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ORIGINAL ARTICLE

Prostate Cancer

Metabolic syndrome, levels of androgens, and changes of erectile dysfunction and quality of life impairment 1 year after radical prostatectomy

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Robust data evaluating the association of preoperative parameters of the patients with quality of life after radical prostatectomy are lacking. We investigated whether clinical and biological preoperative characteristics of the patients were associated with impaired patient-reported quality of life (QoL) and sexual outcomes 1 year after radical prostatectomy. We evaluated patient-reported outcomes among the 1343 men participating in the AndroCan trial (NCT02235142). QoL and erectile dysfunction (ED) were assessed before and 1 year after radical prostatectomy using validated self-assessment questionnaires (Aging Male's Symptoms [AMS] and the 5-item abridged version of the International Index of Erectile Function [IIEF5]). At baseline, 1194 patients (88.9%) accepted to participate. A total of 750 (55.8%) patients answered the 1-year postoperative questionnaires. Out of them, only 378 (50.4% of responders) provided answers that could be used for calculations. One year after prostatectomy, ED had worsened by 8.0 (95% confidence interval [CI]: 7.3–8.7; $P < 0.0001$) out of a maximum of 20. The global AMS score has worsened by 2.8 (95% CI: 1.7–3.8; $P < 0.0001$). ED scores 1 year postsurgery were positively correlated with preoperative age and percentage of fat mass, and negatively correlated with total cholesterol, dehydroepiandrosterone (DHEA), and androstenediol (D5); AMS were poorly correlated with preoperative parameters. QoL and sexual symptoms significantly worsened after radical prostatectomy. Baseline bioavailable testosterone levels were significantly correlated with smaller changes on AMS somatic subscores postprostatectomy. These findings may be used to inform patients with newly diagnosed prostate cancer.

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INTRODUCTION

Prostate cancer is one of the most commonly diagnosed cancer types worldwide and one of the leading causes of cancer death among men.[1] Most prostate cancer patients are localized and about two-thirds of these patients will be alive 10 years later.[2] Therefore, the aim of any primary treatment besides maximizing survival is to preserve quality of life (QoL).[3–7] Since the adverse effects of primary treatments can negatively affect disease-specific QoL especially due to sexual function impairment,[8] it is important to delineate how these issues may be perceived by patients once the immediate effects of surgery have waned.

We recently reported some preoperative results on the QoL and erectile dysfunction (ED) in patients from a cohort study (AndroCan) involving men with localized prostate cancer about to undergo robotic radical prostatectomy (not published). The present paper reports the changes noted on QoL and ED during the first postoperative year and the 1 year after surgery and how they relate to preoperative clinical/demographic signs and symptoms, symptoms and biological parameters that are generally considered as pertaining to the metabolic syndrome, and levels of circulating sexual hormones.

PARTICIPANTS AND METHODS

Study population

AndroCan trial (ClinicalTrials.gov identifier: NCT02235142) is a prospective longitudinal cohort study conducted in 4 academic institutions, on newly diagnosed patients with localized prostate cancer referred for robot-assisted radical prostatectomy.[8,9] Demographic and clinical data were collected on the day before surgery. Circulating androgens were measured prior to surgery, in accordance with the Endocrine Society guidelines and assayed in a single central laboratory.[10]

Patients who received previous local treatment or systemic treatment that could interfere with hormonal status were excluded. The study protocol was approved by the locally competent institutional (CPP Ile-de-France VIII Ethic Committee, Boulogne-Billancourt, France; approval number 130207) review board and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from each patient.

Questionnaires

All patients had to complete, prior to surgery and one year later, the Aging Male's Symptom (AMS) scale and the 5-item abridged version

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of the International Index of Erectile Function (IIEF5) self-assessment questionnaire.[11,12] For the latter, the patient could indicate that he was willing to answer but unable to do so due to the absence of a partner or the lack of sexual life. Item scores were adjusted so that a score of 0 coded no symptom and a score of 4, the higher severity. The IIEF5 and AMS scores and subscores were only calculated if at least 80% of items had been properly completed.

Statistical analyses

To determine if a dichotomous variable was associated with differences on IIEF5 and AMS scores and subscores, comparisons were done on the scores for the 2 levels of each variable using bootstrap confidence intervals and permutation *t*-tests to avoid artifacts that might be linked to the nonnormal distribution of variables. Since the 1-year postoperative sample was about 3 times smaller than the preoperative one, in order to allow comparisons between factors in the twin articles, we retained a bilateral significance threshold of 0.05 but also outlined as trends values between 0.05 and 0.085. Spearman's nonparametric coefficient was used to test the correlations. Again, *P* values between 0.05 and 0.085 were outlined.

Robust multiple regression[13] was used to define optimal parsimonious models for the IIEF5 and AMS scores and score changes from pre- to 1-year postsurgery. "Parsimonious" in this context is defined by a model with less than 10 independent variables, all of them being individually significant. Huber's procedure with a tuning constant of 1.345 and fixed regression coefficients was used. The following categorical variables were initially entered into the model: ethnicity, history of cancer, biopsy staging (the tumor, node, and metastasis [TNM] classification), biopsy dominant grade (3 and less *vs* 4 and more), presence of diabetes mellitus, cardiovascular disorder, high blood pressure, hypogonadism (bioavailable testosterone [BT] <0.8 ng ml^{-1} or serum total testosterone [TT] <3 ng ml^{-1}), anatomopathological dominant grade for the removed prostate (III or IV), and node involvement. The following continuous variables were initially included in the model: age, height, weight, body mass index (BMI), percentage of fat mass, waist circumference, biopsy Gleason score, prostate-specific antigen (PSA), percentage of high-density lipoprotein (HDL) cholesterol, total cholesterol, triglycerides, blood sugar, number of symptoms that may pertain to a metabolic syndrome, number of concomitant medication, follicle-stimulating hormone (FSH), luteinizing hormone (LH), sex hormone-binding globulin (SHBG), BT, TT, dihydrotestosterone (DHT), dehydroepiandrosterone (DHEA), DHEA-sulfate, androstenediol (D5), androstenedione (D4), estrone (E1), estradiol (E2), weight of removed prostate, preoperative IIEF5 score, preoperative AMS somatic, psychological, sexual subscores, and preoperative AMS global score. Since this was a hypothesis-generating study, no correction (such as Bonferroni's) was applied to probability values; a bilateral probability lower than 0.05 was considered significant. All calculations were done using NCSS 2020 (NCSS LLC, Kaysville, UT, USA).

RESULTS

Population cohort study

A total of 750 patients (55.8% of all patients) answered the 1-year postoperative questionnaires. Out of them, only 378 (28.2% of all patients and 50.4% of responders) provided answers that could be used for calculations; 335 patients (25.0% of all cases, 32.9% of those answering preoperatively [n = 1019 patients]) provided suitable answers to the 4 questionnaires (2 preoperative and 2 in one year after surgery). Those who were responding at 1 year postsurgery, even if they indicated that they could not provide suitable scores for some items, were found, to be significantly younger, to have less concomitant medications, higher BT, and less ED and sexual problems preoperatively than those who elected not to answer (**Supplementary Table 1**). Among those who were responding to the self-assessment questionnaires 1 year postsurgery, those who were unable to provide suitable scores for erectile function due to the unavailability of sexual experiences were found, on their preoperative parameters to be significantly older, to have significantly lower BT, DHEA, and D5 and to have significantly more diabetes and erectile and sexual troubles (**Supplementary Table 2**).

Demographic and clinical characteristics of patients

The mean age of the sample was 64.6 (range: 41.5–79.1) years at the time they completed the 1-year postsurgery questionnaire. Among the 378 respondents, 93 (24.6%) had indicated that, one year before, prior to surgery, they suffered from diabetes mellitus and 76 patients (20.1%) have a cardiovascular disorder. Some characteristics of the global sample are displayed in **Supplementary Table 3**.

One year after prostatectomy, ED (*i.e.*, the global IIEF5 score) had increased (worsened) by 8.0 (95% CI: 7.3–8.7; $P < 0.0001$) out of a maximum of 20. The global AMS score has increased (worsened) by 2.8 (95% CI: 1.7–3.8; $P < 0.0001$). Among subscores, the somatic subscore did not change significantly whereas the psychological subscore significantly decreased (improved) by a mean of 0.6 (95% CI: 0.3–1.0; $P = 0.0003$) and the sexual subscore worsened significantly by a mean of 3.6 (95% CI: 3.1–4.0; $P < 0.0001$).

Baseline parameters associated with QoL 1 year postsurgery

Non-Caucasian had significantly higher scores for erectile dysfunction, and the sexual AMS subscore and the global score for aging symptoms. If they were free of concomitant treatment at baseline, their health-related QoL scores and subscores and IIEF5 score were significantly lower 1 year postsurgery. Not surprisingly, patients with more aggressive forms of cancer as ascertained by pathology fared significantly worse on QoL one year after surgery (**Supplementary Table 1**).

