

Utility of Power Doppler Transrectal Ultrasound in Targeting Prostatic biopsy

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Abstract: Objective: The aim of this study is to compare the effect of transrectal power Doppler ultrasound (PDUS) and conventional transrectal ultrasound (TRUS) in targeting Prostatic biopsy in men with prostate specific antigen (PSA) levels above 4 ng/mL and its impact on prostate cancer (PCa) diagnosis. **Patients and Methods:** A total of 150 consecutive men with serum total PSA levels above 4 ng/mL (mean age 61 ± 8 years, range (50 –78) were included. Gray-scale transrectal ultrasound (TRUS) and PD-TRUS were performed before and during the biopsy procedure. Abnormal vascularity and perfusion characteristics were recorded and graded as normal or abnormal in the peripheral zone of the prostate in addition to histological diagnosis. Regime of twelve systematic TRUS guided core needle biopsies were performed in all patients and additional biopsies from abnormal sites on grey scale TRUS and PD-TRUS. **Results:** PDUS sensitivity, specificity, positive predictive value (PPV) and negative predictive values were 81%, 67.12%, 69.7% and 94%, respectively. PDUS had a greater sensitivity and specificity than TRUS (43.75% and 60%, respectively) and The PCa detection rate in all patients with and without PD-TRUS abnormal vascularity was detect cancer cases more accurately 20/27 (74%), versus 26% 7/27(PD-TRUS –ve) diagnosed patients harboring cancer ($p < 0.003$). **Conclusion:** PDUS increases the cancer detection rate with additional biopsies from suspicious hypervascular foci. Transrectal PDUS guided biopsy should be combined with gray scale TRUS guided biopsy to increase accuracy in the diagnosis.

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Key Words: Biopsy; Prostate cancer; Power Doppler; PSA; Ultrasound; TRUS.

1. Introduction

Prostate cancer is the most common malignancy among men in the United States, and rated second in mortality after lung cancer, accounting for estimated 9.3% of all cancer-related deaths of male adults (28,170 out of 301,820) in 2012 [1]. Prostate cancer was found to be generally smaller, of lower-grade and more often observed in younger men. These changes in detection may allow for increased use of active surveillance for prostate cancer. Transrectal ultrasound (TRUS), magnetic resonance imaging (MRI) and computed tomography (CT) were playing an important role in the diagnosis and in therapeutic decision-making. It has been demonstrated that TRUS gives more detailed information than either CT or MRI [2]. Prostate cancer was found to be correlated with hypervascularity due to angiogenesis [3]. TRUS was highly sensitive but with low positive predictive value (PPV) in the assessment of early malignant lesions decreases its strength. The reason for this low PPV due to hypoechoic lesions in malignant tumors can also be seen in other pathologies. This has led to the investigation of various methods to decrease the cost and morbidity, and to prevent unnecessary biopsies (18-53%) predictive values with prevalence around 33%. Thus, in the era of PSA, searching for hypoechoic lesion on Grey scale ultrasound only is insufficient to diagnose most prostate malignancy [4].

The combination of Color and Power Doppler ultrasound and grey-scale TRUS increased the sensitivity of detecting prostate cancer while it was not decreasing the specificity. This may lead to a biopsy from patients with indistinct findings on grey-scale TRUS but with positive Color and Power Doppler ultrasound findings, which otherwise might not be taken and thus miss the cancer. Lesions with positive Color and Power Doppler ultrasound findings and negative grey-scale imaging results may be significant cancers. [5].

The aim of this study is to demonstrate the beneficial effect of power Doppler ultrasound (PDUS) combined with gray scale TRUS guided systematic biopsy Doppler in targeting Prostatic biopsy.

2. Patients and Subjects

One hundred-fifty men aged 49-78 years (mean age: 61 ± 8 years) with a serum prostate specific antigen above 4 ng/mL were included in the study and the patients presenting to out-patient clinics of Urology and ultrasonographic unit of Al-Azhar University hospitals between November 2010 and May 2015 The protocol of this study has been approved by Al-Azhar Medical Research Ethical committee and written consent was obtained from all patients.

Patients were prescribed the day before to the

examination, ciprofloxacin 500mg twice daily and metronidazole 400 mg three times per day was prescribed, which was continued for 2 days post procedure and instructed to give a self-administered cleansing enema before examination to remove gas and feces and recommend that aspirin and non-steroidal anti-inflammatory (NSAIDS) are to be stopped for 10 and 5 days respectively prior to the procedure. Patients on anticoagulation therapy are not examined until the anticoagulant dosage is adjusted or stopped to allow the coagulation status to normalize.

