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Basal total testosterone serum levels predict biopsy and pathological ISUP grade group in a large cohort of Caucasian prostate cancer patients who underwent radical prostatectomy

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Abstract

Aims: The study aimed to evaluate associations of preoperative total testosterone (TT) with the risk of aggressive prostate cancer (PCA).

Materials & methods: From 2014 to 2018, basal TT levels were measured in 726 consecutive PCA patients. Patients were classified according to the International Society of Urologic Pathology (ISUP) system. Aggressive PCA was defined by the detection of ISUP > 2 in the surgical specimen. The logistic regression model evaluated the association of TT and other clinical factors with aggressive PCA.

Results: On univariate analysis, there was a significant association of basal TT with the risk of aggressive PCA as well as age, prostate-specific antigen (PSA), percentage of biopsy positive cores (BPC), tumor clinical stage (cT), and biopsy ISUP grade groups. On multivariate analysis, two models were considered. The first (model I) excluded biopsy ISUP grading groups and the second (model II) included biopsy ISUP grade groups. Multivariate model I, revealed TT as well as all other variables, was an independent predictor of the risk of aggressive disease [odds ratio (OR) = 1.585; 95% confidence interval (CI): 1.113–2.256; $p = 0.011$]. Elevated basal PSA greater than 20 µg/dl was associated with the risk of aggressive PCA. Multivariate model II revealed that basal TT levels maintain a positive association between aggressive PCA, whereas age, BPC, and clinical stage cT3 lost significance. In the final adjusted model, the level of risk of TT did not change from univariate analysis (OR = 1.525; 95% CI: 1.035–2.245; $p = 0.011$).

Conclusion: Elevated preoperative TT levels are associated with the risk of aggressive PCA in the surgical specimen. TT may identify patients who are at risk of aggressive PCA in the low and intermediate European Association of Urology (EAU) risk classes.

Keywords: prostate cancer, prostate biopsy, radical prostatectomy, testosterone serum level, prostate cancer grade, ISUP grade groups

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Introduction

Prostate cancer (PCA) is a critical issue because it is the second most common male cancer worldwide and its incidence increases with age.[1] When patients receive a PCA diagnosis, it is important to stage and classify them into risk groups according to the D'Amico criteria or European Association of Urology (EAU) risk classes,[1] in

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order to define the prognosis and plan appropriate treatments. Tumor grade groups, prostate-specific antigen (PSA), and clinical tumor stage are parameters used in this process to classify patients into prognostic risk groups.[2] Recently, the International Society of Urologic Pathology (ISUP) has classified prostate tumors into five grade groups that correlate with the natural history of the disease, and, as it has been reported, ISUP tumor grade group classification is the most important, since expressing PCA biology will affect the natural history of the disease.[3] Moreover, it is known that PCA is a hormonally influenced disease, and that systemic serum androgen levels play a pivotal role in its biological course. However, the relationship between preoperative testosterone serum levels and PCA stage and grade is debated. Indeed, some studies suggests a linear correlation between preoperative androgen levels and aggressveness of PCA.[4–6] On the contrary, other authors found that low levels of testosterone are associated with more aggressive PCA.[7–9] It is known that many emerging chronic diseases, such as obesity,[10,11] may influence testosterone levels in middle-aged men either by directly influencing the hypothalamic-pituitary-testicular axis or through a peripheral effect.[12]

The aim of this study was to evaluate associations of basal total testosterone (TT) with biopsy and pathology tumor grade groups in a large cohort of PCA patients who underwent radical prostatectomy (RP).

Materials and methods

Study population

Institutional Review Board approval was obtained from Azienda Ospedaliera Universitaria Integrata of Verona ethical committee, and a retrospective analysis of prospectively collected data was done. Each patient provided informed signed consent for data collection. In a period ranging from November 2014 to December 2018, preoperative basal levels of TT and PSA were measured in 726 consecutive patients who were not under androgen deprivation therapy and underwent RP with or without extended pelvic lymph node dissection (ePLND). Serum samples of TT and PSA were obtained from a cubital vein at least 1 month after biopsies; between 8.00 and 8.30 a.m. All samples were analyzed in our laboratory. Plasma levels of TT (ng/dl) and PSA (ng/ml) were determined by radioimmunoassay. Age (years), body mass index (BMI; kg/m^2), prostate volume (ml) and biopsy positive cores (BPC; percentage) were calculated for each case.

