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"IMAGING AND HISTOPATHOLOGICAL CORRELATION OF PROSTATIC LESIONS"

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ABSTRACT **Background:** To evaluate the role of a transrectal ultrasound (TRUS) guided biopsy and a color doppler test in the detection of prostate cancer in patients with increased serum prostate-specific antigen (PSA) levels and/or an abnormal digital rectal examination (DRE). **Methods:** A total of 30 cases, ranging in age from 50 to 80 years and showing increased serum PSA levels (>4ng/ml) and/or abnormal DRE, were enrolled and underwent TRUS evaluation followed by color Doppler flowmetric studies. A TRUS-guided FNAC/biopsy was performed in all the cases. The findings were confirmed histopathologically. Data were analyzed using the chi-square test. **Results:** Histopathologically, a total of 11 cases (36.66%) were malignant. On TRUS, irregular shape, heterogeneous echotexture loss of differentiation between the peripheral and internal zones, and capsular invasion were significantly associated with malignancy. On flowmetry, moderate vascularity and focal asymmetry were significantly associated with malignancy. The combined use of TRUS and color Doppler flowmetry was found to be 100% sensitive and 89.5% specific and had a positive predictive value (PPV) and a negative predictive value (NPV) of 84.6% and 100%, respectively. **Conclusions:** Trus with color doppler ultrasound plays an important role in the detection of prostatic malignancy with high sensitivity as well as specificity. The high negative predictive value, as observed in the present study could avoid unnecessary diagnostic invasive intervention.

KEYWORDS : PSA (Prostate-Specific Antigen), DRE (Digital Rectal Examination), TRUS (Transrectal Ultrasonography), CAP (Carcinoma Prostate).

INTRODUCTION

Prostate cancer is the most common malignant tumor in men all over the world. Incidence of prostatic cancer increases proportionally after the age of 50 years.[1] In approximately, 70% of cases it arises in the peripheral zone of the gland, particularly in the posterior location.[2] Adenocarcinoma is its most common histological variant.[1]

Carcinoma Prostate is globally the second most frequently diagnosed cancer and the sixth leading cause of cancer death in males. The worldwide incidence of Carcinoma Prostate has been rising rapidly, likely due to intensified effort in early detection and screening.[3]

95% of prostate cancers are adenocarcinomas that develop from the acini of the prostatic ducts. Acinar-type adenocarcinoma is the most common malignancy of the prostate, comprising more than 90 % of malignant lesions.[4] Acinar type adenocarcinoma typically involves the peripheral zones and is associated with high-grade prostatic intraepithelial neoplasia (HGPIN) which is the only recognized premalignant prostate lesion. PSA is currently the only serological marker routinely used in the diagnosis, staging, and monitoring of treatment response or failure in prostate cancer [9]. PSA remains a better predictor of prostate cancer than DRE or transrectal ultrasound. TRUS with or without biopsy and to a lesser extent DRE is also a good predictor for diagnosing Carcinoma Prostate. Prostate biopsy remains the gold standard investigation for diagnosing prostate cancer [9].

Prostate cancer often develops very slowly compared with most other cancers and its natural history often spans several decades. However, some cancers grow fast and will give rise to early metastases and death. At diagnosis, it is still difficult to differentiate those prostate cancers that remain indolent and those that will proliferate more quickly. There is no fixed pattern of proliferation; it is often multifocal and usually grows locally.

Prostate cancer can infiltrate and penetrate the prostatic (pseudo)capsule; often penetration is basal and lateral and continues towards the seminal vesicles or follows the neurovascular bundles [14]. It may spread into regional lymph nodes to finally give rise to distant metastases. The risk of lymph node metastasis increases with increased tumor volume and poor histological differentiation.

Prostate cancer can spread by local invasion (typically into the bladder and seminal vesicles, urethral and rectal involvement are rare), lymphatic spread (pelvic nodes first followed by para-aortic and inguinal nodes), or hematogenous metastasis.

PSA is a tissue and not tumor-specific marker, which is important because elevated levels of PSA may occur in: instrumentation of the urinary tract, BPE, urinary tract infection, prostatitis, acute urinary retention, or large urinary residual [9].

