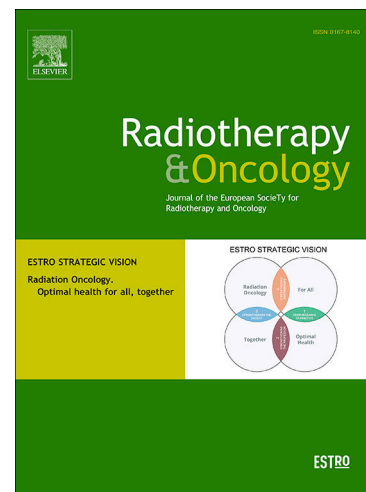


Original Article

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Testosterone recovery after androgen deprivation therapy in localised prostate cancer: long-term data from two randomised trials

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Abstract

Background and purpose

To determine the rate and time of testosterone (T) recovery in patients (pts) with localised prostate cancer treated with radiotherapy plus 0-, 6-, 18- or 36-month of androgen deprivation therapy (ADT).

Materials and methods

In 1230 pts with prostate cancer randomised into two phase III trials, serum T was measured at baseline, then regularly. T recovery rate was compared between normal vs. abnormal baseline T and with ADT duration with Chi-square test or Fisher's exact test. A multivariable logistic regression model to predict the probability of recovering normal T was performed.

Results

Overall, 87.4% (167/191), 75.9% (293/386), 54.8% (181/330) and 43.2% (80/185) of pts, recovered normal T on the 0-, 6-, 18- or 36-month schedule, respectively ($p<0.001$). In patients recovering normal T, the median time to T recovery increased with ADT duration ranging from 0.31, 1.64, 3.06 to 5.0 years for the 0-, 6-, 18- or 36-month schedules, respectively ($p<0.001$) and was significantly faster for those with a normal T at baseline ($p<0.001$). On multivariable analysis, older age and longer ADT duration are associated with a lower T recovery.

Conclusions

Testosterone recovery rate after ADT depends on several factors including hormonal duration, normal baseline T, age and medical comorbidities. A longer ADT duration is the most important variable affecting T recovery. The data from this report might be a valuable tool to help physicians and patients in evaluating risks and benefits of ADT.

Keywords: Localised prostate cancer; Androgen Deprivation therapy; Testosterone recovery

Journal Pre-proofs

Introduction

Androgen deprivation therapy (ADT) is an effective, commonly used treatment in localised prostate cancer¹. In the National Comprehensive Cancer Network guidelines Version 1.2024², the recommendation of ADT plus radiotherapy (RT) for unfavorable intermediate risk prostate cancer (IRPC) is listed as category 2a evidence and as category 1 evidence for high-risk prostate cancer (HRPC). However, ADT is also associated with a long list of hypogonadal side effects that significantly affect patients' quality of life³, including hot flashes⁴, fatigue⁵, anemia⁶, decrease muscle strength, increase body fat⁷⁻⁸ depression, anxiety⁹⁻¹⁰, metabolic syndromes¹¹, decrease penile and testicular size¹², sexual dysfunction¹³⁻¹⁴, increase of cardiovascular risk¹⁵, osteoporosis and bone fractures¹⁶⁻¹⁷⁻¹⁸⁻¹⁹.

Despite these known potential harmful outcomes, there is a lack of prospective data in the literature on the kinetics of testosterone (T) recovery after ADT use. Addressing T recovery, also involves considering the actual place of T replacement therapy in patients remaining persistently hypogonadal after ADT²⁰.

Based on the long-term follow-up of two randomised trials in localised prostate cancer, we report herein our prospectively collected data on T recovery in patients with IRPC and HRPC treated with RT and different duration of ADT.

Patients and methods

Between October 2000 and January 2010, 1230 patients with either IRPC (600 patients – PCS III trial, Clinicaltrials.gov, #NCT00223145) or HRPC (630 patients - PCS IV trial, Clinicaltrials.gov NCT00223171)¹ were randomised into two multicentre phase III trials and are the subjects of this study. Details of both trials have been published previously²¹⁻²². Briefly, IRPC patients, defined as clinical stage T1-T2, PSA 10-20 ng/ml and Gleason score < 7, or T1-T2, PSA ≤ 20 and Gleason score 7, were randomised to RT alone at 76 Gy (200 pts) vs. 6 months of ADT and 2 levels of RT doses, 70 Gy (200 pts) vs. 76 Gy (200 pts). The group of 200 patients treated with RT alone will serve as a reference to evaluate T variation without the use of ADT. HRPC was defined as clinical stage T3-4, PSA level >20 ng/ml or a Gleason score ≥8. Patients with at least one of these 3 factors were eligible for the study. They were randomised to 36 (310 pts) vs. 18 months of ADT (320 pts). All HRPC patients received pelvic RT (44 Gy) and prostate RT (70 Gy). In both trials, ADT consisted of bicalutamide 50 mg for one month plus goserelin acetate.

Testosterone

As per protocol, in both trials, serum T was measured at baseline, then at every 3 months for the first 18 months, every 6 months up to year three and yearly thereafter until death or end of the study. T level is reported using the International System of Units taking in account normal values for each participating center (normal inferior range varying from 5.7 to 9.9 nmol/L), most of the centers had normal T values between 9 and 25 nmol/L. We defined an abnormal T when baseline measurement was below the normal defined level.

¹ AstraZeneca Pharmaceuticals funded PCS III and PCS IV studies but was not involved in any step of the trial design or manuscript preparation

We defined T recovery as a return of T to within the normal range value of each participating institution, regardless of whether it was initially normal or abnormal. Time to T recovery was measured from baseline measurement to T recovery. Patients who had not T measured at baseline or during follow-up visits were excluded. To avoid subsequent T variations due to reintroduction of ADT for recurrence, we selected, for this analysis, only patients with either no biochemical recurrence (BCR) or up to when they developed BCR, according to the Phoenix definition (PSA ≥ 2 ng/mL over the nadir PSA).

Statistical analysis

Patient characteristics were evaluated with frequencies and percentages for categorical variables or with median and interquartile range percentile (IQR:25th-75th) for continuous variables. Comparison between groups of ADT schedules was done with ANOVA and Fisher's exact test. Using the Chi-square test, we compared the rates of T recovery between baseline normal or abnormal T and also compared them against ADT duration. Time to T recovery rates were calculated from baseline pre-treatment T and analyzed with sub distribution (sHR) analysis of competing risks methods. Results are presented with cumulative incidence risk. Because at least 50% of patients in some subgroups did not recover T to a normal level, it was unfeasible to estimate a median time for a normal T recovery with competing risk analysis. We, therefore, describe the median time only in subjects who recovered T to a normal range and compared normal vs. abnormal baseline T recovery with the Mann-Whitney test. Multivariable logistic regression and multivariable competing risk analyses were computed to evaluate predictors of T recovery and predictor of time to T recovery. To increase results reliability about the accurate ADT duration, we did not perform an intent to treat analysis, but rather selected only IRPC and HRPC patients who received exactly 6, 18 or 36 months of ADT ± 1 dose of goserelin acetate therapy.

