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Original Article

Prognostic value of testosterone castration levels following androgen deprivation and high-dose radiotherapy in localized prostate cancer: Results from a phase III trial

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ABSTRACT

Background/objective: The optimal prognostic value of testosterone following androgen deprivation therapy (ADT) is controversial. We studied the effect of serum testosterone levels on clinical outcome in localized prostate cancer (PCa) treated with ADT and high-dose radiotherapy (HRT).

Patients and methods: The DART01/05 trial randomized 355 men with intermediate and high-risk PCa to 4 months of ADT plus HRT (STADT, $N = 178$) or the same treatment followed by 24 months of ADT (LTADT, $N = 177$). This study included patients treated with LTADT who had at least 3 determinations of testosterone during ADT ($N = 154$). Patients were stratified into 3 subgroups by testosterone level: minimum <20 ng/dL; median 20–49 ng/dL; and maximum ≥50 ng/dL. Kaplan–Meyer and Cox regression analysis were used for overall survival (OS) and Fine & Gray regression model for metastasis free survival (MFS), biochemical disease-free survival (bDFS) and time to TT recovery.

Results: There were no statistically significant differences in 10-year bDFS, MFS, or OS between the <20 ng/mL and 20–49 ng/dL subgroups. Multivariate analysis showed that a median testosterone ≥50 ng/dL was significantly associated with a decrease in bDFS (HR: 6.58, 95%CI 1.28–33.76, $p = 0.03$). Time to testosterone recovery after ADT did not correlate with bDFS, MFS, or OS and was not significantly associated with any of the testosterone subgroups.

Conclusions: Our results do not support the concept that additional serum testosterone suppression below 20 ng/dL is associated with better outcomes than 20–49 ng/dL. Time to testosterone recovery after ADT and HRT did not impact clinical failure.

Androgen deprivation therapy (ADT) is currently the standard systemic approach for management of localized high-risk prostate cancer (PCa) in combination with high-dose radiotherapy (HRT) [1–4]. The regulatory authorities have traditionally set target testosterone level during ADT at <50 ng/dL. Over the last decade, several authors [5–7] have considered the 50 ng/dL cut point a potential artefact of the lower limit of quantitation of older testosterone assays, thus raising the question of whether achieving <50 ng/dL might be clinically relevant with new testosterone assays. Recent data suggest that additional suppression of serum testosterone to <20 ng/dL might improve clinical outcomes [8–10]. Similarly, it remains unknown whether maintenance of castrate testosterone levels after discontinuation of ADT could also impact biochemical control rates [11–16].

The DART 01/05 trial is a randomized phase III study comparing 4 versus 28 months of ADT combined with HRT. The 5-year results showed that 2 years of adjuvant ADT was significantly superior to 4 months of treatment [17]. In this post hoc analysis, we studied the effect of serum testosterone levels and testosterone recovery on clinical outcome in a subgroup of localized prostate cancer patients treated in the long-term arm of the DART 01/05 trial.

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Material and methods

The DART 01/05 multicenter, phase III randomized trial was designed to determine the optimal duration of ADT in patients receiving HRT. Full methods and preliminary results are detailed in the primary report [17]. Between November 2005 and December 2010, 355 eligible patients were randomly assigned to the short-term ADT arm (STADT, 178 patients) or the long-term ADT arm (LTADT, 177 patients). Patients assigned to the STADT arm received 4 months of neoadjuvant and concomitant ADT with subcutaneous goserelin, namely, 2 months before radiotherapy and 2 months combined with HRT (minimum dose of 76 Gy, range 76–82 Gy). Antiandrogen therapy (flutamide 750 mg per day or bicalutamide 50 mg per day) was added during the first 2 months of treatment. The patients assigned to long-term suppression (LTADT arm) continued with the same luteinizing hormone-releasing analogue every 3 months for another 24 months. This trial is registered at ClinicalTrials.gov (NCT 02175212) and in the EU Clinical Trials Register (EudraCT 2005-000417-36).

Follow-up visits were at intervals of 3 months after radiotherapy during the first year, every 6 months for 5 years, and yearly thereafter. PSA concentrations, serum testosterone concentration, and a complete blood count were obtained at every visit. We included in the study only those patients treated with LTADT who had at least 3 determinations of serum testosterone during the 2 years of ADT (N = 154). Serum testosterone was not centrally measured. Each centre measured the serum testosterone in a certified laboratory for clinical research purpose using an automated chemiluminescent immunoassay method.

