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REPORT

2020

RAPID REVIEW FOR PATIENT DECISION AID:

Treatment options for metastatic prostate cancer

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Title	Treatment options for metastatic prostate cancer: rapid review for patient decision aid
Norwegian title	Behandlingsalternativer for prostatakreft med spredning: hurtigoversikt for samvalgsverktøy
Director	Camilla Stoltenberg
Authors	Liv Merete Reinar Hege Kornør
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Content

Key messages

Prostate cancer is one of the most common types of cancer and it affects an increasing number of mainly elderly men. Usually prostate cancer grows slowly and is initially confined to the prostate gland, where it may not cause serious harm. In advanced metastatic prostate cancer hormone therapy (medical and/or surgical) is the first choice of treatment.

We aimed to summarise findings about the effectiveness of androgen suppression therapy, chemotherapy, radiation and radioactive treatment in addition to standard care (medical or surgical castration) for metastatic prostate cancer.
We found seven reviews and supplied with two newer trials. Based on our summary of the findings:

- Maximal androgen blockade
  compared to monotherapy probably
    - improves survival slightly at two years follow up
    - improves survival at five years follow up
- Taxane-based chemohormonal therapy with standard care compared to standard care alone in hormone sensitive phase
    - probably reduces prostate-cancer specific death
    - may increase quality of life (one year follow up)
    - may increase adverse events (four years follow up)
- Chemotherapy (prednisone plus cabazitaxel) plus standard care compared to other chemotherapy (prednisone plus mitroxantrone) plus standard care in castration-resistant patients
    - probably reduces death during study (2.5 years)
    - may make little or no difference on pain
    - probably increases nausea
    - probably reduces disease progression
    - probably slightly reduces death
- Radiotherapy plus standard care compared to standard care alone
    - probably make little or no difference on survival (at three years)
    - increases urinary tract infection (at three to seven months)
- Radiocative treatment in addition to or compared to standard care
    - we are not sure if radioactive treatment influence overall survival
    - may slightly delay symptomatic skeletal events
    - may slightly improve quality of life
- Docataxel, chemotherapy in addition to standard care may slightly increase survival
- Active treatment with noncytotoxic agents, abiraterone acetate plus prednisone and enzalutamide, and radium-223 dichloride (Ra-223) is associated with varying levels of improvement in health related quality of life

Title:
Treatment options for metastatic prostate cancer: rapid review for patient decision aid

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Publication type:
Rapid review

We cannot answer everything:
No recommendations
No economic evaluation

Publisher
The Institute of Public Health was commissioned by the University Hospital of Northern Norway

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Updated
Search for literature was conducted in September 2019.

Peer review
Tove Skjelbakken
and Hege Sagstuen Haugnes

Hovedbudskap

Prostatakreft er en av de vanligste former for kreft og den rammer et økende antall i hovedsak eldre menn. Vanligvis vil en lokal prostatakreftsvulst vokse langsomt og ikke være svært alvorlig eller gi alvorlig skade. I alvorlig prostatakreft med spredning vil hormonell behandling (medisinsk eller kirurgisk kastrering) være første valg for mange.

Vi hadde til hensikt å oppsummere forskning om effekten av androgen suppresjonsterapi (hormonell behandling), cellegift, røntgenstrålebehandling eller radioaktiv behandling sammenliknet med standard behandling (medisinsk/kirurgisk kastrering) for alvorlig prostatakreft med spredning.

Vi fant sju systematiske oversikter og supplerte med to nyere studier. Basert på vår oppsummering av resultater:

- Maksimal androgenblokkade
  sammenliknet med monoterapi vil trolig gi
  - bedre overlevelse etter ved to år
  - bedre overlevelse etter fem år
- Taxanbasert hormonbehandling med standard behandling i hormonfølsom fase
  sammenliknet med standard behandling alene
  - vil trolig føre til færre dødsfall spesifikt relatert til prostatakreft
  - kan muligens øke livskvalitet (ved ett års oppfølging)
  - kan muligens øke bivirkninger/uønskede hendelser (fire års oppfølging)
- Cellegift (prednison pluss cabazitaxel) pluss standard behandling sammenliknet med annen cellegift (prednison pluss mitroxantrone) pluss standard behandling i kastrasjonsresistent fase
  - reduserer trolig dødelighet i studieperioden (2.5 år)
  - gir liten eller ingen forskjell på smerter
  - øker trolig kvalme
  - reduserer trolig sykdomsprogresjon
  - reduserer trolig dødelighet noe
- Røntgenstrålebehandling pluss standard behandling sammenliknet med standard behandling alene
  - gjør trolig liten eller ingen forskjell på overlevelse (ved tre års oppfølging)
  - øker antall urinveisinfeksjoner (ved tre til sju måneder)
- Radioaktiv behandling i tillegg til eller sammenliknet med standard behandling:
  - vi er ikke sikre på om radioaktiv behandling påvirker overlevelse
  - kan muligens forsinke symptomer i skjellet
  - kan muligens gi litt bedre livskvalitet
- Cellegift (docetaxel)i tillegg til standard behandling kan muligens øke overlevelse
- Aktiv behandling med ikke- cytotoksiske midler, hormonhemmende tabletter som abiraterone pluss prednison og enzalutamid, og radium-223 diklorid (Ra-223) er assosiert med varierende grad bedring i helserelatert livskvalitet.

