The Combined Diagnostic Role of Digital Rectal Examination, Prostate Specific Antigen, Transrectal Ultrasound and Transrectal Ultrasound Guided Biopsy to Differentiate Benign Versus Malignant Prostatic Enlargement

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Abstract

Introduction: The term prostatomegaly encompasses both Benign Prostatic Hyperplasia and Carcinoma of the Prostate. This study aimed to find a screening tool for the early diagnosis of prostate carcinoma so that that specific treatment can be instituted at an early stage in the Indian population. **Objectives**: To establish the role of digital Rectal Examination (DRE), Prostate-Specific antigen (PSA), transrectal ultrasound (TRUS) and transrectal ultrasound guided biopsy in differentiating benign enlargement from the malignancy of the prostate. **Methods**: This was a prospective observational study conducted over two years in 130 men above 40 years with Lower Urinary Tract Symptoms specifically attributed to prostate problems. Utility of PSA, DRE, TRUS and TRUS guided biopsy for diagnosis of prostate carcinoma were evaluated and compared. **Results**: Among the benign cases, 1.72% had PSA ≤ 4 ng/mL, 86.21% had PSA between > 4 to 10 ng/mL and 12.07% had PSA > 10 ng/mL. Among the malignant cases, 9.09% had PSA ≤ 4 ng/mL, 4.55% had PSA between >4 to 10 ng/mL and 86.36% had PSA more than 10 ng/mL. The sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy of DRE for diagnosis of malignancy were 54.55%, 98.28%, 92.31%, 85.07% and 86.25%, respectively. The sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy of TRUS for diagnosis of malignancy were 72.73%, 94.83%, 84.21%, 90.16% and 88.75%, respectively. The sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy of PSA for diagnosis of malignancy were 90.91%, 22.41%, 30.77%, 86.67% and 41.25%, respectively. **Conclusion**: The proportion of suspicion of malignancy by DRE increased significantly, with an increase in the Gleason score. As the PSA level increases, the chances of biopsy having malignancy also increased significantly. Therefore, it is suggested to do TRUS-guided transrectal Biopsy in patients with abnormal DRE and PSA more than 10 ng/mL

Keywords: Digital rectal examination, hyperplasia, prostate specific antigen, transrectal ultrasound, prostate cancer

Introduction

The term prostatomegaly encompasses both Benign Prostatic Hyperplasia and Carcinoma of the Prostate. Men with lower urinary tract symptoms are screened for prostate cancer with prostate-specific antigen (PSA) testing and a digital rectal examination (DRE) as part of routine prostate assessment[1,2].

While prostate cancer survival rates are excellent overall, there is a significant discrepancy between five-year survival rates for patients diagnosed with locally or regionally contained disease and those with distant metastases at the time of diagnosis. With distant metastases at the time of diagnosis, the five-year survival rate falls from 100% to a low 28.2%[3]. It is clear that prostate cancer is a disease with a broad range of lethality, considering the disparity in mortality between locally contained and disseminated disease, as well as the prevalence of incidental disease found on autopsy. In response, physicians have attempted to optimize population screening guidelines to prevent life-threatening cases while avoiding overdiagnosis of nonlethal disease.

The oldest screening test for prostate cancer is digital rectal examination (DRE). It has been performed to detect nodules, asymmetry, or induration that may suggest a tumour in the posterior and lateral aspects of the gland. Unfortunately, not all tumours arise in these locations[4]. Furthermore, the effectiveness of the DRE as an examination has been called into question given the subjective nature of the test and the fair but not great level of inter-rater agreement.

Prostate cancer has many faces, ranging from low-grade, low-volume cancers, often referred to as clinically insignificant or indolent prostate cancer, to more aggressive cancers, which are likely to progress to or present with metastatic disease. While low-risk prostate cancer is not likely to influence an individual patient's morbidity and mortality, importantly, intermediate and high-risk prostate cancer have the potential of severely limiting the patient's quality of life and overall survival depending on age and comorbidity. In addition, the incidence of prostate cancer has dramatically risen with the advent of prostate-specific antigen (PSA) testing, leading only to a modest decrease in prostate cancer-specific mortality. This suggests an increase in the diagnosis of low-risk prostate cancer by PSA testing predominantly, and it has turned prostate cancer diagnosis into a challenging field of research[5].

