

Cytoreductive radical prostatectomy versus no local treatment in patients with metastatic prostate cancer

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Citation

González-Browne C, Díaz J, Pinto I, Recabal P, Sandoval C, Vidal Á, et al.

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Medwave 2023;23(4):e2661

DOI

10.5867/medwave.2023.04.2661

Submission date

Sep 22, 2022

Acceptance date

Apr 28, 2023

Publication date

May 25, 2023

Keywords

Metastatic prostate cancer, cytoreductive radical prostatectomy, Epistemonikos, prostate cancer, Advanced prostate cancer

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Abstract

Introduction

Prostate cancer is one of the most frequent cancers in Chile, with 8157 new cases in 2020. Worldwide, 5 to 10% of men have metastatic disease at diagnosis, and androgen deprivation therapy with or without chemotherapy is the standard of care for these patients. The use of local treatment in this setting has no formal recommendation due to the lack of high-quality evidence. Some retrospective studies have sought to elucidate the benefit of surgery on the primary tumor in the setting of metastatic disease since it has been proven to be an effective local treatment for other metastatic malignant diseases. Despite these efforts, the benefit of cytoreductive radical prostatectomy as local treatment in these patients remains unclear.

Methods

We searched Epistemonikos, the largest database of systematic reviews in health, which is maintained by screening multiple information sources, including MEDLINE, EMBASE, and Cochrane, among others. We extracted data from systematic reviews, reanalyzed data from primary studies, conducted a meta-analysis, and generated a summary results table using the GRADE approach.

Results and conclusions

We identified 12 systematic reviews, including seven studies in total, none of which was a trial. Only six of those seven primary studies were used in the results summary. Despite the lack of high-quality evidence, the results summary shows the benefits of performing surgery on the primary tumor in terms of all-cause mortality, cancer-specific mortality, and disease progression. There was also a potential benefit in local complications related to the progression of the primary tumor, supporting the implementation of this intervention in patients with metastatic disease. The absence of formal recommendations highlights the need to evaluate the benefits of surgery on a case-by-case basis, presenting the available evidence to patients for a shared decision-making process and considering future local complications that could be difficult to manage.

MAIN MESSAGES

- ◆ Cytoreductive radical prostatectomy probably reduces the risk of cancer-specific mortality compared to no local treatment in patients with metastatic prostate cancer.
- ◆ All-cause mortality, disease progression, and local complications related to metastatic prostate cancer may be reduced when using cytoreductive radical prostatectomy compared to no local treatment (low certainty of evidence).
- ◆ We are uncertain whether cytoreductive radical prostatectomy reduces the probability of developing castration resistance compared to no local treatment.

PROBLEM

Prostate cancer is the most frequent solid tumor in the Western world. It represents 7.3% of all new cancer cases worldwide, being responsible for 375 304 deaths yearly. In Chile, prostate cancer is the most frequent cancer, with 8157 new cases in 2020, corresponding to 15% of all new cancer cases registered for that year [1,2].

In general, 5 to 10% of men with prostate cancer exhibit metastatic disease at diagnosis[3]. The standard of care for these patients has not changed in recent years, corresponding to a systemic treatment targeting the androgen axis through hormonal deprivation, using drugs, or surgical castration. In recent years, it has been established that androgen deprivation therapy may be administered with chemotherapy using docetaxel or second-generation hormonal therapy [4,5].

Due to the lack of high-quality evidence, there is no formal recommendation to use local treatments for primary tumors (i.e., surgery or radiation therapy) in patients with metastatic prostate cancer. Particularly, several retrospective studies have sought to elucidate the benefit of surgery on the primary tumor in the setting of metastatic disease since there is evidence of its efficacy on other metastatic malignancies, such as ovarian and renal cancer [6,7]. The evidence supporting this idea is based on multiple biological foundations, establishing that the cells in the primary tumor may have the ability to maintain the sowing of

metastases to distant organs. Moreover, untreated local tumors could act as a source of remote seeding and for seeding and resistance in the tumor itself [8,9].

