression compared with RP alone in any of the four trials. The trial comparing 3 months and 8 months neoadjuvant ADT with RP reported greater AEs in the 8-month group than the 3-month group (4.5 percent vs. 2.9 percent) and higher incidence of hot flashes (87 percent vs. 72 percent).				
External beam radiotherapy: comparison of EBRT regimens (5 RCTs). No RCTs compared EBRT and WW. It is not known if using higher doses of EBRT by increasing either the total amount or type of radiation (e.g., via high-dose intensity modulated or proton beam or by adding brachytherapy) improves overall or disease specific survival compared with other therapies. No EBRT regimen, whether conventional, high dose conformal, dose fractionation, or hypofractionation, was superior in reducing overall or disease-specific mortality. Increasing the total amount of radiation or adding brachytherapy after EBRT decreased cancer recurrence compared with lower doses of radiation. One trial (N=936) found that the probability of biochemical or clinical progression at 5 years was lower in the long-arm group (66 Gy in 33 fractions) than the	A systematic review (Bannuru) that evaluated radiation treatments and concluded that the lack of high-quality comparative evidence precludes conclusions about the efficacy of radiation treatments compared with no treatments for localized prostate cancer. 1 study (Kuban) reported that moderate dose escalation (78 Gy) decreases biochemical and clinical failure as well as prostate cancer deaths in patients with pretreatment PSA >10 ng/mL or high-risk disease. 1 meta-analysis (Viani) concluded that high dose radiotherapy is superior to conventional dose radiotherapy in preventing biochemical failure in low-, intermediate-, and high-risk prostate cancer patients, suggesting that this should be offered as a treatment for all patients, regardless of their risk	Not reported	1 expert opinion did not know. 2 experts thought this was out of date.	Original conclusion is probably/possibly out of date and this portion of the original report may need updating.

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
short-arm group (52.5 Gy in 20 fractions). Conventional dose EBRT (64 Gy in 32 fractions) and hypofractionated EBRT (55 Gy in 20 fractions) resulted in similar PSA relapse. One trial (N=104) found that brachytherapy combined with EBRT reduced biochemical or clinical progression compared with EBRT alone. One trial (N=303) found that high-dose EBRT (79.2 Gy that included 3D conformal proton 50.4 Gy with 28.8 Gy proton boost) was more effective than conventional-dose EBRT (70 Gy that included 19.8 Gy proton boost) in the percentage of men free from biochemical failure at 5 years (80 percent in the high-dose group and 61 percent in the conventional-dose group). Effectiveness was evident in low-risk disease (PSA <10 ng/ml, stage ²T2a tumors, or Gleason ²6) and higher risk disease. Acute combined gastrointestinal (GI) and genitourinary (GU) toxicity was lower in the long arm (7.0 percent) than in the short arm (11.4 percent). Late toxicity was similar. There were no significant differences between conventional and hypofractionated EBRT with the exception of rectal bleeding at 2 years after therapy, which had a higher prevalence in the hypofractionated group. Acute GI or GU symptoms of at least	status. 1 study (Hoskin) found relapse free survival was higher in patients treated with EBRT + high-dose-rate brachytherapy p=0.04. 1 study (Arcangeli) found that hypofractionated was superior in freedom from biochemical failure compared to conventional fractionation in patients with high-risk prostate cancer. 1 study (Pollack) found no difference between conventional and hypofractionated radiotherapy.			

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
moderate severity were similar in the trial comparing high and conventional doses.				
External beam radiotherapy combined with androgen deprivation therapy compared with EBRT alone (3 RCTs). ADT combined with EBRT (ADT + EBRT) may decrease overall and disease-specific mortality but increase AEs compared with EBRT alone in high-risk patients defined by PSA levels and Gleason histologic score (PSA >10 ng/ml or Gleason >6). One RCT (N=216) found that conformal EBRT combined with 6 months of ADT reduced all-cause mortality, disease-specific mortality, and PSA failure compared with conformal EBRT alone after a median follow-up of 4.5 years. There were significant increases in gynecomastia and impotence in the ADT + EBRT group compared with EBRT alone. One RCT (N=206) found that 6 months of ADT + EBRT did not significantly reduce disease-specific mortality compared with conformal EBRT alone in T2b and T2c subjects after a median follow-up of 5.9 years. Six months of combination therapy reduced clinical failure, biochemical failure, or death from any cause compared with EBRT alone in subjects with T2c disease but not in T2b subjects.	1 new RCT (Warde) compared the addition of EBRT to ADT and found that this combination improved overall survival at 7 years compared to ADT alone. 1 RCT (Jones) showed that ADT + EBRT reduced prostate-cancer mortality only among intermediate-risk, but not low-risk, patients through 9 years of follow up. 1 RCT (Hanks) showed no statistical difference between patients treated with an additional 24 months of androgen deprivation therapy compared to a standard short term androgen deprivation with radiotherapy. 1 abstract (Mottet) showed that the addition of local radiotherapy to androgen deprivation therapy reduced the risk of clinical progression. 1 abstract (Bolla) showed that survival with 6 months of androgen deprivation therapy after radiotherapy was significantly shorter than with 3 years of androgen deprivation therapy. 1 study (Widmark) showed the addition of local radiotherapy to endocrine treatment reduced the	Not reported	1 expert opinion did not know. 2 experts thought this was out of date.	Original conclusion is out of date.

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
	prostate cancer mortality.			
Different doses of adjuvant external beam radiotherapy combined with brachytherapy (1 RCT). One small trial comparing different doses of supplemental EBRT, 20 Gy (N=83) vs. 44 Gy (N=76), adjuvant to brachytherapy (103Pd) implant found no significant differences in the number of biochemical failure events and freedom from biochemical progression at 3 years.	No new data	Not reported	2 experts did not know. 1 expert thought this was still supported by the literature.	Original conclusion is still valid and this portion of the original report does not need updating.
Brachytherapy compared with brachytherapy (1 RCT). No RCTs compared brachytherapy alone with other major treatment options. Preliminary results from one small trial (N=126) comparing ^{125}I with ^{103}Pd brachytherapy found similar biochemical control at 3 years. There was a trend toward more radiation proctitis, defined aspersistent bleeding, with ^{125}I.	No new data	Not reported	2 experts did not know. 1 expert thought this was still supported by the literature.	Original conclusion is still valid and this portion of the original report does not need updating.
Bicalutamide combined with standard care: RP, EBRT, or WW (3 RCTs). Androgen deprivation with bicalutamide alone or in addition to RP or EBRT did not reduce cancer recurrence or mortality. There was no difference in total number of deaths between the bicalutamide and placebo groups for men receiving RP or EBRT at the median follow-up of 5.4 years. Among WW subjects,	No new data	Not reported	2 experts did not know. 1 expert thought this was still supported by the literature.	Original conclusion is still valid and this portion of the original report does not need updating.