Clinical staging and surgery

Tumor, nodal, and metastatic status was assessed according to the TNM system. Pelvic lymph node staging (cN) was performed by axial imaging modalities. Enlarged pelvic nodes measuring more than 1 cm in diameter were staged as cN1 disease. The metastatic status was investigated by both axial imaging and total bone scans. Patients were classified according to EAU risk classes.[1]

Skilled and experienced surgeons performed RP with ePLND specifically using the robot-assisted (RARP) or open retro-pubic (RRP) approach. RARP was delivered by the da Vinci Robot System (Intuitive Surgical, Inc., Sunnyvale, CA, USA) and was performed through the trans-peritoneal approach with anterograde prostatic dissection.[13] RRP was performed according to the technique described by Walsh. The decision to perform an extended lymph node dissection was based mainly on pre-operative nomograms showing a risk of lymph node invasion (LNI) greater than 5%.[1] In low-risk patients, the decision to perform an ePLND was based on clinical factors indicating increased risk of tumor upgrading in the surgical specimen according to our prior experience.[14–17]

Assessment of prostate biopsies and surgical specimens

Biopsies performed elsewhere were assessed for the following features: (a) at least 12 biopsy cores; (b) the reported number of positive cores; (c) measurement of prostate volume (ml). In our Institution, a 14-core trans-perineal guided prostate biopsy technique was used.[18] Prostate volume (ml) was measured by standard methods. Tumors were classified into grade groups according to the ISUP system.[19] Our dedicated pathologist assessed all specimens, which were processed according to the Stanford protocol.[20] The ISUP grade group system was applied to classify tumors.[19] Surgical margins were stated positive when cancer invaded the inked surface of the specimen. Nodal packets were grouped according to a standard template and submitted in separate packages. Lymph nodes were assessed

for histopathology after hematoxylin and eosin staining. Immunohistochemical staining was performed when appropriate. In each case, the number of removed lymph nodes and LNI was assessed. Prostate and nodal specimens were then staged according to the TNM system.

Study design and statistical methods

The aim of the study was to test the hypothesis that basal TT is associated "with aggressive" disease, which is defined as the presence of ISUP grade group > 2 in the surgical specimen. The patient population was classified into two groups according to tumor classification detected in the surgical specimen: those having an ISUP grade system $\leqslant 2$ (non-aggressive PCA) and those with ISUP grade > 2 (aggressive PCA). To assess the relationship between TT and PCA aggressiveness, TT was categorized by the first quartile in order to assess its ability in predicting aggressive disease.

Furthermore, the population was stratified according to TT, dividing patients at the median (low TT below the median and high TT above the median), then the association between the risk of aggressive disease (ISUP grade 3–5 *versus* 1–2) and high-grade disease defined as ISUP grade 4–5 (*versus* 1–3) in the pathological specimen was evaluated. Other significant variables were also categorized in order to evaluate their ability to predict aggressive PCA.

Summary statistics and distributions of factors between groups were assessed. Data on continuous variables are reported as medians and interquartile (IQR) ranges. Data on categorical variables are presented as frequencies (percentages). The logistic regression model evaluated the association of TT with the risk of aggressive PCA (univariate and multivariate analysis). The software used to run the analysis was IBM-SPSS version 20. All tests were two-sided with $p < 0.05$ considered to indicate statistical significance.

Results

Increased detection of aggressive prostate tumors in surgical specimens

Overall, 726 cases were evaluated. Demographics of the PCA population and groups are reported in Table 1.

Considering EAU risk classes in our cohort, intermediate was the most prevalent (53.2%), followed by low (24.2%), high (16.3%), and locally advanced (6.3%) classes. Overall, high-risk and locally advanced risk classes represented 22.6% of the population.