In order to establish the potential clinical impact of a low nadir (<20 ng/dl) of testosterone compared to the classical castration definition (<50 ng/dl), we defined 3 testosterone subgroups (<20, 20–49, and ≥50 ng/dl) for each patient. Then, we stratified the patients by the minimum, median, and maximum testosterone levels reached into the 3 testosterone subgroups as follows: (1) minimum (minTT), <20 ng/dL (<0.7 nmol/L); (2) medium (medTT), 20–49 ng/dL (0.7 to < 1.7 nmol/L); and maximum (maxTT), ≥50 ng/dL (≥1.7 nmol/L). For patients with documented baseline testosterone, we also evaluated the impact of testosterone recovery, defined according to measured testosterone levels with a lower laboratory limit above the threshold of 150 ng/dL.

Endpoints, definitions, and statistical analysis

Overall survival (OS) was analyzed by Kaplan–Meier analysis and Cox proportional hazards regression models. Biochemical disease-free survival (bDFS), metastasis-free survival (MFS), cause-specific survival (CSS) and time to testosterone recovery were compared between the subgroups using Gray's test in the univariate analyses and multivariate Fine & Gray regression in the adjusted analyses to account for the competing risk of non-PCa mortality. Death from any cause was considered a competitive risk for MFS, bDFS, and time to testosterone recovery. Death from prostate cancer or a complication of cancer treatment was considered for CSS analysis. All endpoints were calculated from the date of randomization. Time to testosterone recovery was calculated as the interval between the last trimestral ADT injection and testosterone values within the normal range (>150 ng/dL). The t and chi-square tests were used to assess associations with other clinical variables. Two-sided p values <0.05 were considered statistically significant. The covariates used in the analysis were patient age, T stage, Gleason group, pre-treatment prostate-specific antigen (PSA), risk group, and testosterone recovery. All analyses were performed using IBM SPSS Statistics v22. The Fine & Gray analyses were performed using SAS version 9.4.

Results

Of the 355 patients randomized, 154 LTADT were eligible for the analysis. The characteristics of the patients are shown in Table 1. The median age was 71.3 years (IQR 67.6–74.9), and the median follow-up was 109.6 months (IQR: 100.6–115.3). The median and range of testosterone determinations performed per patient during ADT was 5 (range 3–7) for intermediate and 5 (IQR 3–6) for high risk patients.

The median testosterone nadir was 19 ng/dL (IQR: 10–27 ng/dL), with a median time to nadir of 10.2 months (IQR: 7.3–15.9 months). A total of 82 (53.2%) patients had a minTT < 20 ng/dL, 69 (44.8%) patients had a minTT between 20 and 49 ng/dL, and only 3 (1.9%) patients had a minTT ≥ 50 ng/dL. The corresponding values for medTT and maxTT are shown in Table 2.

Overall, 21 (13.6%) patients developed biochemical failure during follow-up, and 9 (5.8%) patients developed distant metastasis. Twenty-nine (18.8%) patients died, although only 4 died from PCa. At 10 years, bDFS, MFS, CSS, and OS were 69.6% (95% CI: 61.6%–77.5%), 66.3% (95% CI: 47.8%–84.9%), 95.8% (95% CI: 91.7%–99.9%), and 77.8% (95% CI: 70.6%–85.1%), respectively.

Table 1
Patients' characteristics.

	TOTAL N = 154
Median (IQR) follow-up, months	109.6 (100.6–115.3)
Median (IQR) age, years	71.3 (67.6–74.9)
Clinical T stage	
T1	43 (28.0%)
T2	82 (53.2%)
T3	29 (18.8%)
Gleason group (ISUP 2014/WHO 2016)	
1	16 (10.3%)
2	62 (40.3%)
3	33 (21.5%)
4	30 (19.5%)
5	13 (8.4%)
Pre-treatment PSA, ng/mL	
Median (IQR)	10.8 (6.7–17.0)
<10	70 (45.5%)
0–20	53 (34.4%)
>20	31 (20.1%)
NCCN Risk Groups	
Intermediate	73 (47.4%)
High	81 (52.6%)
Median (IQR) PSA nadir, ng/mL	0.01 (0.0–0.03)
Median (IQR) testosterone nadir, ng/dL	19 (10.0–27.0)
Testosterone recovery (>150 ng/dL)	
Yes	114 (74.0%)
No	40 (26.0%)
Median (IQR) time to testosterone recovery, months)	16.3 (1.7–70.9)

IQR: Interquartile range; ISUP: International Society of Urological Pathology; WHO: World Health Organization; NCCN: National Comprehensive Cancer Network.