Correlations

ED scores 1 year postsurgery were positively correlated with (worsened by) preoperative age and percentage of fat mass and negatively with (improved by) total cholesterol, DHEA, and D5; aging male symptoms were poorly correlated with preoperative parameters (<10% of significant correlation; **Table 1**).

Multivariate models

Preoperative predictors from 303 patients allowed calculating a model that explained 14.4% of the 1-year postoperative score on IIEF5. Height and BMI were independently negative predictors of this score, while waist circumference and preoperative IIEF5 were positively correlated with it. The 3 preoperative subscores of the AMS were negatively correlated with the IIEF5 postoperative score, while the global AMS score was a positive correlate (**Table 2**).

Using predictors from 335 patients, a model was developed from preoperative predictors, which explained 41.2% of the variance of the AMS global score 1 year after surgery. BMI, E2, preoperative IIEF, AMS somatic subscore, AMS psychological subscore, and pathological aggressiveness were positive predictors of the score, while weight was an independent negative correlate (**Table 3**).

QoL evolution from pre-operation to 1 year postsurgery

Factors related to score evolution were studied. For the change of the IIEF5 score, there were a few parameters that showed significant differences: presence of diabetes mellitus (worsening by 8 points against worsening by 6 points), high blood pressure (worsening by 9

Table 1: Correlation of preoperative parameters and 1-year postoperative quality of life and erectile dysfunction scores

Parameter	*Patient (n)*	*IIEF5 (P)*	*AMS somatic (P)*	*AMS psychological (P)*	*AMS sexual (P)*	*AMS global (P)*
Age (year)	348	0.25 (<0.0001)	–0.03 (0.52)	–0.01 (0.86)	0.20 (0.0002)	0.04 (0.41)
Height (cm)	351	0.02 (0.67)	0.03 (0.63)	0.02 (0.66)	–0.03 (0.56)	0.01 (0.84)
Weight (kg)	351	0.09 (0.10)	0.02 (0.68)	0.04 (0.48)	0.01 (0.90)	0.02 (0.70)
Fat mass (%)	340	0.13 (0.018)	0.04 (0.48)	0.01 (0.91)	0.01 (0.79)	0.02 (0.65)
Gleason score (biopsy)	355	–0.02 (0.66)	0.04 (0.40)	0.04 (0.25)	0.06 (0.052)	0.04 (0.19)
PSA (ng ml^{-1})	352	0.06 (0.31)	–0.005 (0.92)	0.06 (0.30)	0.01 (0.80)	0.02 (0.73)
Total cholesterol (mg dl^{-1})	290	–0.14 (0.015)	–0.04 (0.45)	–0.01 (0.89)	–0.12 (0.040)	–0.08 (0.18)
FSH (mUI ml^{-1})	352	0.01 (0.90)	–0.04 (0.42)	–0.09 (0.08)	0.02 (0.73)	–0.06 (0.28)
LH (mUI ml^{-1})	351	–0.02 (0.69)	–0.08 (0.14)	–0.10 (0.06)	–0.03 (0.57)	–0.09 (0.11)
SHBG (µg ml^{-1})	351	0.03 (0.60)	–0.07 (0.16)	0.01 (0.86)	0.07 (0.18)	–0.02 (0.69)
DHT (ng ml^{-1})	350	–0.07 (0.18)	–0.06 (0.24)	–0.05 (0.39)	–0.04 (0.41)	–0.07 (0.21)
DHEA (µg dl^{-1})	351	–0.13 (0.014)	0.04 (0.50)	0.01 (0.82)	–0.11 (0.042)	–0.02 (0.71)
D5 (ng dl^{-1})	352	–0.16 (0.002)	0.01 (0.79)	–0.004 (0.93)	–0.09 (0.08)	–0.03 (0.55)
D4 (ng dl^{-1})	350	–0.06 (0.24)	0.03 (0.53)	0.03 (0.53)	–0.04 (0.45)	0.01 (0.80)
E1 (pg ml^{-1})	355	0.06 (0.29)	0.06 (0.30)	0.02 (0.64)	0.03 (0.55)	0.04 (0.40)
E2 (pg ml^{-1})	352	–0.02 (0.74)	–0.02 (0.78)	–0.004 (0.95)	0.03 (0.60)	–0.004 (0.94)
DHEA-sulfate (µg dl^{-1})	352	–0.08 (0.16)	–0.04 (0.46)	–0.05 (0.33)	–0.12 (0.019)	–0.08 (0.14)
Prostate volume (weight, g)	343	0.05 (0.33)	0.05 (0.38)	–0.04 (0.46)	0.004 (0.94)	0.01 (0.82)

IIEF5: the 5-item abridged version of the International Index of Erectile Function; AMS: Aging Male's Symptoms; PSA: prostate-specific antigen; FSH: follicle-stimulating hormone; LH: luteinizing hormone; SHBG: sex hormone-binding globulin; DHT: dihydrotestosterone; DHEA: dehydroepiandrosterone; D5: androstenediol; D4: androstenedione; E1: estrone; E2: estradiol

Table 2: Multiple regression model for the 5-item abridged version of the International Index of Erectile Function (baseline preoperative variables used as independent predictors)

Independent variable	*Regression coefficient*	*SE*	*Standardized coefficient*	*T-statistic to test H0: β(i)=0*	*Probability level*
Intercept	38.098	8.8629		4.30	0.0000
Height (cm)	–0.173	0.05168	–0.192	–3.34	0.0009
BMI (kg m^{-2})	–0.350	0.1681	–0.208	–2.08	0.038
Wais circumference (cm)	0.128	0.05728	0.229	2.23	0.027
Preoperative IIEF5 global score	0.296	0.08196	0.242	3.61	0.0004
Preoperative AMS somatic subscore	–8.216	3.5632	–6.660	–2.31	0.0218
Preoperative AMS psychological subscore	–8.240	3.5695	–4.873	–2.31	0.022
Preoperative AMS sexual subscore	–8.250	3.5722	–5.003	–2.31	0.0216
Preoperative AMS global score	8.290	3.5647	14.076	2.33	0.0207

Postoperative IIEF5 = 38.098 – 0.173 × height – 0.350 × BMI + 0.128 × waist circumference + 0.296 × preoperative IIEF5 score – 8.216 × preoperative AMS somatic subscore – 8.240 × preoperative AMS psychological subscore – 8.250 × preoperative AMS sexual subscore + 8.290 × preoperative AMS global score. IIEF5: the 5-item abridged version of the International Index of Erectile Function; AMS: Aging Male's Symptoms; BMI: body mass index; SE: standard error

Table 3: Multivariate model 1-year postoperative Aging Male's Symptoms global score (baseline preoperative variables used as independent predictors)

Independent variable	*Regression coefficient*	*SE*	*Standardized coefficient*	*T-statistic to test H0: β(i)=0*	*Probability level*
Intercept	3.153	3.4189	0.0000	0.922	0.36
Weight (kg)	–0.162	0.06632	–0.207	–2.45	0.015
BMI (kg m^{-2})	0.547	0.2437	0.191	2.25	0.025
E2 (pg ml^{-1})	0.130	0.05061	0.110	2.57	0.011
Preoperative IIEF5 score	0.212	0.09113	0.104	2.32	0.021
Preoperative AMS somatic subscore	0.681	0.1145	0.329	5.95	<0.0001
Preoperative AMS psychological subscore	0.873	0.1547	0.310	5.64	<0.0001
Prostate anatomopathological dominant grade 4	1.945	0.8744	0.095	2.22	0.027

Estimated equation: AMS score = 3.153–0.162 × weight + 0.547 × BMI + 0.130 × E2 + 0.212 × IIEF5 preoperative score + 0.681 × preoperative AMS somatic subscore + 0.873 × preoperative AMS psychological subscore + 1.944 × prostate anatomopathological dominant grade 4. IIEF5: the 5-item abridged version of the International Index of Erectile Function; AMS: Aging Male's Symptoms; BMI: body mass index; E2: estradiol; SE: standard error

points against 7 points), and TNM (worsening by 7 points for TNM1, and by 9 points for TNM2). For the change of AMS, lower waist circumference, lack of hypertension, 3-dominant grade for biopsy, normal BT and TT, hypogonadism, and lower cancer aggressiveness were significantly associated with a smaller deterioration of QoL (**Supplementary Table 4**).

Correlates of score changes were subsequently defined. Height, preoperative IIEF5 score, and preoperative sexual and global AM scores were positively and significantly correlated with erectile function deterioration. Height, preoperative IIEF, AMS somatic, psychological and sexual subscore, and AMS global scores were significantly and positively correlated with AMS deterioration. On the contrary, E2

levels were significantly negatively associated with AMS deterioration (**Table 4**).