However, PSA screening is accumulating evidence for reducing prostate cancer-specific mortality at the cost of significant overtreatment of patients diagnosed with low-risk prostate cancer. The European Randomized Study of Screening for Prostate Cancer (ERSPC), the most referenced study on this subject, showed a 20% mortality reduction at the cost of 1410 men needed to screen and 48 additional cases of prostate cancer treated. In the landmark series, Schröder et al.[6] defined the substantial rate of overdiagnosis as the main limitation for PSA as a screening tool. The diagnosis of prostate cancer is dependent on histologic analysis of biopsy specimens. 18G (Tru-Cut) core biopsy needles are currently accepted as the standard for the histological diagnosis of prostate cancer. The number of biopsies has increased since the original sextant biopsy developed by Hodge et al.[7]. Current guidelines recommend a 10-12 core peripheral zone (PZ) baseline set of TRUS-guided biopsies while recommending against incorporating standard transition zone (TZ) biopsies.

The present study attempted to compare the sensitivity, specificity, positive predictive value, and negative predictive value of DRE, serum PSA, TRUS and TRUS guided biopsy. This study may enable us to find a screening tool for the early diagnosis of prostate carcinoma so that that specific treatment can be instituted at an early stage in the Indian population. In our country, where there is a lack of quality health care in remote areas, DRE and PSA can become instrumental in the early diagnosis of carcinoma of the prostate at a minimal cost.

Aims and Objective

The study aimed to establish the role of Digital Rectal Examination, Prostate-Specific Antigen, transrectal ultrasound and transrectal ultrasound guided biopsy in differentiating benign enlargement from the malignancy of the prostate. Objectives of the study were to study sensitivity and specificity of Digital Rectal Examination, Prostate Specific Antigen and transrectal ultrasound in the diagnosis of malignancy and to correlate the findings of digital rectal examination with gleason Score on transrectal biopsy.

Materials and Methods

This was a prospective observational study conducted over two years in 130 men above 40 years with lower urinary tract symptoms after taking approval from Institutional Ethics committee (IEC/VKC-025/2018). Exclusion criteria were lower urinary tract symptoms due to causes other than prostate enlargement, other concurrent malignancy and immuno compromised patients. Demographics and other data like the patient's medical history, surgical and other significant histories were noted in case record form. In addition, DRE and other specific investigations like Serum PSA, transrectal Biopsy under transrectal USG (TRUS) guidance were done. Severity of symptoms was classified according to International Prostate Symptom Score (IPSS).[8]
Serum PSA: Specimens for PSA testing were drawn by the investigator before prostatic manipulations such as digital rectal exams (DRE), prostatic massage, transrectal ultrasound, and prostatic biopsy. Blood samples were collected aseptically by using regular vacutainers and the serum separated by standard laboratory techniques. Samples were processed within 24 hours of collection and stored at 2-8°C before processing by the pathologist.

Digital rectal examination: DRE was performed by only one investigator in all the patients in the study. On DRE grade, consistency, surface and tenderness were examined. In addition, the prostatic size was graded as described by Barnes RW et al.[9] Grade of Prostate on DRE were:

- Normal : Encroaches 0-1 cm into the rectal lumen
- Grade 1: Encroaches 1-2 cm into the rectal lumen
- Grade 2: Encroaches 2-3 cm into the rectal lumen
- Grade 3: Encroaches 3-4 cm into the rectal lumen
- Grade 4: Encroaches more than 4 cm into rectal lumen.

Hard consistency (induration) and nodular surface were considered as findings suggestive of malignancy.

