

RESEARCH ARTICLE

Impact of PSA and DRE on Histologic Findings at Prostate Biopsy in Turkish Men Over 75 Years of Age

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Abstract

Prostate specific antigen (PSA) and digital rectal examination (DRE) are the known predictive factors for positive prostate biopsies differing according to the age, region and race. There have been only very limited studies about the impact of PSA on histological findings at prostate biopsy in Turkey. The aim of this study was to evaluate the impact of PSA and clinical stage on histologic findings of prostate biopsy in men older than 75 years of age as a first study in the Turkish population. A total of 1,645 consecutive prostate biopsies were included, with 194 men aged 75 or older. Cancer was identified in 104 patients (53.6%). Of the 104 positive biopsies, Gleason scores were less than 7 in 53 (49%) patients, 7 or greater in 51 (51%) patients. Positive prostate biopsies were significantly correlated with advanced age ($p=0.0001$), abnormal DRE ($p=0.0001$) and raised PSA ($p=0.0001$). The prostate volume was significantly correlated with advanced age especially in prostate cancer patients over 75 years, compared with those under 75 ($p=0.0001$). These results are useful for counseling men older than 75 years for prostate cancer detection. However, PCa screening decisions are currently based on urologist judgment and detection of latent asymptomatic disease is an important concern regarding costs, overdiagnosis, overtreatment and quality of life (QOL) for men aged 75 years and older. Healthy old patients with a long life expectancy need to be carefully evaluated for eligibility for PCa screening.

Keywords: Elderly patient - PCa screening - prostate biopsy - histological findings

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Introduction

Prostate cancer (PCa) is one of the most common cancers in the male population and diagnosed in 1 out of 6 men (Jemal et al., 2010). Its incidence among Turkish men was determined as 6.1 per 100,000 (Tuncer, 2007). PCa usually affects elderly men and has increasing incidence rates with PSA testing especially in the developed countries (Taichman et al., 2007). However PSA-based screening in patients older than 75 years has long been controversial although being an easy procedure, acceptable sensitivity and low costs. Health status and life expectancy were frequently used to select the patients for PSA-based screening to avoid over diagnosis and overtreatment (Welch, 2010). There are significant different therapeutic strategies in older and younger patients. This indicates that age alone has influenced urologist's selection of therapeutic modalities (Situmorang et al., 2012). Prostate biopsies in elderly men are only justified in the age group of 75-79 years with PSA < 20 ng/ml and with no comorbidities, as this is the group of patients who could benefit from radical treatment (Carter et al., 2006; Parker

et al., 2006). But, U.S. Preventive Services Task Force (USPSTF) recommendation statement about screening for PCa is not to screen for PCa in men age of 75 years or older (US Preventive Services Task Force, 2008; Schröder et al., 2009). However the results of PSA values and autopsies suggest that insignificant PCa may be found even in about 80% of males over 80 year-old (Haas et al., 2007). The prevalence of incidental PCa appears to be low in the Turkish population because the prevalence of PCa and high-grade prostatic intraepithelial neoplasia (HGPIN) were 33.3% and 16.7% beyond age 80, respectively in the limited number of autopsy study following trauma induced death (Polat et al., 2007).

PCa in elderly men are frequently treated with a 'watch and wait' policy or with hormonal withdrawal alone. The elderly should request more effective treatment and should be willing to tolerate less treatment-related complication (Dale et al., 2005). The purpose of our study was to determine the impact of PSA and clinical stage on histological findings of prostate biopsy in men older than 75 and also necessity of prostate biopsy of elderly men as a first study in the Turkish population.

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Materials and Methods

A high volume tertiary center's prospectively maintained prostate biopsy database was reviewed retrospectively between January 2001 and June 2008. An abnormal digital rectal examination (DRE) or an elevated age-specific PSA according to reference ranges were accepted as indication for prostate biopsy. PSA screening was performed by Beckman Coulter Kit, Hybritech, San Diego, CA, USA. A written consent paper about the biopsy procedure and explanation of possible complications was taken from patients. A total of 1645 consecutive prostate biopsies were included to the study and 194 of them were 75 year-old and older. Exclusion criteria were prior history of prostate cancer, a history of cancer treatment or known history of metastatic disease. And results of previous biopsies were also excluded. All men underwent transrectal ultrasound-guided prostate biopsies in the lateral decubitus position by using topical anesthesia with 2% lidocaine gel. All patients began to use Levofloxacin (500mg BID) one day before the operation and went on to receive the drug during one week. We used an ultrasound machine (Toshiba Sonalayer SSA-250AR) equipped with 5Mhz rectal probe and automatic core biopsy device (TruCare MD-TechR) with 18 gauge core tissue biopsy needle. Prostate biopsies were performed as 8, 10 and 12-core protocol. The biopsy specimens were put in a container with 10% formaldehyde and all samples had been examined by the same uropathologist. All the cases were stratified by age, PSA levels, free and total PSA ratio, DRE findings, prostate volumes measured with transrectal ultrasound, results of cancer positive biopsies, Gleason scores according to histopathological results. The statistical analysis in this study was performed with NCSS 2007 software program. The methods of descriptive statistics such as the mean, standard deviation as well as Chi-square test for comparing the qualitative variables and independent t-test for comparing two groups on a given variable were used in the study. The p value less than 0.05 were judged as statistically significant.