In the patient population, RARP was performed in 640 cases (88.2%) and RPP in 86 subjects (11.8%). ePLND was performed in 446 RARP cases (69.7%) and in 79 RRP (91.9%) patients. Of the 525 patients who underwent ePLND, the median number of nodes removed was 26 (IQR = 20–33) and LNI was detected in 61 cases (11.6%).

Although biopsy and pathology ISUP grade groups were highly correlated (Pearson's correlation coefficient, $r = 0.457$; $p < 0.0001$), there was increased detection of more aggressive PCA in the surgical specimens (from 31.5% to 53.3%; difference = 21.8%).

Positive association of basal TT with the risk of aggressive PCA (ISUP > 2)

Median TT levels were 410 ng/dl (IQR: 320.5–513.0 ng/dl). Basal TT correlated with both biopsy ($r = 0.109$; $p = 0.003$) and pathology ($r = 0.089$; $p = 0.016$) ISUP grade groups. There was a significant positive association of TT with the risk of detecting aggressive PCA as well as age, PSA, percentage of biopsy positive cores (BPC), tumor clinical stage, and ISUP biopsy tumor grade groups. Details are illustrated in Table 1. Specifically, median levels of TT were higher in aggressive PCA compared with ISUP 1–2 (432 ng/dl *versus* 385.6 ng/dl; $p = 0.007$); moreover, TT was a positive predictor of the risk of detecting aggressive PCA in the surgical specimen (OR = 1.001; 95% CI: 1.000–1.002; $p = 0.044$).

Figure 1 illustrates the risk of TT predicting aggressive PCA; as shown, there is an increasing risk of detecting aggressive PCA in the surgical specimen as basal TT increases.

Independent positive association of preoperative TT with the risk of aggressive PCA

Significant continuous variables associated with the risk of aggressive PCA were then categorized as follows: TT by the first quartile (TT $\geqslant$ 304 ng/dl *versus* TT $<$ 304 ng/dl), age by the third quartile (age $\geqslant$ 69 years *versus* age $<$ 69 years), PSA by

Table 1. Distribution and association of clinical factors with the risk of aggressive PCA in the patient population.

Clinical factors	Population of patients	Non-aggressive PCA (ISUP 1–2)	Aggressive PCA (ISUP 3–5)	*p*-value	OR (95% CI)	*p*-value
n (%)	726	339 (46.7)	387 (53.3)			
Age (years); median (IQR)	65 (60.7–70)	65 (60–69)	66 (61–70)	0.006	1.037 (1.013–1.061)	0.002
BMI (kg/m^2); median (IQR)	25.6 (23.9–28.1)	25.7 (23.9–27.7)	25.6 (23.8–28.4)	0.46		
TT (ng/dl); median (IQR)	410 (320.5–512)	385.6 (304–501)	432 (340.6–519)	0.007	1.001 (1.000–1.002)	0.044
PSA (µg/l); median (IQR)	6.7 (4.9–9)	6.2 (4.9–8.5)	7 (5.1–9.8)	0.006	1.055 (1.022–1.088)	0.001
PV (cc); median (IQR)	40 (30–53)	41 (30–54)	40 (30–52)	0.32		
BPC (%); median (IQR)	30 (20–50)	28 (17–42)	33 (21–50)	<0.0001	1.017 (1.010–1.024)	<0.0001
cT; *n* (%)				<0.0001		
cT1	438 (60.3)	234 (69)	204 (52.7)		1	
cT2	256 (36.7)	100 (29.5)	166 (42.9)		1.904 (1.395–2.599)	<0.0001
cT3	22 (3.0)	5 (1.5)	17 (4.4)		3.900 (1.414–10.758)	0.009
cN; *n* (%)				0.13		
cN0	702 (96.7)	331 (97.6)	371 (99.9)			
cN1	24 (3.3)	8 (2.4)	16 (4.1)			
ISUP (biopsy); *n* (%)				<0.0001		
1–2 (non-aggressive PCA)	497 (68.5)	309 (91.2)	188 (48.6)		1	
3–5 (aggressive PCA)	229 (31.5)	30 (8.8)	199 (61.4)		10.903 (7.131–16.669)	<0.0001

BMI, body mass index; BPC, biopsy positive cores; CI, confidence interval; cN, nodal clinical stage; cT, clinical tumor stage; IQR, interquartile range; ISUP, International Society of Urologic Pathology system for PCA; OR, odds ratio; PCA, prostate cancer; PSA, prostate specific antigen; PV, prostate volume; TT, total testosterone.

