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Garcia-Albeniz, Xabier
Chan, June M
Paciorek, Alan T
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Immediate versus deferred initiation of androgen deprivation therapy in prostate cancer patients with PSA-only relapse. An observational follow-up study

X. Garcia-Albeniz [a,*], J.M. Chan [b,c], A. Paciorek [b], R.W. Logan [a], S.A. Kenfield [c], M.R. Cooperberg [b,c], P.R. Carroll [c], M.A Hernán [a,d,e]

[a] *Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, United States*
[b] *Departments of Epidemiology and Biostatistics, University of California, San Francisco, San Francisco, CA, United States*
[c] *Department of Urology, University of California, San Francisco, San Francisco, CA, United States*
[d] *Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston, MA, United States*
[e] *Harvard-MIT Division of Health Sciences and Technology, Boston, MA, United States*

Abstract *Background:* The optimal timing to start androgen deprivation therapy (ADT) in prostate cancer patients with rising prostate-specific antigen (PSA) as the only sign of relapse is unknown.

Methods: We identified men with prostate cancer in the Cancer of the Prostate Strategic Urologic Research Endeavour (CaPSURE) study who would have been eligible ($\leqslant$ cT3aN0M0, primary radical prostatectomy or radiotherapy, PSA relapse as the only evidence of recurrence) for a randomised trial comparing 'immediate' versus 'deferred' ADT initiation. We emulated such trial by assigning patients to the 'immediate' strategy if they initiated ADT within 3 months of PSA relapse and to the 'deferred' strategy if they initiated ADT when they presented with metastasis, symptoms or a short PSA doubling time. We censored patients when they deviated from the assigned strategy and adjusted for this censoring via inverse probability weighting.

Results: Of 2096 eligible patients (median age 69, interquartile range 63–75 years), 88% were white, 35% had a Gleason score $\geqslant 7$, 69% were treated with radical prostatectomy and 31% received radiotherapy only as primary treatment. The mean time from primary treatment to PSA relapse was 37.4 (standard deviation [SD] 34.2) months. Mean follow-up from primary treatment was 91.4 (SD 48.4) months. The adjusted mortality hazard ratio for immediate

* *Corresponding author at:* Department of Epidemiology, Harvard T.H. Chan School of Public Health, 677 Huntington Ave. Boston, MA 02115, United States.
E-mail address: xabi@post.harvard.edu (X. Garcia-Albeniz).

versus deferred ADT was 0.91 (95% confidence interval (CI), 0.52–1.60), which would be translated into a similar 5-year survival (difference between groups: −2.0% (95% CI: −10.0 to 5.9%).

Conclusion: Our analysis suggests that prostate cancer patients undergoing immediate ADT initiation within three months after PSA-only relapse had similar survival to those who deferred ADT initiation within 3 months after clinical progression.

1. Introduction

Androgen deprivation therapy (ADT) is the first line of therapy for advanced prostate cancer [1]. However, the optimal timing to administer ADT is unknown in patients diagnosed with localised disease and treated with curative intention that later present a prostate-specific antigen (PSA)-only relapse (no symptoms, no detectable metastasis) [2]. Specifically, there are no published randomised trials of immediate versus deferred ADT initiation in this subset of patients [3]. The American Society of Clinical Oncology guidelines state that 'the Panel cannot make a strong recommendation for the early use of ADT', and that 'the critical issue is to determine whether there is benefit and how large it is for starting ADT while patients are asymptomatic' [4].

Randomised controlled trials have shown that castration of asymptomatic patients not suitable for curative treatment resulted in longer time to disease progression [5,6] and lower prostate cancer mortality [4,7] as compared with castration at symptom onset. On the other hand, deferring ADT until overt progression (metastases or symptoms) may preserve quality of life [6,8,9] and cognitive function [10] for a longer period.

An intermediate strategy for patients with PSA-only relapse would be to use PSA levels and clinical events to decide the timing of ADT initiation. The National Comprehensive Cancer Network considers asymptomatic patients with rising PSA level as a 'therapeutic dilemma regarding the role of ADT' [11]. Given the strong association of PSA dynamics (i.e. PSA doubling time) with disease progression and prognosis [12–14], PSA evolution and clinical events-based initiation may provide the optimal balance between deferring ADT for patients who do not need it and starting ADT immediately in patients with an aggressive disease. Results from an ongoing phase III clinical trial that uses PSA and clinical events-based ADT initiation are not yet available [ClinicalTrials.gov identifier: NCT00110162].

Here we used observational data from a prospective study to emulate this trial. Because, PSA was both a time-varying confounder (it affects timing of treatment, it is associated with survival through biological aggressiveness of the tumour and other unmeasured variables) and was itself affected by prior therapy, we used statistical methods designed to appropriately adjust for time-varying confounders that are affected by prior treatment. [15,16]) Our goal was to provide a preliminary answer to the question 'when to start ADT therapy in PSA-only relapsed patients'.

