Topic Brief: Locally Advanced Prostate Cancer

Date: 11/1/2019
Nomination Number: 0825

Purpose: This document summarizes the information addressing a nomination submitted on September 17, 2018 through the Effective Health Care (EHC) Website. This information was used to inform the Evidence-based Practice Center (EPC) Program decisions about whether to produce an evidence report on the topic, and if so, what type of evidence report would be most suitable.

Issue: The nominator, the American Urological Association (AUA), is interested in using a new systematic review to aid in developing clinical practice guidelines pertaining to management of locally advanced prostate cancer.

Key findings

- This nomination meets all selection criteria.
- A new review would not be duplicative of an existing product. We identified an ongoing systematic review conducted by the European Association of Urology (EAU) on PROSPERO, which is relevant to Key Question 2 (KQ2) and KQ3 of the original nomination. However, this review will not include focal therapy interventions such as cryotherapy and high-intensity focused ultrasound (HIFU) with or without systemic neoadjuvant/adjuvant interventions (androgen deprivation therapy and chemotherapy). We modified KQ2 and KQ3 to focus on these interventions not covered by the EAU review. We did not find any existing or ongoing systematic review that adequately addressed KQ1 or KQ4.

Program Decision: Though the scope of this topic met all EHC Program selection criteria and was considered for a systematic review. However, it was not selected.

Background

In 2018, the American Cancer Society projects prostate cancer to be the most frequently diagnosed non-dermatologic malignancy (164,690 new cases) and the second leading cause of cancer death (29,430 deaths) among men in the United States.[1] Prostate cancer also represents a significant cost burden. The total national medical costs attributable to treatment for prostate cancer was $11 billion in 2010 and is projected to rise to $16 billion by 2020.[2] Locally advanced prostate cancer (LAPC) is characterized by spread of the tumor beyond the capsule of the prostate gland to invade the seminal vesicles (T3 disease), the urinary sphincter, bladder, rectum or pelvic wall (T4 disease), or to the pelvic lymph nodes (N+ disease).[3] LAPC portends a poorer prognosis than organ confined disease. Identifying the optimal treatment strategy for this subset of high-risk patients has become a complex problem due to availability of multiple treatment options such as open and robotic-assisted laparoscopic prostatectomy and external beam

radiation therapy as well as emergence of more recent ablative focal therapies such as cryotherapy and high-intensity focused ultrasound (HIFU).[4-6] The advent of multi-modal treatment strategies that combine primary surgical, focal ablative or radiation treatment with neoadjuvant or adjuvant androgen deprivation therapy (ADT) or chemotherapy has further contributed to this complexity.[7, 8]

In addition to therapeutics, recent advances in diagnosis and staging to accurately identify LAPC at the treatment naïve phase of disease management using enhanced scanning technologies could prove beneficial in selection of an optimal multi-modal therapeutic strategy with curative intent for these high-risk patients.[9]

Nomination Summary

The American Urological Association nominated this topic on September 17, 2018. It is a resubmission of a nomination first submitted in March 1, 2018 with the addition of a key question related to effectiveness and harms of surveillance protocols used to monitor patients after receiving treatment for LAPC. When we first worked up the topic in March 2018, we found a systematic review in progress being conducted by the European Association of Urology (EAU). In this resubmitted nomination, we likewise worked with the nominator to revise the key questions to prevent duplication.

Scope

1. What is the optimal diagnostic strategy, or combination of diagnostic strategies to stage locally advanced prostate cancer (LAPC: T3/T4 N0/N+ M0 prostate adenocarcinoma)?

2. For men with LAPC, what are the effectiveness and comparative effectiveness of various focal therapy interventions, alone or in combination with systemic therapies, on oncological, functional, and quality of life/other patient reported outcomes?

3. For men with LAPC receiving any type of focal therapy interventions, alone or in combination with systemic therapies, what are the harms and comparative harms associated with these interventions?

4. What is the comparative effectiveness and harms of survivorship surveillance protocols for men who elected treatment following a diagnosis of LAPC?

Table 1. Questions and PICOTS (population, intervention, comparator, outcome, timing and setting)

