Associations of Transitional Zone Volume with Intraprostatic Chronic Inflammation and Prostate Cancer Risk in Patients Undergoing a First Random Biopsy Set

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Key Words

Prostate cancer • Chronic prostate inflammation •
Prostate-specific antigen • Prostate biopsy •
Prostate volume • Transitional zone volume

Abstract

Objectives: To investigate associations of the transitional zone volume (TZV) with intraprostatic chronic inflammatory infiltrate (CII) and prostate cancer (PCa) risk in patients undergoing a first random biopsy set. **Materials and Methods:** The study included a homogenous population of 596 patients. The volume of the prostate and TZV were separately measured. Independent associations were investigated by multivariate logistic regression analysis. **Results:** The median TZV was 18 ml, CII was detected in 157 cases (26.3%), and PCa was present in 292 patients (49%). TZV was the only independent clinical factor associated with CII risk (OR = 1.014). After correcting for CII (OR = 0.276; $p < 0.0001$), independent factors associated with PCa risk included age (OR = 1.066), prostate specific antigen (OR = 1.177), TZV (OR = 0.919), and an abnormal digital rectal exam (OR = 2.024). **Conclusion:** In a patient population undergoing a first random prostate

biopsy set because of suspected cancer, independent associations were detected among TZV, CII, and PCa. The association between TZV and CII was direct, but the relation between TZV and PCa was inverse. The measurement of the volume of the transitional zone was a useful parameter for evaluating chronic intraprostatic inflammation and PCa risk.

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Introduction

In clinical practice, the zonal anatomy of the prostate is important in assessing the origin and location of disorders affecting the gland [1]. Benign prostate hyperplasia (BPH) and prostate cancer (PCa) represent the two main growth disorders. The former develops in the transition zone while the latter in the peripheral part of the gland.

The measurement of prostate volume (PV) is important when considering medical and surgical treatments of both BPH and PCa. Moreover, measurements of volumes of the prostate zonal anatomy are even more important

because they are related to the development of both BPH and PCa which are independent from each other and do not show any causal association [1–3]. When considering BPH pathophysiology, it is important to evaluate the transitional zone volume (TZV) because its variations relate to the anatomy of the aging prostate. It is also important to evaluate the volume and anatomy of the peripheral zone when assessing PCa.

The prostate may also be affected by inflammatory disorders. Clinically, the prostatitis syndromes have been classified into 4 categories by the National Institutes of Health [4]. The last category, type IV, is diagnosed in patients who have no history of genitourinary tract pain complaints, but undergo prostate biopsy for evaluation of possible PCa because of an increased serum prostate-specific antigen (PSA) level, abnormal digital rectal exam (DRE) or both. In biopsy cores, histology shows the presence of chronic inflammatory infiltrate (CII) that might associate with both PCa and/or BPH [5, 6]. The nature of the association between CII and PCa represents a controversial subject that is still unsettled.

We have shown that there is a negative association between chronic inflammation and PCa risk in patients undergoing biopsy because of suspected cancer [7, 8]. We have also demonstrated that the relations between TZV and the peripheral zone volume (PZV) play an important role in evaluating the risk of detecting PCa in patients electing a first random biopsy set [7, 9]. In addition, we have shown that the ratio of TZV and PZV, and the prostate volume (PV) index are associated with a decreased risk of detecting PCa. The aim of the present study was to investigate associations of TZV with chronic inflammation and PCa risk in patients electing a first random biopsy set.

Materials and Methods

Collection and use of patient data had Institutional Board Review approval. All patients signed informed consent for using the data. The study was retrospective and evaluated the records of 1,327 patients who underwent prostate biopsy in the period ranging from September 2010 to September 2015. The exclusion criteria were as follows: (i) repeat biopsy (68.5%), (ii) active surveillance (15%), (iii) previous BPH surgery (3.7%), (iv) medical treatment with inhibitors of enzyme 5-alpha reductase (3.7%), or (v) biopsy samples of less than 14 cores (9.1%). In the design of the study, patients having biopsy samples less than 14 cores were excluded in order to evaluate a homogenous patient population undergoing a first set of random biopsies. As a result, the study excluded 731 cases. The analysis deliberately excluded additional targeted cores in order to avoid a skewed phenomenon. According

to the aim of the study, additional targeted cores were ignored in order to assess a homogenous population. Biopsy indications were as follows: (i) increased PSA levels (73.7%), (ii) abnormal DRE findings (4.76%), (iii) abnormal DRE with increased PSA levels (14.9%), and (iv) abnormal imaging findings (6.5%).