2. Methods

2.1. Study population

CaPSURE is a prostate cancer registry study of over 14,000 men with biopsy-proven prostate adenocarcinoma enrolled consecutively from over 45 community-based clinics, three academic institutions and three Veterans Administration hospitals since 1995 [17]. Urologists ascertain clinical data at baseline and subsequent clinic visits. Baseline recorded variables include results of biopsy of the prostate and clinical TNM staging, complete pathology report of the surgical specimen, medical history and demographic characteristics. In addition, time-varying information is recorded at clinical visits (current disease stage, clinic procedures performed, new diagnoses, laboratory and imaging tests, signs and symptoms, Karnofsky functional status, and international prostate symptom score), hospital admissions (diagnosis and procedures) and with patient-directed questionnaires specifically designed to record information on health-related quality of life [18]. Additional details about CaPSURE have been previously reported [19].

Following the design of trial NCT00110162, our study was restricted to patients with ⩽cT3a, N0, M0, who had primary treatment with either radical prostatectomy or radiotherapy (external beam radiotherapy or brachytherapy) and a subsequent PSA relapse, defined as a PSA determination ⩾0.2 ng/mL if the primary treatment was radical prostatectomy, or three rising levels one month apart if the primary treatment was radiation-based as the only sign of relapse. Patients fulfilling these criteria in the first postoperative assessment were included. We excluded patients with relapse diagnosed via computed tomography (CT) scan, bone scan, pelvic magnetic resonance imaging (MRI) or symptoms (fatigue, bone pain, weight loss, anorexia, abdominal pain) at the time of PSA relapse. We also excluded patients with an orchiectomy before PSA relapse and patients who had received ADT in the 12 months before PSA relapse.

The outcome of primary interest was all-cause mortality. We also studied prostate cancer-specific

mortality. CaPSURE obtains mortality information from the Bureau of Vital Statistics or National Death Index to verify the date and primary cause of death. Follow-up started at the time of PSA relapse and finished at the time of death or 12 months after the most recent contact with the study (i.e. questionnaire, physician reporting patient withdrawal from the study, PSA determination, clinical visit, or treatment change).

2.2. ADT initiation strategies

Similarly to the trial NCT00110162, we compared two dynamic PSA-based strategies: ADT initiation at PSA relapse (immediate initiation) and ADT initiation at disease progression (deferred initiation). ADT was defined as the use of any LHRH-agonist or orchiectomy and progression as cancer relapse based on any imaging technique, severe cancer-related symptoms (fatigue, bone pain, weight loss or anorexia), a PSA doubling time <12 months for PSA ⩾ 10 ng/mL, or PSA doubling time ⩽ 6 months based on three consecutive measurements obtained ⩾ 2 months apart. For our analysis, we considered strategies under which ADT initiation occurred uniformly [16] during a 3-month grace period. Local relapses candidate to rescue radiotherapy were allowed to be treated with radiotherapy (i.e. they do not influence the ADT initiation strategies under study).

The 'deferred initiation' strategy of the trial NCT00110162 was ADT initiation at disease progression or more than 2 years after PSA relapse regardless of progression. We implemented this strategy as a secondary analysis for direct comparability with the trial. See Table 1 and the Appendix for a description of the protocol of trial NCT00110162 (information extracted from www.clinicaltrials.gov on 1st March 2014). Table 1 also summarises how we used the observational data to emulate the trial protocol.

2.3. Statistical analysis

Patients were assigned to the initiation strategy (immediate or deferred ADT) that was consistent with their observed data at PSA relapse (baseline). We then estimated the mortality hazard ratio for 'immediate ADT' versus 'deferred ADT' via a weighted (see below) pooled logistic model that included the indicator for strategy, a flexible function of time (restricted cubic splines to estimate the baseline hazard) and the following baseline covariates: Gleason score, percentage of positive biopsies at diagnosis, T-stage, type of primary treatment (radical prostatectomy ± radiotherapy versus radiotherapy-only based treatment), time from primary treatment to PSA relapse, calendar year of PSA relapse, and age. We calculated robust standard errors to compute conservative 95% confidence intervals for the hazard ratio estimate.

Patients who did not start ADT immediately at baseline could be assigned to either strategy. For example, a patient who did not progress and did not initiate ADT at month 2 had data consistent with both the 'immediate ADT' strategy (which allows for a 3-month grace period), and with the 'deferred ADT' strategy. We therefore created an exact copy of the data of these patients, assigned each copy to one of the strategies, and censored the copy assigned to one strategy when data stopped being consistent with that strategy [16]. To adjust for the potential selection bias due to censoring [20,21] we used inverse probability weighting. Informally, the denominator of the weights is each subject's time-varying probability of having his own ADT history conditional on the previously listed baseline covariates and the time-varying covariates PSA, Karnofsky functional status, fatigue, and bone pain.

