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Normal preoperative endogenous testosterone levels predict prostate cancer progression in elderly patients after radical prostatectomy

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Antonio Benito Porcaro*, **Andrea Panunzio***, **Alberto Bianchi**, **Clara Cerrato**, **Sebastian Gallina**, **Emanuele Serafin**, **Giovanni Mazzucato**, **Stefano Vidiri**, **Damiano D'Aietti**, **Rossella Orlando**, **Davide Brusa**, **Matteo Brunelli**, **Salvatore Siracusano**, **Vincenzo Pagliarulo**, **Maria Angela Cerruto**, **Alessandro Tafuri** and **Alessandro Antonelli**

Abstract

Background: The impact of senior age on prostate cancer (PCa) oncological outcomes following radical prostatectomy (RP) is controversial, and further clinical factors could help stratifying risk categories in these patients.

Objective: We tested the association between endogenous testosterone (ET) and risk of PCa progression in elderly patients treated with RP.

Design: Data from PCa patients treated with RP at a single tertiary referral center, between November 2014 and December 2019 with available follow-up, were retrospectively evaluated.

Methods: Preoperative ET (classified as normal if >350 ng/dl) was measured for each patient. Patients were divided according to a cut-off age of 70 years. Unfavorable pathology consisted of International Society of Urologic Pathology (ISUP) grade group >2, seminal vesicle, and pelvic lymph node invasion. Cox regression models tested the association between clinical/pathological tumor features and risk of PCa progression in each age subgroup.

Results: Of 651 included patients, 190 (29.2%) were elderly. Abnormal ET levels were detected in 195 (30.0%) cases. Compared with their younger counterparts, elderly patients were more likely to have pathological ISUP grade group >2 (49.0% *versus* 63.2%). Disease progression occurred in 108 (16.6%) cases with no statistically significant difference between age subgroups. Among the elderly, clinically progressing patients were more likely to have normal ET levels (77.4% *versus* 67.9%) and unfavorable tumor grades (90.3% *versus* 57.9%) than patients who did not progress. In multivariable Cox regression models, normal ET [hazard ratio (HR) = 3.29; 95% confidence interval (CI) = 1.27–8.55; $p = 0.014$] and pathological ISUP grade group >2 (HR = 5.62; 95% CI = 1.60–19.79; $p = 0.007$) were independent predictors of PCa progression. On clinical multivariable models, elderly patients were more likely to progress for normal ET levels (HR = 3.42; 95% CI = 1.34–8.70; $p = 0.010$), independently by belonging to high-risk category. Elderly patients with normal ET progressed more rapidly than those with abnormal ET.

Conclusion: In elderly patients, normal preoperative ET independently predicted PCa progression. Elderly patients with normal ET progressed more rapidly than controls, suggesting that longer exposure time to high-grade tumors could adversely impact sequential cancer mutations, where normal ET is not anymore protective on disease progression.

Keywords: age, elderly, progression, prostate cancer, radical prostatectomy, total testosterone

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Correspondence to:
Antonio Benito Porcaro
Department of Urology, University of Verona and Azienda Ospedaliera Universitaria Integrata Verona, Piazzale Stefani 1, 37126 Verona, Italy.
drporcaro@yahoo.com

Andrea Panunzio
Alberto Bianchi
Clara Cerrato
Sebastian Gallina
Emanuele Serafin
Giovanni Mazzucato
Stefano Vidiri
Damiano D'Aietti
Rossella Orlando
Davide Brusa
Maria Angela Cerruto
Alessandro Antonelli
Department of Urology, University of Verona and Azienda Ospedaliera Universitaria Integrata, Verona, Italy

Matteo Brunelli
Department of Pathology, University of Verona, Azienda Ospedaliera Universitaria Integrata, Verona, Italy

Salvatore Siracusano
Department of Life, Health and Environmental Sciences, University of L'Aquila, L'Aquila, Italy

Vincenzo Pagliarulo
Alessandro Tafuri
Department of Urology, Vito Fazzi Hospital, Lecce, Italy

*These authors contributed equally to this manuscript.

Introduction

Prostate cancer (PCa) represents the second most diagnosed tumor worldwide with an increasing incidence due to prostate-specific antigen (PSA) testing and the aging population. PCa is classified into three main prognostic groups according to the European Association of Urology (EAU) and the National Comprehensive Cancer Network guidelines.[1,2] In treating clinically localized disease, robot-assisted radical prostatectomy (RARP) with or without extended pelvic lymph node dissection (ePLND) is the most performed surgical procedure at tertiary referral centers, where it is also increasingly performed in elderly people with a life expectancy of at least 10 years. Although surgery in older patients is safe and feasible, functional outcomes related to urinary continence and erectile function are worse compared with their younger counterparts.[1–7] In addition, elderly patients undergoing surgery are more likely to have unfavorable disease characteristics, which implicates an increased risk of death due to PCa.[1–6,8–10] The potential unfavorable impact of senior age and related factors on oncological outcomes following PCa surgery remains controversial, however, and further clinical factors are required to stratify PCa risk classes, which are heterogeneous. In this perspective, molecular tumor analysis appears promising, but is still far from widespread use in clinical routine.[1,2]