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
there were significantly more deaths with bicalutamide compared with placebo. The addition of bicalutamide to standard care did not reduce progression.				
Comparative outcomes data from nonrandomized reports				
Cryosurgery. No randomized trials evaluated cryosurgery, and the majority of reports included patients with T3-T4 stages. Overall or prostate-cancer specific survival was not reported. Progression-free survival in patients with T1-T2 stages ranged from 29 to 100 percent. AEs were often not reported but, when described, included bladder outlet obstruction (3 to 21 percent), tissue sloughing (4 to 15 percent), and impotence (40 to 100 percent). Outcomes may be biased by patient and provider characteristics.	No new data	Not reported	1 expert did not know.	Original conclusion is still valid and this portion of the original report does not need updating.
Laparoscopic and robotic assisted prostatectomy. Three reviews estimated the effectiveness and AEs of laparoscopic and robotic assisted prostatectomy from 21 nonrandomized trials and case series. Most originated from centers outside of the United States. Median follow-up was 8 months. Laparoscopic RP had longer operative time but lower blood loss and improved wound healing compared with open retropubic RP. Reintervention rates were similar. Results from	1 study (Barry) did not show fewer adverse effects following robotic prostatectomy.	Not reported	2 experts thought this was still supported by the literature.	Original conclusion is still valid and this portion of the original report does not need updating.

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
eight nonrandomized reports suggested that total complications, continence rates, positive surgical margins, and operative time were similar for robotic assisted and open RP. Median length of hospital stay (1.2 vs. 2.7 days) and median length of catheterization (7 vs. 13 days) were shorter after robotic assisted RP than open RP.				
Intensity modulated radiation therapy. There was no direct evidence that IMRT results in better survival or disease-free survival than other therapies for localized prostate cancer. Based on nonrandomized data, the absolute risks of clinical and biochemical outcomes (including tumor recurrence), toxicity, and quality of life after IMRT are comparable with conformal radiation. There is low-level evidence that IMRT provides at least as good a radiation dose to the prostate with less radiation to the surrounding tissues compared with conformal radiation therapy.	No new data	Not reported	2 experts did not know. 1 expert thought this was out of date.	Original conclusion is still valid and this portion of the original report does not need updating.
Proton EBRT. There were no data from randomized trials comparing EBRT using protons vs. conventional EBRT or other primary treatment options. In one randomized trial, men with localized prostate cancer had statistically significantly lower odds of biochemical failure (increase in PSA) 5 years after	No new data	Not reported	2 experts did not know. 1 expert thought this was still supported by the literature.	Original conclusion is still valid and this portion of the original report does not need updating.

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
the higher dose of EBRT with a combination of conformal photon and proton beams without increased risk of adverse effects. Based on nonrandomized reports, the rates of clinical outcomes and toxicity after proton therapy may be comparable with conformal radiation. There was no direct evidence that proton EBRT results in better overall or disease-free survival than other therapies.				
High-intensity focused ultrasound therapy. There were no data from randomized trials comparing HIFU with other primary treatment options. Biochemical progression-free survival rates of 66 to 87 percent and negative biopsy rates of 66 to 93 percent were reported from non-controlled studies. The absolute risk of impotence and treatment-related morbidity appeared to be similar to other treatments. Follow-up duration was <10 years.	No new data	Not reported	2 experts did not know. 1 expert thought this was out of date.	Original conclusion is still valid and this portion of the original report does not need updating.
Health status, quality of life, and treatment satisfaction. Eight studies of health status and quality of life, including a U.S. population-based survey, were eligible. Bother due to dripping or leaking of urine was more than six fold greater in RP-treated men than in men treated with EBRT after adjusting for baseline factors. Bother due to	1 article (Johannson) reported on 12-year follow-up QOL data from the SPCG-4 trial and men in both the radical prostatectomy and watchful waiting groups reported higher levels of anxiety than the control group. In a longitudinal analysis of men in SPCG-4 who provided information at two follow-up points 9 years apart, 45%	Not reported	1 expert did not know. 1 expert though this was out of date. 1 expert thought this was still supported by the literature.	Original conclusion is possibly out of date and this portion of the original report may need updating.

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
bowel dysfunction (4 vs. 5 percent) or sexual dysfunction (47 vs. 42 percent) was similar for RP and EBRT. In a subgroup of men ages 70 and over, bother due to urine, bowel, or sexual dysfunction was 5.1, 2.4, and 2.8 times higher, respectively, for aggressive (RP/EBRT) vs. conservative (WW/ADT) therapy. Satisfaction with treatment was high, with less than 5 percent reporting dissatisfaction, unhappiness, or feeling terrible about their treatment, although the highest percent was among those treated with RP. Treatment satisfaction was highly correlated with bowel, bladder, and erectile function; general health status; belief that the respondent was free of prostate cancer; and whether cancer treatments limited activity or relationships. More than 90 percent said they would make the same treatment decision again, regardless of treatment received.	allocated radical prostatectomy and 60% allocated watchful waiting reported an increase in number of physical symptoms; 61% allocated radical prostatectomy and 64% allocated watchful waiting reported a reduction in quality of life. 1 article (Cook) found that men receiving brachytherapy scored better in urinary (91.8 v 88.1; p=0.02) and sexual (52.5 v 39.2; p=0.001) domains, and in patient satisfaction (93.6 v 76.9; p=0.001) compared with men receiving radical prostatectomy. 1 study (Malcolm) found that brachytherapy and cryotherapy were associated with higher urinary function compared to open radical and robotic radical prostatectomy. Brachytherapy was associated with higher sexual function compared to open radical prostatectomy, robotic radical prostatectomy and cryotherapy.			
Key Question 2. How do patient characteristics affect outcomes?				
No RCTs reported head-to-head comparisons of treatment outcomes stratified by race/ethnicity, and most did not provide baseline racial characteristics. Available data were largely from case series. Few studies reported head-to-head comparisons, and there was limited adjustment for confounding factors. Modest	The Prostate Intervention versus Observation Trial (PIVOT) trial results were presented by Dr. Timothy Wilt at the American Urology Association ~~last May~~May 2011. Sub-group analysis did not vary by age, race, Charleson score, or performance status.	Not reported	2 experts thought this was out of date. 1 expert thought this was still supported by the literature.	Original conclusion is out of date.

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
treatment differences reported in some on randomized studies have not been consistently reported in well powered studies. There was little evidence of a differential effect of treatments based on age. While differences exist in the incidence and morbidity of prostate cancer based on patient age and there are differences in the treatments offered to men at different age ranges, few studies directly compared the treatment effects of different therapies across age groups. Most RCTs did not have age exclusion criteria. The mean/median age ranged from a low of 63 years for trials of RP to 72 years for trials of EBRT. Only one RCT provided subgroup analysis according to age. Results suggest that survival benefits of RP compared with WW may be limited to men under 65 years of age. Practice patterns from observational studies show that RP is the most common treatment option in younger men with localized prostate cancer.				
Key Question 3. How do provider and hospital characteristics affect outcomes?				
Results from national administrative databases and surveys suggested that provider/hospital characteristics, including RP procedure volume, physician specialty, and geographic region, affect outcomes. (There was no information on volume and	No new data	Not reported	2 experts thought this was still supported by the literature. 1 expert did not know.	Original conclusion is still valid and this portion of the original report does not need updating.

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
outcomes for brachytherapy, cryotherapy, or EBRT.) Patient outcomes varied in different locations and were associated with provider and hospital volume independent of patient and disease characteristics. Screening practices can influence the characteristics of patients diagnosed and tumors detected. Screening practices and treatment choices varied by physician specialty and across regions of the United States. These did not correlate with clinician availability. Clinicians were more likely to recommend procedures they performed regardless of tumor grades and PSA levels.				
Regional variation existed in physician availability, ratio of urologists and radiation oncologists per 100,000 adult citizens, screening practice, incidence, mortality, and treatment selection. The direction of regional variation was not always consistent.	No new data	Not reported	2 experts did not know.	Original conclusion is still valid and this portion of the original report does not need updating.
Surgeon RP volume was not associated with RP-related mortality and positive surgical margins. However, the adjusted relative risk of surgery-related complications was lower in patients treated by higher volume surgeons. Urinary complications and incontinence were lower for patients whose surgeons performed more than 40 RPs per year. The length of hospital stay	No new data	Not reported	2 experts did not know. 1 expert thought this was still supported by the literature.	Original conclusion is still valid and this portion of the original report does not need updating.

