Effective Health Care

Therapies for Clinically Localized Prostate Cancer

Results of Topic Selection Process & Next Steps

The nominator, a regulatory executive from EDAP Technomed, Inc. – a manufacturer of a medical device used to treat prostate cancer – is interested in an update of the AHRQ systematic review on therapies for clinically localized prostate cancer. We contacted the American Urological Association (AUA), the nominators of the previous systematic review update of the same topic and found that they were also interested in an updated review to inform development of a planned clinical practice guideline update. AUA also shared a supplementary evidence report that they commissioned from the Evidence-based Practice Center (EPC) that performed the systematic review update.

This topic will go forward as a new systematic review update based on both the 2014 AHRQ update and the supplementary evidence report provided by the AUA. To sign up for notification when this and other Effective Health Care (EHC) Program topics are posted for public comment, please go to https://effectivehealthcare.ahrq.gov/email-updates.

Topic Brief

Topic Number and Name: #0829, Therapies for Clinically Localized Prostate Cancer

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Authors

Lionel L. Bañez
Robin Paynter

Conflict of Interest: None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

Background

In 2019, the American Cancer Society projects prostate cancer to be the most frequently diagnosed non-dermatologic malignancy (174,650 new cases) and the second leading cause of cancer death (31,620 deaths) among men in the United States.[1] Plainly stated, about one in every nine men in the U.S. will be diagnosed with prostate cancer in their lifetime. Prostate cancer also represents a significant cost burden. The total national medical costs attributable to prostate cancer treatment was $11 billion in 2010 and is projected to rise to $16 billion by 2020.[2]

About 90% of men who receive a diagnosis of prostate cancer have localized disease confined to the prostate gland. Clinically localized prostate cancer (CLPC) is characterized by organ-confined tumors (T1 and T2 disease) or tumors that have spread beyond the capsule of the prostate gland but *not* invading the seminal vesicles, the urinary sphincter, bladder, rectum or pelvic wall or the pelvic lymph nodes (T3a disease).[3] The primary goal in the management of this patient subset is to target men most likely to need therapeutic intervention to prevent death or disability while minimizing treatment-related complications. There are numerous treatments available to treat CLPC.[4] Mainstay treatments include surgery, radiation therapy, and hormonal therapy. For these treatment categories, multiple approaches have been developed in the past two decades. This includes laparoscopic and robot-assisted laparoscopic surgical approaches, intensity modulated radiation therapy (IMRT), three-dimensional conformal radiation therapy (3D-CRT), stereotactic body radiation therapy, and proton beam radiation therapy approaches,[5] and various drug preparations for hormonal therapy such as luteinizing hormone-releasing hormone (LHRH) agonists, LHRH antagonists, and antiandrogens.[6]

Focal therapies such as high-intensity focused ultrasound (HIFU), cryotherapy, and brachytherapy have also been developed that allows partial ablation of the prostate gland with the goal of minimizing unwanted side-effects such as urinary/bowel incontinence and erectile dysfunction which usually results from mainstay treatments.[6] Providers have developed protocols for watchful waiting and active surveillance where prostate tumors are not immediately removed or ablated but rather monitored for growth and progression to determine whether more definitive treatments should be employed at a later time.[7] For these less aggressive interventions, the goal is to extend a more favorable quality of life for patients without increasing risk for morbidity and mortality due to CLPC.

Availability of numerous treatments with varying profiles for effectiveness and safety have thus become the crux of a decisional dilemma for men with CLPC. Moreover, there is some uncertainty as to how patient characteristics (ex. age, ethnicity, etc.), provider/hospital characteristics (ex. case volume, learning curve, etc.), and tumor characteristics (ex. tumor grade, tumor volume, etc.) potentially influence effectiveness and harms of the various treatments. In 2014, AHRQ produced a systematic review (SR) update titled "*Therapies for Clinically Localized Prostate Cancer: Update of a 2008 Systematic Review"* to help address these issues.[4] The SR update was used by the American Urological Association (AUA), the American Society for Radiation Oncology (ASTRO), and the Society of Urologic Oncology (SUO) to develop joint clinical practice guidelines.[8, 9] Since publication of the SR update, a number of clinical trials on this topic have completed long-term follow-up[10] and the results could further clarify the comparative long-term benefits and risks associated with the various CLPC

treatments. For example, two separate trials comparing surgery and/or radiotherapy versus active surveillance including the Prostate cancer Intervention Versus Intervention Trial (PIVOT) have published long-term results in 2016/17.[10, 11] Furthermore, there have been technological developments that could redefine the safety profiles for some of these interventions such as use of carbon ions, which causes less tissue toxicity than proton ions, and hydrogel spacers to better protect the rectum during prostate and pelvic irradiation.[12, 13]

Nominator and Stakeholder Engagement: The nominator is a regulatory executive from EDAP Technomed, Inc., a device company that manufactures HIFU machines (see Appendix C). The 2014 AHRQ SR update collected and evaluated evidence on HIFU and the nominator expressed interest in acquiring a new SR update for 2019.