Results

1645 men who underwent transrectal ultrasound guided needle biopsy were prospectively studied. 194 (11%) patients were 75 years-old or older and the mean age at biopsy was 77.8 years (range 75-88). Of the 194 men, 161 were 75-80 years of age (83%), 33 were over 80 years (17%). Table 1 shows the demographics of patients stratified by age. Only 5 men had a history of familial PCa. DRE findings were reported as abnormal in 105 men (54.13%), normal in 89 men (45.87%) in group 1 patients (≥ 75 years) and abnormal in 923 (63.6%) men, normal in 528 men (36.4%) in group 2 patients (< 75 years). Positive prostate biopsies in group 1 patients were significantly correlated with abnormal DRE ($p=0.0001$). Group 1 patients were found to be at more advanced clinical stage than the other group ($p=0.0001$). PSA values were higher in Group 1 patients than the group 2 patients. Patients with PSA value higher than 20 ng/ml was observed in 73 (37.5%) and 261 (17.5) patients in group 1 and group 2

Table 1. Demographics of Men Stratified by Age

		<75 year	≥ 75 year	Statistics
DRE	Negative	923 63.60%	89 45.87%	$\chi^2:22.7$ $p=0.0001$
	Suspected	528 36.4%	105 54.13%	
C	T1c	923 63.62%	89 45.87%	$\chi^2:30$ $p=0.0001$
	T2	495 34.11%	92 47.42%	
STAGE	T3	32 2.21%	13 6.71%	$\chi^2:60.7$ $p=0.0001$
	T4	1 0.06%		
PSA (mg/ml)	<4	110 7.5%	4 2.0%	$\chi^2:28.6$ $p=0.0001$
	4.1-10	789 54.3%	68 35.0%	
	10.1-20	291 20.0%	49 25.2%	
	20.1-30	87 5.9%	18 9.2%	
	30.1-40	43 2.9%	9 4.6%	
	>40	131 9.0%	46 23.7%	
Pathologic Diagnose	bph	945 65.1%	90 46.40%	$\chi^2:17.6$ $p=0.0001$
	Cancer	506 34.9%	104 53.60%	
Pathology	None	1387 95.5%	187 96.3%	$\chi^2:0.635$ $p=0.728$
	PIN high grade	44 3.0%	4 2.0%	
	ASAP	19 1.4%	3 1.5%	
Prostate Volume	<40 ml.	754 51.9%	73 37.6%	$\chi^2:17.6$ $p=0.0001$
	>40 ml.	697 48.1%	121 62.4%	
Gleason Score	<7	277 58.1%	52 50.9%	$\chi^2:4.35$ $p=0.113$
	>7	138 28.9%	29 28.4%	

*Abbreviations: DRE: digital rectal examination; PIN: prostatic intraepithelial neoplasia

Table 2. Mean PSA Values, Prostate Volumes and Gleason Scores Men Stratified by Age

	<75 year	≥ 75 year	t	p
PSA	20.50 \pm 58.37	47.51 \pm 116.95	-3.15	0.002
Prostate volume	35.9 \pm 21.25	45.14 \pm 25.66	-4.04	0.0001
Gleason Score	6.23 \pm 1.31	6.49 \pm 1.32	-1.8	0.071

respectively ($p=0.0001$)

Prostate biopsy was performed in only 4 patients (2%) who had a PSA level lower than 4ng/ml but had abnormal DRE findings. PSA values of 4-10ng/ml were found in 67 men (34.5%), 10, 1-20ng/ml in 45 men (25.2%), more than 20ng/ml in 68 men (35%) in group 1 patients. PCa was identified histopathologically in 106 men (54.7%) 75 year-old or older and 506 men (34.9%) younger than 75 years old. patients with a prostate volume ≥ 40 cc was observed in 697 (48.1%) and 121 (62.4%) in group 2 and group 1 respectively. Elderly patients had significantly higher prostate volumes than the younger patients. The prostate volume was positively correlated with advanced age ($p=0.0001$). Gleason >7 was found more frequently in elderly group than younger group. Gleason scores in both age group were statistically insignificant. Mean PSA values and prostate volumes were significantly higher in men ≥ 75 years ($p<0.005$). But there was no statistically significant difference for Gleason scores between 2 groups. ($p>0.005$) (Table 2.)

Almost 15% of these men had complication following biopsy, of which 8% need hospitalization within the first 6 months after biopsy.