Transrectal Ultrasound and TRUS guided Biopsy: All patients with abnormal DRE or PSA > 4ng/mL or both were subjected to TRUS examination followed by TRUS guided prostate biopsy. Cleansing enema was administered before procedure. Single-dose oral fluoroquinolones were given before procedure. Patients were placed in the left lateral decubitus position with knees and hips flexed at 90 degrees. During the procedure an ultrasound transducer was inserted into the patient's rectum, and ultrasound survey of the prostate was performed using a real time Biplanar 7.0 or 7.5 MHz ultrasound probe and the prostate volume was estimated. The whole of the prostate gland was carefully evaluated for any hypoechoic, anechoic, hyperechoic, or isoechoic lesion and capsular distortion. The suspicion of prostate cancer on TRUS was hypoechoic space occupying lesion (SOL) and capsular distortion. The biopsy was performed after a regional block was administered around both neurovascular bundles. A biopsy gun was passed through the needle guide attached to the ultrasound probe. The biopsy gun used was Bard Max-Core Disposable Biopsy Gun 18GX25CM - MC1825 which advances

the needle 0.5 cm and samples the subsequent 1.5 cm or 2 cm of tissue with the tip extending 0.5 cm beyond the area sampled. Biopsies were obtained as systematic 12 cores and additional lesion guided. Biopsies were placed in multipack container kit and sent for histopathology.
Histopathological examination reports were entered in the Performa sheet. Patients diagnosed to have malignancy were classified according to WHO "Gleason Grade Group" system [Table 1].[10]

Table 1: WHO Gleason grade group system

Gleason Group	Gleason score and pattern
1	Grade 6 (3+3)
2	Grade 7 (3+4)
3	Grade 7 (4+3)
4	Grade 8 (4+4, 3+5, or 5+3)
5	Grade 9 or 10 (4+5,5+4 or 5+5)

Statistical analysis: Data were compiled and entered using Epi Info version 7.2. The quantitative data was expressed in terms of mean and standard deviation. The qualitative data was expressed in terms of percentages. Prostate biopsy was considered as gold standard and sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy for diagnosis of malignancy were calculated separately for Digital rectal examination, Transrectal ultrasound and Prostate specific antigen. A cut off of > 5.4 ng/mL (suspicion of malignancy) was considered for prostate specific antigen. Further, the cut off was reduced to > 4 ng/mL and increased to > 10 ng/mL to find the trend of the performance statistics. To analyze the trend of the detection rates, we used chi square test. All p values were two tailed and the significance level was set at 0.05.

Results

The mean age of the study subjects was 69.06 ± 9.22 years. The most common age group was 61 to 70 years (53, 40.77%), followed by 71 to 80 years (38, 29.23%) and 81 to 90 years (19, 14.62%).

In our study, the majority of the patients had an International Prostate Symptom Score (IPSS) of moderate (72, 55.38%) followed by severe (37, 28.46%) and mild (21, 16.15%).

Digital rectal examination was done in all the study subjects. Based on the surface characteristics, the majority of them had smooth surface (118, 90.77%), and a few had nodular surface (12, 9.23%). Upon evaluation based on the consistency, 118 (90.77%) had firm consistency, and 12 (9.23%) had hard consistency. Among 130 cases, 75 (57.89%) were Grade II, 50 (38.46%) were Grade III, and 5 (3.85%) were Grade I based on DRE.

Among the 88 cases who underwent TRUS 19 (21.59%) had a hypoechoic lesion, and 7 (7.95%) had capsular distortion.
Among the benign cases, 1 (1.72%) of them had PSA ≤ 4 ng/mL, 50 (86.21%) had PSA between > 4 to 10 ng/mL and 7 (12.07%) had PSA > 10 ng/mL. Among the malignant cases, 2 (9.09%) had PSA ≤ 4 ng/mL, 1 (4.55%) had PSA between > 4 to 10 ng/mL and 19 (86.36%) had PSA more than 10 ng/mL. As the PSA levels increased, the chances of biopsy having malignancy also increased significantly ($p < 0.001$).
The mean PSA level was 12.75 ± 9.05 ng/mL. Among 130 cases, 48.46% of cases had PSA of ≤ 5.4 ng/mL, and 51.54% had more than 5.4 ng/mL. A cut off of 5.4 ng/ml was obtained from a study done by Agnihotri S et al.[21] done in Indian study subjects [Table 2].