Transrectal ultrasonography (TRUS) has received increasing attention recently because of its potential for early detection of prostate cancer. It provides greater detail on the zonal anatomy of the prostate and the echo pattern of the gland and its various lesions. The prostate gland can be visualized with a transrectal probe allowing close-contact scanning. Ultrasound is essential for examining the echotexture and size of the gland and to aid precision biopsies. It is more accurate than a DRE examination in measuring prostate size. It is routine to measure the prostate volume which may be important in offering treatment options. The prostate is measured in 3 planes. In the transverse view 1,) anterior to posterior (width) 2) height and in the longitudinal plane 3) from the bladder neck to the apex (length). In the evaluation for suspicion of prostate cancer, TRUS also provides information regarding the existence and location of cancer foci. Prostate cancer is typically visualized as a hypoechoic lesion in the peripheral zone, and at times it is accompanied by asymmetry or protrusion into the prostatic capsule. In advanced disease, the asymmetry between the seminal vesicles is seen through TRUS. The limitation of TRUS is the reliability of the findings is operator-dependent, and TRUS suffers from poor test characteristics for the diagnosis of prostate cancer.

Transrectal ultrasound (TRUS) is generally recognized as the method of choice for prostatic biopsy guidance, however, only 20% of urologists perform targeted biopsies based on sonographic findings. Most contemporary prostate biopsy protocols have concentrated on the use of the systematic prostate biopsy approach and currently require the acquisition of 10 or more cores. This investigation though sensitive and specific however is a very painful and invasive procedure rendering it unfit for screening [11]. Moreover, the

low positive predictive value (PPV) for the presence of prostate cancer remains a considerable weakness. Doppler and gray-scale ultrasound are the two modes generally used to examine the prostate after contrast administration. Echogenic material within the vasculature is visible on grayscale and the Doppler signal is greatly enhanced, particularly within areas of cancer. Color and power Doppler biopsy targeted at such areas of abnormal flow is more sensitive than random biopsy. Color Doppler ultrasonography is an adjunct technique to traditional gray-scale imaging. It is designed to help clinicians better identify areas of increased vascularity that are associated with tumors. Malignant lesions are characterized by asymmetrically increased flow patterns, particularly in higher-grade prostate cancers with a Gleason score of above 8. CD-US correlates positively with the grade and stage, as well as biochemical recurrence of prostate cancer, after initial treatment.

Although increased cancer detection has been reported for the use of color Doppler US, the combined sensitivity of gray-scale and color Doppler imaging is insufficient to preclude the need for systemic biopsies.[12]

Hence, there is a need for an alternate, cost-effective and efficient modality of screening, detection, and differentiation of prostatic diseases, the present study is done to study the role of "transrectal ultrasonography (TRUS) and color doppler to evaluate the prostatic lesions and comparing this modality with the histopathology".

METHODS

The study was carried out on a total of 30 male patients aged 50-80 years, with raised serum PSA levels and/or having a hard, enlarged nodular prostate on Digital Rectal Examination (DRE). The study was prospective, conducted in the Department of Radiodiagnosis, PGIMS Rohtak. All suspected patients attending the surgical outpatient/ inpatients department who fulfilled the inclusion criteria of Age > 50 years, raised PSA levels and having a hard and enlarged nodular prostate on DRE were thoroughly examined by general physical examination and systemic examination followed by TRUS with a color Doppler for the detection of the prostatic lesion. TRUS was done on an ultrasonography (USG) color Doppler machine (with a transrectal probe (6-10 MHz)), in the proper position (knee-chest position). To assure acoustic contact the sheath contained ultrasound gel. The sheath was coated with gel for adequate lubrication and was inserted into the rectum. Then FNAC/Biopsy was taken under TRUS guidance from the suspected lesions.

On TRUS, the number of nodules, zone involved, size and shape of the lesion, echogenicity, difference between peripheral and internal zone, prostate weight, and capsular invasion were noted. Doppler color flowmetry studies were done for the extent of vascularity (mild/moderate) and vascular asymmetry (focal/diffuse). Then FNAC/Biopsy was taken under TRUS guidance from the suspected lesions.

Data Analysis

Collected data were analyzed for sensitivity, specificity, positive predictive value, negative predictive value, and accuracy by applying the p-value in the chi-square test to assess the statistical significance.

RESULTS

The age of patients in the present study ranged from 51 years to 80 years (n = 30). The mean age was 67.53 years. Most of the patients were in the age group 71-80 years (n = 14). In our study, with an increase in age, there is an increase in the frequency of prostatic disease. The main clinical presentation of the patients was nocturia (26.7 %) and acute retention (26.7 %) followed by frequency and hesitancy (23.3 %).

