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Characteristics of Prostate Cancers Detected at Prostate-Specific Antigen Levels Less than 2.5 ng/ml

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Abstract

Introduction—The Prostate Cancer Prevention Trial (PCPT) reported that 15% of men with a PSA value < 4 ng/ml and a normal digital rectal examination (DRE) have biopsy-detectable prostate cancer (PCa). However, limited published data describe the tumor features of PCa detected at very low PSA levels (< 2.5 ng/ml).

Methods—A total of 934 men underwent radical retropubic prostatectomy (RRP) by one surgeon between 2003 and 2007. Herein, we describe the clinico-pathological features of 77 patients with a preoperative PSA < 2.5 ng/ml.

Results—Of the men with a low-PSA (<2.5 ng/ml) tumor, 51 (66%) had findings suspicious for PCa on DRE. Indications for prostate biopsy in the remainder included an elevated PSA velocity, hematospermia, and abnormal transrectal ultrasound findings. PCa was detected at transurethral resection of the prostate (TURP) in the remaining 8%. Despite their low PSA at diagnosis, 8 (10.4%) and 20 (26%), respectively, had a biopsy and RRP Gleason grade ≥7, while 7 (9%) and 6 (7.8%) had extracapsular tumor extension or positive surgical margins. Compared to men with a normal DRE, the mean tumor volume was significantly higher in those with a suspicious DRE (3.3 cc vs. 1.7 cc, p=0.018).

Conclusions—Despite PSA levels <2.5 ng/ml at diagnosis, a considerable proportion of men had aggressive pathology features at RRP. DRE remains an important component of early PCa detection.

Keywords

Prostate Cancer; PSA; Prostate Cancer Screening

Introduction

Serum prostate specific antigen (PSA) and digital rectal examination (DRE) form the basis for modern prostate cancer (PCa) screening and early PCa detection programs[1]. The widespread application of PCa testing has resulted in a stage migration, as many PCa's are now detected at lower PSA levels.

The Prostate Cancer Prevention Trial (PCPT) reported that 15% of men with a PSA < 4 ng/ml and a normal digital rectal examination (DRE) have biopsy-detectable prostate cancer[2]. Subgroup analysis revealed that prostate cancer was even present in 10% of men with PSA levels < 1 ng/ml and a normal DRE[3].

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A recent publication from the placebo arm of the PCPT reported that only 33% of tumors could be considered “clinically insignificant” in men with a PSA < 2.5 ng/ml[4]. Overall, there are limited published data on the prostatectomy pathology features or treatment outcomes among patients with prostate cancer detected at very low PSA levels (< 2.5 ng/ml). Thus, our objective was to describe the pathological features after radical prostatectomy for prostate cancer detected at low PSA levels in daily clinical practice.

Materials and Methods

A total of 1278 men underwent radical retropubic prostatectomy (RRP) by one surgeon (WJC) between 2003 and September of 2008. All men were referred for prostate cancer treatment, and none were enrolled in a formal screening study. Of these men, 77 had a maximum preoperative PSA level of 2.5 ng/ml. We recorded clinical and pathological patient information in a prospective database. The indications for prostate biopsy are listed in Table 1.

Tumor volumes were calculated by multiplying the prostate weight at the time of RRP by the percentage of tumor in the prostatectomy specimen, estimated visually by the attending surgical pathologist. This technique has been previously demonstrated to correlate closely with tumor extent determined by morphometric analysis[5]. Chi square and Fisher's exact tests were used to compare patient subsets. In addition, we calculated the proportion of men who met published criteria for pathologically “insignificant” prostate cancer [6] including tumor volume < 0.5 cc, and biopsy Gleason score < 7 and no evidence of extracapsular tumor extension. All statistical analyses were performed using Statistical Analysis Systems (version 9.1; SAS Institute, Inc., Cary, NC) and SPSS 10.0 for Windows (SPSS Inc., Chicago, IL).

Results

Of the 77 men with a PSA <2.5 ng/ml, the digital rectal exam findings were suspicious for PCa in 51 (66%) and normal in 26 (34%) (Table 2). At the time of diagnosis, 8 (10.4%) had a Gleason sum ≥7, whereas 20 (26%) had a Gleason sum ≥ 7 at RRP. Thus, upgrading occurred in 15.6% of the study population.

The mean tumor volume was 2.76 cc, and extracapsular tumor extension was present in 9% of patients. Positive surgical margins and seminal vesicle invasion were found in 7.8% and 1.3%, respectively. When men with low PSA were categorized based upon DRE findings, there was a trend toward more aggressive tumor features in those with palpable tumors (Table 3). This difference was statistically significant for tumor volume (p= 0.018).

Although most tumors were identified because of suspicious DRE findings and thus would typically be considered clinically significant by many, we nevertheless determined the proportion of men with low PSA levels at diagnosis who met previously published criteria for clinical significance. Overall, only 20% of cases would have considered “clinically insignificant” based upon these criteria (including 46% with a normal DRE and 20% with an abnormal DRE, p = 0.019).

Discussion

At the conclusion of the PCPT, all men who had not reached the 4.0 ng/ml PSA threshold for biopsy and who had a normal digital rectal examination throughout the study period were recommended to undergo an empiric prostate biopsy. This resulted in a PCa detection rate of 15% among men with clinically “undetectable” PCa.