Tittel:
Behandlingsalternativer for prostatakreft med spredning: hurtig metodevurdering for samvalgsverktøy

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Publikasjonstype:
Hurtigoversikt

Svarer ikke på alt:
Gir ingen anbefaling
Gir ingen økonomisk vurdering

Hvem står bak denne publikasjonen?
Folkehelseinstituttet har gjennomført oppdraget etter forespørsel fra Universitetssykehuset Nord-Norge

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Når ble litteratursøket utført?
Søk etter studier ble avsluttet september 2019

Preface

The Centre for Shared decision making at the University Hospital North Norway (UNN) and Norwegian Institute of Public Health, Division for Health Services, have since 2017 co-operated in a pilot to develop evidence based patient decision aids.

The patient decision aids are published on www.helsenorge.no/samvalg.

The aim of our methodology is to:
- be resource effective
- be trustworthy and in line with national quality criteria for patient decisison aids
- present updated and evidence based information in a format that is understood by everybody (including patients and their carers).

The authors have not reported any conflict of interest.

For this rapid review we aim to summarise findings about the effectiveness of relevant treatment for metastatic prostate cancer.

Thanks for peer review from Tove Skjelbakken (Centre for Shared decision making, UNN) and Hege Sagstuen Haugnes (Department of oncology, UNN).
We would like to thank Runar Eggen, Severin Zinöcker and Tonje Lehne Refsdal, all at the Norwegian Institute of Public Health, Division for Health Services. Runar Eggen assessed the risk of bias (independently, in pair with Liv Merete Reinar) in the included primary studies. Severin Zinöcker screened some of the titles and abstracts and helped draft the report. Tonje Lehne Refsdal conducted the additional searches.

Hege Kornør
Department Director

Liv Merete Reinar
Senior Adviser

Background

The prostate gland is a common site of cancer, mostly in older men. Prostate cancer is cancer that occurs in the prostate — a small walnut-shaped gland in men that produces the seminal fluid that nourishes and transports sperm. Prostate cancer is the most common type of cancer in men in Norway and it affects an increasing number of mainly elderly men. Usually prostate cancer grows slowly and is initially confined to the prostate gland, where it may not cause serious harm. In advanced metastatic prostate cancer hormone therapy (medical and/or surgical) is the first choice of treatment. Those affected will have a reduced life expectancy, and treatments will cause side effects.

For advanced cancer, treatments include surgical and/or medical castration (androgen deprivation therapy) alone or supplied with maximal androgen blockade, chemotherapy, radiation, radioactive treatment and/or palliative care.

Method

We searched the Cochrane Library and Epistemonikos for relevant systematic reviews based on inclusion criteria defined in coalition with the Centre of shared decision making. The aim was to provide an evidence base for treatments, and treatment choices, for people with metastatic prostate cancer. We also searched Cochrane CENTRAL and Epistemonikos for single trials to update some of the research evidence.

Inclusion criteria

Population	People with metastatic prostate cancer (primary or secondary diagnosis)
Interventions	Standard care (medical or surgical castration) in addition to: Androgen suppression therapy/ maximal androgen blockade Radioactive treatment (radium-223 dichlorid) Chemotherapy (docetaxel or cabazitaxel) Radiation
Comparators	Radiation Any chemotherapy Standard care
Study design	Systematic reviews Randomised controlled trials (RCTs)

Literature search

We searched for systematic reviews in Cochrane Database of Systematic Reviews and randomised trials in Cochrane CENTRAL and in Epistemonikos (Supplement 1). The searches were conducted in March 2019 and in September 2019. We also identified some ongoing trials and protocols for systematic reviews.

Selection of studies

We screened the titles and abstracts identified through the searches. Relevant systematic reviews were presented and discussed with the commissioner. Data were extracted from included systematic reviews and single studies.

Presenting the results and judging the quality of the evidence

We used GRADE (Grading of Recommendations Assessment, Development and Evaluation) to judge our confidence in the results for each predefined outcome with a summarised effect estimate. We presented the results in Summary of Findings tables.

Table 1. GRADE Working Group grades of evidence

High certainty ⊕⊕⊕⊕	We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty ⊕⊕⊕⊖	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty ⊕⊕⊖⊖	Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect
Very low certainty ⊕⊖⊖⊖	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

We also present the results by using standardised statements about effects developed by the Cochrane collaboration (Figure 1).

Figure 1. Standardised statements about effect

Table of standardised statements about effect

	Important benefit/harm	Less important benefit/harm	No important benefit/harm
High quality / certainty[1] evidence	[*Intervention*] improves/reduces [*outcome*] (high quality / certainty evidence)	[*Intervention*] slightly improves/reduces [*outcome*] (high quality / certainty evidence)	[*Intervention*] makes little or no difference to [*outcome*] (high quality / certainty evidence)
Moderate quality / certainty[1] evidence	[*Intervention*] probably improves/reduces [*outcome*] (moderate quality / certainty evidence)	[*Intervention*] probably slightly improves/reduces / probably leads to slightly better/worse [*outcome*] (moderate quality / certainty evidence)	[*Intervention*] probably makes little or no difference to [*outcome*] (moderate quality / certainty evidence)
Low quality / certainty[1] evidence	[*Intervention*] may improve/reduce [*outcome*] (low quality / certainty evidence)	[*Intervention*] may slightly improve/reduce [*outcome*] (low quality / certainty evidence)	[*Intervention*] may make little or no difference to [*outcome*] (low quality / certainty evidence
Very low quality / certainty[1] evidence	We / The review authors are uncertain whether [*intervention*] improves/reduces [*outcome*] as the quality / certainty of the evidence has been assessed as very low		
No studies	No studies were found that looked at [*outcome*]		

[1]Within GRADE, the phrase "quality of the evidence" is increasingly referred to as "certainty of" the evidence. Use the same term that has been used elsewhere in the review.