Out of the 30 patients, 12 patients (40 %) had nodularity on digital rectal examination and 10 patients (33.3 %) had induration. 6 patients had a PSA value (4-5ng/ml), 10 patients had a PSA level (15-50ng/ml) and 14 had a PSA value >50ng/ml, a minimum serum PSA level of the patients was 5.14ng/ml whereas the maximum serum PSA level was 168.73ng/ml. The mean serum PSA level of the patients was 54.59ng/ml. Raised PSA levels were found in concordance with malignancy. 12 (40 %) out of 30 patients had heterogeneous echotexture of prostatic tissue on TRUS, of which 10 patients were malignant on histology and 2 patients were benign whereas 18 (60 %) out of 30 patients had homogenous echotexture, of which only 1 patient was malignant on histology.

In our study of 30 patients, on TRUS examination we found that the differentiation between peripheral and internal zone was lost in 10 patients (33.3 %). Out of which 8 patients (80 %) had malignant lesions proven on histology. Out of 20 patients (66.7 %) with maintained differentiation between peripheral and internal zone 2 (10 %) were found to be malignant. Hence, proving the significance of the study that loss of differentiation between peripheral and internal zone is associated with malignancy (p-value <0.01).

On TRUS examination, out of 30 patients, 6 patients (20%) showed capsular invasion and peripheral spread in all positive patients had malignant histology.

TRUS done for zonal distribution in 24 patients with focal lesions (out of 30 patients24 had focal lesions) showed that out of 3 patients (12.5 %) with focal lesions found at apex, none were found to be malignant. Out of 7 patients (27.2 %) with focal lesions found in the basal region, 1(14.3 %) was found malignant. Out of 12 patients (50%) with lesions found in the peripheral zone unilaterally, 4 (33.3 %) were found to be malignant. Out of 2 patients (8.3%) with lesions found in the transitional zone unilaterally, none were found to be malignant. The location of the lesion in the peripheral zone was significantly associated with the malignancy of the prostate (p < 0.01).

Considering the sizes of the focal lesion, out of 15 patients (62.5 %) showing lesions of size <2 cm 3 (20%) were found to be malignant, out of 8 patients (33.5 %) showing lesions of sizes 2-5 cm, one (12.5 %) was found to be malignant, the single patient showing lesion of size > 5 cm was found to be malignant (100 %).

Considering the shape of the nodule, out of 6 patients (25 %) showing irregular nodules 4 (66.7 %) were found to be malignant, and out of 12 patients (50 %) showing regular and round-shaped nodules, none were found to be malignant and out of 6 patients (25 %) showing oval-shaped nodules only one was found to be malignant (16.7 %). Therefore, the nodules appearing irregular in shape were more consistently associated with malignancy (p < 0.03).

Based on the echo pattern of the focal lesions, out of 11 patients (45.8 %) showing hypoechoic nodules on TRUS 5 (45.5%) were found to be malignant, out of the remaining 13 patients (54.2 %), none of the lesions were found to be malignant. Hence, the study was found to be significant as all the malignant lesions appeared hypoechoic on TRUS (p <0.01).

Out of 30 patients, 24 were found to have single or multiple focal lesions on TRUS evaluation out of which 5 (20.8%) were found to be malignant, and out of the remaining 6 patients (20 %) showed no focal lesion but appeared heterogeneous in echotexture and showing loss of differentiation between peripheral and transitional zone and capsular invasion all

were found to be malignant. Hence proving that the features such as heterogeneous echotexture, loss of differentiation between peripheral and transitional zone, and capsular invasion are more associated with malignancy as compared to a focal lesion itself (p-value < 0.01).

On color doppler assessment, 28 patients showed abnormal vascularity on color doppler, out of which 15 patients (50 %) showed abnormal moderate vascularity out of which 90.9 % patient have malignant lesions and 13 patients (43.3 %) showed abnormal focal vascularity out which 90 % patient has malignant lesion suggesting vascularity to be significantly associated with malignancy.

