African Journal of Urology

ORIGINAL RESEARCH

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Endogenous testosterone density associates with predictors of tumor upgrading and disease progression in the low through favorable intermediate prostate cancer risk categories: analysis of risk factors and clinical implications

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Abstract

Background The study aimed to test the hypothesis that endogenous testosterone density (ETD), in the low through favorable intermediate PCa risk classes patients undergoing surgery, might be associated with disease progression.

Materials and methods ETD, PSAD, and percentage of biopsy positive cores density (BPCD) were calculated in relation to prostate volume (PV). Tumor load density (TLD) was estimated as the tumor load (TL) ratio to prostate weight. ET was considered low if < 230 ng/dL. Tumor upgrading (ISUP > 2), upstaging (pT > 2) and their related features were investigated.

Results 433 patients were included, 249 (57.5%) from the favorable intermediate-risk class. Upgrading occurred in 168 (38.8%) cases and upstaging in 62 (14.3%). ETD above the median (9.9 ng/(dL x mL)), was discriminated by PSAD (AUC = 0.719; 95% CI: 0.671–0.766; $p < 0.0001$), BPCD (AUC = 0.721; 95% CI: 0.673–0.768; $p < 0.0001$), TLD (AUC = 0.674; 95% CI: 0.624–0.724; $p < 0.0001$) with accuracy improved by the multivariable model (AUC = 0.798; 95% CI: 0.724–0.811; $p < 0.0001$). In linear multivariable models as ETD increased, so did TLD (rc = 0.019; 95% CI: 0.014; 0.025; $p < 0.0001$), further increased by low ET (rc = 0.097; 95% CI: 0.017; 0.176; $p = 0.017$). After adjusting for clinical and pathological features, ETD correlated with TLD above the first quartile. Disease progression occurred in 43 (11.9%) patients, independently predicted by PSAD (hazard ratio, HR = 99.906; 95% CI: 6.519–1531.133; $p = 0.001$) and tumor upgrading (HR = 3.586; 95% CI: 3.586–6.863; $p < 0.0001$).

Conclusions ETD was associated with unfavorable PCa, and men with tumor upgrading were at increased risk of disease progression. ETD was related to predictors of PCa progression and could provide pivotal biological information about aggressive disease.

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Keywords Prostate cancer, Open or robotic radical prostatectomy, Endogenous testosterone density, Prostate-specific antigen density, Percentage of biopsy positive cores density, Tumor load density

1 Background

Prostate cancer (PCa) still represents a major health problem, being the second most diagnosed tumor in the aging male [1, 2]. Clinically localized PCa is classified into risk classes. Although both the European Association of Urology (EAU) and National Comprehensive Cancer Network (NCCN) guidelines identify three categories according to the risk of developing metastases, the two systems are not equivalent [1, 2]. Tumor grading is based on the International Society of Urological Pathology (ISUP) classification, which predicts the risk of disease progression more accurately than the previous Gleason system [1–5]. Treatment options include monitoring strategies (active surveillance, AS; watchful waiting, WW) and active treatments (radical prostatectomy, RP, conformal radiation therapy, RT, and brachytherapy) [1, 2]. For patients who are candidates to RP, the detection of unfavorable disease, tumor upgrading and upstaging as well as positive surgical margins play a key role because of the prognostic drawbacks [1–3]. On the contrary, clinical under-grading and under-staging are essential, especially for low and favorable intermediate-risk classes, needing more stratifying parameters [1, 2]. In this perspective, molecular tumor analysis represents a promising tool, but still far from widespread use in clinical practice [1, 2]. Tumor quantitation is a potential parameter for patient stratification. Tumor quantitation on biopsy specimens is an independent predictor of aggressive disease in definitive histopathologic analysis [1, 2]. On the other hand, tumor quantitation in the surgical specimen, considered as the percentage of prostate gland involved by cancer, has been under-evaluated [1]. Further studies are needed to identify factors associated with specimen tumor quantitation.

The risk of PCa has been associated with several factors including genetic, dietary, environmental, physical (obesity, metabolic syndrome), and hormonal factors [1]. Endogenous testosterone (ET) is the main androgen related to prostatic diseases including either benign prostatic hyperplasia (BPH) or PCa, which may also coexist [1, 6]. Our group has extensively investigated the association of ET with the unfavorable disease in surgical specimens [6–9]. Recently, our efforts have focused on associations of ET density (ETD), defined as the ratio of ET to prostate volume (PV). Tumor quantitation features at biopsy and pathology reports, in low-risk patients, showed a positive association with ETD [10, 11]. The same findings were observed in the intermediate-risk group. Moreover, low ET levels imposed a higher risk of hiding unfavorable disease, tumor upgrading and upstaging as well as lymph node invasion, regardless of ETD measurements [12, 13]. In the low through favorable intermediate PCa risk classes treated with RP, we hypothesized a relationship between ETD and aggressive cancer features, influencing the natural history of the disease.

2 Methods

The study was approved by Institutional Review Board. Informed consent was obtained from all subjects. Data were collected prospectively but evaluated retrospectively. In a period ranging from November 2014 to December 2019, ET (ng/dL) of 805 consecutive PCa patients not receiving any antiandrogen therapy was measured at our institution's laboratory before surgery. The test was performed at least one month after biopsies between 8.00–8.30 a.m. by radioimmunoassay. Data about prostate-specific antigen (PSA; ng/mL), age (years), body mass index (BMI; kg/m^2), PV (mL) and percentage of biopsy positive cores (BPC), the ratio of positive and total cores taken (%), were collated for each patient. PV was calculated with transrectal ultrasound (TRUS) and biopsies performed elsewhere were reviewed for the number of cores taken, tumor grade, and PV. For procedures carried out at our Institution, the 14-core transperineal technique was used. In any case, the ratios of BPC, PSA, ET, and PV were calculated, and relative densities were given as BPCD (%/mL), PSAD (ng/ml^2), and ETD (ng/(dL x mL)), respectively. Clinical staging was assessed by the TNM system (8th edition) with clinical T stage only based on direct rectal examination. Patients' risk was stratified as recommended by EAU guidelines [1]. Preoperative physical status was evaluated by the American Society of Anesthesiologists (ASA) system [14]. Surgery was performed by experienced surgeons with a robot-assisted (RARP) or open approach (ORP). As previously reported, extended pelvic lymph node dissection (ePLND) was performed according to the guidelines [1, 2, 9]. Nodal packets were submitted in separate packages according to a standard anatomical template including external iliac, internal iliac plus obturator, Marcille's fossa, and Cloquet's nodal stations, bilaterally. Prostates were weighted and tumors were graded according to the ISUP system [1, 2, 4, 5]. Tumor quantitation was assessed as tumor load (TL), defined as the percentage of prostate involved by cancer; specifically,

the pathologist assessed tumor quantitation by visual estimation of all glass slides after all microscopically identifiable foci of carcinoma were circled with a marked pen, as considered by ISUP association [15]. Tumor load density (TLD) was calculated as the ratio of TL to prostate weight (%/gr). Surgical margins were considered positive when cancer invaded the inked surface of the specimen. Removed lymph nodes were counted and assessed for cancer invasion. Prostate surgical specimens were staged by the 2017 version of the TNM system (8th edition) [1, 2].