EAU risk levels (below 10 µg/l, between 10 and 20 µg/l and above 20 µg/l), and BPC by percentage of positive cores (below 50% *versus* equal or above 50%). TT was categorized by the first quartile in order to stratify the risk of predicting aggressive PCA. Results are shown in Table 2.

On univariate analysis, all significant variables were positively associated with the risk of aggressive PCA except PSA between 10 and 20 ng/dl. Specifically, TT equal to, or above, the first quartile was positively associated with the risk of detecting aggressive disease in the surgical specimen [odds ratio (OR) = 1.553; 95% confidence interval (CI): 1.089–2.216; $p = 0.001$]. Among patients with aggressive disease, 79.1% had basal TT ⩾ 304 ng/dl.

Multivariate models

On multivariate analysis, two models were considered. In model I, biopsy ISUP grade groups were excluded (ISUP > 2 *versus* ISUP ⩽ 2; aggressive *versus* non-aggressive PCA at biopsy). In model II, biopsy ISUP grade groups were included.

In multivariate model I, TT, as well as all other variables, were independent predictors of the risk of aggressive disease; moreover, the level of association of the risk changed compared with univariate analysis (OR = 1585; CI: 1113–2256; $p = 0{,}011$). Basal PSA remained associated with the risk of aggressive PCA, but only above 20 µg/dl, including only 6.5% of subpopulation with ISUP > 2.

In multivariate model II, basal TT levels remained positively associated with aggressive PCA, whereas age, BPC, and clinical stage cT3 lost significance because of their high correlation and dependence on the biopsy ISUP grade, which is closely associated with the risk of harboring aggressive disease in the specimen.

In the final adjusted model, the level of risk of TT did not change from univariate analysis (OR = 1.525; 95% CI: 1.035–2.245; $p = 0.011$). Details relative to other clinical factors are shown in Table 2.

As illustrated in Figure 2, the distribution of aggressive PCA along TT quartiles, percentages of aggressive disease increase along TT quartiles while those with non-aggressive disease are decreasing. Because of the close association between TT and tumor grade, basal TT is also correlated with EAU risk classes ($r = 0.098$; $p = 0.008$).

Figure 3 shows median TT basal levels among EAU risk classes. As depicted, median TT levels were significantly higher in aggressive disease along EAU classes, as well as increasing along EAU risk classes for both aggressive and non-aggressive PCA.

TT serum levels and categorization of aggressiveness in the surgical specimen

The association between TT serum levels (stratified into two groups divided at the median, where low TT is below the median and high TT is above the median) and both aggressive and high-grade PCA was evaluated.

The stratification of clinical factors in the general population divided at the TT median is depicted in supplemental Table S1. As shown, there was a significant positive correlation between biopsy aggressive disease (ISUP grade group 3–5) and high TT serum levels ($p = 0.027$).

Considering the relationship among clinical factors and the risk of having ISUP grade 3 to 5 in the pathological specimen (supplemental Table S2), high TT serum levels were associated with aggressive disease after adjusting for age, BPC, clinical stage >cT1, and node stage (OR 1.446, 95% CI 1.065–1.962, $p = 0.018$).

When we evaluated the association among clinical factors and the risk of high-grade disease (ISUP 4–5) in the pathological specimen (supplemental Table S3), high TT levels were associated with high grade disease in univariate analysis (OR 1.842, 95% CI 1.48–2.83; $p = 0.005$), but this association was lost in multivariate analysis (OR: 1.356, 95% CI 0.948–1.939; $p = 0.095$).