Results

Patient characteristics are shown in Table 1. Results are reported with a median follow-up of 15.3 years (IQR: 12.2-18.4). Median age at randomisation was 71 years (range: 50-80) and 82 (range: 57-100) at the time of the last follow-up.

Table 1. Patient characteristics

Parameters	No ADT (n=191)	6 mo ADT (n=386)	18 mo ADT (n=330)	36 mo ADT (n=185)	p-value
Age (years)					
Median	72	71	71	71	0.9114
Range	50-79	54-80	51-80	51-79	
IQR	66-74	66-74	66-74	66-74	
Zubrod Performance Scales - n (%)					
0	168 (88)	355 (92)	294 (89.1)	169 (91.4)	
1	23 (12)	31 (8)	36 (10.9)	16 (8.6)	0.361
Co-morbidities - n (%)					
Cardiac disease	67 (35.4)	112 (29.1)	97 (29.4)	52 (28.1)	0.364
COPD	15 (7.9)	35 (9.1)	34 (10.3)	16 (8.6)	0.822
Hypertension	96 (50.8)	200 (51.9)	158 (47.9)	96 (51.9)	0.71
Diabetes	27 (14.3)	62 (16.1)	58 (17.6)	29 (15.7)	0.799
Baseline testosterone - n (%)					
Normal	143 (74.9)	311 (80.6)	250 (75.8)	152 (82.2)	0.146
Abnormal	48 (25.1)	75 (19.4)	80 (24.2)	33 (17.8)	

Clinical tumor stage**(AJCC 1997) - n (%)**

T1-T2a	148 (77.5)	282 (73.1)	154 (46.7)	81 (43.8)	<0.001
T2b-T2c	43 (22.5)	104 (26.9)	105 (31.8)	49 (26.5)	
T3-T4	0 (0)	0 (0)	71 (21.5)	55 (29.7)	

Gleason score - n (%)

6	44 (23)	98 (25.4)	41 (12.4)	26 (14.1)	<0.001
7	147 (77)	288 (74.6)	84 (25.5)	53 (28.6)	
8-10	0 (0)	0 (0)	205 (62.1)	106 (57.3)	

PSA (ng/ml)

PSA >10 ng/ml	108 (56.5)	206 (53.4)	211 (63.9)	128 (69.2)	0.001
Median	10.5	10.44	15.05	16	<.0001
Range	0.33-19.7	0.5-20	0.6-252	1.12-153	
IQR	6.8-13.5	6.35-13.53	8-28.12	9-29.58	

ADT: androgen deprivation therapy; mo: month; n: number; IQR: inter-quartile range, COPD: chronic obstructive pulmonary disease; AJCC: American Joint Committee on Cancer

Of the 1230 patients, 90 (7.3%) were excluded from the analysis for the following reasons: 50 had no baseline T, 37 had no T during subsequent follow-up and 3 had no T measured at all. From the 1140 remaining patients, 48 were further excluded because they did not receive exactly 6, 18 or 36 months of ADT. A total of 1092 patients were retained for this analysis. Of these, 191 IRPC patients received RT alone and will serve as reference. 386 IRPC patients received 6 months of ADT, 330 HRPC patients received ADT for 18 months while another 185 had ADT for 36 months.

Groups are comparable for age, Zubrod performance scale and medical co-morbidities. At baseline, 856/1092 (78.4%) patients presented a normal T value and there was no significant difference in normal T between those receiving no ADT (74.9%) vs. those receiving ADT for 6 (80.6%), 18 (75.8%) or 36 (82.2%) months, $p=0.15$. Similarly, there was no significant difference in age between patients presenting with a normal vs. abnormal T at baseline (age ≥ 70 years, 60% (515/856) vs. 58% (137/236), $p=0.558$). As expected, clinical stage, Gleason score, and PSA levels are significantly different given patients' different risk stratifications. For the whole group, a total of 12 522 T measurements were available over a period of 21 years. Of these, 1813 T measurements in 191 patients receiving RT alone, 4543 in 386 patients receiving 6 months of ADT, 3737 in 330 patients receiving 18 months and 2429 in 185 patients receiving 36 months.

The rate of T recovery was higher in subjects under 70 years of age than in subjects older than 70 years (71.6% vs. 62.3%, $p=0.001$). With a longer ADT duration, fewer patients recovered T to a normal level. T recovery rates for ADT of 0-, 6-, 18- or 36-month were 87.4% (167/191), 75.9% (293/386), 54.8% (181/330) and 43.2% (80/185), respectively, ($p<0.001$). In patients with a baseline abnormal T, the rate of T recovery to normal level, was similarly lower and ranged from 68.8% to 30.3%, depending upon ADT duration, $p<0.001$ (Table 2).

Table 2. Testosterone recovery rates in reference to baseline T level and ADT duration.

ADT duration (months)	T measurements at baseline				p-value
	Normal T		Abnormal T		
	n pts	T recovery (%)	n pts	T recovery (%)	
0	143	134 (93.7)	48	33 (68.8)	<0.001
6	311	252 (81.0)	75	41 (54.7)	<0.001
18	250	153 (61.2)	80	28 (35.0)	<0.001
36	152	70 (46.1)	33	10 (30.3)	0.01

ADT: androgen depletion therapy; n: number; pts: patients; T: testosterone

Patients' testosterone variation over time is reported in the supplement material where each line represents a T variation per patient over a given time (Supp Fig. 1).

In patients recovering T to a normal level, the median time to T recovery increased with ADT duration and ranged from 0.31, 1.64, 3.06 to 5.0 years for 0-, 6-, 18- or 36-month schedules, respectively ($p < 0.001$). There was a strong inverse linear association ($R^2 = 0.97$) when calculating a curve of best fit considering that a shorter time to T recovery was associated with a higher recovery rate (**Suppl Fig. 2**). A faster recovery time was seen in patients with a normal T at baseline ($p < 0.001$) (**Table 3**).

Table 3. Median time to T recovery based on baseline T level and ADT duration.