Source: https://www.cochrane.no/sites/cochrane.no/files/public/uploads/how_to_write_a_cochrane_pls_15th_june_2018.pdf

Results

The searches identified 533 reviews and 188 single studies (Figures 2 and 3). Nineteen reviews were read in full text. We included five systematic reviews (Schmitt 1999, Shelley 2006, Sathianathen 2018, Burdett 2019, Kunath 2019) (1-5), two non-systematic reviews (Goyal 2012, Nussbaum 2016) (6;7) and two single studies (Akaza 2004, de Bono 2010) (8;9).

Figure 2. Flow chart, Cochrane Library search, March 2019

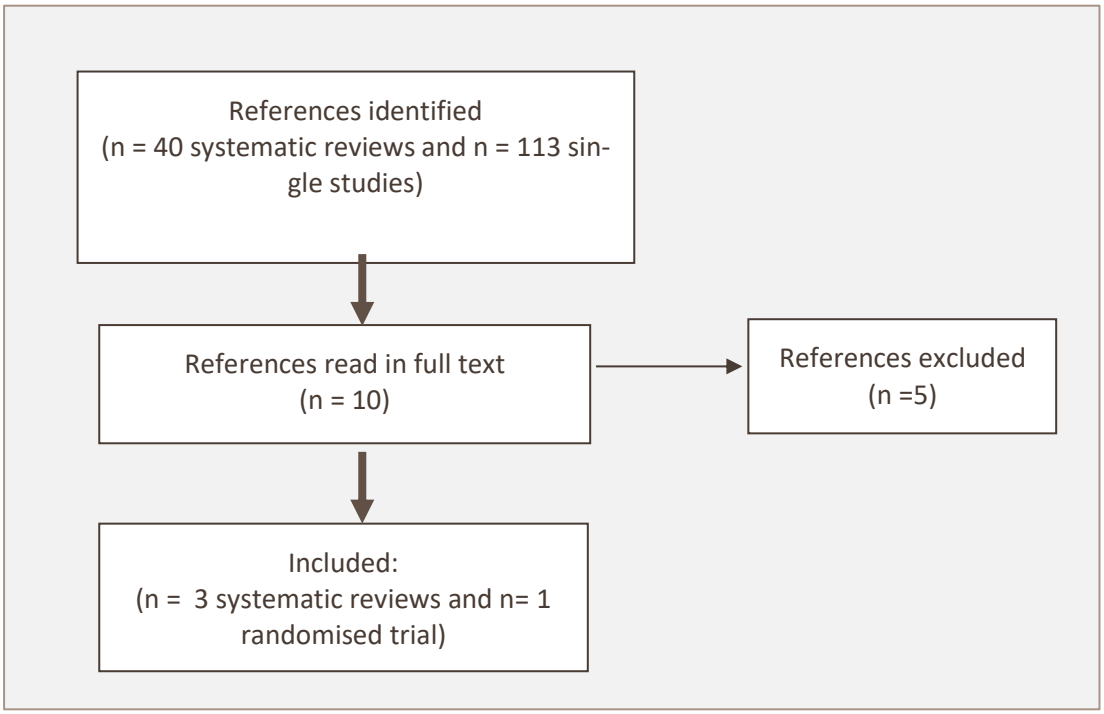
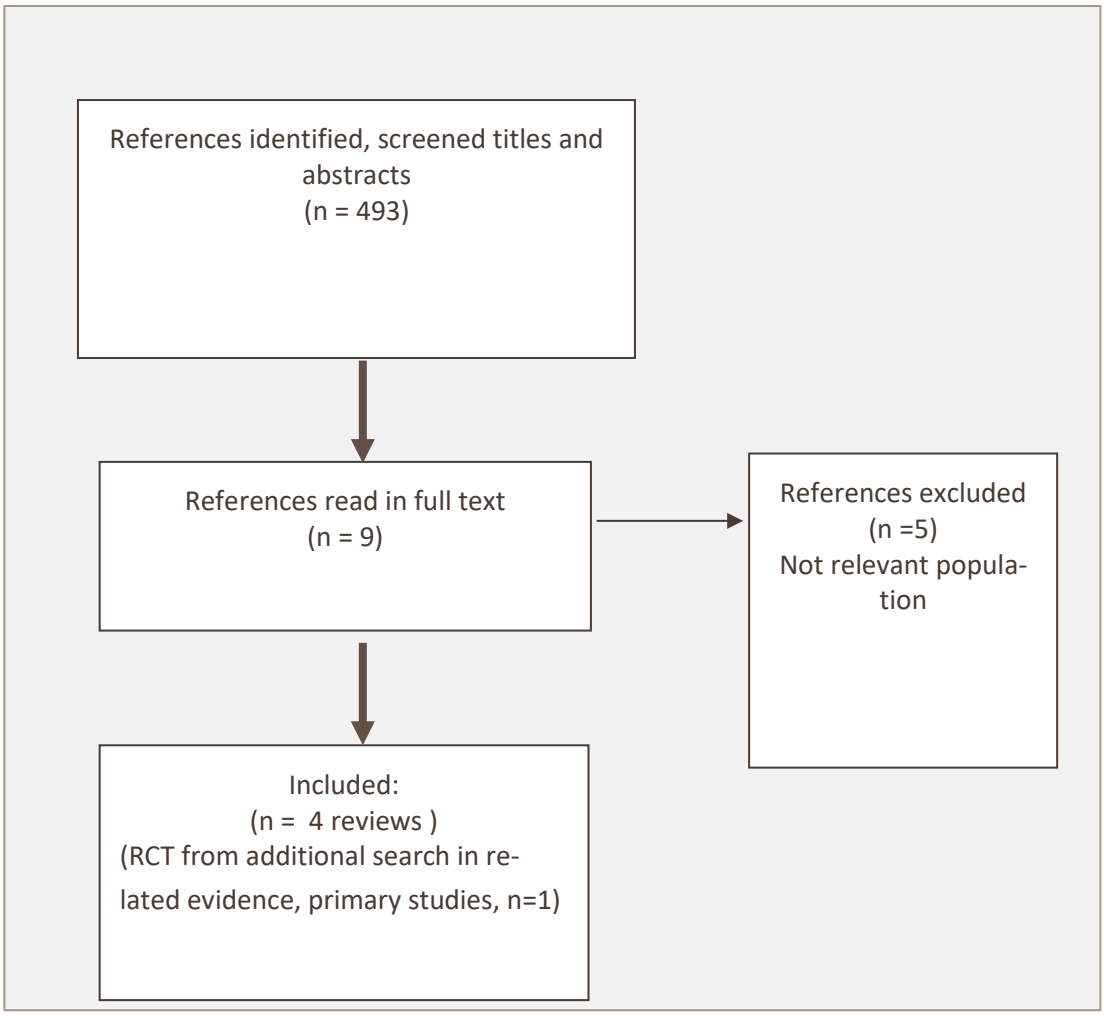