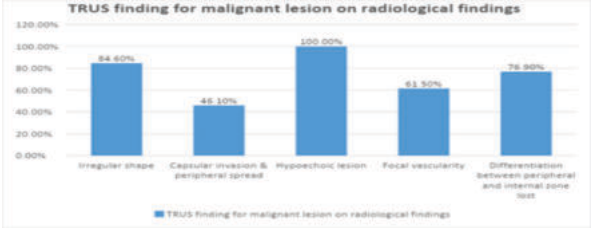
Overall out of the 30 patients referred for TRUS 17 patients (56.7 %) were diagnosed with BPH and 13 patients (43.3 %) were diagnosed to have malignancy on TRUS evaluation and after histopathological examination 19 cases (63.3 %) were found to be benign (BPH), 11 cases (36.7 %) were malignant (out of which 2 cases (6.7 %) were carcinoma in situ).

On clinical examination, abnormal DRE, and PSA level >4ng/ml, 19 patients were suspected of having malignant lesions, after histopathological examination, we concluded that clinical diagnosis had a diagnostic accuracy of 73.3 % in determining prostatic malignancy with a specificity of 57.9 %, the sensitivity of 100 %, PPV of 57.9 % and NPV of 100 %.

Hence concluding that the combination of TRUS and color doppler has resulted in increased specificity and accuracy as compared to clinical diagnosis. The sensitivity of the combined evaluation appears to be 100 % and the specificity has been shown to lie between 66.9 % - 98.7 %. Colour doppler improves the sensitivity of endorectal ultrasound despite some false-negative results. It demonstrates tumor vascularity, detects capsular extension, and aids in image-guided FNAC/biopsy. TRUS with color doppler had a diagnostic accuracy of 93.3%, PPV of 84.6 %, and NPV of 100 %

S. No	Characteristics	Statistics
1	Mean age ± SD (range) in years Most of the patients were in the age group 71-80 years(n=14)	67.53 ± 8.36(51-80)
2	DRE findings	
	Induration	10(33.3%)
	Nodularity	12 (40%)
3	Mean PSA (ng/ml) 54.59	
	4-15	6(20.0%)
	15-50	10(33.3%)
	>50	14(46.7.0%)
4	Histopathological diagnosis	
	Benign	19(63.3%)
	Carcinoma prostate	9(30%)
	Carcinoma in situ	2 (6.7%)
5	TRUS (grey scale diagnosis)	
	Benign	17 (56.7%)
	Malignant	13 (43.3%)
6	TRUS + color doppler	
	Normal vascularity Moderate vascularity Focal vascularity	2 (6.7%) 15 (50%) 13 (43.3%)

Table 2. TRUS finding for Malignant Lesion on Radiological findings (n = 13)



A focal lesion with an irregular shape and hypoechoic nodules with moderate and focal vascularity were considered malignant. In cases where focal lesions were not there, heterogeneous echotexture with loss of differentiation between peripheral and transitional zone and capsular invasion were considered malignant features.

Characteristics	Total		Benign		Malignant		P-value
	No.	%	No.	%	No.	%	
No. of nodules							
1	11	45.8	9	81.8	2	18.2	0.02
2	05	20.8	3	60	2	40	
>2	08	33.3	7	87.5	1	12.5	
Zone							
Apex	3	12.5	3	100	0	0.0	0.01
Basal	7	29.2	6	85.7	1	14.3	
Unilateral peripheral	12	50.0	8	66.7	4	33.3	
Unilateral transtional	2	8.3	2	100	0	0.0	
Size							
<2 cm	15	62.5	12	80	3	20	0.06
2-5 cm	08	33.3	7	87.5	1	12.5	
>5 cm	01	4.2	0	0.0	1	100	
Shape							
Irregular	06	25	2	33.3	4	66.7	0.03
Regular	06	25	6	100	0	0.0	
Round	06	25	6	100	0	0.0	
Oval	06	25	5	83.3	1	16.7	
Echopattern of focal lesion							
Hypoechoic	11	45.8	6	54.5	05	45.5	<0.01
Isoechoic	01	4.2	1	100	0	0.0	
Iso to hypoechoic	12	50	12	100	0	0.0	

Table 3. Characteristics Of Focal Lesions On TRUS (n= 24)