2.1 Study population and design

The study aimed at demonstrating that ETD of patients with low through favorable intermediate EAU risk categories undergoing radical prostatectomy associates with aggressive tumor characteristics, thus being able to predict disease upgrading and progression. The favorable intermediate risk category was defined according to the following criteria: PSA within 10 ng/mL with ISUP grade group 2 and clinical stage < cT2c. Of the total patient population, 433 cases met the inclusion criteria. Tumor upgrading was defined as ISUP grade group > 2 in the final pathology report. After surgery, patients were followed-up according to EAU recommendations [1]. Specifically, disease clinical history and PSA measurements were obtained at 3, 6, and 12 months after treatment, then every 6 months for 3 years and yearly then after. At PSA persistence/recurrence, restaging imaging modalities were considered to plan further treatments. Disease progression was defined as the occurrence of biochemical recurrence and/or local recurrence and/or distant metastases. According to the EAU guidelines, biochemical recurrence after surgery was defined as PSA ≥ 0.2 ng/mL with a second confirmatory level of PSA > 0.2 ng/mL [1].

2.2 Statistical analysis

Continuous variables were measured for medians and interquartile ranges (IQR). Categorical factors were assessed by frequencies (percentages). Associations of ETD and TLD with clinical and pathological factors, including tumor upgrading and upstaging, were investigated with a logistic regression model. The discriminatory performance of ETD and TLD was assessed by plotting a receiver operating curve (ROC) for each significant predictor and then for all clinical predictors, computing the area under the curve (AUC). Linear associations of ETD and PSAD with clinical and pathological features were investigated with correlation analysis and a multivariable linear regression model that included low ET (less than 230 ng/dL) versus intermediate/normal ET (superior to 230 ng/dL), according to international standard consensus [16]. Bivariate models of correlation between ETD and tumor density features (BPCD, TLD) stratified by ET (low versus intermediate/normal) were computed with relative boxplots. Time elapsed between surgery and the clinical outcome of interest (disease progression) or last follow-up was measured as time to event occurrence. Univariate and multivariable Cox proportional hazards model was used to estimate the association of clinical and pathological factors with the risk of disease progression; additionally, hazard ratios and relative 95% confidence intervals (CI) were evaluated. Where appropriate, unadjusted Kaplan–Meier estimator curves of factors associated with the risk of disease progression were displayed. The software used to run the analysis was IBM-SPSS version 26. All tests were two-sided, and $p < 0.05$ was an index of statistical significance.

3 Results

3.1 Demographics of the low through favorable intermediate risk classes stratified by ETD

The study included 433 patients, of whom 184 (42.5%) were classified as low and 249 (57.5%) as favorable intermediate risk classes. Demographics of the patient population are reported in Table 1. Median age was 65 years, median PSA was 5.9 ng/mL, and clinical stage cT1c was detected in 73.9% of patients. RARP was performed in 388 (89.6%) cases. In the surgical specimen, upgrading occurred in 168 (38.8%) cases and upstaging in 62 (14.3%), while surgical margins were involved in 106 (24.5%) subjects. A total of 18 (6.3%) out of 285 patients who underwent ePLND had nodal involvement. The cohort was stratified according to median ETD (9.9 ng/(dL x mL)). A positive correlation with tumor parameters (PSA, PSAD, BPC, BPCD, TL, TLD) and a negative relationship with BMI, PV, and PW were observed. Figure 1 shows the ROC curves of factors associated with ETD above the median. The AUC was improved by the multivariable model (AUC = 0.798; 95% CI: 0.724–0.811; $p < 0.0001$).

3.1.1 Linear associations of ETD and PSAD with biopsy and specimen tumor density features

Linear associations of ETD and PSAD with clinical and pathological factors are reported in Additional file 1. At univariate analysis, ETD and PSAD showed a high correlation to each other ($r = 0.498$; $p < 0.0001$) and a positive correlation with both tumor quantitation (BPC, BPCD, TL, TLD) and grading factors; PSAD was also related to unfavorable pathologic features (upgrading, upstaging and positive surgical margins).

Considering pathological multivariable models, ETD and TLD showed a positive correlation with each other

Table 1 Demographics of patients stratified by ETD including low and intermediate risk categories who underwent radical prostatectomy

	Population (*)	ETD < 10	ETD > 9,9	P-value
Number	433	219	214	
Clinical features				
Age (years), medians (IQR)	65 (60–70)	65 (61–70)	65 (60–70)	0.53
Body mass index; BMI (kg/m^2), medians (IQR)	25.6 (23.7–27.1)	26.1 (24.3–28.1)	25 (23.4–27.1)	< 0.0001
ET (ng/dL), medians (IQR)	403 (308.3–504.1)	320 (266–400)	482 (406.5–565.9)	< 0.0001
ETD (ng/(dL x mL)), medians (IQR)	9.9 (6.8–14.8)	6.8 (5.3–8.8)	14.8 (12.4–18.3)	< 0.0001
PSA (ng/mL), medians (IQR)	5.9 (4.5–7.4)	6.2 (4.7–7.8)	5.5 (4.3–7.0)	0.022
PSAD (ng/(mL x mL)), medians (IQR)	0.14 (0.10–0.20)	0.12 (0.08–0.16)	0.18 (0.12–0.24)	< 0.0001
PV (mL), medians (IQR)	40 (30–50)	49 (40–60)	30 (24.7–40)	< 0.0001
BPC (%), medians (IQR)	28.5 (17–45)	27 (14.2–42.0)	30 (20–50)	0.016
BPCD (%/mL), medians (IQR)	0.74 (0.40–1.25)	0.54 (0.31–0.93)	1.00 (0.60–17.3)	< 0.0001
ASA score, n (%)				
ASA 1	46 (10.6)	20 (9.1)	26 (12.1)	0.011
ASA 2	351 (81.3)	173 (79)	179 (83.6)	
ASA 3	35 (8.1)	26 (11.9)	9 (4.2)	
Clinical stage, n (%)				0.363
cT1c	320 (73.9)	166 (75.8)	154 (72)	
cT 2a/2b	113 (26.1)	53 (24.2)	60 (28)	
ISUP, n (%)				0.006
ISUP 1	215 (49.7)	123 (56.2)	92 (43)	
ISUP 2	218 (50.3)	96 (43.8)	122 (57)	
Pathological features				
PW (grams; gr), medians (IQR)	52 (40–65)	60 (50–73)	45 (36.3–55)	< 0.0001
TL (%), medians (IQR)	15 (10–22)	15 (10–20)	20 (10–25)	0.001
TLD (%/gr), medians (IQR)	0.28 (0.15–0.51)	0.22 (0.12–0.40)	0.38 (0.21–0.66)	< 0.0001
ISUP, n (%)				0.558
ISU $p < 3$	265 (61.2)	137 (62.6)	128 (59.8)	
ISUP > 2	168 (38.8)	82 (37.4)	66 (40.2)	
Pathologic tumor stage, n (%)				0.933
pT2	371 (85.7)	189 (86.3)	182 (85)	
pT3a	33 (7.6)	16 (7.3)	17 (8.0)	
pT3b	29 (6.7)	14 (6.4)	15 (7.0)	
Surgical margins status (SM), n (%)				0.931
negative (NSM)	327 (75.5)	165 (75.3)	162 (75.7)	
positive (PSM)	106 (24.5)	54 (24.7)	52 (24.3)	