In each patient, measurements included age (years), body mass index (BMI, kg/m²), levels of PSA (µg/l), PV (ml), PSA density (PSAD, µg/l/ml), and DRE findings (normal, abnormal). PV was measured by transrectal ultrasound (TRUS) and was determined by using the formula for the ellipsoid that was transformed into volume (ml). The TZV was measured in the same fashion. Moreover, measurement of the TZV also included an evaluation of the median lobe volume when present [7, 9]. PV and TZV were separately measured and PZV was determined by subtracting PV from TZV. The random 14-core TRUS-guided prostate biopsy was routinely performed by the trans-perineum technique [7, 9]. For each core, a dedicated pathologist systematically assessed the following issues: (i) length, (ii) PCa and its grade according to the new tumor prognostic grading system related to biopsy Gleason score and pattern [10–12], (iii) percentage of cancer involving the core, (iv) prostatic intraepithelial neoplasia, (v) CII, (vi) glandular atrophy, and (vii) atypical small acinar cell proliferation. Chronic inflammation criteria, which have already been reported [7, 8], included inflammatory cell infiltrates composed predominantly of lymphocytes associated with admixed plasma cells showing a peri-glandular distribution pattern. Sheets of neutrophils around and within the glands as well as aspects of granulomatous prostatitis were excluding criteria.

Statistical Design and Methods

The population was first clustered in 2 groups by the presence or absence of CII in order to assess associated clinical factors. Patients were then grouped in cases with or without PCa with the aim of evaluating associated clinical factors. Data on continuous variables are reported as medians with their respective ranges and differences between groups were analyzed with the Mann-Whitney test. Data on categorical variables are presented as proportions, and differences between groups were analyzed with Pearson's chi-squared test or Fisher exact test as appropriate.

The multivariate logistic regression model assessed independent factors associated with CII and PCa risk. The mean probability logistic regression model was computed after assessing independent predictive variables. The goodness of fit of the final model was assessed by the Hosmer-Lemeshow test, which assesses the model by the deciles of risk grouping strategy of the estimated probabilities generated by the model. Finally, clinical probability risk models predicting CII and PCa were computed. The software used to run the analysis was IBM-SPSS version 20. All tests were two-sided, with a significance level of $p < 0.05$.

Results

The statistical summary of the evaluated cohort ($n = 596$) is reported in table 1. The median volume of the transitional zone was 18 ml, CII was detected in 157 cases (26.3%), and PCa was present in 292 patients (49 %).

Table 1. Demographics of the patient population (n = 596) undergoing a first biopsy set

Variables	Median (range)	n (%)
Age, year	67.0 (40–90)	
BMI, kg/m ²	26.1 (18.2–42.6)	
PSA, µg/l	6.2 (0.3–524)	
PV, ml	38.2 (9.2–182.8)	
TZV, ml	18.0 (2.0–112.5)	
PSAD, µg/l/ml	0.16 (0.01–106.2)	
L, mm	15.4 (10–40)	
DRE		
Normal		425 (71.3%)
Abnormal		171 (28.7%)
PCa		
No		304 (51.0%)
Yes		292 (49.0%)
CII		
No		438 (73.7%)
Yes		157 (26.3%)
BGS		
6		151 (51.7%)
7		101 (34.6%)
> 7		40 (13.7%)

BMI = Body mass index; L = length of the biopsy core; BGS = biopsy Gleason score.

Table 2. Cross-classification of factors associated with intraprostatic CII in patients undergoing a first biopsy set (n = 596)

Variables	CII		p
	No	Yes	
PSA, µg/l			0.682
median (range)	6.1 (0.26–465)	6.2 (0.90–524.45)	
PV, ml			0.002
median (range)	36.7 (11.2–180.9)	44.6 (9.2–182.8)	
TZV, ml			< 0.00001
median (range)	17.2 (2–112.5)	22.8 (4.6–76.9)	
PSAD, µg/l/ml			0.008
median (range)	0.16 (0.01–6.90)	0.15 (0.01–27.8)	
DRE, n (%)			0.830
Normal	312 (71.1%)	113 (72.0%)	
Abnormal	127 (28.9%)	44 (28.0%)	
PCa, n (%)			< 0.0001
No	188 (42.8%)	116 (73.9%)	
Yes	251 (57.2%)	41 (26.1%)	

Association between TZV and CII in patients undergoing first random biopsy set because of suspected cancer. The probability of detecting CII in the biopsy cores is directly associated with increasing measurements of TZV.

Table 3. Multivariate logistic regression analysis of factors associated with the risk of chronic intraprostatic inflammation in patients undergoing a first biopsy set (n = 596)

Factors	Model A			Model B		
	OR	95%CI of OR	p	OR	95%CI of OR	p
PV	0.985	0.960–1.012	0.275			
TZV	1.036	0.996–1.078	0.078	1.014	1.001–1.028	0.039
PSAD	1.122	0.958–1.134	0.153			
PCa	0.290	0.189–0.445	< 0.0001	0.300	0.197–0.457	< 0.0001

Model A: model including all significant variables in the univariate analysis; Model B: model after removing not significant variables and correcting PCa.

