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ORIGINAL ARTICLE

Prostate Cancer

The role of the serum testosterone levels as a predictor of prostate cancer in patients with atypical small acinar proliferation at the first prostate biopsy

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The current literature does not support the usefulness of clinical markers on predicting which patients with atypical small acinar proliferation (ASAP) are more likely to progress to prostate cancer (PCa). Androgens have long been considered to be the potential risk factors for PCa. However, the role of testosterone is controversial. The present study aims to analyze the relationship between serum testosterone (TS) levels and the diagnosis of PCa after a first prostate biopsy in patients affected by ASAP. This retrospective study included 143 patients diagnosed with ASAP in an initial transrectal ultrasound-guided prostate biopsy for suspicious PCa according to the European Association of Urology guidelines. Their TS levels, age, PSA, prostate volume, digital rectal examination, and prostate biopsy Gleason score (GS) were collected retrospectively for statistical analysis. All patients included in the study had a second biopsy and were suitable for further analysis. Re-biopsy was carried out 3–6 months after the first diagnosis of ASAP. Low and normal TS groups were composed of 29 (20.3%) and 114 (79.7%) patients, respectively. The diagnosis of the second biopsy was ASAP in 25.2% and PCa in 36.4% of patients. The comparison between patients with PCa and those with negative or an ASAP result in the second biopsy reported that men with cancer had significantly higher levels of TS ($P < 0.001$). However, there was no statistically significant association between GS postbiopsy and TS ($P = 0.324$). Our experience demonstrated that eugonadal patients may be a clinical risk factor for the diagnosis of PCa on re-biopsy after ASAP diagnosis than hypogonadal.
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INTRODUCTION

Atypical small acinar proliferation (ASAP) is a diagnosis that occurs in about 1%–5% of prostate biopsies.[1] The term ASAP represents a small area composed of few glands with atypical epithelium suspect, but nondiagnostic, for prostate cancer (PCa).[2] Previous authors have reported that 17%–70% of patients with ASAP have adenocarcinoma present on subsequent prostate biopsies.[3] The guidelines recommend immediate repeat biopsy within 3–6 months after the initial diagnosis of ASAP.[2,3] The current literature does not support the usefulness of clinical markers on predicting which patients with ASAP are more likely to progress to PCa.[1,4] The role of testosterone is controversial.[5,6] Testosterone levels are required for the normal growth and development of the prostate gland.[7] In many observational studies, high levels of testosterone have long been considered to be potential risk factors for PCa.[8] However, recent studies show that PCa has often been associated with low testosterone levels.[9,10] In our opinion, it is therefore important to define whether, in the early stages of PCa carcinogenesis, there is a relationship between testosterone levels and PCa. In this retrospective study, we wished to analyze the relationship between serum testosterone levels and the diagnosis of PCa after a first prostate biopsy in patients affected by ASAP.

PATIENTS AND METHODS

Between March 2008 and December 2015, we retrospectively reviewed the medical records of 327 patients diagnosed with ASAP in an initial transrectal ultrasound-guided prostate biopsy (TRUSBx) for suspicious PCa according to the European Association Urology (EAU) guidelines at two tertiary referral urological centers. For a standardization of the clinical data, patients with a history of biopsy, surgical treatment for prostatic disease, neoadjuvant therapy, and incomplete clinical data were excluded from our study. Of the 327 patients, 143 patients for whom preoperative testosterone serum (TS) levels were available were eligible for this study. The patients enrolled in this study were largely men referred for erectile dysfunction in our andrology clinics, and the TS levels were measured as part of their tests for erectile dysfunction. These patients were also found to have a suspicious for PCa and thus underwent prostate biopsy. The study was conducted in accordance with the Declaration of Helsinki and was approved by the institutional ethics committees of University Hospital St. Anna (Ferrara, Italy), and University Hospital Ospedali Riuniti (Ancona, Italy). All patients enrolled in the study signed a consent form for the procedure.

