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ORIGINAL REPORT

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

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ABSTRACT

Purpose
Uncertainty exists regarding benefits of intermittent androgen deprivation (IAD) compared with continuous androgen deprivation (CAD) for treatment of prostate cancer. On the basis of a systematic review of evidence, our aim was to formulate a recommendation for either IAD or CAD to treat relapsing, locally advanced, or metastatic prostate cancer.

Methods
We searched literature published up to September 2012 from MEDLINE, EMBASE, the Cochrane Library, and major conference proceedings. We included randomized controlled trials comparing IAD and CAD if they reported overall survival (OS) or biochemical/radiologic time to disease progression.

Results
Nine studies with 5,508 patients met our criteria. There were no significant differences in time-to-event outcomes between the groups in any studies. The pooled hazard ratio (HR) for OS was 1.02 (95% CI, 0.94 to 1.11) for IAD compared with CAD, and the HR for progression-free survival was 0.96 (95% CI, 0.76 to 1.20). More prostate cancer–related deaths with IAD tended to be balanced by more deaths not related to prostate cancer with CAD. Superiority of IAD for sexual function, physical activity, and general well-being was observed in some trials. Median cost savings with IAD was estimated to be 48%.

Conclusion
There is fair evidence to recommend use of IAD instead of CAD for the treatment of men with relapsing, locally advanced, or metastatic prostate cancer who achieve a good initial response to androgen deprivation. This recommendation is based on evidence against superiority of either strategy for time-to-event outcomes and substantial decrease with IAD in exposure to androgen deprivation, resulting in less cost, inconvenience, and potential toxicity.

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INTRODUCTION

It is estimated there will be about 240,000 diagnoses and about 28,000 deaths from prostate cancer in 2012 in the United States.[1] Death of men with prostate cancer is caused frequently by other medical illnesses,[2,3] and treatment for prostate cancer may contribute to morbidity and mortality. For men with locally advanced, recurrent, or metastatic prostate cancer, the main goal of treatment is to prolong survival, delay progression, and control symptoms. Androgen-deprivation therapy (ADT) achieved with either surgical or medical castration remains the mainstay of initial management for such men. 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. Similarly, there is little evidence to support use of ADT in most men with increasing prostate-specific antigen (PSA) after local treatment, although it is reasonable to treat men with a short PSA doubling time.

Medical ADT consists generally of a gonadotropin-releasing hormone (GnRH) agonist combined, at least for a short time initially, with a peripheral antiandrogen. Use of ADT has been associated with long-term and short-term adverse effects, including decreased bone mineral density, loss of muscle mass, increased body fat, hot flashes, gynecomastia, impotence, anemia, and small increases in risk of diabetes, coronary artery disease, and sudden death.[4-8] Given these toxicities, the optimal timing of ADT is debatable.[9-13] The concept of intermittent androgen deprivation (IAD), where ADT is interrupted in responding patients and guided by serum PSA, is based on the principle that

development of a castration-independent state is at least in part a result of adaptive survival of prostate cancer cells. The concept was supported by preclinical models showing longer time to hormone resistance with IAD.[14,15] 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. 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.

METHODS

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. We followed the Preferred Reporting for Systematic Reviews and Meta-Analyses (PRISMA) statement whenever applicable.

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.

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. 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.

Studies were rated by their quality as good, fair, or poor based on predefined criteria (Appendix Table A1, online only). Grades of recommendation were allocated according to the US Preventive Services Task Force (Appendix Table A2, online only),[17] and level of evidence was allocated as per the criteria in Appendix Table A3 (online only). 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.

Interventions were as follows. ADT treatment was given using a GnRH agonist with or without a concurrent peripheral antiandrogen. Initial ADT was given to all patients (usually for a minimum of about 6 months), and those having a satisfactory decline in serum PSA (generally < 4 ng/mL) were randomly assigned to IAD or CAD. In the intermittent group, ADT was discontinued when serum PSA decreased below a predefined level, and reinstitution of ADT was guided by the level of PSA. Testosterone levels did not guide reinstitution of IAD.