These time-varying prognostic factors can influence the decision to initiate ADT (i.e. they are time-varying confounders) and are affected by ADT initiation. PSA doubling time, which may also influence the decision to initiate ADT [12–14], is implicitly adjusted for because both baseline PSA and time-varying PSA are included in the model.

We then stabilised the weights to emulate a uniform ADT initiation during the grace period [16]. Like previous applications of inverse probability weighting to compare dynamic strategies [22–24], we truncated them at percentile 99 to avoid undue influence of outliers. As a sensitivity analysis we repeated the analyses censoring patients at 24 months (as opposed to 12 months) after last contact.

To estimate survival probabilities under both strategies, we fit a weighted outcome model like the one described above that also included product ('interaction') terms for strategy and time variables. The model's predicted values were then used to estimate the 10-year predicted probability of survival from the moment when patients fulfilled the inclusion criteria until death. We used a non-parametric bootstrap based on 1000 resamplings to compute 95% CIs.

All analyses were conducted with SAS, version 9.3 (SAS Institute, Cary, North Carolina). The institutional review boards at University of California, San Francisco and Harvard School of Public Health approved our research.

3. Results

Of 9344 patients staged ⩽ cT3aN0M0 with PSA determinations and imaging tests after primary treatment, 5351 underwent radical prostatectomy (with or without additional external beam radiotherapy) and 2368 received external beam radiotherapy and/or brachytherapy as their primary treatment. Of these, 2096 patients who never underwent orchiectomy (1437 treated primarily with radical prostatectomy) were eligible for our analysis. See Fig. 1 for a detailed flowchart

Table 1
Abbreviated protocols of the NCT00110162 randomised trial and the emulated trial using observational Cancer of the Prostate Strategic Urologic Research Endeavour (CaPSURE) data.

Components	NCT00110162 randomised trial	Emulated trial using observational CaPSURE
Primary aim	To compare the survival of prostate cancer patients assigned to immediate versus deferred androgen deprivation therapy (ADT), defined as either bilateral orchiectomy OR luteinising hormone-releasing hormone agonist with or without oral antiandrogen therapy	Same
Study population[*]	Patients with prostate cancer treated with curative intention with a prostate-specific antigen (PSA)-only relapse	Same
Eligibility	Histologically confirmed adenocarcinoma of the prostate No symptomatic disease requiring therapy PSA relapse after definitive radical treatment (prostatectomy or radiotherapy), as evidenced by one of the following: • Post-prostatectomy PSA $\geqslant 0.2$ ng/mL • At least 3 rising PSA levels (post-radiotherapy) $\geqslant 1$ month apart, with the last PSA within the past 2 monthsNo metastatic disease by bone scan or abdomino-pelvic CT scan	Same
Follow-up	Patients are followed up from randomisation at PSA relapse every 3 months for 2 years, every 6 months for 3 years, and then periodically thereafter at the discretion of the principal investigator	Patients are followed up from PSA relapse. Participating urologist reports clinical data at follow-up visits under usual practice. Patients complete study-specific surveys at baseline and every six months thereafter
Treatment assignment	Patients are randomised to one of the following two dynamic strategies: • Deferred ADT: initiation at progression[**] or any time after 2 years since baseline, (continuous or intermittent) • Immediate ADT: initiation (continuous or intermittent) at baseline	Patients are classified as following the same strategies (with a 3-month grace period): • Deferred ADT: initiation at progression[**] (continuous or intermittent) • Immediate ADT: initiation (continuous or intermittent) at baselineSupplementary analyses: 1. Patients are classified as following the same strategies of NCT00110162 (with a 3-month grace period) 2. PSA relapse after radiotherapy is defined using the 'Phoenix' definition (a rise by 2 ng/mL above the nadir PSA after radiation therapy)
ADT definition	LHRH agonist with or without antiandrogens or orchiectomy	Same
Primary endpoint	Death from any cause	Same
Statistical analysis	Information not provided.	Observational analogue of a per protocol analysis, adjusted for baseline variables (Gleason score, percentage of positive biopsies at diagnosis, T-stage, type of primary treatment, time from primary treatment to PSA relapse, calendar year of PSA relapse and age), and time-varying variables (PSA, Karnofsky functional status, fatigue, and bone pain)

[*] The trial also included a second group of patients not candidate for curative treatment and not requiring immediate ADT.
[**] Progression defined as PSA doubling time of <12 months with PSA $\geqslant 10$ ng/mL OR PSA doubling time of $\leqslant 6$ months based on three consecutive measurements obtained $\geqslant 2$ months apart OR development of metastases or symptoms.

that shows patients assigned to each strategy, including those initially assigned to both. Table 2 shows the baseline characteristics of the eligible patients. Mean age was 68.7 (standard deviation [SD] 8.4) years and mean time since primary treatment to PSA relapse was 37.4 (SD 34.2) months. The biopsy Gleason score was $\geqslant 7$ in 34.8% of patients.