We contacted the AUA, the lead organization for the joint clinical practice guidelines and original topic nominator of the 2014 SR update, and found that they are very interested in using a new evidence report on CLPC to update their practice guidelines, which they are planning to release in 2021. The AUA also shared a supplementary evidence report that they commissioned from the EPC that performed the 2014 update. Both the AHRQ update and the supplementary report were used to develop the current practice guidelines.

Key Questions and PICOs

The key questions were adapted from the previous SR update and are as follows:

Key Question 1: What are the comparative risks and benefits of the following therapies for CLPC?

a. Radical prostatectomy, including open (retropubic and perineal) and laparoscopic (with or without robotic assistance) approaches
b. External beam radiation therapy, including standard therapy and therapies designed to decrease exposure to normal tissues such as three-dimensional conformal radiotherapy, intensity-modulated radiation therapy, proton beam therapy, and stereotactic body radiation therapy
c. Interstitial brachytherapy
d. Cryotherapy
e. Watchful waiting
f. Active surveillance
g. Hormonal therapy
h. High-intensity focused ultrasound

Key Question 2: How do specific patient characteristics affect the outcomes of these therapies overall and differentially?

Key Question 3: How do provider/hospital characteristics affect outcomes of these therapies overall and differentially?

Key Question 4: How do tumor characteristics affect the outcomes of these therapies overall and differentially?

To define the inclusion criteria for the key questions we specify the population, interventions, comparators, outcomes, timing, and setting (PICOTS) of interest (Table 1).

Table 1. Key Questions and PICOTS

	KQ1: Comparative effectiveness and harms	KQ2: Patient characteristics as effectiveness and harms modifiers	KQ3: Provider/hospital characteristics as effectiveness and harms modifiers	KQ4: Tumor characteristics as effectiveness and harms modifiers
Population	Adult male patients with clinically localized prostate cancer (T1–T3a, N0–X,M0–X)	Adult male patients with clinically localized prostate cancer (T1–T3a, N0–X,M0–X) <u>*Modifiers of interest*</u>*:* o *Age,* o *Race/ethnicity,* o *Presence or absence of comorbid illness* o *Patient preferences*	Adult male patients with clinically localized prostate cancer (T1–T3a, N0–X,M0–X) <u>*Modifiers of interest*</u>*:* o *Geographic region* o *Case volume* o *Learning curve*	Adult male patients with clinically localized prostate cancer (T1–T3a, N0–X,M0–X) <u>*Modifiers of interest*</u>*:* o *Gleason score* o *Tumor volume* o *Screen-detected vs. clinically detected tumors* o *PSA levels*
Interventions	▪ Radical prostatectomy (including retropubic, perineal, laparoscopic, robotic-assisted) ▪ External beam radiation (including conventional radiation, intensity-modulated radiation therapy, 3D conformal radiotherapy, proton beam, stereotactic body radiation therapy) ▪ Interstitial brachytherapy ▪ Cryotherapy ▪ Watchful waiting ▪ Active surveillance ▪ Hormonal therapy ▪ HIFU	▪ Radical prostatectomy (including retropubic, perineal, laparoscopic, robotic-assisted) ▪ External beam radiation (including conventional radiation, intensity-modulated radiation therapy, 3D conformal radiotherapy, proton beam, stereotactic body radiation therapy) ▪ Interstitial brachytherapy ▪ Cryotherapy ▪ Watchful waiting ▪ Active surveillance ▪ Hormonal therapy ▪ HIFU	▪ Radical prostatectomy (including retropubic, perineal, laparoscopic, robotic-assisted)	▪ Radical prostatectomy (including retropubic, perineal, laparoscopic, robotic-assisted) ▪ External beam radiation (including conventional radiation, intensity-modulated radiation therapy, 3D conformal radiotherapy, proton beam, stereotactic body radiation therapy) ▪ Interstitial brachytherapy ▪ Cryotherapy ▪ Watchful waiting ▪ Active surveillance ▪ Hormonal therapy ▪ HIFU

	KQ1: Comparative effectiveness and harms	KQ2: Patient characteristics as effectiveness and harms modifiers	KQ3: Provider/hospital characteristics as effectiveness and harms modifiers	KQ4: Tumor characteristics as effectiveness and harms modifiers
Comparators	Any of the interventions above compared to each other	Any of the interventions above compared to each other **May include non-comparative high-quality studies*	Any of the interventions above compared to each other **May include non-comparative high-quality studies*	Any of the interventions above compared to each other **May include non-comparative high-quality studies*
Outcomes	Primary: Overall mortality Secondary: Disease-specific mortality, biochemical (PSA) progression, metastatic and/or clinical progression-free survival, health status, quality of life, and harms/adverse events	Primary: Overall mortality Secondary: Disease-specific mortality, biochemical (PSA) progression, metastatic and/or clinical progression-free survival, health status, quality of life, and harms/adverse events	Primary: Overall mortality Secondary: Disease-specific mortality	Primary: Overall mortality Secondary: Disease-specific mortality, biochemical (PSA) progression, metastatic and/or clinical progression-free survival, health status, quality of life, and harms/adverse events
Timing	Minimum duration of one year post-treatment follow-up	Minimum duration of one year post-treatment follow-up	Minimum duration of one year post-treatment follow-up	Minimum duration of one year post-treatment follow-up
Setting	No restriction by setting	No restriction by setting	No restriction by setting	No restriction by setting

