RESEARCH ARTICLE

Utility of Digital Rectal Examination, Serum Prostate Specific Antigen, and Transrectal Ultrasound in the Detection of Prostate Cancer: A Developing Country Perspective

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Abstract

Purpose: To determine the utility of digital rectal examination (DRE), serum total prostate specific antigen (tPSA) estimation, and transrectal ultrasound (TRUS) for the detection of prostate cancer (PCa) in men with lower urinary tract symptoms (LUTS). Materials and Methods: All patients with abnormal DRE, TRUS, or serum tPSA >4ng/ml, in any combination, underwent TRUS-guided needle biopsy. Eight cores of prostatic tissue were obtained from different areas of the peripheral prostate and examined histopathologically for the nature of the pathology. Results: PCa was detected in 151 (50.3%) patients, remaining 149 (49.7%) showed benign changes with or without active prostatitis. PCa was detected in 13 (56.5%), 9 (19.1%), 26 (28.3%), and 103 (74.6%) of patients with tPSA <4 ng/ml, 4-10 ng/ml, 10-20 ng/ml and >20 ng/ml respectively. Only 13 patients with PCa had abnormal DRE and TRUS with serum PSA <4 ng/ml. The detection rate was highest in patients with tPSA >20 ng/ml. The association between tPSA level and cancer detection was statistically significant (p<0.01). Among 209 patients with abnormal DRE and raised serum PSA, PCa was detected in 128 (61.2%). Conclusions: The incidence of PCa increases with increasing serum level of tPSA. The overall screening and detection rate can be further improved by using DRE, TRUS and TRUS-guided prostate needle biopsies.

Keywords: Biopsy - digital rectal examination - prostate cancer - transrectal ultrasound - Pakistan

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Introduction

Prostate cancer (PCa) is the most common cancer in American men, and the second leading cause of cancer deaths in men, exceeded only by lung cancer (Woolf, 1995). Ahmed et al. (2007) reported that almost 1% of men aged around 50 years are diagnosed with PCa. The incidence of PCa in American population has increased around 50% between 1989 and 1993 (Shapiro et al., 1994) and is expected to increase at even higher rates across the globe due in part to improvement in longevity, with more men living to the age when prostate cancer is more likely to develop (Lalitha et al., 2012; Verim et al., 2013). Several Indian tumor registries have also revealed a rising trend in the incidence of PCa and the mean annual percent change has ranged from 0.14 to 8.6% (Lalitha et al., 2012). No such analysis of changing incidence of PCa has been reported from Pakistan till date.

Men with early stages of PCa are usually asymptomatic. If symptoms are present, they are often confused with normal signs of aging (Kavasmaa et al., 2013). Many times, benign prostatic conditions, such as benign prostatic hyperplasia (BPH), have the same symptoms as PCa (Pinnock et al., 1998). Men with lower urinary tract symptoms (LUTS) are also reported to harbor PCa. A substantial number of clinicians perceive that there is a link between LUTS and PCa and recommend screening for early cancer in men with urinary symptoms (Martin et al., 2008; Hoffman, 2011; Belbase et al., 2013). The screening programs for PCa in healthy adult men are however, not completely without fault. The detection of latent asymptomatic disease in very old men (>75 years) is an important concern, for example, with regard to increasing costs, overdiagnosis, overtreatment and quality of life (Verim et al., 2013).

To improve the prognosis of patients with PCa, early detection is necessary. Methodologies used today to identify PCa include the serum total prostate specific antigen (PSA) test, digital rectal examination (DRE), transrectal ultrasound (TRUS), and TRUS-guided needle biopsy. The DRE screening significantly improved the staging of PCa in the early 1900s and was recommended annually for men fifty years of age and older. Torp-Pederson et al., (1988) described the DRE as simple to perform, noninvasive, and a relatively inexpensive screening tool. It is a subjective evaluation and dependent on the physician's skill in recognizing the feel of the tumor. Unfortunately, this method does not allow the physician to

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manually feel the entire prostate. As a result, the DRE often detects the disease when it is no longer organ confined. Currently, the DRE is an important assessment when used in conjunction with other diagnostic tools. Technologic advances in ultrasound and biopsy since the 1940s have made TRUS an integral tool in detecting early stages of PCa (Applewhite et al., 2001). TRUS is an imaging technique that uses harmless sound waves and their echoes to "map" the prostate. Radiologist use TRUS to guide their biopsy needles through the perineum into the prostate (directed biopsies). This procedure detects about 68% of cancers in the prostate peripheral zone and 8% from the central zone (McNeal et al., 1988). Since Kuriyama et al. (1980) found the detectable and quantifiable antigen in human serum in 1980, PSA had become the most useful tumor marker for PCa. PSA is superior to DRE and TRUS for screening due to its objectivity and cost-effectiveness. These diagnostic modalities and their combinations have improved the detection rate of clinically organ-confined PCa (Strohmaier et al., 1999; Nath et al., 2012; Poudel et al., 2012; Zheng et al., 2012).