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
was shorter in patients operated on by surgeons who performed more RPs per year. Surgeon volume of robotic laparoscopic RP was marginally associated with lower adjusted odds of extensive (but not any or focal) positive margins. Pooled analysis showed that surgery-related mortality and late urinary complications were lower and length of stay was shorter in hospitals that performed more RPs per year. Hospital readmission rates were lower in hospitals with greater volume. Teaching hospitals had a lower rate of surgery-related complications and higher scores of operative quality.				
Key Question 4. How do tumor characteristics affect outcomes?				
Little data existed on the comparative effectiveness of treatments based on PSA levels, histologic score, and tumor volume to identify low-, intermediate-, and high risk tumors.	The Prostate Intervention versus Observation Trial (PIVOT) trial results were presented by Dr. Timothy Wilt at the American Urology Association ~~last May~~May 2011. A subgroup analysis suggested that men with high-risk features (PSA > 10, and intermediate risk) might have a survival benefit.	Not reported	3 experts thought this was out of date.	Original conclusion is out of date.
Secondary analysis of one randomized trial concluded that disease-specific mortality at 10 years for men having RP compared with WW differed according to age but not baseline PSA level or Gleason score.	The Prostate Intervention versus Observation Trial (PIVOT) trial results were presented by Dr. Timothy Wilt at the American Urology Association ~~last May~~May 2011. A subgroup analysis did not find that younger men benefited from surgery, though did not look at the interaction between age and	Not reported	2 experts thought this was out of date. 1 expert thought this was still supported by the literature.	Original conclusion is out of date.

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
	tumor-risk.			
Based on very limited nonrandomized trial data, disease-specific survival was similar for men treated with EBRT or with RP in men with baseline PSA >10 ng/ml. Men with Gleason scores 8-10 were more likely to have biochemical recurrence than men with Gleason scores 2-6, regardless of type of treatment.	No new data	Not reported	1 expert did not know. 1 expert thought this was out of date. .	Original conclusion is still valid and this portion of the original report does not need updating.

ADT = androgen deprivation therapy; AE = adverse effects; EBRT = external beam radiotherapy; GnRH = gonadotropin-releasing hormone; Gy = gray; IMRT = intensity modulated radiation therapy; mL = milliliters; ng = nanogram; PSA = prostate specific antigen; RCT = randomized controlled trial; RP = radical prostatectomy; SCEPC = Southern California Evidence-based Practice Center; SPCG = Scandinavian Prostate Cancer Group; WW = watchful waiting

References

1. Wilt TJ, Shamliyan TA, Taylor B, et al. Comparative Effectiveness of Therapies for Clinically Localized Prostate Cancer. Comparative Effectiveness Review No. 13. (Prepared by Minnesota Evidence-based Practice Center under Contract No. 290-02-0009.) Agency for Healthcare Research and Quality. February 2008. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

2. Shekelle PG, Newberry SJ, Maglione M, et al. Assessment of the Need to Update Comparative Effectiveness Reviews: Report of an Initial Rapid Program Assessment (2005-2009) (Prepared by the Southern California Evidence-based Practice Center). Rockville, MD: Agency for Healthcare Research and Quality; October 2009.

3. Shojania KG, Sampson M, Ansari MT, et al. How quickly do systematic reviews go out of date? A survival analysis. Ann Intern Med. 2007 Aug 21;147(4):224-33. PMID: 17638714.

4. Hu JC, Gu X, Lipsitz SR, et al. Comparative effectiveness of minimally invasive vs open radical prostatectomy. JAMA. 2009 Oct 14;302(14):1557-64. PMID: 19826025.

5. Keating NL, O'Malley AJ, Freedland SJ, et al. Diabetes and cardiovascular disease during androgen deprivation therapy: observational study of veterans with prostate cancer. J Natl Cancer Inst. 2010 Jan 6;102(1):39-46. PMID: 19996060.

6. Kibel AS, Ciezki JP, Klein EA, et al. Survival Among Men With Clinically Localized Prostate Cancer Treated With Radical Prostatectomy or Radiation Therapy in the Prostate Specific Antigen Era. J Urol. 2012 Feb 13. PMID: 22335870.

7. Dosoretz AM, Chen MH, Salenius SA, et al. Mortality in men with localized prostate cancer treated with brachytherapy with or without neoadjuvant hormone therapy. Cancer. 2010 Feb 15;116(4):837-42. PMID: 20052734.

8. Warde P, Mason M, Ding K, et al. Combined androgen deprivation therapy and radiation therapy for locally advanced prostate cancer: a randomised, phase 3 trial. Lancet. 2011 Dec 17;378(9809):2104-11. PMID: 22056152.

9. Jones CU, Hunt D, McGowan DG, et al. Radiotherapy and short-term androgen deprivation for localized prostate cancer. N Engl J Med. 2011 Jul 14;365(2):107-18. PMID: 21751904.

10. Johansson E, Steineck G, Holmberg L, et al. Long-term quality-of-life outcomes after radical prostatectomy or watchful waiting: the Scandinavian Prostate Cancer Group-4 randomised trial. Lancet Oncol. 2011 Sep;12(9):891-9. PMID: 21821474.

11. Bannuru RR, Dvorak T, Obadan N, et al. Comparative evaluation of radiation treatments for clinically localized prostate cancer: an updated systematic review. Ann Intern Med. 2011 Aug 2;155(3):171-8. PMID: 21646550.

12. Malcolm JB, Fabrizio MD, Barone BB, et al. Quality of life after open or robotic prostatectomy, cryoablation or brachytherapy for localized prostate cancer. J Urol. 2010 May;183(5):1822-8. PMID: 20303100.

13. Donnelly BJ, Saliken JC, Brasher PM, et al. A randomized trial of external beam radiotherapy versus cryoablation in patients with localized prostate cancer. Cancer. 2010 Jan 15;116(2):323-30. PMID: 19937954.

14. Widmark A, Klepp O, Solberg A, et al. Endocrine treatment, with or without radiotherapy, in locally advanced prostate cancer (SPCG-7/SFUO-3): an open randomised phase III trial. Lancet. 2009 Jan 24;373(9660):301-8. PMID: 19091394.

15. Barry MJ, Gallagher PM, Skinner JS, et al. Adverse effects of robotic-assisted laparoscopic versus open retropubic radical prostatectomy among a nationwide random sample of medicare-age men. J Clin Oncol. 2012 Feb 10;30(5):513-8. PMID: 22215756.

16. Crook JM, Gomez-Iturriaga A, Wallace K, et al. Comparison of health-related quality of life 5 years after SPIRIT: Surgical Prostatectomy Versus Interstitial Radiation Intervention Trial. J Clin Oncol. 2011 Feb 1;29(4):362-8. PMID: 21149658.

17. Kuban DA, Levy LB, Cheung MR, et al. Long-term failure patterns and survival in a randomized dose-escalation trial for prostate cancer. Who dies of

disease? Int J Radiat Oncol Biol Phys. 2011 Apr 1;79(5):1310-7. PMID: 20493642.