The risk of PCa is multifactorial, and it has been associated with genetic, dietary, environmental, metabolic, and hormonal factors with endogenous testosterone (ET) being the main investigated androgen. Moreover, aging itself is a risk factor, as well.[1,2,11,12] We previously investigated the relationship between preoperative ET and PCa showing that total ET is associated with the risk of unfavorable disease in the surgical specimen.[13–18] In this study, we specifically aimed to test whether an association between preoperative ET levels and the risk of cancer progression in elderly with PCa exists.

Materials and methods

Population, data collection, and evaluation of parameters

Continuously collected data from 805 consecutive PCa patients treated with RP at the Department of Urology of Verona Integrated University Hospital, between November 2014 and December 2019 were retrospectively evaluated. All patients, who were not under androgen blockade, had ET (ng/dL) measured at our lab before surgery. The test was performed at least 1 month after prostate biopsies between 8.00 and 8.30 a.m. by radioimmunoassay. Age (years), body mass index (BMI; kg/m^2), and preoperative PSA (ng/ml) were collected for each patient. At our institution, the 14-core trans-perineal prostate biopsy technique was used. Prostate volume (PV; ml), evaluated by trans-rectal ultrasound (TRUS) standard methods, tumor grade, and percentage of biopsy positive cores (BPC), defined as the ratio between positive and total taken cores, was also recorded. Clinical staging was assessed using the 2017 version of the TNM staging system (8th edition) with clinical T stage only referring to digital rectal exam findings. Patients were classified into risk classes, as recommended by the EAU guidelines.[1] Preoperative physical status was evaluated by the American Society of Anesthesiologists (ASA) system.[19] Surgery was delivered by RARP or open radical prostatectomy (RP) and was performed by experienced surgeons. As previously reported, ePLND was performed according to international guidelines recommendations.[1,2] Nodal packets were submitted in separate packages according to a standard anatomical template including external iliac, internal iliac and obturator, Marcille's common iliac, and Cloquet's nodal stations, bilaterally.[20] Specimens including prostate and dissected lymph nodes were placed into formalin and evaluated by a dedicated uro-pathologist. Prostates were weighted (PW; grams), and tumors were graded according to the International Society of Urologic Pathology (ISUP) system.[1,2] Tumor quantitation was assessed as tumor load (TL), which was defined as the percentage of prostate involved by cancer; specifically, our dedicated pathologist assessed tumor quantitation by visual estimation of all the glass slides after all microscopically identifiable foci of carcinoma have been circled with a marked pen, as considered by the ISUP association.[21] Surgical margins were stated as 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 using the 2017 version of the TNM staging system (8th edition), accordingly.[1,2]

Oncological and survival outcomes

Supposing the interaction between advancing age and unfavorable PCa, this study aimed to test the

hypothesis of an association between preoperative ET levels and PCa progression in elderly patients. Specifically, a cut-off age of 70 years was decided according to EAU recommendations, which suggest that patients aged ⩾70 years (senior age) should receive a comprehensive geriatric assessment before any treatment. Preoperative total ET levels were classified as low (<230 ng/dl), intermediate (230–350 ng/dl), and normal (>350 ng/dl) according to an international standard consensus.[22] In this study, low through intermediate ET levels were both coded as abnormal. Unfavorable pathology included ISUP grade group >2, seminal vesicle invasion (SVI), and pelvic lymph node invasion (PLNI). Patients were followed-up, according to the EAU recommendations.[1] At PSA persistence/recurrence, imaging modalities were considered to restage the disease and plan further treatments. Disease progression was defined as the event of biochemical recurrence (BCR) and local recurrence and distant metastases, as well.

Statistical analysis

Descriptive statistics included frequencies and proportions for categorical variables. Medians and interquartile ranges (IQRs) were reported for continuously coded variables. Univariable and multivariable logistic regression models tested the associations between clinical and pathological factors and age, dichotomized as <70 *versus* ⩾70 years. The length of time between surgery and PCa progression or the last available follow-up was measured as time to event occurrence. In each specified age subgroup, univariable and multivariable Cox proportional hazards regression models tested the associations between ET levels and the risk of PCa progression; accordingly, hazard ratios (HRs) and relative 95% confidence intervals (CIs) were evaluated. Clinical models including EAU risk classes and ET categories stratified by age subgroups were computed, and appropriate survival risk curves were generated. The software used to run the analysis was IBM-SPSS version 26.0 (IBM Corp., Armonk, NY, USA). All tests were two-sided with $p < 0.05$ considered to indicate statistical significance.