This summary aims to review the available literature published on this matter to determine the impact of cytoreductive radical prostatectomy compared to no local treatment in patients with metastatic prostate cancer.

METHODS

We searched Epistemonikos, the largest database of systematic reviews in health, which is maintained by screening multiple information sources, including MEDLINE, EMBASE, and Cochrane, among others, to identify systematic reviews and their included primary studies. We extracted data from the identified reviews and reanalyzed data from primary studies included in those reviews. With this information, we generated a structured summary denominated FRISBEE (Friendly Summary of Body of Evidence using Epistemonikos) using a pre-established format, which includes key messages, a summary of the body of evidence (presented as an evidence matrix in Epistemonikos), a meta-analysis of the studies, and when possible, a summary-of-findings table following the GRADE approach and a table of other considerations for decision-making.

THE BODY OF EVIDENCE FOR THIS QUESTION

<p>What is the evidence See the evidence matrix in Epistemonikos later</p>	<p>Twelve systematic reviews [3,10–20] were found, including seven primary studies [21–27], none of which were trials. Two were case-control reports [22,27], and five corresponded to cohort studies [21,23–26]. One study was not used in the analyses presented below [25] because it analyzes the same database as another included study [24], where the latter uses a more updated version of the database, and the data were supplemented with other sources.</p>
<p>What types of patients were included*</p>	<p>All selected studies included men with metastatic prostate adenocarcinoma at diagnosis. Three studies excluded patients with visceral metastases [23,27], and one also excluded lymph node metastases [22]. One study included men with bone, visceral, and lymph node metastases [26], and two did not report information on this matter [21,24]. The average age of the patients was reported only in five studies, ranging from 61 to 78 years old.</p>

<p>What is the evidence See the evidence matrix in Epistemonikos later</p>	<p>Twelve systematic reviews [3,10–20] were found, including seven primary studies [21–27], none of which were trials. Two were case-control reports [22,27], and five corresponded to cohort studies [21,23–26]. One study was not used in the analyses presented below [25] because it analyzes the same database as another included study [24], where the latter uses a more updated version of the database, and the data were supplemented with other sources.</p>
<p>What types of interventions were included*</p>	<p>All primary studies aimed to evaluate the effect of local treatment in patients with metastatic prostate cancer compared to no local treatment. The interventions included in the local treatment group varied across studies, but all included radical prostatectomy or cytoreductive prostatectomy. Two studies included other interventions [24,26], termed: conformal radiation therapy, intensity-modulated radiation therapy, and radiotherapy, but only outcomes related to surgery of the primary tumor were reported in this summary. Neoadjuvant and adjuvant treatment with androgen deprivation therapy was allowed in this group. The comparator, no local treatment, was defined as androgen deprivation therapy with or without chemotherapy.</p>
<p>What types of outcomes were measured</p>	<p>The studies evaluated multiple outcomes, which were grouped by the systematic reviews as follows:</p> <ol style="list-style-type: none"> 1. All-cause mortality 2. Cancer-specific mortality 3. Disease progression 4. Development of castration resistance 5. Complications grade (Clavien-Dindo classification) 6. Severe local complications <p>Outcomes only reported for the group with local treatment:</p> <ol style="list-style-type: none"> 1. Operating room time 2. Blood loss 3. Blood transfusions 4. Length of hospital stay 5. Catheterization time 6. Biochemical relapse 7. Urinary continence <p>Outcomes reported only for the group without local treatment:</p> <ol style="list-style-type: none"> 1. Urinary tract complications for patients without local treatment 2. Surgical or percutaneous interventions for patients without local treatment <p>The median follow-up of the studies ranged from 20 to 82.2 months.</p>

*Information about primary studies is not extracted directly from primary studies but from identified systematic reviews unless otherwise stated.

SUMMARY OF FINDINGS

Information about the effect of cytoreductive radical prostatectomy on metastatic prostate cancer is based on six observational studies, including 10 731 patients in total.

All studies analyzed in this summary were observational with two different designs, cohort and case-control studies. Given this fact, only studies with the same design were pooled in the analysis of each reported outcome.