Discussion

PCa is the second most common cancer in male population and ranks sixth in terms of cancer-related mortality worldwide (Ferlay et al., 2010). So, it is important to remember that younger men (under 60

years) may be at risk, even if asymptomatic. In general, cancer-related mortality can be reduced by early detection and treatment. Early detection through screening is recommended but whether PCa screening lowers PCa mortality remains controversial by the discrepant results of the prostate large-scale randomized controlled trials (Andriole et al., 2009; Wolf et al., 2010). Lumen et al. (2012) reported that PSA-based screening did not lower Pca-specific mortality but did increase diagnosis of stage 1 PCa in a retrospective databases study (Lumen et al., 2012). However, the Rotterdam section of the European Randomized Study of Screening for Prostate Cancer (ERSPC) has a large randomized screening trials at a total of 34,833 men and published the latest article of reduced risk of dying from PCa up to 51% for an individual man choosing to be screened repeatedly compared with a man who was not screened. This benefit of cancer screening should be balanced against the harms of over diagnosis and subsequent overtreatment under the age 70 year-old but no benefit over 70 year-old (Bokhorst et al., 2013). Although, several guidelines consider PSA to be a major cancer screening test and PSA testing in primary care has increased over the last decade. However, PSA alone is not a reliable parameter to predict the likelihood of cancer histopathology on TRUS-guided prostate biopsy (Roobol et al., 2007; Heidenreich et al., 2011) A PSA threshold of 4ng/ml, as traditionally used, will miss a substantial proportion of cancers, but wide-spread adoption of lower thresholds to increase sensitivity would expose many men to an unnecessary biopsy. Therefore many parameters other than PSA like f PSA, PSA velocity, PSA density, Age-adjusted PSA values, DRE, prostate volumes have been used to predict more accurate result of prostate biopsies (Barry, 2006; Alibhai et al., 2003). PCa, a disease that causes serious health problems especially in older population and the definitive diagnosis is only made by TRUS-guided biopsy (Scattoni et al., 2005). According to the aforementioned report, The USPSTF recommends against screening for PCa in men ≥ 75 years. Because, patients who have less than 10 years of life expectancy are rarely candidates for curative treatment (Eastham et al., 1999; Schröder et al., 2009). However, some studies showed that radical prostatectomy increases the survival in selected patients ≥ 75 years (Froehner et al., 2013). In this study, we aim to evaluate the impact of PSA and clinical stage on histological findings of prostate biopsy and also to discuss the indication of prostate biopsy in Turkish men older than 75 years of age.

We analyzed age, PSA, DRE, prostate volumes and Gleason scores. We analyzed prostate volume to find the direct effect of prostate volume on prediction of histopathology of biopsy rather than the calculation PSA density. According to the study of Shigemura et al. in Japanese men with PSA levels < 10 ng/ml showed that prostate volume was the significant predictor for a positive biopsy (Shigemura et al., 2008). Based on our findings, prostate volume > 40 cc should be considered a predictive factor for a positive biopsy ($p=0.0001$). On the other hand prostate volume was not included in Garzotto's study which reports independent factors associated with positive biopsy (Garzotto et al., 2003).

Total PSA alone has been reported to be a weak predictor of a positive biopsy result (Ferlay et al., 2010). However in our study total PSA was a significant predictive factor for positive biopsy result in men older than 75 years ($p=0.0001$). The reason for this result is that we performed prostate biopsy in older patient population with higher PSA values than the younger patients .

DRE is sensitive, specific, predictive or accurate enough on its own to be an ideal screening or diagnostic test for PCa (Ojewola et al., 2013). Nomikos et al reported that abnormal DRE helped significantly in the diagnosis of prostate cancer in older men with PSA < 20 ng/ml (Nomikos et al., 2010). However in our study DRE with the age, PSA and prostate volume were significant predictive factors for positive biopsy result in men older than 75 years ($p=0.0001$). The reason for this is that older patients have higher probability of prostate cancer with advanced clinical stage. In our study; abnormal DRE was associated with higher positive cancer detection results ($p < 0.005$) and additionally PSA values and increasing prostatic volumes were found higher and statistically significant ($p < 0.005$) in men 75 years and older according to the more younger group.

In conclusion, PSA testing often leads to discovery of nonmortal cancers in the elderly. But PSA was the only clinical variable associated with an increased rate of cancer detection on prostate biopsy in men 75 years and older . Our current study shows significant predictors for positive prostate biopsies in Turkish men ≥ 75 years. DRE, PSA and prostate volumes were the important parameters associated with an increase rate of cancer detection on prostate biopsy in men ≥ 75 years. These results are useful when counseling men older than 75 years of age for detection of PCa. However, PCa screening decision is currently based on urologist's judgment. While PSA-based screening and detect latent asymptomatic disease lead to important concerns regarding the costs, over diagnosis, over treatment and quality of life (QOL) for men aged 75 years and older. On the other hand, a strict age cut-off of 75 years also prohibits screening in healthy older men with a long life expectancy. So, these limited number of healthy old patients had to be carefully evaluated for eligibility of PCa screening. Furthermore, extensive studies for prostate biopsy outcomes in elderly Turkish population are also needed.

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