Mean follow-up after primary treatment and after PSA-only relapse was 91.4 (SD 48.4) months and 54.0 (SD 38.6) months respectively. Progression occurred in 337 patients: 86 developed symptoms, 226 had progression detected via imaging techniques and 92 had short PSA doubling time. Mean time from PSA relapse to

progression was 35.8 months (SD 35.3). Four hundred and seventy-three patients initiated ADT during the follow-up, 13 in the form of orchiectomy as the first ADT. One hundred and eighty patients received rescue radiotherapy and 53 of them are treated with ADT at some point afterwards.

At baseline 2096 patients were assigned to the 'immediate ADT' strategy and 2058 to the 'deferred ADT' strategy. As described in the Methods section, 38 patients contributed only to the 'immediate ADT' strategy because they initiated ADT at PSA relapse; all other patients contributed to both strategies for at least one month of follow-up.

Inclusions
10,140 patients with a histological diagnosis of prostate adenocarcinoma, PSA measurements and imaging tests after diagnosis and no orchiectomy at the time of primary treatment.
9,344 staged ≤ T3aN0M0.
7,719 treated with curative intention (5,351 with RP ± EBRT and 2,368 with EBRT and/or brachytherapy).
2,341 relapsed by PSA (1,577 in the subset treated with RP± EBRT and 765 in the subset treated with EBRT and/or brachytherapy)

Exclusions
20 patients underwent orchiectomy before PSA relapse
154 patients received pharmacological ADT in the 12 months preceding to PSA relapse.
70 patients presented overt relapse on bone scan , abdominopelvic CT scan or pelvic MRI.
13 patients suffered from cancer-related symptoms

2096 eligible patients[1]

Immediate ADT strategy
2,096 patients

Deferred ADT strategy
2,058 patients

1,984 censored due to no initiation of ADT during the grace period
79 administrative end of follow-up

318 censored due to initiation of ADT without progression
152 censored due to not initiating ADT after progression
1448 administrative end of follow-up

14,881 months of follow-up
33 deaths (27 unique[2])

85,727 months of follow-up
140 deaths (134 unique[2])

[1]38 patients contributed only to the "Early ADT" strategy because they initiated ADT at PSA relapse; all other patients contributed to both strategies for at least one month of follow-up. See Methods section.
[2]Six deaths occurred during months assigned to both strategies and are thus counted under both strategies
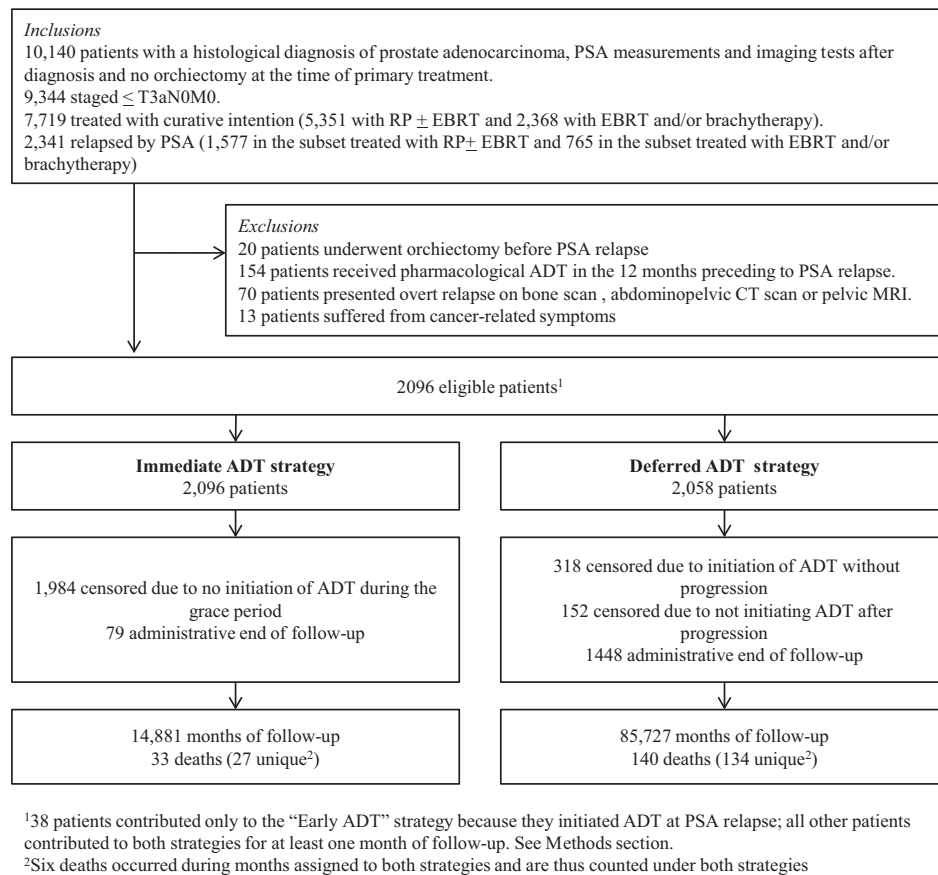
Fig. 1. Flowchart of patient selection into the study, Cancer of the Prostate Strategic Urologic Research Endeavour (CaPSURE).

