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Long-term castration-related outcomes in patients with high-risk localized prostate cancer treated with androgen deprivation therapy with or without docetaxel and estramustine in the UNICANCER GETUG-12 trial

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Declaration of interest: none

Abstract

Introduction. Neoadjuvant chemotherapy with docetaxel and estramustine (DE) significantly improved relapse-free survival in patients with high-risk localized prostate cancer (HRLPC) treated with androgen deprivation therapy (ADT) for 3 years and a local treatment in the GETUG-12 phase 3 trial. We sought to explore whether addition of DE impacts long-term treatment-related side effects.

Patients and methods. Patients randomized within the UNICANCER GETUG-12 trial at Gustave Roussy who were alive when ADT was discontinued were followed-up prospectively. Serum testosterone levels (STLs) and clinical data regarding body weight, libido, erection, and cardiovascular events, were collected.

Results. Seventy-eight patients were included: 36 patients had been treated with ADT plus a local treatment and 42 with ADT+DE plus a local treatment. With a median follow-up of 5.9 years after ADT discontinuation, STLs returned to normal values (>200 ng/mL) for 57 out of 72 evaluable patients (78%), and 29 out of 68 evaluable patients (43%) reported erections allowing intercourse without medical assistance. No impact of DE on testosterone level recovery, libido, quality of erections, and changes in body weight after ADT discontinuation was detected. The incidence of cardiovascular events was low and similar in both treatment arms.

Conclusion. Treatment with docetaxel and estramustine was not associated with excess long-term castration-related toxicity in men with high-risk localized prostate cancer. The relapse-free survival improvement seen with DE in GETUG-12 is likely not related to differed testosterone recovery.

Introduction

Prostate cancer is the most common cancer in developed countries, with a majority of patients presenting with localized disease at diagnosis¹. Treatment modalities for localized prostate cancer are based on risk factors predictive for cancer recurrence and death from the disease, mainly the TNM stage, the Gleason score, and serum PSA level. In patients with high-risk localized prostate cancer (HRLPC), the current standard of care is mostly based on prostate-focused external beam radiation therapy (EBRT) combined with androgen deprivation therapy (ADT) with LH-RH agonists for 18 to 36 months²⁻⁴.

Chemotherapy with docetaxel given concomitantly with ADT is a time-honored standard for patients with metastatic castration-resistant prostate cancer⁵. More recently, this treatment has also been shown to improve overall survival when administered in the castration-naive setting^{6,7}. Whether combining chemotherapy with ADT even earlier in the natural history of prostate cancer might benefit the patients, it has been a subject of inquiry for almost two decades⁸.

The UNICANCER GETUG 12 trial was the first phase III trial to assess the role of docetaxel-based chemotherapy in men with localized prostate cancer: 413 patients with previously untreated HRLPC were randomized to receive ADT with or without concomitant chemotherapy with docetaxel plus estramustine (DE) before local treatment, which turned out to be EBRT in 87% of patients⁹. The addition of chemotherapy resulted in significantly improved relapse-free survival¹⁰, the primary endpoint of the trial. With a median follow-up of 12 years, this trial showed that DE reduces biochemical failures, but also improves clinical or radiological relapse-free survival with events including metastases, local relapses, and deaths¹¹. Since GETUG-12 primary analysis read out in 2015, other trials randomly testing docetaxel in men with HRLPC have also reported early relapse-free survival, with some showing relapse-free survival improvement^{3,7,12-15}. The benefit of adjuvant/neoadjuvant docetaxel on relapse-free survival was further confirmed by a meta-analysis including the first four trials with available data⁸. In the GETUG 12 trial, the on-treatment toxicity of chemotherapy was manageable, with only a 2% febrile neutropenia rate, and its negative impact on quality of life was only transient, with patient-reported outcomes being similar in both arms one year after the end of DE treatment⁹. These observations are supported by similar data obtained in the metastatic setting¹⁶.