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]

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.

RESULTS

Our initial search retrieved 1,311 references from electronic databases and 12 from meeting proceedings. Nine of these studies with a total of 5,019 randomly assigned patients fulfilled criteria for inclusion (Fig 1). The overall strategy used in the studies is shown in Figure 2. Characteristics of specific studies are described in Table 1, and the main results are listed in Table 2. All studies had comparable groups at baseline, had clear definition of the intervention, and used consistent measurements in the groups. A summary of the other predefined quality criteria for each study with assignment of a quality grade is presented in Table 3. The κ for agreement in the collected data between two authors was 0.80.

OS was the primary end point of three studies[21-23] and the secondary end point in four studies.[24-27] Time to biochemical or radiologic progression (defined as progression while on ADT or not prevented by reinstitution of ADT) was the primary end point of five studies[24-28] and the secondary end point in three studies.[21,22,27] The remaining study[29] aimed to measure rate of progression and tolerability, but the primary end point was not stated explicitly. Other secondary end points were QoL parameters.

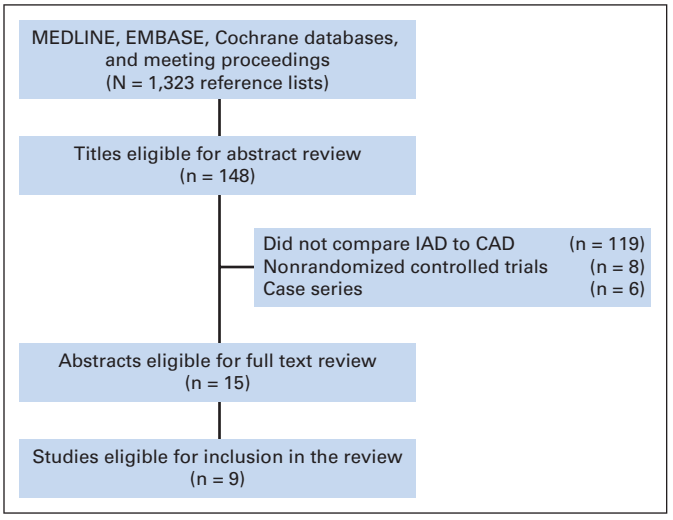

Fig 1. Flow chart of search results. CAD, continuous androgen deprivation; IAD, intermittent androgen deprivation.

