Original Article

Archives of Clinical & Experimental Surgery

Role of Prostate Specific Antigen, Digital Rectal Examination and Trans Rectal Ultrasonography in the Diagnosis of Prostate Cancer in Patients with Lower Urinary Tract Symptoms

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Received: January 12, 2013
Accepted: April 26, 2013
Arch Clin Exp Surg 2014;3:40-46
DOI:10.5455/aces.20130426015426

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Abstract

Objectives: The aim of this study is to compare the roles of prostate-specific antigen (PSA), digital rectal examination (DRE) and transrectal ultrasonography (TRUS) in the detection of prostate cancer among patients presenting with lower urinary tract symptoms (LUTS) and having an International Prostate Symptoms Score (IPSS) of not less than 7.

Material and Methods: This study was carried out in I.P.G.M.E.R and S.S.K.M Hospital, Kolkata, West Bengal, India, from March 2011 to March 2012. Sixty patients presenting with LUTS and with an IPSS not less than 7 had been screened for prostate cancer using PSA estimation, DRE and TRUS. Transrectal sextant prostate biopsy was performed in all patients.

Results: The PSA estimation revealed 85% sensitivity and 72.5% specificity for the patients with a serum total PSA level >10 ng/ml. The positive predictive value (PPV) was 60.7%. If 4 ng/ml is taken as a lower cutoff value for serum total PSA, the sensitivity increases to 95%, whereas specificity reduces to 46.66% and PPV becomes 50%. DRE alone showed 60% sensitivity, 92.5% specificity and 80% PPV for the diagnosis of carcinoma prostate. TRUS has the highest sensitivity (75%) and highest specificity (85%). However, the PPV was 71.43%. When DRE and serum PSA >10 ng/ml were combined, the sensitivity and specificity were raised to 90% and 70% respectively. The PPV was 60%. This was almost comparable with the combination of DRE, serum PSA >10 ng/ml, and TRUS, which has a 90% sensitivity and 85% specificity. The PPV was 75%.

Conclusion: None of the single screening tools had that much efficacy in differentiating carcinoma of prostate from benign prostatic hyperplasia in patients with LUTS. Combining PSA, DRE and TRUS increases sensitivity, specificity and PPV of PC detection.

Key words: *LUTS, prostate-specific antigen, digital rectal examination, transrectal ultrasound, prostate cancer*

Introduction

Prostatomegaly is a condition where the patients present with both obstructive and irritative voiding symptoms collectively known as Lower Urinary Tract Symptoms (LUTS) [1]. The symptoms of LUTS can be quantified by an International Prostate Symptoms Score (IPSS) questionnaire [2]. This questionnaire has been validated as a useful means for assessing and following symptoms resulting from prostatomegaly [3]. These symptoms consist of incomplete emptying, frequency, intermittency, urgency, weak stream,

straining, and nocturia.

The term prostatomegaly encompasses both Benign Prostatic Hyperplasia (BPH) and Carcinoma of Prostate (PC). Men with LUTS are screened for prostate cancer with prostate-specific antigen (PSA) testing and a digital rectal examination (DRE) as part of routine prostate assessment [4]. There is a general agreement among clinicians that the PSA test has the highest predictive value for prostate cancer, as compared to DRE or transrectal ultrasound (TRUS) alone [5,6]. In clinical practice, biopsies are generally performed only when the results of a PSA test or DRE are abnormal. This leads to misdiagnosis of most of the small PCs present in many older men.

Patients with LUTS who have PSA levels higher than 4 ng/ml are primarily advised to undergo prostate biopsy to rule out cancer [7]. PSA is organ-specific but not cancer-specific, so the presence of other prostate diseases such as BPH, and prostatitis may influence its effectiveness for cancer detection [8]. Thus, the PSA-based prostate cancer detection is fraught with a high false-positive rate.

An early detection of the cause of LUTS is necessary to offer selective treatment to the concerned subjects and also for selecting patients for such curative treatment as radical prostatectomy or radiation therapy in organ-confined disease. The present study is an attempt to have a comparative analysis among the sensitivity, specificity and positive predictive value of DRE, serum PSA and TRUS. This study may enable us to find out an ideal diagnostic tool for the early diagnosis of the cause of LUTS so that specific treatment can be instituted at an early stage.

Material and Methods

This prospective descriptive study was carried out in I.P.G.M.E.R and S.S.K.M Hospital, Kolkata, West Bengal, India, in the period of March 2011 to March 2012. The patients were selected from the outdoor of the Department of Urology. Institutional ethical committee clearance and informed consent of all patients were obtained. Sixty men at or above fifty years of age and presenting with LUTS specifically attributed to prostate problems and with an IPSS score not less than 7 were included in the study. Men with calcified or fibrotic prostate, with skeletal or distant metastasis or LUTS caused by any urological malignancy other than prostate and who had previous prostatic surgery or pelvic radiotherapy or complications of urinary obstruction, were excluded from the study.

