Méta-analyse et cancer

Atelier pratique :
lecture critique de méta-analyses

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Lecture critique d'un article avec PRISMA

- **PRISMA : Preferred reporting items for systematic reviews and meta-analyses**
- **Objectif : aider les auteurs à améliorer leur manuscrit de revues systématiques et de méta-analyses**
- **27 items**

Lecture critique d'un article avec PRISMA

- **Article :**

Treatment of Prostate Cancer With Intermittent Versus Continuous Androgen Deprivation: A Systematic Review of Randomized Trials

Saroj Niraula, Lisa W. Le, and Ian F. Tannock

Journal of Clinical Oncology

Juin 2013

Titre

Section/topic	Item No	Checklist item
Title		
Title ✓	1	Identify the report as a systematic review, meta-analysis, or both

Treatment of Prostate Cancer With Intermittent Versus Continuous Androgen Deprivation: A Systematic Review of Randomized Trials

Abstract

Abstract		
Structured summary	2	Provide a structured summary including, as applicable, background, objectives, data sources, study eligibility criteria, participants, interventions, study appraisal and synthesis methods, results, limitations, conclusions and implications of key findings, systematic review registration number

Data sources :

We searched literature published up to September 2012 from MEDLINE, EMBASE, the Cochrane Library, and major conference proceedings.

Study eligibility criteria :

We included randomized controlled trials comparing IAD and CAD if they reported overall survival (OS) or biochemical/radiologic time to disease progression.

Abstract

Abstract		
Structured summary	2	Provide a structured summary including, as applicable, background, objectives, data sources, study eligibility criteria, participants, interventions, study appraisal and synthesis methods, results, limitations, conclusions and implications of key findings, systematic review registration number

Background, objectives	✓
Data sources	✓
Study eligibility criteria	✓
Participants	✓
Interventions	✓
Study appraisal and synthesis methods	✓
Results	✓
Limitations	✗
Conclusions and implications	✓
Systematic review registration number	✗

Introduction

Introduction		
Rationale	3	Describe the rationale for the review in the context of what is already known

ADT provides biochemical response and symptomatic benefit in more than 80% of patients, but ADT is frequently overused in men without evident metastases, who may not benefit from treatment.

Use of ADT has been associated with long-term and short-term adverse effects

Given these toxicities, the optimal timing of ADT is debatable.

Introduction

Introduction			
Rationale	✓	3	Describe the rationale for the review in the context of what is already known

The concept of intermittent androgen deprivation (IAD), where ADT is interrupted in responding patients and guided by serum PSA

The first clinical trial assessing IAD in prostate cancer was reported in 1986,[16] and there have been several randomized controlled trials (RCTs) comparing continuous and intermittent ADT.

Introduction

Objectives	✓	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS)

Here, we review the results of these RCTs to address the following questions: What is the evidence for or against use of IAD compared with continuous androgen deprivation (CAD) in terms of overall survival (OS) and time to progression (TTP), where progression occurs despite ongoing ADT? What is the difference in adverse effects and quality of life (QoL) between patients receiving IAD and CAD? We also estimate cost savings from adopting a policy of IAD as opposed to CAD.

Méthodes

Methods		
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (such as web address), and, if available, provide registration information including registration number

Pas d'indication
Pas de protocole relu et accessible

Méthodes

Eligibility criteria	6	Specify study characteristics (such as PICOS, length of follow-up) and report characteristics (such as years considered, language, publication status) used as criteria for eligibility, giving rationale
Information sources	7	Describe all information sources (such as databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated

Table 1. Important Features of Included Studies

Studies were eligible for inclusion if they were RCTs comparing IAD and CAD for men with increasing serum PSA after local treatment or who had locally advanced or metastatic disease and if they reported time-to-event outcomes.