Table 2: Distribution of study subjects based on PSA level

Serum PSA	Frequency(n)	Percentage (%)
≤5.4ng/ml	63	48.46
>5.4ng/ml	67	51.54
Total	130	100
Mean	9.05	NA
SD	12.75	NA

On evaluation by ultrasonography, prostatic enlargement was Grade II in 57.69% and Grade III in 42.31% of patients. The post-void volume was >100 mL in 48.46%, between > 50 to 100 mL in 36.92% and ≤ 50 mL in 14.62% of the patients. The Median lobe was enlarged in the case of 56.92%, and hydrouretronephrosis (bilateral) was present in 2.31% of patients [Table 3]. The grading of the prostate gland enlargement was done as follows: Grade I - 21 – 30 cc, Grade II - 31 – 50 cc, Grade III – 51 – 80 cc and Grade IV –80 cc and above.[11]

Table 3: Characteristics of the study subjects based on the parameters of Ultrasonography of Abdomen and Pelvis

Ultrasonography	Frequency(n)	Percentage (%)
Grade of prostate		
I	0	0
II	75	57.69
III	55	42.31
Post void volume		
≤ 50 mL	19	14.62
> 50ml to 100 mL	48	36.92
> 100 mL	63	48.46
Median lobe		
Not enlarged	56	43.06
Enlarged	74	56.92
HDUN (Bilateral)		
Absent	127	97.69
Present	3	2.31

On DRE, 13 (16.25%) cases had a suspicion of malignancy of the prostate. Later, when the transrectal biopsy was done, we found that 12 among 13 suspected cases had malignancy. We also found that 67 (83.75%) cases had a suspicion of benign hypertrophy of the prostate. Among these, 10 cases had malignancy on transrectal biopsy report, and 57 cases were benign. Upon detailed statistical analysis, the sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy of DRE for diagnosis of malignancy were 54.55%, 98.28%, 92.31%, 85.07% and 86.25%, respectively.

Among the 65 (81.25%) cases with PSA > 5.4 ng/mL, we found 20 cases were malignant, and 45 cases were benign on biopsy. Among the 15 (18.75%) cases with PSA ≤ 5.4 ng/mL, we found that 13 of them were benign, and 2 were malignant on Biopsy. Upon detailed statistical analysis, the sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy of PSA for diagnosis of malignancy were 90.91%, 22.41%, 30.77%, 86.67% and 41.25%, respectively.

If the cut-off value of PSA was reduced to > 4 ng/mL, we found 77 (96.25%) cases of suspicion of malignancy. Among these, 20 cases were malignant on biopsy, and 57 cases were benign. Among 3 (3.75%) cases suspected of having benign lesion, 2 cases were malignant on biopsy, and 1 case was benign lesion. Upon detailed statistical analysis, the sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy of PSA (cut off > 4 ng/mL) for diagnosis of malignancy were 90.91%, 1.72%, 25.97%, 33.33% and 26.25% respectively.

In our study, based on TRUS, there were 19 (23.75%) cases suspected of having malignancy, among which 16 cases were malignant by biopsy, and 3 cases were benign. Among the 61 (76.25%) cases suspected to have a benign lesion, 6 cases were malignant on biopsy, and 55 cases were benign. Upon detailed statistical analysis, the sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy of TRUS for diagnosis of malignancy were 72.73%, 94.83%, 84.21%, 90.16% and 88.75%, respectively.

The Gleason Grade group was Grade II in 8.33%, Grade III in 33.33%, Grade IV in 50%, Grade V in 8.33% cases suspected of malignancy by DRE. The proportion of suspicion of malignancy by DRE increased significantly with an increase in the Gleason Grade Group (Gleason Score) ($p < 0.05$) [Table 4].