The study was performed using Doppler ultrasound devices (B & K console (B & K Medical, Denmark) with color monitor 15 inch and 7 MHz). The patient is positioned in left lateral position. This allows for easier insertion of the rectal probe. A topical anesthetic gel is applied prior to performing the

examination. A 5.0 to 7.5 MHz endocavitary transducer is used for transrectal imaging of the prostate. Grayscale scanning was done from the base to the apex of the prostate, as well as the surrounding structures such as the seminal vesicles, urethra and rectum to look for areas that appear suspicious.

This was followed by Color Doppler and power Doppler to assess the blood flow through the entire prostate and suspicious foci. The flow signals from Color Doppler were evaluated and categorized into hypervascular, hypovascular lesions and normal vascular areas. (Fig 1). Grading of PDUS was classified as following: - Grade (G) 0 No abnormal vascularity, G1 Low focal vascular clustering, G2 Intensive focal vascular clustering and G3 Diffuse vascular clustering.

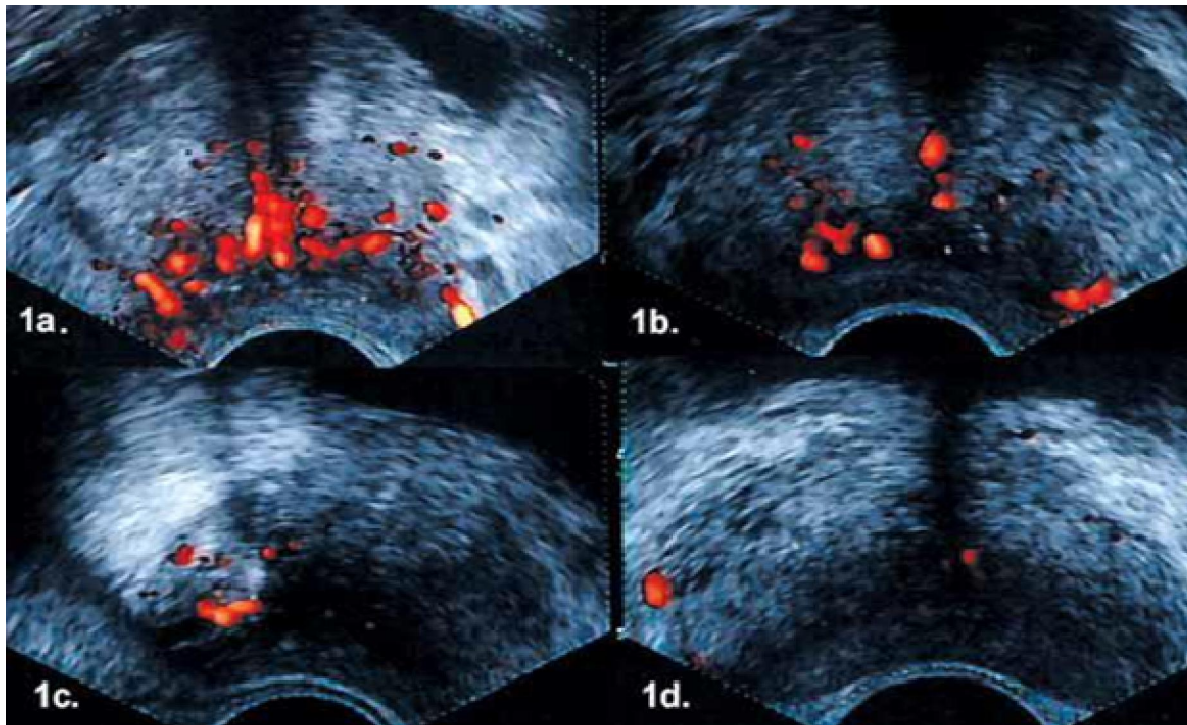


Figure (1): A) G 3 (Diffuse flow), B) G 2 (focally intense flow in right peripheral zone), C) G 1 (Focally low flow), D) G 0 (Scarce flow).

Transrectal ultrasound-guided needle biopsies were performed to obtain 12 core samples using an 18 gauge biopsy cut needle driven by spring loaded biopsy gun including areas that showed increased flow on color Doppler and hypoechoic lesion. The patients was followed up for the management of complications if occur and to discuss the results of the histopathological examination of the biopsy.

Statistical analysis: The data were analyzed using Microsoft Excel 2010 and statistical package for social science (SPSS version 20.0) for windows (SPSS IBM.,

Chicago, IL). Results will be expressed as mean \pm SE with 95% confidence interval using medians for quantitative variables, and using the frequencies and percentage for qualitative ones; a p value $<$ 0.05 was considered statistically significant. To analyze data sensitivity, specificity, positive predictive value (PPV) and negative predictive value were evaluated using MedCalc1 V.7.1.0.1.