*Population including European Association of Urology (EAU) low and intermediate risk categories with PSA up to 10 ng/mL, ISUP grade group 1 or 2 and cT1c-2b;

(rc = 5.033; 95% CI: 3.489; 6.581; $p < 0.0001$) but a negative association with low ET levels (-6.756; 95% CI: -7.922; -5.591; $p < 0.0001$). PSAD was correlated with TLD (rc = 0.045; 95% CI: 0.025; 0.065; $p < 0.0001$), ETD (rc = 0.007; 95% CI: 0.006; 0.008; $p < 0.0001$), and low ET levels (rc = 0.050; 95% CI: 0.033; 0.066; $p < 0.0001$).

Figures 2 and 3 depict the scatterplot of the bivariate model of ETD predicting BPCD and TLD, respectively, stratified by ET levels. As ETD measurements increased, BPCD values increased accordingly (rc = 0.061; 95% CI: 0.050; 0.071; $p < 0.0001$). In addition, higher BPCD corresponded to lower ET levels (rc = 0.318; 95% CI: 0.168; 0.469; $p < 0.0001$). ETD increased with increasing TLD (rc = 0.019; 95% CI: 0.014; 0.025; $p < 0.0001$); however, at a given ETD value, TLD was inversely correlated with low ET levels (rc = 0.097; 95% CI: 0.017; 0.176; $p = 0.017$) (Fig. 4).

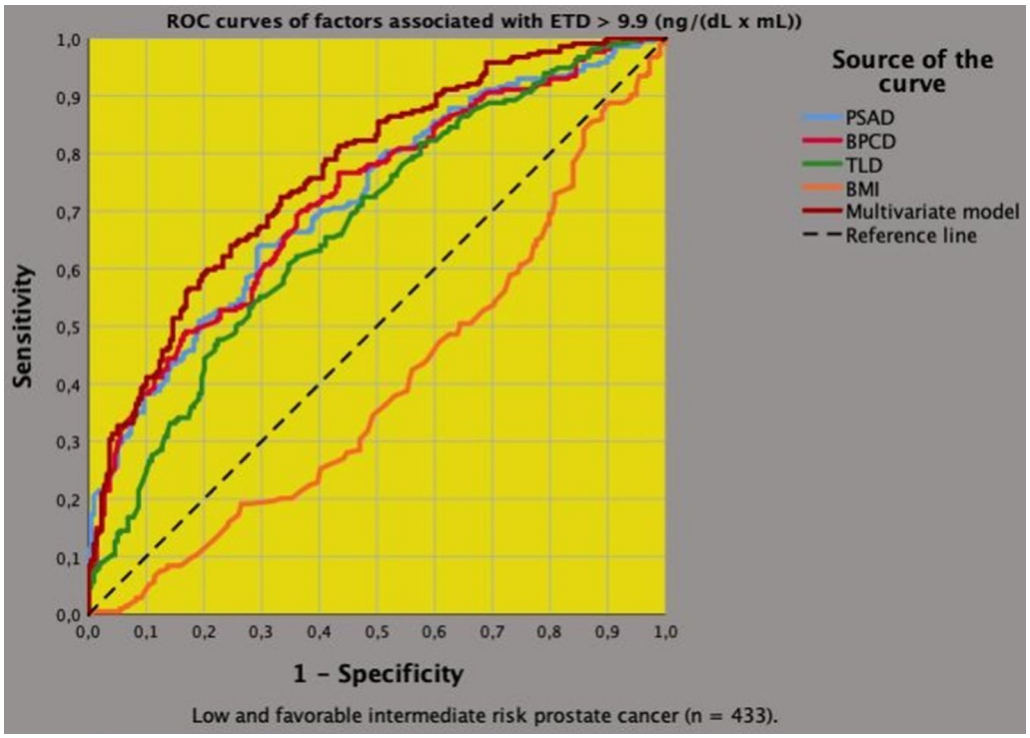

Fig. 1 ROC curves and AUC of factors associated with ETD including PSAD (AUC = 0.719; 95% CI: 0.671–0.766; $p < 0.0001$), BPCD (AUC = 0.721; 95% CI: 0.673–0.768; $p < 0.0001$), TLD (AUC = 0.674; 95% CI: 0.624–0.724; $p < 0.0001$) and BMI (AUC = 0.348; 95% CI: 0.345–0.451; $p = 0.027$). The multivariable model including PSAD, BPCD, TLD, and BMI improved predicting accuracy (AUC = 0.798; 95% CI: 0.724–0.811; $p < 0.0001$)