18. Viani GA, Stefano EJ, Afonso SL. Higher-than-conventional radiation doses in localized prostate cancer treatment: a meta-analysis of randomized, controlled trials. Int J Radiat Oncol Biol Phys. 2009 Aug 1;74(5):1405-18. PMID: 19616743.

19. Hoskin PJ, Rojas AM, Bownes PJ, et al. Randomised trial of external beam radiotherapy alone or combined with high-dose-rate brachytherapy boost for localised prostate cancer. Radiother Oncol. 2012 Feb 16. PMID: 22341794.

20. Arcangeli G, Saracino B, Gomellini S, et al. A prospective phase III randomized trial of hypofractionation versus conventional fractionation in patients with high-risk prostate cancer. Int J Radiat Oncol Biol Phys. 2010 Sep 1;78(1):11-8. PMID: 20047800.

21. Hanks GE, Pajak TF, Porter A, et al. Phase III trial of long-term adjuvant androgen deprivation after neoadjuvant hormonal cytoreduction and radiotherapy in locally advanced carcinoma of the prostate: the Radiation Therapy Oncology Group Protocol 92-02. J Clin Oncol. 2003 Nov 1;21(21):3972-8. PMID: 14581419.

22. Mottet N, Peneau M, Mazeron J. Impact of radiotherapy (RT) combined with androgen deprivation (ADT) versus ADT alone for local control in clinically locally advanced prostate cancer. J Clin Oncol. 2010;28(abstract 4505).

23. Pollack A, Walker G, Buyyounouski M, et al. Five year results of a randomized external beam radiotherapy hypofractionation trial for prostate cancer Int J Radiat Oncol Biol Phys. 2011;81(S1).

24. Bolla M, De Reijke TM, Van Tienhoven GJ, et al. Six-month concomitant and adjuvant hormonal treatment with external beam irradiation is inferior to 3-years hormonal treatment for locally advanced prostate cancer: results of the EORTC randomized phase 3 trial 22961. European Urology Supplements 2008;7 (117):(abstract 86).

25. The VA/NCI/AHRQ CSP #407: Prostate Cancer Intervention Versus Observation Trial (PIVOT): Main Results From a Randomized Trial Comparing Radical Prostatectomy to Watchful Waiting in Men With Clinically Localized Prostate Cancer AUA Annual Meeting; 2011; Washington, DC.

Appendices

Appendix A: Search Methodology

Appendix B: Evidence Table

Appendix C: Questionnaire Matrix

Appendix A. Search Methodology

ALL SEARCHES WERE LIMITED TO THE FOLLOWING JOURNALS:
Annals of Internal Medicine
BMJ
JAMA
Lancet
New England Journal of Medicine

Cancer
Journal of Urology
Journal of the National Cancer Institute
Journal of Clinical Urology (0 hits)
European Urology

KEY QUESTION 1-
SEARCH 1:
DATABASE SEARCHED & TIME PERIOD COVERED:
PubMed® – 2007-3/5/2012

LANGUAGE:
English

SEARCH STRATEGY:
prostatic neoplasms OR "prostate cancer"
AND
ultrasound, high-intensity focused, transrectal OR radiotherapy, intensity-modulated OR radiotherapy OR proton OR cryosurgery OR (laparoscopy AND prostatectomy) OR (robotic* AND prostatectomy) OR (transrectal AND ultrasound) OR radiotherap* OR cryosurg* OR (laparoscop* AND prostatectom*) OR therapy[ti] OR therapies[ti] OR treatment*[ti] OR treating[ti] OR treat[ti] OR therapy/mh
AND
Limits: Clinical Trial, Randomized Controlled Trial, Clinical Trial, Phase I, Clinical Trial, Phase II, Clinical Trial, Phase III, Clinical Trial, Phase IV
NOT
metasta*[ti]
NOT
review OR case report* OR case-report* OR letter OR editorial
NOT
animal* NOT (human OR humans)

SEARCH STRATEGY #2:

prostatic neoplasms OR "prostate cancer"
AND
radical prostatectom* OR brachytherap* OR "adjuvant androgen deprivation" OR bicalutamide
AND
Limits: Clinical Trial, Randomized Controlled Trial, Clinical Trial, Phase I, Clinical Trial, Phase II, Clinical Trial, Phase III, Clinical Trial, Phase IV

SEARCH STRATEGY #3:
prostatic neoplasms OR "prostate cancer"
AND
Limits: Meta-Analysis
OR
prostatic neoplasms OR "prostate cancer"
AND
systematic[sb]
NOT
Results of previous searches

SEARCH STRATEGY #4:
prostatic neoplasms OR "prostate cancer"
AND
“quality of life" OR quality of life[mh] OR qol OR hrqol OR "health status" OR satisfaction OR satisfied OR or dissatisf*
NOT
animal* NOT (human OR humans)
NOT
Results of previous searches

TOTAL OF ALL KEY QUESTION 1 SEARCHES AFTER LIMITING TO SPECIFIED JOURNALS: 473

==========

KEY QUESTION 2-
DATABASE SEARCHED & TIME PERIOD COVERED:
PubMed – 2007-3/7/2012

LANGUAGE:
English

SEARCH STRATEGY:
prostatic neoplasms OR "prostate cancer"
AND

"age factors"OR age [ti] OR ethnicityOR ethnic groups OR race OR racial OR co-morbidit* OR comorbid*

NUMBER OF RESULTS AFTER REMOVING DUPLICATES & REFERENCES TO METASTATIC CANCER & LIMITING TO SPECIFIED JOURNALS: 267

==========

KEY QUESTION 3-
DATABASE SEARCHED & TIME PERIOD COVERED:
PubMed – 2007-3/12/2012

SEARCH STRATEGY:
prostatic neoplasms OR "prostate cancer"
AND
"hospital volume" OR "surgeon volume" OR "clinical competence" OR "physician's practice patterns" OR practice pattern* OR "health services research" OR "learning curve" OR malpractice OR physician*[ti] OR physicians[mh] OR hospital*[ti] OR hospitals[mh] OR epidemiology[mh] OR epidemiolog*[ti]

KEY QUESTION 3 revision (adding term "Case load")
DATABASE SEARCHED & TIME PERIOD COVERED:
PubMed – 2007-3/13/2012

SEARCH STRATEGY:
prostatic neoplasms OR "prostate cancer"
AND
caseload* OR case load* OR case volume*

NUMBER OF RESULTS AFTER REMOVING DUPLICATES & LIMITING TO SPECIFIED JOURNALS: 38

==========

KEY QUESTION 4-
DATABASE SEARCHED & TIME PERIOD COVERED:
PubMed – 2007-3/9/2012

SEARCH STRATEGY:
prostatic neoplasms OR "prostate cancer"
AND
prostate-specific antigen OR "tumor characteristics" OR "tumor volume" OR "tumour characteristics" OR "tumour volume" OR histologic OR histology OR psa OR gleason
AND

mortality[ti] OR mortality[mh] OR survival[ti] OR survival[mh] OR prognos*[ti] OR prognos*[mh] OR outcome*[ti] OR treatment outcome[mh] OR dying OR died OR death OR predict*[ti]
NOT
animal* NOT (human OR humans)