ADT duration (months)	n pts	Median time (year)	Initial baseline T	n pts	Median time (year)	p-value
0	167	0.31 (0.25-0.92)	Normal	134	0.29 (0.25-0.58)	<.0001
			Abnormal	33	2.76 (0.89-5.20)	
6	293	1.64 (1.42-2.23)	Normal	252	1.59 (1.32-2.10)	<.0001
			Abnormal	41	2.01 (1.61-3.48)	
18	181	3.06 (2.57-3.65)	Normal	153	3.07 (2.55-3.66)	0.6211
			Abnormal	28	3.02 (2.57-3.54)	
36	80	5.00 (4.49-5.95)	Normal	70	5.00 (4.55-5.96)	0.3016
			Abnormal	10	4.53 (4.31-5.20)	

ADT: androgen depletion therapy; n: number; pts: patients; T: testosterone

Based on the competing risks analysis, 5-year T recovery rates for 0-, 6-, 18- or 36-month ADT schedules were 83%, 73%, 50%, and 23%, while 10-year rates were 90%, 77%, 57% and 44%, respectively. When compared to no ADT, recovery time to normal T decreased with prolonged duration of ADT [6 months ADT: sHR (95% CI) = 0.44 (0.33-0.59), $p < 0.001$; 18 months ADT: sHR = 0.20 (0.15-0.27), $p < 0.001$; 36 months ADT: sHR = 0.11 (0.08-0.16), $p < 0.001$] (**Fig. 1**). Patients with a normal baseline T had a significantly faster recovered T than patients with an abnormal baseline T. With respect to ADT duration, the following outcomes were seen: no ADT [sHR (95% CI) = 4.08 (2.71-6.13), $p < 0.001$], 6 months ADT [sHR (95% CI) = 2.45 (1.81-3.34), $p < 0.001$], 18 months ADT [sHR (95% CI) = 2.26 (1.49-3.45), $p < 0.001$]. No significant difference was observed between normal vs. abnormal baseline T for 36 months ADT [sHR (95% CI) = 1.75 (0.87-3.50), $p = 0.12$] (**Fig. 2**).

A proportion of patients did not recover normal T levels despite a long-term follow-up. The unrecovered T level rates for 0-, 6-, 18- or 36-month ADT schedules were 12.6% (24/191), 24.1% (93/386), 45.2% (149/330) and 56.8% (105/185), respectively, for an overall unrecovered rate of 34.0% (371/1092). It is noteworthy that 25.6% (148/577) of IRPC patients and 31.5% (162/515) of HRPC patients, none receiving T replacement therapy, eventually developed BCR over time, as shown on supplement figure 3.

We studied a multivariable model with baseline normal T, Zubrod scale, age, cardiac disease, chronic obstructive pulmonary disease, hypertension, diabetes and ADT duration schedules. A normal baseline T was a strong predictor of T recovery using a logistic regression or a competing risk analysis. Older age, chronic pulmonary obstructive disease, diabetes, and longer ADT duration significantly reduced the likelihood of T recovery to normal level (**Table 4**).

Table 4. Multivariable models with logistic regression and competing risk analysis.

	Logistic regression		Competing risk analysis	
	OR (95% CI)	p-value	sHR (95% CI)	p-value
Baseline normal T	3.10 (2.16-4.45)	<0.001	2.46 (1.90-3.19)	<0.001
Zubrod Scales	0.79 (0.47-1.32)	0.360	1.24 (0.87-1.76)	0.237
Age	0.92 (0.89-0.94)	<0.001	0.94 (0.93-0.95)	<0.001
Cardiac disease	0.95 (0.68-1.32)	0.751	0.92 (0.73-1.15)	0.474
COPD	0.49 (0.29-0.82)	0.006	0.54 (0.36-0.82)	0.004
Hypertension	1.25 (0.91-1.70)	0.165	1.07 (0.88-1.29)	0.494
Diabetes	0.48 (0.32-0.72)	<0.001	0.55 (0.42-0.73)	<0.001
ADT				

6	1	1		
18	0.36 (0.26-0.51)	0.248	0.34 (0.28-0.42)	<0.001
36	0.19 (0.13-0.28)	<0.001	0.16 (0.13-0.21)	<0.001

ADT: androgen deprivation therapy; T: testosterone; COPD: chronic obstructive pulmonary disease; OR: odds ratio; sHR: Sub distribution Hazard ratio; CI: Confidence interval

Discussion

To our knowledge, this report represents the largest prospectively collected data on T recovery after both a short or prolonged ADT use in patients with localised prostate cancer and a long-term follow-up. Previous series reported in the literature are mainly from retrospective data, involving small number of patients with non-uniform clinical stages, a variety of regimens and duration of ADT and, most importantly, without an adequately acceptable T measurement frequency and/or baseline T documentation²³⁻²⁴⁻²⁵⁻²⁶⁻²⁷. Moreover, the definition of T recovery varied significantly and included return to supra or non-castrate level, out of hypogonadism after ADT withdrawal⁵, a T >50 ng/dl²⁴, supra castrate level, recovery to baseline and/or normal T levels²⁵⁻²⁶, and back to normal T with low T cut-off²⁷. Overall, most studies report that older patients receiving a longer duration of ADT have more prolonged T recovery rates after ADT cessation²³⁻²⁵⁻²⁶.

Our report is unique because it also includes a cohort of randomised patients receiving RT alone who had their T measured in a similar manner to those receiving combined RT plus ADT. The lack of added ADT to this cohort, allowed us to assess the potential impact of RT on T changes. As reported, most patients (94%) with baseline normal T maintained a normal T over time after completion of RT, indicating the small, if any, impact of RT alone on T level. Pickles et al²⁸ have reported similar rates in 666 patients with prostate cancer treated with RT alone. Thus, we can use this cohort as a reference for T variation over a prolonged period. The small percentage of this cohort developing abnormal T over time can be explained by a natural decline of T with advancing age, as shown by several reports²⁹⁻³⁰⁻³¹⁻³².

Our study confirms that the prolonged use of ADT significantly affects and delays T recovery rates, even after a long-term follow-up. This important side effect related to the hormonal treatment should not be overlooked, considering its detrimental impact on quality of life and the potential aggravation of associated medical issues that a prolonged castration status may have in this, generally, elderly population. Life style modifications should be discussed with these patients, including alcohol and caffeine consumption, smoking cessation, healthy food habits, exercise, optimal calcium and vitamin D intake. Because of the potential development of osteoporosis and the known bone fracture risk after ADT¹⁸⁻¹⁹, long term bone health surveillance including a bone density scan should be performed and appropriate therapy³³⁻³⁴⁻³⁵⁻³⁶ given if osteoporosis or fracture shall be prevented.

Moreover, we performed multivariable analyses with logistic regression or with competing risks using ADT duration as outcomes variable and determined that a normal T at baseline is indeed a strong predictor for T recovery. On MVA, other factors affecting an optimal T recovery included age and medical comorbidities.