Five studies reported the outcome of *all-cause mortality* [21,22,24,26,27]; however, the data needed for the analysis could not be extracted from one of them [22], and an additional study was excluded since it presented a different design [27]. Three studies reported cancer-specific mortality [22,23,26], but one was also excluded [22]. One study evaluated disease

progression [23], and two reported the development of castration resistance [22,27]. Outcomes related to complications were reported in three studies, but only the information available in two could be used in the analysis [22,27].

The summary of findings is as follows:

- 1) Cytoreductive radical prostatectomy probably reduces cancer-specific mortality compared to no local treatment.
- 2) Local treatment using cytoreductive radical prostatectomy may reduce the risk of all-cause mortality compared to no local treatment.
- 3) The treatment with cytoreductive radical prostatectomy may reduce disease progression compared to no local treatment.
- 4) Cytoreductive radical prostatectomy may reduce severe local complications compared to no local treatment.
- 5) Cytoreductive radical prostatectomy may reduce grade IIIb complications, as measured by the Clavien-Dindo classification, compared to no local treatment.

- 6) We are uncertain whether cytoreductive radical prostatectomy reduces the probability of developing castration resistance compared to no local treatment.

Cytoreductive radical prostatectomy versus no local treatment for patients with metastatic prostate cancer				
Patients	Men with metastatic prostate cancer			
Intervention	Cytoreductive radical prostatectomy			
Comparison	No local treatment (androgen deprivation therapy with or without chemotherapy)			
Outcome	Absolute effect*		Relative effect (95% CI)	Certainty of evidence (GRADE)
	No local treatment	Cytoreductive radical prostatectomy		
	Difference: patients per 100			
Cancer-specific mortality	54	26	HR 0.39 (0.22 to 0.69)	⊕ ⊕ ⊕ O ^{1,2} MODERATE
	Difference: 28 fewer (Margin of error: 38 fewer to 13 fewer)			
All-cause mortality	67	43	HR 0.50 (0.44 to 0.57)	⊕ ⊕ OO ¹ LOW
	Difference: 24 fewer (Margin of error: 28 fewer to 20 fewer)			
Disease progression	55	27	HR 0.39 (0.21 to 0.73)	⊕ ⊕ OO ^{1,2,3} LOW
	Difference: 28 fewer (Margin of error: 40 fewer to 11 fewer)			
Severe local complications**	35	7	RR 0.20 (0.06 to 0.64)	⊕ ⊕ OO ^{1,3,4,5} LOW
	Difference: 28 fewer (Margin of error: 33 fewer to 13 fewer)			
Grade IIIb complications***	24	4	RR 0.18 (0.02 to 1.36)	⊕ ⊕ OO ^{1,3,5,6} LOW
	Difference: 20 fewer (Margin of error: 23 fewer to 9 more)			
Development of castration resistance	73	64	HR 0.78 (0.48 to 1.27)	⊕ OO ^{1,3,4,6} VERY LOW
	Difference: 9 fewer (Margin of error: 26 fewer to 8 more)			

Margin of error: 95% confidence interval (CI).
HR: Hazard ratio.
RR: Risk ratio.
GRADE: Evidence grades of the GRADE Working Group (see later).
 *The risk with **No local treatment** is based on the risk in the control group of the observational study. The risk with **Cytoreductive radical Prostatectomy** (and its margin of error) is calculated from relative effect (and its margin of error).
 ** Severe complications in the group with cytoreductive radical prostatectomy were stenosis and severe urinary incontinence, and in the group with no local treatment were ureter obstructions and urinary retentions requiring catheterization and/or transurethral resection of the prostate.
 *** Grade IIIb complications were measured using the Clavien-Dindo classification. These complications are related to additional interventions requiring general anesthesia.
¹ Observational studies
² The certainty of the evidence was raised one level because of the large effect size
³ The certainty of the evidence was downgraded one level for publication bias since only small studies were included in this analysis.
⁴ The certainty of the evidence was downgraded one level due to risk of bias since one of the studies was rated at moderate risk of bias using the Newcastle-Ottawa scale.
⁵ The certainty of the evidence was raised two levels due to a very large effect size.
⁶ The certainty of the evidence was downgraded one level for imprecision since the 95% CI includes a null benefit of the intervention in relation to the comparator.
 Control risk of dying at three years (all-cause mortality rate) = 67%
 Control risk of dying at three years (cancer-specific mortality rate) = 54%
 Control risk of dying or with evidence of disease progression at three years (disease progression rate) = 55.1%
 Control risk of dying or developing castration resistance at three years (development of castration resistance rate) = 73.2%
 Control risk of developing complications represented as severe local complications and grade IIIb complications in the group with no local treatment.