Results

Demographics and tumor characteristics of the study population

Overall, 651 surgically treated PCa patients with available follow-up data were included (Table 1). Of these, 190 (29.2%) were elderly (age ⩾70 years) with a median age of 72 (IQR = 71–74) years. RARP was performed in 580 (89.1%) patients with no statistically significant difference between age subgroups. Clinically, patients aged ⩾70 years were more likely to have high-grade tumors compared with their younger counterparts (21.6% *versus* 10.4% ISUP 4–5) and to belong to the high-risk EAU class, accordingly. Overall, abnormal ET levels were detected in 195 (30%) patients, with no statistically significant differences between the age subgroups (30.5% *versus* 29.7%). Regarding pathological tumor features, compared with their younger counterparts, elderly patients were more likely to bear larger prostates (56 *versus* 50 g), and to have adverse pathology concerning tumor stage (12.6% *versus* 7.8% pT3a and 16.3% *versus* 10.8% pT3b), as well as tumor grade (63.2% *versus* 49.0% ISUP >2).

Adverse impact of ET on PCa progression according to age subgroups

Median follow-up was 39.0 (IQR = 22.0–53.0) months being 39.0 (IQR = 23.0–52.5) and 36.0 (IQR = 20.7–53.0) months for younger and elderly patients, respectively. Overall, PCa progression occurred in 108 (16.6%) patients, resulting in 77 (16.7%) and 31 (16.3%) younger and elderly patients, respectively.

The association between clinical and pathological factors and the risk of PCa progression for the younger age subgroup is reported in Supplementary Table 1. Patients having unfavorable pathology including ISUP grade groups >2 (HR = 2.35; 95% CI = 1.39–3.97; $p < 0.001$) and SVI (HR = 1.87; 95% CI = 1.09–3.19; $p = 0.023$) were more likely to progress as those presenting clinically with smaller prostates (HR = 0.98; 95% CI = 0.97–0.99; $p = 0.021$) and with features of intermediate risk category [ISUP 2–3 (HR = 1.70; 95% CI = 1.06–2.73; $p = 0.027$) and PSA between 10 and 20 ng/ml (HR = 1.97; 95% CI = 1.12–3.47; $p = 0.019$)] and of high-risk category [PSA >20 ng/ml, (HR = 4.88; 95% CI 2.52–9.50; $p < 0.001$)], as well.

The association between clinical and pathological factors and the risk of PCa progression for the elderly subgroup is reported in Table 2. Clinically progressing elderly patients were more likely to have normal ET levels (HR = 3.29; 95% CI = 1.27–8.55; $p = 0.014$) and unfavorable tumors grade [ISUP 4–5 (HR = 6.89; 95% CI = 1.94–24.44; $p = 0.003$)]. Also, progressing

Table 1. Demographics and tumor characteristics of 651 prostate cancer patients treated with radical prostatectomy, stratified according to age groups (<70 *versus* ⩾70 years).

	Age <70 years	Age ⩾70 years	Univariate analysis		Multivariate analysis	
Number	461 (70.8)	190 (29.2)	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Age (years)	63 (58–66)	72 (71–74)				
Clinical factors						
Endogenous testosterone (ng/dl)						
Abnormal	137 (29.7)	58 (30.5)	Reference	–	Reference	–
Normal	324 (70.3)	132 (69.5)	0.96 (0.67–1.39)	0.8	0.87 (0.60–1.28)	0.5
BMI (kg/m^2)	25.4 (23.7–28.2)	25.7 (24–28.1)	1.00 (0.95–1.05)	0.9	0.99 (0.93–1.04)	0.6
ASA score system						
1	51 (11.1)	13 (6.8)	Reference	–	Reference	–
2	377 (81.8)	160 (84.2)	1.61 (0.87–2.98)	0.1	1.48 (0.79–2.78)	0.2
3	33 (7.2)	17 (8.9)	1.95 (0.85–4.47)	0.1	1.56 (0.66–3.70)	0.3
Prostate volume (ml)	40 (30–51)	45 (30.4–58)	1.01 (1.00–1.02)	0.06	1.01 (0.99–1.02)	0.07
PSA (ng/ml)						
<10	373 (80.9)	152 (80.0)	Reference	–	Reference	–
10–20	68 (14.8)	31 (16.3)	1.12 (0.70–1.78)	0.6	0.96 (0.59–1.56)	0.9
>20	20 (4.3)	7 (3.7)	0.86 (0.36–2.07)	0.7	0.63 (0.25–1.60)	0.3
Percentage of biopsy positive cores (%)						
<50	327 (70.9)	135 (71.1)	Reference	–	Reference	–
⩾50	134 (29.1)	55 (28.9)	0.99 (0.69–1.44)	0.9	0.94 (0.63–1.39)	0.8
Clinical tumor stage						
cT1	302 (65.5)	130 (68.4)	Reference	–	Reference	–
cT2/cT3	159 (34.5)	60 (31.6)	0.88 (0.61–1.26)	0.5	0.75 (0.51–1.10)	0.1
ISUP grade group						
1	164 (35.6)	55 (28.9)	Reference	–	Reference	–
2–3	249 (54)	94 (49.5)	1.13 (0.77–1.66)	0.5	1.20 (0.81–1.78)	0.4
4–5	48 (10.4)	41 (21.6)	2.55 (1.52–4.27)	**<0.001**	3.08 (1.74–5.45)	**<0.001**
Clinical node stage						
cN0-cNX	438 (95.0)	182 (95.8)	Reference	–	Reference	–
cN1	23 (5.0)	8 (4.2)	0.88 (0.61–1.26)	0.5	0.75 (0.51–1.10)	0.1

