original article

Relative contribution of digital rectal examination and transrectal ultrasonography in interpreting serum prostate-specific antigen values for screening prostate cancer in Arab men

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BACKGROUND: This study was conducted to determine the utility of digital rectal examination (DRE), transrectal ultrasonography (TRUS) and serum prostate-specific antigen (PSA) in the diagnosis of prostate cancer in men in Arabia, an are of the world with a relatively low incidence of this disease.

PATIENTS AND METHODS: 329 patients suspected of having prostate cancer on account of raised serum PSA level (> 4 ng/ml), DRE or TRUS findings, underwent TRUS-guided prostate biopsy. Raised PSA individually as well as combined, or a lesion suspicious of carcinoma on DRE or TRUS was recorded as PSA (+), DRE (+) or TRUS (+), respectively. The contribution of DRE, TRUS and serum PSA to the diagnosis of prostate cancer was analysed.

RESULTS: Of the 329 patients who had prostate biopsies 109 cases (33.1%) had PCa. Of these 109 patients 56 (51%) had DRE (+), 77 (42%) had TRUS (+) and 49 (66%) had both DRE (+) and TRUS (+). Statistical analysis revealed that DRE (+) tripled the probability for cancer. PSA over a range of 10-50 ng/mL demonstrated an increasing cancer probability ranging from 2 to 3 fold. TRUS (+) was only significantly associated with cancer risk if PSA was elevated. The presence of all three factors increased the cancer probability by 6 to 7 fold.

CONCLUSION: TRUS findings are dependent on PSA for interpretation while DRE (+) with elevated PSA makes PCa more likely.

Prostate cancer (PCa) is the most common neoplasm affecting elderly men. Radical prostatectomy is a curative method when the disease is organ confined. Therefore, early diagnosis of the disease is essential in lowering the morbidity and mortality of PCa. The detection of PCa is generally based on digital rectal examination (DRE), transrectal ultrasonography (TRUS) findings and serum prostate-specific antigen (PSA) determination.[1] Several investigators have reported the feasibility of early PCa detection using DRE, TRUS, and PSA.[2-4] Although DRE remains an efficient and cost-effective investigation procedure for PCa, it is rather subjective and empirical. The cancer detection rate of TRUS has been reported to be approximately 2-fold higher than that of DRE when used as a screening tool.[5] The development of high definition TRUS probes has facilitated the detection of small prostatic lesions, which can be biopsied. This has probably increased the detection rate of early PCa, but the value of this modality in relation to the traditional method of DRE has not been finally determined. Serum PSA in asymptomatic men varies with race and age,[6-9] and as such, the specificity of PSA is not high, particularly for intermediate values (4-10 ng/mL), and an excess of unnecessary prostate biopsies are performed on that basis. Attempts have been made to increase the specificity of PSA using PSA derivatives such as PSA density,[10] PSA velocity[11] and age-adjusted reference ranges,[12] but none of these methods has significantly improved the predictive value in patients with intermediate total PSA values (4-10 ng/mL).[13] The predictive capacity of DRE, PSA and TRUS, individually and in combination, has been

reported predominantly from large North American institutions.[14-21] This study was conducted to determine the utility of DRE, TRUS and PSA in the diagnosis of prostate cancer in Arab men, an area of the world with a relatively low incidence of the disease.

PATIENTS AND METHODS

This study was conducted on 329 consecutive men referred to the Radiology Department of Mubarak Al-Kabeer Teaching Hospital, Kuwait, as part of an investigation to exclude prostate cancer. All the men were of Arab origin (North Africa and the Middle East). The reasons for referral included suspected PCa on account of a raised serum PSA level (> 4 ng/mL), the finding of a palpable nodule or greater firmness of one prostatic lobe than the other on DRE, or the finding of a focal area suspicious of a neoplasm on TRUS of the prostate. A lesion suspicious of carcinoma on DRE or TRUS was recorded as DRE (+) or TRUS (+), respectively.