Abbreviations: PSA=prostate specific antigen; 3D=three dimensional; HIFU=high intensity focused ultrasound

Methods

We assessed nomination #0829, Therapies for Clinically Localized Prostate Cancer for priority for a systematic review or other AHRQ EHC report with a hierarchical process using established selection criteria. Assessment of each criteria determined the need to evaluate the next one. See Appendix A for detailed description of the criteria.

1. Determine the *appropriateness* of the nominated topic for inclusion in the EHC program.
2. Establish the overall *importance* of a potential topic as representing a health or healthcare issue in the United States.
3. Determine the *desirability of new evidence review* by examining whether a new systematic review or other AHRQ product would be duplicative.
4. Assess the *potential impact* a new systematic review or other AHRQ product.
5. Assess whether the *current state of the evidence* allows for a systematic review or other AHRQ product (feasibility).
6. Determine the *potential value* of a new systematic review or other AHRQ product.

Appropriateness and Importance

We assessed the nomination for appropriateness and importance.

Desirability of New Review/Duplication

We searched for high-quality, completed or in-process evidence reviews published in the last three years on the key questions of the nomination. See Appendix B for sources searched.

Impact of a New Evidence Review

The impact of a new evidence review was qualitatively assessed by analyzing the current standard of care, the existence of potential knowledge gaps, and practice variation. We considered whether it was possible for this review to influence the current state of practice through various dissemination pathways (practice recommendation, clinical guidelines, etc.).

Feasibility

We conducted a literature search using the search strategy employed in the previous SR update. Since the previous SR update search range ended in March 2014, we conducted a new search from 2014 to December 2018. Due to the large number of articles identified, we reviewed a random sample of 200 titles and abstracts for inclusion and classified identified studies by study design to help assess the size and scope of a potential SR update. We then calculated the projected total number of included studies based on the proportion of studies included from the random sample in the new search. See Table 2, Feasibility Column, Size/Scope of Review Section for the citations of included studies. See Appendix C for the PubMed search strategy and links to the ClinicalTrials.gov search.

Value

We assessed the nomination for value. We considered whether or not the clinical, consumer, or policymaking context had the potential to respond with evidence-based change; and if a partner organization would use this evidence review to influence practice.

Results

See Appendix A for detailed assessments of all EPC selection criteria.

Appropriateness and Importance

This is an appropriate and important topic.

Impact of a New Evidence Review

A new systematic review update has a high impact potential because it would help resolve current controversies surrounding the various treatments for CLPC and lead to clinical practice guidelines that will promote better patient outcomes.

Desirability of a New Review/Duplication

A new evidence review update would not be duplicative of an existing evidence review. We did not find any high-quality systematic reviews that fully addressed the four KQs. We found two Cochrane reviews but these focused on specific treatments or treatment categories such as cryotherapy[14] or various radical prostatectomy approaches (laparoscopic/robotic-assisted laparoscopic vs. open).[15] See Table 2, Duplication column.

Feasibility of New Evidence Review

We found 15 studies that were relevant to KQ1 which includes three RCTs,[16-18] six prospective non-randomized studies,[19-24] and six retrospective studies.[25-30] Comparison of interventions categorized by type of outcome include:

- Clinical Effectiveness Outcomes
  - Conventional vs. hypo-fractionated radiotherapy [16]
  - Radiation therapy with proton vs. carbon ions [17]
  - Radical prostatectomy with vs. without adjuvant radiotherapy [18]
  - Laparoscopic vs. open radical prostatectomy [19]
  - Continuous vs. intermittent hormonal therapy [26]
  - Radical prostatectomy vs. radiation therapy [27]
  - Radiotherapy plus total androgen blockade vs. radiotherapy plus LHRH analog monotherapy [28]
  - Brachytherapy with vs. without neoadjuvant combined androgen blockade [29]

- Conformal external beam radiotherapy with vs. without high-dose-rate brachytherapy boost [30]

- Quality of Life/Patient-Reported Outcomes
  - Active surveillance vs. radiation therapy [20]
  - Brachytherapy vs. robotic-assisted laparoscopic radical prostatectomy [21]
  - Radical prostatectomy vs. external beam radiotherapy vs. brachytherapy vs. active surveillance [22]
  - Surgery vs. radiotherapy [23]
  - External beam radiation therapy or brachytherapy with vs. without neoadjuvant androgen deprivation therapy [24]

We found one retrospective study that examined race as a modifier of effectiveness and harms relevant to KQ2[31] and one retrospective study that examined supervisor case volume on clinical outcomes of patients operated on by surgical trainees pertinent to KQ3.[32] Finally, we found three studies that examined various tumor characteristics such as tumor volume and grade that were relevant to KQ4.[19, 25, 33] Thus, we estimate that a new SR update on this topic would be medium-sized.