Our study raises the question of the potential benefit and safety of use of T replacement therapy in persistently hypogonadal patients (low T with attributable symptoms) post-ADT and without evidence of disease recurrence. The saturation model³⁷ based on androgen receptors in prostate cancer cells already saturated at low level of T, would theoretically prevent exogenous T impacting on prostate cancer cells growth, supporting the use of T replacement therapy in these situations. Retrospective data in the literature confirm the safety of the use of T replacement therapy after active surveillance³⁸, prostatectomy³⁹⁻⁴⁰, radiation therapy⁴¹⁻⁴² and brachytherapy⁴³⁻⁴⁴. Despite several caveats from the retrospective methodology, including small series, mainly low risk or intermediate favorable risk prostate cancers, short follow up, lack of Gleason score report and objective measures to properly evaluate symptoms of hypogonadism²³⁻²⁴⁻²⁵⁻²⁶⁻²⁷⁻²⁸, there appears to be a major trend to consider T replacement therapy in patients cured from prostate cancer with the goal of improving hypogonadism symptoms and quality of life.

Guidelines from the European Association of Urology⁴⁵ and the American Urology Association⁴⁶ acknowledge the shift in concept and practice in T replacement therapy in men with history of persistent hypogonadism post-ADT, although a shared decision with a well-informed patient and a vigorous surveillance protocol is strongly recommended. Despite that none of our patients received replacement therapy, we generally agree with these recommendations. Further studies in this matter are clearly warranted. Advances in the field hopefully will be solved through randomised trials like the one started by Valderrábano et al⁴⁷.

Our study has limitations including the potential variability in T measurement essays among the institutions participating in our trials. We also acknowledge that variation in T level is related to several factors beyond age and ADT duration, including cultural and geographical location, exercise, obesity, comorbid conditions and circadian rhythms⁴⁸⁻⁴⁹⁻⁵⁰. For these reasons, we are aware that some T that were called abnormal may indeed represent a borderline normal T due, for example, to a diurnal variation. To overcome some of these limitations, we opted to use a straightforward definition of T recovery (return to normal level) and for abnormal T value (defined as below the normal range). Despite these potential caveats, strengths of the current study include the randomisation aspect of both trials (preventing patient selection to different ADT duration arms), the availability of a baseline T measurement prior to ADT and rigorous and controlled T measurements during follow-up schedule for all patients. Furthermore, it has an arm that received no ADT and, importantly, it is the largest study looking at T kinetics over a long-term follow-up.

Conclusion

In patients with localised prostate cancer treated with different ADT duration, our prospective data provide investigators and patients useful information and guidance on the frequency of an initial normal T level measurement, on the probability of testosterone recovery post medical castration, and on the time required for a full recovery to a normal gonadal status. The testosterone recovery rate after exposure to ADT is dependent on several factors including duration of the hormonal manipulation, a normal baseline T, age, and medical comorbidities. Longer ADT duration is the most important variable affecting T recovery kinetics that may last for a long time after hormonal cessation. Special attention should be addressed to patients considered cured from prostate cancer, but with a continuing low testosterone level and symptoms of hypogonadism. Consideration of T replacement therapy after

careful evaluation and strict follow up seems to be an attractive option that requires further studies. The data from this report might be a valuable tool to help physicians and patients in evaluating risks and benefits of ADT and in facilitating the design of treatment optimization in future trials.

Journal Pre-proofs

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Figure captions

Figure 1. Testosterone recovery rates depending upon androgen deprivation therapy duration

ADT: androgen deprivation therapy; mo: month; yr: years

Figure 2. Testosterone recovery rates based on initial normal vs abnormal values

ADT: androgen deprivation therapy; mo: month

Suppl. Figure 1 patients' testosterone variation over time.

(each line represents a T variation per patient over a given time).

Suppl. Figure 2. Best fit curve showing association between testosterone recovery rates and time to testosterone recovery.

T: Testosterone

Suppl. Figure 3. Biochemical recurrence over time.

The curves shown the cumulative rate of biochemical recurrence (BCR) over time among patients who had a recurrence. IRPC: intermediate risk prostate cancer; HRPC: high risk prostate cancer; yr: years

Testosterone recovery after androgen deprivation therapy in localised prostate cancer: long-term data from two randomised trials

Highlights

- Prospective data in intermediate and high-risk prostate cancer
- Testosterone measurements per protocol, initially and at each visit
- Different durations of ADT (6, 18, 36 months) compared to a group of patients without ADT
- Long term follow-up
- Testosterone recovery and time to recovery

- Largest series in the literature

Journal Pre-proofs

Parameters	No ADT (n=191)	6 mo ADT (n=386)	18 mo ADT (n=330)	36 mo ADT (n=185)	p-value
Age (years)					
Median	72	71	71	71	0.9114
Range	50-79	54-80	51-80	51-79	
IQR	66-74	66-74	66-74	66-74	
Zubrod Performance Scales - n (%)					
0	168 (88)	355 (92)	294 (89.1)	169 (91.4)	
1	23 (12)	31 (8)	36 (10.9)	16 (8.6)	0.361
Co-morbidities - n (%)					
Cardiac disease	67 (35.4)	112 (29.1)	97 (29.4)	52 (28.1)	0.364
COPD	15 (7.9)	35 (9.1)	34 (10.3)	16 (8.6)	0.822
Hypertension	96 (50.8)	200 (51.9)	158 (47.9)	96 (51.9)	0.71
Diabetes	27 (14.3)	62 (16.1)	58 (17.6)	29 (15.7)	0.799
Baseline testosterone - n (%)					
Normal	143 (74.9)	311 (80.6)	250 (75.8)	152 (82.2)	0.146
Abnormal	48 (25.1)	75 (19.4)	80 (24.2)	33 (17.8)	
Clinical tumor stage					

Table 1. Patient characteristics**(AJCC 1997) - n (%)**

T1-T2a	148 (77.5)	282 (73.1)	154 (46.7)	81 (43.8)	<0.001
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T2b-T2c	43 (22.5)	104 (26.9)	105 (31.8)	49 (26.5)	
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T3-T4	0 (0)	0 (0)	71 (21.5)	55 (29.7)	
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Gleason score - n (%)

6	44 (23)	98 (25.4)	41 (12.4)	26 (14.1)	<0.001
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7	147 (77)	288 (74.6)	84 (25.5)	53 (28.6)	
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8-10	0 (0)	0 (0)	205 (62.1)	106 (57.3)	
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PSA (ng/ml)

PSA >10 ng/ml	108 (56.5)	206 (53.4)	211 (63.9)	128 (69.2)	0.001
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Median	10.5	10.44	15.05	16	<.0001
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Range	0.33-19.7	0.5-20	0.6-252	1.12-153	
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IQR	6.8-13.5	6.35-13.53	8-28.12	9-29.58	
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ADT: androgen deprivation therapy; mo: month; n: number; IQR: inter-quartile range, COPD: chronic obstructive pulmonary disease; AJCC: American Joint Committee on Cancer

Table 2. Testosterone recovery rates in reference to baseline T level and ADT duration.