Finally, multivariate models were done. The model for IIEF5 score changes only explains 14.0% of the difference variance whereas the model for AMS changes in global score explains 28.0% of the difference variance (**Table 5**). In the latter case, preoperative weight and preoperative global AMS score were independent correlates of an increased magnitude of the difference (QoL improvement), whereas preoperative BMI, and E2, preoperative IIEF5, AMS somatic and psychological subscores, and cancer aggressiveness were independent correlates of QoL worsening.

Table 4: Correlates of changes in erectile dysfunction and Aging Male's Symptoms scores from baseline, preoperative, to 1 year postsurgery

Parameter	*Patient (n)*	*Pre-/post-IIEF5 (P)*	*Pre-/post-AMS somatic (P)*	*Pre-/post-AMS psychological (P)*	*Pre-/post-AMS sexual (P)*	*Pre/post-AMS global (P)*
Age (year)	330	0.07 (0.18)	–0.05 (0.33)	–0.03 (0.61)	0.06 (0.24)	0.004 (0.94)
Height (cm)	333	0.13 (0.016)	0.06 (0.24)	0.18 (0.001)	0.10 (0.06)	0.13 (0.014)
Weight (kg)	333	0.09 (0.10)	–0.03 (0.51)	0.09 (0.12)	0.07 (0.21)	0.06 (0.31)
Fat mass (%)	324	0.08 (0.13)	–0.07 (0.23)	–0.07 (0.19)	0.06 (0.29)	–0.02 (0.66)
Gleason score (biopsy)	332	–0.05 (0.34)	–0.06 (.29)	–0.05 (0.34)	–0.06 (0.27)	–0.07 (0.20)
PSA (ng ml^{-1})	328	–0.04 (0.41)	–0.01 (0.80)	0.01 (0.80)	–0.05 (0.40)	–0.01 (0.81)
Total cholesterol (mg dl^{-1})	279	–0.04 (0.54)	0.001 (0.99)	0.002 (0.97)	–0.05 (0.38)	–0.03 (0.61)
FSH (mUI ml^{-1})	334	–0.02 (0.74)	–0.003 (0.96)	–0.05 (0.36)	0.02 (0.70)	–0.004 (0.94)
LH (mUI ml^{-1})	333	–0.04 (0.46)	–0.08 (0.12)	–0.08 (0.13)	–0.04 (0.45)	–0.07 (0.15)
SHBG (µg ml^{-1})	333	0.04 (0.51)	–0.07 (0.18)	0.03 (0.52)	0.04 (0.42)	0.002 (0.98)
DHT (ng ml^{-1})	332	–0.01 (0.87)	–0.04 (0.41)	–0.04 (0.45)	–0.07 (0.20)	–0.06 (0.27)
DHEA (µg dl^{-1})	333	–0.08 (0.17)	–0.03 (0.54)	0.01 (0.82)	–0.08 (0.17)	–0.05 (0.38)
D5 (ng dl^{-1})	334	–0.04 (0.43)	–0.08 (0.14)	–0.05 (0.37)	–0.09 (0.12)	–0.08 (0.15)
D4 (ng dl^{-1})	332	–0.09 (0.11)	–0.02 (0.76)	0.05 (0.35)	–0.09 (0.12)	–0.03 (0.58)
E1 (pg ml^{-1})	332	–0.01 (0.79)	–0.04 (0.44)	0.08 (0.15)	–0.004 (0.95)	0.01 (0.84)
E2 (pg ml^{-1})	334	–0.03 (0.63)	–0.14 (0.013)	0.02 (0.73)	–0.10 (0.06)	–0.09 (0.09)
DHEA-sulfate (µg dl^{-1})	334	–0.03 (0.56)	–0.08 (0.16)	–0.02 (0.66)	–0.05 (0.32)	–0.08 (.0.15)
Prostate volume (weight, g)	325	–0.01 (0.80)	–0.01 (0.86)	0.01 (0.83)	0.02 (0.70)	0.01 (0.87)
IIEF5 preoperative score	334	0.40 (<0.0001)	0.08 (0.16)	0.06 (0.31)	0.25 (<0.0001)	0.17 (0.001)
AMS preoperative somatic subscore	334	0.07 (0.19)	0.45 (<0.0001)	0.28 (<0.0001)	0.17 (0.002)	0.38 (<0.0001)
AMS preoperative psychological subscore	334	0.04 (0.45)	0.20 (0.0002)	0.52 (<0.0001)	0.16 (0.003)	0.32 (<0.0001)
AMS preoperative sexual subscore	334	0.21 (0.0001)	0.25 (<0.0001)	0.21 (0.0001)	0.47 (<0.0001)	0.40 (<0.0001)
AMS preoperative global score	334	0.13 (0.019)	0.39 (<0.0001)	0.40 (<0.0001)	0.30 (<0.0001)	0.45 (<0.0001)

IIEF5: the 5-item abridged version of the International Index of Erectile Function; AMS: Aging Male's Symptoms; PSA: prostate-specific antigen; FSH: follicle-stimulating hormone; LH: luteinizing hormone; SHBG: sex hormone-binding globulin; DHT: dihydrotestosterone; DHEA: dehydroepiandrosterone; D5: androstenediol; D4: androstenedione; E1: estrone; E2: estradiol

Table 5: Multiple regression for the change in the 5-item abridged version of the International Index of Erectile Function scores and in Aging Male's Symptoms global score (from preoperation to 1 year postoperation)

Scores	*Independent variable*	*Regression coefficient*	*SE*	*Standardized coefficient*	*T-statistic to test H0: β(i)=0*	*Probability level*
IIEF5	Intercept	–34.039	8.1896	0.0000	–4.16	0.0000
	Height (cm)	0.130	0.04663	0.133	2.79	0.006
	Number of concomitant medications	–0.543	0.1947	–0.159	–2.79	0.006
	Preoperative IIEF5 score	0.720	0.08003	0.533	8.99	<0.0001
	Preoperative AMS somatic subscore	7.960	3.5270	5.851	2.26	0.025
	Preoperative AMS psychological subscore	7.993	3.5331	4.347	2.26	0.024
	Preoperative AMS sexual subscore	7.901	3.5333	4.407	2.24	0.026
	Preoperative AMS global score	–7.997	3.5278	–12.445	–2.27	0.024
	High blood pressure: Yes	2.152	0.7175	0.166	3.00	0.003
AMS global	Intercept	–3.745	3.4652	0.000	–1.08	0.28
	Weight (kg)	0.163	0.06721	0.231	2.43	0.016
	BMI (kg m^{-2})	–0.527	0.2470	–0.203	–2.13	0.034
	E2 (pg ml^{-1})	–0.130	0.05078	–0.123	–2.56	0.011
	Preoperative IIEF5 score	–0.212	0.1081	–0.116	–1.97	0.050
	Preoperative AMS somatic subscore	–0.729	0.2333	–0.390	–3.12	0.002
	Preoperative AMS psychological subscores	–0.852	0.2682	–0.337	–3.18	0.002
	Preoperative AMS global score	1.011	0.1710	1.141	5.91	<0.0001
	Prostate anatomopathology: 4-dominant	–1.864	0.8811	–0.101	–2.12	0.035

IIEF5 score (preoperative-postoperative difference) = –34.039 + 0.130 × height (cm) – 0.543 × number of concomitant medications + 0.720 × IIEF5 preoperative score + 7.960 × AMS preoperative somatic subscore + 7.993 × AMS preoperative psychological subscore + 7.901 × AMS preoperative sexual subscore –7.997 × AMS preoperative global score + 2.152 × presence of high blood pressure. AMS global score (difference between preoperative and 1 year postoperative) = –3.745 + 0.163 × weight (kg) – 0.527 × BMI (kg m^{-2}) – 0.130 × E2 – 0.212 × IIEF5 preoperative score –0.729 × AMS preoperative somatic subscore –0.852 × AMS preoperative psychological subscore + 1.011 × AMS preoperative global score –1.864 × 4 – dominant for prostate anatomopathology. IIEF5: the 5-item abridged version of the International Index of Erectile Function; AMS: Aging Male's Symptoms; BMI: body mass index; E2: estradiol; SE: standard error

DISCUSSION

To our knowledge, we report for the first time an evaluation of aging male symptoms and circulating sexual hormones together with QoL and sexual function, 1 year after surgery in a cohort of newly diagnosed prostate cancer patients treated by radical prostatectomy. There was a significant alteration of sexual outcomes 1 year after surgery, and this effect is one of the main reasons for the alteration of their QoL. Recent analyses from a large prospective cohort and from the ProtecT trial identified similar patterns of adverse effects in patients with clinically localized prostate cancer following radical prostatectomy.[4,14] In the study reported by Chen and colleagues,[4] radical prostatectomy (n = 469 mostly robot assisted) was associated with sexual dysfunction and urinary incontinence over two years. In our study, we evaluated QoL and ED, and outcomes with their relation to baseline levels of circulating sexual hormones, and of clinical and biological parameters. Baseline testosterone levels and metabolic syndrome parameters were independent factors associated with impaired QoL and sexual functioning 1 year after surgery in men aged 40–80 years, found to have a localized prostate cancer requiring robot-assisted surgery. Correlations of clinical factors and preoperative testosterone and its precursors and metabolites could also be ascertained.