Méthodes

Non précisé

Non précisé

Eligibility criteria	6	Specify study characteristics (such as PICOS, length of follow-up) and report characteristics (such as years considered, language, publication status) used as criteria for eligibility, giving rationale
Information sources	7	Describe all information sources (such as databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated

An electronic search was performed of articles in MEDLINE from 1948 to September 2012, in EMBASE from 1980 to September 2012, and in the Cochrane Library up to September 2012. The search used the following terms: "hormone therapy" OR "hormone blockade" OR "intermittent androgen suppression" OR "continuous androgen suppression" OR "antiandrogen" OR "LHRH" OR "leuprolide" OR "goserelin" OR "flutamide" OR "bicalutamide" OR "cyproterone" OR "nilutamide." References provided in review articles and proceedings of major oncology/genitourinary conferences were also searched. Authors were contacted if the publication/presentation was more than 2 years old to request updates of time-to-event end points and information about study methodology, such as intent-to-treat analysis and adequacy of follow-up.

+++

Méthodes

Study selection	9	State the process for selecting studies (that is, screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis)
Data collection process	10	Describe method of data extraction from reports (such as piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators
Data items	11	List and define all variables for which data were sought (such as PICOS, funding sources) and any assumptions and simplifications made

Data Collection

Data regarding study methodology, results, quality, and validity were collected on predesigned forms independently by the first and second authors. Any conflicts were resolved by consensus. Information on all important outcomes (such as those listed in Tables 1 and 2) was collected, including time-to-event outcomes, QoL, and adverse effects. Descriptive comparisons were undertaken for results, such as QoL, that could not be quantified.

Méthodes

Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis

Non précisé

Risk of Bias

For eligible RCTs, we evaluated the adequacy of random assignment, baseline comparability of groups, description of the intervention, uniformity of outcome measurement, extent of loss to follow-up, outcome reporting bias, and intent-to-treat analysis.

Studies were rated by their quality as good, fair, or poor based on pre-defined criteria (Appendix Table A1, online only).

Méthodes

Critère principal non précisé
Pas de définition des critères de jugement (TTP)

Summary measures	13	State the principal summary measures (such as risk ratio, difference in means).
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (such as I^2 statistic) for each meta-analysis

Meta-Analysis

All hazard ratios (HRs) reported for time-to-event data in this review are for men on IAD compared with men on CAD. Estimates of HR reported in the opposite direction were adjusted accordingly. We pooled separately the HR for OS and the HR for TTP from those studies that reported these outcomes in meta-analyses using RevMan 5.1 analysis software (The Cochrane Collaboration, Copenhagen, Denmark). Pooled estimates of HR outcomes were computed using the random-effects model[18] according to the generic inverse-variance approach.[19] In this method, studies are weighted by the SE for their individual HR rather than by sample size. Statistical heterogeneity was assessed by χ^2 and I^2 statistics (an expression of the inconsistency of study results).[20]

Méthodes

Risk of bias across studies	✗	15	Specify any assessment of risk of bias that may affect the cumulative evidence (such as publication bias, selective reporting within studies)

Publiées sous forme d'abstract

We included unpublished studies to minimize publication bias, but a formal test using funnel plot was judged to be futile because of the limited number of studies; publication bias was minimized by searching multiple sources.