We also found 18 comparative interventional trials on ClinicalTrials.gov relevant to KQ1. We found no trials relevant to KQ2, KQ3, and KQ4. See Table 2 and Appendix C for hyperlinks.

Table 2. Key Questions and Results for Duplication and Feasibility

Key Question	Duplication (01/2016-12/2018)	Feasibility (01/2014-12/2018)
KQ1: Comparative effectiveness and harms of various treatments	Total number of identified systematic reviews: • Cochrane – 2[14, 15]	Size/scope of review Relevant Studies Identified: 15 • RCT – 3[16-18] • Prospective non-randomized studies – 6[19-24] • Retrospective studies – 6[25-30] Clinicaltrials.gov • Recruiting: 12 • Active, Not Recruiting: 6
KQ2: Patient characteristics as effectiveness and harms modifiers	Total number of identified systematic reviews: 0	Size/scope of review Relevant Studies Identified: 1 • Retrospective studies – 1[31] Clinicaltrials.gov • None
KQ3: Provider/ hospital characteristics as effectiveness and harms modifiers	Total number of identified systematic reviews: 0	Size/scope of review Relevant Studies Identified: 1 • Retrospective studies – 1[32] Clinicaltrials.gov • None

Key Question	Duplication (01/2016-12/2018)	Feasibility (01/2014-12/2018)
KQ4: Tumor characteristics as effectiveness and harms modifiers	Total number of identified systematic reviews: 0	Size/scope of review Relevant Studies Identified: 3 • Prospective non-randomized studies – 1[19] • Retrospective studies – 2[25, 33] Clinicaltrials.gov • None

Abbreviations: KQ=Key Question; RCT=Randomized Controlled Trial

Value

The potential for value is high because the AUA will use the new evidence report to update practice guidelines developed in collaboration with various other medical society stakeholders such as ASCO, ASTRO, SUO, the European Association of Urology (EAU), and the National Comprehensive Cancer Network (NCCN). Furthermore, CLPC is a disease entity that imposes a high cost burden to the United States healthcare system.

Summary of Findings

- Appropriateness and importance: The topic is both appropriate and important.
- Duplication: A new review update would not be duplicative of an existing product. We found no published or in-process systematic reviews that fully address all four KQs.
- Impact: A new systematic review update has high impact potential.
- Feasibility: A new review update is feasible. We estimate enough new evidence base to generate a large SR update.
- Value: The potential for value is high.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin. 2019 Jan;69(1):7-34. doi: 10.3322/caac.21551. PMID: 30620402. [https://www.ncbi.nlm.nih.gov/pubmed/30620402].

2. Mariotto AB, Yabroff KR, Shao Y, et al. Projections of the cost of cancer care in the United States: 2010-2020. J Natl Cancer Inst. 2011 Jan 19;103(2):117-28. doi: 10.1093/jnci/djq495. PMID: 21228314. [https://www.ncbi.nlm.nih.gov/pubmed/21228314].

3. Buyyounouski MK, Choyke PL, McKenney JK, et al. Prostate cancer - major changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA Cancer J Clin. 2017 May 6;67(3):245-53. doi: 10.3322/caac.21391. PMID: 28222223. [https://www.ncbi.nlm.nih.gov/pubmed/28222223].

4. Sun F, Oyesanmi O, Fontanarosa J, et al. Therapies for Clinically Localized Prostate Cancer: Update of a 2008 Systematic Review. Rockville (MD); 2014. [https://www.ncbi.nlm.nih.gov/pubmed/25610935]

5. Lee DJ, Barocas DA, Zhao Z, et al. Contemporary prostate cancer radiation therapy in the United States: Patterns of care and compliance with quality measures. Pract Radiat Oncol. 2018 Sep - Oct;8(5):307-16. doi: 10.1016/j.prro.2018.04.009. PMID: 30177030. [https://www.ncbi.nlm.nih.gov/pubmed/30177030].

6. Ashrafi AN, Tafuri A, Cacciamani GE, et al. Focal therapy for prostate cancer: concepts and future directions. Curr Opin Urol. 2018 Nov;28(6):536-43. doi: 10.1097/MOU.0000000000000539. PMID: 30102623. [https://www.ncbi.nlm.nih.gov/pubmed/30102623].