TRUSBx was performed with the patient in the left lateral decubitus using an ultrasound machine equipped with a 5–9 MHz multi-frequency convex probe "end-fire" (Logiq 7, GE Healthcare, Milwaukee, WI, USA). Each transrectal ultrasound (TRUS) performed

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included an assessment of the volume of the whole prostate, the transition zone, capsular, seminal vesicle characteristics, and a morphological description of potential pathological features. The prostate volume was invariably calculated using prostate ellipse formula (0.52 × length × width × height). After having images of the prostate, sampling was carried out with an 18-gauge Tru-Cut (Bard Biopsy Systems, Tempe, AZ, USA) needle powered by an automatic spring-loaded biopsy disposable gun. Three experienced urologists of our department performed a 14-core biopsy scheme, as first intention, including two basal samples (lateral and medial), two parasagittal samples (lateral and medial), two apical samples (lateral and medial), and one transitional zone sample on each side. This biopsy scheme was changed based on TRUS findings concerning the size of the prostate and possibility suspicious regions and varied from 8 cores for a small prostate to 18 cores for large prostatic glands. Blood samples for TS measurement were obtained in the morning when testosterone levels were relatively stable at their high serum concentration. Based on our clinical practice, we chose 300 ng dl^{-1}, as the lower limit of normal for TS. Prebiopsy parameters (age, PSA, prostate volume [PV], and digital rectal examination [DRE]) were collected retrospectively for analysis. The decision for a second biopsy was based on ASAP diagnosis in the initial biopsy. The second biopsy was performed within 6 months from the first one. The Gleason grading was based on the recommendations of the 2005 International Society of Urological Pathology Consensus Conference. All histological specimens were analyzed internally by our Pathology Department specializing in genitourinary pathology. Cases were not reviewed for this study. Patients were then categorized into the following Gleason score (GS) according to the biopsy and prostatectomy: low (Gleason 2–6), moderate (Gleason 7), and high (Gleason 8–10).

Statistical analysis

The one-tailed Student's *t*-test was used to study the distribution of TS within the variables of age, PSA, PV, and DRE. The Pearson's Chi-square test and Fisher's exact test were used to analyze TS groups and histopathological features. All statistical analyses were conducted on Microsoft Excel 2010 platform version 10.1 (Microsoft, Los Angeles, CA, USA). $P < 0.05$ was considered statistically significant.

RESULTS

Of the 143 patients included in the study, all patients had a second biopsy and were suitable for further analysis. Re-biopsy was carried out 3–6 months after the first diagnosis of ASAP. The clinical and pathological characteristics of these 143 patients are shown in **Table 1**. Prebiopsy TS ranged widely from 153 to 968 ng dl^{-1} (median: 462 ng dl^{-1}). TS levels were <299 ng dl^{-1} in 29 (20.3%), 300–399 ng dl^{-1} in 47 (32.9%), and equal to or >400 ng dl^{-1} in 67 (46.9%). Thus, low and normal TS groups were composed of 29 (20.3%) and 114 (79.7%) patients, respectively. There was no statistically significant association between prebiopsy clinicopathologic parameters and prebiopsy TS levels (**Table 1**). The diagnosis of the second biopsy was ASAP in 36 patients (25.2%) and PCa in 52 patients (36.4%). The comparison between patients with PCa and those with negative or an ASAP result in the second biopsy reported that men with cancer had significantly higher levels of TS ($P < 0.001$). The prevalence of PCa by decade of age was 25.0% (1 of 4), 33.3% (9 of 27), 30.2% (13 of 43), and 42.0% (29 of 69) in patients aged 40–49, 50–59, 60–69, and 70 years or older, respectively. The cancer detection rate in patients aged 70 years or older was greater than the rest of the patients ($P < 0.001$). Patients with abnormal DRE findings had a greater prevalence of PCa compared to patients with normal DRE findings. The cancer rate was 37.9% (50/132) in men whose biopsies involved more than 8 cores and was 18.2% (2/11) in those with 8 cores only.

Finally, the rate of cancer detection in low TS patients was 24.1% (7/29) and 39.5% (45/114) in eugonadal patients ($P < 0.002$). The Gleason scores were assigned as follows: for patients with TS level of 300 ng dl^{-1} or less, 57.1% (4/7) had a low GS, 28.6% (2/7) had a moderate GS, and 14.3% (1/7) had a high GS; for patients with TS level greater than 300 ng dl^{-1}, 53.3% (24/45) had a low GS, 33.3% (15/45) had a moderate GS, and 13.3% (6/45) had a high GS. These findings were not statistically significant ($P = 0.623$).