Table 2
Distribution of nadir, median, and maximum testosterone level of every patient within 3 testosterone subgroups: minimum < 20 ng/dL (<0.7 nmol/L); medium 20–49 ng/dL (0.7 to <1.7 nmol/L); and maximum ≥ 50 ng/dL (≥1.7 nmol/L).

Variable	Testosterone value, ng/dL		
	<20 N (%)	20–49 N (%)	≥50 N (%)
Testosterone level during ADT			
Minimum	82 (53.2%)	69 (44.8%)	3 (1.9%)
Median	30 (19.5%)	109 (70.8%)	15 (9.7%)
Maximum	7 (4.5%)	73 (47.4%)	74 (48.1%)

ADT: Androgen deprivation therapy.

There were no statistically significant differences in 10-year bDFS, MFS, CSS, or OS between the testosterone values of <20 ng/dL and 20–49 ng/dL for the 3 testosterone subgroups (min, med, and max TT levels) (Table 3). In the univariate analysis, the presence of a medTT value ≥50 ng/dL, the Gleason group 4–5, a pre-treatment PSA > 20 ng/mL, and the high-risk subgroup were variables significantly associated with a decrease in bDFS. The results of the multivariable Fine & Gray regression analysis showed that a medTT value ≥ 50 ng/dL remained significantly associated with a decrease in bDFS (HR: 6.42; 95% CI: 1.19–34.51; $p = 0.04$) (Table 4, Fig. 1). A minTT value ≥ 50 ng/dL was also found to be associated with a lower MFS (HR: 13.08; 95% CI: 2.00–106.14; $p = 0.02$); however, since there were only 3 patients in the minTT subgroup ≥ 50 ng/dL, this finding should be considered non-valuable.

A total of 114 patients (74%) recovered testosterone values within the normal range (>150 ng/dL) on completion of ADT, with a median time to testosterone recovery of 16.3 months (IQR: 1.7–70.9). Time to testosterone recovery was not significantly associated with any of the testosterone subgroups (minTT $p = 0.34$; medTT $p = 0.14$; max TT $p = 0.11$) or with any of the other clinical variables (patient age, $p = 0.27$; pre-treatment PSA, $p = 0.45$; T stage, $p = 0.12$; and Gleason group, $p = 0.07$), with the exception of the risk subgroup. The median time to testosterone recovery was 14.5 and 17.8 months for intermediate and high-risk prostate cancer, respectively ($p = 0.02$).

Time to testosterone recovery after ADT did not associate with bDFS, MFS, or OS. However, our data revealed a significant association with CSS (HR: 0.91; 95% CI: 0.85–0.98; $p = 0.02$). Again, since

Table 3
Results of the univariate analysis for biochemical disease-free survival, metastasis-free survival (Fine & Gray) and overall survival (Cox regression).

Covariate	Metastasis-free survival HR (95% CI) *p* value	Biochemical disease–free survival HR (95% CI) *p* value	Overall Survival HR (95% CI) *p* value
Minimum testosterone	$p = 0.06$	$p = 0.29$	$p = 0.47$
<20 ng/dL ***(Ref. v)***			
20–49 ng/dL	2.08 (0.50–8.66)	1.53 (0.64–3.66)	1.26 (0.60–2.65)
≥50 ng/dL*	13.08 (2.00–106.14)	5.41 (0.52–56.54)	3.35 (0.43–25,96)
Median testosterone	$p > 0.99$	$p = 0.03$	$p = 0.56$
<20 ng/dL (***Ref. v)***			
20–49 ng/dL	NOT ESTIMABLE	1.96 (0.46–8.47)	1.05 (0.39–2,80)
≥50 ng/dL		6.58 (1.28–33.76)	1.86 (0.50–6 0.96)
Maximum testosterone	$p > 0.99$	$p > 0.99$	$p = 0.22$
<20 ng/dL ***(Ref. v)***			
20–49 ng/dL	NOT ESTIMABLE	NOT ESTIMABLE	NOT ESTIMABLE
≥50 ng/dL			
Time to testosterone recovery	$p = 0.16$	$p = 0.14$	$p = 0.10$
	0.95 (0.86–1.02)	0.97 (0.94–1.01)	0.96 (0.91–1.01)
Clinical T stage	$p = 0.31$	$p = 0.18$	$p = 0.37$
T1-2 (***Ref.v***)			
T3	2.11 (0.49–9.01)	1.93 (0.74–5.01)	0.62 (0.21–1.77)
Gleason Group	$p = 0.71$	$p = 0.03$	$p = 0.20$
Groups 1–3 (***Ref. v***)			
Groups 4–5	1.29 (0.33–5.01)	2.57 (1.10–5.99)	0.54 (0.20–1.40)
Pre-treatment PSA	$p = 0.19$	$p = 0.03$	$p = 0.04$
<10 ng/mL (***Ref. v***)			
10–20 ng/mL	0.35 (0.04–3.03)	0.94 (0.30–2.93)	3.25 (1.32–7.99)
>20 ng/mL	2.34 (0.60–9.16)	3.09 (1.17–8.16)	2.14 (0.75–6.09)
Risk group	$p = 0.15$	$p = 0.01$	$p = 0.47$
Intermediate (***Ref.v***)			
High	3.15 (0.66–15.03)	4.21 (1.45–12.29)	0.77 (0.37–1.59)
Patient age	$p = 0.73$	$p = 0.22$	$p = 0.09$
	0.97 (0.83–1.14)	0.95 (0.87–1.03)	1.07 (0.99–1.16)