Figure 3. Flow chart, Epistemonikos search, September 2019



Included evidence

We found systematic reviews on androgen suppression therapy, chemotherapy and radiotherapy. We also included a review on radioactive treatment (Ra-223), that summarised three relevant single RCTs (6). We included one review that summarised quality of life measures across all types of interventions in patients with metastatic prostate cancer (7). See table 2. We summarised the results of four reviews in summary of findings tables (See table 4 to 7 in Supplement 2).

Table 2. Included reviews

Study ID (reference)	No of included studies	Intervention(s) (in addition to standard care)	Comparator
Schmitt 1999 (4)	20	Maximal androgen blockade	Monotherapy
Shelley 2006 (5)	4	Chemotherapy + other agent	Placebo or other chemotherapy + other agent
Sathianathen 2018 (3)	3	Chemotherapy	Standard care
Goyal 2012 (6)	3	Radioactive treatment	Standard care
Nussbaum 2016 (7)	19	Androgen suppression therapy Chemotherapy Radioactive treatment	Standard care
Kunath 2019 (2)	10	Early androgen suppression therapy	Deferred androgen suppression therapy + standard care
Burdett 2019 (1)	3	Radiation	Standard care

To update the included review on androgen suppression therapy from 1999, we searched for single studies in Cochrane CENTRAL and in Epistemonikos and added two more RCTs (Akaza 2004, de Bono 2010) (8;9). See table 3.

Table 3. Included randomised controlled trials

Study ID (reference)	Intervention (in addition to standard care)	Comparison
De Bono 2010 TROPIC (9)	Chemotherapy + prednisone	Other chemotherapy + prednisone (+ standard care)
Akaza 2004 (8)	Maximal androgen blockade	Monotherapy

We narratively summarised three reviews and one trial (Akaza 2004; Shelley 2006, Goyal 2012, Nussbaum 2016) (5-8) (Supplement 3).

Summary of our findings

What are the effects of surgical and/or medical androgen suppression therapy, chemotherapy or radiation on survival, quality of life, relief of symptoms, adverse events or

unwanted incidents for people with metastatic prostate cancer? Based on our summary of findings we found that:

- Maximal androgen blockade compared to monotherapy probably improves survival slightly at two years follow up
- Maximal androgen blockade compared to monotherapy probably improves survival at five years follow up
- Taxane-based chemohormonal therapy with androgen deprivation therapy compared to androgen deprivation alone probably reduces prostate-cancer specific death in hormone sensitive patients
- Taxane-based chemohormonal therapy with androgen deprivation therapy compared to androgen deprivation alone may increase quality of life (one year) in hormone sensitive patients
- Taxane-based chemohormonal therapy with androgen deprivation therapy compared to androgen deprivation alone may increase adverse events (four years) in hormone sensitive patients
- Prednisone plus cabazitaxel compared to prednisone plus mitroxantrone probably reduces death during study (30 months) in castration resistant patients
- Prednisone plus cabazitaxel compared to prednisone plus mitroxantrone may make little or no difference on pain in castration resistant patients
- Prednisone plus cabazitaxel compared to prednisone plus mitroxantrone probably increases nausea in castration resistant patients
- Prednisone plus cabazitaxel compared to prednisone plus mitroxantrone probably reduces disease progression in castration resistant patients
- Radiotherapy plus standard care compared to standard care alone probably make little or no difference on survival
- Radiotherapy plus standard care compared to standard care alone increases urinary tract infection (12- 28 weeks)
- Early androgen suppression therapy probably reduces death from any cause at five years follow-up
- Early androgen suppression therapy probably reduces death from prostate cancer at five years follow-up
- Quality of life is probably similar between early or deferred androgen suppression treatment after two years
- Early androgen suppression therapy may make little or no difference in serious adverse events five to 13 years follow-up
- Early androgen suppression therapy may slightly decrease skeletal events after 5 years
- Early androgen suppression therapy may slightly increase fatigue at 9 to 11 years follow-up
- Early androgen suppression therapy may increase heart failure at 9.7 years follow-up

What are the effects of chemotherapy or radioactive treatment on survival, quality of life, relief of symptoms, adverse events or unwanted incidents for people with metastatic prostate cancer? Based on our narrative summaries we found that:

- We are uncertain if Ra-223 increases overall survival. Ra-223 may delay symptomatic skeletal events and improve quality of life
- Docetaxel, chemotherapy in addition to standard care may slightly increase survival

Active treatment with noncytotoxic agents, abiraterone acetate plus prednisone and enzalutamide, and Ra-223 is associated with varying levels of improvement in health related quality of life.