(Continued)

Table 1. (Continued)

	Age <70 years	Age ⩾70 years	Univariate analysis		Multivariate analysis	
Pathological factors						
Prostate weight (g)	50 (40–64)	56 (45–70.4)	1.02 (1.01–1.03)	**<0.001**	1.02 (1.01–1.03)	**<0.001**
Tumor load (%)	20 (10–30)	18.7 (10–30)	0.99 (0.70–1.01)	0.7	0.99 (0.98–1.00)	0.1
ISUP grade group						
⩽2	235 (51.0)	70 (36.8)	Reference	–	Reference	–
>2	226 (49.0)	120 (63.2)	1.78 (1.22–2.65)	**0.003**	1.79 (1.22–2.65)	**0.003**
Pathological tumor stage						
pT2	375 (81.3)	135 (71.1)	Reference	–	Reference	–
pT3a/ECE	36 (7.8)	24 (12.6)	1.85 (1.07–3.22)	**0.029**	1.69 (0.94–3.03)	0.08
pT3b/SVI	50 (10.8)	31 (16.3)	1.72 (1.06–2.81)	**0.029**	1.65 (0.93–2.94)	0.09
Surgical margins						
Negative (R0)	339 (73.3)	138 (72.6)	Reference	–	Reference	–
Positive (R1)	122 (26.5)	52 (27.4)	1.05 (0.72–1.53)	0.8	1.06 (0.70–1.61)	0.8
Pathological node stage						
pN0-pNX	422 (91.5)	169 (88.9)	Reference	–	Reference	–
pN1	39 (8.5)	21 (11.1)	1.35 (0.77–2.35)	0.3	0.86 (0.45–1.64)	0.7

BMI, body mass index; CI, confidence interval; ECE, extra-capsular extension; ISUP, International Society of Urologic Pathology; OR, odds ratio; PSA, prostate-specific antigen; SVI, seminal vesicle invasion.
Continuous variables are reported as medians (IQR, interquartile ranges) and categorical factors as frequencies (percentages).
Bold values are those that are statistically significant ($p < 0.05$).

Table 2. Association between clinical and pathological factors and the risk of prostate cancer (PCa) progression among 190 patients with age ⩾70 years.

	No PCa progression	PCa progression	Univariable analysis		Multivariable analysis (*)	
	159 (83.7)	**31 (16.3)**	**HR (95% CI)**	***p* value**	**HR (95% CI)**	***p* value**
Clinical model						
ET abnormal	51 (32.1)	7 (22.6)	Reference	–	Reference	–
ET normal	108 (67.9)	24 (77.4)	3.41 (1.35–8.61)	**0.010**	3.29 (1.27–8.55)	**0.014**
Age	72 (71–74)	72 (70–73)	0.95 (0.78–1.17)	0.6		
BMI	25.7 (23.8–28.4)	25.7 (24.2–27.4)	0.96 (0.85–1.09)	0.3		
ASA 1	11 (6.9)	2 (6.5)	Reference	–		
ASA 2	132 (83.0)	28 (98.3)	1.26 (0.30–5.37)	0.7		
ASA 3	16 (10.1)	1 (3.2)	0.48 (0.04–5.26)	0.5		
PV	42.9 (30–57)	50 (36–51)	1.02 (0.99–1.04)	0.2		

(Continued)

Table 2. (Continued)