Ref. v: Reference value; *: Only 3 cases; **: Only 1 event.
HR: hazard ratio; CI: confidence interval; ISUP: International Society of Urological Pathology; PSA: prostate-specific antigen.

Table 4
Results of Fine & Gray multivariable regression for biochemical disease-free survival.

Variables	P value	Hazard Ratio (HR)	95% CI	
			Lower limit	Upper limit
Median testosterone	0.04			
Median testosterone (20–49 ng/dL)		1.83	0.44	7.69
Median testosterone (≥50 ng/dL)		6.42	1.19	34.50
Gleason groups 4–5	0.49	1.46	0.50	4.25
Pre-treatment PSA	0.47			
PSA 10 ng/mL ≤ PSA ≤ 20 ng/mL		0.97	0.31	3.08
PSA > 20 ng/mL		1.89	0.59	6.13
High-risk subgroup	0.20	2.65	0.60	11.67

Reference values:
Median testosterone: < 20 ng/dL.
Pre-treatment PSA: < 10 ng/dL.
Gleason Groups: 1–3.
Risk subgroup: Intermediate.
CI: confidence interval; PSA: prostate-specific antigen.

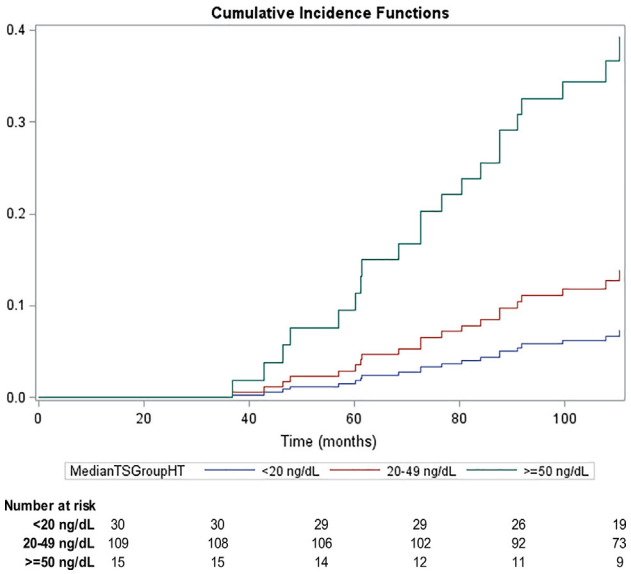

Fig. 1. Cumulative incidence estimates of biochemical failure according to median testosterone level.

only 4 patients died from PCa, these data should be interpreted with caution.

Discussion

Our results do not support the notion that better outcomes are associated with testosterone below 20 ng/dL. Similarly, we did not observe an independent association between the kinetics of testosterone recovery and the risk of clinical failure.

As most studies investigating the prognostic value of testosterone levels following ADT have been performed in advanced or metastatic PCa, available information in localized PCa patients is scant and controversial. Nabid et al. [18] reported in abstract form their results from a subgroup of 796 patients in 2 randomized trials of ADT combined with radiotherapy in localized PCa. With a median follow-up of 9.15 years, the authors found no significant differences in outcome between testosterone levels <20 and <50 ng/dL. Conversely, recent data from a retrospective study of 764 patients with localized PCa from the Veterans Affairs database who had received ADT (median duration 12 months) and radiotherapy showed that additional serum testosterone suppression <20 ng/dL was associated with lower rates of biochemical recurrence and metastasis [10]. Other authors have also reported similar results [19].