7. Garisto JD, Klotz L. Active Surveillance for Prostate Cancer: How to Do It Right. Oncology (Williston Park). 2017 May 15;31(5):333-40, 45. PMID: 28512731. [https://www.ncbi.nlm.nih.gov/pubmed/28512731].

8. Sanda MG, Cadeddu JA, Kirkby E, et al. Clinically Localized Prostate Cancer: AUA/ASTRO/SUO Guideline. Part I: Risk Stratification, Shared Decision Making, and Care Options. J Urol. 2018 Mar;199(3):683-90. doi: 10.1016/j.juro.2017.11.095. PMID: 29203269. [https://www.ncbi.nlm.nih.gov/pubmed/29203269].

9. Sanda MG, Cadeddu JA, Kirkby E, et al. Clinically Localized Prostate Cancer: AUA/ASTRO/SUO Guideline. Part II: Recommended Approaches and Details of Specific Care Options. J Urol. 2018 Apr;199(4):990-7. doi: 10.1016/j.juro.2018.01.002. PMID: 29331546. [https://www.ncbi.nlm.nih.gov/pubmed/29331546].

10. Wilt TJ, Jones KM, Barry MJ, et al. Follow-up of Prostatectomy versus Observation for Early Prostate Cancer. N Engl J Med. 2017 Jul 13;377(2):132-42. doi: 10.1056/NEJMoa1615869. PMID: 28700844. [https://www.ncbi.nlm.nih.gov/pubmed/28700844].

11. Hamdy FC, Donovan JL, Lane JA, et al. 10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer. New England Journal of Medicine. 2016 10 13;375(15):1415-24. doi: https://dx.doi.org/10.1056/NEJMoa1606220. PMID: 27626136.

12. Maruyama K, Tsuji H, Nomiya T, et al. Five-year quality of life assessment after carbon ion radiotherapy for prostate cancer. J Radiat Res. 2017 Mar 1;58(2):260-6. doi: 10.1093/jrr/rrw122. PMID: 28043947. [https://www.ncbi.nlm.nih.gov/pubmed/28043947].

13. Karsh LI, Gross ET, Pieczonka CM, et al. Absorbable Hydrogel Spacer Use in Prostate Radiotherapy: A Comprehensive Review of Phase 3 Clinical Trial Published Data. Urology. 2018 May;115:39-44. doi: 10.1016/j.urology.2017.11.016. PMID: 29174940. [https://www.ncbi.nlm.nih.gov/pubmed/29174940].

14. Jung JH, Risk MC, Goldfarb R, et al. Primary cryotherapy for localised or locally advanced prostate cancer. Cochrane Database Syst Rev. 2018 May 30;5:CD005010. doi:

10.1002/14651858.CD005010.pub3. PMID: 29845595. [https://www.ncbi.nlm.nih.gov/pubmed/29845595].

15. Ilic D, Evans SM, Allan CA, et al. Laparoscopic and robotic-assisted versus open radical prostatectomy for the treatment of localised prostate cancer. Cochrane Database Syst Rev. 2017 Sep 12;9:CD009625. doi: 10.1002/14651858.CD009625.pub2. PMID: 28895658. [https://www.ncbi.nlm.nih.gov/pubmed/28895658].

16. Arcangeli G, Saracino B, Arcangeli S, et al. Moderate Hypofractionation in High-Risk, Organ-Confined Prostate Cancer: Final Results of a Phase III Randomized Trial. J Clin Oncol. 2017 Jun 10;35(17):1891-7. doi: 10.1200/JCO.2016.70.4189. PMID: 28355113. [https://www.ncbi.nlm.nih.gov/pubmed/28355113].

17. Habl G, Uhl M, Katayama S, et al. Acute Toxicity and Quality of Life in Patients With Prostate Cancer Treated With Protons or Carbon Ions in a Prospective Randomized Phase II Study--The IPI Trial. Int J Radiat Oncol Biol Phys. 2016 May 1;95(1):435-43. doi: 10.1016/j.ijrobp.2016.02.025. PMID: 27084659. [https://www.ncbi.nlm.nih.gov/pubmed/27084659].

18. Wiegel T, Bartkowiak D, Bottke D, et al. Adjuvant radiotherapy versus wait-and-see after radical prostatectomy: 10-year follow-up of the ARO 96-02/AUO AP 09/95 trial. Eur Urol. 2014 Aug;66(2):243-50. doi: 10.1016/j.eururo.2014.03.011. PMID: 24680359. [https://www.ncbi.nlm.nih.gov/pubmed/24680359].

19. Alessandro S, Alessandro G, Susanna C, et al. Laparoscopic versus open radical prostatectomy in high prostate volume cases: impact on oncological and functional results. Int Braz J Urol. 2016 Mar-Apr;42(2):223-33. doi: 10.1590/S1677-5538.IBJU.2015.0385. PMID: 27256175. [https://www.ncbi.nlm.nih.gov/pubmed/27256175].