	No PCa progression	PCa progression	Univariable analysis		Multivariable analysis (*)	
	159 (83.7)	**31 (16.3)**	**HR (95% CI)**	***p* value**	**HR (95% CI)**	***p* value**
PSA <10 ng/ml	131 (82.4)	21 (67.7)	Reference	–		
PSA 10–20 ng/ml	23 (14.5)	8 (25.8)	2.11 (0.93–4.80)	0.08		
PSA > 20 ng/ml	5 (3.1)	2 (6.5)	2.66 (0.62–11.42)	0.2		
BPC <50%	115 (72.3)	20 (64.5)	Reference	–		
BPC ⩾50%	44 (27.7)	11 (35.5)	1.13 (0.54–2.36)	0.8		
cT1	110 (69.2)	20 (64.5)	Reference	–		
cT2-cT3	49 (30.8)	11 (35.5)	1.67 (0.80–3.52)	0.2		
ISUP 1	52 (32.7)	3 (9.7)	Reference	–	Reference	-
ISUP 2–3	80 (50.3)	14 (45.2)	3.45 (0.99–12.03)	0.052		
ISUP 4–5	27 (17.0)	14 (15.2)	7.21 (2.05–25.36)	**0.002**	6.89 (1.94–24.44)	**0.003**
cN0-cNx	155 (97.5)	27 (87.1)	Reference	–		
cN1	4 (2.5)	4 (12.9)	4.59 (1.59–13.24)	**0.005**		
Pathological model						
PW	55 (45–70)	59 (45–77)	1.00 (0.99–1.02)	0.7		
TL	15 (10–30)	20 (10–40)	1.05 (1.02–1.07)	<**0.001**	1.03 (1.01–1.05)	**0.016**
ISUP ⩽2	67 (42.1)	3 (9.7)	Reference	–	Reference	
ISUP >2	92 (57.9)	28 (90.3)	9.37 (2.82–31.15)	<**0.001**	5.62 (1.60–19.79)	**0.007**
pT2	117 (73.6)	18 (51.8)	Reference	–		
ECE	21 (13.2)	3 (9.7)	0.95 (0.28–3.26)	0.9		
SVI	21 (13.2)	10 (32.3)	2.54 (1.15–5.61)	**0.021**		
R0	117 (73.6)	21 (67.7)	Reference	–		
R1	42 (26.4)	10 (32.3)	1.46 (0.68–3.12)	0.3		
pN0-pNx	150 (94.3)	19 (61.3)	Reference	–	Reference	
pN1	9 (5.7)	12 (38.7)	5.11 (2.45–10.63)	<**0.001**	3.13 (1.48–6.62)	**0.003**

ASA, American Society of Anesthesiologists; BMI: body mass index; BPC, biopsy positive core; CI, confidence interval; ECE, endogenous testosterone; ET, endogenous testosterone; HR, hazard ratio; ISUP, International Society of Urologic Pathology; PCa, prostate cancer; PSA, prostate-specific antigen; PV, prostate volume; PW, prostates were weighted; SVI, seminal vesicle invasion; TL, tumor load.
Continuous variables are reported as medians and interquartile range (IQR), and categorical factors as frequencies and percentages.
*By the Wald forward method (see also Table 1).

elderly patients were more likely to have unfavorable pathology such as higher TLs (HR = 1.03; 95% CI = 1.01–1.05; $p = 0.016$) and higher rates of ISUP grade group >2 (HR = 5.62; 95% CI = 1.60–19.79; $p = 0.007$) and of PLNI (HR = 3.13; 95% CI = 1.48–6.62; $p = 0.003$).

Table 3. Multivariable clinical model predicting prostate cancer progression by endogenous testosterone and EAU clinical risk classes in population and age groups of patients treated with radical prostatectomy.

Statistics (*)	Overall population ($n=651$)	Age <70 years ($n=461$)	Age ≥ 70 years ($n=190$)
	HR (95% CI)	HR (95% CI)	HR (95% CI)
ET			
Abnormal	Reference		Reference
Normal	1.66 (1.07–2.58)		3.42 (1.34–8.70)
p value	0.024		0.010
EAU class risk			
Low	Reference	Reference	Reference
Intermediate	2.85 (1.49–5.44)	2.86 (1.40–2.65)	
p value	0.002	0.004	
High	4.16 (2.12–8.17)	3.54 (1.65–7.70)	2.66 (1.30–5.42)
p value	<0.001	0.001	0.007

CI, confidence interval; EAU, European Association of Urology; ET, endogenous testosterone; HR, hazard ratio.
*Multivariable analysis by the Wald forward method excluding not significant variables.

On clinical multivariable models testing preoperative ET levels as an independent predictor of PCa progression, that also adjusted for EAU risk classes, elderly patients were more likely to progress for normal ET levels (HR = 3.42; 95% CI = 1.34–8.70; $p = 0.010$), independently by belonging to the high-risk category, as detailed in Table 3. Interestingly, high-risk PCa was more aggressive in elderly with 50% progressing at the time of 57 months compared with their younger counterparts, where 50% progressed at the time of 67 months, as depicted in Figures 1 and 2, respectively. Also, normal preoperative ET had a negative prognostic impact in elderly patients, who progressed more rapidly than those with abnormal preoperative ET levels, as shown in Figure 3.