Table 4: Distribution of the study subjects based on the Gleason Grade Group (Gleason Score) on Transrectal Biopsy and type of tumor as assessed by DRE

Gleason Grade Group (Gleason Score)	Suspicion of Benign on DRE		Suspicion of Malignant on DRE	
	No^r	%	No^r	%
I (≤ 6 score)	1	10.00	0	0
II (3 + 4)	4	40.00	1	8.33
III (4 + 3)	3	30.00	4	33.33
IV (8)	2	20.00	6	50.00
V (9 to 10)	0	0	1	8.33
Total	10	100	12	100
Chi square for trend = 4.42	p-value = 0.0354			

Discussion

Prostate cancer is the second most common cause of cancer and the sixth leading cause of cancer death among men worldwide[12]. The worldwide prostate cancer burden is expected to grow to 1.7 million new cases and 499000 new deaths by 2030 simply due to the growth and ageing of the global population[13]. Digital rectal examination and prostate-specific antigen have been some methods in diagnosing prostate malignancy. Keeping this background, we conducted a cross-sectional study on the efficacy of digital rectal examination, prostate-specific antigen and transrectal ultrasound in differentiating BPH and prostate carcinoma. We included 130 cases in our study; it was a single-centre study conducted in our hospital. The mean age of our study subjects was 69.06 ± 9.22 years. Studies done by Aslan G et al.[14] had a mean age of 67 ± 7.8 years, Lee A et al.[15] had 68.2 ± 8.9 years, Akdas AM et al.[16] reported the mean age to be 66.7 years with a range of 50 to 83 years. These studies had the mean age almost similar to our study. Of

the summary, the most common age group of either benign or malignancy of prostate were more common among the age group of more than 60 years.

According to the international prostate symptom scale, we found 16.15% had mild scores, 55.38% had moderate scores, and 28.46% had severe scores. One study done by Su MZ et al.[17] reported a median international prostate symptom score of 10 with a range of 5 to 17. Another study done in India by De S et al.[18] reported that 36.67% had IPSS score between 7 to10, 53.34% had scores of 11 to 14, and the rest had scores more than 14. Our results are in accordance with these studies.

The mean PSA level in our study was 9.05 ± 12.75 ng/mL. Studies done by Su MZ et al.[17] reported a mean PSA level of 5.7 ng/mL with a range of 3.6 to 8.0 ng/mL, Aslan G et al.[14] reported 19.4 ± 43.5 ng/mL, De S et al.[18] reported the mean to be 12.09 ng/mL and Lee A et al. [15] reported a mean of 8.6 ng/mL with a range of 6.0 to 16.4 ng/mL. The high mean PSA level was likely due to a large proportion of subjects presenting for assessment of suspected malignancy in our study.

The cancer detection rate based on biopsy in our study was 27.5%. However, Lee A et al.[15] had reported the cancer detection rate to be 35.1%, Akdas AM et al.[16] had reported the cancer detection rate to be 35.22%, Aslan G et al.[14] had reported the cancer incidence to be 48.17%, De S et al.[18] had reported the cancer detection rate to be 33.33% in their study. Our study lacks data on the cancer detection rate in men with PSA 0–3.99 ng/mL and normal DRE for comparison. With only a small number of men with PSA 0–3.99 ng/mL in our study, cancer detection rate is low compared to other studies.

In our study, the proportion of suspicion of malignancy by DRE increased significantly with an increase in the Gleason score ($p < 0.05$). Another study done by Walsh AL et al.[19] had reported that those who were DRE positive had a proportion of Gleason score 3+3, 3+4, 4+3, 4+4, 4+5 in 24.1%, 41.4%, 17.2%, 10.3% and 7% of their study, respectively. A study done by Borden LS et al.[20] inferred that the digital rectal examination positivity was an independent factor for the Gleason score of the cases. They reported that 54% of DRE positive cases had ≤6 Gleason score, and 45% of DRE positive cases had a Gleason score of 7 to 10. This difference between the two proportions was significant ($p < 0.05$). In our study, the sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy of digital rectal examination were 54.55%, 98.28%, 92.31%, 85.07% and 86.25%, respectively. A study by Manyahi P et al.[21] reported the sensitivity, specificity, diagnostic accuracy to be 67%, 88.6% and 82.6%, respectively. In a study done by Lee A et al.[15] the sensitivity, specificity, positive predictive value and negative predictive value were 50%, 81.4%, 59.2% and 75.1%, respectively. Finally, a study done by Walsh AL et al.[19] reported the sensitivity, specificity and positive predictive value of digital rectal examination to be 81%, 40% and 42%, respectively.