20. Banerji JS, Hurwitz LM, Cullen J, et al. A prospective study of health-related quality-of-life outcomes for patients with low-risk prostate cancer managed by active surveillance or radiation therapy. Urol Oncol. 2017 May;35(5):234-42. doi: 10.1016/j.urolonc.2016.12.015. PMID: 28110975. [https://www.ncbi.nlm.nih.gov/pubmed/28110975].

21. Blanchard P, Davis JW, Frank SJ, et al. Quality of life after brachytherapy or bilateral nerve-sparing robot-assisted radical prostatectomy for prostate cancer: a prospective cohort. BJU Int. 2018 Apr;121(4):540-8. doi: 10.1111/bju.14021. PMID: 28941030. [https://www.ncbi.nlm.nih.gov/pubmed/28941030].

22. Chen RC, Basak R, Meyer AM, et al. Association Between Choice of Radical Prostatectomy, External Beam Radiotherapy, Brachytherapy, or Active Surveillance and Patient-Reported Quality of Life Among Men With Localized Prostate Cancer. JAMA. 2017 Mar 21;317(11):1141-50. doi: 10.1001/jama.2017.1652. PMID: 28324092. [https://www.ncbi.nlm.nih.gov/pubmed/28324092].

23. Donovan JL, Hamdy FC, Lane JA, et al. Patient-Reported Outcomes after Monitoring, Surgery, or Radiotherapy for Prostate Cancer. N Engl J Med. 2016 Oct 13;375(15):1425-37. doi: 10.1056/NEJMoa1606221. PMID: 27626365. [https://www.ncbi.nlm.nih.gov/pubmed/27626365].

24. Gay HA, Sanda MG, Liu J, et al. External Beam Radiation Therapy or Brachytherapy With or Without Short-course Neoadjuvant Androgen Deprivation Therapy: Results of a Multicenter, Prospective Study of Quality of Life. Int J Radiat Oncol Biol Phys. 2017 Jun 1;98(2):304-17. doi: 10.1016/j.ijrobp.2017.02.019. PMID: 28463150. [https://www.ncbi.nlm.nih.gov/pubmed/28463150].

25. Bolton DM, Papa N, Ta AD, et al. Predictors of prostate cancer specific mortality after radical prostatectomy: 10 year oncologic outcomes from the Victorian Radical Prostatectomy Registry. BJU Int. 2015 Oct;116 Suppl 3:66-72. doi: 10.1111/bju.13112. PMID: 26176738. [https://www.ncbi.nlm.nih.gov/pubmed/26176738].

26. Ku JY, Lee JZ, Ha HK. The effect of continuous androgen deprivation treatment on prostate cancer patients as compared with intermittent androgen deprivation treatment. Korean J Urol. 2015 Oct;56(10):689-94. doi: 10.4111/kju.2015.56.10.689. PMID: 26495069. [https://www.ncbi.nlm.nih.gov/pubmed/26495069].

27. Lee BH, Kibel AS, Ciezki JP, et al. Are biochemical recurrence outcomes similar after radical prostatectomy and radiation therapy? Analysis of prostate cancer-specific mortality by nomogram-predicted risks of biochemical recurrence. Eur Urol. 2015 Feb;67(2):204-9. doi: 10.1016/j.eururo.2014.09.017. PMID: 25294696. [https://www.ncbi.nlm.nih.gov/pubmed/25294696].

28. Marvaso G, Viola A, Fodor C, et al. Radiotherapy Plus Total Androgen Block Versus Radiotherapy Plus LHRH Analog Monotherapy for Non-metastatic Prostate Cancer. Anticancer Res. 2018 May;38(5):3139-43. doi: 10.21873/anticanres.12576. PMID: 29715154. [https://www.ncbi.nlm.nih.gov/pubmed/29715154].

29. Senzaki T, Fukumori T, Mori H, et al. Clinical Significance of Neoadjuvant Combined Androgen Blockade for More Than Six Months in Patients with Localized Prostate Cancer Treated with Prostate Brachytherapy. Urol Int. 2015;95(4):457-64. doi: 10.1159/000439573. PMID: 26461847. [https://www.ncbi.nlm.nih.gov/pubmed/26461847].

30. Smolska-Ciszewska B, Miszczyk L, Bialas B, et al. The effectiveness and side effects of conformal external beam radiotherapy combined with high-dose-rate brachytherapy boost compared to conformal external beam radiotherapy alone in patients with prostate cancer. Radiat Oncol. 2015 Mar 7;10:60. doi: 10.1186/s13014-015-0366-z. PMID: 25884489. [https://www.ncbi.nlm.nih.gov/pubmed/25884489].

31. Bryant C, Mendenhall NP, Henderson RH, et al. Does Race Influence Health-related Quality of Life and Toxicity Following Proton Therapy for Prostate Cancer? Am J Clin Oncol. 2016 Jun;39(3):261-5. doi: 10.1097/COC.0000000000000050. PMID: 24710124. [https://www.ncbi.nlm.nih.gov/pubmed/24710124].