Table 1: Demographic and clinicopathologic features of patients undergoing transrectal ultrasound prostate biopsy after atypical small acinar proliferation diagnosis

Variable	*Testosterone serum levels*		*P*
	≤300 ng dl^{-1} (n=29)	*>300 ng dl^{-1} (n=114)*	
Age (year), mean±s.d.	64.3±6.2	63.5±6.4	NS
Prostate volume (ml), mean±s.d.	46.4±18.5	47.4±7.3	NS
PSA level (ng ml^{-1}), mean±s.d.	6.7±4.8	7.1±5.3	NS
Number of biopsy cores, mean±s.d.	12.5±4.2	12.2±4.4	NS
Abnormal DRE, *n* (%)	6 (20.7)	38 (33.3)	<0.001
Prostate cancer, *n* (%)	7 (24.2)	45 (39.5)	<0.002
ASAP, *n* (%)	5 (17.3)	31 (27.2)	<0.001
HGPIN, *n* (%)	2 (6.9)	6 (5.3)	NS
Biopsy Gleason score, *n* (%)			
≤6	4 (57.1)	24 (53.4)	NS
7	2 (28.6)	15 (33.3)	
≥8	1 (14.3)	6 (13.3)	

ASAP: atypical small acinar proliferation; DRE: digital rectal examination; HGPIN: high grade intraepithelial prostatic neoplasia; NS: not significant; PSA: prostate-specific antigen; s.d.: standard deviation

DISCUSSION

ASAP is a diagnosis that represents suspicious glands without adequate histologic atypia for a definitive diagnosis of prostate adenocarcinoma.[1] Conflicting opinions regarding the pathologic aggressiveness of PCa identified following the diagnosis of ASAP have been shown. In men with ASAP, some authors reported that only 5%–20% of cancers are high grade, while other authors reported that clinically significant PCa is up to 51%.[11] In a multi-institutional review of 264 men who underwent prostate biopsy and were diagnosed with ASAP and subsequently underwent a repeat TRUSBx, Leone *et al.*[4] showed that 34% of patients were diagnosed PCa, but only 8% had Gleason score ≥7. The current guidelines recommend immediate repeat biopsy within 3–6 months after the initial diagnosis of ASAP, although the recent literature has demonstrated an increase in the incidence of significant postbiopsy infections.[12] However, the pathologic features of cancers identified following a diagnosis of ASAP have been relatively understudied and existing data are conflicting. While some studies have noted a predominance of low-grade cancer following ASAP, other studies have observed a relatively high incidence of clinically significant disease, occurring in up to 51% of men.[13,14] Currently, there are no clinical predictors that seem to be helpful in identifying which patients with ASAP are at risk of cancer progression.[15] Only ASAP multifocality seems to be systematically related to a higher risk of a positive re-biopsy.[16] Androgen hormones are necessary for the development, maintenance, and activity of the prostate gland.[7]

The association of TS levels with PCa development is not completely understood.[9] The relationship between PCa and testosterone has

been controversial since 1941 when Huggins and Hodges showed a PCa regression after testosterone deprivation.[17] Several authors have investigated whether the incidence of PCa is associated with serum androgen levels.[9,18] Massengill *et al.*[19] analyzed 879 patients treated with radical prostatectomy (RP) and reported that patients with nonorgan-confined PCa have significantly lower preoperative TS levels than those with organ-confined PCa, and that lower preoperative TS levels are significant predictors of extraprostatic disease in multivariate analysis. Many groups reported that the risk of PCa was higher in men with lower total testosterone levels.[6,20] Yano *et al.*[21] reported that TS levels were lower in patients with PCa than in those with benign prostatic hyperplasia. Sofikerim *et al.*[22] found similar findings, with patients affected by PCa having lower testosterone levels than men with a negative biopsy. In our study, we try to define whether TS levels are associated with a positive second prostate biopsy in patients that were found harboring ASAP at the first biopsy. According to our current knowledge, this is the first study that correlates the TS level as a clinical predictor in identifying which patients with ASAP are at risk of PCa progression.

In fact, in literature, few studies determined an association between a high grade intraepithelial prostatic neoplasia (HGPIN) diagnosis and TS levels at the second biopsy in terms of cancer progression, but not between ASAP and TS levels.[6,23,24] Recently, Fiamegos *et al.*[5] showed that patients with a positive re-biopsy after HGPIN had higher free testosterone and bioavailable testosterone levels than patients with negative re-biopsy. In our study, we related an association between higher TS levels and PCa at the second biopsy ($P < 0.001$). However, cancer patients at second biopsy were found harboring localized cancer, mostly well or moderately differentiated and only six cases of a high GS. A few authors reported the association between GS and TS levels in PCa. Schatzl *et al.*[25] also reported statistically significant difference in mean GS between patients with partial androgen deficiency and those without androgen deficiency, suggesting that PCa with high GS had lower TS levels. Hoffman *et al.*[26] proved that lower serum-free testosterone might be a marker for more aggressive cancer (any clinical stage with high GS). Unfortunately, our data cannot be compared with their results, because metastatic or locally advanced cancers were included in their study cohort. However, in the future, larger studies will be needed to confirm this relationship.