About the certainty of the evidence (GRADE)*

⊕ ⊕ ⊕ ⊕

High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low.

⊕ ⊕ ⊕ ○

Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate

⊕ ⊕ ○ ○

Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high.

⊕ ○ ○ ○

Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high.

*This concept is also called ‘quality of the evidence’ or ‘confidence in effect estimates’.

† Substantially different = a large enough difference that might affect a decision.

Other considerations for decision-making

To whom this evidence does and does not apply

The evidence applies to patients with metastatic prostate cancer that will undergo surgery on the primary tumor. Patients with oligometastatic disease are included in this analysis.

The results do not apply to patients in earlier prostate cancer stages undergoing local treatment or patients with metastatic disease treated with a local treatment different from cytoreductive radical prostatectomy.

About the outcomes included in this summary

The most frequently reported outcomes in the systematic reviews are all-cause mortality, also named overall survival, and cancer-specific mortality, also called cancer-specific survival. The authors of this summary agree that these outcomes are of great importance for the decision-making process of the treatment for metastatic prostate cancer.

Other secondary oncological outcomes reported were progression-free survival, referred to as disease progression in this summary, and castration-free survival, named development of castration resistance here, but only in systematic reviews without meta-analysis due to the low frequency in which they are reported. These outcomes provide relevant information about the benefit of the intervention; however, outcomes related to mortality are essential for patients' and doctors' decision-making.

Regarding complications, the outcomes reported in this summary are critical for decision-making since they represent local complications derived from disease progression. Severe local complications represent a more general outcome that may be more understandable to patients, including complications related to disease and surgery. Complications reported using the Clavien-Dindo classification are informative for clinicians because they report complications specifically associated with surgical procedures. Only complications graded IIIb or greater were reported, reflecting the need for further surgeries. No grade IV or V complications were presented in either group; therefore, those results were not reported in the summary.

Surgical or percutaneous intervention and urinary tract complications in patients without local treatment and urinary continence in patients undergoing prostatectomy are also important outcomes to declare, as they represent what can be avoided when deciding to use one treatment or the other. However, since these outcomes cannot be reported for both groups, they were excluded from this summary.

Balance between benefits and risks and certainty of the evidence

Cytoreductive radical prostatectomy was associated with improved cancer-specific mortality, reducing the risk of death because of cancer by 61% compared to no local treatment (HR = 0.39; CI 0.22 to 0.69). The risk of all-cause mortality was reduced by 50% in patients undergoing surgery (HR = 0.50; CI 0.44 to 0.57), but this result is less probable since it was obtained from low-quality evidence.

Cytoreductive radical prostatectomy may also reduce disease progression and showed a potential benefit in preventing secondary local complications related to the primary tumor progression.

The benefit of cytoreductive radical prostatectomy compared to no local treatment in the development of castration resistance is uncertain because the quality of the evidence reporting this outcome was very low.

Resource considerations

None of the systematic reviews reported analyses of the cost of surgery in relation to its benefits for patients with metastatic prostate cancer. The nature of available evidence makes it inappropriate for estimating the benefits of the intervention to determine its cost-benefit since it comes from observational studies. Further high-quality studies (i.e., randomized trials) are needed to determine the cost-effectiveness of cytoreductive radical prostatectomy compared to no local treatment.

Despite the lack of formal analyses in this matter, it is important to notice that even though the surgery implies more costs for patients than no local treatment, cytoreductive radical prostatectomy may avoid the need for future surgeries related to complications derived from disease progression, reducing future costs.