In the scenario of patients with more advanced PCa, the available evidence comes mainly from the subanalysis of clinical trials of intermittent ADT, where data are also contradictory. The results published by Tombal et al. [20] in a subgroup of 345 patients from the ICELAND trial receiving continuous androgen deprivation did not reveal a significant difference between the 3 testosterone subgroups in time to CSS and progression of PSA. These data are in contrast to the results of the PR7 trial of intermittent versus continuous ADT reported by Klotz et al. [8]. Several other studies have also reported a correlation between lower testosterone levels ($\leq$0.7 nmol/L) and a longer time to castration-resistant PCa and/or death [6,21]. Interestingly, most of these studies were performed in patients with more advanced or metastatic PCa, a noticeably different scenario.

The discrepancies between studies and the contradictory data reported can be explained by factors such as the retrospective approach, differences in serum testosterone determinations, and differences in study design, regimen, and duration of ADT. The variety of LHRH agonists used, different cohort sizes, and the wide range of the target populations also make the results difficult to interpret. A recent systematic review and meta-analysis [22] analyzed the impact of testosterone levels in different clinical settings during the natural history of PCa. The authors reported a dynamic interplay between serum testosterone and PCa biology that changes during the natural history of the disease.

The rate and the time course of testosterone recovery after ADT and radiotherapy is not well characterized [11–13,23]. Multiple small series have shown that the use of STADT (3–6 months) results in a reversible effect on serum testosterone in most patients within 1 year of cessation of ADT. However, data regarding testosterone recovery after LTADT are more limited and conflicting [24,25]. In the present analysis, 74% of patients recovered testosterone values within the normal range (>150 ng/dL) after the end of adjuvant ADT, with a median time to recovery of 16.3 months (IQR: 1.7–70.9). We observed a shorter median time to testosterone recovery for intermediate versus high-risk prostate cancer (14.5 and 17.8 months respectively, p = 0.02). We cannot provide a satisfactory explanation for this finding other than sample bias related to the number of determinations.

It remains unclear whether maintaining castrate testosterone levels is associated with a risk of relapse [12,16]. In our study, time to testosterone recovery did not correlate with bDFS, MFS, or OS. Similarly, a recent report from a secondary analysis of a phase III trial analyzing a 6-month ADT regimen revealed no significant association between the kinetics of testosterone recovery and the risk of subsequent relapse [26]. Interestingly, other authors have observed a correlation between time to testosterone rebound and PCa mortality in patients treated with 6 months of ADT and radiotherapy irrespective of the degree of comorbidity, although cardiovascular mortality increased in patients with moderate-severe comorbidity [12]. Whether there is a difference in biological behavior depending on the duration of ADT remains to be determined. A previous report on toxicity from the DART trial showed that LTADT was significantly associated with an increase in nonfatal cardiovascular toxicity (HR: 2.090; 95% CI: 1.170–3.720, p = 0.012) [27]. Shore et al. have recently reported the results of HERO phase III trial that compared the efficacy and safety of relugolix (an oral GnRh antagonist) with leuprolide in patients with advanced PCa [28]. Although data on survival are awaited, the results showed that relugolix achieved a lower and quicker testosterone nadir, a shorter time of testosterone recovery and a 54% lower risk of major adverse cardiovascular events than leuprolide.

The present study was subject to several limitations, mainly the relatively small sample size and the low number of events that restricts the power of the analysis. Another potential limitation was that testosterone values were not centrally measured. Nevertheless, we cannot obviate the strengths of this report, which lie in its prospective design, the use of a similar formulation and duration for adjuvant ADT, and the HRT schedule. The analysis also required documented baseline testosterone before initiation of ADT and during follow-up. Finally and noteworthy, the long-term follow-up of this study enabled us to evaluate the association with clinical outcome. To our knowledge, this is the first full-text prospective report to show the effect of serum testosterone levels and testosterone recovery on long-term survival in localized PCa treated with HRT combined with LTADT.

Conclusion

Our results show that additional suppression of serum testosterone to <20 ng/dL is not associated with better outcomes than 20–49 ng/dL. We were unable to prove a correlation between time

to testosterone recovery after ADT and radiotherapy and biochemical failure or distant metastasis.

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Declaration of interest statement

Other than the grants from the GICOR/SEOR (Grupo de Investigación en Oncología Radioterápica/Sociedad Española de Oncología Radioterápica) and AstraZeneca, the authors declare no potential conflicts of interest.

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