There was a clear worsening of ED (loss of a mean 1.5 points per item) and QoL (loss of about one-sixth of a level per item for each AMS item). Some preoperative parameters are associated with the 1-year outcome on ED and QoL, namely concomitant medications, a surrogate marker of good/poor health status, and the results of anatomopathological examination of the resected prostate. With regard to sexual hormones, FSH, LH, DHEA, D5, and DHEA-sulfate are significantly correlated with IIEF5, AMS psychological subscore, or AMS global score. E2 also appears as a significant independent factor of IIEF5 one year after surgery. On the contrary, AMS somatic subscore does not seem to be significantly associated with any androgen level.

Low levels of bioavailable and total testosterone were found to be significantly associated with a higher deterioration of the AMS sexual subscore; preoperative ED and moreover QoL preoperative values were significantly and positively associated with the changes in IIEF5 and AMS scores and subscores (the higher the initial levels, the larger the changes from pre- to postoperative for the relevant score). E2 is the only androgen that is significantly correlated with changes in QoL subscores – the lower its preoperative levels, the larger the changes from pre- to postoperative QoL.

In addition, lower levels of BT are associated with a lower AMS somatic subscore, whereas such a relation is lacking for TT. Baseline parameters that are generally related to a metabolic syndrome are associated with a few significant differences on QoL and/or ED.

Reduced testosterone levels have been increasingly recognized to be a risk factor for high-grade prostate cancer.[14] In the AndroCan trial, we observed that baseline testosterone deficiency, *i.e*., low total testosterone and/or low bioavailable testosterone, was independently associated with higher prostate cancer aggressiveness.[8]

The physiological mechanisms underlying the detrimental effect of testosterone deficiency in the early stages of prostate cancer are still debated. Population-based studies have shown that obesity, diabetes mellitus, and metabolic syndrome could be linked to aggressive prostate cancer,[15] the risk of biochemical recurrence, and prostate cancer mortality.[16,17] Interestingly, recently reported data showed that testosterone therapy following radical prostatectomy reduced biochemical recurrence by about 50%.[18]

It has also been recently suggested that prostate cancer risk might be reduced by testosterone therapy owing to improvements in metabolic syndrome components, such as elevated blood sugar levels or elevated insulin levels.[19,20] The complex relationship of testosterone and prostate cancer allows speculations on the possible positive effect (notably on sexual outcomes) of supplementation of testosterone in patients with low baseline testosterone even if this approach challenges the current paradigms.

Previously, questionnaire studies evaluating QoL and sexual function have been reported in advanced and metastatic cancer patients.[21,22] Even in these patients, the response rate to mailings confirms that QoL and sexual function in particular continue to be major issues for patients with an active disease and cancer survivors. In our study, we noted a slight but significant reduction (improvement) of the psychological subscore (irritability, nervousness, and anxiety) of the AMS (0.58, 95% CI: 0.25–0.91; P = 0.0003) 1 year after radical prostatectomy. This result is in line with the improved emotional and cognitive functioning 12 months after radical prostatectomy reported in a prospective longitudinal cohort (n = 209) of prostate cancer patients treated with radical prostatectomy,[23] possibly consequent to patients' relief as the expected that the malignant tumor had been removed. One should be aware that this improvement was not sufficient to compensate for the sexual dysfunction as shown by the worsening of the global AMS score.[4] Physicians may use these data to better individualize counseling when baseline risk factors are not decisive.

Unfortunately, our data do not provide a straightforward and definite answer on the possible relationship between cancer aggressiveness and QoL. The cancer aggressiveness, dominant grade 4 on the anatomopathological examination of the resected prostate, independently increases (worsens) the AMS global score. Although statistically significant, this effect is moderate with increases of 2 points of the 1-year AMS global score, *i.e*., about 10%; this impairment of QoL may be a direct effect of cancer or a consequence of more aggressive cancer treatments being administered to such patients.

One limitation of our study is not to connect our results on QoL and ED to current levels of androgens. However, this would have severely hampered our initial recruitment as most patients would not have agreed to come back as inpatients, even for one night, one year after surgery, just to have blood collected. In addition, our own pilot study and the 3 published ones do show that confounding factors are so important in nomad assessment that the latter are extremely unlikely to clarify the results based on the recommended assessment done preoperatively.

Another severe limitation is the large number of patients that did not answer the questionnaires after a 1-year follow-up. In fact, the IIEF5 score is actually designed as a screening tool and thus uses quite direct questions about erectile function. It was retained because of its brevity to limit the number of intimate questions. Unfortunately, the wording of the items is probably too direct and led about half of the responders to state they could not provide a suitable answer. Thus, our final sample was reduced to about one-third of our initial sample. If such a study was to be reproduced, one should consider amending the questionnaire in order to assess ED in ways that would not deter participants with limited or no recent sexual encounters. The loss of such a large proportion of patients makes it difficult to establish if some parameters are truly not associated with QoL or ED or whether the absence of a significant association is related to the vastly reduced power of the experiment. Nevertheless, the size of our analyzable patients' sample (that is 350 at 1 year) gives us some protection in terms of power. Last but not least, no standard procedure for nerve sparing surgery was stated in the study protocol as this type of surgery is highly operator dependent. However, the recommendation to use

such a procedure was reiterated at each monitoring visit. Nevertheless, it cannot be assumed that such a procedure was used and was successful in all study participants. While we have undertaken to produce videos to standardize such an approach in a forthcoming study, many surgeons were highly reluctance to switch to an unfamiliar procedure and this issue is likely to be a recurrent problem in future studies.

Regarding to methodology, since the study is ongoing, we are not yet able to determine if one year is adequate to observe period for the whole effects on QoL. Prior trials showed that there may be little change in sexual outcomes after 1 year.[4,5,24] Finally, concomitant medications during the 1-year postoperative period may have affected patients' QoL and ED independently of radical prostatectomy. Limited data are available on this topic.

CONCLUSIONS

In this cohort of men with localized prostate cancer, general QoL and sexual symptoms were, as expected, significantly affected by some demographic/clinical characteristics. TT and BT had different effects on our outcome parameters. In addition, testosterone precursors and metabolites also show differential effects on the same outcome parameters. These findings may be used to inform patients with newly diagnosed prostate cancer. Further study of the influence of concomitant medications on QoL/ED would be desirable.

AUTHOR CONTRIBUTIONS

YN drafted the manuscript and helped with data acquisition. JFD drafted the manuscript and performed statistics. JPR helped with establishing the study design and reviewing the manuscript. M Rouanne drafted the manuscript and helped with data acquisition. MS, M Roupret, SD, MG, XC, and TL helped with data acquisition and reviewing the manuscript. HB established the study design and helped with drafting the manuscript. All authors read and approved the final manuscript.

COMPETING INTERESTS

All authors declared no competing interests.

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Supplementary Information is linked to the online version of the paper on the *Asian Journal of Andrology* website.

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Supplementary Table 1: Significant differences between patients providing suitable scores at 1 year and patients not provide them

Parameter	*Group without proper answers*			*Group with suitable answers*			*Difference between groups*		*P*[n]
	Sample	*Mean*	*95% CI*	*Sample*	*Mean*	*95% CI*	*Mean of the difference*	*95% CI*	
Age (year)	959	65.5	64.1–64.8	373	62.9	62.3–63.5	1.6	0.9–2.3	0.0002
Total cholesterol	712	193	189–196	305	200	194–205	–7.0	–13.3––0.6	0.026
Triglycerides	655	1.47	1.42–1.53	281	1.37	1.29–1.44	0.11	0.02–0.20	0.028
Number of concomitant medications	966	1.94	1.81–2.07	377	1.65	1.46–1.84	0.30	0.06–0.52	0.011
Bioavailable testosterone	964	1.26	1.23–1.29	376	1.33	1.28–1.37	–0.07	–0.12–0.01	0.015
E1	964	33.9	33.0–34.7	375	32.3	31.1–33.5	1.5	0.01–3.1	0.043
Preoperative IIEF5	721	6.6	6.3–7.0	352	5.3	4.8–5.8	1.3	0.7–2.0	0.0002
Preoperative AMS sexual subscore	826	5.5	5.3–5.8	355	4.6	4.3–5.0	0.9	0.4–1.3	0.0004
Ethnicity (%)	926	12.5	10.5–14.6	364	6.9	4.4–9.3	5.6	2.3–9.1	0.002
Node extension (%)	471	8.1	5.5–10.4	190	3.6	1.1–6.3	4.4	0.6–8.0	0.034