Formal analyses are needed to elucidate the cost-effectiveness of cytoreductive radical prostatectomy compared to no local treatment in metastatic prostate cancer.

What would patients and their doctors think about this intervention

Other considerations for decision-making

The management of metastatic prostate cancer considers systemic hormonal deprivation as the main treatment, with no localized therapy on the prostate. This could be a difficult fact for patients to understand, especially for those with *de novo* metastases, where primary tumor treatment has not been formally recommended. Additionally, a part of the urologist community may reject the idea of performing surgery on these patients because they consider surgery a more complex, high-risk procedure with no proven clinical benefit.

The decision to use this surgical treatment must be discussed and evaluated jointly by patients and doctors since cytoreductive prostatectomy is not the standard of care for metastatic prostate cancer. It is important to clarify and explain the procedure's potential risks and benefits, focusing on the possible benefits of disease control regarding mortality, disease progression, time to castration resistance, and complication. The benefit of providing information on the time to castration resistance to patients is still unclear.

Additionally, it must be explained to the patients that this intervention aims to prolong survival and improve local control regarding long-term symptoms. Patients value this last point because they are afraid of feeling pain and of the need for additional surgeries, which could be more complex in patients that did not undergo cytoreductive radical prostatectomy as a first treatment.

It is very unlikely that the results of this summary influence the recommendations in the clinical guidelines; however, they provide important information that should be shared with patients about oncological and symptomatic management.

Differences between this summary and other sources

The results of this summary are consistent with those reported in the systematic reviews included in this summary, where cytoreductive radical prostatectomy was associated with a reduction in mortality compared to no local treatment in terms of all-cause mortality and cancer-specific mortality. Disease progression and development of castration resistance were less reported in primary studies and systematic reviews; therefore, no clear conclusions can be reported about these outcomes. Despite these conclusions about survival benefits, all systematic reviews acknowledge the need for randomized trials to elucidate the real benefit of prostatectomy on patients with metastatic prostate cancer.

Regarding non-oncological outcomes, the systematic reviews agree that cytoreductive radical prostatectomy is a beneficial intervention for these patients since it reduces local complications compared to no local treatment. Our results are consistent with this conclusion, as severe local complications and grade IIIb complications in the Clavien-Dindo classification were reduced in the group undergoing surgery.

Guidelines establish that the standard of care for patients with metastatic disease at presentation is androgen deprivation therapy with or without chemotherapy. The evaluation of the role of cytoreductive radical prostatectomy in these patients has not been described yet, as results of ongoing trials assessing its benefit have not been reported yet [4,5].

Could this evidence change in the future?

In general, the results of this summary are likely to change due to the low and very low certainty of the evidence for overall survival, progression-free survival, castration-resistance-free survival, and the outcomes related to complications. Only the result of cancer-specific survival had moderate certainty of evidence; therefore, in the presence of new studies, the effect found may change, but it is less likely. Cohort studies have an inherent selection bias, where patients in the group with cytoreductive radical prostatectomy were normally younger and had fewer comorbidities, lower T-stage, and lower initial level of prostate-specific antigen, among other characteristics. Some of the included studies used a propensity score matching to deal with this issue; however, those results were not included in this summary since, in some cases, their sample size was not reported. This is important to mention since this problem may influence our results, and randomized trials are needed to confirm our findings.

We found one prospective cohort study [28] that could be relevant. Still, it was not cited in any of the systematic reviews included in this summary or the clinical guidelines used in our institution.

Six ongoing randomized trials evaluating cytoreductive radical prostatectomy versus no local treatment in patients with metastatic prostate cancer were reported in the systematic reviews, and the clinical trials register (clinicaltrials.gov) [29–34]. Additionally, two ongoing systematic reviews were found in the International Prospective Register of Systematic Reviews (PROSPERO) [35,36].

HOW WE CONDUCTED THIS SUMMARY

Using automated and collaborative means, we compiled all the relevant evidence for the question of interest and presented it as a matrix of evidence.

Follow the link to access the interactive version: Cytoreductive radical prostatectomy versus no local treatment in patients with metastatic prostate cancer.