NUMBER OF RESULTS IN SPECIFIED JOURNALS: 683

==========

TOTAL NUMBER OF RESULTS IN SPECIFIED JOURNALS FOR ALL KEY QUESTIONS: 1458

Appendix B. Evidence Table

Article ID, Author, year	Trial	n	Subjects	Primary Outcome	Duration	Findings
Key Question 1. What are the comparative risks, benefits, and outcomes of therapies?						
Randomized comparisons across primary treatment categories						
Wilt, not yet published, but presented at the American Urological Association 2011 Annual Meeting in Washington, DC[25]	PIVOT Prostate Cancer Intervention Versus Observation Trial	n = 731 Radical prostatectomy: n = 364 Observation: n = 367	Age ≤ 75, T1-2, N0, M0, PSA <50 ng/mL, diagnosed ≤12 months, candidate for radical prostatectomy	All cause mortality	Median follow-up 10 years	Non-significant absolute risk reduction in patients undergoing radical prostatectomy Adjusted risk ratio 2.9% (-4.1-10.3). Sub-group analysis did not vary by age, race, Charlson score, performance status, or Gleason score, but did vary by PSA and tumor risk. In men with low risk radical prostatectomy did not reduce all-cause mortality (HR = 1.15 p=0.045) but in men with intermediate risk, radical prostatectomy decreased overall mortality (HR = 0.69; p=0.04). In men with PSA >10, radical prostatectomy reduced overall mortality (HR = 0.36, p=0.03).
Randomized comparisons within primary treatment categories						
Warde, 2011[8]	--	n =1201	Locally advance (T3 or T4) prostate cancer, organ confined disease (T2) with a PSA >40 ng/mL, or PSA > 20 ng/mL and a Gleason ≥8	Overall survival	7 years	The addition of radiation therapy to androgen deprivation therapy improved overall survival at 7 years (74%, 95% CI 70– 78 *vs* 66%, 60–70; hazard ratio [HR] 0·77, 95% CI 0·61–0·98, p=0·033).
Jones, 2011[9]	--	EBRT alone: n= 992 EBRT + ADT: n = 987	T1b, T1c, T2a, or T2b prostate adenocarcinoma and a PSA level ≤ 20 ng /mL	Overall survival	Median follow-up 9.1 years	Overall survival was 62% among patients receiving EBRT + ADT, as compared with 57% among patients receiving EBRT alone (hazard ratio for death with radiotherapy alone, 1.17;

Article ID, Author, year	Trial	n	Subjects	Primary Outcome	Duration	Findings
						P=0.03). Reanalysis according to risk showed reductions in overall and disease-specific mortality primarily among intermediate-risk patients, with no significant reductions among low-risk patients.
Hanks, 2003[21]	Radiation Therapy Oncology Group (RTOG) Protocol 92-02	n =1554	T2c-4 prostate cancer treated with androgen deprivation therapy, radiotherapy and either no additional therapy or 24 months of androgen deprivation therapy	Overall survival	5 years	No statistical difference in overall survival p=0.73.
Banniru, 2011[11]	--	n = 75 studies	Published English-language comparative studies involving adults with localized prostate cancer who either had first-line radiation therapy or received no initial treatment	Clinical and biochemical out-comes of radiation therapies for localized prostate cancer.	--	75 studies (10 randomized, controlled trials [RCTs] and 65 nonrandomized studies) met the inclusion criteria. A lack of high-quality comparative evidence precludes conclusions about the efficacy of radiation treatments compared with no treatments for localized prostate cancer.
Mottet, 2010[22]	--	N = 263 Androgen deprivation therapy: n = 130 Androgen deprivation therapy + radiotherapy: n = 133	Histologically confirmed PCa, T3- 4, or pT3 (biopsy) N0, M0 were treated with androgen deprivation therapy with or without the addition of localized radiotherapy	Progression free survival	5 years	The cumulative incidence of loco-regional progression at 5 years was 9.7% (combined group) versus 29% (ADT group) ($p<0.0002$) and the cumulative incidence of metastatic progression at 5 years respectively 3% vs 10.8% ($p<0.018$).
Bolla, 2008[24]	EORTC 22961	n = 970 Short androgen deprivation therapy: n = 483 Long androgen deprivation therapy: n = 487	T1c-2b N1-2 or pN1-2, or T2c-4 N0-2 M0	Overall survival and progression free survival.	Median follow-up 6.4 years	Survival with 6 months of androgen deprivation therapy was significantly shorter than with 3 years of adjuvant androgen deprivation therapy.
Widmark, 2009[14]	--	n = 875	T3; PSA<70; N0; M0	Prostate cancer	Median follow-up	Addition of local radiotherapy

Article ID, Author, year	Trial	n	Subjects	Primary Outcome	Duration	Findings
		Endocrine treatment only: n = 439 Endocrine treatment and radiotherapy: n = 436		specific mortality	7.6 years	to endocrine treatment halved the 10-year prostate-cancer-specific mortality.
Kuban, 2011[17]		n= 301	T1b-T3 prostate cancer treated to 70 Gy vs 78 Gy of radiation therapy.	Incidence of death from prostate cancer versus other causes.	9 years	Moderate dose escalation (78 Gy) decreases biochemical and clinical failure as well as prostate cancer death in patients with pretreatment PSA >10 ng/mL or high-risk disease.
Viani, 2009[18]	--	Total patient population = 2812; 7 studies included	Randomized, controlled studies comparing high dose radiation therapy with conventional dose radiation therapy for localized prostate cancer.	Biochemical failure, all-cause mortality rate, and prostate cancer mortality rate.	--	High dose radiotherapy is superior to conventional dose radiotherapy in preventing biochemical failure in low-, intermediate-, and high-risk prostate cancer patients p<0.001.
Hoskin, 2012[19]	--	n = 218 EBRT: n = 108 EBRT + high-dose-rate brachytherapy boost: n = 110	Stage T1 to T3, with no evidence of metastatic disease, a PSA <50 ug/l.	Relapse free survival	Median follow-up 85 months	Relapse free survival was higher in patients treated with EBRT + high-dose-rate brachytherapy p=0.04
Arcangeli, 2010[20]	--	n = 168	High risk patients that received 9 months of androgen deprivation therapy.	Freedom from biochemical failure.	Median follow-up for hypofractionated group: 32 months; median follow-up for conventional fractionation: 35 months.	Hypofractionated was superior in freedom from biochemical failure compared to conventional fractionation in patients with high-risk prostate cancer.
Pollack, 2011[23]	--	n = 303 Conventional: n = 152 Hypofractionated: n = 151	Age 65 years or older and were diagnosed with prostate cancer from 1995 to 2005 from the Surveillance, Epidemiology, and End Results (SEER)-Medicare database.	Biochemical failure	Median follow-up 60 months	No statistically significant differences between the treatment arms for biochemical failure, any failure, or late side effects.

Article ID, Author, year	Trial	n	Subjects	Primary Outcome	Duration	Findings
Donnelly, 2010[13]	--	n = 244 Cryoablation: n = 122 EBRT: n = 122	Eligibility criteria: histologically proven adenocarcinomaof the prostate, a biopsy tumor classification ofT2 or T3, no evidence of lymph node or distant metastases, a pretreatment PSA level#20 ng/mL, and a gland volume #60 cm3	Disease progression	36 months	No statistically significant disease progression.
Comparative outcomes data from nonrandomized reports						
Hu, 2009[4]	--	Minimally-invasive prostatectomy: n = 1938 Open radical prostatectomy: n = 6899	Population-based cohort study using US Surveillance, Epidemiology, and End Results Medicare linked data from 2003-2007	Postoperative 30-day complications, Anastomotic strictures 31-365 days post-operatively, incontinence, erectile dysfunction, and postoperative use of cancer therapies.	1.5 years	Minimally invasive prostatectomy compared to open radical prostatectomy was associated with shorter length of stay, lower rates of blood transfusions, fewer postoperative respiratory complications, fewer miscellaneous surgical complications, fewer anastomotic strictures, but increased risk of genitourinary complications, increased incontinence, and increased erectile dysfunction.
Keating, 2010[5]	--	n = 37,443	Men diagnosed with local or regional prostate cancer in the Veterans Healthcare Administration from 1/2001-12/2004	Association of androgen deprivation therapy with GnRH agonists, oral antiandrogens, the combo of the two, or orchiectomy with diabetes, coronary heart disease, myocardial infarction, sudden cardiac death, or stroke.	Through 12/2005	Treatment with GnRH agonists was associated with increased risk of diabetes, coronary heart disease, myocardial infarction, sudden cardiac death, and stroke. Combined androgen blockade and orchiectomy were associated with increased risk of coronary heart disease.