Questions	1. Diagnostic strategy	2. Focal therapy effectiveness	3. Focal therapy harms	4. Surveillance protocol effectiveness and harms
Population	Adult males aged ≥18 years with non-metastatic clinical and pathologic T3/T4 treatment naïve prostate adenocarcinoma who may or may not have clinically suspicious pelvic lymph nodes			Adult males aged ≥18 years treated for non-metastatic clinical and pathologic T3/T4 prostate adenocarcinoma
Interventions	Diagnostic/staging interventions • *MRI* • *CT scan* • *PET (choline, gallium, sodium fluoride, PSMA) scans* • *Bone scintigraphy* • *Lymph node biopsy* • *Others*	Focal therapy interventions* • *Cryotherapy* • *HIFU* *With or without neoadjuvant/adjuvant therapy • *ADT* • Chemotherapy		Surveillance protocols consisting of one or more of the following: • *Imaging (CT, MRI, PET, Bone scan* • *PSA/biomarkers* • *Physical examination*
Comparators	Interventions/combinations of interventions compared to each other Comparisons of particular interest include: • *MRI vs. CT of the abdomen and pelvis (± contrast)* • *PET (choline vs. gallium vs. sodium fluoride vs. PSMA) scans of the abdomen and pelvis* • *MRI vs. CT vs. PET scans of the abdomen and pelvis* • *Staging CT vs. bone scan* • *LN biopsy alone vs. with any combination of the above pelvic imaging techniques*	Surgical interventions** • *Radical prostatectomy (open, robot-assisted, laparoscopic) ± cystectomy ± resection of the rectum (aka pelvic exenteration)* • *Lymph node dissection* Radiation therapy** • *Interstitial Brachytherapy (low dose rate and high dose rate)* • *EBRT* **With or without neoadjuvant / adjuvant therapy • *ADT* • Chemotherapy		No protocol (usual care) Other survivorship surveillance protocols including variations in dose (when appropriate), phase (when appropriate), use of contrast (when appropriate), timing, frequency

Questions	1. Diagnostic strategy	2. Focal therapy effectiveness	3. Focal therapy harms	4. Surveillance protocol effectiveness and harms
Outcomes	Primary outcomes • *Sensitivity/specificity to diagnose and stage T3/T4 disease and/or lymph node involvement*	Primary outcomes • *Overall survival* • *Cancer-specific survival* • *Progression-free survival* • *Metastasis-free survival* Secondary outcomes • *Biochemical recurrence* • *Quality of life/patient-reported outcomes*		Primary outcomes • *Overall survival* • *Progression-free survival* • *Metastasis-free survival* • *Short- and long-term morbidity (ex. bone health, sexual dysfunction, anemia, psychological/cognitive effects, cardiovascular morbidity, secondary malignancies, infections)* Secondary outcomes • *Biochemical recurrence* • *Quality of life/patient-reported outcomes*
Timing	Any duration of follow-up			
Setting	All settings			

Abbreviations: ADT - Androgen Deprivation Therapy; CT: Computed Tomography; EBRT - External Beam Radiation Therapy; HIFU - High Intensity Focused Ultrasound; LAPC - Locally Advance Prostate Cancer; MRI - Magnetic Resonance Imaging; PET - Positron Emission Tomography; PSA - Prostate Specific Antigen; PSMA - Prostate Specific Membrane Antigen

Assessment Methods

See Appendix A.

Summary of Literature Findings

We found an ongoing SR being conducted by the EAU, which is partially duplicative of the two KQs on treatment of LAPC proposed by the nominator.[10] Specifically, all surgical approaches and radiation therapy modalities with or without systemic therapy (ADT and/or chemotherapy) will be covered by the EAU review; however, focal therapies such as cryotherapy and HIFU will not be covered. After consultation with nominator, we modified KQ2 and KQ3 to focus on these focal ablative interventions with or without systemic therapies. We found one systematic review, which is relevant to the revised KQ2 and KQ3; however, the search date was limited to articles published prior to April 2015 and thus not sufficiently recent for the nominator.

There were four systematic reviews related to KQ1 but they were focused on a single diagnostic staging modality rather than comparatively appraising several modalities in a single review. Thus, we found no review that is substantially duplicative of KQ1. We did not find any systematic reviews relevant to KQ4.

We estimate that the total size of the relevant literature from April 2013 to the present may be approximately 20 studies, which addresses KQ1. We found no studies addressing the remaining KQs. We found two studies that led to this estimate. The first is a retrospective study of 45 men examining the diagnostic accuracy of multi-parametric MRI coupled with an automated analysis tool in detecting the presence and extent of prostate cancer. The second involves secondary data analysis on 38,340 men from the prostate arm of the Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trial that examined the ability of PSA-derived growth curves to predict occurrence of high-risk prostate cancer. Thus, the evidence base will likely encompass a variety of interventions that include diagnostic imaging and biomarker studies.

We also identified 16 trials relevant to KQ1 on ClinicalTrials.gov. Though we did not identify studies that addressed KQ2/KQ3 in our random sample, we found 12 trials that were relevant on ClinicalTrials.gov. We did not identify any studies relevant to KQ4 in our random sample or on ClinicalTrials.gov.

See Appendix A for the PubMed search strategy and links to the ClinicalTrials.gov search. See Appendix B for detailed assessments of all EPC selection criteria.