NOTES

The upper portion of the evidence matrix will display a warning of “new evidence” if new systematic reviews are published after this summary's publication. Even though the project considers the periodic update of these summaries, users are invited to comment in Medwave or to contact the authors through

email if they find new evidence, and the summary should be updated earlier.

After creating an account in Epistemonikos, users can save the matrixes and receive automated notifications whenever new evidence potentially relevant to the question appears. This article is part of the Epistemonikos Evidence Synthesis project. It is elaborated with a pre-established methodology, following rigorous methodological standards and an internal peer review process. Each of these articles corresponds to a summary, denominated FRISBEE (Friendly Summary of Body of Evidence using Epistemonikos), whose main objective is to synthesize the body of evidence for a specific question with a friendly format to clinical professionals.

Its main resources are based on the evidence matrix of Epistemonikos and analysis of results using GRADE methodology. Further details of the methods for developing this FRISBEE are described here: (<http://dx.doi.org/10.5867/medwave.2014.06.5997>)

Epistemonikos Foundation is a not-for-profit organization aiming to bring information closer to health decision-makers with technology. Its main development is the Epistemonikos database (www.epistemonikos.org).

Notes

Contributor roles

Conceptualization: JAV, ID, IP, PR, CS, AV. Formal analysis: CGB. Investigation: JAV, CGB. Data curation: CGB. Writing: JAV, CGB. Visualization: JAV, CGB. Supervision: JAV, CGB. Project administration: CGB.

Competing interests

The authors do not have a relevant conflict of interest to declare.

Provenance and peer review

Not commissioned. Externally peer-reviewed by three reviewers, double-blind.

Language of submission

English.

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Prostatectomía radical citorreductora comparado a no realizar tratamiento local en pacientes con cáncer de próstata metastásico

Resumen

Introducción

El cáncer de próstata es uno de los cánceres más frecuentes en Chile, con 8157 nuevos casos en 2020. A nivel mundial, 5 a 10% de los hombres presentan metástasis al diagnóstico, y la terapia de deprivación androgénica con o sin quimioterapia es el estándar de cuidado para estos pacientes. El uso de tratamiento local en este contexto tiene una recomendación formal debido a la falta de evidencia de alta calidad. Algunos estudios retrospectivos han intentado dilucidar el beneficio de la cirugía sobre el tumor primario en el contexto de la enfermedad metastásica, ya que se ha demostrado que es un tratamiento local eficaz para otras neoplasias metastásicas. A pesar de estos esfuerzos, el beneficio de la prostatectomía radical citorreductora como tratamiento local en estos pacientes sigue sin estar claro.

Métodos

Se realizó una búsqueda en Epistemonikos, la mayor base de datos de revisiones sistemáticas en salud, que se mantiene mediante el cribado de múltiples fuentes de información, incluyendo MEDLINE, EMBASE y Cochrane, entre otras. Se extrajeron los datos de las revisiones sistemáticas, se volvieron a analizar los datos de los estudios primarios, se realizó un metanálisis y se generó una tabla de resumen de resultados utilizando el enfoque GRADE.

Resultados y conclusiones

Se identificaron 12 revisiones sistemáticas, que incluían siete estudios primarios en total, ninguno de los cuales era un ensayo aleatorizado controlado. Sólo seis de esos siete estudios primarios se utilizaron en el resumen de resultados. A pesar de la falta de evidencia de alta calidad, los resultados de este resumen muestran los beneficios de realizar la cirugía en el tumor primario en términos de mortalidad por cualquier causas, mortalidad específica por cáncer y progresión de la enfermedad. También se observó un beneficio potencial en las complicaciones locales relacionadas con la progresión del tumor primario, lo que apoya la realización de esta intervención en pacientes con enfermedad metastásica. La ausencia de recomendaciones formales subraya la necesidad de evaluar los beneficios de la cirugía caso por caso, presentando la evidencia disponibles a los pacientes para un proceso de toma de decisiones compartido, teniendo en cuenta las futuras complicaciones locales que podrían ser difíciles de manejar.



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