With reference to the different modalities used for the detection of PCa, this study was planned to determine the usefulness of serum PSA, DRE, and TRUS for the detection of PCa in patients having LUTS in our set up.

Materials and Methods

Patients

This study was conducted at Sindh Institute of Urology and Transplantation (SIUT) from May 2012 to Nov 2013. A total of 300 men (≥45 years) underwent testing for the detection of PCa using the diagnostic modalities of DRE, serum tPSA measurement, TRUS and TRUS-guided prostate biopsies. The sample size was calculated using WHO software with the incidence rate of prostate cancer found in literature. All included patients had LUTS with negative urine culture. LUTS included urgency, frequency, reduced flow, hesitancy, nocturia, dribbling, incontinence and incomplete emptying of the bladder. The prostate was examined among these patients to explore the relationship between diagnostic tools including serum PSA, DRE, TRUS and TRUS-guided biopsy. Since this study is interested in early diagnosis of PCa, therefore, patients clinically identified as either stage C or D disease by DRE or by radiographic examinations were excluded from this study.

Methods

All patients underwent DRE, serum tPSA estimation, and TRUS, followed by TRUS-guided needle biopsy which was performed due to suspicion of PCa on DRE (abnormal DRE) or raised serum PSA >4 ng/ml or abnormal TRUS finding. PSA was measured prior to DRE, which was performed by two urologists and TRUS was performed by one experienced radiologist. Initially, each patient was scanned transversally and sagittally from the level of seminal vesicles to the apex of the prostate. Abnormality of any of the three diagnostic modalities were labeled as positive and the absence of abnormality as negative. TRUS-guided biopsies were taken transrectally using an 18 gauge automated biopsy gun needle. In case, a hypoechoic area specifying localized PCa was noticed in the prostate with TRUS, both TRUS-guided systematic as well as directed needle biopsy was carried out. In almost all cases, at least eight cores were obtained from predetermined areas of the prostate zones as detailed in our previous study (Rashid et al., 2013). Each biopsy core was separately labeled and processed and examined. Standardized approach to prostate core biopsy handling and interpretation was adopted as given in detail in our earlier report by an experienced uropathologist (MM). An additional core was obtained from a hypoechoic areas if that area did not fall in the systematic biopsy sites. All patients received Ciproxin 500 mg 12 hourly and Flagyl 800 mg every 8 hourly per day for five days after the procedure.

Data analysis

The data was compiled and analyzed in SPSS version 10.0 (SPSS, Chicago, IL, USA). The frequency and percentages were calculated for quantitative variables i.e., findings of DRE, TRUS, and biopsy results. Mean±SD and median were calculated for quantitative variables i.e., age and serum tPSA level. Chi square test and student's T-test were applied as appropriate for statistical significance of the differences between the groups. p value ≤0.05 was considered as significant.

Results

A total of 300 men were included in the study. The mean age of all patients was 63.5±8.5 years. Out of these, PCa was detected in 151 (50.3%) patients and 149 (49.7%) showed benign changes with or without active prostatitis. The mean age of patients with PCa was 64.7±8.04 years, while the mean age of patients with benign changes was 62.3±8.8 years. There was no statistically significant difference in the age between the groups (p>0.05). The median age for both groups was 65 years. The distribution of pathological lesions according to age groups is shown in Table 1. It is evident the rate of cancer detection increases with increasing age and this was statistically significant (p=0.034).

The mean serum tPSA level was 19.6±10.5 ng/ml for all patients. It was 23.8±10.5 ng/ml in cancer cases and 15.3±8.7 ng/ml in benign cases. The difference in the mean tPSA levels was statistically significant (p <0.001). The median serum tPSA levels were 26.7 and 14.7 ng/ml for malignant and benign lesions, respectively.

Serum PSA level was elevated (>4.0 ng/ml) in majority of patients (277/300: 92.3%). PCa was detected in 13 (56.5%), 9 (19.1%), 26 (28.3%), 103 (74.6%) of the patients with PSA values of <4 ng/ml, 4-10 ng/ml, 10.01-20 ng/ml and >20 ng/ml, respectively. The rate of PCa detection increased with the increasing tPSA level; the cancer detection rate was highest in patients with serum tPSA >20 ng/ml, as shown in Table 2. The association between PSA level and cancer detection was statistically significant (p<0.001).