Discussion

At tertiary referral centers, elderly patients diagnosed with PCa are increasingly treated with surgery, which is almost exclusively delivered by RARP with rates ranging from 7.7% up to 26.8%.[3,5,7–9,23,24] Generally, these patients show lower survival rates, more frequently harbor high-risk disease, and less likely receive local therapy,[1,2,10] In contemporary series, oncological outcomes are controversial; accordingly, although elderly patients are more likely to harbor unfavorable pathology, this might or might not translate into an increased risk of disease progression and reduced cancer-specific survival.[1–5,9,25,26] Different meta-analyses investigated the relationship between endogenous and exogenous testosterone and the risk of developing PCa,[27–30] but, to the best of our knowledge, no meta-analysis has investigated the role of preoperative testosterone levels as predictors of postoperative outcomes yet. In this context, the exact relationship between preoperative total testosterone levels and clinically relevant PCa and PCa progression is still controversial for the relation being reported as positive, inverse, or even null.[31,32] There are studies showing that normal ET levels protect against the risk of unfavorable pathology, but do not have any influence on BCR or disease progression.[33–36] Conversely, it has also been demonstrated that low ET was a significant predictor for PSA failure after surgery in localized PCa,[37,38] and could be predictive of higher-stage and higher-grade disease.[39] Nevertheless, Salonia *et al.*[40] found that preoperative serum sex steroids were independent predictors of early BCR in a cohort of 605 patients treated with RP with no significant association between low testosterone levels and early BCR. Despite many studies on the topic, however, the specific association between preoperative ET and

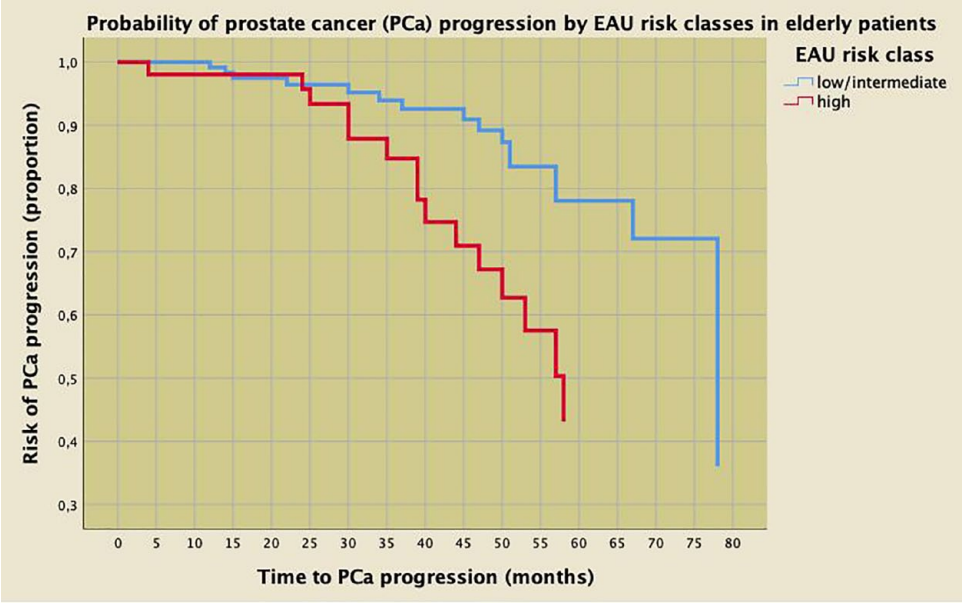

Figure 1. Risk curves of time to prostate cancer (PCa) progression in patients aged ⩾70 years comparing high-risk *versus* low-/intermediate-risk classes according to the European Association of Urology (EAU) system. High-risk patients progressed more rapidly than low-/intermediate-risk patients with a median time of about 57 months for the former and 78 months for the latter.