3.1. All-cause mortality

Of 161 total deaths during the follow-up, six occurred during months assigned to both strategies and are thus counted under both strategies. Of those assigned to the deferred ADT strategy, 117 (5.7%) died before documented progression and without initiating ADT (six of these were considered deaths secondary to prostate cancer).

The mortality HR for 'immediate ADT' versus 'deferred ADT' was 0.91 (95% CI: 0.52–1.60) (Table 3). The corresponding estimated 5-year survival (95% CI) was 85.7% (77.7–93.7%) under the immediate ADT strategy and 87.7% (84.8–90.6%) under the deferred ADT strategy (Fig. 2). The 5-year survival difference was −2.0% (95% CI: −10.0% to 5.9%). The 10-year estimated survival (95% CI) was 69.8.1% (54.5–85.1%) under the immediate ADT strategy and 69.3% (60.7–77.9%) under the deferred ADT strategy. The 10-year survival difference was 0.5% (95% CI: −16.7% to 17.6%).

3.2. Prostate cancer-specific mortality

There were few prostate cancer specific deaths, 15 under the immediate ADT strategy and 18 under the deferred ADT strategy. Two deaths occurred during

months assigned to both strategies and are thus counted under both strategies. The HR of prostate cancer mortality was 1.09 (95% CI 0.31–3.78) for immediate versus deferred ADT (Table 3). The estimated 5-year prostate cancer-specific survival (95% CI) was 92.8% (86.7–98.9%) under the immediate ADT strategy and 95.8% (92.7–98.9%) under the deferred ADT strategy (Fig. 2). The 5-year survival difference was −3.0% (95% CI: −8.7 to 2.7). The corresponding 10-year estimated survival (95% CI) was 83.1% (71.8–94.4%) under the immediate ADT strategy and 84.5% (76.6–92.3%) under the deferred ADT strategy. The 10-year survival difference (95% CI) was −1.3 (−14.6% to 11.9%).

Results did not materially change in sensitivity analyses that censored patients 24 months after the most recent contact (Supplemental Table 1), that employed the same deferred strategy as trial NCT00110162 (Supplemental Table 2) and that employed the 'Phoenix' definition for biochemical relapse (a rise by 2 ng/mL above the nadir PSA after radiation therapy [25], Supplemental Table 3).

4. Discussion

Our study suggests little or no survival benefit of immediate ADT initiation compared with deferred

Table 2

Baseline characteristics for 2096 men presenting a prostate-specific antigen (PSA)-only relapse after treatment of localised prostate cancer treated with curative intention and enrolled in Cancer of the Prostate Strategic Urologic Research Endeavour (CaPSURE), 1974–2014.

Median age at relapse, years (IQR)		69.1 (63.0–74.7)
PSA at diagnosis (%),[1] ng/mL	≤6	703 (33.5)
	6.1–10	624 (29.8)
	10.1–20	428 (20.4)
	20.1–30	101 (4.8)
	30+	115 (5.5)
Median PSA at relapse (IQR), ng/mL		0.50 (0.22–1.51)
Total Gleason score (%)[2]	2–5	396 (18.9)
	6	838 (40.0)
	7–10	729 (34.8)
Percentage of positive biopsies (%)[3]	<34%	878 (41.9)
	≥34	932 (44.5)
Primary treatment (%)	RP ± EBRT	1437 (68.6)
	EBRT and/or brachytherapy	659 (31.4)
Race (%)	White	1842 (87.9)
	Black	195 (9.3)
	Other	59 (2.8)
cT stage (%)	cT1	843 (40.2)
	cT2	1205 (57.5)
	cT3	48 (2.3)
Median time since primary treatment, months (IQR)		26.8 (13.4–50.6)
Year (%)	1988–1992	50 (2.4)
	1993–1997	550 (26.2)
	1998–2002	651 (31.1)
	2003–2007	724 (34.5)
	2008–2014	121 (5.8)

IQR, interquartile range; RP, radical prostatectomy; EBRT, external beam radiotherapy.