ADT duration (months)	T measurements at baseline				p-value
	Normal T		Abnormal T		
	n pts	T recovery (%)	n pts	T recovery (%)	
0	143	134 (93.7)	48	33 (68.8)	<0.001
6	311	252 (81.0)	75	41 (54.7)	<0.001
18	250	153 (61.2)	80	28 (35.0)	<0.001
36	152	70 (46.1)	33	10 (30.3)	0.01

ADT: androgen depletion therapy; n: number; pts: patients; T: testosterone

Table 3. Median time to T recovery based on baseline T level and ADT duration.

ADT duration (months)	n pts	Median time (year)	Initial baseline T	n pts	Median time (year)	p-value
0	167	0.31 (0.25-0.92)	Normal	134	0.29 (0.25-0.58)	<.0001
			Abnormal	33	2.76 (0.89-5.20)	
6	293	1.64 (1.42-2.23)	Normal	252	1.59 (1.32-2.10)	<.0001
			Abnormal	41	2.01 (1.61-3.48)	
18	181	3.06 (2.57-3.65)	Normal	153	3.07 (2.55-3.66)	0.6211
			Abnormal	28	3.02 (2.57-3.54)	
36	80	5.00 (4.49-5.95)	Normal	70	5.00 (4.55-5.96)	0.3016
			Abnormal	10	4.53 (4.31-5.20)	

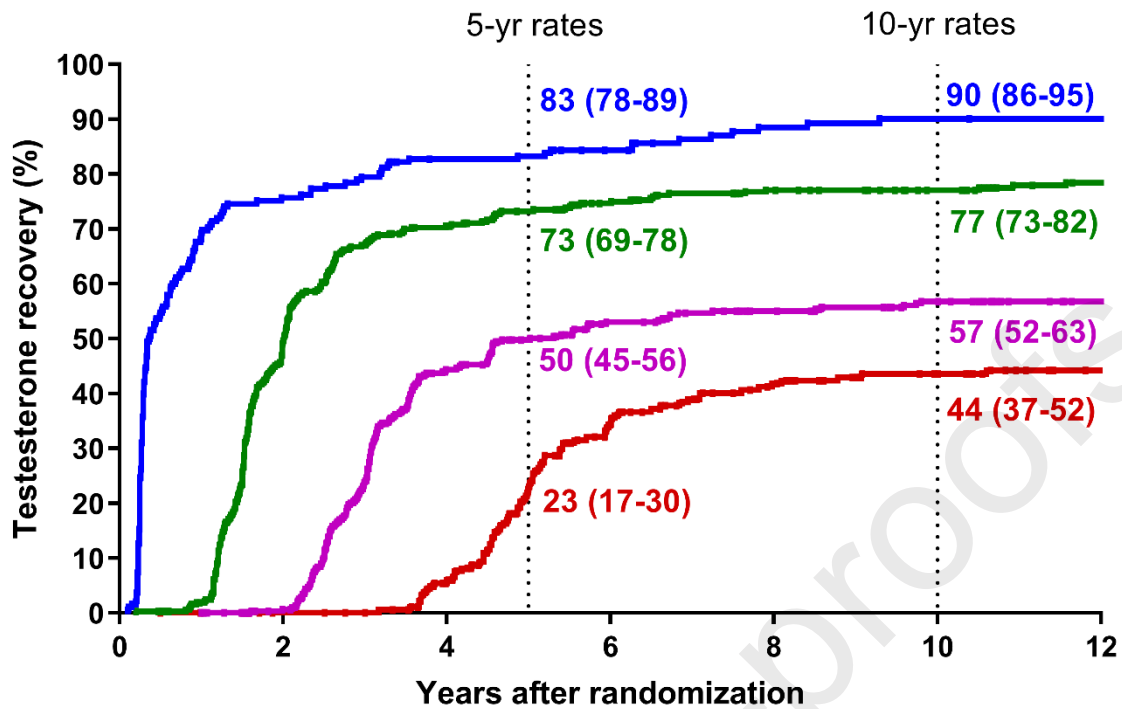
ADT: androgen depletion therapy; n: number; pts: patients; T: testosterone

Table 4. Multivariable models with logistic regression and competing risk analysis.

Logistic regression		Competing risk analysis	
OR (95% CI)	p-value	sHR (95% CI)	p-value

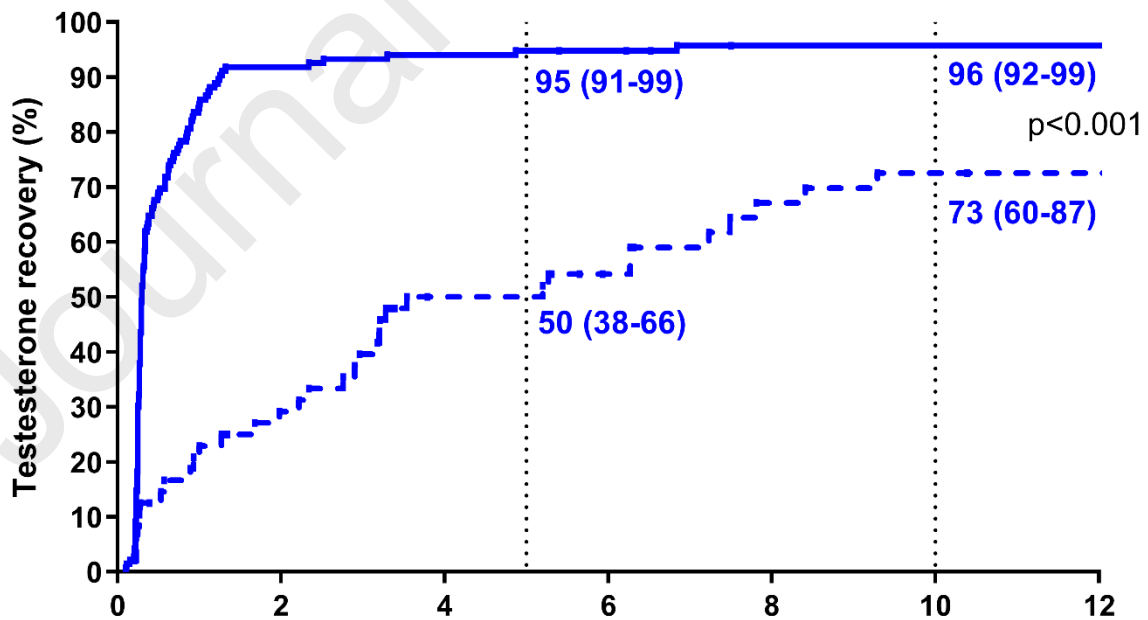
Baseline normal T	3.10 (2.16-4.45)	<0.001	2.46 (1.90-3.19)	<0.001
Zubrod Scales	0.79 (0.47-1.32)	0.360	1.24 (0.87-1.76)	0.237
Age	0.92 (0.89-0.94)	<0.001	0.94 (0.93-0.95)	<0.001
Cardiac disease	0.95 (0.68-1.32)	0.751	0.92 (0.73-1.15)	0.474
COPD	0.49 (0.29-0.82)	0.006	0.54 (0.36-0.82)	0.004
Hypertension	1.25 (0.91-1.70)	0.165	1.07 (0.88-1.29)	0.494
Diabetes	0.48 (0.32-0.72)	<0.001	0.55 (0.42-0.73)	<0.001
ADT				
6	1		1	
18	0.36 (0.26-0.51)	0.248	0.34 (0.28-0.42)	<0.001
36	0.19 (0.13-0.28)	<0.001	0.16 (0.13-0.21)	<0.001