Table 2. Literature identified for each Question

Question	Systematic reviews (4/2013-12/2018)	Primary studies (4/2013-12/2018)
Question 1: Diagnostic strategy	Total: 4 • Other - 4[11-14]	Total: 2 • Secondary analysis of RCT: 1[15] • Observational: 1[16] Clinicaltrials.gov • Recruiting/Enrolling: 11 • Completed: 5

Question	Systematic reviews (4/2013-12/2018)	Primary studies (4/2013-12/2018)
Question 2: Focal therapy effectiveness	Total: 1 • Other - 1[17]	Total: 0 • RCT: 0 • Observational: 0 Clinicaltrials.gov • Recruiting: 10 • Active, not recruiting: 1 • Completed: 1
Question 3: Focal therapy harms	Total: 1 Other - 1[17]	Total: 0 • RCT: 0 • Observational: 0 Clinicaltrials.gov • Recruiting: 10 • Active, not recruiting: 1 • Completed: 1
Question 4: Surveillance protocol effectiveness and harms	Total: 0	Total: 0 • RCT: 0 • Observational: 0 Clinicaltrials.gov • Recruiting: 0 • Completed: 0

Abbreviations: RCT=randomized controlled trial

Summary of Selection Criteria Assessment

This nomination meets all selection criteria. We found five non-duplicative systematic reviews and estimate 20 primary studies covering the revised KQs of this topic on locally advanced prostate cancer. We did not consider the systematic reviews duplicative because they only partially addressed the revised list of interventions of interest to the nominator. A new systematic review on management of LAPC may have a high impact because the standard of care is unclear due to a multitude of available treatment strategies. Recommendations among clinical experts differ and there is practice variation due to conflicting data/opinion and existing recommendations. The potential for value is high given that AUA will use a systematic review to formulate a new guideline. It could potentially be used by EAU, ASCO, ASTRO and other medical organizations.

Please see Appendix B for detailed assessments of individual EPC Program selection criteria.

References

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

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Appendix A: Methods

We assessed nomination for priority for a systematic review or other AHRQ Effective Health Care report with a hierarchical process using established selection criteria. Assessment of each criteria determined the need to evaluate the next one. See Appendix B for detailed description of the criteria.

Appropriateness and Importance

We assessed the nomination for appropriateness and importance.

Desirability of New Review/Absence of Duplication

We searched for high-quality, completed or in-process evidence reviews published in the last three years up to December 27, 2018 on the questions of the nomination from these sources:

- AHRQ: Evidence reports and technology assessments
  - AHRQ Evidence Reports https://www.ahrq.gov/research/findings/evidence-based-reports/index.html
  - EHC Program https://effectivehealthcare.ahrq.gov/
  - US Preventive Services Task Force https://www.uspreventiveservicestaskforce.org/
  - AHRQ Technology Assessment Program https://www.ahrq.gov/research/findings/ta/index.html
- US Department of Veterans Affairs Products publications
  - Evidence Synthesis Program https://www.hsrd.research.va.gov/publications/esp/
  - VA/Department of Defense Evidence-Based Clinical Practice Guideline Program https://www.healthquality.va.gov/
- Cochrane Systematic Reviews https://www.cochranelibrary.com/
- University of York Centre for Reviews and Dissemination database https://www.crd.york.ac.uk/CRDWeb/
- PROSPERO Database (international prospective register of systematic reviews and protocols) http://www.crd.york.ac.uk/prospero/
- PubMed https://www.ncbi.nlm.nih.gov/pubmed/

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 of New Evidence Review

Since we conducted a feasibility search for KQ1-3 back in April 2018 that used a PubMed search for the last five years, we conducted an updated search to include abstracts up until December 27, 2018 and used the search results to augment the previous feasibility search. We reviewed a random sample of 13 new abstracts, which is proportional with the 200 abstracts previously reviewed, and combined them. Thus, for KQ1-3, we reviewed a total of 213 abstracts. For KQ4, we reviewed a separate random sample of 200 titles and abstracts since it was not included in the previous feasibility search. For all KQs, we classified identified studies by question and study design, to assess the size and scope of a potential evidence review. We then calculated the projected total number of included studies based on the proportion of studies included from the random sample.

We also searched ClinicalTrials.gov for related trials.