Bootstrap mean and 95% CI is obtained with 3000 replications. [n]*P* for differences by permutation *t*-test with 5000 replications. IIEF5: the 5-item abridged version of the International Index of Erectile Function; AMS: Aging Male's Symptoms; E1: estrone; CI: confidence interval

Supplementary Table 2: Significant differences among responders at 1 year between patients providing suitable answers and patients indicating they could not provide appropriate answers

Parameter	*Group unable to provide appropriate answers*			*Group with suitable answers*			*Difference between groups*		*P*[n]
	Sample	*Mean*	*95% CI*	*Sample*	*Mean*	*95% CI*	*Mean of the difference*	*95% CI*	
Percentage of fat mass	373	26.3	25.6–27.0	364	25.2	24.5–25.8	1.1	0.2–2.1	0.021
Age (year)	389	65.5	64.9–66.0	373	62.9	62.3–63.5	2.6	1.8–3.4	0.0002
Triglycerides	270	1.56	1.45–1.67	281	1.37	1.29–1.45	0.19	0.06–0.32	0.005
Number of concomitant medications	392	2.0	1.9–2.2	377	1.6	1.5–1.8	0.4	0.1–0.6	0.011
Bioavailable testosterone (μg ml^{-1})	392	1.21	1.7–1.25	376	1.33	1.28–1.37	–0.11	–0.18––0.05	0.001
DHEA	390	2.45	2.29–2.61	376	2.71	2.54–2.88	–0.26	–0.50––0.03	0.030
D5	391	0.81	0.77–0.84	377	0.89	0.84–0.93	–0.08	–0.13––0.03	0.007
Prostate volume (g)	386	53	51–55	368	49	47–51	4.2	1.4–6.9	0.004
IIEF5 preoperative score	301	7.5	6.9–8.1	352	5.3	4.8–5.8	2.2	1.4–3.0	0.0002
AMS preoperative sexual subscore	372	5.9	5.5–6.3	355	4.6	4.3–5.0	1.3	0.8–1.8	0.0002
Diabetes mellitus	338	12.4	9.3–16.4	345	7.5	4.8–10.2	4.9	9.4–0.4	0.024

Bootstrap mean and 95% CI is obtained with 3000 replications. [n]*P* for differences by permutation *t*-test with 5000 replications. DHEA: dehydroepiandrosterone; D5: androstenediol; IIEF5: the 5-item abridged version of the International Index of Erectile Function; AMS: Aging Male's Symptoms; CI: confidence interval

Supplementary Table 3: Preoperative factors for the 1-year postoperative quality of life and erectile dysfunction scores

Parameters	*Levels: Group 1 (n) Group 2 (n)*	*Variable*	*Group 1: mean (95% CI) versus Group 2: mean (95% CI)§*	*Difference: Group 1– Group 2, mean (95% CI)§*	*P**
Ethnicity	G1: Caucasian (339) (93.1%) G2: Non-Caucasian (25)	IIEF5	13.3 (12.7–14.0) versus 15.8 (14.4–17.3)	–2.5 (–4.1–0.8)	0.009
		AMS_{som}	6.2 (5.6–6.7) versus 7.3 (5.2–9.2)	–1.0 (–3.1–1.0)	0.29
		AMS_{psy}	2.9 (2.6–3.3) versus 3.8 (2.1–5.4)	–0.9 (–2.5–0.9)	0.22
		AMS_{sex}	8.2 (7.8–8.6) versus 10.5 (9.5–11.6)	–2.3 (–3.4–-1.2)	0.001
		AMS_{glo}	17.3 (16.2–18.4) versus 21.6 (17.6–25.3)	–4.4 (–8.2–-0.1)	0.047
Obesity (kg m^{-2})	G1: BMI≤30 (309) (82.4%) G2: BMI≥30 (66)	IIEF5	13.5 (12.8–14.1) versus 13.7 (12.4–14.9)	–0.2 (–1.6–1.2)	0.77
		AMS_{som}	6.1 (5.6–6.6) versus 6.7 (5.4–8.0)	–0.6 (–2.0–0.8)	0.36
		AMS_{psy}	2.9 (2.5–3.3) versus 3.3 (2.5–4.2)	–0.4 (–1.4–0.5)	0.37
		AMS_{sex}	8.4 (8.0–8.8) versus 8.1 (7.1–9.1)	0.3 (–0.7–1.4)	0.53
		AMS_{glo}	17.4 (16.3–18.5) versus 18.1 (15.2–20.8)	–0.7 (–3.6–2.4)	0.60
Waist circumference (cm)	G1: <102 (207) (62.2%) G2: ≥102 (126)	IIEF5	13.0 (12.2–13.8) versus 14.5 (13.7–15.4)	–1.5 (–2.7–-0.4)	0.012
		AMS_{som}	5.7 (5.1–6.3) versus 6.7 (5.8–7.6)	–1.0 (–2.1–0.1)	0.06
		AMS_{psy}	2.8 (2.3–5.2) versus 3.1 (2.4–3.7)	–0.3 (–1.0–0.4)	0.41
		AMS_{sex}	8.4 (7.9–8.9) versus 8.2 (7.5–8.9)	0.2 (–0.7–1.0)	0.64
		AMS_{glo}	16.8 (15.6–18.0) versus 17.9 (16.0–20.0)	–1.1 (–3.5–1.1)	0.33
Metabolic syndrome	G1: No (310) (82.4%) G2: Yes (66)	IIEF5	13.4 (12.7–14.0) versus 14.1 (12.8–15.4)	–0.7 (–2.2–0.7)	0.38
		AMS_{som}	6.0 (5.5–6.6) versus 7.1 (5.9–8.3)	–1.0 (–2.4–0.3)	0.13
		AMS_{psy}	2.9 (2.5–3.3) versus 3.3 (2.4–4.1)	–0.4 (–1.3–0.6)	0.39
		AMS_{sex}	8.5 (8.1–8.9) versus 7.6 (6.6–8.5)	1.0 (–0.1–2.0)	0.07
		AMS_{glo}	17.4 (16.3–18.6) versus 17.9 (15.2–20.5)	–0.4 (–3.4–2.5)	0.76
Diabetes mellitus (reported by patient)	G1: No (345) (92.5%) G2: Yes (28)	IIEF5	13.5 (12.9–14.1) versus 13.5 (11.4–15.6)	0.1 (–2.1–2.2)	0.92
		AMS_{som}	6.1 (5.6–6.6) versus 7.9 (6.2–9.5)	–1.7 (–3.5–0.1)	0.07
		AMS_{psy}	2.9 (2.6–3.3) versus 3.7 (2.1–5.1)	–0.7 (–2.2–0.9)	0.29
		AMS_{sex}	8.4 (8.0–8.8) versus 8.1 (6.8–9.5)	0.3 (–1.1–1.6)	0.73
		AMS_{glo}	17.4 (16.3–18.6) versus 19.6 (15.7–23.5)	–2.2 (–6.2–1.9)	0.30
Cardiovascular disorder (reported by patient)	G1: No (344) (92.0%) G2: Yes (30)	IIEF5	13.4 (12.8–14.0) versus 14.7 (13.0–16.5)	–1.3 (–3.1–0.5)	0.25
		AMS_{som}	6.1 (5.6–6.7) versus 7.4 (5.4–9.4)	–1.3 (–3.3–0.8)	0.16
		AMS_{psy}	2.9 (2.5–3.3) versus 3.6 (2.3–4.8)	–0.6 (–1.9–0.7)	0.34
		AMS_{sex}	8.3 (7.9–8.7) versus 9.4 (8.1–10.8)	–1.1 (–2.6–0.2)	0.11
		AMS_{glo}	17.3 (16.3–18.4) versus 20.4 (16.4–24.2)	–3.1 (–7.0–1.0)	0.12
High blood pressure (reported by patient)	G1: No (243) (65.1%) G2: Yes (130)	IIEF5	13.6 (12.9–14.3) versus 13.4 (12.5–14.4)	0.2 (–1.0–1.4)	0.70
		AMS_{som}	5.9 (5.3–6.5) versus 6.9 (6.0–7.8)	–1.0 (–2.1–0.1)	0.06
		AMS_{psy}	2.9 (2.4–3.3) versus 3.2 (2.6–3.8)	–0.4 (–1.1–0.4)	0.33
		AMS_{sex}	8.3 (7.8–8.7) versus 8.5 (7.8–9.2)	–0.2 (–1.1–0.6)	0.56
		AMS_{glo}	17.0 (15.7–18.2) versus 18.6 (16.7–20.5)	–1.6 (–3.8–0.6)	0.17
HDL cholesterol	G1: ≥40 (237) G2: <40 (66)	IIEF5	13.3 (12.5—14.1) versus 13.3 (11.9–14.7)	–0.02 (–1.6–1.5)	0.99
		AMS_{som}	6.0 (5.4–6.7) versus 6.9 (5.6–8.1)	–0.8 (–2.2–0.6)	0.24
		AMS_{psy}	3.0 (2.6–3.5) versus 2.9 (2.1–3.7)	0.1 (–0.8–1.0)	0.87
		AMS_{sex}	8.5 (8.0–8.9) versus 7.6 (6.6–8.5)	0.9 (–0.2–2.0)	0.10
		AMS_{glo}	17.5 (16.2–18.8) versus 17.4 (14.8–19.8)	0.1 (–2.7–2.9)	0.94
Triglycerides	G1: <1.5 (194) G2: ≥1.5 (87)	IIEF5	13.3 (12.5–14.2) versus 12.9 (11.7–14.1)	0.4 (–1.1–1.9)	0.62
		AMS_{som}	6.2 (5.5–6.9) versus 5.9 (4.8–6.9)	0.4 (–0.9–1.6)	0.58
		AMS_{psy}	2.8 (2.4–3.3) versus 3.3 (2.4–4.1)	–0.4 (–1.4–0.5)	0.32
		AMS_{sex}	8.4 (7.8–8.9) versus 7.8 (7.0–8.6)	0.5 (–0.4–1.5)	0.27
		AMS_{glo}	17.4 (15.9–18.9) versus 16.9 (14.6–19.1)	0.5 (–2.2–3.1)	0.74
Blood sugar (g l^{-1})	G1: ≤1 (198) G2: >1 (102)	IIEF5	13.2 (12.3–13.9) versus 13.8 (12.7–14.9)	–0.6 (–2.1–0.7)	0.37
		AMS_{som}	6.1 (5.3–6.8) versus 6.6 (5.7–7.6)	–0.5 (–1.7–0.7)	0.40
		AMS_{psy}	2.8 (2.4–3.3) versus 3.3 (2.6–4.0)	–0.5 (–1.3–0.3)	0.26
		AMS_{sex}	8.4 (7.9–8.9) versus 8.0 (7.3–8.8)	0.4 (–0.6–1.3)	0.43
		AMS_{glo}	17.3 (15.8–18.8) versus 17.9 (15.9–19.8)	–0.6 (–3.1–1.8)	0.62
Concomitant medication	G1: At least one (230) G2: None (147)	IIEF5	14.2 (13.4–14.9) versus 12.4 (11.5–13.4)	1.7 (0.5–3.0)	0.006
		AMS_{som}	6.9 (6.2–7.6) versus 5.1 (4.5–5.7)	1.8 (0.9–2.7)	0.001
		AMS_{psy}	3.3 (2.8–3.8) versus 2.4 (2.0–2.9)	0.9 (0.2–1.5)	0.012
		AMS_{sex}	9.0 (8.4–9.5) versus 7.4 (6.8–7.9)	1.6 (8–2.3)	0.0002
		AMS_{glo}	19.1 (17.7–20.6) versus 14.9 (13.6–16.2)	4.2 (2.3–6.2)	0.0002