The cross-classification of clinical factors with CII is shown in table 2. Intraprostatic CII was associated with PV, TZV, and PSAD and there was an inverse association between PCa and CII.

Multivariate logistic regression analysis (table 3) showed that TZV was an independent factor associated with chronic intraprostatic inflammation (OR = 1.014, 95%CI: 1.001–1.028, p = 0.039) after removing confounders (PV and PSAD) and correcting PCa (OR = 0.300, 95%CI: 0.197–0.457, p < 0.0001). Figure 1 shows

the probability model of detecting CII in the biopsy cores by TZV measurements.

Age, PSA, PV, TZV, PSAD, abnormal DRE, and CII were associated with PCa (table 4). The association between factors and PCa was direct for age, PSA, PSAD, and abnormal DRE, but inverse for PV, TZV, and CII. The multivariate model showed that age (OR = 1.066, 95%CI: 1.039–1.093, p < 0.0001), PSA (OR = 1.177, 95%CI: 1.108–1.251, p < 0.0001), TZV (OR = 0.919, 95%CI: 0.901–0.938, p < 0.0001), abnormal DRE (OR

Table 4. Cross-classification of factors associated with PCa in the patient population (n = 596)

Variables	PCa		Range
	No (n = 304, 51%)	Yes (n = 292, 49%)	
Age, year			< 0.0001
median (range)	65.0 (42–90)	68.5 (40–90)	
BMI, kg/m ²			0.253
median (range)	26.0 (18.3–42.6)	26.1 (18.2–39.1)	
PSA, µg/l			< 0.0001
median (range)	6.03 (0.3–26)	6.28 (1–524)	
PV, ml			< 0.0001
median (range)	44.1 (9.2–180.9)	32.3 (12.2–182.4)	
TZV, ml			< 0.0001
median (range)	23.2 (4–12.5)	14.6 (2–76.9)	
PSAD, µg/l/ml			< 0.0001
median (range)	0.13 (0.01–0.73)	0.20 (0.02–27.8)	
DRE, n (%)			< 0.0001
Normal	243 (79.9)	182 (62.3)	
Abnormal	61 (20.1)	110 (37.7)	
CII, n (%)			< 0.0001
No	188 (61.8)	251 (86.0)	
Yes	116 (38.2)	41 (14.0)	

BMI = Body mass index.

Fig. 1. Association between TZV and CII in patients undergoing the first random biopsy set because of suspected cancer. The probability of detecting CII in the biopsy cores is directly associated with increasing measurements of TZV.

Table 5. Multivariate logistic regression analysis of factors associated with PCa risk in the population of patients undergoing a first random biopsy set (n = 596)

Factors	Model A			Model B		
	OR	95%CI of OR	p	OR	95%CI of OR	p
Age	1.066	1.038–1.093	< 0.0001	1.066	1.039–1.093	< 0.0001
PSA	1.056	0.933–1.195	0.388	1.177	1.108–1.251	< 0.0001
PV	1.023	0.986–1.061	0.233			
TZV	0.916	0.872–0.962	< 0.0001	0.919	0.901–0.938	< 0.0001
PSAD	6.546	0.827–9152.472	0.060			
CII	0.271	0.170–0.433	< 0.0001	0.276	0.174–0.439	< 0.0001
DRE	2.316	1.478–3.628	< 0.0001	2.024	1.415–3.428	< 0.0001

Model A: model including all significant variables in the univariate analysis, Model B: model after removing not significant variables and correcting intraprostatic CII.

Table 6. Multivariate logistic regression model of clinical factors predicting PCa risk stratified by TZV in patients undergoing a first random biopsy set (n = 596)

Factors	OR	95%CI of OR	p
Age	1.059	1.033–1.085	< 0.0001
PSA	1.147	1.088–1.210	< 0.0001
TZV(1) *	0.476	0.284–0.799	0.005
TZV(2) *	0.214	0.126–0.364	< 0.0001
TZV(3) *	0.064	0.035–0.119	< 0.0001
DRE **	2.134	1.394–3.266	< 0.0001

TZV (1), TZV first quartile (TZV ≤ 12.3 ml); TZV (2), TZV second quartile (12.3 < TZV ≤ 18.0 ml); TZV (3), TZV third quartile (18.0 < TZV ≤ 27.7 ml); TZV (4), TZV fourth quartile (27.7 < TZV ≤ 112.5 ml); *reference TZV (4); **reference normal DRE.