The relationship between the results of DRE, tPSA levels, TRUS and TRUS-guided biopsy for pathological

Table 1. The Prevalence of Prostate Cancer and Benign Changes on Histology According to Different Age Groups of Patients

		Cancer n (%)	Benign changes n (%)	Total	p value
No of patients		151(50.3)	149 (49.7)	300	
Age groups (in years)	40-50	8(34.8%)	15(65.2%)	23	0.034
	51-60	29 (39.2%)	45(60.8%)	74	
	61-70	72(55.8%)	57(44.2%)	129	
	>70	42(56.8%)	32(43.2%)	74	

Table 2. Serum Total Prostate Specific Antigen (PSA) Levels and the Prevalence of Prostate Cancer and Benign Changes on Histology According to Different Degrees of PSA Elevation

	Cancer n (%)	Benign changes n (%)	Total	p value
Number of patients	151(50.3)	149 (49.7)	300	
PSA, mean±SD (ng/ml)	23.8±10.5	15.3±8.7	19.6±0.5	0.001
PSA, median (ng/ml)	26.7	14.7		
PSA levels (ng/ml)				
< 4	13(56.5%)	10(43.5%)	23	0.001
4.0-10.0	9(19.1%)	38(80.9%)	47	
10.01-20	26(28.3%)	66(71.7%)	92	
> 20	103(74.6%)	35(25.4%)	138	

Table 3. Relationship between Results of Digital Rectal Examination (DRE), Serum Prostate Specific Antigen (PSA), Transrectal Ultrasound (TRUS) and Biopsy Findings of Benign and Malignant Lesions

	TRUS-		TRUS+	
	Benign	Malignant	Benign	Malignant
DRE(-)/PSA(+)	25/-	33/-	10	68
DRE(+)/PSA(+)	81/30	-/-	98	209
DRE(+)/PSA(-)	5/-	-/5	13	23
Total	111/30	-/38	121	300

lesions is presented in Table 3. The frequency of findings visualized by TRUS and TRUS biopsy in patients with both DRE (+) and PSA (+) was evidently very high as compared to frequency of findings in patients with other combinations. Among 209 patients with DRE (+) and PSA (+), PCa was detected in 128 (61.2%) patients. Of the 111 patients with combination of DRE(+)/PSA(+)/TRUS(-), 30 patients were identified as having PCa. Of the 98 patients with combination of DRE(+)/PSA(+)/TRUS(+), all patients were identified as having PCa. Of the 43 patients with combination of DRE(-)/PSA(+)/TRUS(+), only 10 patients were identified as having PCa. Of the 18 patients with combination of DRE(+)/PSA(-)/TRUS(+), 13 patients were identified as having PCa. No cancer was identified in patients with DRE(-)/PSA(+)/TRUS(-) and DRE(+)/PSA(-)/TRUS(-).

Discussion

This is the first and largest study from Pakistan which systematically analyzes the role of different diagnostic modalities commonly used for an early diagnosis of PCa. However, it must be noted that almost all patients included in this study presented with signs and symptoms of prostatism. There is still no national or regional prostate cancer screening program in place in Pakistan. The results of this study will provide the presentation characteristics of patients with PCa in our set up. This will help in devising the screening strategies for this common tumor in future.

The overall detection rate of PCa in our study was 50.3% which was slightly higher than the 48.8% rate, reported in an earlier study from our center (Rashid et al., 2013). This finding is also not consistent with earlier Asian studies. The incidence rates of PCa found in earlier studies were 36.26% and 44.5% in Chinese (Hua et al., 2011) and Turkish (Baruteuoglu et al., 2009) studies, respectively. The incidence of PCa varies even in different parts of the same country. An Indian study found higher incidence rates in metropolitan cities and very low incidences in rural areas (Lalitha et al., 2012). A clear period effect was also noted in that study, with a statistically significant rise in incidence rates of PCa in many tumor registries from different parts of India over the period of 1983-2002. Unfortunately, such an analysis is still lacking in this country. The incidence of PCa also increases with increases in the serum level of tPSA. The highest incidence of PCa was seen in patients whose serum tPSA levels were >20 ng/ml. Other studies have also reported similar results (Barakzai et al., 2011). On the other hand, some studies have found decreasing levels of prostate biomarkers, notably PSA, with increasing duration of PCa and increasing body mass index (BMI) (Poudel et al., 2012).