Méthodes

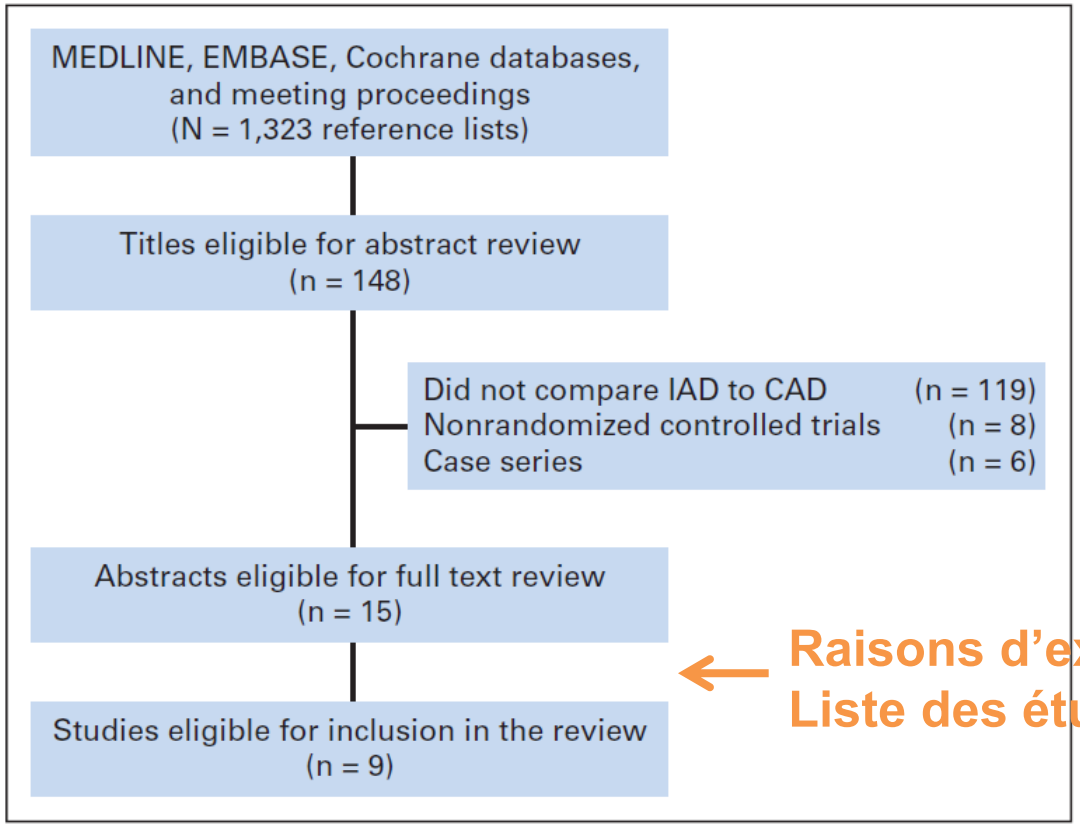
Additional analyses	✓	16	Describe methods of additional analyses (such as sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified

Descriptive comparisons were undertaken for results, such as QoL, that could not be quantified.

To obtain a simple estimate of cost savings, we calculated median cost of treatment in both arms of the studies per patient per year (in US dollars) according to the drug price listed in the pharmacy's reference Red Book (Thomson Reuters, New York, NY) for the GnRH agonists and peripheral antiandrogens used in the studies. The cost saving for IAD was estimated according to the median percentage of time off treatment observed in individual studies.

Résultats

Results			
Study selection		17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram



Raisons d'exclusion ?
Liste des études exclues ?

Fig 1. Flow chart of search results. CAD, continuous androgen deprivation; IAD, intermittent androgen deprivation.

Résultats

Study characteristics	✓	18	For each study, present characteristics for which data were extracted (such as study size, PICOS, follow-up period) and provide the citations

Dose ?

Table 1. Important Features of Included Studies

Study	Sample Size (No.)	End Points	Median Follow-Up (months)	Study Population	Drugs Used for ADT	Strategy to Stop ADT	Strategy to Start ADT	Predefined QoL Measures

Résultats

Informations sur la qualité de la randomisation ?

Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see item 12).

Table 3. Summary of Quality Criteria of Randomized Controlled Trials Comparing Intermittent and Continuous Androgen-Deprivation Therapy

Study	Quality Rating	Are Survival/Progression Outcomes Considered?	> 20% Loss to Follow-Up	Characteristics Matched?	Major Confounder?	Presence of Contamination?	Adequately Powered?	Intent-to-Treat Analysis
de Leval et al[28] (2002)	Fair	Yes	No	Yes	No	Not obvious	No, but justification provided	Not mentioned
Schasfoort et al[25] (2003)	Poor	Yes	No	Not available	Not available	Not obvious	No justification	Not mentioned
Miller et al[26] (2007)	Fair	Yes	No	Yes	No	Not obvious	No justification	Yes
Calais da Silva et al[24,30] (2011)	Good	Yes	No	Yes	No	Not obvious	Yes	Yes
Tunn et al[29] (2007)	Poor	Yes but not reported	Yes	Yes	No	Not obvious	No justification	Yes
Crook et al[21] (2012)*	Good	Yes	No	Yes	No	Not obvious	Yes	Yes
Mottet et al[22] (2012)	Fair	Yes	No	Yes	No	Not obvious	No justification	Not mentioned
Salonen et al[27] (2012)	Fair	Yes	No	Yes	No	Not obvious	Yes	Not mentioned
Hussain et al[23] (2012)*	Good	Yes	No	Yes	No	Not obvious	Yes	Yes

NOTE. Comparability of groups, definition of intervention, and measurements used in the groups were satisfactory in all studies.