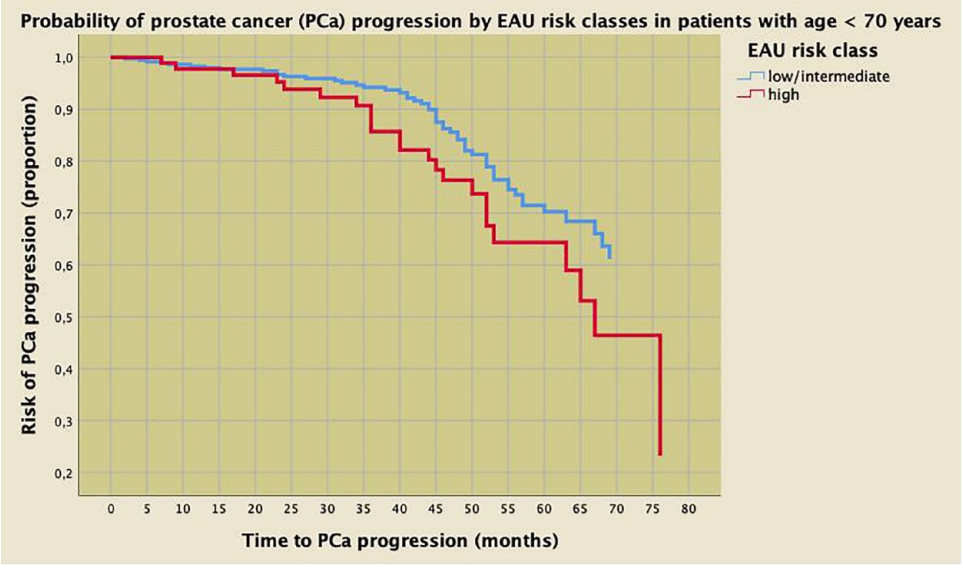

Figure 2. Risk curves of time to prostate cancer (PCa) progression in patients aged <70 years comparing high-risk *versus* low-/intermediate-risk classes according to the European Association of Urology (EAU) system. As shown, median time to disease progression was about 67 months for the high-risk class and not even reached for the low-/intermediate-risk classes, as well.

disease progression in elderly PCa patients is still an unexplored subject.

In this study, about one-third of patients had a senior age and underwent RARP in approximately 90% of cases, thus producing oncological results of an RARP series, as well. Although senior age was associated with high-risk PCa with unfavorable tumor-grade pathology, it did not specifically predict disease progression thus confirming literature results. The natural history of PCa in the elderly was not the same as for their younger counterparts, however. Progressing elderly patients were more likely to have higher

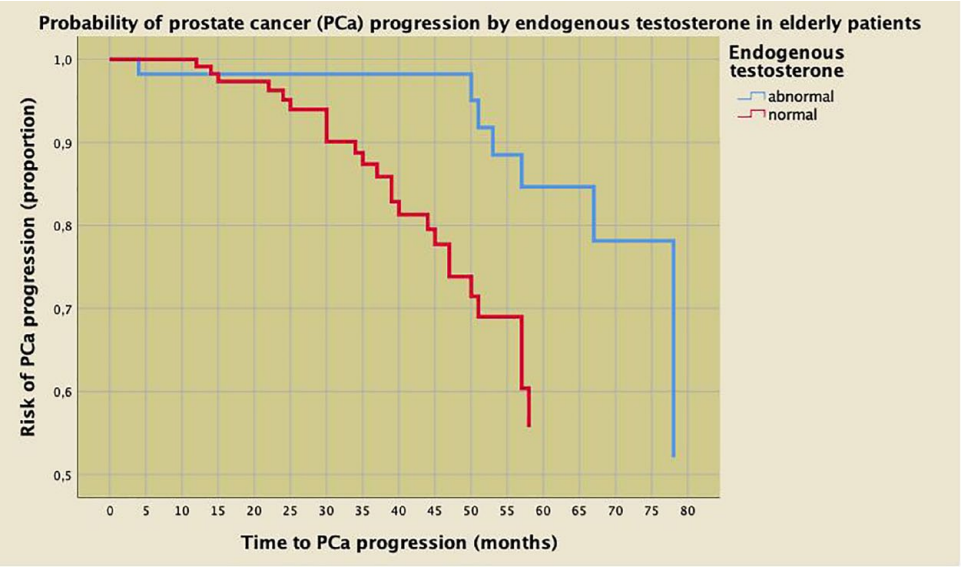

Figure 3. Risk curves of time to prostate cancer (PCa) progression in patients aged ⩾70 years comparing normal *versus* abnormal preoperative endogenous total testosterone levels. According to an international standard consensus, total testosterone was classified normal for levels above 350 ng/dl. Elderly patients with normal total testosterone levels progressed more rapidly than those with abnormal one; specifically, 40% PCa progression occurred at about 57 months for the former and at about 77 months for the latter, as well.

rates of unfavorable pathology, including tumors greater than ISUP 2 and PLNI. Moreover, they were more likely to progress faster than their younger counterparts for the EAU high-risk category, as well. Interestingly, elderly patients presenting preoperatively with normal ET levels were more likely to progress than those having abnormal total ET levels, independently of belonging or not to the high-risk EAU class. Taken together, this study shows two main results, which represent a novelty for the current literature concerning this subject. First, senior age is an adverse prognostic factor for patients belonging to the EAU high-risk class. Second, normal preoperative ET levels are an adverse prognostic factor for PCa progression in elderly patients undergoing surgery, independently of the EAU risk class. These results should be considered when dealing with elderly with PCa because of implications for treatment and for the natural history of the disease.