Discussion

Main findings

We found systematic reviews and randomised trials that covered most of the interventions predefined in the inclusion criteria for this rapid review. However, we did not find evidence on all the prespecified comparisons.

Maximal androgen blockade has beneficial effects on survival. Adding chemotherapy to standard care (androgen suppression therapy – medical or surgical castration) might influence survival in the short (but not the long) run, might give some relief of symptoms and reduce some pain. Adding radiation therapy to standard care probably makes little difference on survival. Radiopharmaceuticals seem to relieve pain related to bone metastatic disease, we are unsure to what extent it is beneficial on survival. The interventions might to some extent improve quality of life. However, the treatments all come at the expense of increased individual non-serious adverse events or have adverse effects that can be serious.

As is concluded in Kunath 2019: "It appears important to share the information on both desirable and undesirable effects with patients considering the treatment options and to facilitate shared decision-making to resolve the resulting trade-offs» (2).

Limitations

There is a limitation that palliative care is not included in our review. It is also a limitation that not all included reviews are up-to date and not all included reviews reported findings in a way that made it possible to GRADE all the evidence.

Update and research gaps

There is a need to update the systematic reviews on androgen suppression therapy and chemotherapy (docetaxel) and to conduct systematic reviews on radiotherapy and radioactive treatment.

In light of how big a burden metastatic prostate cancer can be for many people it is worrying that relatively few conducted studies and reviews identified in our search have reported quality of life measures.

We searched the Cochrane Library for protocols and found several that are relevant for a future update of this rapid review (Supplement 4).

References

Inkluderte studier

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2. Kunath F, Jensen K, Pinart M, Kahlmeyer A, Schmidt S, Price CL, et al. Early versus deferred standard androgen suppression therapy for advanced hormone-sensitive prostate cancer. Cochrane Database Syst Rev 2019;(6).

3. Sathianathen NJ, Philippou YA, Kuntz GM, Konety BR, Gupta S, Lamb AD, et al. Taxane-based chemohormonal therapy for metastatic hormone-sensitive prostate cancer. Cochrane Database of Systematic Reviews 2018;(10).

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7. Nussbaum N, George DJ, Abernethy AP, Dolan CM, Oestreicher N, Flanders S, et al. Patient experience in the treatment of metastatic castration-resistant prostate cancer: state of the science. Prostate cancer and prostatic diseases 2016;19(2):111-21.

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10. Gupta N, Devgan A, Bansal I, Olsavsky TD, Li S, Abdelbaki A, et al. Usefulness of radium-223 in patients with bone metastases. Proceedings (Baylor University Medical Center) 2017;30(4):424-6.

Supplement 1. Search strategy

Database: Cochrane Database of Systematic Reviews (Cochrane Library)
Search date: 19.03.2019
Search performed by: Therese Kristine Dalsbø, Senior Adviser, Norwegian Institute of Public Health

Search terms: prostate cancer in Title Abstract Keyword og MeSH descriptor: [Prostatic Neoplasms] explode all trees

Search hits are limited to reviews, protocols are not included.

Number of hits : 40 (completed reviews, protocols are excluded)

Database: Cochrane Central Register of Controlled Trials
Search terms: metastatic prostate cancer AND radiotherapy OR cabazitaxel in Title
Number of hits: 113

Search update

Database: Epistemonikos (Advanced search – Title/Abstract)
Search date: 27.09.2019
Search performed by: Tonje Lehne Refsdal, Librarian, Norwegian Institute of Public Health

(prostat* AND (cancer* OR tumor* OR tumour* OR neoplasm* OR carcinoma* OR adenocarcinoma*) AND (radium OR radium223 OR Ra223 OR 223Ra* OR cabazitaxel OR docetaxel OR "radiation treatment" OR "radiation treatments" OR "radiation therapy" OR "radiation therapies" OR brachytherap* OR chemoradiotherap* OR irradiation OR radioimmunotherap* OR immunoradiotherap* OR radiotherap* OR "radioactive therapy" OR "radioactive therapies" OR "radioactive treatment" OR "radioactive treatments" OR "x-Ray therapy" OR "x-Ray therapies" OR "xray therapy" OR "xray therapies" OR "x-ray treatment" OR "x-ray treatments" OR "xray treatment" OR "xray treatments" OR "androgen suppression therapy" OR "androgen suppression therapies" OR "androgen suppression treatment" OR "androgen suppression treatments" OR "androgen deprivation therapy" OR "androgen deprivation therapies" OR "androgen deprivation treatment" OR "androgen deprivation treatments" OR ADT OR "castration therapy" OR "castration therapies" OR "castration treatment" OR "castration treatments" OR "hormone deprivation therapy" OR "hormone deprivation therapies" OR "hormone deprivation treatment" OR "hormone deprivation treatments" OR "hormone therapy" OR "hormone therapies" OR "hormone treatment" OR "hormone treatments" OR "anti-androgen therapy" OR "anti-androgen therapies" OR "anti-androgen treatment" OR "anti-androgen treatments" OR "antiandrogen therapy" OR "antiandrogen therapies" OR "antiandrogen treatment" OR "antiandrogen treatments" OR "androgen blockade" OR leuprolide OR goserelin OR triptorelin OR histrelin OR degarelix OR flutamide OR

enzalutamide OR bicalutamide OR nilutamide OR ketoconazole OR aminoglutethimide OR abiraterone))

Broad synthesis: 12 hits (year 2014 -2019)
Systematic review: 499 hits (year 2014 -2019)
511 references exported from Epistemonikos to EndNote (18 duplicates)