Little is known about the very long-term impact of early taxane-based chemotherapy when combined with ADT. Here, we present the results of a longitudinal study of patients from Institute Gustave Roussy treated in the UNICANCER GETUG 12, focusing on recovery from castration and its associated functional and cardiovascular outcomes.

Methods

Patients and treatment

The detailed inclusion criteria and treatment plan for the GETUG 12 trial have been previously described⁹. Briefly, patients had treatment-naive, histologically proven prostate cancer, no evidence of distant metastases on both abdomino-pelvic CT and bone scan performed during the last 6 months, and one or more adverse risk features among: clinical stage T3 or T4, serum PSA level >20 ng/mL, Gleason score ≥ 8 , histologically proven regional lymph node involvement. All patients underwent surgical lymph node staging during the 12 weeks before randomization. All patients were treated with subcutaneous goserelin 10.8 mg every 3 months for 3 years, concomitantly with an androgen receptor inhibitor for the first 3 weeks. For patients allocated to the experimental arm (ADT+DE arm), chemotherapy with intravenous docetaxel 70 mg/m² on day 2 associated with oral prednisone on day 1 to 3 and oral estramustine 10 mg/kg/day on day 1 to 5 were administered every 3 weeks for 4 cycles before local treatment, with concomitant thromboprophylaxis. In both arms, local treatment was performed 3 months after the start of ADT and could consist of either EBRT or prostatectomy for patients with node-negative disease, and either EBRT or no local treatment for patients with node-positive disease. Radiotherapy procedures have been previously described⁹.

Data collection

For the present study, the subgroup of patients enrolled in the GETUG 12 trial at the Institut Gustave Roussy (Villejuif, France) were monitored twice yearly as per protocol after ADT discontinuation. Supplementary clinical data regarding body weight, libido, and quality of erection were collected prospectively during that follow-up. Libido was characterized as either absent, decreased, or normal. Quality of erection was characterized as no erection, erection present but not permitting intercourse (patient complaining or not complaining), erection permitting intercourse with medical assistance, or erection permitting intercourse without medical assistance. Serum testosterone levels (STLs) were collected prospectively. Data was collected annually for up to 10 years after randomization (i.e. 7 years post-ADT). Patients were excluded from the analyses in case of death, prostate cancer recurrence leading to ADT resumption, or any other illness that may interfere with the interpretation of the aforementioned parameters. Baseline data was collected retrospectively using the local computerized individual patient files. Cardiovascular events notified in these files were collected.

Outcomes description and statistical analysis

Changes in body weight were described as percentages of variation from weight at randomization. The distribution of individual changes in body weight between randomization and ADT discontinuation in both treatment arms was compared using a Student's t-test. The percentage of patients with a 10% or more weight gain at the end of ADT was compared using a chi2 test. The timely evolution of the mean change in body weight in each treatment arm was described.

Discreet STL values were dichotomized as either castrate (<50 ng/dL) or supracastrate (≥50 ng/dL), and STLs ≥200 ng/dL were considered as normal¹⁷. The proportion of patients with supracastrate and normal STLs was described at the end of ADT, 6 months post-ADT, and then yearly. The proportion of evaluable patients recovering to normal STLs at any time after ADT discontinuation in both treatment arms was compared using a chi2 test.

Libido was analyzed as a binary parameter, either normal or absent/decreased. The proportion of evaluable patients reporting normal libido at least once at any time after ADT discontinuation in both treatment arms was compared using a chi2 test.

Quality of erection was analyzed as a binary parameter, either erection permitting intercourse without medical assistance or other. The proportion of evaluable patients reporting erections allowing for intercourse without medical help any time after ADT discontinuation in both treatment arms was compared using a chi2 test. For homogeneity concerns, patients treated with radical prostatectomy were excluded from this analysis.

Results

Patients and treatment

Between November 2002 and November 2006, 81 patients were included in the GETUG 12 trial at the Institute Gustave Roussy; 2 patients had died and one patient was lost to follow-up before completion of the 3 years of ADT. Of the remaining 78 patients, 36 patients had been randomized to the ADT arm and 42 patients to the ADT+DE arm. Baseline characteristics as well as the nature of local treatment received by the patients are displayed in Table 1.