Prior to digital or ultrasonographic examination of the prostate, blood was collected for the serum PSA assay. The assay was performed using the chemiluminescent assay method (Roche Elecsys Mannheim, Germany). Patients received prophylactic oral ciprofloxacin 500 mg 60 minutes before the procedure and continued with 12 hourly doses for 2 more days after the procedure (total of 6 doses). DRE was performed with the patient in the left-lateral position, and the results were reported as either normal or suspicious for carcinoma based on the finding of firmness or a nodule in the prostate. All DRE was performed by two urologists (EOK, AA) and the findings indicated on the request forms for TRUS-guided biopsy. TRUS was then performed using a GE Logic 500 scanner (GE Medical systems, Milwaukee, Wisconsin, USA) with a 7.5 MHz endocavity transducer (model E721), scanning the gland in sagittal and axial planes. All TRUS of the prostate plus biopsies were performed by two radiologists (MS, AYTH). The volume of the prostate was calculated using the prostate ellipse formula: Volume (V) =0.52(LxWxH), where L is the cephalocaudal length obtained from the longitudinal sonogram, W is the width obtained from the transaxial view and H is the antero-posterior height obtained transaxially.

All the patients underwent biopsy mapping of the prostate with at least 8 systematic ultrasonography guided biopsies. Additional biopsies up to a maximum of 12 were taken, depending upon the size of the gland. If the gland was bigger, more areas were biopsied so that coverage was uniform. This was done subjectively and no objective criteria were used. The transrectal biopsies were performed at the apex, middle and base of the right and left prostatic lobes in the parasagittal plane. If a hypoechoic defect was demonstrated in the peripheral or central zone, an additional biopsy of that area was also performed. The biopsy specimens were fixed in 4% formaldehyde solution processed into paraffin and haematoxylin and eosin stained sections used to categorize the tissues into benign and cancer by JTA and this was the gold standard.

Binomial logistic regression analysis was used to evaluate the contribution of the various factors to the diagnosis of PCa. In addition we determined the specificity, sensitivity, positive predictive valve (PPV) and negative predictive value (NPV) for DRE in the presence or absence of TRUS findings or PSA positivity (>10 ng/mL).

Analysis was performed for PSA levels 10 ng/mL and above as we have observed in our previous study that the PSA levels between 4-10 ng/mL have poor discriminatory power. This is because PSA testing has a relative lack of specificity within the 4.0-10.0 ng/mL range, a diagnostic grey zone in which prostate cancer is present in only 25% of patients.[9] This is consistent with our previous observation of the optimal cut off of 16.4 ng/mL via ROC analysis in this population.[22]

RESULTS

Of the 329 patients who had prostate biopsies, 109 cases (33.1%) had PCa. The remaining 220 (62.9%) cases had benign lesions comprising benign prostatic hypertrophy (BPH) with or without prostatitis. There was no significant difference between the mean ages of the patients with PCa (66.3 years) and those without PCa 65.8 years, ranges 42-95 years versus 32-90 years, respectively. The mean serum PSA value was 60.80 ng/mL (range, 1.5-1566 ng/mL) and 18.6 ng/mL (range, 0.7-46 ng./mL) for patients with PCa and those without cancer, respectively. Table 1 shows the relationship between PSA values and diagnosis of prostate cancer.

Table 1. The relationship between prostate cancer diagnosis and different prostate-specific antigen values in Arab men.

PSA (ng/mL)	No. of patients	No. with prostate cancer	% with prostate cancer
< 10	113	20	17%
> 10 to < 50	168	54	32%
> 50	48	35	72%
Total	329	109	33.1%

Table 2. Results of binomial logistic regression analysis with digital rectal examination (DRE), prostate-specific antigen (PSA), and transrectal ultrasonography (TRUS) as independent variables and prostate cancinoma outcome as a dependent variable.