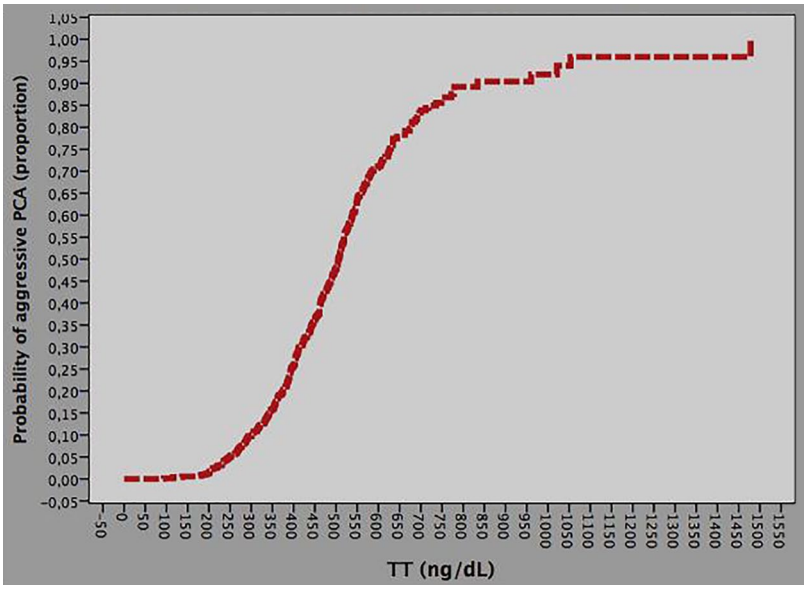

Figure 1. TT curve predicting the risk of aggressive PCA; as shown, there is an increasing risk of detecting aggressive PCA in the surgical specimen along increasing basal levels of TT.
ISUP, International Society of Urologic Pathology; PCA, prostate cancer; TT, total testosterone.

Discussion

Association of basal TT levels with the risk of aggressive PCA biology

Pathological tumor grade plays a pivotal role in the natural history of PCA as well as having important implications for both management and prognosis.[19]

PCA ISUP grade group 3 is a crucial group since it is more closely related to aggressive PCA than grade group 2, which is more closely associated to non-aggressive disease. Although biopsy and pathology ISUP grade systems are highly correlated, upgrading phenomena occur in the surgical specimen. As a result, this will have an impact on predicting the natural history of PCA.[1,19] In our study, aggressive PCA (ISUP > 2 in the surgical specimen) was detected in 53.3% of cases

Table 2. Clinical factors associated with the risk of aggressive prostate cancer in the surgical specimen (ISUP > 2).

	Non aggressive PCA (ISUP < 3)	Aggressive PCA (ISUP > 2)	Univariate model		Multivariate model I*		Multivariate model II**		Multivariate model II**; adjusted)	
Statistics	***n* (%)**	***n* (%)**	**OR (95% CI)**	***p*-value**	**OR (95% CI)**	***p*-value**	**OR (95% CI)**	***p*-value**	**OR (95% CI)**	***p*-value**
TT < 304	110 (29,5)	81 (20,9)	1							
TT ⩾ 304	74 (21,8)	306 (79,1)	1,553 (1,089–2,216)	0.015	1,585 (1,113–2,256)	0.011	1,506 (1,018–2,227)	0.040	1,525 (1,035–2,245)	0.011
Age < 69	265 (78,2)	267 (69)	1							
Age ⩾ 69	74 (21,8)	120 (31)	1,609 (1,150–2,252)	0.005	1,651 (1,165–2,338)	0.005	1,392 (0,948–2,044)	0.091		
PSA < 10	288 (85)	295 (76,2)	1							
PSA 10–20	47 (13,9)	67 (17,3)	1,392 (0,927–2,090)	0.111						
PSA > 20	4 (1,1)	25 (6,5)	6,102 (2,097–17,751)	0.001	6,158 (2,082–18,213)	0.001	4,205 (1,314–13,462)	0.016	4,435 (1,399–14,062)	0.011
BPC < 50%	268 (79,1)	256 (66,1)	1							
BPC ⩾ 50%	71 (20,9)	131 (33,9)	1,932 (1,381–2,702)	<0,0001	1,639 (1,154–2,328)	0.006	1,340 (0,906–1,981)	0.142		
cT1	234 (69)	204 (52,7)	1							
cT2	100 (29,5)	166 (42,9)	1,904 (1,395–2,599)	<0,0001	1,897 (1,377–2,614)	<0,0001	1,811 (1,273–2,577)	0.001	1,802 (1,273–2,552)	0.001
cT3	5 (1,5)	17 (4,4)	3,900 (1,414–10,588)	0.009	3,206 (1,137–9,044)	0.028	2,319 (0,735–7,342)	0.152		
ISUP < 3^	309 (91,2)	188 (48,6)	1							
ISUP > 2^	30 (8,8)	199 (51,4)	10,903 (7,131–10,669)	<0,0001			9,469 (6,141–14,599)	<0,0001	10,293 (6,697–15,821)	<0,0001