[1] Missing in 125 patients.
[2] Missing in 133 patients.
[3] Missing in 286 patients.

ADT initiation (at clinical progression) among prostate cancer patients with PSA-only relapse. No survival comparisons between ADT initiation strategies guided by PSA and clinical events have been previously reported

for patients with biochemical-only relapse. Therefore our study provides at least a first approximation to answer the 'when to start ADT' question in these patients.

Two randomised trials have compared immediate versus deferred ADT in other types of prostate cancer patients. The EORTC 30891 trial [6,26] compared deferred ADT at symptomatic progression versus immediate ADT (either orchiectomy or LHRH-agonist) in 985 patients not eligible for curative treatment. This trial found a 21% increased mortality (95% CI: 5–39%) and no differences in prostate cancer mortality (HR 1.05, 95% CI 0.83–1.33). About 26% of trial participants assigned to deferred initiation died without fulfilling criteria to start ADT, and only 55% of those who started ADT did so according to the protocol. The MRC PR03 trial [27] compared immediate versus deferred ADT initiation at clinical indication for treatment (criteria for 'clinical indication' left to the treating physician) in 938 patients with locally advanced or asymptomatic metastatic prostate cancer. This trial found lower prostate cancer mortality, but not lower overall mortality, in the immediate treatment arm [7].

An observational study compared early versus late ADT initiation in patients with PSA-only relapse using observational data from the Department of Defense Center for Prostate Disease Research Database [28]. This study did not find a lower metastasis-free survival (overall survival was not evaluated) for early ADT, but the study results are hard to interpret because the analysis (i) was based on 'prevalent' users rather than 'incident' users, which may result in selection bias [29], and (ii) adjusted for PSA using standard regression, which may introduce bias because PSA is a time-varying confounder. Standard regression may not appropriately adjust for time-varying confounders affected by treatment [30]. The magnitude and direction of these potential biases cannot be predicted and their results

Table 3

Mortality analyses for immediate versus deferred ADT initiation, Cancer of the Prostate Strategic Urologic Research Endeavour (CaPSURE) 1974–2014 (N = 2096).

	Deferred ADT	Immediate ADT
Person-months	85,727	14,881
Deaths	140	33
Prostate cancer deaths	22	18
All-cause mortality hazard ratio (95% confidence interval)		
Unadjusted	1 (ref)	2.12 (1.42–3.17)
Adjusted for baseline variables[a]	1 (ref)	1.51 (0.99–2.33)
Adjusted for baseline- and time-varying[b] variables	1 (ref)	0.91 (0.52–1.60)
Prostate cancer mortality hazard ratio (95% confidence interval)		
Unadjusted	1 (ref)	7.57 (3.89–14.72)
Adjusted for baseline variables[a]	1 (ref)	4.65 (1.98–10.92)
Adjusted for baseline- and time-varying[b] variables	1 (ref)	1.09 (0.31–3.78)

ADT, androgen deprivation therapy; PSA, prostate-specific antigen.

[a] Gleason score, percentage of positive biopsies at diagnosis, T-stage, type of primary treatment (radical prostatectomy ± radiotherapy versus radiotherapy-only based treatment), time from primary treatment to PSA relapse, calendar year of PSA relapse, and age.
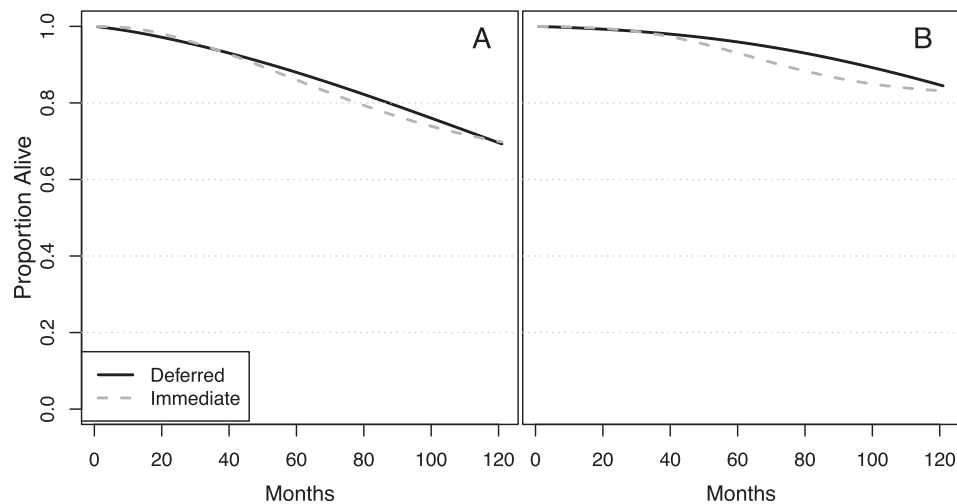[b] PSA, Karnofsky functional status, bone pain, fatigue.