We used PSA level of 5.4 ng/mL as a cut off as reported by Agnihotri A et al.[22], a study done by the Indian Centre of Medical Research on a large sample size in India. For this cut-off, the sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy of prostate-specific antigen for diagnosis of malignancy were 90.91%, 22.41%, 30.77%, 86.67% and 41.25%, respectively. Upon decreasing the PSA level cut off to > 4ng/mL, the sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy of the prostate-specific antigen were 90.91%, 1.72%, 25.97%, 33.33%, 26.25%, respectively. Upon increasing the cut off to > 10ng/mL, the sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy of prostate-specific antigen were 86.36%, 87.93%, 73.08%, 94.14% and 87.5%, respectively. A study done by Prcic A et al.[23] described that the best cut-off of PSA to detect malignancy of prostate to be 6.08 ng/mL as per their study. They applied receiver operating characteristic curves to establish the cut-off. As the PSA levels increased, the sensitivity and specificity attained a peak at the PSA levels of 4 to 10ng/mL, but the positive predictive value showed an increasing pattern, and the negative predictive value showed a decreasing pattern. A study done by Udeh EI et al.[24] had used the cut-off of PSA to be 4ng/ml in their study. They found the sensitivity and specificity to be 95.88% and 28.7%, respectively. Another study by AL Rumaihi KA et al.[25] also used a cut-off of PSA to be 4ng/mL and the sensitivity and specificity to be 93.9% and 8.5%, respectively. However, upon receiver operating characteristic analysis, they found the best cut off to be 7.9ng/mL with sensitivity and specificity

of 56.6% and 52.9%, respectively.

In our study, the sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy of TRUS for diagnosis of malignancy were 72.73%, 94.83%, 84.21%, 90.16% and 88.75%, respectively. A study done by Ahmad S et al.[26] inferred that the sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy were 60%, 70%, 42.6%, 31.6% and 67.3%, respectively. Akdas AM et al.[16] reported almost similar sensitivity but lower specificity when compared to our study. A study done by Manyahi P et al.[21] reported that the sensitivity, specificity, positive predictive value, and diagnostic accuracy were 58.3%, 85.7%, 58% and 78.7%, respectively.

Limitations of our study: It was a single center cross sectional study, affecting the generalizability of the findings reported.

Transrectal ultrasound does not usually allow the direct visualization and targeting of abnormal regions of the prostate for biopsy, although in rare cases a prostate lesion may be directly depicted. As a result, TRUS-guided biopsy has a low sensitivity (range, 39%– 52%), although its specificity is approximately 80%. Because of high false-negative rates, repeat biopsies are often necessary.[27] Most important limitation of the study was the gold standard considered for calculating the performance statistics was transrectal biopsy. But, studies suggest that this investigation also has some limitations and the gold standard is recommended as the biopsy taken up after the radical prostatectomy.

Conclusion

Digital rectal examination is an important screening tool for detection of malignancy. The proportion of suspicion of malignancy by DRE increases with increase in the Gleason score (High grade cancer). As the PSA level increases the chances of biopsy having malignancy also increases significantly. In patients with abnormal DRE and/ or PSA more than 10 ng/mL, TRUS-guided transrectal biopsy is recommended. For patients with normal digital rectal examination and Prostate specific antigen in the "grey zone" of 4-10 ng/mL, it is recommended that various PSA related serum markers or PSA derivatives should be used to decrease the number of negative biopsies.

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