3. Results

The results of positive biopsy cores in correlation

with PDUS and TRUS findings were summarized in **Table 1**. Ten out of 26 hypoechoic hypervascular lesions (38.4%) were found to be adenocarcinoma. Cancer was only diagnosed in two of 28 hypoechoic lesion with non-vascular areas (7.1%), eleven of 24

non-hypoechoic area with hypervascular lesion (34.3%) revealed malignancy. Power doppler positive areas were found in 60 cases (40%), 21 of them were malignant (35%). Twenty seven of 150 patients (18%) had prostate adenocarcinoma.

Table (1): Gray scale and Doppler cross tabulated with histopathology:-

P=0.01	Hypoechoic zone in TRUS (+) (n=54)		Hypoechoic zone in TRUS (-) (n=96)		Total (n= 150)	
Hypervascular zone in PDUS (+)	10/26	38.4	11/23	34.3	21/60	35
Hypervascular zone in PDUS (-)	2/28	7.1	4/64	6.25	6/90	6.66
Total	12/54	22.2	15/96	15.6	27/150	18

The results of positive biopsy cores with hypervascular zone in Power doppler was collected in **Table 2**. According to hypervascularity grading, 93 patients (62%) were diagnosed as normal vasculature.

Fourteen (9.4%), Twenty two (14.6%) and twenty one (14%) lesions were defined as grade 1, grade 2 and grade 3 (**Figure 2 A, B and C**).

Table (2): comparison of cancer positive biopsy with power Doppler ultrasound:-

P=0.03	Grade 0 (normal) (n=93)		Grade 1 (n=14)		Grade 2 (n=22)		Grade 3 (n=21)		Total (n=150)	
	No	%	No	%	No	%	No	%	No	%
Positive biopsy Forcancer	8	8.6	4	28.5	7	31.8	8	38	27	18
Negativefor Biopsycancer	85	91.4	10	71.5	15	68.2	13	62	123	82
Total (n=106)	93	62	14	9.4	22	14.6	21	14	150	100

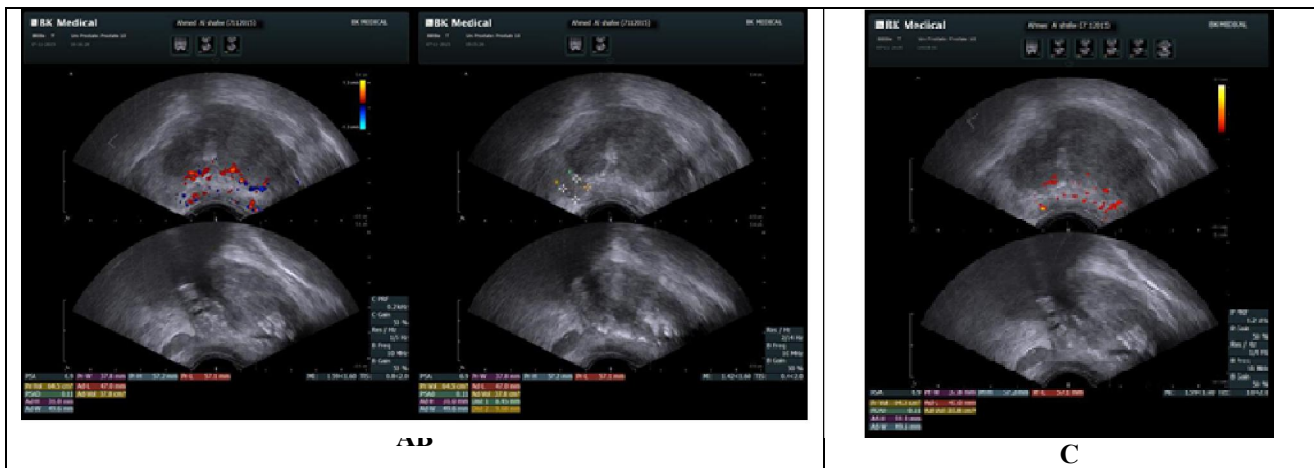


Figure (2): A) Color Scale U/S (Hypervascular Lesion). B) Gray Doppler U/S (Hypoechoic lesion). C) Power Doppler U/S (Hypervascular Lesion). PSA 6.9ng/mL, **Histopathology:** Moderately differentiated prostatic adenocarcinoma, nuclear grade III gleason score 8 (4+4).