ADT: androgen deprivation therapy; T: testosterone; COPD: chronic obstructive pulmonary disease; OR: odds ratio; sHR: Sub distribution Hazard ratio; CI: Confidence interval



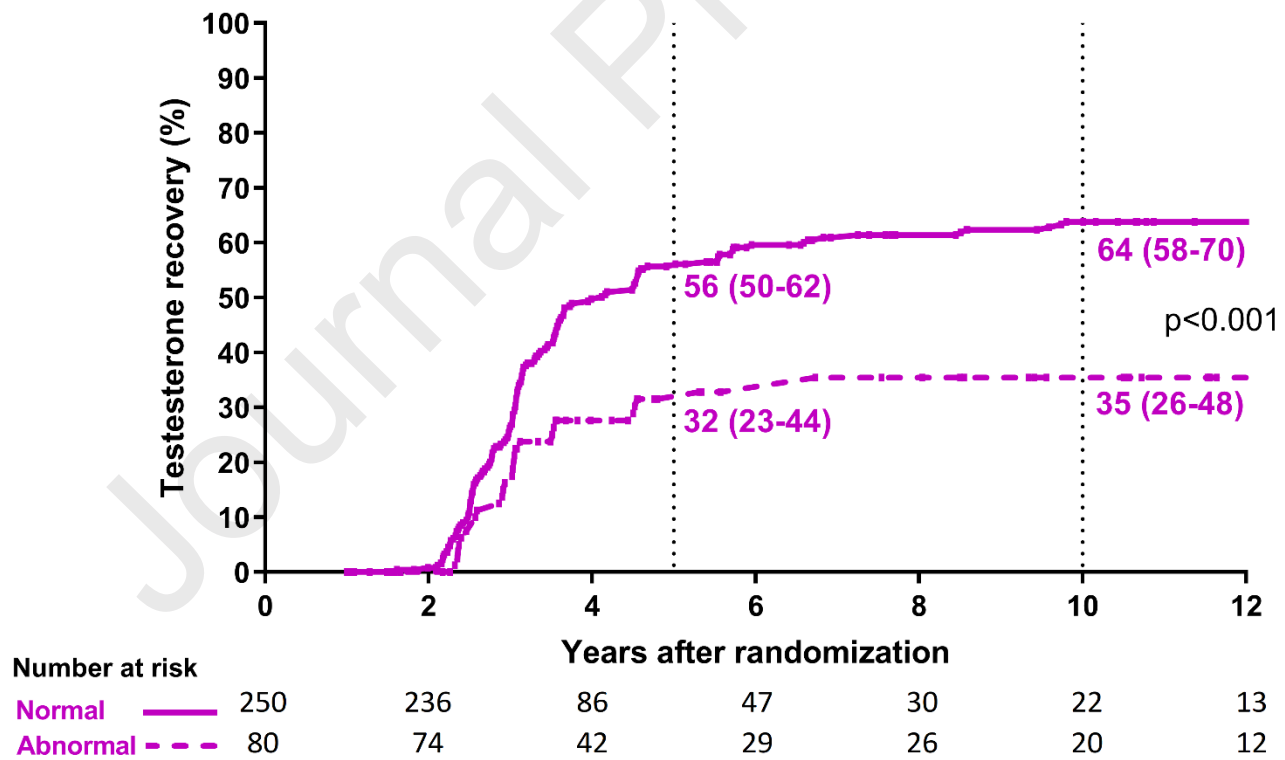
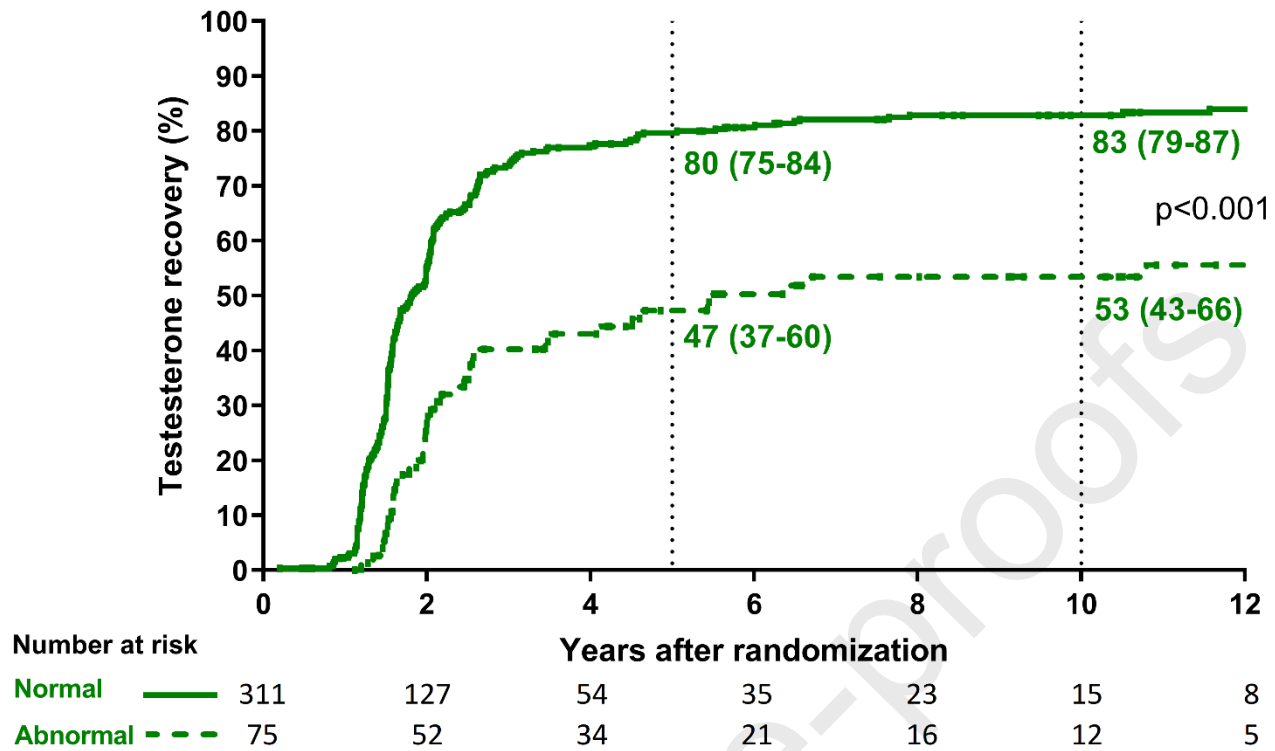
Number at risk