At data cutoff on March 15, 2014, the median follow-up after ADT discontinuation was 5.9 years. Patients were censored from the analyses before data cutoff for the following reasons: prostate cancer recurrence needing ADT resumption (n=6) or salvage radiation therapy (n=1), other medical condition (n=2), death (n=8), or lost to follow-up (n=4).

Changes in body weight

At the end of ADT, 21% and 15% of evaluable patients presented a >10% weight gain in the ADT arm and the ADT+DE arm, respectively ($p=0.51$). There was no difference in the distribution of changes in body weight from baseline in both treatment arms (t-test: $p=0.47$; Figure 1A). The mean weight variation at the end of ADT was similar in both treatment arms (+3.9% and +3.5%, respectively), with a similar trend toward timely normalization in patients with prolonged follow-up (Figure 1B).

Testosterone recovery

As expected, STLs were constantly at castrate levels at the end of ADT in all evaluable patients. The proportion of patients with supracastrate STLs increased to 41%, 81%, and 91% of evaluable patients after 6 months, 1 year, and 3 years of ADT discontinuation, respectively (Figure 2A), and the proportion of patients with normal STLs were 29%, 73%, and 81%, respectively (Figure 2B). In 72 evaluable patients with at least one available STL value after ADT discontinuation, patients recovering to normal STLs at any time point after ADT discontinuation was 80% in the ADT arm and 78% in the ADT+DE arm ($p=0.87$).

Functional outcomes

Similarly, the proportion of patients reporting normal libido and erections allowing for intercourse without medical help increased during the first 4 years following ADT discontinuation (Figure 3). Among evaluable patients, 44% of patients in the ADT arm and 59% in the ADT+DE arm reported normal libido at some point after ADT discontinuation ($p=0.20$), and 37% and 47% reported erections allowing for intercourse without medical help, respectively ($p=0.37$).

Cardiovascular morbidity

As of data cutoff, an arterial thrombotic event had occurred in 6 patients and a venous thrombotic event had occurred in 4 patients (summarized in Table 2). Although this number of events was too small to allow for statistical analysis, no gross excess of cardiovascular events was apparent in one or the other treatment arm.

Discussion

This study provides the first insight on long-term castration-related outcomes in patients treated with upfront docetaxel-based chemotherapy and long-course ADT for HRLPC. The key observation derived from our data is that neither changes in body weight, testosterone recovery, libido or quality of erection seemed to be negatively impacted by chemotherapy. The long follow-up and the randomized nature of this study strengthen these findings.

In our study, restoration of STLs to normal levels was achieved in 78% of evaluable patients within 2 years of ADT discontinuation, then plateaued. Despite methodological discrepancies, the observations seem to be coherent with the rare previous reports of testosterone recovery after long-course adjuvant/neoadjuvant ADT^{18,19}. Although the number of patients was too small to draw any definitive conclusions, baseline body mass index (BMI) seemed to negatively impact testosterone recovery, with evaluable patients with BMI <25 kg/m², 25-29.9 kg/m², and ≥30 kg/m² recovering normal STLs in 87%, 79%, and 67% of cases, respectively. Weight gain on ADT was not associated with a decreased probability of normal testosterone recovery. One limit of our study was the absence of data regarding baseline STLs, which precludes analyzing non-recovery at the individual level; indeed, previous studies have reported that pre-ADT testosterone levels are predictive of testosterone recovery²⁰. Importantly, we observed no apparent delay in testosterone recovery associated with chemotherapy. This is in line with findings from the TAX-3501 trial, in which addition of docetaxel to leuprolide after radical prostatectomy (either as adjuvant therapy or differed until progression) did not impact testosterone recovery¹². An important difference between the two studies is that, in the TAX-3501 trial, ADT was pursued for only 18 months when several reports have concluded that a duration of treatment longer than 18 or 24 months negatively impacts testosterone recovery in patients treated with adjuvant ADT^{17,18,21}. Since 18 months to 3 years of adjuvant ADT are now the standard of care in HRLPC patients treated with EBRT^{3,4}, we felt that confirmation of those findings from TAX-3501 was needed. Other differences include the nature of local treatment, which was radical prostatectomy, and length of follow-up, which was only 3.4 years from treatment initiation in the report from TAX-3501. Finally, a major specificity of the GETUG 12 trial was the addition of estramustine to docetaxel. Estramustine has long been described as having endocrine effects including gonadotropic suppression^{22,23}, and the long-term endocrine toxicity of combined LH-RH agonists and estramustine had been a concern. In our subset of patients from the GETUG-12 trial we observed no excess in long-term endocrine toxicity in estramustine-treated patients. The similarity in the rates and timeliness in testosterone recovery in both arms also does not support the hypothesis that the benefit associated with neoadjuvant docetaxel and estramustine in the GETUG 12 trial was due to deeper or prolonged castration.