Résultats

Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see item 12).

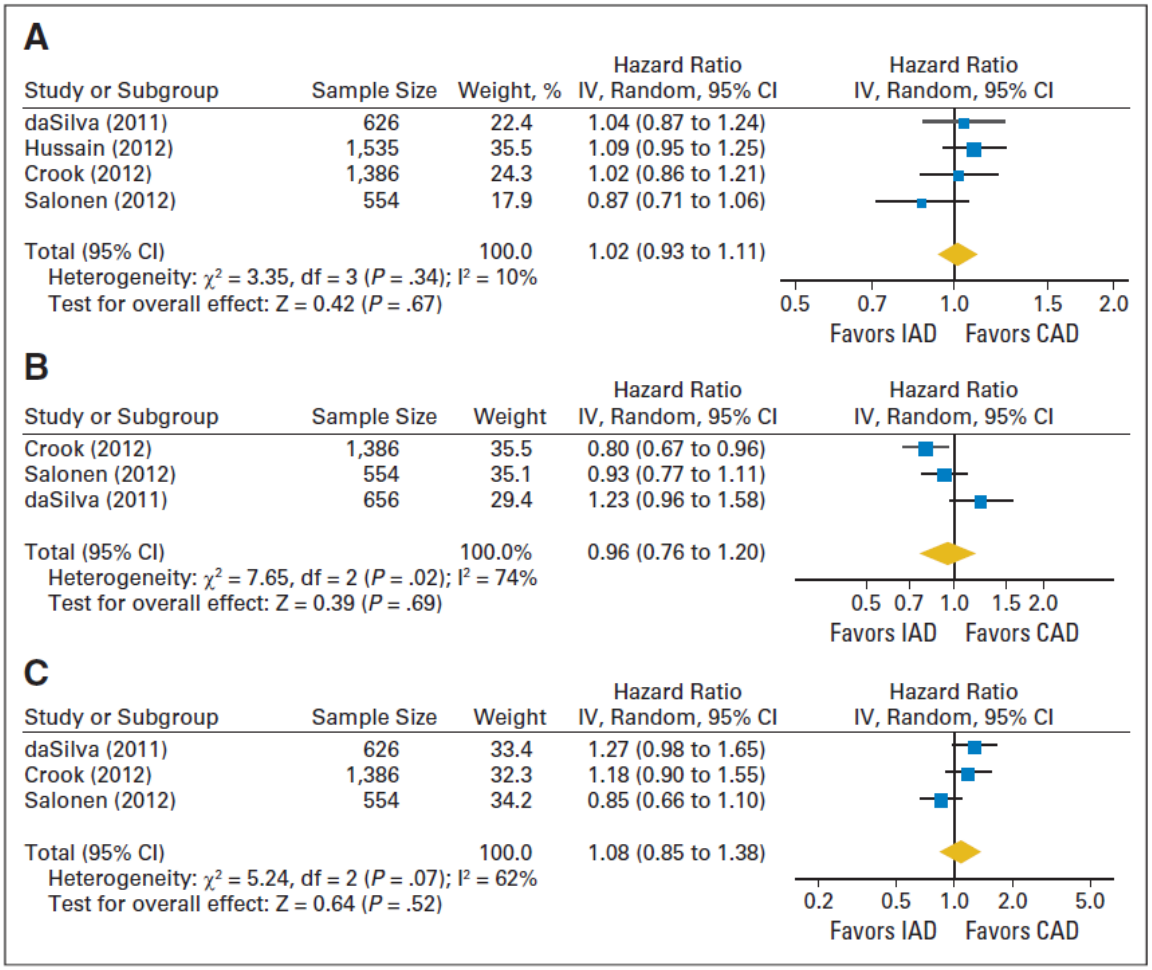
Table A1. Predefined Rating Criteria for Quality of the Included Studies