Legend: OR, odds ratio; CI, confidence interval; (^) biopsy; (*) escluding biopsy tumor grade groups; (**), including biopsy tumor grade groups; see also Table 1.

compared with 31.5% by biopsy ISUP grading; thus, 21.8% of patients were upgraded to aggressive disease after evaluation of the surgical specimen. So far, additional simple parameters predicting the risk of aggressive PCA are required beyond the known parameters currently utilized in daily practice.[1,19]

The association of TT with PCA biology is controversial, and controlled trials evaluating the correlation between high and low TT levels with PCA are missing. Particularly, several studies tried to demonstrate the correlation between low TT serum levels and more aggressive PCA. Among these, Imamoto *et al.* found that lower pretreatment TT serum levels predicted extraprostatic-disease in 82 clinically localized PCA patients treated with RP.[21] Park *et al.* demonstrated that low TT level was an independent risk factor for high-grade PCA detection at the time of biopsy.[22] Dai *et al.* demonstrated that low pretreatment serum TT levels were associated with a higher incidence of Gleason Score 8–10 in prostatectomy specimens.[8] Ferro *et al*. showed that low serum TT levels were a predictor of upstaging and upgrading in low risk PCA patients who had met the inclusion criteria for active surveillance.[9]

On the other hand, several studies have reported a positive association between basal TT levels and PCA. One study has documented significant increased androgenic activity in metastatic disease.[23] Another study reported that higher basal TT levels predicts the risk of metastatic progression in patients with clinically localized disease treated by primary radiation.[24] A collaborative analysis of 20 prospective trials demonstrated that higher free testosterone levels increased the risk of developing PCA.[25] A large prospective observational trial demonstrated that exposure of higher levels of free testosterone over time is associated with the risk of developing aggressive cancers.[26] In addition, an Italian study showed that both the lowest and highest TT levels were predictive of high-grade cancers.[27,28] In an previous series, we showed that elevated basal TT levels were associated with high grade tumors in pathologic specimens.[29,30] Subsequently, in a contemporary set of patients, we showed that higher preoperative TT levels were directly associated with upgrading in low-intermediate risk classes using the D'Amico criteria as well as higher biopsy ISUP groups[6]; furthermore, basal TT levels were related to the risk of focal and non-focal positive surgical margins in a linear manner.[5,31]