Our study is the first to report on long-term functional outcomes in patients treated with neoadjuvant chemotherapy in combination with ADT for HRLPC. The drastic on-treatment impact of ADT on sexuality-related patient-reported outcomes (PROs) is well-described^{24,25}. In accordance with previous reports²⁶, the castrate STLs observed in all patients at the end of ADT in our study were associated with dramatic decreased libido, and virtually no patient reported the possibility of sexual intercourse without medical assistance. Few studies have focused on such functional outcomes

beyond treatment discontinuation. For patients undergoing short-term ADT and radiation therapy, conflicting reports exist as to the reversibility of ADT-induced changes in sexual activity and sexual functioning within 2 years of treatment discontinuation^{27,28}; this may be the reflection of methodological discrepancies in PRO measurement. In any case, we feel that a 2-year follow-up may be too short to evaluate such outcomes since a decline in erectile function may be observed even later in these patients²⁹. Data regarding recovery after long-term ADT is even more scarce³⁰. We did not use validated questionnaires regarding libido and quality of erection, which is a limitation of our study. Nevertheless, we were able to observe that both symptoms significantly improved over time, with about 40% of patients regaining the possibility of intercourse without medical assistance within 2 to 3 years of ADT discontinuation. We did not find any association between baseline erectile dysfunction and post-ADT functional outcomes, possibly because of a lack of statistical power and of missing data. The frequent discrepancy between normalized STLs and abnormal functional outcomes in most patients pleads for non-endocrine causes. Indeed, most men in GETUG-12 also received radiotherapy to the prostate, this may have impaired their erectile function.

Cardiovascular morbidity and mortality are chief concerns in prostate cancer patients treated with long-term ADT³¹⁻³³. Nevertheless, the incidence of cardiovascular or thrombotic events was low in GETUG-12 and, in the subgroup of patients analyzed in the present paper, we did not observe any gross increase in those randomized in the chemotherapy arm. This is reassuring regarding the long-term toxicity of neoadjuvant docetaxel, especially when considering that in the GETUG 12 trial chemotherapy also included estramustine, which is a known pro-thrombotic drug³⁴. Also, no excess in second cancers was observed in the recently reported long-term analysis of the trial¹¹.

The benefit of docetaxel-based chemotherapy in HRLPC is suggested by a building corpus of evidence, although not yet mature enough to support its implementation in routine practice in most countries^{8,3,15}. While the long-term results of pioneer studies such as the GETUG-12 trial are made available^{11,15}, other studies are ongoing such as the PEACE-2/GETUG-AFU 23 trial (NCT01952223) which explores the benefit of neoadjuvant cabazitaxel, a taxane active in metastatic patients pretreated with docetaxel³⁵, in HRLPC patients treated with EBRT with or without pelvic irradiation. The data we derived from a subset of the GETUG 12 trial population is reassuring as of the long-term endocrine or cardiovascular side effects associated with additional chemotherapy in this setting and encourages pursuing such trials. Nevertheless, because the present study is a subgroup analysis, results are only informative and need to be interpreted cautiously. In our opinion, any future studies of early chemotherapy in HRLPC patients large enough to address these issues, such as the PEACE-2 trial, should include a prospective survey of the long-term biochemical and functional recovery from castration, as well as of metabolic and cardiovascular morbidity.