Search Strategy

Topic: Locally-Advanced Prostate Cancer Date: December 27, 2018 Database Searched: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present	
Concept	**Searches**
Prostate cancer	(prostate/ and (adenocarcinoma/ or exp neoplasms/)) or prostatic neoplasms/
OR	
Non-metastatic Locally Advanced Prostate Cancer	(prostat* adj10 (local* or nonmetast* or non-metast* or pre-cancer* or precancer* or situ or T3 or T4)).ti,ab,kf.
Limit to up to April 2013	
N=2,119	

ClinicalTrials.gov

KQ1
Recruiting
11 studies found for: prostate cancer & staging | studies received on or after 04/11/2013
https://clinicaltrials.gov/ct2/results?cond=Prostate+Cancer&intr=staging&strd_s=04%2F11%2F2013&strd_e=04%2F11%2F2018&Search=Apply&recrs=a&age_v=&gndr=&type=&rslt=

Completed
5 studies found for: prostate cancer & staging | studies received on or after 04/11/2013
https://clinicaltrials.gov/ct2/results?cond=Prostate+Cancer&intr=staging&strd_s=04%2F11%2F2013&strd_e=04%2F11%2F2018&Search=Apply&recrs=e&age_v=&gndr=&type=&rslt=

KQ2 / KQ3
Recruiting
10 studies found for: prostate cancer/HIFU or prostate cancer/cryotherapy | studies received on or after 04/11/2013
https://clinicaltrials.gov/ct2/results?cond=Prostate+Cancer&term=&intr=HIFU&strd_s=04%2F11%2F2013&strd_e=04%2F11%2F2018&cntry=&state=&city=&dist=&Search=Search&recrs=a
https://clinicaltrials.gov/ct2/results?cond=Prostate+Cancer&intr=cryotherapy&strd_s=04%2F11%2F2013&strd_e=04%2F11%2F2018&Search=Apply&recrs=a&age_v=&gndr=&type=&rslt=

Active, not recruiting
1 study found for: prostate cancer/HIFU or prostate cancer/cryotherapy | studies received on or after 04/11/2013
https://clinicaltrials.gov/ct2/results?cond=Prostate+Cancer&intr=cryotherapy&strd_s=04%2F11%2F2013&strd_e=04%2F11%2F2018&Search=Apply&recrs=d&age_v=&gndr=&type=&rslt=

Completed
1 study found for: prostate cancer/HIFU or prostate cancer/cryotherapy | studies received on or after 04/11/2013
https://clinicaltrials.gov/ct2/results?cond=Prostate+Cancer&intr=HIFU&strd_s=04%2F11%2F2013&strd_e=04%2F11%2F2018&Search=Apply&recrs=e&age_v=&gndr=&type=&rslt=

KQ4
No studies found for: prostate cancer/surveillance or prostate cancer/monitoring | studies received on or after 04/11/2013

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.

Appendix B. Selection Criteria Assessment

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 United States.
1b. Is the nomination a request for an evidence report?	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 effectiveness and 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 burden. In 2018, the ACS projects prostate cancer to be the most frequently diagnosed non-dermatologic malignancy and the second leading cause of cancer death among men in the United States.
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. Incorporates issues around both clinical benefits and potential clinical harms	Yes, this nomination addresses both benefits and potential harms of focal therapy to treat LAPC.
2d. 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 is projected to rise to $16 billion by 2020.
3. Desirability of a New Evidence Review/Absence of Duplication	
3. A recent high-quality systematic review or other evidence review is not available on this topic	A new review would not be duplicative. We identified five SRs related to the scope of this review. One was partly duplicative of portions of KQ2 and KQ3 in the original nomination but we had revised it to exclude what was covered by the SR. The remaining reviews were not considered duplicative because they were not recent enough or did not cover the range of interventions of interest.

Selection Criteria	Assessment
	We found an ongoing SR being conducted by the EAU, which is partially duplicative of the two KQs on treatment of LAPC originally proposed by the nominator. Specifically, all surgical approaches and radiation therapy modalities with or without systemic therapy (ADT and/or chemotherapy) will be covered by the EAU review; however, focal therapies such as cryotherapy and HIFU will not be covered. After consultation with nominator, we modified KQ2 and KQ3 to focus on these focal ablative interventions with or without systemic therapies. We found one systematic review, which is relevant to the revised KQ2 and KQ3; however, the search date was limited to articles published prior to April 2015 and thus not sufficiently recent for the nominator. There were four systematic reviews related to KQ1 but they were focused on a single diagnostic staging modality rather than comparatively appraising several modalities in a single review. Thus, we found no review that is substantially duplicative of KQ1. We did not find any systematic reviews relevant to KQ4.
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, because guidelines are not available.
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 but likely due to various treatment modalities and absence of a guideline rather than a gap in implementation.
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 (April 2013 – present) may be approximately 20 studies across key questions (low confidence). All studies were related to KQ1. Scope of the review is likely small. *ClinicalTrials.gov*: We found 16 trials relevant to the KQ1 and 12 trials relevant to KQ2/KQ3. No trials were found relevant to KQ4.

Selection Criteria	Assessment
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 LAPC.
6b. Identified partner who will use the systematic review to influence practice (such as a guideline or recommendation)	Yes, the nominator plans to use the findings of the report to formulate new clinical practice guidelines.

Abbreviations: ACS=American Cancer Society; ADT=androgen deprivation therapy; EAU=European Association of Urology; KQ=key question; LAPC=locally advanced prostate cancer; US=United States