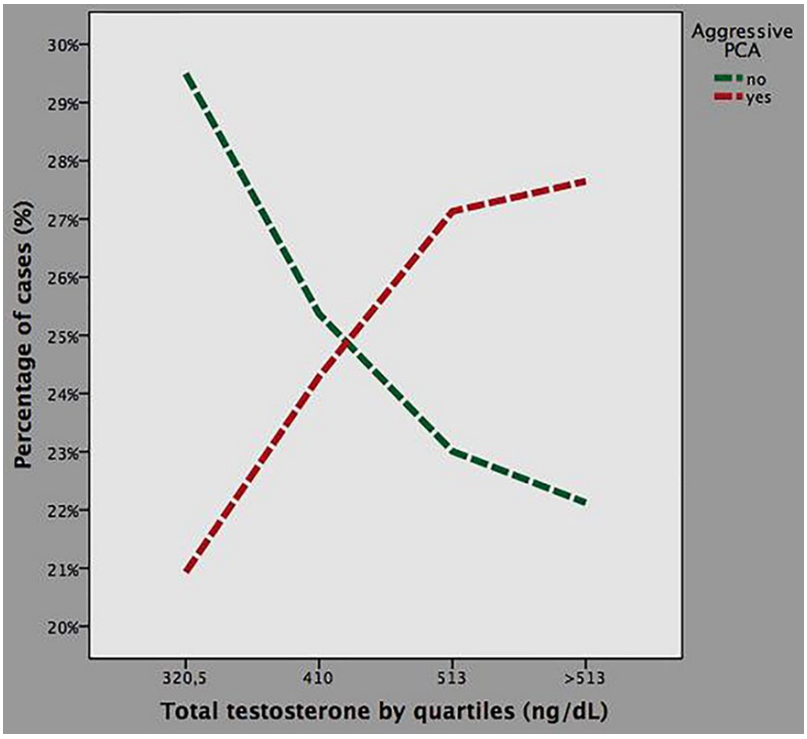

Figure 2. Distribution of aggressive PCA along TT quartiles, percentages of aggressive disease are increasing along TT quartiles while those with non-aggressive disease are decreasing.
PCA, prostate cancer; TT, total testosterone.

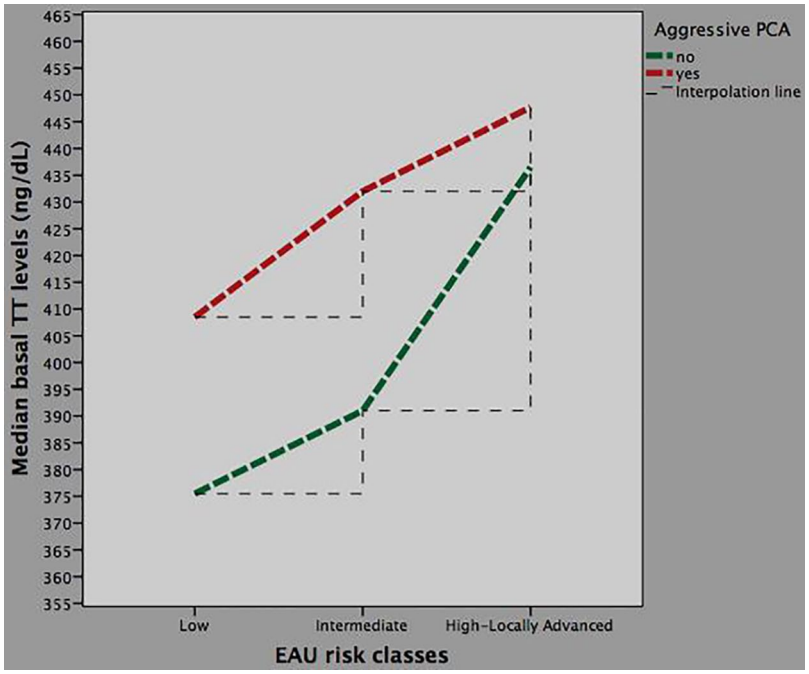

Figure 3. Median TT basal levels in EAU risk classes: median TT levels were significantly higher in aggressive disease along EAU classes as well as increasing for both aggressive and non-aggressive PCA along EAU risk classes.
EAU, European Association of Urology; PCA, prostate cancer; TT, total testosterone.

In the present study, we have shown that there is an independent positive association between basal TT and the risk of aggressive PCA in the surgical specimen. We also identified a cut-off value of basal TT that allowed us to stratify the patient population into two subgroups. As shown in Table 2, when TT levels were equal or above the first quartile, aggressive PCA was detected in 79.1% of cases. On the other hand, when basal TT levels were below the first quartile, aggressive disease was detected in a limited subset (20.9%) of the PCA population. In both multivariate models, TT was an independent predictor of the risk of aggressive PCA. Multivariate models were computed by considering stratification of clinical factors according to EAU risk class features, and TT was demonstrated to be a strong independent predictor of the risk of aggressive PCA in the surgical specimen, thus suggesting its potential use as an adjunctive clinical parameter for stratifying patients inside each EAU risk class, which are extremely heterogeneous, especially the low and intermediate risk classes.

