Evidence-based Practice Center Systematic Review Protocol

Project Title: Therapies for Clinically Localized Prostate Cancer

Initial Publication Date: September 12, 2019
Amendment Date: November 2, 2019
(Amendments Details-see Section VII)

I. Background and Objectives for the Systematic Review

Prostate cancer is common and results in considerable morbidity, mortality, and costs. The American Cancer Society projects that in 2019, prostate cancer will 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 US.[1] Annual medical costs for prostate cancer treatment are projected to rise to $16 billion by 2020.[1] About 90 percent of men diagnosed with prostate cancer have cancer confined to the prostate gland or clinically localized prostate cancer (CLPC).[2] Most cases of CLPC grow slowly and remain asymptomatic, even if untreated. However, for some men, disease progression can cause bothersome, and even fatal, results.

CLPC treatment aims to identify men most likely to benefit from early intervention while minimizing treatment-related complications. Watchful waiting (WW) monitors patients for signs or symptoms of progression, focuses on avoidance of unnecessary or ineffective early interventions, and uses treatment mainly for palliative purposes. For men with low-risk CLPC, active surveillance (AS) is often recommended. With AS, tumors are not immediately removed, irradiated, or ablated.[3, 4] Instead, tumors are monitored through surveillance of prostate specific antigen (PSA) testing, Gleason score, MRI images, or biopsy. Meanwhile, androgen deprivation therapy (ADT) (luteinizing hormone-releasing hormone [LHRH] agonists, LHRH antagonists, anti-androgens, and orchiectomy) have historically been the first-line treatment for biochemically recurrent and metastatic prostate cancer. However, ADT had also been used alone or in combination (adjuvant) with surgical or radiation therapies in CLPC.[5, 6]

Other CLPC treatments are intended to cure disease. These include radical prostatectomy (RP) and radiation therapy (RT). RP can be open or laparoscopic. Laparoscopic prostatectomy (RALP) is now commonly performed using a robotic-assisted approach. External beam radiation therapy includes a variety of approaches such as intensity modulated radiation therapy (IMRT), three-dimensional conformal radiation therapy (3D-CRT), stereotactic body radiation therapy (SBRT), and proton beam radiation therapy. These interventions treat the whole prostate gland and can have adverse effects such as urinary, bowel, and erectile/sexual dysfunction.

Therefore, more attention is turning to potentially lower-risk focal therapies including brachytherapy, high-intensity focused ultrasound (HIFU), and cryotherapy that focus

treatment on the so-called index lesion.[7-9] Use of these options has increased as magnetic resonance imaging (MRI) technology has advanced, allowing better imaging. In addition, awareness has grown regarding treatment benefits and harms relative to men's preferences.[10]

Since the original 2008 AHRQ report[11] and subsequent updates in 2014[5] and 2016,[12] new research has been published and existing trials have reported new and longer-term outcomes. Also, technology has advanced and clinical interest increased around additional focal therapies such as laser ablation, photodynamic therapy, and irreversible electroporation. New approaches to radiation therapy, such as hypofractionation, have also been tested.[13] These developments may redefine our understanding of the comparative effectiveness of CLPC treatments both for effectiveness and harms.

This broad spectrum of treatments with varying effectiveness and safety has become the crux of decisional dilemmas. Further, we do not know how effectiveness and safety are modified by patient characteristics (e.g., age, ethnicity, comorbidities, preferences), tumor characteristics (e.g., PSA, histologic grade, volume, presence of specific biomarkers); or provider/hospital characteristics (e.g., case volume, etc.).

The purpose of this systematic review is to update the previous reviews evaluating treatments for CLPC and inform clinical practice guideline committees as they update relevant guidelines.

II. Key Questions

The following populations, interventions, comparators, outcomes, timing, and settings (PICOTS) addressed with select study designs will be eligible for our review to answer the Key Questions (KQs).