The sampling technique is as follows: considering the 15% prevalence of LUTS patients in this region, out of the 4000 patients at the urology outdoor/year, 600 patients with LUTS were expected to present in one year. Taking into account the feasibility and available resources, around ten percent of this subset, i.e., sixty patients, were proposed for the study. Random sampling was done for case selection.

The findings of systemic digital rectal examination (DRE) performed by a urologist were noted for all patients as subjective examination according to the following true findings: hard swelling of the prostate, firm swelling, nodular swelling, irregular surface, and obligation of middle sulcus attachment to the mucosal of the rectum. As a routine practice, DRE examination was scheduled after collection of blood samples to avoid an increase in serum PSA that may follow digital manipulation of the gland.

Blood samples were collected in a 5ml sterile container containing ethylene diamine tetra acetic acid (EDTA). The samples were centrifuged within 20 minutes after collection at 500 x g for 10 min, and sera were stored at -20 oC until assay. The total prostate-specific antigen was assessed using enzyme-linked immune sorbent assay (ELISA).

PSA levels less than 4 ng/ml were considered normal, those between 4 and 10 ng/ml as being in a diagnostic gray zone, and above 10 ng/ml as being indicative of cancer [9,10].

All the patients were subjected to TRUS examination and followed by TRUS-guided biopsy. TRUS was performed using a real time Biplanar 7.0 or 7.5 MHz ultrasound probe. The whole of the prostate gland was carefully evaluated for any hypo-echoic, an-echoic, hyper-echoic or iso-echoic zone. The classical description of prostate cancer on TRUS is a hypo-echoic space-occupying lesion (SOL) [11]. Bulging or irregularity of the prostate capsule, extension of hypo-echoic areas from the central zone into the seminal vesicles, and any area corresponding to an abnormality on DRE were carefully evaluated.

TRUS-guided biopsy was performed in all patients at the time of TRUS examination through the peri-anal route. Biopsies were done under antibiotic cover. Systematic sector (Sextant) biopsies were taken with an "Autovac" biopsy gun (Autovac, Angiomed, Karlsruhe, Germany) from the base, mid-gland and apex of the right and left sides as well as from any suspicious area. Each of the samples was submitted for pathological examination. The post-intervention patients were kept for observation overnight and discharged the next morning with the advice to continue antibiotics for 48 hours and to attend the outpatient department or emergency room in case any problem like hematuria, fever, dysuria or hemospermia arises.

Data were analyzed using the Statistical Package for Social Sciences software version 17 for Windows. Sensitivity, specificity, and positive predictive values (PPV) were calculated.

Results and Analysis

A total of 60 male patients presenting with lower urinary tract symptoms (LUTS) were included in this study. Their mean age was 66 years (range 50–82). The patients were selected according to IPSS scores, which were not less than 7. Among 60 patients, 22 had IPSS of 7–10, 32 had IPSS between 11 and 14, and 6 patients had IPSS >14.

IPSS is a screening tool used to assess the lower urinary tract symptoms. IPSS more than 7 indicates moderately symptomatic patients [2]. But the predictive value of IPSS to diagnose PC is not well established. Several studies tried to find the sensitivity and specificity of IPSS for the screening of patients with PC, but varied observations were obtained. While one study showed significant sensitivity and specificity of IPSS to diagnose PC [12], some others demonstrated no significant difference in the IPSS scores between men with cancer and the others with the same age group [13]. In our study, we used IPSS to quantify LUTS. Only the patients with IPSS not less than 7 were included in the study. The detection of PC in these patients was done by more confirmatory tools like PSA estimation, DRE and TRUS, with their results being compared statistically.

Out of 60 men presented with LUTS, 66.66% (40 men) were diagnosed with benign prostatic hyperplasia (BPH), and 33.33% (20 men) with prostate cancer (PC). The mean of total PSA was 12.09 ng/ml. Out of 40 men with BPH, 52.5% (21 men) had total PSA below 4.0 ng/ml, 20% (8 men) had total PSA between 4.0 and 10.0 ng/ml, and 27.5% (11 men) had total PSA >10 ng/ml. While in the case of PC (20 men), 5% (1 man) showed total serum PSA below 4.0 ng/ml, 10% (2) had total PSA between 4.0 and 10.0 ng/ml, and 85% (17 men) showed total PSA >10.0 ng/ml.

Table 1: Results of prostate-specific antigen (PSA), digital rectal examination (DRE) and TRUS in detection of prostate cancer (PC).

