Effective Health Care

Locally Advanced Prostate Cancer

Results of Topic Selection Process & Next Steps

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.

Due to limited program resources, the program is unable to develop a review at this time. No further activity on this topic will be undertaken by the Effective Health Care (EHC) Program.

Topic Brief

Topic Name: Locally Advanced Prostate Cancer (LAPC) #0773

Nomination Date: 03/01/2018

Topic Brief Date: 05/11/2018

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.

Summary of Key Findings:

- Appropriateness and importance: The topic is both appropriate and important.
- Duplication: 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 KQ2 and KQ3 of the original nomination. However, this review will not include focal therapy interventions such as cryotherapy and HIFU with or without systemic neoadjuvant/adjuvant interventions (ADT 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.
- Impact: A new systematic review would have high impact. Optimal strategies for diagnostic staging and treatment of LAPC are currently under debate. Recommendations among clinical experts differ greatly resulting in wide practice variation. An AHRQ report will complement the ongoing EAU report and help resolve controversies.
- Feasibility: A new review is feasible. The evidence base is likely limited to small.
    - *Size/scope of review:* Our search of PubMed resulted in a total of 1,983 unique titles. Upon title and abstract review, we identified two studies potentially relevant to KQ1 in the nomination, for a projected total of 20 studies. We did not find studies relevant to KQ2 and KQ3.
    - *ClinicalTrials:* We identified 28 open or recently closed relevant clinical trials on ClinicalTrials.gov.

- Value: The potential for value is high because AUA will use a new AHRQ evidence review to update clinical practice guidelines on a topic that imposes a high mortality burden on the US male population. In addition, the AUA will work closely with EAU and several other national and international stakeholder organizations, which would help disseminate the AHRQ report findings including the Urology Care Foundation, the Canadian Urological Association (CUA), the American Society for Radiation Oncology (ASTRO), and the Society of Urologic Oncology (SUO).

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Introduction

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]

The American Urological Association nominated this topic on 03/01/2018. During the search for duplicative reviews, we found a systematic review in progress being conducted by the European Association of Urology (EAU).[10] We worked with the nominator to revise the KQs to prevent duplication. The revised key questions are:

Key Question 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)?

Key Question 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?

Key Question 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?

In Table 1, we define the population, interventions, comparators, outcomes, and timing, and setting (PICOTS) for each Key Question.

Table 1. Key Questions and PICOTs

Key Questions	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?
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 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 with non-metastatic clinical and pathologic T3/T4 treatment naïve prostate adenocarcinoma who may or may not have clinically suspicious pelvic lymph nodes
Interventions	Diagnostic and 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*	Focal therapy interventions* • *Cryotherapy* • *HIFU* *With or without neoadjuvant/adjuvant therapy • *ADT* • *Chemotherapy*
Comparators	Interventions and 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*	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*
Outcomes	Primary outcomes	Primary outcomes • Overall survival • Cancer-specific survival	Primary outcomes • Short- and long-term morbidity including: o *bone health status with ADT*

Key Questions	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?
	• Sensitivity and Specificity to diagnose and stage T3/T4 disease and/or lymph node involvement	• Progression-free survival/Metastatic-free survival • PSA biochemical recurrence • Quality of Life and other Patient Reported Outcomes	o *pathological fractures* o *sexual dysfunction* o *anemia* o *psychological and cognitive effects* o *cardiovascular morbidity* o *secondary malignancies* o *infections* o *others* o
Timing	Any duration of follow-up	Any duration of follow-up	Any duration of follow-up
Setting	Outpatient	Inpatient or outpatient	Inpatient or outpatient

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;

Methods

To assess the topic nomination Locally Advanced Prostate Cancer (#773), for priority for a systematic review or other AHRQ EHC report, we used a modified process based on established criteria. Our assessment is hierarchical in nature, with the findings of our assessment determining the need for further evaluation. Details related to our assessment are provided in Appendix A.

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 qualitatively assessed the nomination for appropriateness and importance.

Desirability of New Review/Duplication

We searched for relevant high-quality, completed or in-process evidence reviews from the last five years. Databases searched included AHRQ Effective Health Care Program website, VA Evidence Synthesis Program website, PubMed, Cochrane Collaboration, and PROSPERO register of systematic reviews.

Impact of a New Evidence Review

The impact of a new evidence review was assessed by analyzing the current standard of care, the existence of potential knowledge gaps, and practice variation. We considered whether it was hypothetically 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

We conducted a literature search in PubMed from 11 April 2013 to 11 April 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 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. 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 topic would inform clinical policy in community and/or clinical settings, and if there was a partner organization that would use this evidence review to do disseminate this policy.

Compilation of Findings

We constructed a table outlining the selection criteria (Appendix A).

Results

Appropriateness and Importance

This is an appropriate and important topic. This topic represents a significant burden, affects heath care decisions for a large proportion of the US population, and represents important uncertainty for decision makers. In 2018, the American Cancer Society 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. The total national medical cost attributable to treatment for prostate cancer was $11 billion in 2010 and is projected to rise to $16 billion by 2020.