Supplement 2. Summary of findings tables

Table 4. Maximal androgen blockade vs monotherapy

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with monotherapy	**Risk with maximal androgen blockade**				
Survival follow up: 2 years	561 per 1 000	**593 per 1 000** (561 to 626)	**OR 1.14** (1.00 to 1.31)	5286 (14 RCTs)	⊕⊕⊕◯ MODERATE [a]	Maximal androgen blockade compared to monotherapy probably slightly improves survival
Survival follow-up: 5 years	249 per 1 000	**300 per 1 000** (269 to 333)	**OR 1.29** (1.11 to 1.50)	3550 (7 RCTs)	⊕⊕⊕◯ MODERATE [a]	Maximal androgen blockade compared to monotherapy probably improves survival

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **OR:** Odds ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Reference: Schmitt 1999 “Maximal androgen blockade for advanced prostate cancer” (4)

Explanations

a. High risk of bias in majority of studies

Table 5. Chemohormonal combination therapy vs standard care

Participants: men with metastatic hormone-sensitive prostate cancer
Setting: multicenter
Intervention: early docetaxel with androgen deprivation therapy
Control: androgen deprivation therapy only

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with monotherapy	**Risk with chemohormonal combination therapy**				
Prostate-cancer specific death	371 per 1 000	**293 per 1 000** (260 to 330)	**RR 0.79** (0.70 to 0.89)	2261 (3 RCTs)	⨁⨁⨁◯ MODERATE [a]	Chemohormonal combination therapy compared to monotherapy probably reduces prostate-cancer specific death
Quality of life 12 months	The mean quality of life was **116.4**	MD **2.85 higher** (0.13 higher to 5.57 higher)	-	790 (1 RCT)	⨁⨁◯◯ LOW [b]	Chemohormonal combination therapy compared to monotherapy may increase quality of life
Adverse events follow up: median 50 months	898 per 1 000	**997 per 1 000** (952 to 1 000)	**RR 1.11** (1.06 to 1.17)	375 (1 RCT)	⨁⨁◯◯ LOW [c]	Chemohormonal combination therapy compared to monotherapy may increase adverse events

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Reference: Sathianathen 2018 “Early taxane-based chemohormonal therapy in addition to androgen deprivation therapy versus androgen deprovation therapy alone” (3)

Explanations

a. Severe concerns regarding study limitations (high risk of performance bias and unclear risk of detection bias) contributed to authors' decision to downgrade by one level overall.
b. Very severe concerns regarding study limitations (high risk of detection, performance and attrition bias) contributed to authors' decision to downgrade by two levels overall.
c. Severe concerns regarding study limitations (high risk of performance and detection bias), imprecision (wide CI consistent with both large and very large increase in grade III to V adverse events), and additional concerns about selective reporting (outcome only adequately reported by one of three trials) contributed to authors' decision to downgrade by two levels overall.

Table 6. Comparing two chemohormonal combination therapies

Participants: men with metastatic castration-resistant prostate cancer who had received previous hormone therapy
Setting: multicenter
Intervention: prednisone + cabazitaxel
Control: prednisone + mitoxantrone

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with mitoxantrone	Risk with cabazitaxel				
Deaths during study follow up: 30 months	741 per 1 000	615 per 1 000 (556 to 675)	**RR 0.83** (0.75 to 0.91)	742 (1 RCT)	⨁⨁⨁◯ MODERATE [a]	Cabazitaxel compared to mitoxantrone probably reduces death during study
Relief of symptoms (response rate pain)	77 per 1 000	92 per 1 000 (46 to 185)	**RR 1.19** (0.59 to 2.39)	342 (1 RCT)	⨁⨁◯◯ LOW [a,b,c]	Cabazitaxel compared to mitoxantrone may make little or no difference on pain
Side effects (nausea)	229 per 1 000	341 per 1 000 (270 to 433)	**RR 1.49** (1.18 to 1.89)	742 (1 RCT)	⨁⨁⨁◯ MODERATE [a,b]	Cabazitaxel compared to mitoxantrone probably increases nauasea
Adverse events (discontinued study treatment due to disease progression)	708 per 1 000	475 per 1 000 (418 to 538)	**RR 0.67** (0.59 to 0.76)	755 (1 RCT)	⨁⨁⨁◯ MODERATE [a,b]	Cabazitaxel compared to mitoxantrone probably reduces disease progression

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Reference: De Bono 2010 “Androgen deprivation therapy and prednisone plua cabazitaxel or mitoxantrone” (9)

Explanations

a. open label phase 3, sponsor funded trial
b. Patients and physicians unblinded
c. Confidence interval includes both higher and lower risk of response rate pain

Table 6. Radiotherapy plus standard care compared to standard care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standard care	**Risk with radiotherapy plus standard care**				
Survival death of any cause	467 per 1,000	**28 fewer per 1,000** (68 fewer to 13 more)	**HR 0.92** (0.81 to 1.04)	2126 (2 RCTs)	⨁⨁⨁◯ MODERATE [a]	Radiotherapy plus standard care compared to standard care alone probably make little or no difference on survival
Adverse events (urinary tract infection)	48 per 1,000	**73 per 1,000** (51 to 103)	**RR 1.53** (1.08 to 2.16)	2061 (1 RCT)	⨁⨁⨁⨁ HIGH	Radiotherapy plus standard care compared to standard care alone increases urinary tract infection

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

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High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
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Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Reference: Burdett 2019 "Prostate radiotherapy for metastatic hormone-sensitive prostate cancer" (1)