PICOTS Framework

Population(s)

- Treatment naïve men with CLPC (stages T1 to T3)

Interventions

KQ1 to 3

1) Watchful waiting (WW)
2) Active surveillance (AS)
3) Androgen deprivation therapy (ADT)
4) Focal therapies
    a) Brachytherapy
    b) Cryotherapy
    c) High-intensity focused ultrasound (HIFU)
    d) Laser ablation
    e) Photodynamic therapy
    f) Irreversible electroporation
5) Whole gland therapies
    a) Brachytherapy

b) Cryotherapy
c) External beam radiation therapy
    i) Three-dimensional conformal radiotherapy
    ii) Intensity-modulated radiation therapy
    iii) Proton beam therapy
    iv) Stereotactic body radiation therapy
d) Radical prostatectomy
    i) Open
    ii) Laparoscopic
        (1) Without robotic assistance
        (2) With robotic assistance
6) Combination of above

KQ4
1) Radical prostatectomy (RP)

Comparators
KQ1 to KQ4
- Any other intervention of listed above except certain within category comparisons (e.g., nerve-sparing vs non-nerve sparing prostatectomy; different dosage/frequency/timing/duration of same therapy)

Outcomes
KQ1 to KQ3
- Overall survival/mortality
- Prostate cancer specific survival/mortality
- Metastatic-progression free survival
- Metastases (lymph nodes/distant)
- Health status
- Quality of life (measured with validated instruments)
- Prostate-cancer related quality of life (measured with validated instruments)

KQ4
- Overall survival/mortality
- Prostate cancer specific survival/mortality
- Metastatic free survival/metastases (lymph nodes/distant)

Harms
KQ1 to KQ3
Common and serious treatment side effects
- Bowel, bladder, and sexual/erectile dysfunction
- Serious adverse effects associated with ADT such as cognitive impairment, MACE, fractures

Timing

KQ1 to KQ3
Follow up from treatment initiation:

- Mortality/survival outcomes/metastases: 5 years or more
- Health status, quality of life and harms: 1 year or more

KQ4
Follow up from treatment initiation:

- Mortality/survival outcomes/metastases: 5 years or more

Setting
KQ1 to KQ4

- All settings

Study Design
KQ1 to KQ4

1) RCTs
2) Non-RCT if:
    a) Comparative
    b) Concurrent
    c) Multicenter (enrolling patients treated at multiple locations)
    d) ≥500 patients
    e) Some method to control for selection bias (propensity scores, instrumental variables, multivariate regression)
    f) Prospective data collection

Key Questions

Project Title: Therapies for Clinically Localized Prostate Cancer

KQ 1: What are the comparative effectiveness and harms of CLPC therapies?

1) Watchful waiting
2) Active surveillance
3) Androgen deprivation therapy (ADT)
4) Focal therapies
    a) Brachytherapy
    b) Cryotherapy
    c) High-intensity focused ultrasound (HIFU)
    d) Laser ablation
    e) Photodynamic therapy
    f) Irreversible electroporation
5) Whole gland therapies
    a) Brachytherapy
    b) Cryotherapy
    c) External beam radiation therapy
        i) three-dimensional conformal radiotherapy
        ii) intensity-modulated radiation therapy
        iii) proton beam therapy
        iv) stereotactic body radiation therapy
    d) Radical prostatectomy
        i) open
        ii) laparoscopic
            (1) without robotic assistance
            (2) with robotic assistance
6) Combination of above

KQ 2: How do patient characteristics modify comparative effectiveness and harms of CLPC therapies?

1) Age
2) Race/ethnicity
3) Comorbidities
4) Health status

KQ 3: How do tumor characteristics modify comparative effectiveness and harms of CLPC therapies?