Article ID, Author, year	Trial	n	Subjects	Primary Outcome	Duration	Findings
Kibel, 2012[6]	--	Radical prostatectomy: n = 6,485 EBRT: n = 2,264 Brachyotherapy: n = 1,680	Men with localized prostate cancer	Overall survival and prostate specific mortality	10 year	EBRT was associated with decreased overall survival and increased prostate cancer specific mortality compared to radical prostatectomy. Brachytherapy was associated with decreased overall survival compared to radical prostatectomy.
Dosoretz, 2010[7]	--	Brachyotherapy + neoadjuvant hormone therapy: n = 1,083 Brachyotherapy alone: n = 1,391	Men with localized prostate cancer treated between 1991 and 2005 at centers within the 21st Century Oncology Consortium	All cause mortality	Median follow-up: 4.8 years (3.3-7.5)	Men $\geq$ 73 years who received brachytherapy and neoadjuvant hormone therapy had an increased risk of all cause mortality compared to men who only received brachyotherapy.
Johansson, 2011[10]	SPCG-4	Radical prostatectomy: n = 182 Watchful waiting: n = 167 Control: n = 214	All Swedish and Finnish men (400 of 695) assigned to radical prostatectomy or watchful waiting and a population-based control.	Quality of life	Median follow-up of 12.2 years	Anxiety was higher in the radical prostatectomy and watchful waiting groups (77 [43%] of 178 and 69 [43%] of 161 men) than in the control group (68 [33%] of 208 men; relative risk 1·42, 95% CI 1·07–1·88). Prevalence of erectile dysfunction was 84% (146 of 173 men) in the radical prostatectomy group, 80% (122 of 153) in the watchful-waiting group, and 46% (95 of 208) in the control group and prevalence of urinary leakage was 41% (71 of 173), 11% (18 of 164), and 3% (six of 209), respectively. In a longitudinal analysis of men in SPCG-4 who provided information at two follow-up points 9 years apart, 38 (45%) of 85 men allocated radical prostatectomy and 48 (60%) of 80 men allocated watchful waiting reported an increase in

Article ID, Author, year	Trial	n	Subjects	Primary Outcome	Duration	Findings
						number of physical symptoms; 50 (61%) of 82 and 47 (64%) of 74 men, respectively, reported a reduction in quality of life.
Crook, 2011[16]	SPIRIT: Surgical Prostatectomy versus Interstitial Radiation Intervention Trial	n = 168 (60.7% brachytherapy; 39.3% radical prostatectomy)	Men recruited for the SPIRIT trial	Health related quality of life	5 years	No difference in bowel or hormonal domains, but men treated with brachytherapy scored better in urinary (91.8 v 88.1; p=0.02) and sexual (52.5 v 39.2; p=0.001) domains, and in patient satisfaction (93.6 v 76.9; p=0.001).
Malcolm, 2010 [12]	--	n= 785	From February 2000 to December 2008 all patients undergoing operative treatment of localized prostate cancer at UCLA were asked to participate.	Health related quality of life	24 months	Brachytherapy and cryotherapy were associated with higher urinary function compared to open radical and robotic radical prostatectomy. Brachytherapy was associated with higher sexual function compared to open radical prostatectomy, robotic radical prostatectomy and cryotherapy.
Barry, 2012[15]	--	n = 797 Robotic surgery: n = 406 Open surgery: n = 220	Random population sample from Medicare claims	Adverse effects (sexual dysfunction and incontinence)	14 months postoperatively	There were no statistical difference in adverse effects.
Key Question 2. How do patient characteristics affect outcomes?						
Wilt, not yet published, but presented at the American Urological Association 2011 Annual Meeting in Washington, DC[25]	PIVOT Prostate Cancer Intervention Versus Observation Trial	n = 731 Radical prostatectomy: n =364 Observation: n =367	Age $\leq$ 75, T1-2, N0, M0, PSA <50 ng/mL, diagnosed $\leq$12 months, candidate for radical prostatectomy	All cause mortality	Median follow-up 10 years	Non-significant absolute risk reduction in patients undergoing radical prostatectomy Adjusted risk ratio 2.9% (-4.1-10.3). Sub-group analysis did not vary by age, race, Charlson score, performance status, or Gleason score, but did vary by PSA and tumor risk. In men with low risk radical prostatectomy did not reduce all-cause mortality

Article ID, Author, year	Trial	n	Subjects	Primary Outcome	Duration	Findings
						(HR = 1.15 p=0.045) but in men with intermediate risk, radical prostatectomy decreased overall mortality (HR = 0.69; p=0.04). In men with PSA >10, radical prostatectomy reduced overall mortality (HR = 0.36, p=0.03)
Key Question 3. How do provider and hospital characteristics affect outcomes?						
Wilt, not yet published, but presented at the American Urological Association 2011 Annual Meeting in Washington, DC[25]	PIVOT Prostate Cancer Intervention Versus Observation Trial	n = 731 Radical prostatectomy: n = 364 Observation: n = 367	Age ≤ 75, T1-2, N0, M0, PSA <50 ng/mL, diagnosed ≤12 months, candidate for radical prostatectomy	All cause mortality	Median follow-up 10 years	Non-significant absolute risk reduction in patients undergoing radical prostatectomy Adjusted risk ratio 2.9% (-4.1-10.3). Sub-group analysis did not vary by age, race, Charlson score, performance status, or Gleason score, but did vary by PSA and tumor risk. In men with low risk radical prostatectomy did not reduce all-cause mortality (HR = 1.15 p=0.045) but in men with intermediate risk, radical prostatectomy decreased overall mortality (HR = 0.69; p=0.04). In men with PSA >10, radical prostatectomy reduced overall mortality (HR = 0.36, p=0.03).
Key Question 4. How do tumor characteristics affect outcomes?						
Wilt, not yet published, but presented at the American Urological Association 2011 Annual Meeting in Washington, DC[25]	PIVOT Prostate Cancer Intervention Versus Observation Trial	n = 731 Radical prostatectomy: n = 364 Observation: n = 367	Age ≤ 75, T1-2, N0, M0, PSA <50 ng/mL, diagnosed ≤12 months, candidate for radical prostatectomy	All cause mortality	Median follow-up 10 years	Subgroup analyses suggested that men with high-risk features (PSA > 10, and intermediate risk) might have a survival benefit and did not find that younger men benefited from surgery, though did not look at the interaction between age and tumor-risk.