Desirability of New Review/Duplication

A new evidence review would not be duplicative of an existing product. We found an ongoing SR being conducted by the EAU for development of clinical guidelines, which is 90% 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 KQ2 and KQ3; however, the search date was limited to articles published prior to April 2015 and is 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, no review has been found that is substantially duplicative of KQ1. See Table 2, Duplication column for the systematic review citations that were determined to address the key questions.

Impact of a New Evidence Review

A new systematic review on management of LAPC may have 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 wide practice variation due to conflicting data/opinion and existing recommendations.

Feasibility of a New Evidence Review

A new evidence review examining management of LAPC is feasible. 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 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. See Table 2, Feasibility column for the citations that were determined to address the key questions.

Table 2. Key questions, relevant evidence reviews, and original research

Key Question	Duplication (Completed or In-Process Evidence Reviews)	Feasibility (Published and Ongoing Original Research)
KQ 1: Diagnostic staging	Total number of completed or in-progress systematic reviews - 4 • Other - 4[11-14]	Size/scope of review Relevant Studies Identified: 2 • Secondary analysis of RCT - 1[15] • Retrospective Cohort - 1[16] Projected Total: 20 ClinicalTrials.gov Relevant Trials: 16 • Recruiting – 11 • Complete – 5
KQ 2: Focal therapy effectiveness	Total number of completed or in-progress systematic reviews - 1 • Other - 1[17]	Size/scope of review Relevant Studies Identified: 0 Projected Total: 0 ClinicalTrials.gov Relevant Trials: 12 • Recruiting – 10 • Active, not recruiting – 1 • Complete – 1
KQ 3: Focal therapy harms	Total number of completed or in-progress systematic reviews - 1 • Other - 1[17]	Size/scope of review Relevant Studies Identified: 0 Projected Total: 0 ClinicalTrials.gov Relevant Trials: 12 • Recruiting – 10 • Active, not recruiting – 1 • Complete – 1

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

Value

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 and other medical organizations.

Summary of Findings

- Appropriateness and Importance: The topic is both appropriate and important.
- Duplication: A new review would not be duplicative of an existing product. We identified an ongoing systematic review on PROSPERO conducted by the EAU, which is relevant to KQ2 and KQ3 of the original nomination. However, this review will not include focal therapy interventions such as cryotherapy and HIFU with or without systemic neoadjuvant/adjuvant interventions (ADT 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 addressed KQ1.
- Impact: A new systematic review would have high impact. Optimal strategies for diagnostic staging and treatment LAPC are currently under debate. Recommendations among clinical experts differ greatly resulting in wide practice variation. An AHRQ report could complement the ongoing EAU report and help resolve controversies.
- Feasibility: A new review is feasible. The evidence base is likely limited to small.

    - *Size/scope of review:* Our search of PubMed resulted in a total of 1983 unique titles. Upon title and abstract review, we identified two studies potentially relevant to KQ1 in the nomination, for a projected total of 20 studies. We did not find studies relevant to KQ2 and KQ3.
    - *ClinicalTrials:* We identified 28 open or recently closed relevant clinical trials on ClinicalTrials.gov.
- Value: The potential for value is high because AUA will use a new AHRQ evidence review to update clinical practice guidelines on a clinical topic that imposes a high mortality burden on the US male population. In addition, the AUA will work closely with EAU and several other national and international stakeholder organizations, which would help disseminate the AHRQ report findings including the Urology Care Foundation, the Canadian Urological Association (CUA), the American Society for Radiation Oncology (ASTRO), and the Society of Urologic Oncology (SUO).

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Appendix A. Selection Criteria Summary

Selection Criteria	
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 health care drugs and 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 both 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. Yes, it is consistent with what is known about the topic.
2a. Represents a significant disease burden; large proportion of the population	Yes, this topic represents a significant burden. In 2018, the American Cancer Society 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. 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	Yes, this nomination addresses both benefits and potential harms of therapeutic interventions for LAPC patients.
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 is projected to rise to $16 billion by 2020.
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. We have revised the KQs to focus on interventions not covered by an ongoing review being conducted by the EAU. No completed or ongoing review has been found that is duplicative of KQ1 which focuses on diagnostic staging of LAPC.
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 multitude of available treatment strategies. Recommendations among clinical experts differ.
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 data/opinion and existing recommendations.

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). Scope of the review is likely limited/small. *ClinicalTrials.gov*: We found 15 trials relevant to KQ1 and 12 trials relevant to KQ2 / KQ3.
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, AUA will use a systematic review to formulate a new guideline. It may potentially be used by EAU as well.

Abbreviations: AHRQ=Agency for Healthcare Research and Quality; KQ=Key Question; LAPC - Locally Advance Prostate Cancer; EAU=European Association of Urology; RCT=Randomized Controlled Trial; AUA=American Urological Association

Appendix B. Search for Systematic Reviews (Duplication)

Listed below are the sources searched and results of our search for existing guidance.

Locally Advanced Prostate Cancer
Source
Search for Duplication: April 11, 2018
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 https://www.ncbi.nlm.nih.gov/pubmed/
PROSPERO Database (international prospective register of systematic reviews and protocols) http://www.crd.york.ac.uk/prospero/

Appendix C. Search Strategy & Results (Feasibility)

Topic: Locally Advanced Prostate Cancer Date: April 11, 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 last 5 years	Filter activated: published in the last 5 years
N=1983	

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=