The results of this study need explanation and interpretation, as well. We have shown that senior age has an indirect adverse impact on disease progression because elderly patients were more likely to harbor adverse pathology that associated with high-grade tumors. There are theories stressing the importance of physiological total testosterone levels in order to maintain the prostate dependent cells healthy and functional.[31,32] Notably, although a decrease in total testosterone is physiological in middle-aged males, its decrement can reach critical points that destabilize androgen receptors of prostate cells, which undergo dedifferentiation and tumor induction.[41] This study has implications in interpreting the natural history of PCa in elderly people. First, we have shown that these individuals were more likely to have unfavorable pathology including high-grade tumors and PLNI, as well as to progress more rapidly than their younger counterparts. Second, we have demonstrated that normal preoperative ET levels were not protective in the elderly, as well. These findings might be explained by the fact that elderly patients with PCa could have a longer time exposure to high-grade tumors, which will have the potential to undergo multiple sequential mutations leading to more lethal cancers progressing to PLNI, when compared with those detected in younger patients, as well. Moreover, normal ET levels are no more protective in elderly patients because of the advanced sequence of mutations that makes androgen receptors insensible to total testosterone levels for the induced intra-tumoral production of testosterone, accordingly. These interpretations, however, need controlled studies to verify these hypotheses, which could have important clinical implications and could lead to

strategies for treating PCa in elderly patients, in the near future.

This study may have implications in clinical practice, as well. First, senior age is a further risk factor for disease progression in high-risk PCa, which shows faster dynamics than in younger patients. Accordingly, neoadjuvant and adjuvant treatments should be considered in elderly patients with PCa, who present with high-risk disease and are fit for radical prostate surgery, as well. Second, abnormal ET levels in elderly patients undergoing surgery are protective while normal levels represent a further risk factor of progression, independently of the EAU risk category. Accordingly, neoadjuvant and adjuvant androgen blockade with first- and second-line medications is an option to consider in these individuals, especially if belonging to the EAU high-risk class, as well. Multicenter prospective controlled studies are required to assess the hypothesis, however.

Several limitations need to be acknowledged. First, this is a retrospective and single-center study. Second, there was a preselection bias of elderly patients, who were more likely to receive surgical treatment, accordingly. Third, total testosterone was measured only once and not on a periodic base. Fourth, central pathology review of external biopsies was not performed. Fifth, the results of multiparametric magnetic resonance imaging were not evaluated for not being available in all patients. Sixth, genomic tests were not performed. Seventh, the percentage of pattern 4 in biopsy ISUP grade group 2 has not been evaluated. Nevertheless, this study has several strengths, as well. For example, all prostate specimens were assessed by our dedicated uro-pathologist; total testosterone was measured in the morning, which is the appropriate period for evaluating hormonal levels, which decrease in the afternoon; data were prospectively collected. As, according to the existing literature, the relationship between ET and PCa oncological outcomes is still a controversial topic, future controlled studies are needed to better define its role in the biology of PCa.

Conclusion

In elderly patients with PCa treated with RP, high-grade tumors, and normal ET independently predicted cancer progression. Notably, elderly patients with normal ET progressed more rapidly than controls suggesting that longer exposure time to high-grade tumors could adversely impact sequential cancer mutations, where normal total testosterone is not anymore protective on disease progression. Confirmatory studies are required.

Declarations

Ethics approval and consent to participate

Institutional Review Board approval was obtained from Azienda Ospedaliera Universitaria Integrata of Verona's Ethical Committee. An approval ID was not provided. Written informed consent was obtained from all individual participants included in the study.

Consent for publication

Informed consent to publish was obtained from all individual participants included in the study.

Author contributions

Antonio Benito Porcaro: Conceptualization; Formal analysis; Methodology; Project administration; Writing – original draft; Writing – review & editing.

Andrea Panunzio: Data curation; Writing – original draft; Writing – review & editing.

Alberto Bianchi: Data curation.

Clara Cerrato: Data curation.

Sebastian Gallina: Data curation.

Emanuele Serafin: Data curation.

Giovanni Mazzucato: Data curation.

Stefano Vidiri: Data curation.

Damiano D'Aietti: Data curation.

Rossella Orlando: Data curation.

Davide Brusa: Data curation.

Matteo Brunelli: Supervision.

Salvatore Siracusano: Supervision.

Vincenzo Pagliarulo: Supervision.

Maria Angela Cerruto: Supervision.

Alessandro Tafuri: Writing – original draft; Writing – review & editing.

Alessandro Antonelli: Supervision.

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ORCID iDs

Antonio Benito Porcaro https://orcid.org/0000-0002-7890-040X
Emanuele Serafin https://orcid.org/0000-0002-5646-9719
Alessandro Tafuri https://orcid.org/0000-0003-1404-2925

Supplemental material

Supplemental material for this article is available online.

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