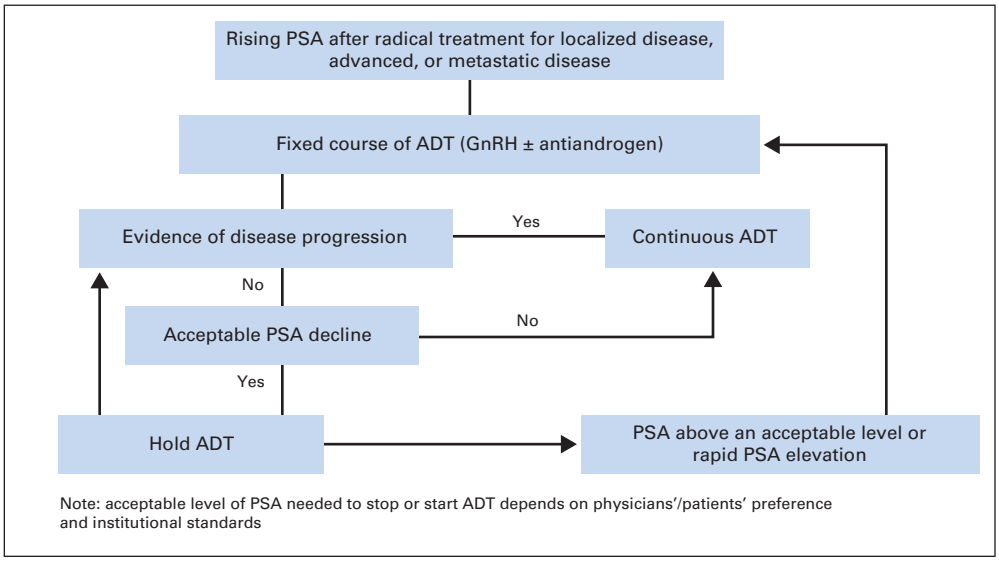

Fig 2. General algorithm for institution of intermittent androgen deprivation. ADT, androgen-deprivation therapy; GnRH, gonadotropin-releasing hormone; PSA, prostate-specific antigen.

Risk of Bias

We assigned quality ratings according to the risk of bias within studies as indicated in Table 3. Duplicate publication was noted for two studies,[23,27] both of which reported QoL results separately. Studies were carried out in different parts of the world but had comparable results indicating minimal location bias. Three studies were rated as good quality, four were of fair quality, and two were of poor quality. Most studies rated as fair quality either failed to mention or ignored important sources of bias such as failure to use intent-to-treat analysis or adjustment for confounders, or they had unclear results on one or more end points. Two studies were graded as poor quality mainly because one was unclear about adjustment to major confounders[25] and another reported no numerical result for the time-to-event end points.[29]

Three authors replied to our queries regarding updated results and/or methodology. One study[30] was upgraded from fair to good quality based on this response. There was no updated analysis in one study,[26] two authors described the use of intent-to-treat analysis in their studies,[21,30] and information on adequacy of power, acceptable follow-up, and updated results were provided by one author.[30]

Four studies, totaling 4,101 patients, reported HRs for OS comparing IAD and CAD (Fig 3A). The pooled estimate of HRs for OS was 1.02 (95% CI, 0.93 to 1.11). The test of heterogeneity among included studies was statistically insignificant ($\chi^2 = 3.35$, $P = .34$, $I^2 = 10\%$). Similarly, the HR for TTP was reported in three studies, which yielded a pooled HR estimate of 0.96 (95% CI, 0.76 to 1.20), but there was statistical heterogeneity (Fig 3B). There were generally more prostate cancer–specific deaths in the IAD group in the studies that reported it, counterbalanced by more deaths not related to prostate cancer in the CAD group. The pooled HR for prostate cancer–specific survival for IAD compared with CAD was 1.08 (95% CI, 0.85 to 1.38) in the three studies[21,24,27] that reported it (Fig 3C).

Six of the nine included studies reported differences in QoL using well-validated QoL questionnaires (Table 1). 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

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.

To be eligible for random assignment, postinduction PSA was set to be less than 4 ng/mL in most of the included studies; there was no information about patients who were registered but did not achieve sufficient reduction in PSA for random assignment. In routine clinical practice, men who respond to ADT with less stringent levels of PSA suppression (and no clinical progression) might also benefit from use of IAD. Applying IAD to such men would further lower the cost, although clinical trials are required to assess outcome using more relaxed criteria of PSA response. Of note, one study reported pre–random assignment PSA $\geq$ 4 ng/mL to be associated with a greater risk of progression and death.[30]

One of six studies that reported data on QoL reported significant superiority for IAD, particularly with respect to physical activity and capacity and sexual functioning.[31] Other studies reported improvement in some domains of QoL but no significant overall difference.