= 2.024, 95%CI: 1.415–3.428, p < 0.0001), and CII were independent predictors of PCa (table 5). The volume of the transitional zone and the presence of chronic intraprostatic inflammation were independently associated with a reduced risk of PCa.

The volume of the transitional zone was categorized by quartiles as follows: (i) first quartile: TZV ≤ 12.3 ml), (ii) second quartile: 12.3 < TZV ≤ 18.0 ml, (iii) third quartile: 18.0 < TZV ≤ 27.7 ml), and (iv) fourth quartile: 27.7 < TZV ≤ 112.5 ml. The fourth quartile was the reference category. The final model showed that age, PSA, and categorized TZV were independent clinical predictors of PCa risk (table 6). The Hosmer-Lemeshow test assessed the efficacy of the model (Chi squared = 5.435, p = 0.710).

Fig. 2. Association of TZV and age with PCA risk in patients electing a first random biopsy set. The probability of PCA is directly associated with age. However, when we stratified the population into 4 groups of increasing TZV quartiles, the risk of PCA was decreased at the same age levels because of the inverse association between TZV and PCA. The patient population was clustered in 4 groups according to ranking TZV quartiles as follows: (i) group 1: TZV within the first quartile, (ii) group 2: TZV above the first quartile but within the median (second quartile), (iii) group 3: TZV above the median and within the third quartile, and (iv) group 4: TZV above the third quartile.

PCA risk models including age and PSA with categorized TZV (normal DRE) are shown in figure 2 and 3. The PCA model predicted by TZV and stratified by chronic intraprostatic inflammation is depicted in figure 4.

Discussion

The present investigation showed that TZV was associated with CII in patients electing a first random biopsy set because of suspected cancer. The probability of detecting CII in the biopsy cores was directly related to increasing measurements of TZV (see fig. 1). This study showed associations between chronic intraprostatic inflammation and growth of the transitional zone. The relationships between chronic inflammation and BPH are controversial [2, 3] and our study brings new evidence to this subject.

Fig. 3. Association of TZV and PSA with PCA risk in patients electing a first random biopsy set. The probability of PCA is associated with increasing PSA levels. However, when we stratified the population into 4 groups of increasing TZV quartiles, the PCA risk was decreased at the same PSA levels because of the inverse association between TZV and PCA. Patients presenting with the same PSA level of 5 ng/ml might show different probabilities of PCA by TZV measurements. PCA risk is about 0.10 in group 4, close to 0.30 in group 3, about 0.45 in group 2, and just above 0.60 in group 1. As a result, the model stratifies the risk of detecting PCA in the different groups having the same PSA levels.

In a patient population undergoing a first random biopsy set, the study showed that TZV was associated with a decreased risk of PCA.

PCA clinical models including age and PSA stratified by TZV quartiles were proposed (fig. 2 and 3). The proposed models might have potential applications in clinical practice when patients undergo a first random biopsy set. The subject dealing with associations between CII and PCA is controversial. However, the results of the present study confirmed an inverse association between CII and PCA, which has been reported in clinical studies [6–8, 13–16]. It was also shown that baseline prostate inflammation is associated with a reduced risk of PCA in men undergoing repeat prostate biopsies [17].

In the present investigation, TZV was an independent predictor of both CII (direct association) and PCA risk (inverse association). The evidence of our study stresses the importance of evaluating the volume of the prostate according to the evolving zonal anatomy, which depends

on aging and hormonal variations of total testosterone and oestrogens [18, 19].

There are limits in our study. First, it was a single center study, but the sample size was large enough. Second, we measured PV by means of TRUS and not by prostatectomy specimens. However; TRUS is widely used and it is considered an effective technique. Third, the inverse association of chronic inflammation with PCa might be confounded by PSA. PSA may be elevated by both inflammation and cancer, and hence, if biopsies are performed in cases with increased PSA, some patients will have cancer and others CII [20–22]. Patients with inflammation may undergo biopsy procedures more readily than men without inflammation because of potential higher PSA levels. As a result, men with CII will automatically be less likely to have cancer and vice versa. However, beyond the limits and because of the inclusion criteria, we are confident that our study gives evidence of the independent associations of CII and PCa when related to TZV.

Conclusion

In a patient population undergoing a first random prostate biopsy set because of suspected cancer, independent associations were detected among TZV, CII, and PCa. The association between TZV and CII was direct, but the relation between TZV and PCa was inverse. The

Fig. 4. The diagram illustrates the independent relations among PCa, TZV, and intraprostatic CII. The risk of detecting PCa is decreased by both TZV and intraprostatic CII.

measurement of TZV is a useful parameter for evaluating chronic intraprostatic inflammation and PCa risk. Our study outlines the importance of evaluation of the prostate according to the zonal anatomy of the gland.

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