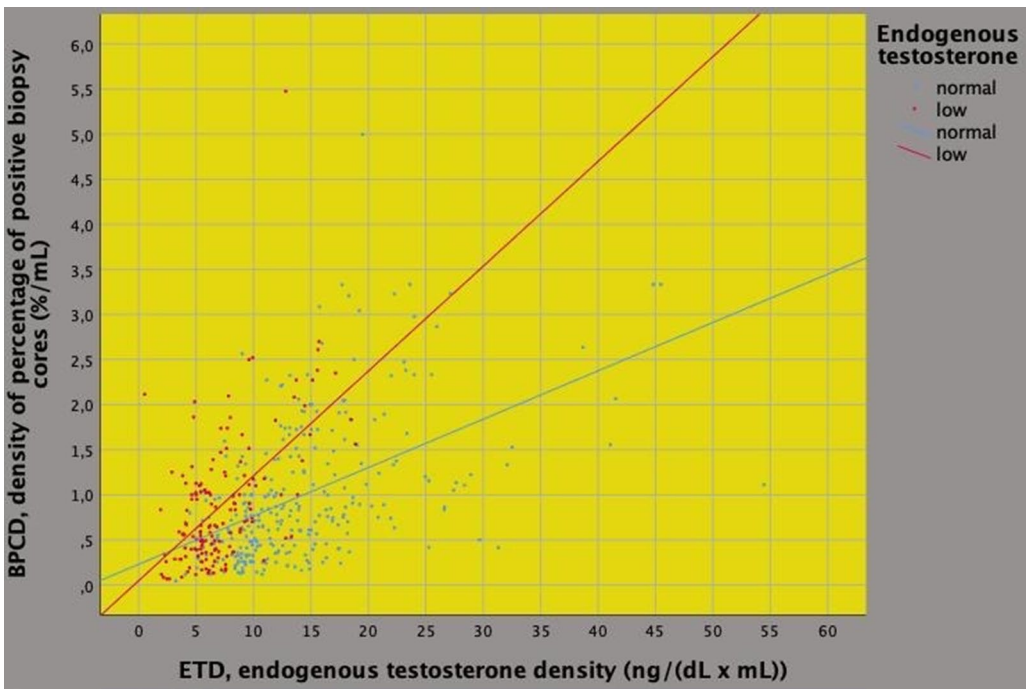

Fig. 2 Scatterplot of the bivariate model of endogenous testosterone density (ETD) predicting biopsy positive cores percentage density (BPCD) stratified by endogenous testosterone (ET) levels; as ETD measurements increased, BPCD values increased accordingly (regression coefficient, rc = 0.061; 95% CI: 0.050; 0.071; $p < 0.0001$), but low ET levels (below 230 ng/dL) also increased biopsy tumor load density (rc = 0.318; 95% CI: 0.168; 0.469; $p < 0.0001$)

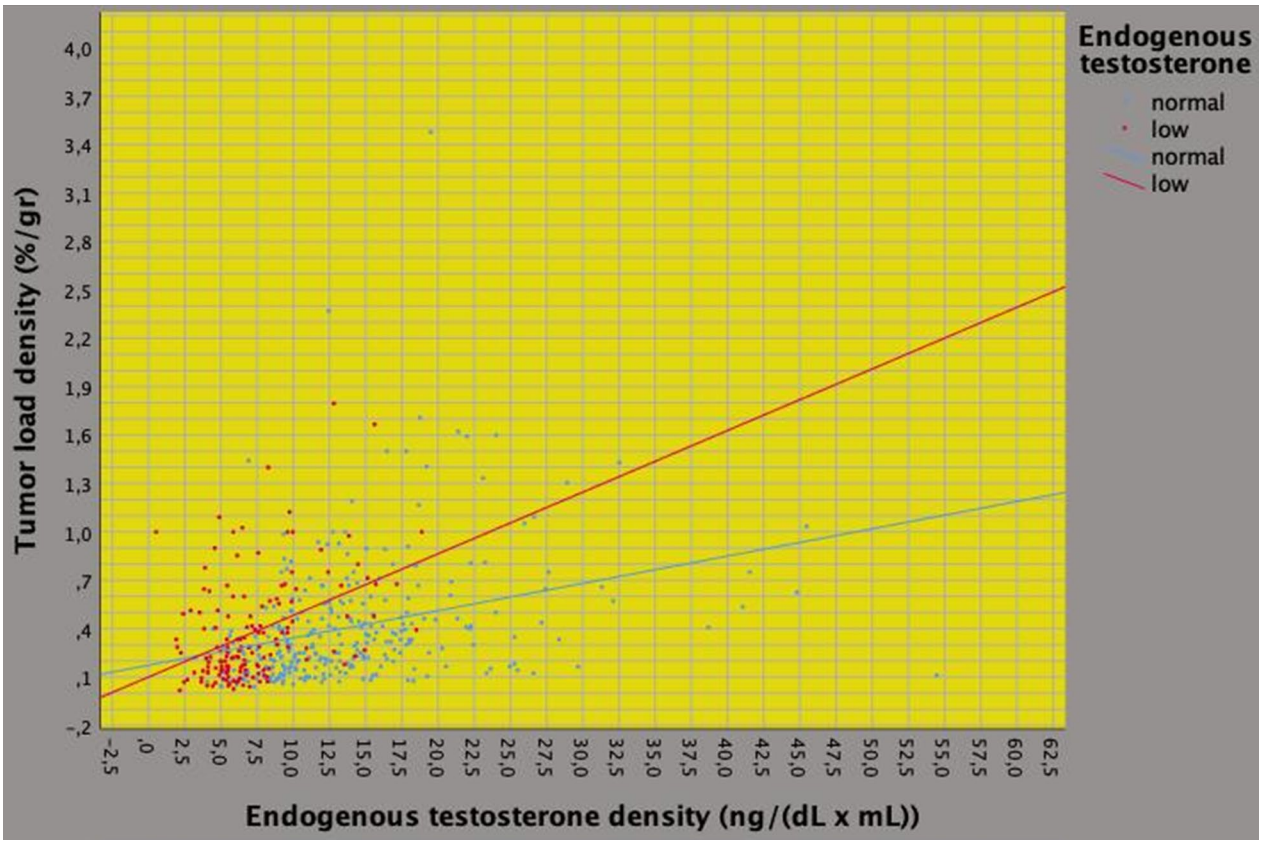

Fig. 3 Scatterplot of the bivariate model of ETD predicting TLD stratified by ET levels; as ETD increased, TLD increased accordingly (rc = 0.019; 95% CI: 0.014; 0.025; $p < 0.0001$), but low ET levels (below 230 ng/dL) further increased TLD (rc = 0.097; 95% CI: 0.017; 0.176; $p = 0.017$)

3.1.2 Associations of ETD with the risk of high TLD predicting PCa upgrading

On multivariable analysis, high TLD was positively correlated with ETD, PSAD, BPC, and BPCD, but inversely with age on clinical models. Regarding pathological models, TLD has shown a direct correlation with tumor upgrading and upstaging. The overall multivariable model is displayed in Table 2.

3.1.3 Associations of ETD with factors predicting disease progression

Follow-up data were available for 361 (83.4%) of the 433 patients. Table 3 shows the clinical outcomes of patients with low through favorable intermediate risk classes after surgery. The median follow-up (IQR) was 37 (21–54) months, with no significant difference between patients with and without disease progression. Of the 5 deaths, none was imputable to PCa (overall survival 98.6%), and disease progression occurred in 43 (11.9%) cases. In the univariate analysis, neither ET nor ETD were significantly associated with disease progression. Thus, there is no direct correlation between testosterone and PCa progression. On the contrary, in a multivariable model including clinical and pathological factors, the risk of disease progression was independently predicted by PSAD (hazard ratio, HR = 99.906; 95% CI: 6.519–1531.133; $p = 0.001$), tumor upgrading (HR = 3.586; 95% CI: 3.586–6.863; $p < 0.0001$) and seminal vesicle invasion (HR = 2.811; 95% CI: 1.369–5.818; $p = 0.005$). Figure 5 depicts unadjusted Kaplan–Meier survival curves for the association between tumor upgrading and disease progression. As shown, the upgraded group had a significantly higher risk of disease progression (hazard ratio, HR = 3.790; 95% CI: 2.035–7.061; $p < 0.0001$) compared to the control group; furthermore, at a follow-up of 60 months, 45% of upgraded patients had disease progression, compared with a rate of 15% in the control group.