Conclusion

Additional neoadjuvant chemotherapy with docetaxel and estramustine did not negatively impact neither testosterone recovery nor long-term functional outcomes, changes in body weight or the incidence of cardiovascular events in the first years following treatment discontinuation after long-course androgen deprivation therapy for high-risk localized prostate cancer.

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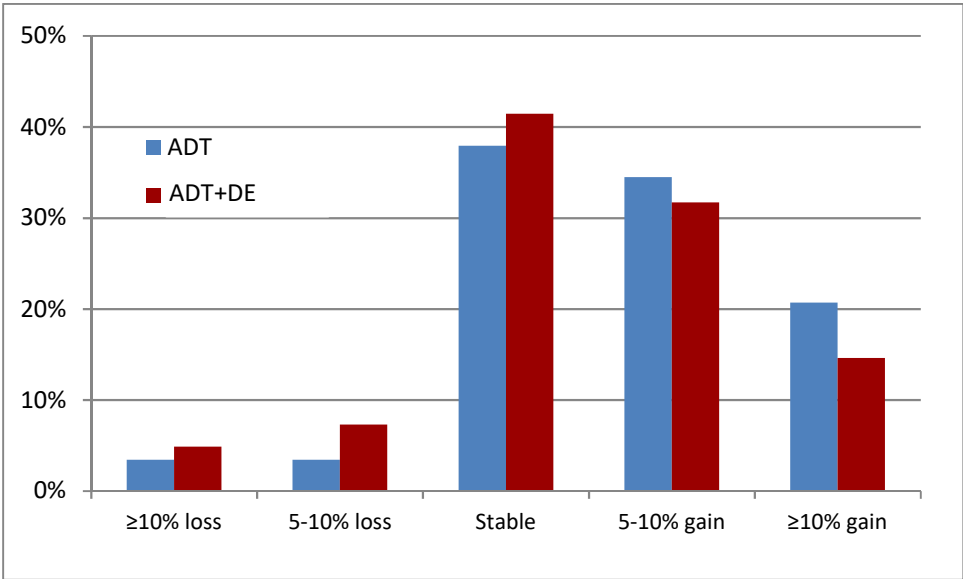
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Figure 1 – Changes in body weight

A. Distribution of changes in body weight at the time of ADT discontinuation (ADT arm: 29 evaluable patients; ADT+DE arm: 41 evaluable patients)



B. Timely evolution of mean weight variation from baseline after ADT discontinuation (numbers of evaluable patients in each treatment arm at each time point are shown)