	Variables in the equation	Sig.	Exp (B)	95% confidence interval for exp (b)	
				Lower	Upper
PSA 10	FOC	.009	2.093	1.202	3.646
	DRE	.000	3.437	1.941	6.087
	PSA 10	.010	2.210	1.214	4.026
	Constant	.000	.114		
PSA 20	FOC	.017	1.983	1.132	3.473
	DRE	.000	3.267	1.831	5.831
	PSA 10	.000	2.654	1.568	4.492
	Constant	.000	.144		
PSA 30	FOC	.050	1.757	1.001	3.085
	DRE	.000	3.288	1.846	5.859
	PSA 10	.000	2.875	1.609	5.135
	Constant	.000	.169		
PSA 40	FOC	.033	1.835	1.051	3.205
	DRE	.000	3.156	1.771	5.625
	PSA 10	.004	2.577	1.361	4.881
	Constant	.000	.182		
PSA 50	FOC	.048	1.762	1.005	3.089
	DRE	.000	3.210	1.802	5.718
	PSA10	.001	3.249	1.626	6.488
	Constant	.000	.184		

DRE: (Firmness or nodule on rectal examination), FOC: (Focal lesion on U/S), PSA: 10-50 ng/mL (PSA < or > 10-50 ng/mL)

Of the 109 patients with PCa, 56 cases (51%) were DRE (+), 77 cases (42%) were TRUS (+) and 49 cases (66%) were both DRE (+) and TRUS was (+).

DRE and PSA were independent determinants of the probability of PCa (Table 2). The strongest effect was seen for DRE as the presence of any positive sign on DRE tripled the probability of cancer. An intermediate effect was demonstrable for PSA and over a range of 10-50 ng/mL there was an increasing cancer probability, ranging 2 to 3 fold. Focal lesions on TRUS in those with raised PSA was also associated with a 2-fold increased probability for cancer. The presence of all three factors therefore increased cancer risk 6 to 7 fold. Above a PSA cut-off of 20 ng/mL, TRUS loses significance and mainly DRE and PSA retained significance in the model. The sensitivity, specificity, the PPV and the NPV for PSA are shown in Table 3.

DISCUSSION

DRE is the initial step in the diagnosis of PCa, and when an abnormal DRE is present, irrespective of the PSA level, a biopsy of the gland is recommended.

Screening asymptomatic men in the cancer age group by this method has shown a detection rate of 1.3% to 1.7%.[23,24] Wanatabe et al[25] reported detection of 48 cases in 7235 apparently normal men over the age of 55 years (0.6%), while Lee et al[26] detected 20 cases in 784 men over the age of 60 years (2.6%). The detection rates of the two methods are thus very similar and this rate represents only a small percentage of men with occult carcinoma. For the purpose of early diagnosis, however, even an isolated elevation in serum PSA has been suggested as an indication for biopsy, which yields an increased number of patients diagnosed with PCa, but also an increase in the number of unnecessary bi-

opsies as well.

Although DRE is a simple method employed for the detection of PCa, it is not useful for detecting early stage cancer since studies show its PPV is 22% to 33%,[3,27-30] and more than 10% of examined patients with normal DRE findings have been found to have PCa.[1,31] Philip et al[32] in a study reported that 47% of patients with PCa were DRE (+), while 38.8% with DRE (-) had cancer. These authors concluded that DRE does not significantly contribute to the diagnosis of PCa, especially with PSA levels in the range of 2.5 to 10 ng/mL. In our study it was noted that DRE had a poor sensitivity for detecting PCa, being negative in about 85% of the cancer patients. On the other hand it was quite specific and a DRE (+) was only present in 15.4% of patients without cancer and as expected the highest PPV for PSA >10ng/mL was for DRE (+) and TRUS (+) patients as well.

The average cancer detection rates in the presence of a negative DRE in the literature are 21.6% (present study 12-22%) and 32% (present study 19-37%) when the PSA level was between 4 and 10 ng/mL or greater than 10 ng/mL, respectively. If PSA is positive then a DRE (-) must be viewed with caution and even more so if TRUS is also negative. In other words PSA is not very accurate in screening if both DRE and TRUS are negative.