4 Discussion

In the low through favorable intermediate PCa risk classes, disease progression occurred in 11.9% of cases and was independently predicted by tumor upgrading after adjusting for PSAD. Therefore, upgraded patients were more likely to experience disease progression than the control group (45% versus 15%, respectively). In this highly selected cohort, our results confirm that the ISUP

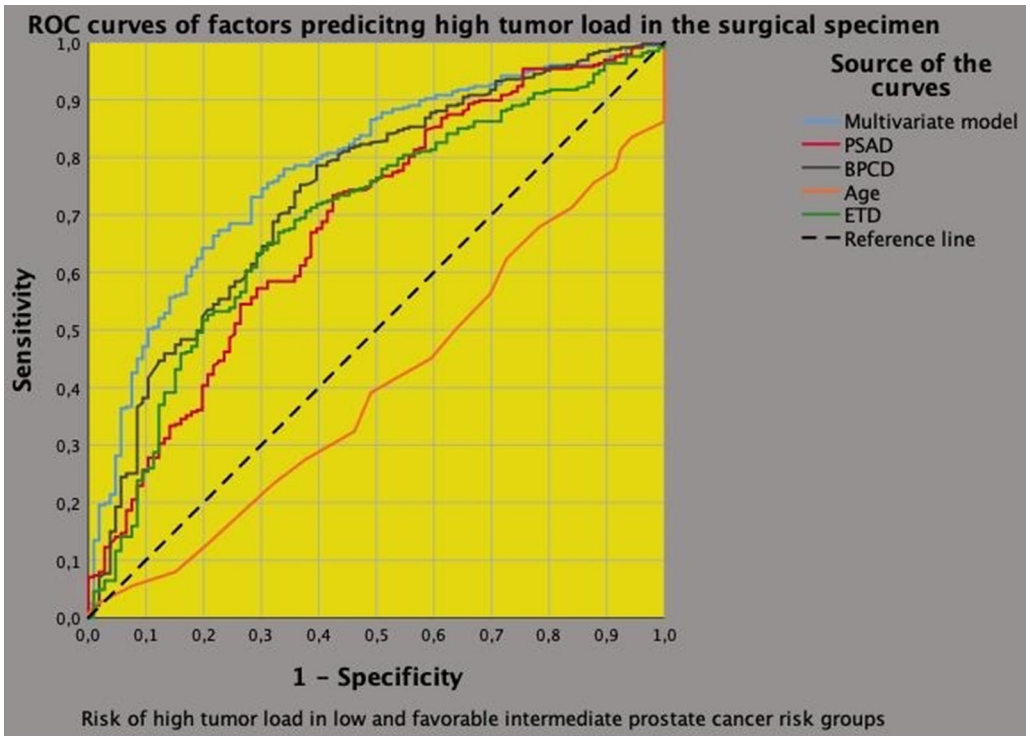

Fig. 4 Comparing ROC and AUC of clinical factors associated with high tumor load density (TLD above the first quartile), which was predicted by ETD (AUC = 0.692; 95% CI: 0.634–0.749; $p < 0.0001$), PSAD (AUC = 0.684; 95% CI: 0.634–0.749; $p < 0.0001$), BPCD (AUC = 0.738; 95% CI: 0.683–0.793; $p < 0.0001$) and age (AUC = 0.401; 95% CI: 0.342–0.401; $p = 0.002$). The multivariable model including ETD, PSAD, BPCD, and age improved prediction accuracy (AUC = 0.762; 95% CI: 0.709–0.816; $p < 0.0001$)

grading group formulation predicts PCa progression: the higher the tumor grade, the greater the likelihood of recurrence [4, 5]. The 5-year biochemical risk-free survival of grade groups 1 to 5 after RP was 96%, 88%, 63%, 48%, and 26%, respectively; moreover, the hazard ratios of groups 2 to 5 were 2.2, 7.3, 12.3, and 23.9 [4]. Nevertheless, tumor upgrading in the surgical specimen remains a major concern in clinical decision-making [1, 2, 4, 5]. For instance, disease progression due to tumor upgrading may explain the 1% cancer-specific mortality encountered in patients undergoing AS, which represents one of its main drawbacks [1]. A large study including 1113 patients has shown that tumor upgrading leads to adverse pathological features and biochemical progression; however, its limitations such as its retrospective design, a historical and non-homogenous cohort, and the omission of PV and PSAD measurement must be taken into account [17]. Although our study has similarities with the aforementioned one, it differs in that the cohort is contemporary and highly selected, and in that it assesses density factors related to PCa (ETD, PSAD, BPCD, TLD) and basal PSAD, which represent important prognostic factors [1–3].

Notably, tumor upgrading, which predicts disease progression, occurred in 38.8% of cases, with higher rates for patients with TLD above the first quartile compared with the control group (44.3% versus 21%), even after adjustment for ETD, PSAD, and other clinical (age, BMI) and pathological (seminal vesicle invasion) aspects. In addition, an association between ETD and predictors of disease progression was observed, either directly with PSAD or indirectly through TLD. Our results confirm the ability of some tools (PSA, BPC) used in daily clinical practice to predict tumor upgrading and also demonstrate the efficacy of density parameters (ETD, PSAD, BPCD, TLD) in assessing the risk of upgrading in the low through favorable intermediate PCa risk classes [1, 2]. Our findings could shed light on the dynamics of tumor events that induce to end of AS [1, 2]. The utility of tumor-related density parameters was recently confirmed by a study showing that PSAD predicted tumor upgrading at confirmatory biopsy in men undergoing AS, including low and favorable intermediate-risk patients with negative mpMRI findings; however, the power of the study was limited by the small number of patients, loss of RP specimens, and the inclusion of two different AS protocols; moreover, it did not investigate ET, ETD, and tumor

Table 2 Low and favorable intermediate risk prostate cancer patients stratified by tumor load density (TLD) in the the surgical specimen ($n=433$)