ADT = androgen deprivation therapy; EBRT = external beam radiotherapy; GnRH = gonadotropin-releasing hormone; HR = hazard ratio; mL = milliliters; ng = nanogram; Gy = gray

Appendix C. Questionnaire Matrix

Surveillance and Identification of Triggers for Updating Systematic Reviews for the EHC Program

Title: **Comparative Effectiveness of Therapies for Clinically Localized Prostate Cancer**

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
Key Question 1. What are the comparative risks, benefits, and outcomes of therapies?			
No one therapy can be considered the preferred treatment for localized prostate cancer due to limitations in the body of evidence as well as the likely tradeoffs an individual patient must make between estimated treatment effectiveness, necessity, and adverse effects. All treatment options result in adverse effects (primarily urinary, bowel, and sexual), although the severity and frequency may vary between treatments. Even if differences in therapeutic effectiveness exist, differences in adverse effects, convenience, and costs are likely to be important factors in individual patient decision making. Patient satisfaction with therapy is high and associated with several clinically relevant outcome measures. Data from nonrandomized trials are inadequate to reliably assess comparative effectiveness	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
and adverse effects. Additional randomized controlled trials (RCTs) are needed.			
Randomized comparisons across primary treatment categories			
Radical prostatectomy compared with watchful waiting (2 RCTs). Compared with men who used watchful waiting (WW), men with clinically localized prostate cancer detected by methods other than PSA testing and treated with radical prostatectomy (RP) experienced fewer deaths from prostate cancer, marginally fewer deaths from any cause, and fewer distant metastases. The greater benefit of RP on cancer-specific and overall mortality appears to be limited to men under 65 years of age but is not dependent on baseline PSA level or histologic grade. Two RCTs compared WW with RP. The Scandinavian Prostate Cancer Group (SPCG) trial found significantly lower incidences of all-cause deaths (24 vs. 30 percent), disease-specific deaths (10 vs. 15 percent), and distant metastases (14 vs. 23 percent) for subjects treated with RP than for subjects assigned WW after a median follow-up of 8.2 years. Surgery was associated with greater urinary and sexual dysfunction than WW. An older trial of 142 men found no significant differences in overall survival between RP and WW after	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
a median follow-up of 23 years, although small sample size limited study power.			
Radical prostatectomy vs. external beam radiotherapy (1 RCT). One small (N=106), older trial indicated that, compared with EBRT, RP was more effective in preventing progression, recurrence, or distant metastases in men with clinically localized prostate cancer detected by methods other then PSA testing. Treatment failure at 5 years of follow-up, defined as acid phosphatase elevation on two consecutive follow-up visits or appearance of bone or parenchymal disease with or without concomitant acid phosphatase elevation, occurred in 39 percent for EBRT compared with 14 percent for RP.	☐	New Evidence:	☐
Cryotherapy, laparoscopic or robotic assisted radical prostatectomy, primary androgen deprivation therapy, high-intensity focused ultrasound (HIFU), proton beam radiation therapy, or intensity modulated radiation therapy (IMRT) (0 RCTs). It is not known whether these therapies are better or worse than other treatments for localized prostate cancer because these options have not been evaluated in RCTs.	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
Randomized comparisons within primary treatment categories			
Radical prostatectomy combined with neoadjuvant androgen deprivation therapy (5 RCTs). The addition of neoadjuvant hormonal therapy to RP did not improve survival or cancer recurrence rates, defined by PSA recurrence, but increased AEs. One small RCT comparing RP alone and RP combined with neoadjuvant ADT found no overall or disease-specific survival benefit with the addition of neoadjuvant ADT after a median follow-up of 6 years. The addition ofneoadjuvant ADT did not prevent biochemical progression compared with RP alone in any of the four trials. The trial comparing 3 months and 8 months neoadjuvant ADT with RP reported greater AEs in the 8-month group than the 3-month group (4.5 percent vs. 2.9 percent) and higher incidence of hot flashes (87 percent vs. 72 percent).	☐	New Evidence:	☐
External beam radiotherapy: comparison of EBRT regimens (5 RCTs). No RCTs compared EBRT and WW. It is not known if using higher doses of EBRT by increasing either the total amount or type of radiation (e.g., via high-dose intensity modulated or proton beam or by adding brachytherapy) improves overall or disease specific survival compared with other therapies. No EBRT regimen, whether conventional, high dose conformal, dose	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
fractionation, or hypofractionation, was superior in reducing overall or disease-specific mortality. Increasing the total amount of radiation or adding brachytherapy after EBRT decreased cancer recurrence compared with lower doses of radiation. One trial (N=936) found that the probability of biochemical or clinical progression at 5 years was lower in the long-arm group (66 Gy in 33 fractions) than the short-arm group (52.5 Gy in 20 fractions). Conventional dose EBRT (64 Gy in 32 fractions) and hypofractionated EBRT (55 Gy in 20 fractions) resulted in similar PSA relapse. One trial (N=104) found that brachytherapy combined with EBRT reduced biochemical or clinical progression compared with EBRT alone. One trial (N=303) found that high-dose EBRT (79.2 Gy that included 3D conformal proton 50.4 Gy with 28.8 Gy proton boost) was more effective than conventional-dose EBRT (70 Gy that included 19.8 Gy proton boost) in the percentage of men free from biochemical failure at 5 years (80 percent in the high-dose group and 61 percent in the conventional-dose group). Effectiveness was evident in low-risk disease (PSA <10 ng/ml, stage ²T2a tumors, or Gleason ²6) and higher risk disease. Acute combined gastrointestinal (GI) and genitourinary (GU) toxicity was lower in the long arm (7.0 percent) than in the short arm (11.4 percent). Late toxicity was similar. There			