Lucia et al. recently reported on the PSA-stratified pathological data from a subset of men in the PCPT placebo group[4]. In 161 men with PSA levels of 0 to 1.0 ng/ml and 1.1 to 2.5 ng/ml, 51.7% and 33.7% met the Epstein biopsy criteria for potentially insignificant cancer, respectively[7]. Among men from the placebo group with a preoperative PSA of 1.1 to 2.5 ng/ml, 13% had extracapsular tumor extension, 19% had positive surgical margins, and 2.9% had lymph node metastases at radical prostatectomy. It is noteworthy that these rates of adverse pathology features are higher than those observed in our patient cohort with similar PSA levels whose prostate cancer was detected in a clinical setting.

In the European Randomized Study of Screening for Prostate Cancer (ERSPC), Lujan et al also reviewed the pathology characteristics of PCa detected at low PSA levels[8]. Specifically, they identified 15 cancers detected at a PSA less than 2.99 ng/ml. Of these cancers, 11(73%) were considered “significant,” and 2 (13%) had extracapsular tumor extension. Although the frequency of “insignificant” cancer was therefore slightly higher in their study than in ours or in the PCPT, the ERSPC data similarly suggests that a considerable proportion of men with prostate cancer detected at low PSA levels have aggressive tumor features.

Finally, Stephenson et al recently compared the pathology features and treatment outcomes between men whose PCa was diagnosed at a PSA < 2.5 ng/ml versus a PSA between 2.5 and 4.0 ng/ml[9]. Of the 84 men with a PSA <2.5 ng/ml in their series, 62 (74%), 6 (7%), and 16 (19%) were treated with radical prostatectomy, external beam radiation therapy, and brachytherapy, respectively. Among surgically treated patients, the proportion of tumors with a prostatectomy Gleason score ≥7 was similar between the 2 PSA strata (44 vs. 56%, p=0.11). Moreover, Kaplan-Meier analysis revealed a similar progression-free probability after local therapy between the groups. This data further confirms that a proportion of men diagnosed at very low PSA levels have aggressive tumor features.

While the importance of the DRE in early PCa detection remains controversial, more than 66% of the low-PSA tumors in our series were identified exclusively by DRE. In particular, it has been suggested that the positive predictive value of DRE is low for men with low PSA levels[10]. We have previously demonstrated in a separate screening population that a substantial (20%) proportion of prostate cancer cases detected by DRE alone had non-organ-confined disease[11]. Furthermore, Okotie et al. showed that serially screened men with a concomitant abnormality in PSA and DRE had a lower progression-free survival rate than those with an abnormal DRE alone or elevated PSA alone. Taken together, these studies suggest that DRE plays an important role in early PCa detection, even in men with low PSA levels.

The mean tumor volume in our series was 2.76 cc. This value is relatively high compared to other series, such as Koboyashi et al describing the pathology of men with PSA between 2.5 and 4.0 ng/ml[12]. This may likely be explained by the high frequency of clinical stage T2 cancers in our series. Also, in contrast to some other studies which only calculate the volume of the largest tumor, we report the total tumor volume.

There are several limitations of our study that deserve mention. First, the overall number of patients in our radical prostatectomy referral series with a preoperative PSA <2.5 ng/ml is relatively small. Second, our data may be biased due to the high proportion of patients with clinical stage T2 disease. However, outside of a clinical trial (such as the PCPT) with empiric prostate biopsies done in men with no clinical indication, this bias is likely to be present.

Conclusions

Despite a PSA level < 2.5 ng/ml at diagnosis, a substantial proportion of PCa patients may have aggressive pathology features in the radical prostatectomy specimen. DRE plays an important role for prostate cancer detection and risk stratification, even among men with total PSA levels <2.5 ng/ml.

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Table 1

Indication for Prostate Biopsy

Abnormal DRE	51 (66%)
Elevated PSA	
Velocity	12 (16%)
Hematospermia	4 (5%)
Abnormal TRUS for BPH	4 (5%)

* An additional 6 (8%) patients were diagnosed at transurethral resection of the prostate.

Table 2

Clinical Characteristics

Preoperative		
Age (years)		56
PSA (ng/ml)		1.63
Clinical Stage (%)		
T1a/b		8%
T1c		26%
T2		66%
Biopsy Gleason Score		
	6	89%
	7	7.8%
	8	2.6%
Postoperative		
Tumor Volume		2.76 ml
RRP Gleason Score		
	6	73%
	7	21%
	8	5%
(+) Surgical Margins		7.8%
Extracapsular Tumor Extension		9.1%
Seminal Vesicle Invasion		1.3%
(+) Lymph Nodes		0%
Gleason Upgrading from Biopsy to RRP		15.6%

Table 3

Pathological characteristics of cases of abnormal vs normal DRE

	Suspicious DRE	Normal DRE	p-value
Mean ml tumor vol	3.27	1.72	0.02
% Biopsy Gleason ≥7	11.7	8	0.60
% RRP Gleason ≥7	27.7	23.1	0.67
% Gleason upgrading	19.6	16	0.2
% Positive surgical margins	7.8	7.7	1
% Extracapsular tumor extension	11.8	3.9	0.41
% Seminal vesicle invasion	2	0	1
% Insignificant tumors	20	46	0.019