TRUS of the prostate gland has developed into an important adjunct for the diagnosis of PCa. The sonographic appearance of PCa is variable. With the early techniques it was reported that these carcinomas were hyperechoic.[33] With the development of high frequency transducers and improved instrumentation, investigators reported that carcinomas, particularly when small, were most commonly seen as localized hypoechoic areas and that as the lesions enlarged, invaded other structures, and developed associated calcifications, they could appear hypoechoec, hyperechoic, isoechoic or of mixed-type echogenicity.[34] Approximately 60% to 76% of the lesions appear as hypoechoic lesions on sonogram and in the other 24% to 40% the tumour is isoechoic and cannot be distinguished clearly from the surrounding tissue.[35] Although TRUS is particularly useful in demonstrating that 70% of prostate cancers arise in the peripheral zone of the gland,[36] it must be realized that a large percentage of hypoechoic lesions in the peripheral zone result from benign pathology. Hence the most important limitation of TRUS is that the majority of hypoechoic areas are not cancerous. TRUS-directed biopsies of such lesions reveal cancer in 20% to 40% of cases.[3,33] This results in the strong interdependence of TRUS with PSA due to the increase in the specificity of TRUS findings as PSA increases.

The specificity of serum PSA is only about 60% and 10% to 45% of patients with biopsy-confirmed PCa have serum PSA levels within the normal range.[1,16,27,37,38] In the USA and Europe the detection rate of PCa increases with serum PSA above 10 ng/mL.[7,39] In Arab men the total PSA valve >10 ng/mL appears to be the result of BPH with or without prostatitis (89%) rather than PCa (11%).[9] In our study, 32% of the patients with PSA between 10 and 50 ng/mL had PCa whereas in

Table 3. Operating characteristics of prostate-specific antigen.

	DRE and TRUS (positive) (74)		DRE alone (positive) (16)		TRUS alone (positive) (90)		DRE and TRUS (negative) (149)		
PSA Status	+	-	+	-	+	-	+	-	**Total**
Cancer	46	3	5	2	20	8	18	7	109
Not Cancer	14	11	6	3	34	28	75	49	220
	60	14	11	5	54	36	93	56	
Sensitivity	94		100		71		72		
Specificity	44		45.5		45		39.5		
Positive Predictive Value	77		45.5		37		19		
Negative Predictive Value	79		100		78		87.5		

PSA (+) = Serum PSA > 10 ngm/ml, PSA (-) = Serum PSA < 10 ngm/ml
TRUS (+) = Focal lesion suspicious of cancer on transrectal Ultrasound
TRUS (-) = No focal lesion seen on transrectal Ultrasound

patients with PSA above 50ng/mL, 72% had PCa.

Lee et al[3] reported that in a study of 256 pre-screened patients, the PPV of TRUS alone, TRUS with DRE, and TRUS with DRE and serum PSA was 41%, 61%, and 71%, respectively. Cooner et al[16] studied patients with hypoechoic findings visualized by TRUS and reported that in those with normal DRE findings, the PPV was 2.1%, 7.0%, and 28.1% for serum PSA levels of <4 ng/mL, 4-10 ng/mL, and > 10 ng/mL, respectively. On the other hand, in the same study population, they also found that when the DRE findings suggested cancer the PPV for serum PSA increased to 11.7%, 42.6%, and 76.2% at the respective levels noted above. As such, TRUS features of cancer are associated strongly with an increase in PSA and once PSA levels are high, the usefulness of ultrasonogpaphy is reduced. On the other hand, the combination of DRE and TRUS increases the PPV for PSA, i.e., the highest (77%) suggesting that PSA (+) with TRUS (+) and a DRE (+) usually indicate Pca pathology. The TRUS findings should, therefore, only be interpreted in the context of PSA.

Our study suggests that TRUS and DRE findings are only relevant if PSA is elevated. The first step in screening should, therefore, be PSA estimation followed by TRUS if the PSA is raised. However, since the clinical examination is always performed first, patients with normal PSA and DRE (+) should also be biopsied. We recommend routine biopsy in those patients with either elevated PSA or DRE (+), but not in those with TRUS (+) findings alone.

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