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
were no significant differences between conventional and hypofractionated EBRT with the exception of rectal bleeding at 2 years after therapy, which had a higher prevalence in the hypofractionated group. Acute GI or GU symptoms of at least moderate severity were similar in the trial comparing high and conventional doses.			
External beam radiotherapy combined with androgen deprivation therapy compared with EBRT alone (3 RCTs). ADT combined with EBRT (ADT + EBRT) may decrease overall and disease-specific mortality but increase AEs compared with EBRT alone in high-risk patients defined by PSA levels and Gleason histologic score (PSA >10 ng/ml or Gleason >6). One RCT (N=216) found that conformal EBRT combined with 6 months of ADT reduced all-cause mortality, disease-specific mortality, and PSA failure compared with conformal EBRT alone after a median follow-up of 4.5 years. There were significant increases in gynecomastia and impotence in the ADT + EBRT group compared with EBRT alone. One RCT (N=206) found that 6 months of ADT + EBRT did not significantly reduce disease-specific mortality compared with conformal EBRT alone in T2b and T2c subjects after a median follow-up of 5.9 years. Six months of combination therapy reduced clinical failure, biochemical failure, or death from any cause compared with EBRT alone in	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
subjects with T2c disease but not in T2b subjects.			
Different doses of adjuvant external beam radiotherapy combined with brachytherapy (1 RCT). One small trial comparing different doses of supplemental EBRT, 20 Gy (N=83) vs. 44 Gy (N=76), adjuvant to brachytherapy (103Pd) implant found no significant differences in the number of biochemical failure events and freedom from biochemical progression at 3 years.	☐	New Evidence:	☐
Brachytherapy compared with brachytherapy (1 RCT). No RCTs compared brachytherapy alone with other major treatment options. Preliminary results from one small trial (N=126) comparing ^{125}I with ^{103}Pd brachytherapy found similar biochemical control at 3 years. There was a trend toward more radiation proctitis, defined as persistent bleeding, with ^{125}I.	☐	New Evidence:	☐
Bicalutamide combined with standard care: RP, EBRT, or WW (3 RCTs). Androgen deprivation with bicalutamide alone or in addition to RP or EBRT did not reduce cancer recurrence or mortality. There was no difference in total number of deaths between the bicalutamide and placebo groups for men receiving RP or EBRT at the median follow-up of 5.4 years. Among WW subjects, there were significantly more deaths with bicalutamide	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
compared with placebo. The addition of bicalutamide to standard care did not reduce progression.			
Comparative outcomes data from nonrandomized reports			
Cryosurgery. No randomized trials evaluated cryosurgery, and the majority of reports included patients with T3-T4 stages. Overall or prostate-cancer specific survival was not reported. Progression-free survival in patients with T1-T2 stages ranged from 29 to 100 percent. AEs were often not reported but, when described, included bladder outlet obstruction (3 to 21 percent), tissue sloughing (4 to 15 percent), and impotence (40 to 100 percent). Outcomes may be biased by patient and provider characteristics.	☐	New Evidence:	☐
Laparoscopic and robotic assisted prostatectomy. Three reviews estimated the effectiveness and AEs of laparoscopic and robotic assisted prostatectomy from 21 nonrandomized trials and case series. Most originated from centers outside of the United States. Median follow-up was 8 months. Laparoscopic RP had longer operative time but lower blood loss and improved wound healing compared with open retropubic RP. Reintervention rates were similar. Results from eight nonrandomized reports suggested that total complications, continence rates, positive surgical margins, and operative	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
time were similar for robotic assisted and open RP. Median length of hospital stay (1.2 vs. 2.7 days) and median length of catheterization (7 vs. 13 days) were shorter after robotic assisted RP than open RP.			
Intensity modulated radiation therapy. There was no direct evidence that IMRT results in better survival or disease-free survival than other therapies for localized prostate cancer. Based on nonrandomized data, the absolute risks of clinical and biochemical outcomes (including tumor recurrence), toxicity, and quality of life after IMRT are comparable with conformal radiation. There is low-level evidence that IMRT provides at least as good a radiation dose to the prostate with less radiation to the surrounding tissues compared with conformal radiation therapy.	☐	New Evidence:	☐
Proton EBRT. There were no data from randomized trials comparing EBRT using protons vs. conventional EBRT or other primary treatment options. In one randomized trial, men with localized prostate cancer had statistically significantly lower odds of biochemical failure (increase in PSA) 5 years after the higher dose of EBRT with a combination of conformal photon and proton beams without increased risk of adverse effects. Based on nonrandomized reports, the rates of clinical outcomes and toxicity after proton therapy may be comparable with conformal radiation. There was no direct	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
evidence that proton EBRT results in better overall or disease-free survival than other therapies.			
High-intensity focused ultrasound therapy. There were no data from randomized trials comparing HIFU with other primary treatment options. Biochemical progression-free survival rates of 66 to 87 percent and negative biopsy rates of 66 to 93 percent were reported from noncontrolled studies. The absolute risk of impotence and treatment-related morbidity appeared to be similar to other treatments. Followup duration was <10 years.	☐	New Evidence:	☐
Health status, quality of life, and treatment satisfaction. Eight studies of health status and quality of life, including a U.S. population-based survey, were eligible. Bother due to dripping or leaking of urine was more than six fold greater in RP-treated men than in men treated with EBRT after adjusting for baseline factors. Bother due to bowel dysfunction (4 vs. 5 percent) or sexual dysfunction (47 vs. 42 percent) was similar for RP and EBRT. In a subgroup of men ages 70 and over, bother due to urine, bowel, or sexual dysfunction was 5.1, 2.4, and 2.8 times higher, respectively, for aggressive (RP/EBRT) vs. conservative (WW/ADT) therapy. Satisfaction with treatment was high, with less than 5 percent reporting dissatisfaction, unhappiness, or feeling terrible about their treatment, although the highest percent was	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
among those treated with RP. Treatment satisfaction was highly correlated with bowel, bladder, and erectile function; general health status; belief that the respondent was free of prostate cancer; and whether cancer treatments limited activity or relationships. More than 90 percent said they would make the same treatment decision again, regardless of treatment received.			
Key Question 2. How do patient characteristics affect outcomes?			
No RCTs reported head-to-head comparisons of treatment outcomes stratified by race/ethnicity, and most did not provide baseline racial characteristics. Available data were largely from case series. Few studies reported head-to-head comparisons, and there was limited adjustment for confounding factors. Modest treatment differences reported in some on randomized studies have not been consistently reported in well powered studies. There was little evidence of a differential effect of treatments based on age. While differences exist in the incidence and morbidity of prostate cancer based on patient age and there are differences in the treatments offered to men at different age ranges, few studies directly compared the treatment effects of different therapies across age groups. Most RCTs did not have age exclusion criteria. The mean/median	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
age ranged from a low of 63 years for trials of RP to 72 years for trials of EBRT. Only one RCT provided subgroup analysis according to age. Results suggest that survival benefits of RP compared with WW may be limited to men under 65 years of age. Practice patterns from observational studies show that RP is the most common treatment option in younger men with localized prostate cancer.			
Key Question 3. How do provider and hospital characteristics affect outcomes?			
Results from national administrative databases and surveys suggested that provider/hospital characteristics, including RP procedure volume, physician specialty, and geographic region, affect outcomes. (There was no information on volume and outcomes for brachytherapy, cryotherapy, or EBRT.) Patient outcomes varied in different locations and were associated with provider and hospital volume independent of patient and disease characteristics. Screening practices can influence the characteristics of patients diagnosed and tumors detected. Screening practices and treatment choices varied by physician specialty and across regions of the United States. These did not correlate with clinician availability. Clinicians were more likely to recommend procedures they performed regardless of tumor grades and PSA levels.	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
Regional variation existed in physician availability, ratio of urologists and radiation oncologists per 100,000 adult citizens, screening practice, incidence, mortality, and treatment selection. The direction of regional variation was not always consistent.	☐	New Evidence:	☐
Surgeon RP volume was not associated with RP-related mortality and positive surgical margins. However, the adjusted relative risk of surgery-related complications was lower in patients treated by higher volume surgeons. Urinary complications and incontinence were lower for patients whose surgeons performed more than 40 RPs per year. The length of hospital stay was shorter in patients operated on by surgeons who performed more RPs per year. Surgeon volume of robotic laparoscopic RP was marginally associated with lower adjusted odds of extensive (but not any or focal) positive margins. Pooled analysis showed that surgery-related mortality and late urinary complications were lower and length of stay was shorter in hospitals that performed more RPs per year. Hospital readmission rates were lower in hospitals with greater volume. Teaching hospitals had a lower rate of surgery-related complications and higher scores of operative quality.	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
Key Question 4. How do tumor characteristics affect outcomes?			
Little data existed on the comparative effectiveness of treatments based on PSA levels, histologic score, and tumor volume to identify low-, intermediate-, and high risk tumors.	☐	New Evidence:	☐
Secondary analysis of one randomized trial concluded that disease-specific mortality at 10 years for men having RP compared with WW differed according to age but not baseline PSA level or Gleason score.	☐	New Evidence:	☐
Based on very limited nonrandomized trial data, disease-specific survival was similar for men treated with EBRT or with RP in men with baseline PSA >10 ng/ml. Men with Gleason scores 8-10 were more likely to have biochemical recurrence than men with Gleason scores 2-6, regardless of type of treatment.	☐	New Evidence:	☐
Are there new data that could inform the key questions that might not be addressed in the conclusions?			