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
de Leval et al[28] (2002)	68	Primary: TTP	31 (mean)	Locally advanced, metastatic, or relapsing PSA after radical prostatectomy for localized CaP	Goserelin + flutamide	PSA ≤ 4 ng/mL on 2 successive measurements 2-3 months apart	PSA ≥ 10 ng/mL	Not mentioned
Schasfoort et al[25] (2003)	193	Primary: TTP; secondary: OS, QoL	25	Locally advanced or metastatic CaP	Buserelin + nilutamide	PSA < 4 ng/mL	PSA ≥ 20 ng/mL (for metastatic); PSA ≥ 10 ng/mL (for locally advanced)	Not mentioned
Miller et al[26] (2007)	335	Primary: TTP; secondary: OS, QoL, tolerability	51	Locally advanced or metastatic CaP	Goserelin + bicalutamide	PSA < 4 ng/mL or < 90% of baseline	PSA ≥ 10 ng/mL	EORTC/AUO questionnaire
Calais da Silva et al[24,30] (2011)	626	Primary: TTP; secondary: OS, QoL	57	Locally advanced or metastatic CaP	GnRH agonist (not named) + cyproterone	PSA < 4 ng/mL or < 80% of baseline after 3 months of ADT	PSA ≥ 10 ng/mL or ≥ 20% above nadir	EORTC QLQ-C30 QoL questionnaire and the EORTC Prostate Cancer Module
Tunn et al[29] (2007)	167	Primary: TTP; secondary: QoL	Not given	Localized CaP with relapsing PSA after radical prostatectomy	Leuprolide + cyproterone	PSA < 0.5 ng/mL	PSA ≥ 3 ng/mL	Not mentioned
Crook et al[21] (2012)*	1,386	Primary: OS; secondary: TTP, QoL	83	Localized RT-treated CaP with relapsing PSA	Multiple combinations	PSA < 4 ng/mL and no clinical progression	PSA ≥ 10 ng/mL	EORTC QLQ-C30 QoL questionnaire and trial-specific questionnaires
Mottet et al[22] (2012)	173	Primary: OS; secondary: TTP, QoL	47	Metastatic CaP	Leuprolide + flutamide	PSA < 4 ng/mL	PSA > 10 ng/mL or symptomatic progression	EORTC QLQ-C30 QoL
Salonen et al[27,31] (2012, 2013)	554	Primary: TTP; secondary: OS, treatment failure	65	Locally advanced or metastatic CaP	Goserelin + cyproterone (first 12 days)	PSA < 10.0 ng/mL or decreased at least by 50% (baseline PSA < 20.0 ng/mL)	PSA > 20 ng/mL or > baseline	Validated 30-item questionnaire
Hussain et al[23] (2012)*	1,535	Primary: OS, QoL; secondary: TTP	100	Metastatic hormone-sensitive CaP	Goserelin + bicalutamide	PSA ≤ 4 ng/mL	PSA ≥ 20 ng/mL or > baseline if baseline PSA < 20 ng/mL	SWOG QOL questionnaire: impotence, libido, energy, physical and emotional function

NOTE. TTP and progression-free survival have been used interchangeably.

Abbreviations: ADT, androgen-deprivation therapy; AUO, Association of Urologic Oncology; CaP, prostate cancer; EORTC, European Organisation for Research and Treatment of Cancer; GnRH, gonadotropin-releasing hormone; OS, overall survival; PSA, prostate-specific antigen; QLQ-C30, Quality of Life Questionnaire C30; QoL, quality of life; RT, radiotherapy; SWOG, Southwest Oncology Group; TTP, time to progression.

*Designed to test noninferiority of intermittent androgen deprivation compared with continuous androgen deprivation.

More treatment-related adverse effects were observed with CAD compared with IAD in most studies. Inconsistent methods used to collect and report QoL data among the studies did not allow us to quantify it as a summary estimate. Patients with minimal comorbidity are generally selected to participate in RCTs, and larger health outcome studies may be necessary to detect rare adverse effects such as cardiovascular disease or diabetes.

The studies included patients with different stages of disease (Table 1) and from multiple countries, thus increasing the generalizability of this review. We used systematic grading of methodologic quality (Table 3), but there are some caveats because of concerns regarding study design, power, and duration of follow-up. Despite clinical heterogeneity of the population among the included studies, the reported HR for OS consistently did not favor a particular strategy with a summary estimate of 1.02 (95% CI, 0.0.93 to 1.11).