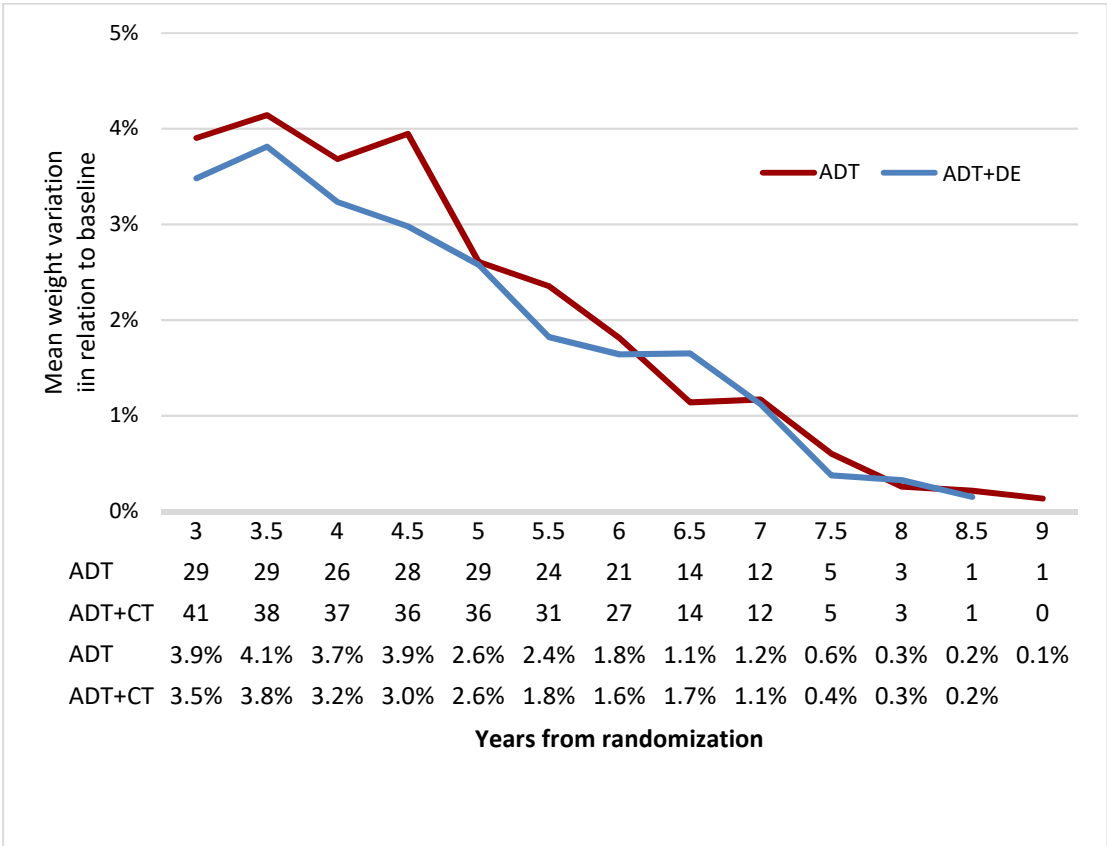
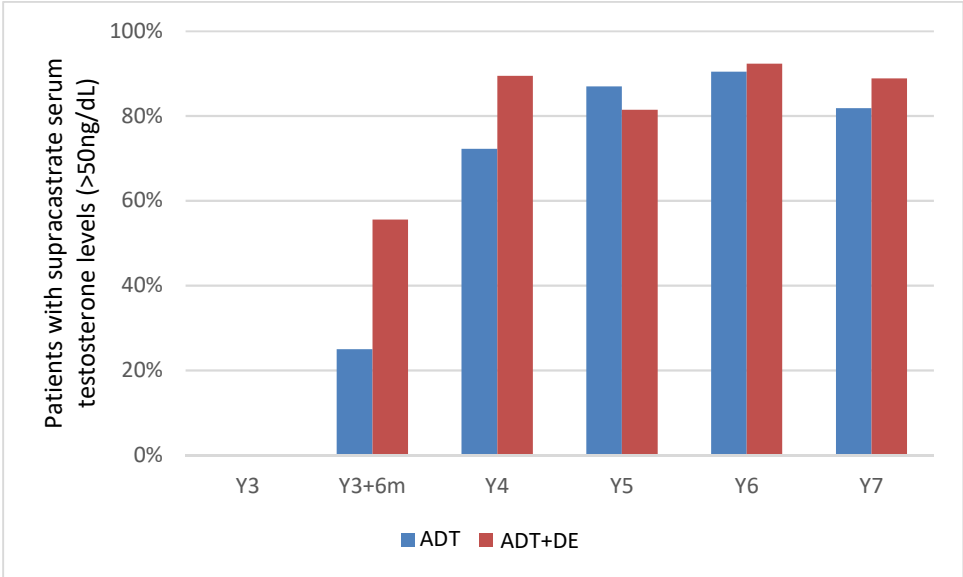