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Supplementary Table 3: Contd...

Parameters	*Levels: Group 1 (n) Group 2 (n)*	*Variable*	*Group 1: mean (95% CI) versus Group 2: mean (95% CI)*[§]	*Difference: Group 1– Group 2, mean (95% CI)*[§]	*P*[†]
TNM (biopsy)	G1: T1 (174) G2: T2 (162)	IIEF5	13.1 (12.3–14.0) versus 13.8 (13.0–14.6)	–0.7 (–1.9–0.6)	0.29
		AMS_{som}	6.3 (5.6–7.1) versus 6.4 (5.6–7.2)	–0.1 (–1.1–1.0)	0.89
		AMS_{psy}	3.0 (2.5–3.5) versus 3.1 (2.5–3.5)	–0.02 (–0.76–0.70)	0.97
		AMS_{sex}	8.6 (8.1–9.2) versus 8.3 (7.7–8.9)	0.3 (–0.5–1.1)	0.42
		AMS_{glo}	18.0 (16.5–19.5) versus 17.7 (16.0–19.3)	0.2 (–1.9–2.5)	0.82
Dominant grade for biopsy	G1: 3– (298) G2: 4+ (76)	IIEF5	13.4 (12.8–14.1) versus 13.9 (12.6–15.2)	–0.5 (–2.0–1.0)	0.53
		AMS_{som}	6.1 (5.5–6.6) versus 6.9 (5.7–8.1)	–0.9 (–2.2–0.4)	0.18
		AMS_{psy}	2.9 (2.5–3.3) versus 3.4 (2.6–4.3)	–0.6 (–1.5–0.4)	0.22
		AMS_{sex}	8.2 (7.8–8.6) versus 8.9 (8.0–9.9)	–0.7 (–1.8–0.3)	0.15
		AMS_{glo}	17.1 (16.0–18.3) versus 19.2 (16.6–21.8)	–2.1 (–4.9–0.7)	0.11
Bioavailable testosterone[#] ($\mu g\ ml^{-1}$)	G1: ≥0.8 (339) G2: <0.8 (37)	IIEF5	13.6 (13.0–14.2) versus 12.6 (10.7–14.6)	1.0 (–1.1–3.0)	0.34
		AMS_{som}	6.3 (5.8–6.9) versus 5.1 (4.0–6.3)	1.2 (–0.004–2.5)	0.08
		AMS_{psy}	3.0 (2.6–3.4) versus 2.6 (1.5–3.5)	0.4 (–0.6–1.6)	0.48
		AMS_{sex}	8.4 (8.0–8.8) versus 7.5 (6.4–8.8)	0.9 (–0.4–2.1)	0.19
		AMS_{glo}	17.7 (16.6–18.9) versus 15.2 (12.6–17.7)	2.5 (–0.2–5.4)	0.16
Total testosterone ($\mu g\ ml^{-1}$)	G1: ≥3.0 (339) G2: <3.0 (38)	IIEF5	13.5 (12.9–14.1) versus 13.1 (11.4–15.0)	0.4 (–1.6–2.1)	0.74
		AMS_{som}	6.2 (5.7–6.8) versus 5.8 (4.4–7.3)	0.4 (–1.1–2.0)	0.63
		AMS_{psy}	3.0 (2.6–3.3) versus 3.1 (1.9–4.3)	–0.2 (–1.4–1.1)	0.77
		AMS_{sex}	8.4 (8.0–8.8) versus 7.7 (6.3–9.0)	0.7 (–0.7–2.1)	0.29
		AMS_{glo}	17.6 (16.5–18.7) versus 16.7 (13.1–19.9)	0.9 (–2.5–4.6)	0.60
Hypogonadism (bioavailable testosterone <0.8 $\mu g\ ml^{-1}$ OR total testosterone <3.0 $\mu g\ ml^{-1}$)	G1: No (313) G2: Yes (63)	IIEF5	13.6 (13.0–14.4) versus 12.9 (11.3–14.4)	0.8 (–0.9–2.4)	0.33
		AMS_{som}	6.4 (5.8–6.9) versus 5.4 (4.3–6.4)	1.0 (–0.2–2.2)	0.15
		AMS_{psy}	3.0 (2.6–3.3) versus 2.9 (2.0–3.8)	0.04 (–0.93–1.07)	0.93
		AMS_{sex}	8.5 (8.0–8.9) versus 7.7 (6.7–8.7)	0.8 (–0.3–1.8)	0.14
		AMS_{glo}	17.8 (16.6–18.9) versus 16.0 (13.6–18.3)	1.8 (–0.9–4.5)	0.20
Grade prostate anatomopathology	G1: Grade 3 dominant (267) (70.8%) G2: Grade 4 dominant (110)	IIEF5	13.3 (12.6–14.0) versus 13.9 (12.8–15.0)	–0.6 (–2.0–0.7)	0.38
		AMS_{som}	5.8 (5.2–6.3) versus 7.3 (6.1–8.3)	–1.5 (–2.6––0.3)	0.015
		AMS_{psy}	2.8 (2.4–3.2) versus 3.5 (2.8–4.1)	–0.7 (–1.5–0.1)	0.08
		AMS_{sex}	8.1 (7.6–8.5) versus 8.9 (8.2–9.7)	–0.9 (–1.7–0.1)	0.049
		AMS_{glo}	16.6 (15.4–17.8) versus 19.7 (17.4–21.8)	–3.1 (–5.4––0.5)	0.020
Adenopathy detected at surgery	G1: No (183) (96.3%) G2: Yes (7)	IIEF5	13.1 (12.2–14.0) versus 15.7 (12.5–19.7)	–2.7 (–6.7–0.7)	0.27
		AMS_{som}	6.3 (5.5–7.0) versus 9.9 (6.8–13.5)	–3.6 (–7.1––0.4)	0.08
		AMS_{psy}	3.1 (2.6–3.6) versus 4.7 (2.1–7.3)	–1.6 (–4.3–1.0)	0.26
		AMS_{sex}	8.5 (8.0–9.1) versus 9.3 (6.9–12.0)	–0.8 (–3.6–1.8)	0.59
		AMS_{glo}	17.8 (16.2–19.4) versus 23.9 (17.4–31.3)	–6.1 (–13.5–0.5)	0.15