	TLD up to 0.25	TLD > 0.25	P-value	Multivariable model I		Multivariable model II	
Number	**106**	**327**		**OR (95% CI)**	**P-value**	**OR (95% CI)**	**P-value**
Clinical features				Clinical		Overall	
Age (years), median (IQR)	66 (62–71)	65 (60–69)	0.002	0.940 (0.903–0.978)	0.002	0.924 (0.885–0.964)	< 0.0001
BMI (kg/m^2), median (IQR)	25.9 (23.5–28.1)	25.6 (23.8–27.7)	0.487				
ET (ng/dL), median (IQR)	376.5 (295.5–531.0)	410 (315–504)	0.451				
ETD (ng/(dL x mL)), median (IQR)	7.6 (5.5–10.5)	11.3 (7.8–15.5)	< 0.0001	1.068 (1.108–1.121)	0.007	1.069 (1.015–1.125)	0.011
PSA (ng/mL), median (IQR)	5.6 (4.3–7.8)	5.9 (4.5–7.3)	0.935				
PSAD (ng/(mL x mL)), median (IQR)	0.11 (0.07–0.15)	0.15 (0.11–0.21)	< 0.0001				
PSAD < 0.15, n (%)	76 (71.6)	146 (44.6)	< 0.0001	Ref.		Ref.	
PSAD > 0.14, n (%)	30 (28.3)	181 (55.4)		2.222 (1.317–3.749)	0.003	2.059 (1.197–3.542)	0.009
PV (mL), median (IQR)	50 (40–61.2)	37 (28–47)	< 0.0001				
BPC (%), median (IQR)	20 (14–33)	31 (21–50)	< 0.0001	1.025 (1.011–1.040)	0.035	1.023 (1.009–1.038)	0.001
BPCD (%/mL), median (IQR)	0.40 (0.25–0.75)	0.86 (0.51–1.42)	< 0.0001				
ASA, n (%)			0.466				
ASA 1	8 (7.5)	38 (11.6)					
ASA 2	90 (84.9)	262 (80.1)					
ASA 3	8 (7.5)	27 (8.3)					
cT, n (%)			0.09				
cT1c	85 (80.2)	235 (71.9)					
cT 2a/2b	21 (19.28)	92 (28.2)					
ISUP, n (%)			0.006				
ISUP 1	65 (61.3)	150 (45.9)		Ref.		Ref.	
ISUP 2	41 (38.7)	177 (54.1)		1.667 (1.038–2.708)	0.022	removed by model	
Pathological features				Pathological			
PW (grams; gr), median (IQR)	67.5 (52.7–78)	49 (40–60)	< 0.0001				
TL (%), median (IQR)	5 (5–10)	20 (15–30)	< 0.0001				
TLD (%/gr), median (IQR)	0.09 (0.07–0.12)	0.38 (0.25–0.62)	< 0.0001				
ISUP, n (%)			< 0.0001				
ISU $p < 3$	83 (78.3)	182 (55.7)		Ref.		Ref.	
ISUP > 2	23 (21.7)	145 (44.3)		2.395 (1.416–4.051)	0.001	2.563 (1.460–4.500)	0.001
pT, n (%)			< 0.0001				
pT2	101 (95.3)	270 (82.6)		Ref.		Ref.	
pT3a/b	5 (4.7)	57 (17.4)		2.766 (1.040–2.354)	0.041	2.875 (1.014–8.150)	0.047
SM, n (%)			0.039				
NSM	88 (83)	239 (73.1)		Ref.			
PSM	18 (17)	88 (26.9)		1.457 (0.813–2.612)	0.207		

quantitation density feature [18]. Another large study has demonstrated that basal PSA and BPC were predictors of upgrading of low-risk and very low-risk patients; again, PV, ET, and density parameters were not analyzed; furthermore, 93.8% of patients had cT2a, which represents a significant bias for evaluating this category of patients [19].

Biopsy and specimen tumor quantitation density features were positively associated with both ET and ETD. As ETD increased, TLD and BPCD also increased, with higher variations for lower ET levels, thus relating to aggressive disease features. An upgrade of 86.3% was observed in the high-load TLD group compared to controls (13.7%). This identifies a group of patients at increased risk of upgrading, which is an unfavorable prognostic factor of disease progression. ETD, together with clinical predictors of tumor upgrading (PSAD, BPCD), showed the highest discriminative ability for

Table 3 Tumor progression in low and favorable intermediate risk prostate cancer (PCa) patients

Number (%)	No PCa progression	PCa progression	p-value	Multivariable model I (*)		Multivariable model II (*)	
	318 (88.1)	43 (11.9)		HR (95% CI)			
Follow-up (months), median (IQR)	37 (21–54)	45 (31–53)	0.282				
Clinical features				Clinical			
Age (years), median (IQR)	65 (61–70)	64 (60–68)	0.297				
BMI (kg/m^2), median (IQR)	25.6 (23.7–27.8)	25.4 (23.9–26.8)	0.677				
ET (ng/dL), median (IQR)	410.5 (316.7–510)	412.3 (334.2–490)	0.797				
ETD (ng/(dL x mL)), median (IQR)	10 (7–14.6)	11.7 (6.2–17.9)	0.465				
PSA (ng/mL), median (IQR)	5.7 (4.3–7.3)	6.5 (4.9–8)	0.039	excluded by model			
PSAD (ng/(mL x mL)), median (IQR)	0.13 (0.10–0.19)	0.18 (0.10–0.24)	0.033	66.581 (4.859–912.422)	0.002	99.906 (6.519–1531.133)	0.001
PV (mL), median (IQR)	40 (30–50)	36 (26–51)	0.388				
BPC (%), median (IQR)	28 (17–45.2)	33 (21–50)	0.125				
BPCD (%/mL), median (IQR)	0.70 (0.38–1.22)	0.84 (0.45–1.86)	0.107				
ASA, n (%)			0.768				
ASA 1	36 (11.3)	5 (11.6)					
ASA 2	258 (81.1)	36 (83.7)					
ASA 3	24 (7.5)	2 (4.7)					
cT, n (%)			0.988				
cT1c	237 (74.5)	32 (74)					
cT 2a/2b	81 (25.5)	11 (25.6)					
ISUP, n (%)			0.071				
ISUP 1	165 (51.9)	16 (37.2)					
ISUP 2	153 (48.1)	27 (62.8)					
Pathological features				Pathological			
PW (grams; gr), median (IQR)	52 (40–65)	49 (40 -68)	0.512				
TL (%), median (IQR)	15 (10–25)	20 (10–20)	0.389				
TLD (%/gr), median (IQR)	0.28 (0.16–0.53)	0.33 (0.19–0.50)	0.456				
ISUP, n (%)			< 0.0001				
ISU $p < 3$	211 (66.4)	16 (37.2)		Ref.			
ISUP > 2	107 (33.6)	27 (62.8)		3.203 (1.685–6.089)	< 0.0001	3.586 (1.874–6.863)	< 0.0001
pT, n (%)			< 0.0001				
pT2	282 (88.7)	31 (72.1)		Ref.			
pT3a	24 (7.5)	2 (4.7)		excluded by model			
pT3b	12 (3.8)	10 (23.3)		2.595 (1.222–5.512)	0.013	2.811 (1.359–5.818)	0.005
SM, n (%)			0.001				
NSM	246 (77.4)	23 (53.5)		Ref.			
PSM	72 (22.6)	20 (46.5)		1.984 (1.063–3.705)	0.031	excluded by model	