32. O'Kane D, Papa N, Lawrentschuk N, et al. Supervisor volume affects oncological outcomes of trainees performing open radical prostatectomy. ANZ J Surg. 2016 Apr;86(4):249-54. doi: 10.1111/ans.13112. PMID: 25916513. [https://www.ncbi.nlm.nih.gov/pubmed/25916513].

33. Castiglione F, Dell'Oglio P, Tosco L, et al. Tumor Volume and Clinical Failure in High-Risk Prostate Cancer Patients Treated With Radical Prostatectomy. Prostate. 2017 Jan;77(1):3-9. doi: 10.1002/pros.23242. PMID: 27527377. [https://www.ncbi.nlm.nih.gov/pubmed/27527377].

Appendix A. Selection Criteria Summary

Selection Criteria	Assessment
1. Appropriateness	
1a. Does the nomination represent a health care drug, intervention, device, technology, or health care system/setting available (or soon to be available) in the U.S.?	Yes, this topic represents interventions available in the U.S.
1b. Is the nomination a request for a systematic review?	Yes, this topic is a request for a systematic review.
1c. Is the focus on effectiveness or comparative effectiveness?	The focus of this review is on comparative effectiveness.
1d. Is the nomination focus supported by a logic model or biologic plausibility? Is it consistent or coherent with what is known about the topic?	Yes, it is biologically plausible and is consistent with what is known about the topic.
2. Importance	
2a. Represents a significant disease burden; large proportion of the population	Yes, this topic represents a significant disease burden. One in nine men in the United States will develop prostate cancer in their lifetime.
2b. Is of high public interest; affects health care decision making, outcomes, or costs for a large proportion of the US population or for a vulnerable population	Yes, this topic affects heath care decisions for a large proportion of the US population.
2c. Represents important uncertainty for decision makers	Yes, this topic represents important uncertainty for decision makers.
2d. Incorporates issues around both clinical benefits and potential clinical harms	Yes, this nomination addresses both benefits and potential harms of therapeutic interventions for clinically localized prostate cancer.
2e. Represents high costs due to common use, high unit costs, or high associated costs to consumers, to patients, to health care systems, or to payers	Yes, the total national medical costs attributable to treatment for prostate cancer was $11 billion in 2010. This annual cost is projected to further rise to $16 billion by 2020.
3. Desirability of a New Evidence Review/Duplication	
3. Would not be redundant (i.e., the proposed topic is not already covered by available or soon-to-be available high-quality systematic review by AHRQ or others)	Yes, a new systematic review would not be redundant. We did not find any systematic reviews that fully address the KQs.
4. Impact of a New Evidence Review	
4a. Is the standard of care unclear (guidelines not available or guidelines inconsistent, indicating an information gap that may be addressed by a new evidence review)?	Yes, the standard of care is unclear due to a variety of available treatment strategies. It may also change over time as older treatments evolve and newer ones are developed. Recommendations among clinical experts differ as different subspecialties provide specific treatments.
4b. Is there practice variation (guideline inconsistent with current practice, indicating a potential implementation gap and not best addressed by a new evidence review)?	Yes, there is practice variation due to conflicting opinion. Long-term outcomes are unavailable for the newer treatments. New evidence has been produced in the past four years which could help provide clarity in prescribing one treatment over another.

Selection Criteria	Assessment
5. Primary Research	
5. Effectively utilizes existing research and knowledge by considering: - Adequacy (type and volume) of research for conducting a systematic review - Newly available evidence (particularly for updates or new technologies)	*Size/scope of review:* We estimate that the total size of the relevant literature may be approximately 120 studies across the four key questions (low confidence). The scope of the update is likely medium. *ClinicalTrials.gov*: We found 18 comparative interventional trials relevant to KQ1.
6. Value	
6a. The proposed topic exists within a clinical, consumer, or policy-making context that is amenable to evidence-based change	Yes, this topic will inform clinical decision-making on treating patients with clinically localized prostate cancer.
6b. Identified partner who will use the systematic review to influence practice (such as a guideline or recommendation)	Yes, the AUA will use a systematic review update to formulate a new practice guideline. Historically, AUA develops joint guidelines with ASCO, ASTRO, SUO, EAU, and NCCN.

Abbreviations: AHRQ=Agency for Healthcare Research and Quality; KQ=Key Question; AUA=American Urological Association; ASTRO=American Society for Therapeutic Radiology and Oncology; SUO= Society of Urologic Oncology; EAU=European Association of Urology; NCCN=National Comprehensive Cancer Network

Appendix B. Search for Evidence Reviews (Duplication)

Listed are the sources searched.