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. One study reported in abstract form[23] is a well-designed, landmark international study. Inclusion of unpublished studies is important to minimize publication bias, but relevant studies might have been missed despite our rigorous search

Table 2. Main Results of Included Studies

Study	Results				Estimated Cost per Patient per Year (US$)	
	OS	Median Time to Progression* (biochemical or clinical)	Median % Time Off Hormone Therapy in IAD	Quality of Life/Adverse Effects	CAD	IAD
de Leval et al[28] (2002)	Not reported	3-year progression rate: IAD 7% (± 5%); CAD 39% (± 11%); $P = .005$	59.5%	Hot flashes, loss of libido, and erectile dysfunction improved in men on IAD at least during off-treatment phase	9,930	4,020
Schasfoort et al[25] (2003)	Not reached while reporting	IAD, 18 months; CAD, 24 months	65% (first interval); 31% (second interval); 16% (third interval)	Hot flashes, erectile dysfunction, gynecomastia, liver dysfunction, and visual disturbance did not differ significantly between the groups	11,310	3,960 to 9,500
Miller et al[26] (2007)	Median, 51.4 months with IAD, 53.8 months with CAD; $P = .65$	IAD, 16 months; CAD, 11.5 months; $P = .17$	> 40%	Sexual activity, pain, social functioning, emotional well-being, and vitality better with IAD; other adverse effects including cardiovascular events were similar	12,020	7,210
Calais da Silva et al[24,30] (2011)	239 patients died on IAD *v* 235 on CAD; HR, 1.04; 95% CI, 0.87 to 1.25; $P = .61$	127 patients experienced progression on IAD *v* 107 on CAD; HR, 1.23; 95% CI, 0.96 to 1.59	25.5% (82% of total treatment duration [in patients with good PSA response of < 2 ng/mL])	Following parameters better with IAD: sexual function, hot flashes, gynecomastia, headache, and skin complaints	12,530	9,340
Tunn et al[29] (2007)	Not reported	No difference (numerical values unavailable)	67% of cycle 1 and 49% of cycle 2	Hot flashes/hyperhidrosis better with IAD (mean, 46 days *v* 23 days per quarter); $P < .001$	15,360	5,070 to 7,840
Crook et al[21] (2012)*	HR, 1.02; 95% CI, 0.86 to 1.21; $P = .009$ (for noninferiority)	HR, 0.80; 95% CI, 0.67 to 0.98; $P = .024$	64.9%	Significantly better physical function, fatigue, urinary problems, hot flashes, libido, and erectile function with IAD	12,530	4,400
Mottet et al[22] (2012)	Median, 52 months with CAD; 42.1 months with IAD; $P = .75$	IAD, 20.7 months; CAD, 15.1 months; $P = .74$	49.2%	No QoL difference; significantly fewer treatment-related adverse events in the intermittent group	14,030	7,130
Salonen et al[27,31] (2012, 2013)	HR, 1.15; 95% CI, 0.94 to 1.40; median, 45.2 months with IAD *v* 45.7 months with CAD	HR, 1.08; 95% CI, 0.90 to 1.29; 34.5 months with IAD *v* 30.2 months with CAD	41.7%	QoL with IAD was superior to CAD particularly regarding activity limitation, physical capacity, and sexual functioning; there was no difference in adverse events	5,640	3,290
Hussain et al[23] (2012)*	HR, 1.09; 95% CI, 0.95 to 1.24	Not reported	53%	CAD had significantly more impotence and less libido than IAD; emotional function was also better with IAD; no significant differences in treatment-related adverse events including cardiovascular events	12,030	5,660

Abbreviations: CAD, continuous androgen deprivation; HR, hazard ratio; IAD, intermittent androgen deprivation; OS, overall survival; PSA, prostate-specific antigen.
*Biochemical progression in IAD arm was declared only when it occurred during or after reinstitution of androgen-deprivation therapy.