Figure 2 – Testosterone recovery

A. Proportion of evaluable patients with supracastrate testosterone levels



B. Proportion of evaluable patients with normal testosterone levels

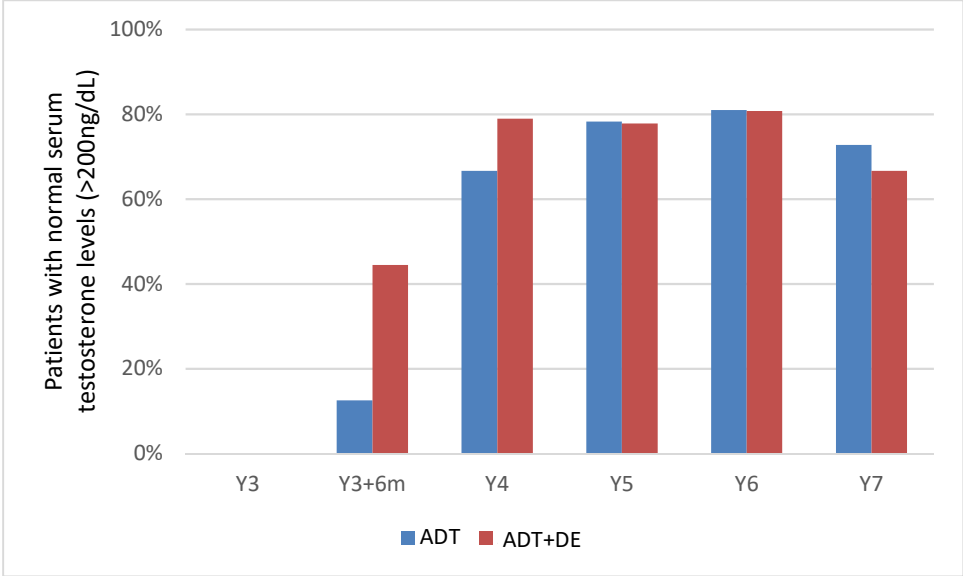
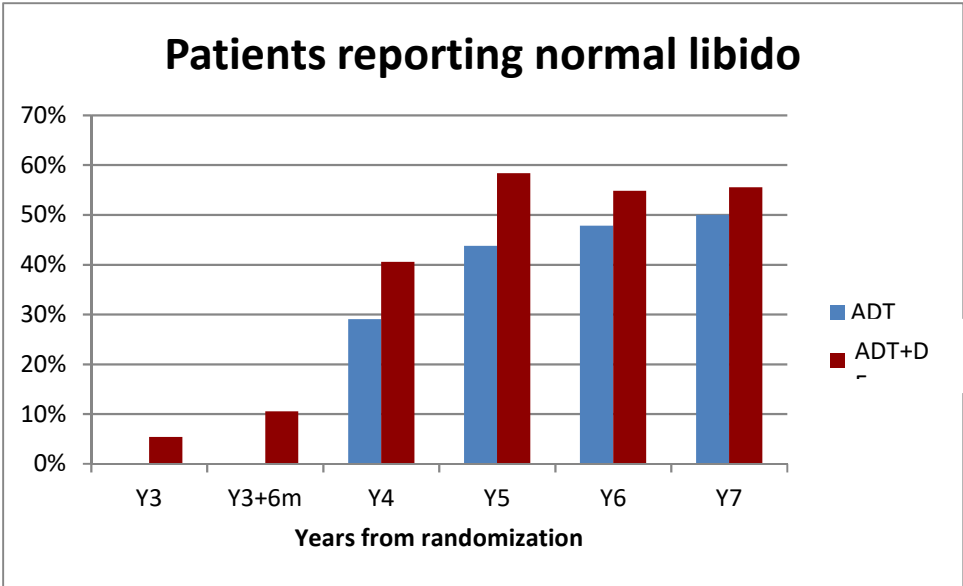