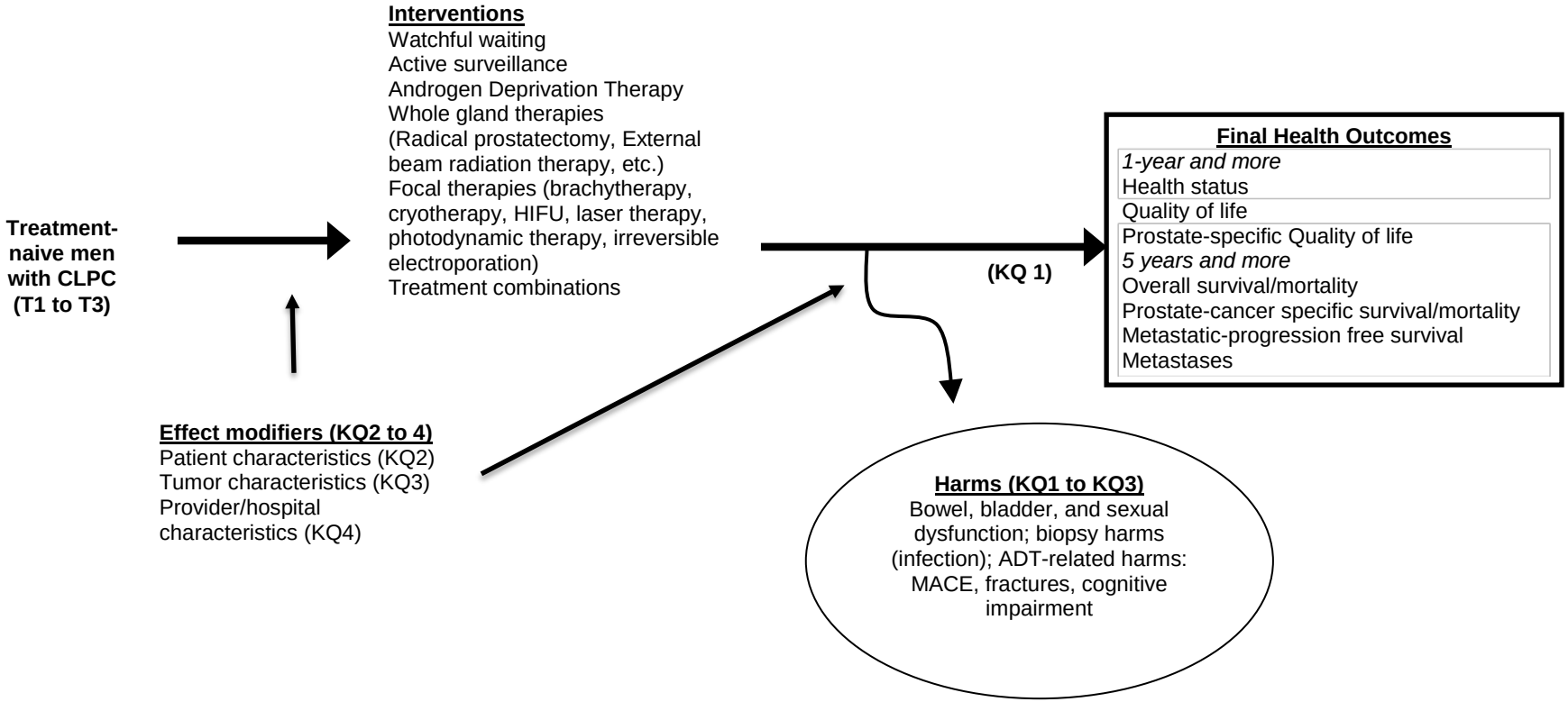
1) Baseline PSA
2) Gleason score
3) Tumor index scores (e.g., Cancer of the Prostate Risk Assessment Score [CAPRA], D'Amico Risk Classification for Prostate Cancer, etc.)
4) Biomarker Status
    a) Decipher (Genomic Classifier)
    b) Oncotype Dx (Genomic Prostate Score)
    c) Prolaris (Cell Cycle Progression)

Key Question 4: How do provider/hospital characteristics modify comparative effectiveness of RP compared to other therapies?

1) Geographic region
2) Hospital Type
3) Provider volume
4) Institutional volume

III. Analytic Framework

Figure 1. Analytical Framework for Therapies for Clinically Localized Prostate Cancer



This figure depicts the key questions within the context of the PICOTS described in the previous section. In general, the figure illustrates how therapies for CPLC may result in final health outcomes such as mortality/survival, health status, and quality of life. It also shows harms that may occur. Finally, it illustrates how therapy may be modified by patient, tumor, and/or provider/hospital characteristics.

IV. Methods

Criteria for Inclusion/Exclusion of Studies in the Review: Studies will be included in the review based on the PICOTS study-specific inclusion criteria outlined above.

Searching for the Evidence: We will develop multiple search strategies for different relevant databases (Medline®, Embase®, and the Cochrane Central trials database) incorporating vocabulary and natural language relevant to the KQs (Appendix A). This search strategy relies heavily on the 2014 AHRQ review search strategy, while limiting the search dates to 2013 forward to identify studies published since 2014 update.[5]

Search results will be downloaded to EndNote X9 and screened in DistillerSR (Evidence Partners, Ottawa, Canada). Two independent investigators will review titles and abstracts using predefined criteria. Two independent investigators will perform full-text screening to determine if inclusion criteria are met. Differences in screening decisions will be resolved by consultation between investigators, and, if necessary, consultation with a third investigator. Throughout the screening process, team members will meet regularly to discuss training material and issues as they arise to ensure consistency of inclusion criteria application. Multiple publications relating to the same study will be grouped together.