Tests	Biopsy +/PC	Biopsy -	Total	Sensitivity, Specificity & PPV
PSA (mean±SD)				
<4.0 ng/ml (2.7±0.81)	1	21	22	Sensitivity=95%, Specificity=46.66%, PPV=50%
4.0–10.0 ng/ml (7.6±1.13)	2	8	10	Sensitivity=10%, Specificity=80%, PPV=20%
>10 ng/ml (21.1±5.54)	17	11	28	Sensitivity=85%, Specificity=72.5%, PPV=60.7%
DRE, n				
Non-suspicious	8	37	45	Sensitivity=60%, Specificity=92.5%, PPV=80%
Suspicious	12	3	15	
TRUS, n				
Hypo-echoic area	15	6	21	
Iso-echoic area	5	25	30	Sensitivity=75%, Specificity=85%, PPV=71.43%
Hyper-echoic area	0	6	6	
Others	0	3	3	

Table 2: Distribution of patients according to DRE + PSA (>10 ng/ml) with biopsy results.

Tests	Biopsy +/PC	Biopsy -	Total	Sensitivity, Specificity & PPV
DRE + &/or PSA >10 ng/ml	18	12	30	Sensitivity=90%, Specificity=70% PPV=60%
DRE - &/or PSA <10 ng/ml	2	28	30	

Table 3: Distribution of patients according to DRE + PSA >10 ng/ml + TRUS findings with biopsy results.

Tests	Biopsy +/PC	Biopsy -	Total	Sensitivity, Specificity & PPV
DRE + &/or PSA >10 ng/ml &/or TRUS +	18	6	24	Sensitivity=90%, Specificity=85% PPV=75%
DRE - &/or PSA <10 ng/ml &/or TRUS -	2	34	36	

For serum PSA >10.0 ng/ml, sensitivity was 85%, specificity was 72.5%, and PPV was 60.7% (Table 1).

The DRE result revealed how 15 patients (25%) had abnormal DRE, whereby suggesting PC, while 45 patients (75%) had no suspicious PC. In the study group, DRE in the detection of PC has sensitivity of 60%, specificity of 92.5%, while the PPV was 80% (Table 1).

On TRUS, 21 patients showed one or more hypoechoic areas, 15 of which had carcinoma on biopsy. 5 out of thirty patients with an iso-echoic area also showed carcinoma on their biopsy. TRUS showed sensitivity of 75%, specificity of 85%, and PPV of 71.43% (Table 1).

When DRE and PSA (>10 ng/ml) were both combined to detect PC, 18 (90%) out of 20 prostate cancer patients were correctly diagnosed to have PC. 28 (70%) out of 40 BPH patients were detected accurately by this method. The sensitivity, specificity and PPV of this method were 90%, 70% and 60%, respectively (Table 2).

When DRE, PSA (>10 ng/ml) and TRUS were combined to detect PC, 18 (90%) out of 20 PC patients were correctly diagnosed to have prostate cancer (Table 3). The sensitivity, specificity and PPV were 90%, 85% and 75%, respectively.

Discussion

Carcinoma of the prostate is the second most common cause of death in males [4]. Therefore, a reliable method for early detection is required to detect PC in patients, especially presenting with LUTS.

In the present study the sensitivity and specificity of PSA assay were found to be 85% and 72.5% respectively for the patients with a serum total PSA level >10 ng/ml. If 4 ng/ml is taken as a lower cutoff value for the serum total PSA value, the sensitivity increases to 95%, whereas specificity reduces to 46.66%. This result is slightly different from what was obtained by Mistry et al. in 2002 [5]. Their meta-analysis showed how the overall sensitivity, specificity, and positive predictive value for PSA (>4 ng/ml) were 72.1%, 93.2% and 25.1%, respectively. In our study, PPV of PSA (>10 ng/ml) in cancer detection was 60.7%, with that of PSA <4 ng/ml being 50%. The result was higher than that reported in two previous studies by Seo et al. [14] in 2007 (PPV=31%) and Manyahi et al. [15] in 2009 (PPV=16%), and close to what was reported by Ng et al. [16] in 2005, who showed that the PPV of PSA is 67% in patients with abnormal findings of DRE. Thus, although some of the previous studies showed PSA, when used alone it cannot be used as an effective screening tool for carcinoma of the prostate due to its low sensitivity and specificity. The result of the present study indicates the importance of a high and intermediate range of PSA in detection of PC among LUTS patients.