[§]Boostrap (3000 replications); [†]Permutation *t*-test accounting for equal/unequal group variances (checked) (5000 permutations); [#]Also applies to free testosterone which is colinear as it is calculated through a mathematical function of bioavailable testosterone; – used as a separator. G1: Group 1; G2: Group 2; BMI: body mass index; IIEF: International Index of Erectile Function; AMS: Aging Male's Symptoms; CI: confidence interval; TNM: tumor, node, and metastasis; HDL: high-density lipoprotein

Supplementary Table 4: Baseline variables and their association to changes in quality of life and erectile dysfunction scores

Parameters	*Levels: Group 1 (n) Group 2 (n) 2*	*Variable*	*Group 1: mean (95% CI) versus Group 2: mean (95% CI)[§]*	*Difference: Group 1– Group 2, mean (95% CI)[§]*	*P[¤]*
Ethnicity	Caucasian (302) Non-Caucasian (20) (6.2%)	IIEF5	–8.0 (–8.7––7.3) versus–9.3 (–11.5––7.0)	1.2 (–1.1–3.7)	0.40
		AMS_{som}	0.1 (–0.4–0.7) versus 0.04 (–1.80–2.05)	–0.1 (–2.0–2.1)	0.94
		AMS_{psy}	0.7 (0.3–1.0) versus 0.4 (–0.5–1.4)	0.2 (–0.8–1.3)	0.74
		AMS_{sex}	–3.6 (–4.1–-3.1) versus–4.2 (–5.9–2.5)	0.6 (–1.1–2.3)	0.56
		AMS_{glo}	–2.8 (–3.9–1.7) versus–3.8 (–7.2–-0.3)	1.0 (–2.5–4.6)	0.67
Obesity (kg m^{-2})	BMI ≤30 (276) BMI ≥30 (56) (16.9%)	IIEF5	–8.2 (–8.9–-7.4) versus–7.2 (–8.8–-5.7)	–1.0 (–2.7–0.9)	0.29
		AMS_{som}	0.2 (–0.3–0.8) versus–0.3 (–1.6–0.9)	0.6 (–0.8–2.0)	0.41
		AMS_{psy}	0.7 (0.4–1.1) versus 0.1 (–0.8–1.1)	0.6 (–0.4–1.6)	0.18
		AMS_{sex}	–3.7 (–4.1–-3.2) versus–3.4 (–0.4.5–-2.1)	–0.3 (–1.6–0.9)	0.58
		AMS_{glo}	–2.7 (–3.8–-1.6) versus–3.5 (–6.2–-0.7)	0.8 (–2.2–3.7)	0.61
Waist circumference (cm)	<102 (190) ≥102 (115) (37.7%)	IIEF5	–8.0 (–8.9–7.0) versus 8.1 (–9.2–7.1)	0.2 (–1.2–1.6)	0.81
		AMS_{som}	0.7 (0.1–1.3) versus–0.5 (–1.4–0.4)	1.2 (0.1–2.2)	0.030
		AMS_{psy}	1.0 (0.6–1.3) versus 0.2 (–0.4–0.8)	0.7 (0.05–1.46)	0.044
		AMS_{sex}	–3.7 (–4.3–3.2) versus–3.3 (–4.2–-2.5)	–0.4 (–1.4–0.6)	0.43
		AMS_{glo}	–2.0 (–3.2–-0.9) versus–3.5 (–5.4–-1.7)	1.5 (–0.7–3.7)	0.17
Metabolic syndrome	No (273) Yes (60) (18.0%)	IIEF5	–8.2 (–8.9–-7.4) versus–7.5 (–9.1–-5.9)	–0.6 (–2.4 *vs* 1.3)	0.49
		AMS_{som}	0.2 (–0.3–0.7) versus–0.1 (–1.3–1.2)	0.2 (–1.1–1.6)	0.70
		AMS_{psy}	0.7 (0.4–1.1) versus 0.3 (–0.7–1.3)	0.5 (–0.6–1.5)	0.38
		AMS_{sex}	–3.8 (–4.3–-3.3) versus–2.8 (–3.9–-1.5)	–1.0 (–2.4–0.2)	0.13
		AMS_{glo}	–2.9 (–3.9–-1.8) versus–2.5 (–5.4–0.6)	–0.3 (–3.6–2.7)	0.83
Diabetes mellitus (reported by patient)	No (307) Yes (24) (7.2%)	IIEF5	–8.2 (8.9–7.5) versus–5.9 (–7.9–3.9)	–2.3 (–4.5–-0.1)	0.08
		AMS_{som}	0.2 (–0.3–0.7) versus–1.0 (–2.9–1.0)	1.2 (–0.8–3.1)	0.22
		AMS_{psy}	0.7 (0.4–1.1) versus–0.4 (–1.8–1.2)	1.1 (–0.5–2.6)	0.09
		AMS_{sex}	–3.7 (–4.2–-3.3) versus–2.4 (–4.1–-0.6)	–1.3 (–3.2–0.4)	0.13
		AMS_{glo}	–2.8 (–3.8–-1.7) versus–3.7 (–7.7–0.9)	0.9 (–3.7–5.1)	0.64
Cardiovascular disorder (reported by patient)	No (306) Yes (26) (7.8%)	IIEF5	–8.1 (–8.8–-7.4) versus–7.7 (–9.9–-5.5)	–0.4 (–2.7–1.9)	0.74
		AMS_{som}	0.1 (–0.4–0.6) versus 0.2 (–1.7–2.3)	–0.1 (–2.2–2.0)	0.91
		AMS_{psy}	0.7 (0.4–1.1) versus–0.3 (–1.4–1)	1.0 (–0.3–2.2)	0.11
		AMS_{sex}	–3.6 (–4.1–-3.2) versus–3.7 (–5.6–-1.9)	0.1 (–1.8–2.0)	0.86
		AMS_{glo}	–2.7 (–3.8–-1.7) versus–3.7 (–7.2–-0.1)	1.0 (–2.8–4.8)	0.61
High blood pressure (reported by patient)	No (216) Yes (115) (34.7%)	IIEF5	–8.7 (–9.6–-7.9) versus–6.8 (–7.8–-5.7)	–2.0 (–3.4–-0.6)	0.004
		AMS_{som}	0.3 (–0.3–0.9) versus (–0.2–0.7)	0.5 (–0.6–1.5)	0.37
		AMS_{psy}	0.7 (0.3–1.1) versus 0.6 (–0.02–1.30)	0.04 (–0.70–0.81)	0.90
		AMS_{sex}	–4.0 (–4.5–-3.4) versus–3.0 (–3.8–-2.1)	–1.0 (–2.01–-0.02)	0.06
		AMS_{glo}	–3.0 (–4.2–-1.7) versus–2.5 (–4.4–-0.5)	–0.5 (–2.7–1.8)	0.70
HDL cholesterol	≥40 (220) <40 (57) (20.6%)	IIEF5	–7.8 (–8.7–-7.0) versus–7.5 (–9.2–-6.1)	–0.3 (–2.0–-1.7)	0.80
		AMS_{som}	0.1 (–0.5–0.7) versus 0.5 (–0.9–1.9)	–0.4 (–1.9–1.0)	0.57
		AMS_{psy}	0.6 (0.2–1.0) versus 0.8 (–0.03–1.65)	–0.2 (–1.2–0.7)	0.63
		AMS_{sex}	–3.7 (–4.2–-3.1) versus–2.9 (–3.9–-1.8)	–0.9 (–2.0–0.3)	0.18
		AMS_{glo}	–3.0 (–4.3–-1.7) versus–1.5 (–4.1–0.9)	–1.5 (–4.2–1.4)	0.30
Triglycerides	<1.5 (177) ≥1.5 (80) (31.1%)	IIEF5	–7.6 (–8.5–-6.7) versus–7.8 (–9.3–-6.4)	0.2 (–1.5–1.9)	0.82
		AMS_{som}	–0.2 (–0.9–0.5) versus 0.8 (–0.1–1.8)	–1.0 (–2.2–0.2)	0.11
		AMS_{psy}	0.6 (0.1–1.1) versus 0.6 (–0.1–1.3)	–0.03 (–0.86–0.83)	0.96
		AMS_{sex}	–3.7 (–4.3–-3.1) versus–3.1 (–4.0–-2.1)	–0.6 (–0.7–0.5)	0.27
		AMS_{glo}	–3.3 (–4.7–-1.8) versus–1.6 (–3.7–0.4)	–1.7 (–4.2–0.8)	0.21
Blood sugar (g l–1)	≤1 (185) >1 (91) (33.0%)	IIEF5	–8.0 (–8.8–-7.0) versus–7.7 (–9.0–-6.4)	–0.3 (–1.8–1.4)	0.74
		AMS_{som}	0.2 (–0.4–0.9) versus 0.04 (–0.94–1.06)	0.2 (–1.1–1.4)	0.79
		AMS_{psy}	0.6 (0.1–1.0) versus 0.7 (0.0–1.4)	–0.1 (–0.9–0.7)	0.81
		AMS_{sex}	–3.7 (–4.3–-3.2) versus–3.2 (–4.1–-2.3)	–0.6 (–1.6–0.5)	0.30
		AMS_{glo}	–3.0 (–4.3–-1.7) versus–2.4 (–4.6–-0.3)	–0.5 (–3.0–2.0)	0.69
Concomitant medication	At least one (204) None (130) (39.0%)	IIEF5	–7.9 (–8.8–-7.0) versus–8.2 (–9.3–-7.1)	0.3 (–1.0–1.7)	0.64
		AMS_{som}	–0.03 (–0.67–0.67) versus 0.4 (–0.3–1.1)	–0.5 (–1.4–0.6)	0.39
		AMS_{psy}	0.7 (0.3–1.2) versus 0.6 (0.1–1.0)	0.1 (–0.5–0.8)	0.78
		AMS_{sex}	–3.6 (–4.2–-3.0) versus–3.5 (–4.1–-2.9)	–0.1 (–1.0–0.8)	0.84
		AMS_{glo}	–2.9 (–4.3–-1.6) versus–2.5 (–3.9–1.1)	–0.4 (–2.4–1.5)	0.68