Out of 37 false positive cases were examined with PDUS, 20 had chronic prostatitis and 5 were diagnosed as PIN and 12 had benign prostate tissue (BPH). As a result, 20 of 27 adenocarcinoma patients

were diagnosed with PDUS and 7 were assessed with TRUS. Seven cases were missed by using Power Doppler guided biopsies, three of which were appeared as a hypoechoic nodule in gray scale TRUS.

The other four adenocarcinoma cases were non hypoechoic in gray scale neither TRUS nor hypervascular in PDUS. The seven missed cases were

diagnosed with systematic TRUS biopsy (-ve PDUS) **Table 3.**

Table (3): Correlation of histological and ultrasonic data of PDUS and TRUS

P=0.04		TRUS		PDU		Both	
		+ve	-ve	+ve	-ve	+ve	-ve
Histological Data	+ve	11	16	20	7	23	4
	-ve	43	80	37	86	65	58
Total		54	96	57	93	88	62

The correlation of Gleason scores of positive biopsy cores with hypervascular zone in PDUS (PDUS grading) is summarized in **Table 4** which show insignificant correlation between Gleason scores and PDUS grading.

Table (4): The correlation of Gleason scores of positive biopsy with PDUS grading

P=0.6	Grade 0 (n=8)	Grade 1 (n=5)	Grade 2 (n=7)	Grade 3 (n=7)	Total (n=27)
	Gleason scores <4	3	3	4	4
Gleason scores 4-7	4	2	3	1	10
Gleason scores 8-10	1	0	0	2	3
Total	8	5	7	7	27

Although 60 cases (40%) were positive by examination with PDUS, 54 cases (36%) were abnormal in conventional TRUS. Power Doppler Ultrasound sensitivity, specificity, positive predictive value (PPV) and negative predictive values were

81.25%, 67.12%, 69.7% and 93.23%, respectively. The above results were show that PDUS had greater sensitivity and specificity than TRUS (43.75% and 60%, respectively) and diagnosis of cancer cases was more accurately **Table 5.**

Table (5): Sensitivity, specificity, PPV, NPV of TRUS and PDUS methods

	Sensitivity	Specificity	PPV	NPV	Accuracy
TRUS	43.75%	60%	22.58%	80%	56.58%
PDUS	81.25%	67.12%	69.7. %	94.23%	69.66%

4. Discussion

TRUS has several benefits including safety, portability, low cost, and the ability to perform real-time imaging and image-guided procedures in an office setting. Gray-scale ultrasound has proved unsuccessful for the detection and local staging of prostate cancer due to limitations in spatial resolution and tumor contrast. The most common appearance of prostate cancer on transrectal ultrasound (TRUS) is an ill-defined hypoechoic region compared to adjacent parenchyma, but it can be isoechoic in up to 30 % of patients. Only rarely is prostate cancer hyperechoic[6].

Conventional transrectal grey scale ultrasound (GSU) is currently the standard imaging tool for the prostate. GSU is used for volumetry, needle guidance for systematic biopsies and guiding seed placement in brachytherapy. The sensitivity of GSU for prospective tumor detection— varying by experience—has been reported to be up to 60 %. This reflects known sonographic properties of PCa: approximately 60 % of

tumors appear hypoechoic. Around 35–39 % of tumours are isoechoic, limiting the detection potential of GSU. The performance was reported in the literature varies widely with sensitivities ranging between 8 and 88 % and specificities ranging from 42.5 to 99 % [7].

In this study, our goal was to evaluate the practical role and limitation of Power Doppler Ultrasound -guided biopsy by comparing it with gray scale TRUS and systematic TRUS guided biopsy. Ten of 26 hypoechoichypervascular lesions were malignant (38.4%) which suggested that biopsies should be taken from PDUS and conventional TRUS positive lesions. We found that hypoechoic area which associated with non-vascular lesion yielded only 7.1% positive cancer diagnosis while the hypervascular non hypoechoic areas identified 34.3% positive cancer detection. These findings support the superiority of PDUS over TRUS in targeting prostatic biopsy foci and suggest that PDUS guided biopsy has a higher sensitivity and

specificity. Prostate cancer is characterized by hypervascularity compared to normal prostate tissue due to growth of the vascular capacity of the existing parenchyma [8].

There has been great interest in using Doppler ultrasound to increase sensitivity and specificity for the targeting of prostate biopsy. Power Doppler imaging are sensitive for detection of flow in vessels as small as 1mm, asymmetrically increased flow patterns around and into areas of tumor with increased number and size of vessels characterize prostate cancer on Doppler imaging. These vessels will show an irregular orientation in contrast to the typical radial pattern of normal prostate flow [9].