All 60 patients of this study were subjected to DRE for any findings suggestive of prostatic disorder. Among them, 15 patients (25%) had positive DRE findings suggestive of PC. And the rest of the 45 patients (75%) had negative DRE findings suggestive of BPH. This finding is comparable with that of Cooner et al. (1990) and Catolina et al. (1994) [17,18] who showed DRE positivity ranges between 21% and 53%. The low value of DRE positivity in our study among the patients with LUTS having IPSS not less than 7 may be due to the high incidence of BPH among the screened population, as the value of DRE largely de-

pends on the type of population screened. Irrespective of DRE findings, all patients were subjected to TRUS examination followed by TRUS-guided biopsy. Twelve patients with positive DRE findings showed cancer on histology, whereas 3 patients with abnormal DRE showed BPH. On the other hand, eight patients with negative DRE showed cancer on histology. These findings suggest 60% sensitivity of DRE, which is sufficiently low for diagnosis of carcinoma prostate, but have a high specificity (92.5%). This finding is in agreement with the results reported by Manyahi et al. [15] who observed 66.7% sensitivity and 88.6% specificity of DRE. The pooled results of a meta-analysis done by K. Mistry et al. [5] also showed 53.2% sensitivity and 83.6% specificity of DRE. However, in most of the previous studies, the PPV of DRE was found to be less. In the meta-analysis, it was only 17.8%; the study of Manyahi et al. found it to be 67%, and the study by Abdelkarim A. et al. [8] observed the PPV of DRE as being 47%.

The PPV of DRE in our study was 80%. It shows that DRE is a necessary screening tool and can never be denied in the detection of prostate cancer.

Although TRUS is not universally accepted as an initial screening test for prostatomegaly, all patients in our study were subjected to TRUS examination followed by TRUS-guided biopsy for the purpose of comparative analysis with DRE and serum PSA in the early detection of prostate cancer among the patients with prostatomegaly. The classical description of prostate cancer on TRUS is a hypo-echoic SOL. In our study, twenty-one patients showed one or more hypo-echoic areas, with 15 of which having carcinoma prostate on biopsy, whereas 5 among thirty patients who showed iso-echoic texture were also shown to have carcinoma prostate on biopsy. Hyperechogenicity is an uncommon finding in prostate cancer, and all six patients with these findings had BPH. In our study, TRUS has the highest sensitivity (75%) among all three screening tools as well as the highest specificity (85%). This result is nearly similar to the observation of Manyahi et al. [15] who observed 58.3% sensitivity and 85.7% specificity of TRUS. But the PPV of TRUS in their study was 58%, whereas we observed it as being 71.43%. Thus, the role of TRUS as a screening tool of PC in the early stage cannot be ruled out.

Although TRUS has the highest sensitivity and specificity among all three screening tools in our study, the positive predictive value and overall accuracy of TRUS were both lower than for DRE, which is in accordance with the result demonstrated by Manyahi et al. [15]. The patients with iso-echoic SOL are the most difficult to diagnose by TRUS. Taking biopsy samples from such lesions is also difficult. In such cases, multiple biopsy samples are taken from the peripheral zone (PZ) of the prostate gland. In our study, none of the patients showed abnormality of the prostatic capsule, ejaculatory ducts and seminal vesicles as well as surrounding organs. Only 4 patients had a capsular breach. Areas of hemorrhages and necrosis were also not found in them, but multiple areas of calcifications were found in two patients.

In order to increase the sensitivity of cancer detection at an early stage in the current study, DRE and serum PSA >10 ng/ml were combined. It was observed that the sensitivity and specificity were raised to 90% and 70% respectively. The PPV was 60%. This is in agreement with the findings observed by Abdelkarim A. et al. [8] who showed 100% sensitivity when total PSA and DRE results were combined to detect PC.

The combination of DRE, serum PSA >10 ng/ml and TRUS showed 90% sensitivity, 85% specificity and 75% PPV in the present study. One of the previous studies done by Manyahi et al. also showed a gradual rise in PPV when a combinatorial screening approach was performed. They showed PPV of 16%, 75% and 80% with PSA >4 ng/ml, with the DRE and PSA combination, and with the DRE, PSA and TRUS combination, respectively. But as abnormal TRUS added only 0.05 to this predictive value in their findings, they suggested that a combination of DRE and PSA is reliable enough to exempt TRUS where it is not available [15].

In the present study, as the combination of TRUS added a significant rise of positive predictive value (75%) to PC detection when compared with single screening tools, it can be concluded that a combinatorial approach of serum total PSA, DRE and TRUS gives the highest possibilities of detection of PC in patients with LUTS at an early stage.

Conclusion

In the present study, it was found that none of the single screening tools, i.e., serum total PSA, DRE or TRUS, had much efficacy in differentiating carcinoma prostate from benign hypertrophy in LUTS patients with IPSS not less than 7. Even the role of TRUS in detecting iso-echoic SOL or organ-confined diseases proved less effective. But the combination of DRE and serum total PSA or DRE, serum total PSA and TRUS showed higher sensitivity, specificity and positive predictive value.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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