The detection rate of cancer was highest in patients with severe elevations of serum tPSA levels. However, the PSA test cannot be used in isolation as an effective screening tool for PCa because it is prone to both false positive and false negative results. Some investigators believe that false positive results of PSA are too high and result in unnecessary and more invasive follow-up procedures such as biopsy. Some other investigators have even suggested that, in general, screening with PSA test results in over-diagnosis of PCA and, hence, over-treatment of indolent forms of PCa that should not be treated due to its non-aggressive and chronic nature (Zappa et al., 1998). On the other hand, PSA test results in false negative outcomes as well (Shiraishi et al., 2012). In this study, we detected 13 cases with PSA level <4 ng/ml, but they were later diagnosed as having PCa. While serum tPSA levels of >4 ng/ml are normally associated with high risk of PCa, studies have shown that certain populations of men with lower levels of PSA also share the same risk level (Djavan et al., 1999). However, in general, the greater the PSA level, more arre the chances of detecting PCa, an experience shared by Yamamoto et al., (2001). PSA tests were often accompanied by abnormalities by palpation on DRE. DRE test is based on the clinical fact that the cancerous tissue is stiffer than normal prostate tissue. When used in combination with PSA levels >4 ng/ml, it was able to correctly detect PCa in 128 (61.24%) patients. This detection rate can be further improved by using TRUS in conjunction with PSA and DRE as is evident by the result of this study, where all 98 cases with this combination were diagnosed as having PCa on TRUS-guided biopsy.

The process of screening and diagnosis of PCa is far from a perfect procedure, especially in healthy men over 75 years of age (Verim et al., 2013). Given all the limitations of the non-invasive diagnostic tests, the current "gold standard" for PCa diagnosis is the histopathologic analysis of biopsy tissue samples obtained under TRUS guidance. During biopsy, a radiologist extracts core samples of prostatic tissue using a needle guided to prostate under ultrasound imaging. The most common prostate biopsy protocol is the systematic sextant approach proposed in 1989 (Hodge et al., 1989). The sextant protocol involves taking tissue samples from the apex (inferior portion), the midsection, and the base (superior portion) of the left and the right lobes of the prostate. Several studies have shown that this protocol is prone to missing cancer in many patients. Therefore, different variations of the sextant biopsy have been suggested in which the number of cores is increased to 10, 12 or even 18 (Stock et al., 2008).

A comparative analysis of DRE, PSA, and TRUS revealed the highest detection rate of PCa in a group who had abnormalities on all three modalities; the PPV in this group being 100% (98/98). Lee et al., (1989) reported PPV of 71% in patients who had abnormal DRE, TRUS and PSA. Conner et al., (1990) found that the combination of DRE, TRUS and PSA abnormalities increased the diagnostic rate of PCa. We also found that a combination of all three diagnostic method abnormalities had significantly higher PPV for the detection of cancer than any other combinations. Our study results support the suggestion that patients with abnormal findings for all three diagnostic methods should undergo the TRUS-guided biopsy of prostate.

The second important group, where DRE and TRUS both were positive, PPV for diagnosis of PCa was 72.2% (13/18) patients. Shapiro et al. (1994) in their study claimed, DRE to be the most valuable single examination in the diagnosis of PCa. TRUS increased the sensitivity of DRE, if both were positive. Their data revealed the highest PPV of 57.5% in their study. Mettlin (1997) in his study maintained that in a group which had positive DRE and TRUS examination, PPV for cancer detection was almost 100%.

And the third group, where DRE and PSA were positive, the PPV was 27% (30/111) in this study. Jabaly and Mohammad (2008) shared almost same experience like our study; they highlighted the significant role of DRE in diagnosis of PCa if combined with PSA; both had highest detection rate for PCa than either alone.

Our study revealed that only raised serum tPSA did not have impact on the detection of PCa. All patients in this group (25/25), with DRE and TRUS negative results, had benign changes on biopsy in spite of raised serum tPSA. Serum tPSA alone could not be used as an effective tool for PCa diagnosis due to its low sensitivity and specificity, especially in the low and intermediate ranges. Khan et al. (2008) presented their data in which in spite of raised serum tPSA, TRUS biopsy turned out to be benign. Gohji et al., (1995) in their study mentioned that if DRE and TRUS both were negative, even the biopsy could be omitted. A number of derived PSA variables such as PSA velocity (PSAV) and PSAV per initial volume (PSAVD) have been demonstrated to be more useful in early diagnosis of PCa, especially in those men undergoing previous TRUS examination (Zheng et al., 2012).

In conclusion, the overall detection rate of PCa in our patients was 50.3%, which was slightly higher than the previous studies from our center. The incidence of PCa increased with increases in the serum level of tPSA. However, PSA alone cannot be used as an effective screening tool for PCa because it is prone to both false positive and false negative results. The overall screening and detection rate can be further improved by using TRUS in conjunction with elevated serum tPSA and abnormal DRE result as evidenced by the results of this study where no false positive or false negatives were reported with this combination of variables.

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