*Cox Proportional Hazards (Wald forward method)

predicting high TLD. The multivariable model including tumor aggressive factors (PSAD, BPCD, TLD) also showed the highest discriminatory ability in predicting high ETD. In either biopsy or surgical specimens, tumor quantitation is an important parameter to assess PCa extension; however, only the former is widely used to predict the risk of tumor upgrading, upstaging, and lymph node invasion, while the latter is rarely considered,

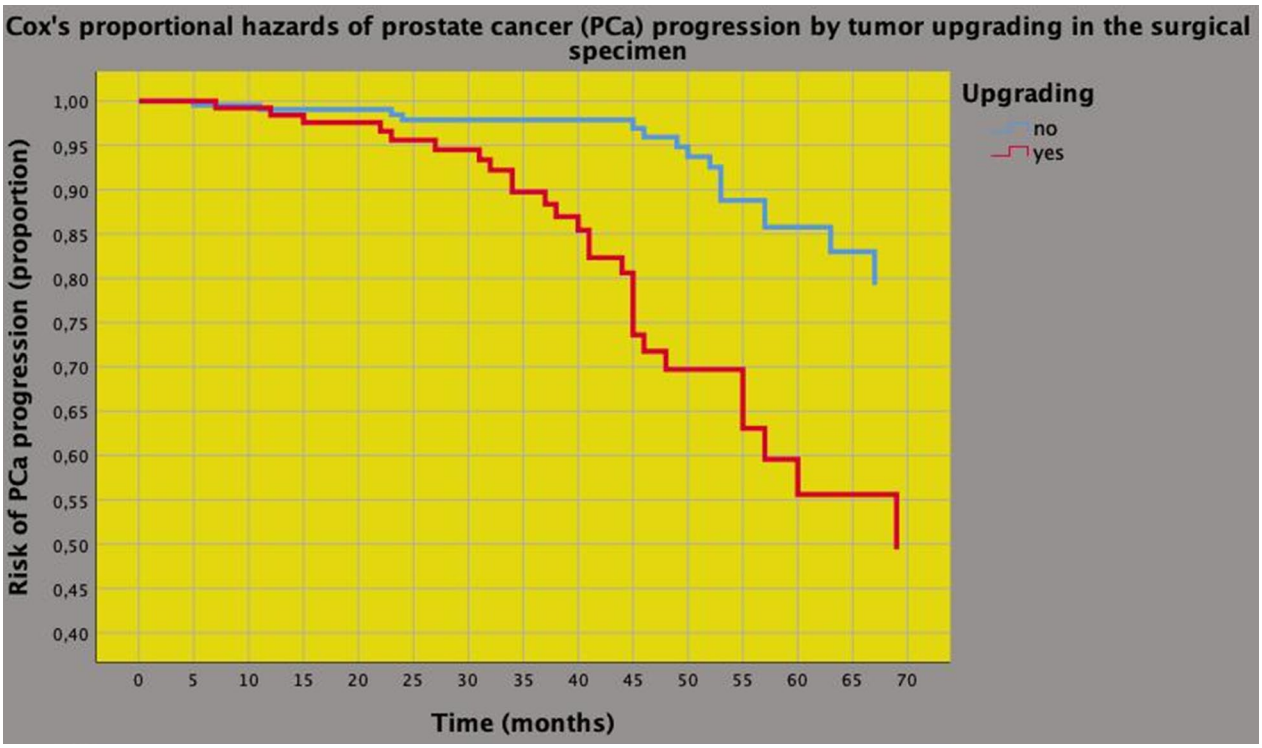

Fig. 5 Unadjusted Kaplan–Meier survival curves for the association between tumor upgrading and disease progression in low through favorable intermediate-risk prostate cancer patients treated with radical prostatectomy. As shown, compared with the not upgraded group, the upgraded group had a significantly increased risk of disease progression (HR = 3.790; 95% CI: 2.035–7.061; $p < 0.0001$). At a 60 months follow-up, 45% of upgraded patients had disease progression, which occurred in only 15% of non-upgraded cases

even though routinely reported [1, 2, 15]. Notably, biopsy tumor quantitation is included in NCCN and CAPRA systems as well as in nomograms for predicting lymph node invasion [1, 2, 20, 21]. Recently, a multicenter study showed that currently available nomograms have similar performances and limitations, with older ones performing better in patients undergoing systematic biopsy. Authors ascribe this result to the hypothesis that mpMRI doesn't add relevant information for the prediction of lymph node invasion (LNI) [22]. Therefore, biopsy tumor quantitation features may impact on stratification of the low through favorable intermediate PCa risk categories [1, 2, 23]. Specimen tumor quantitation, assessed as TL, is considered a surrogate for tumor extension, the association of which with tumor aggressive features is well established [1, 2, 15].

To our knowledge, this is the first study to highlight the implications of ET and tumor quantitation as density factors in low through favorable intermediate-risk classes. According to our multivariable clinical model, the risk of detecting high TLD increased with increasing ETD, but prostates bearing high tumor loads showed lower ET levels. Therefore, for the same prostate weight, patients showed higher tumor loads and lower ET levels. Tumor load density, which can be predicted by standard clinical factors including PSAD and BPCD, correlates with unfavorable disease features in the final pathology report. With our findings, we introduce ETD as a novel tool to better assess and stratify PCa patients in view of their unfavorable disease risk. Since prostate disorders are androgen-related, the association of ET levels and aggressive PCa have been investigated, but the topic is still controversial and controlled studies are lacking. Furthermore, the hormone is not measured periodically in the daily practice [24–26]. There is no clear relationship between ET and the risk of aggressive PCa, although most evidence points to an inverse connection between the two [24, 25]. In a Japanese study, hormonal levels were associated with unfavorable cancer features in the surgical specimen, including tumor upgrading and upstaging; however, it was limited by the small sample size (only 82 cases) and its retrospective nature [27]. An American retrospective study including 326 patients also showed that preoperative low ET levels were associated with features of advanced disease in the surgical specimen, but it did not take into account diurnal variations in testosterone [28]. Another large