There are some limitations in the present study. First, it was a double-center retrospective study with small series of patients and a limited number of repeat biopsies, although a substantial number of patients were lost to follow-up and/or unavailability of TS. A second limitation is that we had no data available regarding the ethnic background of the patients. These details could be of special interest, because in multiethnic populations, some subgroups might have more unfavorable PCa characteristics than others.[27] However, although we did not expressly document race, the majority of the patients of our study cohort were Caucasian and Italian population. Third, this study concerned patients with PCa eligible only for RP; as a consequence, older patients (≥74 years old) who are not candidates for surgery were excluded. This may have influenced the results and precluded comparative investigation of a potentially risky ASAP in hypogonadal versus eugonadal patients.

CONCLUSIONS

Our experience prompts that eugonadal patients may be a clinical risk factor for the diagnosis of PCa on re-biopsy after ASAP than hypogonadal. This reliable biomarker is inexpensive, reproducible, and serves to distinguish men who are otherwise usually obliged to undergo several prostate biopsies. Prostate biopsies can be associated with significant morbidity including pain, bleeding, and infectious complications.[12] Also, a recent study has shown appreciable erectile dysfunction after transrectal prostate biopsy as early as 3 months after the biopsy.[28] However, further studies are required to define the complex mechanism between androgen hormones and genetic factors in PCa etiology.

AUTHOR CONTRIBUTIONS

LDA was the main surgeon of this study, participated in patients enrolls, and drafted the manuscript. ABG performed statistics analysis, participated in its design and coordination. Both authors read and approved the final manuscript.

COMPETING INTERESTS

Both authors declare no competing interests.