When we assessed the relationship among clinical factors and ISUP grade group in the pathological specimen, we found that TT was associated with aggressive disease (ISUP 3–5) in univariate to multivariate models. When we considered ISUP 4 and 5 (high grade), TT retained its predict value on univariate analysis but the correlation was lost upon multivariate analysis ($p = 0.095$). This was probably related to the small number of patients; however, it could be related to an initial loss of androgen sensitivity related to the minor differentiation of PCA cells.[32]

Biological Hypothesis

The results of our study show that there is a complex positive interaction between androgen circulating levels and tumor microenvironment, which varies over time according to tumor biology as defined by the ISUP grading system.

There is evidence that a positive association between circulating TT levels and PCA risk exists. In theory, when a sudden drop in serum testosterone occurs in an aging male, whatever the cause may be,[12] local autocrine-paracrine mechanisms attempt to maintain peri-prostatic testosterone concentrations by testosterone hyper-production and androgen receptor (AR) hyper-expression. This results in an overall hyper-stimulation of luminal glandular cells despite a decrease in TT serum levels. This prostatic cell hyper-stimulation results in DNA damage and uncontrolled luminal cell AR-driven proliferation.[33] These alterations constantly select newer and progressively more aggressive prostatic cellular clones. Initially, this process promotes neoplastic induction and cancer growth. Later, it provides progressive capacity for extracapsular diffusion, ability for nodal invasion, and, finally, the loss of hormonal sensitivity until the PCA becomes castrate-resistant.[34–37] According to this theory, our results mirror these steps: initially patients have lower TT levels, and, in concert with other conditions, PCA induction occurs. Subsequently, additional PCA cellular DNA mutation occurs driving more aggressive disease, with higher ISUP grade and more extensive disease.[32]

Furthermore, this theory supports the evidence that chronic diseases related to lower TT may play an important role in PCA induction and progression. Among these conditions, obesity, which is related with low TT serum levels, has been demonstrated to be associated with more aggressive PCA after RARP and RRP,[10,11] besides being a known factor associated with post-operative high-grade complications.[38]

Strengths, limitations, and clinical implications

Our study has many strengths. First, it was a single institutional study including a contemporary cohort of Caucasian Italian males. Second, all samples were collected in a similar fashion, and the same laboratory in our institution was used. Third, the population is extremely large, representing all ISUP tumor grade groups Fourth, we excluded patients who were under androgen blockade. Fifth, data were collected prospectively. Sixth, it represents one of the largest studies evaluating TT basal levels in patients undergoing RP.

Our study has also limitations. First, although data were collected prospectively, they were analyzed retrospectively. Second, prostate volumes and biopsies performed elsewhere were not re-evaluated; however, inclusion criteria allowed a robust analysis. Third, we did not use gas chromatography-mass spectrometry to measure TT. Fourth, a single measurement of TT was performed, and this might not represent true TT circulating levels; however, the number of patients included in the analysis was large enough to sustain robust statistical analysis. Finally, the hypothalamic-pituitary-testis axis was not functionally explored.

The present study might have important implications for clinical practice. The results show that, beyond known clinical factors defining the different EAU risk classes, basal TT levels can be categorized by the first quartile in order to identify patients who are at risk of aggressive disease in surgical specimens; moreover, these implications apply particularly in the low and intermediate risk classes, which are extremely heterogeneous and for which appropriate decisions on treatment options are pivotal in actual clinical practice.

Conclusion

Preoperative basal TT levels are associated with the risk of aggressive PCA in the surgical specimen. Beyond known clinical parameters defining PCA patients, preoperative basal TT may identify patients who are at increased risk of aggressive PCA in low and intermediate EAU risk classes, and more appropriate treatment decisions may be undertaken.

Conflict of interest statement

The authors declare that there is no conflict of interest.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

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Informed consent

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

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Supplemental material

Supplemental material for this article is available online.

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