American study including 879 patients demonstrated that lower ET levels predict advanced-stage disease in the surgical specimen, regardless of PSA and biopsy Gleason score; however, the study was retrospective and included a historical cohort [29]. Recently, new evidence from a large and heterogenous cohort of 762 patients with localized and metastatic disease showed that ET and clinically unfavorable disease were inversely related to each other; moreover, the same association was observed in the surgical specimen of 152 patients treated with primary RP; however, its retrospective design, the absence of some key features (i.e. PSAD, tumor quantitation, and density features), the adoption of different primary treatments (RP, RT, AS, hormonal therapy) and the presence of metastatic patients lower its quality [30]. Preoperative ET could also have a prognostic impact on the natural history of PCa. Røder et al. demonstrated that, in 277 patients undergoing surgery, low ET levels (≤ 11 nmol/L), equivalent to partial androgen deficiency levels, had a significantly higher risk of biochemical failure than cases with normal ET levels; however, this study suffered from multiple limitations, given the limited number of cases, the inclusion of patients from each risk group and during neoadjuvant treatments; furthermore, authors didn't assess disease progression, and didn't evaluate PV and pathological parameters in the surgical specimen [31]. Yamamoto et al. demonstrated that, in 304 subjects treated with RP, low ET (< 300 ng/dL) was an independent negative predictor of biochemical failure after adjusting for PSA, pathological Gleason score, and positive surgical margins; however, it is not comparable to our study because of its historical nature, inclusion of all risk classes, failure to measure PV, failure to assess disease metastases, and being retrospective [32]. In a large prospective study evaluating 455 patients undergoing surgery, Lane et al. observed that low ET (< 220 ng/mL) did not predict biochemical recurrence or disease progression, but did impose a high-grade tumor risk (predominance of Gleason pattern 4–5 cancer); however, it would be wrong to compare the two studies, the latter being dated, with all risk classes included and not assessing tumor density factors [33].

Our findings could deepen the theories linking ET to PCa biology. Both preoperative ET and PSA measurements adjusted for relative densities showed to be closely related to tumor aggressive features and disease progression. ETD, along with other clinical tumor parameters (PSAD, BPCD) was an independent predictor of high TLD in the surgical specimen. The risk of BPCD or TLD increases with increasing ETD; however, patients having the same ETD presented higher tumor density loads for low ET levels, suggesting that low ET levels have drawbacks on cancer progression. Our results support the pivotal role of low ET levels on androgen-dependent prostate cells. A decrease in ET levels occurs physiologically in middle-aged males [34]. Several studies investigating associations between ET and aggressive PCa have shown that prostate growth is strictly dependent on ET at very low levels, but when it decreases to critical points, it exerts negative feedback on androgen-dependent cell differentiation and division; furthermore, as long as prostate cells are continuously exposed to low ET levels, the risk of cancer induction and progression increases accordingly [34–36].

The main clinical implications of our study involve the management of low through favorable intermediate-risk patients. Although our cohort met the criteria for AS monitoring, 38.8% of patients had to be excluded because of tumor upgrading. Furthermore, final pathology revealed high-grade tumors (ISUP > 3) in 8.5% of the entire cohort. High TLD (above the first quartile) was correlated with the risk of upgrading, which occurred in 86.3% of subjects. Hence, ETD could have helped to discriminate high TLD from the multivariable model. As for linear models, ETD and tumor quantitation density features, including ET (low versus normal), could stratify patients according to the risk of tumor upgrading. These considerations reiterate the importance of ET levels and linear and nonlinear models to predict tumor quantitation density features. This would ensure a modern and simple approach to assess this particular subset of PCa patients; however, confirmatory studies are awaited. According to EAU recommendations, criteria for AS in patients with favorable intermediate-risk include ISUP grade group 2 with PSA < 10 ng/mL, pattern 4 < 10%, cT < 2b, low disease extent on imaging and biopsy; however, there is no agreement on either maximum number of cores that can be involved as well as the percentage of core involvement [1]. According to NCCN, favorable intermediate-risk PCa features include PSA 10–20 ng/mL or ISUP grade group 2 or cT2b-2c and BPC < 50%, as well [2]. To date, other clinical parameters are required to stratify candidates for deferred treatment with AS, and personalized risk-based approaches will ultimately replace protocol-based management. Measurements of ET and relative density features may help urologists and radiation oncologists to stratify patients for appropriate treatments.

Our study has several limitations. First, it has a retrospective design. Prostate volumes were not all measured at our institution. ET, and therefore also ETD,

were measured only once and not on a periodic base. A central pathologic review of external biopsies was not performed. The results of mpMRI were not evaluated because not every patient performed this exam. Genomic tests were not performed. The percentage of pattern 4 in biopsy ISUP grade group 2 and analysis of maximal cancer involvement of each core, which is important to assess indolent cancers, wasn't available for every patient and therefore was not performed [23]. Finally, our statistical analysis didn't reveal a significant association between ET and disease progression. However, our work has several strengths. Data were collected prospectively. A dedicated pathologist evaluated all prostate specimens. ET was measured at our laboratory, always in the morning, the appropriate interval for assessing hormone levels, which decrease in the afternoon [37].

5 Conclusions

In the low through favorable intermediate PCa risk classes, ETD was associated with tumor upgrading predictors. As ETD increased, so did tumor quantitation density factors, which further increased in men with low ET levels. Notably, men with increased PSAD and tumor upgrading were at increased risk of disease progression. In conclusion, ETD can provide pre-treatment information about aggressive PCa and suggest each patient's risk of disease progression.

Abbreviations

AS	Active surveillance
ASA	American Society of Anesthesiologists
AUC	Area under the curve
BPH	Benign prostatic hyperplasia
BPC	Biopsy positive cores
BPCD	Biopsy positive cores density
CAPRA	Cancer of the prostate risk assessment
CI	Confidence intervals
ET	Endogenous testosterone
ETD	Endogenous testosterone density
ePLND	Extended pelvic lymph node dissection
HR	Hazard ratio
IQR	Interquartile ranges
LNI	Lymph node invasion
mpMRI	Multiparametric magnetic resonance imaging
ORP	Open radical prostatectomy
PCa	Prostate cancer
PSA	Prostate specific antigen
PV	Prostate volume
PW	Prostate weight
PSAD	PSA density
RP	Radical prostatectomy
RT	Radiation therapy
ROC	Receiver operating curve
RARP	Robot-assisted radical prostatectomy
TRUS	Transrectal ultrasound
TL	Tumor load
TLD	Tumor load density
WW	Watchful waiting

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12301-023-00366-2.

Additional file 1. Associations of endogenous testosterone densityand prostate specific densitywith clinical and pathological factors in low and favorable intermediate risk prostate cancer patients treated with radical prostatectomy.

Author contributions

ABP provided the study design and conception, the manuscript's drafting, and the statistical analyses. AB provided the manuscript's drafting, analyses, and interpretation of data. SG, FD, PIO, ES, AP, CC, SV, DD, GM, RR, and NA carried out data collection. AT, VDM, FM, SZA, MB, SS, MAC and AA provided supervision and critical revision of the manuscript for important intellectual contents. All authors read and approved the final version of the manuscript.

Funding

This research received no external funding.

Availability of data and materials

All data generated or analyzed during this study are included in this article and its supplementary files. Further enquires can be directed to the corresponding author.

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of the Integrated University Hospital of Verona.

Informed consent

Informed consent was obtained from all subjects involved in the study.

Competing interests

The authors declare no conflict of interest.

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Received: 11 April 2023 Accepted: 16 June 2023
Published online: 29 June 2023

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