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.

strategy. Some of the included studies did not provide information about methodologic standards such as intent-to-treat analysis, power justification, and data on study attrition and were, therefore, graded lower in study quality (Table 3). 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

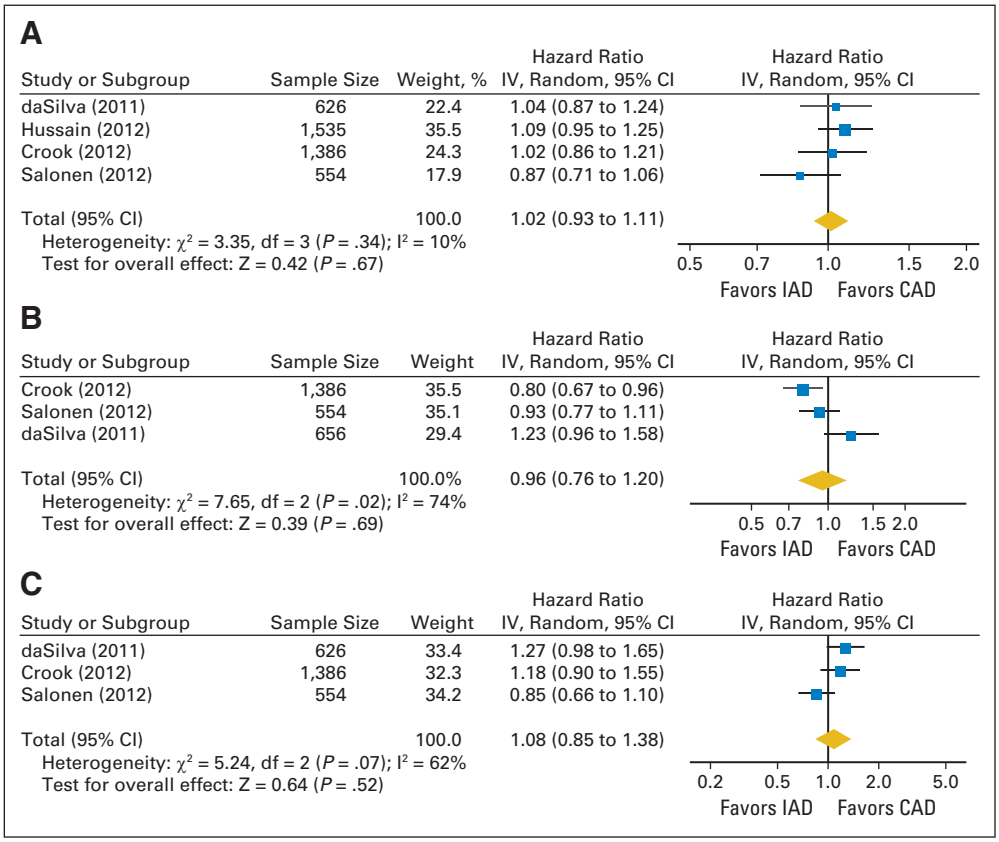

Fig 3. Pooled estimate of hazard ratios for (A) overall survival, (B) time to progression, and (C) prostate cancer–specific survival of intermittent androgen deprivation (IAD) compared with continuous androgen deprivation (CAD) in men with prostate cancer.

after reinstitution of ADT, which may have biased results in favor of that arm.

We were not able to assess individual patient data for survival, TTP, or cost and were not able to perform a formal cost-benefit analysis because none of the studies took cost into account. Our intention to include cost was to provide an estimate of crude savings on drug prices rather than total cost of treatment, which would also consider costs associated with extra hospital visits and treatment of adverse effects. Therefore, the cost difference is likely underestimated.