We will supplement our bibliographic database searches with citation searching of relevant systematic reviews and original research. Additionally, we will search for grey literature on ClinicalTrials.gov to identify completed and ongoing studies. Information from grey literature will also be used to assess publication and reporting bias and inform future research needs. Additional grey literature will be solicited through a notice in the Federal Register and Scientific Information Packets and other information solicited through the AHRQ Effective Health Care website.

Data Abstraction and Data Management: Data fields to be extracted will include author, year of publication, sponsorship, setting, subject inclusion and exclusion criteria, intervention and control characteristics, sample size, follow-up duration, participant baseline age, race, and results of primary outcomes and adverse effects. Relevant data will be extracted into extraction forms created in Microsoft Excel. Data will be extracted to evidence and outcomes tables by one investigator and reviewed and verified for accuracy by a second investigator. We will not extract data from high risk of bias studies or for outcomes that are high risk of bias.

Assessment of Methodological Risk of Bias of Individual Studies: Risk of bias of eligible RCTs will be assessed using the Cochrane Risk of Bias Tool.[14] Components include participant group assignment (random sequence generation, allocation concealment), blinding (performance and detection bias), completeness of follow-up (attrition bias), analyses and outcome reporting consistent with predefined protocols (selective reporting bias) and other issues (such as appropriateness of analytic approach). Risk of bias for non-RCTs will be assessed using the ROBINS-I tool.[15]

One investigator will independently assess risk of bias for eligible studies; a second investigator will review each risk of bias assessment. Investigators will consult to reconcile any discrepancies in risk of bias assessments. Overall risk of bias assessments will be classified as low, high, or unclear based on the collective risk of bias across components and confidence that the study results are believable given the study's limitations.

Data Synthesis: We will not extract data from studies included in previous reviews. We will collect results data from the evidence tables of the previous review when studies and outcomes were assessed as low to medium risk of bias and the comparison is sufficiently similar to one we address and synthesize in this update.

We will summarize the results in evidence tables and synthesize evidence for each unique comparison with meta-analysis when possible and appropriate. We will assess the clinical and methodological heterogeneity and variation in effect size to determine appropriateness of pooling data.[16] We will synthesize data using a Hartung, Knapp, Sidik, and Jonkman (HKSJ)[17] random effects model in Comprehensive Meta-Analysis version 3 (Biostat, Englewood, New Jersey). We will calculate risk ratios (RR) and absolute risk differences (RD) with the corresponding 95 percent confidence intervals (CI) for binary outcomes and weighted mean differences (WMD) and/or standardized mean differences (SMD) with the corresponding 95 percent CIs for continuous outcomes if combining similar outcomes measured with different instruments.

Grading the Evidence Quality for Major Comparisons and Outcomes: We will use the Grading of Recommendations Assessment, Development and Evaluation (GRADE)[19] approach to assess the overall quality of evidence for key outcomes (overall mortality/survival; prostate-specific mortality/survival; metastatic progression) and harms (bowel, bladder, and sexual function). We will present the overall quality or certainty of the evidence for key outcomes according to the GRADE approach.[19] For each comparison, one investigator will rate the quality of evidence for each outcome as high, moderate, low, or insufficient using GRADEpro GDT (www.gradepro.org). These ratings will then be reviewed by a second investigator. We will resolve discrepancies by consensus or discussion with a third reviewer, when necessary.

For each comparison, we will present a summary of the evidence for key outcomes described above in a Summary of Findings table as well as a full Evidence Profile, which provides key information about numbers of participants and studies addressing each important outcome; best magnitude of effect estimate in relative terms and absolute differences for each comparison; and overall confidence in effect estimates for each outcome.[20] If meta-analysis is not possible, we will present results in a narrative Summary of Findings table.

Assessing Applicability: Assessing applicability of studies will be done by analyzing whether eligible studies reflect the relevant population according to the PICOTS framework. The population from which the study participants are enrolled, diagnostic approaches, eligibility criteria, patient and intervention characteristics, and other issues

that differ from those of the population of treatment naïve men with CLPC affect applicability.[21] We will assess the populations and treatments studied to determine applicability of our findings to the population of treatment naïve men diagnosed with CLPC. This will involve comparing of demographics and clinical characteristics of men enrolled in RCTs compared to those analyzed in non-RCT analyses.