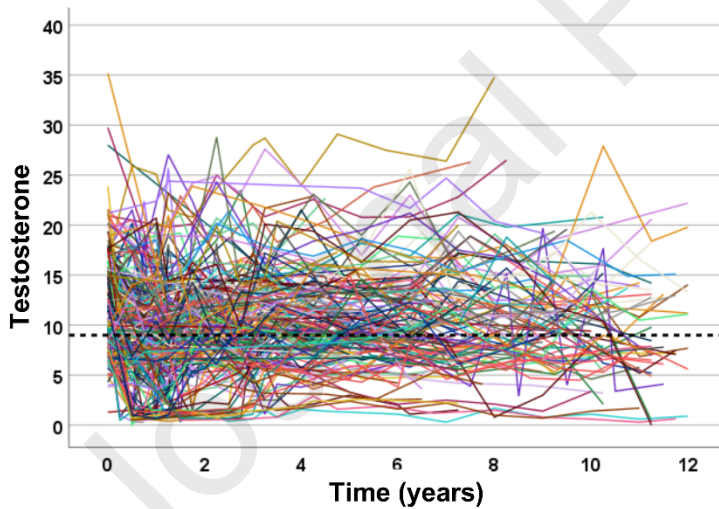
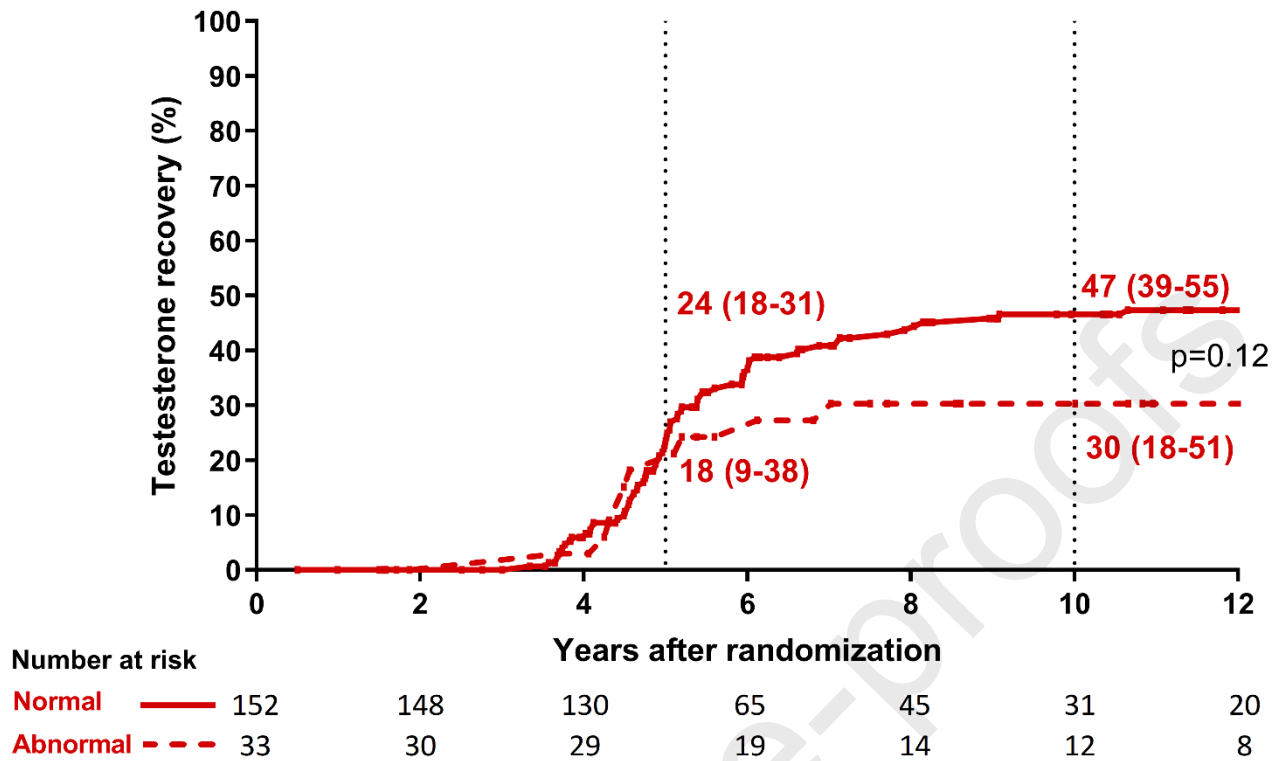
0 mo ADT	191	40	24	17	7	5	4
6 mo ADT	386	179	88	56	39	27	13
18 mo ADT	330	310	128	76	56	42	25
36 mo ADT	185	178	159	84	59	43	28

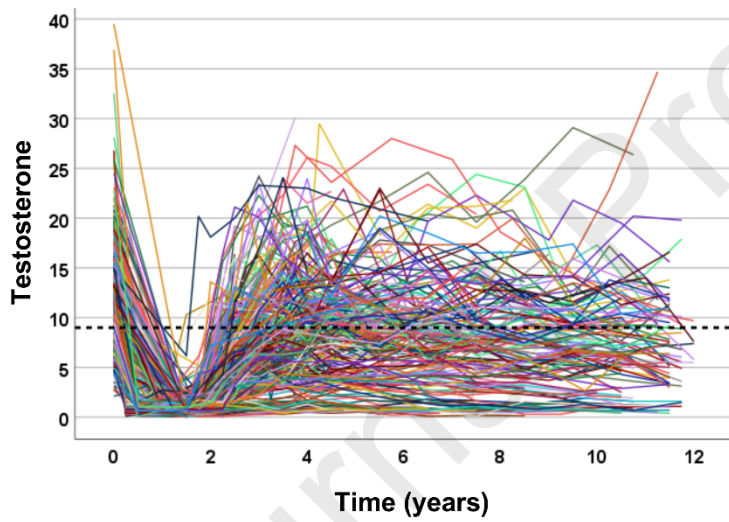
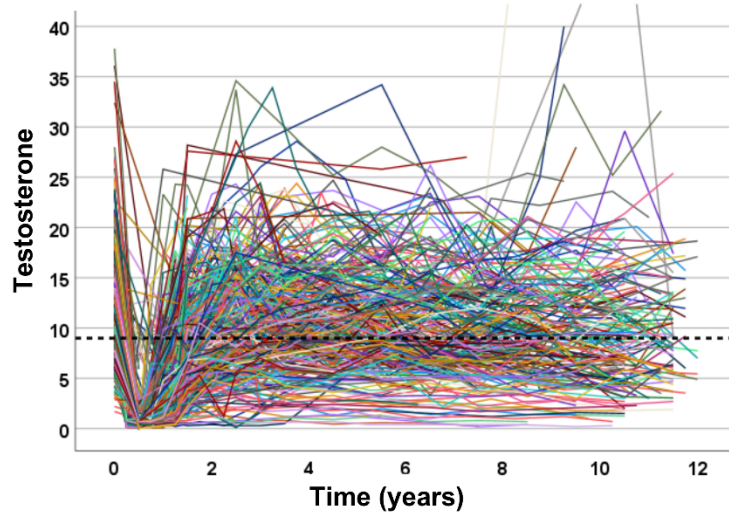