Explanations

a. Confidence interval includes both higher and lower risk of death

Table 7. Early compared to deferred androgen suppression therapy in addition to standard care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with deferred ADT	**Risk difference with early**				
All cause mortality of any cause at five years	390 per 1 000	57 fewer per 1000 (38 fewer to 31 fewer	HR 0.82 (0.75 to 0.90)	4767 (10 RCTs)	⨁⨁⨁◯ MODERATE[a]	Early androgen suppression therapy probably reduces death from any cause at five years follow-up
Time to death from prostate cancer at five years	218 per 1000	62 fewer per 1000 (87 fewer to 31 fewer)	HR 0.69 (0.57 to 0.84	3677 (7 RCTs)	⨁⨁⨁◯ MODERATE[b]	Early androgen suppression therapy probably reduces death from prostate cancer at five years follow-up
Quality of life assessed with EORT QLQ-C30, scale from 0 to 100 (median follow- up 5 years)	The mean global quality of life was 70.83	MD 1.56 lower (4.5 lower to 1.38 higher)	-	285 (1 RCT)	⨁⨁⨁◯ MODERATE[b]	Quality of life is probably similar between early or deferred AST-treatment after two years
Serious adverse events, follow- up range 5 to 13 years	110 per 1000	6 more per 1000 (6 fewer to 18 more)	RR 1.05 (0.95 to 1.16)	10575 (5 RCTs)	⨁⨁◯◯ LOW[b,c]	Early androgen suppression therapy may make little or no difference in serious adverse events five to 13 years follow-up
Skeletal events, follow -up 5 years to unclear years	37 per 1000	23 fewer per 1000 (31 fewer to 7 fewer)	RR 0.37 (0.17 to 0.80)	2209 (3 RCTs)	⨁⨁◯◯ LOW[b,d]	Early androgen suppression therapy may slightly decrease skeletal events after 5 years
Fatigue follow- up median 9.7 to 11.9 years	77 per 1000	31 more per 1000 (18 more to 48 more)	RR 1.41 (1.23 to 1.62)	8209 (2 RCTs)	⨁⨁◯◯ LOW[b,d]	Early androgen suppression therapy may slightly increase fatigue at 9 to 11 years follow-up
Heart failure follow- up median 9.7 years	30 per 1000	27 more per 1000 (3 more to 69 more)	RR 1.90 (1.09 to 3.33)	1214 (1 RCT)	⨁⨁◯◯ LOW[b,d]	Early androgen suppression therapy may increase heart failure at 9.7 years follow-up

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Reference: Kunath 2019 "Early versus deferred standard androgen suppression therapy for advanced hormone-sensitive prostate cancer" (2)

a) Downgraded by one level for performance bias
b) Downgraded by one level for performance and detection bias
c) Concern over selective reporting bias contributed downgrading one level
d) Downgraded by one level for imprecision

Supplement 3. Narrative summary of reviews

Effect of chemotherapy in addition to standard care versus placebo or other chemotherapy in addition to standard care

Shelley 2006 (5) summarised 47 trials that compared chemotherapy with placebo or one chemotherapy regime with another. Four of the included trials in this review concerned docetaxel chemotherapy, a predefined chemotherapy for our evidence base. The results in this systematic review were not pooled and the reporting of the results from the individual trials were limited. We have therefore not summarised the results from this included review in our Summary of Findings tables. For the main outcome overall *survival* we report results from these four individual trials in Table 5.

Standard care (androgen deprivation therapy) for patients with metastatic prostate cancer is almost universally accepted and the trials in the review compared different types of chemotherapy in addition to standard care.

Table 4. Effect of docetaxel on survival

Intervention Comparison	n	Median survival (months)
Docetaxel + thalidomide	50	28.9
Docetaxel alone	25	14.7
Docetaxel + estramustine + prednisone	44	18.6
Mitoxantrone + prednisone	42	13.4
Docetaxel + prednisone	335	18.9
Mitoxantrone + prednisone	337	16.5
Docetaxel + estramustine	386	17.5
Mitoxantrone + prednisone	384	15.6

Radioactive treatment (Radium-223) versus placebo for the treatment of prostate cancer with bone metastases

Patients with metastatic castration-resistant prostate cancer have poor prognosis and expected survival of 18 to 20 months (10). They might experience complications like bone pain, pathological fractures and bone marrow suppression amongst others. According to an overview by Gupta and colleagues (10), "Radium-223 is a first-of-its-kind FDA-approved bone targeting therapeutic agent that positively impacts overall survival, delay in symptomatic skeletal events, and quality of life. Various clinical trials and

their post hoc analyses have proved its safety and efficacy in treating mCRPC with bone metastases. However, its role in managing micro bone metastases in early mCRPC is still ambiguous. Ongoing research and trials are attempting to address various combination therapies and treatment sequencing strategies».

Goyal 2012 (6) summarised the findings of three trials on Ra-223 (one of the interventions in our inclusion criteria). They reported outcomes like overall survival, pain relief, skeletal-related events, and hematological adverse events. One of the trials, a phase-1 trial, included 25 patients with either breast or prostate cancer. The second trial was a phase-2 follow-up study with 64 advanced prostate cancer patients. The third trial, a phase-3 trial with three years follow up, included 922 patients. The authors did not conduct any meta-analyses.