REFERENCES

1 Dorin RP, Wiener S, Harris CD, Wagner JR. Prostate atypia: does repeat biopsy detect clinically significant prostate cancer? *Prostate* 2015; 75: 673–8.
2 Leone L, Lacetera V, Montironi R, Cantoro U, Conti A, *et al.* Biopsy follow-up in patients with isolated atypical small acinar proliferation (ASAP) in prostate biopsy. *Arch Ital Urol Androl* 2014; 86: 332–5.
3 Montironi R, Scattoni V, Mazzucchelli R, Lopez-Beltran A, Bostwick DG, *et al.* Atypical foci suspicious but not diagnostic of malignancy in prostate needle biopsies (also referred to as "atypical small acinar proliferation suspicious for but not diagnostic of malignancy"). *Eur Urol* 2006; 50: 666–74.
4 Leone A, Gershman B, Rotker K, Butler C, Fantasia J, *et al.* Atypical small acinar proliferation (ASAP): is a repeat biopsy necessary ASAP? A multi-institutional review. *Prostate Cancer Prostatic Dis* 2016; 19: 68–71.
5 Fiamegos A, Varkarakis J, Kontraros M, Karagiannis A, Chrisofos M, *et al.* Serum testosterone as a biomarker for second prostatic biopsy in men with negative first biopsy for prostatic cancer and PSA>4ng/mL, or with PIN biopsy result. *Int Braz J Urol* 2016; 42: 925–31.
6 García-Cruz E, Huguet J, Piqueras M, Márquez MP, Peri L, *et al.* Low testosterone bioavailability is related to prostate cancer diagnose in patients submitted to prostate biopsy. *World J Urol* 2012; 30: 361–5.
7 Mearini L, Costantini E, Zucchi A, Mearini E, Bini V, *et al.* Testosterone levels in benign prostatic hypertrophy and prostate cancer. *Urol Int* 2008; 80: 134–40.
8 Bostwick DG, Burke HB, Djakiew D, Euling S, Ho SM, *et al.* Human prostate cancer risk factors. *Cancer* 2004; 101: 2371–490.
9 Khera M, Crawford D, Morales A, Salonia A, Morgentaler A. A new era of testosterone and prostate cancer: from physiology to clinical implications. *Eur Urol* 2014; 65: 115–23.
10 Morgentaler A. Testosterone and prostate cancer: an historical perspective on a modern myth. *Eur Urol* 2006; 50: 935–9.
11 Merrick GS, Galbreath RW, Bennett A, Butler WM, Amamovich E. Incidence, grade and distribution of prostate cancer following transperineal template-guided mapping biopsy in patients with atypical small acinar proliferation. *World J Urol* 2016. doi: 10.1007/s00345-016-1976-2. [Epub ahead of print].
12 Lundström KJ, Drevin L, Carlsson S, Garmo H, Loeb S, *et al.* Nationwide population based study of infections after transrectal ultrasound guided prostate biopsy. *J Urol* 2014; 192: 1116–22.
13 Warlick C, Feia K, Tomasini J, Iwamoto C, Lindgren B, *et al.* Rate of Gleason 7 or higher prostate cancer on repeat biopsy after a diagnosis of atypical small acinar proliferation. *Prostate Cancer Prostatic Dis* 2015; 18: 255–9.
14 Bostwick DG, Meiers I. Atypical small acinar proliferation in the prostate: clinical significance in 2006. *Arch Pathol Lab Med* 2006; 130: 952–7.
15 Bonkhoff H. Significance of prostate cancer missed on needle biopsy tools for retrieving missed cancer. *Prostate* 2016; 76: 369–75.
16 Aglamis E, Kocaarslan R, Yucetas U, Toktas G, Ceylan C, *et al.* How many cores should be taken in a repeat biopsy on patients in whom atypical small acinar proliferation has been identified in an initial transrectal prostate biopsy? *Int Braz J Urol* 2014; 40: 605–12.
17 Huggins C, Hodges CV. Studies on prostatic cancer. I. The effect of castration, of estrogen and androgen injection on serum phosphatases in metastatic carcinoma of the prostate. *Cancer Res* 1941; 1: 293–7.
18 Isom-Batz G, Bianco FJ Jr., Kattan MW, Mulhall JP, Lilja H, *et al.* Testosterone as a predictor of pathological stage in clinically localized prostate cancer. *J Urol* 2005; 173: 1935–7.
19 Massengill JC, Sun L, Moul JW, Wu H, McLeod DG, *et al.* Pretreatment total testosterone level predicts pathological stage in patients with localized prostate cancer treated with radical prostatectomy. *J Urol* 2003; 169: 1670–5.
20 Furuya Y, Nozaki T, Nagakawa O, Fuse H. Low serum testosterone level predicts worse response to endocrine therapy in Japanese patients with metastatic prostate cancer. *Endocr J* 2002; 49: 85–90.

21 Yano M, Imamoto T, Suzuki H, Fukasawa S, Kojima S, *et al.* The clinical potential of pretreatment serum testosterone level to improve the efficiency of prostate cancer screening. *Eur Urol* 2007; 51: 375–80.
22 Sofikerim M, Eskicorapci S, Oruç O, Ozen H. Hormonal predictors of prostate cancer. *Urol Int* 2007; 79: 13–8.
23 García-Cruz E, Piqueras M, Ribal MJ, Huguet J, Serapiao R, *et al.* Low testosterone level predicts prostate cancer in re-biopsy in patients with high grade prostatic intraepithelial neoplasia. *BJU Int* 2012; 110: 199–202.
24 Rhoden EL, Morgentaler A. Testosterone replacement therapy in hypogonadal men at high risk for prostate cancer: results of 1 year of treatment in men with prostatic intraepithelial neoplasia. *J Urol* 2003; 170: 2348–51.
25 Schatzl G, Madersbacher S, Thurridl T, Waldmüller J, Kramer G, *et al.* High-grade prostate cancer is associated with low serum testosterone levels. *Prostate* 2001; 47: 52–8.
26 Hoffman MA, DeWolf WC, Morgentaler A. Is low serum free testosterone a marker for high grade prostate cancer? *J Urol* 2000; 163: 824–7.
27 Ravery V, Dominique S, Hupertan V, Ben Rhouma S, Toublanc M, *et al.* Prostate cancer characteristics in a multiracial community. *Eur Urol* 2008; 53: 533–8.
28 Linden-Castro E, Pelayo-Nieto M, Espinosa-Perezgrovas D, Rubio-Arellano ED, Catalán-Quinto G, *et al.* The impact of transrectal prostate biopsy on erectile function. *Actas Urol Esp* 2016; 40: 453–6.