V. References

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VI. Definition of Terms

Not applicable.

VII. Summary of Protocol Amendments

Date	Section	Original Protocol	Revised Protocol	Rationale
11/5/2019	PICOTs > Population	Treatment naïve men with CLPC (stages T1 to T3).	Treatment naïve men with CLPC (stages T1 to T3a). Studies enrolling 15% or more treatment naïve men with T3b or unspecified T3 will be excluded.	Our original inclusion criteria specified that studies that enrolled treatment naïve men with clinically localized prostate cancer clinically staged as T1 to T3 were eligible. We have changed this to T3a to be consistent with past reports and more accurately synthesize evidence for clinically localized prostate cancer.
11/5/2019	Analytic Framework	Treatment-naive men with CLPC (T1 to T3)	Treatment-naive men with CLPC (T1 to T3a)	Our original inclusion criteria specified that studies that enrolled treatment naïve men with clinically localized prostate cancer clinically staged as T1 to T3 were eligible. We have changed this to T3a to be consistent with past reports and more accurately synthesize evidence for clinically localized prostate cancer.

VIII. Review of Key Questions

The EPC refined and finalized the key questions after review of the public comments, and input from the Technical Expert Panel (TEP). This input is intended to ensure that the key questions are specific and relevant.

IX. Technical Experts

Technical Experts constitute a multi-disciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, or outcomes and identify particular studies or databases to search. They are selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicting opinions are common and perceived as health scientific discourse that results in a thoughtful, relevant systematic review. Therefore,

study questions, design, and methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and recommend approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind nor do they contribute to the writing of the report. They have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Technical Experts must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals are invited to serve as Technical Experts and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

X. Peer Reviewers

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. The EPC considers all peer review comments on the draft report in preparation of the final report. Peer reviewers do not participate in writing or editing of the final report or other products. The final report does not necessarily represent the views of individual reviewers. The EPC will complete a disposition of all peer review comments. The disposition of comments for systematic reviews and technical briefs will be published three months after the publication of the evidence report.

Potential Peer Reviewers must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than $5,000. Peer reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

XI. EPC Team Disclosures

EPC core team members must disclose any financial conflicts of interest greater than $1,000 and any other relevant business or professional conflicts of interest. Related financial conflicts of interest that cumulatively total greater than $1,000 will usually disqualify EPC core team investigators.

XII. Role of the Funder

This project was funded under Contract No. HHSA290201500008I from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The Task Order Officer reviewed contract deliverables for adherence to contract requirements and quality. The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

XIII. Role of the Funder

This protocol will be registered in the international prospective register of systematic reviews (PROSPERO).

Abbreviations

3D-CRT= three-dimensional conformal radiotherapy
ACP= American College of Physicians
ADT= androgen deprivation therapy
AHRQ= Agency for Healthcare Research and Quality
AS= active surveillance
ASCO= American Society of Clinical Oncology
ASTRO= American Society of Therapeutic Radiation Oncology
BT= interstitial brachytherapy
CAPRA= Cancer of the Prostate Risk Assessment Score
CLPC= clinically localized prostate cancer
EAU= European Association of Urology
EBRT= external beam radiotherapy
GRADE= Grading of Recommendations Assessment, Development and Evaluation
FDA= U.S. Food and Drug Administration
HIFU= high-intensity focused ultrasound
IMRT= intensity modulated radiation therapy
KQ= key question
LHRH= luteinizing hormone-releasing hormone
MRI= magnetic resonance imaging
NCCN= National Comprehensive Cancer Network
PSA= prostate-specific antigen
RALP= Robot assisted laparoscopic prostatectomy
RCT= randomized controlled trial
RD= risk difference
RP= radical prostatectomy
RR= risk ratios
RT= radiation therapy
SBRT= stereotactic body radiation therapy
SEER= NIH Surveillance, Epidemiology, and End Results Program
SUO= Society of Urological Oncology
T1= tumor Stage 1
T2= tumor Stage 2
T3= tumor Stage 3
T4= tumor Stage 4
WMD= weighted mean differences
WW= watchful waiting

Appendix A: Search Strategy

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to July 22, 2019>

Search Strategy:

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1 exp Prostatic Neoplasms/ (121506)

2 (prostat* and (neoplasm* or cancer* or carcinoma*)).ti,ab. (142514)

3 watchful waiting.ti,ab. (2445)

4 active surveillance.ti,ab. (6709)

5 LRP.ti,ab. (3691)

6 RLRP.ti,ab. (49)

7 prostatectom*.ti,ab. (28811)

8 radiotherap*.ti,ab. (160155)

9 EBRT.ti,ab. (2881)

10 IMRT.ti,ab. (8899)

11 proton.ti,ab. (96721)

12 (intensity and modulated and therap*).ti,ab. (7554)

13 brachytherap*.ti,ab. (16555)

14 curietherap*.ti,ab. (455)

15 cryosurger*.ti,ab. (3394)

16 cryotherap*.ti,ab. (6900)

17 cryoablat*.ti,ab. (3333)

18 Cyberknife.ti,ab. (1242)

19 freezing.ti,ab. (33279)

20 androgen deprivation.ti,ab. (7147)

21 HIFU.ti,ab. (2163)

22 (high and intensity and focused and ultrasound*).ti,ab. (2918)

23 focal.ti,ab. (144760)

24 laser.ti,ab. (247216)

25 photodynamic.ti,ab. (21944)

26 electroporation.ti,ab. (9712)

27 1 or 2 (165097)

28 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 (763246)

29 27 and 28 (43063)

30 limit 29 to (clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or evaluation studies or meta

analysis or multicenter study or observational study or pragmatic clinical trial or randomized controlled trial) (8866)
31 (clinical trial* or comparative stud* evaluation stud*).tw. (337710)
32 ((singl* or doubl* or trebl* or tripl*) and (mask* or blind*)).tw. (185146)
33 (latin square or placebo or random or control group or prospective* or retrospective* or volunteer* or sham).tw. (2224858)
34 (meta?analysis or cohort or ISRCTN* or ACTRN* or NCT*).tw. (543680)
35 31 or 32 or 33 or 34 (2789597)
36 29 and 35 (13225)
37 30 or 36 (18213)
38 limit 37 to yr="2013 -Current" (7964)

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Database: Embase Classic+Embase <1947 to 2019 July 22>
Search Strategy:
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1 Prostatic Neoplasms/ (9241)
2 (prostat$.ti,ab. or Prostate/) and (cancer.ti,ab. or Neoplasms/ or neoplasm$.mp. or carcinoma$.mp.) [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (218564)
3 1 or 2 (220887)
4 watchful waiting.ti,ab. or Watchful Waiting/ or active surveillance.ti,ab. or prostatectom$.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. or focal.ti,ab. or laser.ti,ab. or photodynamic.ti,ab. or electroporation.ti,ab. (1400768)
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.mp. 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. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (6902131)

6 3 and 4 and 5 (36694)

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.) (35118)

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.) (25188)

9 8 not (case report.de. or case reports.pt. or case report.ti. or (year adj old).ti,ab.) (25151)

10 limit 9 to (english language and yr="2013 -Current") (10638)

11 10 and compar$.ti,hw. (1891)

12 10 and (clinically adj local$).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (526)

13 10 and (stage 1 or stage one).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (16)

14 10 and (early adj3 stage).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (136)

15 10 and (nonmetastatic or non-metastatic).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (286)

16 10 and (gleason 7 or gleason score 7 or gleason 6 or gleason score 6).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (603)

17 10 and (local$ adj advanced).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (315)

18 10 and (T3 or T4).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (288)

19 10 and (high adj risk).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (1867)
20 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 (4642)

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Cochrane

1-prostat* AND (neoplasm* OR cancer* OR carcinoma*)
2-"watchful waiting" OR "active surveillance" OR LRP OR RLRP OR prostatectom* OR radiotherap* OR EBRT OR IMRT OR proton OR (intensity AND modulated AND therap*) OR brachytherap* OR curietherap* OR cryosurger* OR cryotherap* OR cryoablat* OR Cyberknife OR freezing OR "androgen deprivation" OR HIFU OR (high AND intensity AND focused AND ultrasound*) OR focal.ti,ab. OR laser.ti,ab. OR photodynamic.ti,ab. OR electroporation.ti,ab.
3-1 and 2
4- limit 3 to: publication date from 2013 to 2019