Table 5. Efficacy of Ra-223 for advanced prostate cancer

Comparison	Clinical effects	Adverse hematological effects
Escalated doses of Ra-233 (n=25)	At 2 months, pain relief in 56% patients	Thrombocytopenia grade 1 in 3 patients; leukopenia grade 3 in 3 patients; neutropenia grade 3 in 2 patients
Ra-223 vs placebo (n=64)	Change in ALP: 65,6% (Ra-223) vs. 9,3% (placebo), p<0.0001; HR for time to first SRE 1.75 (0.96-3.19); time to PSA progression 26 wks (Ra-223) vs 8 wks (placebo), p=0.048 OS: 65.3 weeks (Ra-223) vs 46.4 weeks (placebo): p=0.068	Thrombocytopenia grade 3: 0% in Ra-223 vs 3.03% in placebo; neutropenia grade 2/3: 9.6% in Ra-223 vs 0% in placebo
Ra-223 vs placebo (n=922)	Overall survival (OS): 14 months (Ra-223) vs 11.2 moths (placebo), HR 0.695, p=0.001; HR time to total ALP progression: 0.163 (p<0.00001); HR time to PSA progression: 0.671 (p=0.0002)	Anemia grade 3/4 in 11% in Ra-223 vs 12% in placebo; neutropenia grade 3/4 in 2% in Ra-223 vs 1 % in placebo; thrombocytopenia grade 3/4 in 4% in Ra-223 vs 2% in placebo

ALP: alkaline phosphatase concentrations; HR: hazard ratio; SRE: skeletal-related events; PSA: prostate spesific antigen
Source: Table 5 in Goyal 2012 (6).

Quality of life in patients with metastatic castration-resistant prostate cancer

When making an informed choice in shared decision making one has to balance the potential health-related quality of life improvements that could result from disease control with potential adverse effects. Nussbaum 2016 (7) summarised findings from ten randomised controlled trials including 50 or more patients with metastatic castration-resistant prostate cancer and reporting patient-reported outcomes. Five of the studies

used patient-completed questionnaires measuring health-related quality of life (HRQoL) post-treatment (Table 6).

Table 6. Post-treatment quality of life in patients with metastatic castration-resistant prostate cancer

Comparison (n)	HRQoL instrument	Results
Abiraterone + prednisone vs placebo + prednisone (1195)	FACT-P	Changes in estimated FACT-P total score from baseline to week 112: 104 to 50 points vs 104 to 30 points
Enzalutamide vs placebo (1199)	FACT-P; EQ-5D	Mean FACT-P total score decreased by 1.5 points with enzalutamide compared with 13.7 points with placebo after 25 weeks (P<0.001). Significantly different mean changes from baseline to week 25 favoring enzalutamide over placebo across all FACT-P subscale and index scores
Ra-223 vs placebo (922)	FACT-P	Less deterioration in mean FACT-P total score from enrollment to week 16 in the radium-223 dichloride arm than the placebo arm (−2.7 vs −6.8; P = 0.006). Clinically meaningful improvements in FACT-P total score also favored radium-223 dichloride over placebo (25% vs 16%; P = 0.02)
Mitoxantrone vs vinorelbine vs etoposide (92)	EORTC QLQ-C30; PR25	HRQoL responses were similar for the three groups
Docetaxel + estramustine vs docetaxel (59)	EORTC QLQ-C30	15 of 59 patients (25%) receiving either docetaxel alone or with estramustine had an improvement in their pain as measured by EORTC QLQ-C30

FACT-P: Functional Assessment of Cancer Therapy-Prostate; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30; PR25: EORTC QLQ-prostate specific module

Maximal androgen blockade compared to usual care in patients with previously untreated advanced prostate cancer.

To supplement the evidence from the review from 1999 on maximal androgen blockade versus monotherapy we included a newer randomised controlled trial (8). The authors evaluated androgen suppression therapy (bicalutamide) plus leuteinizing hormone-releasing hormone agonist versus hormone-releasing hormone agonist.
The study did not report survival. For this rapid review we report adverse events. The trial randomised a total of 205 patients in Japan, 102 to intervention maximum andro-

gen blockade (gosarelin/leuprorepin + bicalutamide 80 mg) and 101 patients to control (LHRH agonist monotherapy (goserelin or leuprorelin). Ten people died during the study period.

Table 7. adverse events, 12 weeks therapy

Outcome	Maximum androgen blockade	LHRH agonist monotherapy
Any adverse events	88.2%	83.2%
Adverse drug reactions	59.8%	58.4%

LHRH: luteinizing hormone-releasing hormone

Supplement 4. Protocols

Protocols for systematic reviews in Cochrane Library

Daly T, Hickey BE, See AM, Francis DP.
Dose-escalated radiotherapy for clinically localised and locally advanced prostate cancer (Protocol). Cochrane Database of Systematic Reviews 2017, Issue 11. Art. No.: CD012817. DOI: 10.1002/14651858.CD012817.

Jakob JJ, Schmidt S, Kunath F, Meerpohl JJ, Blümle A, Schmucker C, Mayer B, Zengerling F. Degarelix for treating advanced hormone-sensitive prostate cancer. Cochrane Database of Systematic Reviews 2017, Issue 2. Art. No.: CD012548. DOI: 10.1002/14651858.CD012548.

Sathianathen NJ, Dahm P, Brown SJ, Oestreich M, Gupta S, Konety BR, Kunath F. Abiraterone acetate in combination with androgen deprivation therapy compared to androgen deprivation therapy only for metastatic hormone-sensitive prostate cancer. Cochrane Database of Systematic Reviews 2019, Issue 1. Art. No.: CD013245. DOI: 10.1002/14651858.CD013245.

Tesfamariam YM, Macherey S, Kuhr K, Becker I, Monsef I, Jakob T, Heidenreich A, Skoetz N. Bisphosphonates or RANK-ligand-inhibitors for men with prostate cancer and bone metastases: a Cochrane Review and network meta-analysis. Cochrane Database of Systematic Reviews 2018, Issue 5. Art. No.: CD013020. DOI: 10.1002/14651858.CD013020.

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P.O.B 4404 Nydalen
NO-0403 Oslo
Phone: + 47-21 07 70 00
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