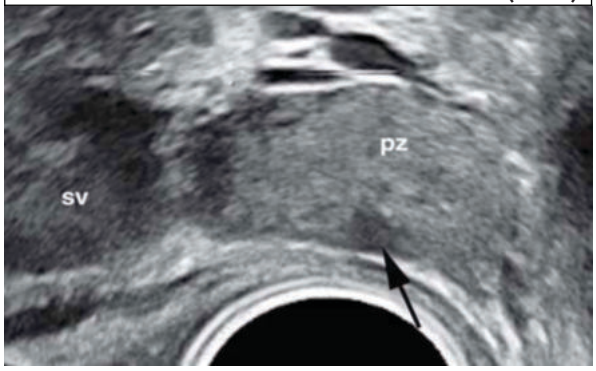


Figure 2. On Transrectal Ultrasonography, Sagital Image showed a Slightly Echogenic Peripheral Zone (pz) and a Hypoechoic Nodule (Arrow) in the Peripheral Zone and the Seminal Vesicle (sv)

TRUS diagnosis	Histopathological diagnosis		Total
	Benign	Malignant	
Benign	17 (TN)	0 (FN)	17
Malignant	02(FP)	11 (TP)	13
Total	19	11	30

Table 4. The Diagnostic Efficacy of TRUS with Colour Doppler Compared to Histopathology

- Sensitivity = 100.0 % (71.5 % - 100 %)
- Specificity = 17/19 = 89.5 % (66.9 % - 98.7 %)
- PPV = 84.6 % (59.7 % - 95.3 %)
- NPV = 100.0 %
- Accuracy = 93.3 % (77.9 % - 99.2 %)

DISCUSSION

The diagnosis and treatment of prostate cancer are very challenging. The current methods of screening for prostate cancer include measuring serum prostate-specific antigen levels (PSA), digital rectal examination (DREs), and transrectal ultrasound (TRUS). Scanning and biopsy confirm the diagnosis; however, the sensitivity and specificity of TRUS

for diagnosing prostate cancer still need further study.

The mean age of patients in the present study was 67.53 years, range of 71-80 years (n = 14). In studies conducted by Vilanova et al(2011),[61] Aydnn et al (2012)· Sakarya et al (1998) and Khanduri et al[64] the study population consisted of men with a mean age of 63.5 years (range 43 - 87 years), 69 years, 66.4 years range (59 - 82 years) and 63.8years range 51 to 77 years respectively. This concludes by our study and other studies that with an increase in age, there is an increase in the frequency of prostatic disease. Raised PSA levels were in concordance with malignancy which is similar to a study done by Prcic et al[69] in which cancer was diagnosed in 57.1 % who had PSA levels more than >20ng/ml.

40 % of patients had heterogeneous echotexture of prostatic tissue on TRUS, of which 83.3% were malignant on histology. Thus concluding that heterogeneous echotexture of the prostate had a significant association with malignancy which was similar to the study done by Khanduri et al.

In this study lesions which were present in the peripheral zone, size more than 5cm, irregular in shape, and hypoechoic in echotexture were more in the favour of malignancy. Another study done by Ahmed et al[60] found that majority of patients with hypoechoic nodules 56.3 % had malignant histology. A study done by Lee et al[58] determined that shape, margin and irregularity and vascularity were factors significantly associated with malignancy. In a study by Khanduri et al[64], 61.54 % of patients of size >5cm have a malignant lesion,76.92 % of a patient having irregular shape shows malignant lesions, and 100 % of patients with round shapes show benign lesion.

Differentiation between peripheral and internal zone was lost in 10 out of 30 patients (33.3 %) in our study. Out of which 8 patients (80 %) had malignant lesions which were similar to the study done by Khanduri et al[64]in which 76.92 % of patients with malignant lesion shows loss of differentiation. Increased vascularity of the focal lesion was more in the favour of malignancy which was similar to the Lee et al[58] in which 57 % of patients with positive color Doppler findings were malignant. In our study on TRUS examination, 6 (20 %) out of 30 patients had capsular invasion and peripheral spread of which 100% showed positive malignant histology which was similar to the study done by Sperandeo et al[55] and Ahmed et al.[60]

In our study, we concluded that TRUS with color doppler had high sensitivity (100%), specificity (89.5%), and high NPV (100 %) which was comparable with a study done by Khanduri et al.

CONCLUSIONS

The findings of the present study showed that TRUS with color doppler ultrasound plays an important role in the detection of prostatic malignancy with high sensitivity as well as specificity. The high negative predictive value, as observed in the present study, could avoid unnecessary diagnostic invasive intervention. However, given the limitation of the sample size, the findings in the present study should be used cautiously with further corroboration by larger sample size.

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