Fig. 2. Overall (A) and prostate cancer-specific (B) survival, standardised for baseline and time-varying variables, for immediate versus deferred androgen deprivation therapy (ADT), Cancer of the Prostate Strategic Urologic Research Endeavour (CaPSURE) 1974–2013.

should be taken with caution. In contrast, our study uses incident users and adjusts for time-varying confounders using inverse probability weighing to emulate the NCT00110162 trial. This methodology has been previously used to appropriately adjust for confounding in several clinical applications [22,24,31]. Had we used a naïve approach such as standard outcome regression with time-varying variables, the adjustment for confounding would have been incomplete (all-cause mortality HR 1.16, 95% CI 0.73–1.83).

Like any observational study, the validity of our estimates requires that all baseline and time-varying confounders are correctly measured. This requirement is especially important in our study because our estimates suggest that there is substantial confounding. The HR in the unadjusted analysis (2.12) went down considerably after adjusting for baseline confounders (1.51), probably because physicians tend to initiate ADT earlier in those patients with worse prognosis (e.g. higher Gleason grade). The HR moved even closer to the null (0.91) after adjusting for time-varying PSA, Karnofsky functional status, fatigue and bone pain. The effect of adjustment was even more evident when analysing prostate-specific mortality. The downward movement of the HR with increasing levels of adjustment makes it conceivable that immediate ADT initiation might actually be beneficial, but that our adjustment for confounding was incomplete.

In summary, our study provides evidence on the when to start ADT question. In the absence of randomised trial results, our findings suggest that starting ADT at PSA relapse does not have a major impact on overall survival compared with deferred ADT initiation at disease progression.

5. Funding

6. Role of the funding source

Conflict of interest statement

None declared.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ejca.2015.03.003.

References

[1] Sharifi N, Gulley JL, Dahut WL. Androgen deprivation therapy for prostate cancer. JAMA 2005;294:238–44.

[2] Walsh PC, DeWeese TL, Eisenberger MA. A structured debate: immediate versus deferred androgen suppression in prostate cancer-evidence for deferred treatment. J Urol 2001;166:508–15.

[3] Scher HI, Heller G. Clinical states in prostate cancer: toward a dynamic model of disease progression. Urology 2000;55:323–7.

[4] Loblaw DA, Virgo KS, Nam R, Somerfield MR, Ben-Josef E, Mendelson DS, et al. Initial hormonal management of androgen-sensitive metastatic, recurrent, or progressive prostate cancer: 2006 update of an American Society of Clinical Oncology practice guideline. J Clin Oncol 2007;25:1596–605.

[5] Studer UE, Hauri D, Hanselmann S, Chollet D, Leisinger H-J, Gasser T, et al. Immediate versus deferred hormonal treatment for patients with prostate cancer who are not suitable for curative local treatment: results of the randomized trial SAKK 08/88. J Clin Oncol 2004;22:4109–18.

[6] Studer UE, Whelan P, Albrecht W, Casselman J, de Reijke T, Hauri D, et al. Immediate or deferred androgen deprivation for patients with prostate cancer not suitable for local treatment with curative intent: European Organisation for Research and Treatment of Cancer (EORTC) Trial 30891. J Clin Oncol 2006;24:1868–76.

[7] Kirk D. Timing and choice of androgen ablation. Prostate Cancer Prostatic Dis 2004;7:217–22.

[8] Tsai HK, D'Amico AV, Sadetsky N, Chen M-H, Carroll PR. Androgen deprivation therapy for localized prostate cancer and the risk of cardiovascular mortality. J Natl Cancer Inst 2007;99:1516–24.

[9] Saigal CS, Gore JL, Krupski TL, Hanley J, Schonlau M, Litwin MS. Androgen deprivation therapy increases cardiovascular morbidity in men with prostate cancer. Cancer 2007;110:1493–500.

[10] Salminen EK, Portin RI, Koskinen A, Helenius H, Nurmi M. Associations between serum testosterone fall and cognitive function in prostate cancer patients. Clin Cancer Res 2004;10:7575–82.

[11] National Comprehensive Cancer Network. Prostate cancer (Version 3.2012); n.d.

[12] Freedland SJ, Humphreys EB, Mangold LA, Eisenberger M, Dorey FJ, Walsh PC, et al. Risk of prostate cancer-specific mortality following biochemical recurrence after radical prostatectomy. JAMA 2005;294:433–9.