Many studies were conducted to assess vascularity in prostate cancer using Color Doppler ultrasound (CDUS). PDUS has the advantage over CDUS of showing very low vascular flows. Studies have been trying to improve cancer diagnosis rates with TRUS –guided biopsy taken from abnormal vascular foci. [10].

In our study, TRUS and PDUS were identified eleven and twenty cancer cases (40.7 % and 74.4%), respectively. PDUS guided biopsy can identify cancers missed by TRUS and twelve systematic biopsy. However, PDUS guided biopsies alone were missed in four of 27 cancer cases diagnosed by a combination of PDUS, TRUS and systematic biopsy. This means that PDUS defined suitable areas for biopsy and increased the cancer identification rate; however, it does not have sufficient accuracy to exclude systematic twelve biopsy.

Radhakrishnan and Vinodh [11], found that high test performances of PDUS for prostate cancer detection with a 98% sensitivity and a 99% NPV. Some studies have reported that Power Doppler is a reliable method for prostate cancer diagnosis and suggest that it can also predict the tumor aggressiveness. [12] & [13].

Halpern et al. [14] evaluated 62 patients with TRUS and PDUS methods, and cancer was detected in 18 patients'. The positive biopsy cores with PDUS were found to be superior to that of systematic biopsy 13% vs. 9.7%. [14]. **Takahashi et al. [15]** evaluated 108 patients, he found that Power Doppler Ultrasound detected 36 cancer patients while only 32 patients were diagnosed by conventional TRUS. They also demonstrated that non-hypoechoic with hypervascular foci yielded higher rates of cancer than non-vascular hypoechoic foci. They suggested that PDUS aids in the identification of additional cancer cases [15].

The relationship between hypervascularity and Gleason scores were studied, the authors concluded that power Doppler US may contribute to the evaluation of prostate cancer aggressiveness and direct biopsies to more aggressive lesions [12].

Our study was found no significant correlation between Gleason scores and flow grading. Gleason scores can be high in low focal flow clustering. While lesions with intensive focal flow clustering can have low Gleason scores. From 14 patients with Gleason scores less than 4, only two had grade 1, three had grade 2 and one had grade 3 flow patterns. Among 10 patients with Gleason scores between 4 and 7, two had grade 1, three had grade 2 and one had grade 3 flow patterns but among 3 patients with Gleason scores greater than 7, two had grade 3.

In chronic prostatitis, increased flow at arteriolar level with inflammatory mediators leading to hypervascular pattern on Power Doppler Ultrasound with an intensive flow clustering. Both prostatitis and prostate cancer were noticed on PDUS as hypervascular foci. [16]. **Radhakrishnan, and Vinodh [11]** demonstrated that in PDUS positive cases without malignancy, prostate size is significantly larger than PDUS negative cases without cancer. They explained that the growing prostatic tissue needed increased blood supply than normal glandular tissue [11].

The sensitivity of gray scale in our study was 43.75% which lies in the range found in the literature (8-88%). The specificity was 60%. The sensitivity of power Doppler was 81.25, specificity was 67.12 % PPV (Positive Predictive Value) was 69.7% and NPV (Negative Predictive Value) was 94.23%. So, we recommend using the two modalities, Gray scale and Doppler in targeting prostatic biopsies and once hypoechoic, hypervascular lesions appeared, directed biopsy should be taken.

When we used power Doppler US in our study we found 77 (51.3%) patients with hypervascular lesions, the results of the histopathological examination of the biopsies revealed adenocarcinoma in 20 (74. %) patients from total number of patients with hypervascular lesions.

When using gray scale and Doppler ultrasound in our study we found lesions hypoechoic, and hypervascular. The results of the histopathological examination of the biopsies revealed adenocarcinoma in 23 (85.1%) while there were 4/27 (14.81%) neither non hypoechoic nor hypervascular from cancerous patients.

In study of 620 radical prostatectomy pathology with preoperative Power Doppler and traditional TRUS findings were recorded. The authors were found that PDUS improve the specificity of TRUS for identifying prostate tumors, we can advise hypervascular area directed biopsy combined with standard 12 core biopsy in patients with suspicious prostates. This finding correlates with the study by [17]. The presence of hypervascularity in hypoechoic nodules has a higher positive predictive value of 98%.

So if a patient has a hypoechoic nodule showing hypervascularity, this is most likely to have a focus of tumor. [17]. **Kahraman, et al.** [18] concluded that PDUS should be combined with conventional TRUS-guided biopsy to increase accuracy in the diagnosis of prostate cancer [18].

Conclusion

Power Doppler imaging guided hypervascular area directed biopsy is efficient in the diagnosis of prostate cancer in comparison to hypoechoic nodule directed biopsy.

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