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Supplementary Table 4: Contd...

Parameters	*Levels: Group 1 (n) Group 2 (n) 2*	*Variable*	*Group 1: mean (95% CI) versus Group 2: mean (95% CI)[§]*	*Difference: Group 1– Group 2, mean (95% CI)[§]*	*P[¥]*
TNM (biopsy)	T1 (148) T2 (146) (49.7%)	IIEF5	–7.4 (–8.4–-6.4) versus–8.7 (–9.8–-7.7)	1.3 (–0.1–2.9)	0.07
		AMS_{som}	0.2 (–0.5–1.0) versus–0.2 (–1.0–0.5)	0.5 (–0.6–1.5)	0.34
		AMS_{psy}	0.9 (0.4–1.5) versus 0.4 (–0.1–0.8)	0.6 (–0.1–1.3)	0.11
		AMS_{sex}	–3.7 (–4.3–-3.0) versus–3.9 (–4.6–-3.3)	0.3 (–0.6–1.2)	0.56
		AMS_{glo}	–2.4 (–4.0–-0.9) versus–3.8 (–5.3–-2.3)	1.3 (–0.8–3.5)	0.23
Dominant grade for biopsy	3– (264) 4+ (67) (20.2%)	IIEF5	–8.0 (–8.7–-7.27) versus–8.3 (–10.0–-6.6)	0.2 (–1.5–2.1)	0.79
		AMS_{som}	0.4 (–0.2–1.0) versus–0.8 (–1.8–0.3)	1.1 (–0.1–2.4)	0.07
		AMS_{psy}	0.7 (0.3–1.1) versus 0.5 (–0.3–1.2)	0.2 (–0.6–1.0)	0.58
		AMS_{sex}	–3.5 (–4.0–-2.9) versus–4.0 (–5.0–-3.0)	0.5 (–0.6–1.7)	0.33
		AMS_{glo}	–2.3 (–3.5–-1.2) versus–4.3 (–6.6–-1.9)	2.0 (–0.6–4.5)	0.13
Bioavailable testosterone[#] ($\mu g\ ml^{-1}$)	≥0.8 (300) <0.8 (33) (9.9%)	IIEF5	–8.2 (–8.9–-7.5) versus–6.4 (–8.6–-4.1)	–1.8 (–4.2–0.6)	0.11
		AMS_{som}	0.1 (–0.4–0.6) versus 0.5 (–1.04–2.2)	–0.4 (–2.2–1.3)	0.62
		AMS_{psy}	0.7 (0.3–1.0) versus 0.5 (–0.6–1.6)	0.2 (–0.9–1.4)	0.73
		AMS_{sex}	–3.7 (–4.2–-3.3) versus–2.4 (–3.9–0.8)	–1.4 (–3.0–0.2)	0.07
		AMS_{glo}	–2.9 (–3.9–-1.8) versus–1.3 (–4.8–2.6)	–1.6 (–5.6–2.0)	0.37
Total Testosterone ($\mu g\ ml^{-1}$)	≥3.0 (300) <3.0 (34) (10.2%)	IIEF5	–8.1 (–8.9–-7.4) versus–6.9 (–8.7–-5.0)	–1.3 (–3.2–0.7)	0.27
		AMS_{som}	0.1 (–0.5–0.6) versus 1.0 (–0.8–3.0)	–1.0 (–3.1–0.9)	0.35
		AMS_{psy}	0.6 (0.3–1.0) versus 0.8 (–0.5–2.3)	–0.2 (–1.7–1.2)	0.79
		AMS_{sex}	–3.7 (–4.2–-3.3) versus–2.2 (–3.5–-0.9)	–1.5 (–2.9–-0.2)	0.047
		AMS_{glo}	–3.0 (–4.0–-2.0) versus–0.4 (–4.2–3.7)	–2.6 (–6.8–1.4)	0.22
Hypogonadism (bioavailable testosterone <0.8 $\mu g\ ml^{-1}$ OR total testosterone <3.0 $\mu g\ ml^{-1}$)	No (277) Yes (56) (16.8%)	IIEF5	–8.3 (–9.0–-7.6) versus–6.6 (–8.2–-4.9)	–1.7 (–3.5–0.1)	0.06
		AMS_{som}	0.01 (–0.58–0.52) versus 0.9 (–0.3–2.2)	–0.9 (–2.3–0.5)	0.17
		AMS_{psy}	0.7 (0.3–1.0) versus 0.4 (–0.5–1.4)	0.3 (–0.8–1.2)	0.62
		AMS_{sex}	–3.8 (–4.3–-3.3) versus–2.3 (–.3.3–-1.3)	–1.5 (–2.6–-0.4)	0.013
		AMS_{glo}	–3.1 (–4.2–-2.0) versus–0.9 (–3.6–2.0)	–2.2 (–5.3–0.8)	0.12
Grade prostate anatomopathology	Grade 3 dominant (235) Grade 4 dominant (99) (29.6%)	IIEF5	–7.9 (–8.7–-7.1) versus–8.3 (–9.6–-7.0)	0.5 (–1.0–2.0)	0.55
		AMS_{som}	0.6 (0.02–1.2) versus–0.9 (–1.8–0.2)	1.5 (0.3–2.6)	0.008
		AMS_{psy}	0.7 (0.4–1.1) versus 0.5 (–0.2–1.1)	0.2 (–0.5–1.0)	0.51
		AMS_{sex}	–3.5 (–4.0–-2.9) versus–3.9 (–4.7–-3.04)	0.4 (–0.5–1.4)	0.39
		AMS_{glo}	–2.1 (–3.3–-0.9) versus–4.2 (–6.4–-2.3)	2.1 (–0.2–4.6)	0.05
Adenopathy detected at surgery	No (162) Yes (6) (3.6%)	IIEF5	–8.0 (–9.1–-7.0) versus–6.4 (–7.7–-5.1)	–1.6 (–3.3–0.1)	0.13
		AMS_{som}	–0.1 (–0.7–0.6) versus–0.1 (–2.1–2.1)	0.01 (–2.25–2.20)	0.99
		AMS_{psy}	0.9 (0.4–1.3) versus–0.7 (–1.7–0.8)	1.52 (0.03–2.70)	0.20
		AMS_{sex}	–4.0 (–4.6–-3.4) versus–3.7 (–6.9–-0.1)	–0.3 (–4.0–3.0)	0.89
		AMS_{glo}	–3.2 (–4.6–-1.8) versus–4.5 (–9.4–1.1)	1.3 (–4.4–6.6)	0.72

G1: Group 1; G2: Group 2; BMI: body mass index; IIEF: International Index of Erectile Function; AMS: Aging Male's Symptoms; CI: confidence interval; TNM: tumor, node, and metastasis; HDL: high-density lipoprotein. [§]Boostrap (3000 replications); [¥]Permutation *t*–test accounting for equal/unequal group variances (checked) (5000 spermutations); [#]also applies to Free testosteron which is colinear as it is calculated through a mathematical function of bioavailable testosterone