Figure 3 – Functional outcomes

A. Proportion of evaluable patients reporting normal libido



B. Proportion of evaluable patients reporting erection allowing for intercourse without medical help

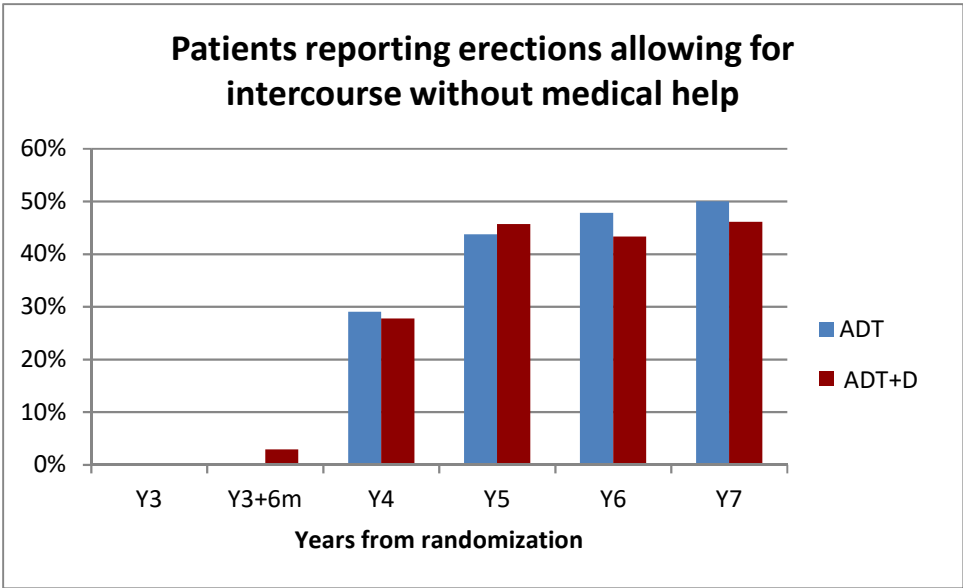


Table 1 – Baseline characteristics for patients alive at the end of ADT

	ADT group		ADT+DE group	
Number of patients	36		42	
Age at randomization				
Median age (years)	60		62	
Patients over 60 (n/%)	18	50%	22	52%
Patients over 70 (n/%)	7	19%	3	7%
Cardiovascular risk factors				
Hypertension (n/%)	7	19%	13	31%
Hypercholesterolemia (n/%)	5	14%	5	12%
Diabetes mellitus (n/%)	2	6%	2	5%
Atheromatosis (n/%)*	2	6%	2	5%
Body weight				
Median BMI (kg.m-2)	25,5		26,8	
Patients with BMI >25 (n/%)	17	47%	28	67%
Patients with BMI >30 (n/%)	6	17%	5	12%
Erectile function				
Reported erectile dysfunction (n/%)	9	25%	13	31%
No reported erectile dysfunction (n/%)	19	53%	13	31%
Missing data (n/%)	8	22%	16	38%
Prostate cancer characteristics				
PSA >20 ng/mL (n/%)	22	61%	30	71%
Gleason score ≥8 (n/%)	18	50%	13	31%
cT3-4 disease (n/%)	20	56%	29	69%
pN+ disease (n/%)	7	19%	6	14%
Local treatment				
EBRT (n/%)	31	86%	41	98%
Prostatectomy (n/%)	5	14%	0	0%
None (n/%)	0	0%	1	2%

ADT: androgen deprivation therapy ; DE: docetaxel and estramustine ; BMI: body mass index ; PSA: prostate-specific antigen ; EBRT: external beam radiotherapy

* Atheromatosis include coronary artery disease, carotid artery disease, and lower limbs artery disease

Table 2 – Cardiovascular events following ADT discontinuation

	ADT group	ADT+DE group
Arterial thrombotic event (n)	4	2
Coronary event (n)	2	2
Stroke (n)	1	0
Lower limb arteritis (n)	1	0
Venous thrombotic event (n)	3	1
Other events (n)		
Cardiac arrest (n)	0	1