AHRQ: Evidence reports and technology assessments, USPSTF recommendations
VA Products: PBM, and HSR&D (ESP) publications, and VA/DoD EBCPG Program
Cochrane Systematic Reviews and Protocols http://www.cochranelibrary.com/
PubMed
PROSPERO Database (international prospective register of systematic reviews and protocols) http://www.crd.york.ac.uk/prospero/

Appendix C. Search Strategy & Results (Feasibility)

We used the search strategy employed by the EPC team that completed the last systematic review update (CER #146: *"Therapies for Clinically Localized Prostate Cancer: Update of a 2008 Systematic Review"*).

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to December 27, 2018

Date Searched: Friday December 28, 2018

#	Searches	Results
1	Prostatic Neoplasms/	115178
2	(prostat$.ti,ab. or Prostate/) and (cancer.ti,ab. or Neoplasms/ or neoplasm$.mp. or carcinoma$.mp.) [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	150550
3	or/1-2	160989
4	watchful waiting.ti,ab. or Watchful Waiting/ or active surveillance.ti,ab. or prostatectom$.ti,ab. or Prostatectomy/ or LRP.ti,ab. or RLRP.ti,ab. or exp Radiotherapy/ or radiotherap$.ti,ab. or EBRT.ti,ab. or IMRT.ti,ab. or proton.ti,ab. or brachytherap$.ti,ab. or Brachytherapy/ or curietherap$.ti,ab. or cryosurger$.ti,ab. or Cryosurgery/ or cryotherap$.ti,ab. or Cyberknife.ti,ab. or Cryotherapy/ or cryoablat$.ti,ab. or Freezing/ or freez$.ti,ab. or androgen deprivation.ti,ab. or High-Intensity Focused Ultrasound Ablation/ or high intensity focused ultrasound.ti,ab. or HIFU.ti,ab. or (high and intensity and focused and ultrasound).ti,ab.	500597
5	Randomized controlled trial/ or random allocation/ or double-blind method/ or single-blind method/ or placebos/ or cross-over studies/ or crossover procedure/ or cross over studies/ or double blind procedure/ or single blind procedure/ or placebo/ or latin square design/ or crossover design/ or double-blind studies/ or single-blind studies/ or triple-blind studies/ or random assignment/ or exp clinical trial/ or exp comparative study/ or cohort analysis.ti,ab. or followup studies/ or intermethod comparison/ or parallel design/ or control group/ or prospective study/ or retrospective study/ or case control study/ or major clinical study/ or evaluation studies/ or followup studies/ or case series.ti,ab. or random$.hw. or random$.ti. or placebo$.ti,ab. or ((singl$ or doubl$ or tripl$ or trebl$) and (dummy or blind or sham)).ti,ab. or latin square.ti,ab. or ISRCTN$.ti,ab. or ACTRN$.ti,ab. or (NCT$ not NCT).ti,ab.	4277902
6	and/3-5	16960
7	6 not ((letter or editorial or news or comment or case reports or note or conference paper).de. or (letter or editorial or news or comment or case reports).pt.)	16332
8	7 not (book/ or edited book/ or case report/ or case reports/ or comment/ or conference abstract/ or conference paper/ or conference review/ or editorial/ or letter/ or news/ or note/ or proceeding/ or (book or edited book or case report or case reports or comment or conference or editorial or letter or news or note or proceeding).pt. or ("comment/reply" or editorial or letter or review-book).pt.)	16329
9	8 not (case report.de. or case reports.pt. or case report.ti. or (year adj old).ti,ab.)	16304
10	limit 9 to (english and humans)	14771
11	limit 10 to yr="2014 - 2019"	3210
12	remove duplicates from 11	3445
13	12 and compar$.ti,hw.	647
14	12 and (clinically adj local$).mp.	141

#	Searches	Results
15	12 and (stage 1 or stage one).mp.	2
16	12 and (early adj3 stage).mp.	37
17	12 and (nonmetastatic or non-metastatic).mp.	78
18	12 and (gleason 7 or gleason score 7 or gleason 6 or gleason score 6).mp.	205
19	12 and (local$ adj advanced).mp.	97
20	12 and (T3 or T4).mp.	83
21	12 and ((high adj risk) or high-risk).mp.	492
22	or/13-21	1654

ClinicalTrials.gov

KQ1

Recruiting
12 comparative interventional studies found for “prostate cancer” & “localized” | studies received on or after 04/01/2014
https://clinicaltrials.gov/ct2/results?term=localized&cond=Prostate+Cancer&sfpd_s=04%2F01%2F2014&sfpd_e=01%2F01%2F2019&Search=Apply&recrs=a&age_v=&gndr=&type=Intr&rslt=

Active, Not Recruiting
6 comparative interventional studies found for “prostate cancer” & “localized” | studies received on or after 04/01/2014
https://clinicaltrials.gov/ct2/results?term=localized&cond=Prostate+Cancer&sfpd_s=04%2F01%2F2014&sfpd_e=01%2F01%2F2019&Search=Apply&recrs=d&age_v=&gndr=&type=Intr&rslt=

KQ2 / KQ3 / KQ4

No studies relevant to these KQs were found.