[13] Antonarakis ES, Chen Y, Elsamanoudi SI, Brassell SA, Da Rocha MV, Eisenberger MA, et al. Long-term overall survival and metastasis-free survival for men with prostate-specific antigen-recurrent prostate cancer after prostatectomy: analysis of the Center for Prostate Disease Research National Database. BJU Int 2011;108:378–85.

[14] Antonarakis ES, Feng Z, Trock BJ, Humphreys EB, Carducci MA, Partin AW, et al. The natural history of metastatic progression in men with prostate-specific antigen recurrence after radical prostatectomy: long-term follow-up. BJU Int 2012;109:32–9.

[15] Young J, Cain L, Robins J, O'Reilly E, Hernan M. Comparative effectiveness of dynamic treatment regimes: an application of the parametric g-formula. Stat Biosci 2011;3:119–43.

[16] Cain LE, Robins JM, Lanoy E, Logan R, Costagliola D, Hernán MA. When to start treatment? A systematic approach to the comparison of dynamic regimes using observational data. Int J Biostat 2010;6. Article 18.

[17] Lubeck DP, Litwin MS, Henning JM, Stier DM, Mazonson P, Fisk R, et al. The CaPSURE database: a methodology for clinical practice and research in prostate cancer. CaPSURE Research Panel. Cancer of the Prostate Strategic Urologic Research Endeavor. Urology 1996;48:773–7.

[18] Glass AS, Cowan JE, Fuldeore MJ, Cooperberg MR, Carroll PR, Kenfield SA, et al. Patient demographics, quality of life, and disease features of men with newly diagnosed prostate cancer: trends in the PSA era. Urology 2013;82:60–5.

[19] Cooperberg MR, Broering JM, Litwin MS, Lubeck DP, Mehta SS, Henning JM, et al. The contemporary management of prostate cancer in the United States: lessons from the cancer of the prostate strategic urologic research endeavor (CapSURE), a national disease registry. J Urol 2004;171:1393–401.

[20] Hernán MA, Lanoy E, Costagliola D, Robins JM. Comparison of dynamic treatment regimes via inverse probability weighting. Basic Clin Pharmacol Toxicol 2006;98:237–42.

[21] Hernán MA, Hernández-Díaz S, Robins JM. A structural approach to selection bias. Epidemiology 2004;15:615–25.

[22] Ray M, Logan R, Sterne JAC, Hernández-Díaz S, Robins JM, Sabin C, et al. The effect of combined antiretroviral therapy on the overall mortality of HIV-infected individuals. AIDS 2010;24:123–37.

[23] Cole SR, Hernán MA. Constructing inverse probability weights for marginal structural models. Am J Epidemiol 2008;168:656–64.

[24] Cain LE, Logan R, Robins JM, Sterne JAC, Sabin C, Bansi L, et al. When to initiate combined antiretroviral therapy to reduce mortality and AIDS-defining illness in HIV-infected persons in developed countries: an observational study. Ann Intern Med 2011;154:509–15.

[25] Roach M, Hanks G, Thames H, Schellhammer P, Shipley WU, Sokol GH, et al. Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO Phoenix Consensus Conference. Int J Radiat Oncol Biol Phys 2006;65:965–74.

[26] Studer UE, Whelan P, Wimpissinger F, Casselman J, de Reijke TM, Knönagel H, et al. Differences in time to disease progression do not predict for cancer-specific survival in patients receiving immediate or deferred androgen-deprivation therapy for prostate cancer: final results of EORTC randomized trial 30891 with 12 years of follow-up. Eur Urol 2013.

[27] Immediate versus deferred treatment for advanced prostatic cancer: initial results of the Medical Research Council Trial. The Medical Research Council Prostate Cancer Working Party Investigators Group. Br J Urol 1997;79:235–46.

[28] Moul JW, Wu H, Sun L, McLeod DG, Amling C, Donahue T, et al. Early versus delayed hormonal therapy for prostate specific antigen only recurrence of prostate cancer after radical prostatectomy. J Urol 2004;171:1141–7.

[29] Hernán MA, Alonso A, Logan R, Grodstein F, Michels KB, Willett WC, et al. Observational studies analyzed like randomized experiments: an application to postmenopausal hormone therapy and coronary heart disease. Epidemiology 2008;19:766–79.

[30] Robins J, Hernan M. Estimation of the causal effects of time-varying exposures. In: Fitzmaurice G, Davidian M, Verbeke G, Molenberghs G, editors. Longitud. Data Anal. 1st ed., Boca Raton: Chapman & Hall/CRC; 2009, p. 553–99.

[31] Toh S, Hernández-Díaz S, Logan R, Robins JM, Hernán MA. Estimating absolute risks in the presence of nonadherence: an application to a follow-up study with baseline randomization. Epidemiology 2010;21:528–39.