The studies of Crook et al[21] and Hussain et al[23] were designed to determine whether IAD could be shown to be noninferior to CAD. Patients in these studies differed (increasing PSA after local treatment in the first and metastatic disease in the second), as did the definition of noninferiority. This required upper limits of the 95% CI of the HR for OS to be less than 1.25 in the former and less than 1.20 in the second; the HRs for OS and their CIs were 1.02 (95% CI, 0.86 to 1.21)[21] and 1.09 (95% CI, 0.95 to 1.24),[23] and the studies were reported as demonstrating noninferiority[21] and not proving noninferiority,[23] respectively, despite rather similar results. The second study was reported at the 2012 American Society of Clinical Oncology annual meeting to show that IAD is inferior to CAD, but this is not supported by the CI on HR that includes 1.0. Patients with minimal disease were reported to have better survival on CAD compared with IAD in the second study, but this subgroup analysis should be interpreted with caution because the definition of extensive disease was nonstandard and included presence of nonaxial skeletal metastasis.

All but one of the included trials used combined androgen blockade (ie, a GnRH agonist plus a peripheral antiandrogen) in both arms. Most studies were initiated when this was the standard of care, but a meta-analysis[32] has shown that CAD using combined androgen blockade adds toxicity and cost but results in no difference in OS compared with initial use of a GnRH agonist alone (with a short initial course of antiandrogen to prevent flare). The concordance of the one study that used such monotherapy[27] makes it probable, although not certain, that comparing CAD with IAD using a GnRH agonist alone would lead to similar conclusions as provided by the present overview. Absolute cost savings with the use of monotherapy would be less, but relative savings would likely be similar.

The studies included in our review included heterogeneous populations, encompassing patients with extensive metastasis who eventually die of prostate cancer to patients with localized disease who normally die with prostate cancer, so perhaps one recommendation should not fit all. However, our review suggested no significant differences in terms of time-to-event outcomes in any of the studies and no compromise of QoL with IAD regardless of the disease stages included. There was a comparable off-treatment period across all studies. Increasing PSA alone or presence of overt metastases represents no more than a difference in the extent of disease (ie, overt *v* occult metastasis). Thus, it seems reasonable to offer a general recommendation for the disease presentations included in the studies that meet the criteria of good initial response.

Caution should be used in initiating hormonal treatment for men with asymptomatic prostate cancer, especially in the absence of overt metastases. There is no evidence that treating asymptomatic patients with increasing PSA improves survival. The majority of such men do not require hormonal treatment, but when treatment is given to a selected group of such patients, particularly those with adverse tumor characteristics, IAD seems to be a rational approach.

In summary, there is no notable compromise in health outcomes in eligible men treated with IAD compared with those treated with CAD despite the heterogeneity in disease stages across the studies. There was either superiority or no difference for IAD compared with CAD in terms of major adverse effects and QoL.

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.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Saroj Niraula, Ian F. Tannock
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Administrative support: Saroj Niraula, Ian F. Tannock
Provision of study materials or patients: Saroj Niraula, Ian F. Tannock
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Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors

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Appendix

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

Table A2. Grades of Recommendation According to the USPSTF

Grade	Definition	Suggestions for Practice
A	The USPSTF recommends the service. There is high certainty that the net benefit is substantial.	Offer or provide this service.
B	The USPSTF recommends the service. There is high certainty that the net benefit is moderate, or there is moderate certainty that the net benefit is moderate to substantial.	Offer or provide this service.
C	The USPSTF recommends against routinely providing the service. There may be considerations that support providing the service in an individual patient. There is at least moderate certainty that the net benefit is small.	Offer or provide this service only if other considerations support the offering or providing the service in an individual patient.
D	The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.	Discourage the use of this service.
I statement	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.	Read the clinical considerations section of USPSTF Recommendation Statement. If the service is offered, patients should understand the uncertainty about the balance of benefits and harms.

Abbreviation: USPSTF, US Preventive Services Task Force.

Table A3. Criteria to Define Levels of Evidence

Criteria to Define Levels of Evidence
I—Evidence from randomized controlled trial(s)
II-1—Evidence from controlled trial(s) without random assignment
II-2—Evidence from cohort or case-control analytic studies, preferably from more than one center or research group
II-3—Evidence from comparisons between times or places with or without the intervention; dramatic results in uncontrolled experiments could be included here
III—Opinions of respected authorities, based on clinical experience; descriptive studies or reports of expert committees