Rating Criteria
Rating was good if study met all of the following criteria
Initial assembly of comparable groups
Maintenance of comparable groups throughout the study with follow-up at least 80%
Measurements: equal, reliable, and valid (includes masking of outcome assessment)
Clear definition of interventions
All important outcomes considered
Analysis: adjustment for potential confounders and intent-to-treat analysis
Rating was fair if any or all of the following problems occurred, without the more serious flaws noted in the poor category
Generally comparable groups assembled initially, but there is some question of whether some (although not major) differences occurred with follow-up
Measurement instruments acceptable (although not ideal)
Some but not all important outcomes considered
No major risk of potential confounding
Not an intent-to-treat analysis or no mention of it
Rating was poor if any of the following fatal flaws existed
Groups assembled initially not comparable or not maintained throughout the study
Unreliable or invalid measurement instruments used or not applied equally among groups
Inattention to key confounders
Sample size < 50

Qualité de la randomisation non prise en compte

Résultats

Results of individual studies	✓	20	For all outcomes considered (benefits or harms), present for each study (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot
Synthesis of results	✓	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency



Résultats

Risk of bias across studies	✗	22	Present results of any assessment of risk of bias across studies (see item 15)

Biais de publication : pas de funnel plot (peu d'études)

Résultats

Additional analysis	✓	23	Give results of additional analyses, if done (such as sensitivity or subgroup analyses, meta-regression) (see item 16)

Patients on IAD had better scores on some domains of QoL and less treatment-related adverse effects such as sexual dysfunction, hot flashes, and impaired physical function, but there was significant superiority of overall QoL for men receiving IAD in only one study.[31]

Estimated cost of treatment per patient per year is listed in Table 2. There was a substantial cost saving with the use of IAD; a median of about US $5,685 per patient per year (48.5%) would be saved of an estimated $11,710 outlay per patient per year for CAD, for those who were able to be randomly assigned in the trials. Studies did not report details of patients with insufficient initial decrease in PSA to render them eligible to receive IAD or of patients who were approached but not randomly assigned, which would give a more precise estimate of the cost savings.

Discussion

Discussion			
Summary of evidence	✓	24	Summarise the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (such as health care providers, users, and policy makers)

We have undertaken a systematic review of RCTs comparing IAD with CAD and have found three RCTs to be of good quality, four of fair quality, and two of poor quality. There were no significant differences in OS and TTP in these studies, although there was a trend toward more deaths related to prostate cancer with IAD and more deaths not related to prostate cancer with CAD in studies that reported cause of death.[21,27,30] The studies do not support the preclinical data suggesting that IAD is superior in delaying progression to hormonal resistance, but they do support its use because of similar survival using less therapy.

Discussion

Limitations		25	Discuss limitations at study and outcome level (such as risk of bias), and at review level (such as incomplete retrieval of identified research, reporting bias)

One limitation of our review is the restricted information about methodology available from studies reported only in abstract form; a full description of the studies might provide more information but is unlikely to change the key findings. Inclusion of unpublished studies is important to minimize publication bias, but relevant studies might have been missed despite our rigorous search strategy.

Although each study defined progression precisely, there were differences among studies, especially for subjective progression or whether testosterone level was considered before declaring castration-resistant disease. For patients randomly assigned to IAD, biochemical progression needed to be confirmed after reinstitution of ADT, which may have biased results in favor of that arm.

Discussion

Conclusions	✓	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research

We conclude that there is fair evidence to recommend the substitution of CAD by IAD to treat relapsing, locally advanced, or metastatic prostate cancer (US Preventive Services Task Force Grade B recommendation). Treatment with IAD requires initial reduction of PSA to a low level, and only patients who have this initial response are eligible to receive it. This recommendation is based on outcomes such as OS and TTP, substantial decrease in duration of exposure to ADT, and considerable saving of cost. The recommendation is valid only within the population used in the included studies and following similar treatment algorithms (Fig 2). There was minimal representation of men in the studies with severe symptoms or visceral metastases, and it is premature to recommend IAD for such men. Overuse of ADT in nonmetastatic settings is an issue that needs to be better addressed with trials that focus on this important question. Future trials should define those that would benefit most from IAD or CAD, the optimal type of ADT, and criteria for stopping and reinitiating treatment when IAD is used.

Conclusions sur cet article

- **Méta-analyse bien rédigée**
- **Présence de la majorité des points importants**
- **Quelques améliorations possibles :**
  - Description du processus de sélection des études (nombre de personnes, décision en cas de désaccord…)
  - Liste des essais exclus en fin de processus
  - Meilleure investigation du biais dans les essais (notamment vérification de la randomisation)
  - Meilleure description des critères de jugement