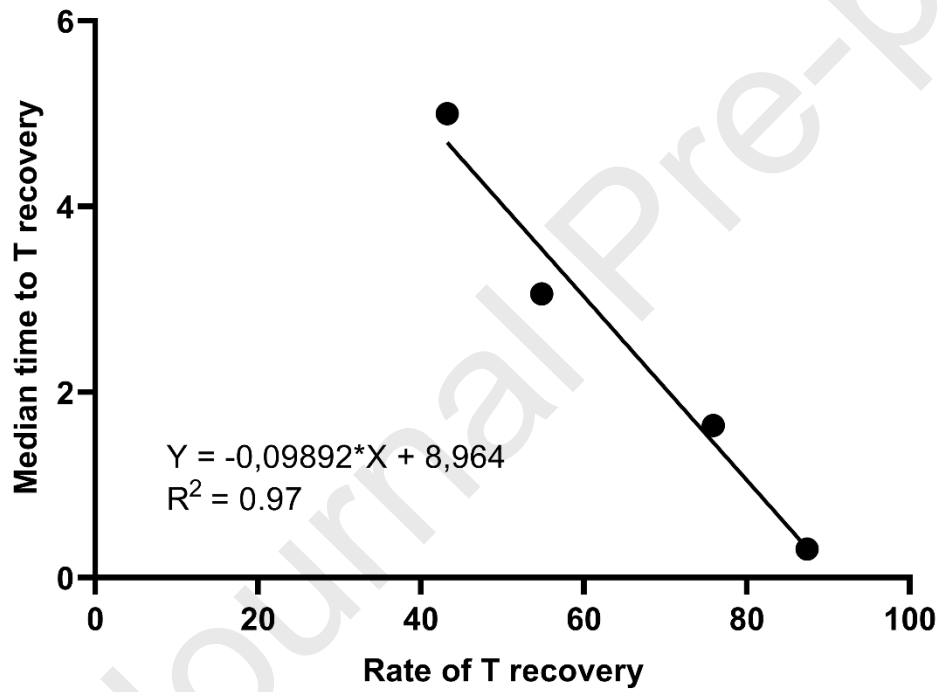
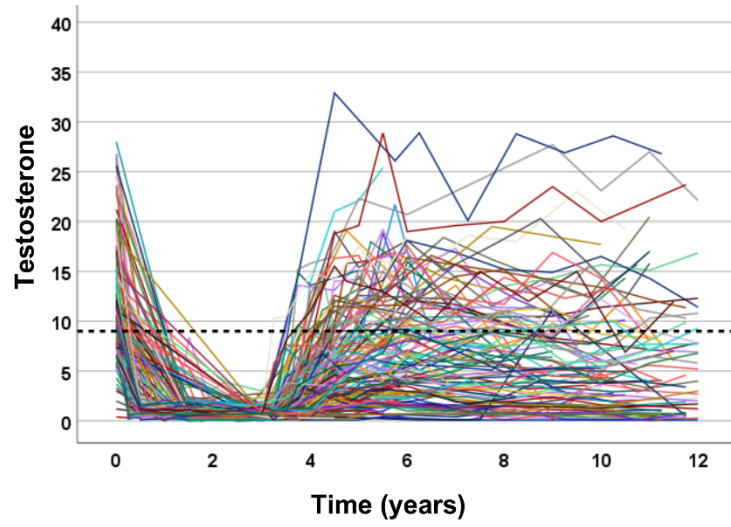
Number at risk

Normal	143	10	7	5	1	1	1
Abnormal	48	30	17	12	6	4	3









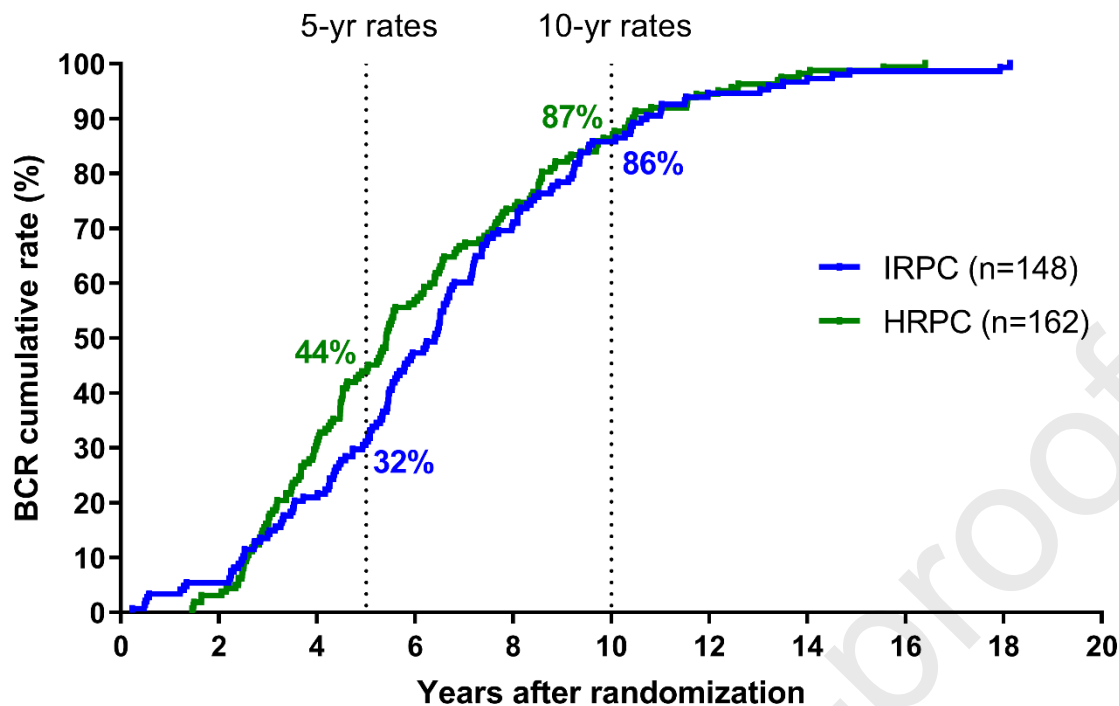


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Conflict of interest

The authors declare that none of them have any conflicts on interest in relation to the present publication