

Genito Urinary Cancer

Hypoechoic lesions on Transrectal Ultrasound and its correlation to Gleason grade in the diagnosis of Clinically Significant Prostate Cancer: A Prospective Study

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Abstract



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Context The importance of hypoechoic lesions on transrectal ultrasound (TRUS) merits re-assessment in the present era of widespread prostate-specific antigen (PSA) testing.

Aims We aimed to investigate the predictive accuracy of hypoechoic lesions on TRUS of prostate in the diagnosis of prostate cancer and to examine the association of hypoechoic lesions with the aggressiveness of prostate cancer.

Settings and Design This prospective study was conducted in a tertiary care center in South India from November 2017 to December 2019.

Methods and Material We included 151 patients undergoing TRUS-guided 12-core prostate biopsy in view of raised serum PSA with or without suspicious digital rectal examination (DRE) findings in the study. Age, DRE findings, serum PSA level, TRUS findings, and histopathology reports were documented. These were compared between patients with and without hypoechoic lesions on TRUS.

Statistical Analysis Used The statistical analysis for this study was performed using SPSS v20.0 software.

Results Among 151 men, prostate cancer was diagnosed in 68 (45.03%) with mean age at presentation 69.81 ± 6.49 years. Fifty-eight cases (38.41%) had hypoechoic lesion on TRUS and the cancer detection rate (68.96%) amongst this group was significantly higher than in those without hypoechoic lesion ($p < 0.0001$). Patients with hypoechoic lesion were more likely to have higher grade cancer. Abnormal DRE findings and hypoechoic lesion on TRUS were independent predictors of a clinically significant cancer ($p < 0.05$).

Conclusion Hypoechoic lesion on TRUS can be considered as an indicator of clinically significant prostate cancer.

Keywords

- ▶ prostate cancer
- ▶ transrectal ultrasonography
- ▶ prostate biopsy
- ▶ hypoechoic lesion

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Introduction

Prostate cancer (PCa) was the second most common cancer affecting the elderly male population in the world and the 5th most common cancer overall as per a 2008 report by Ferlay et al.¹ The updated data from 2018 showed that PCa surpassed lung cancer and was reported to be the most common cancer in men in 12 regions of the world. It is the second most frequent cause of cancer-specific mortality in five regions.² Due to lack of widespread population-based cancer registries and under-reporting, data regarding the true incidence of PCa in India is inadequate.³ As per the Indian Council of Medical Research (ICMR) the incidence rate is nine to ten per 1,00,000 population.⁴ This incidence rate is higher than that reported from other Asian and African countries, however, lower than the incidence rate reported from the West. PCa contributes to a substantial burden on the health care resources in urban India and its incidence is on the rise even in the rural setting.⁵ Urologists are uniquely proficient by training and experience to perform and interpret transrectal ultrasonography (TRUS) of the prostate. TRUS-guided interventions of the prostate hence are an essential part of urological armamentarium. It is a minimally invasive procedure which enhances patient care and management.⁶ The role of TRUS-guided systematic 12-core prostate biopsy in the diagnosis of PCa is proven beyond doubt. Studies have shown that hypoechoic lesions on TRUS study of prostate have an increased likelihood of harboring a cancerous lesion.⁷ When associated with an abnormal digital rectal examination (DRE) finding and an elevated serum prostate-specific antigen (PSA) level, a hypoechoic lesion on TRUS merits a prostatic biopsy. Since the dawn of PSA era in the early 1990s, a majority of cases of PCa are being diagnosed on the basis of raised PSA levels which is classified as T1c disease. This led to an increase in the detection of so-called clinically insignificant cancers. Epstein et al proposed the following criteria to define clinically insignificant cancer: (1) involvement of less than or equal to one-third of cores positive, (2) $\leq 50\%$ involvement of any one core, and (3) PSA density < 0.15 ng/mL².⁸ This was subsequently validated and has proven to be beneficial in making treatment algorithms.⁹ In the present study, we aimed to investigate the predictive accuracy of hypoechoic lesions on TRUS of prostate in the diagnosis of PCa and to examine the association of hypoechoic lesions with the aggressiveness of PCa. Can hypoechoic lesions on TRUS predict the presence of a clinically significant PCa?

Subjects and Methods

This prospective study was conducted from November 2017 to December 2019 by analyzing the data of patients undergoing TRUS-guided prostate biopsy in view of raised serum PSA level (> 4 ng/mL) with or without suspicious DRE findings. Patients with past history of undergoing prostatic biopsy or diagnosed cases of PCa were excluded from the study. A total of 151 men fulfilled the study criteria and comprised the study group. After obtaining approval (KLES Kidney Foundation Institutional Ethics Committee:

KLESKFIEC/2017/013), informed consent was obtained from study subjects. The clinical parameters such as age, DRE findings, prostate volume, serum PSA, prostate-specific antigen density (PSAD), TRUS findings including hypoechoic lesion, and histopathological examination reports with Gleason grade groups were documented.

The following protocol was followed for TRUS-guided prostate biopsy for all the patients by a single investigator. Patients taking antiplatelet or anticoagulant medications were asked to discontinue the drug as per their treating physician's guidance. Sodium phosphate enema was ordered on the morning of the procedure and a single dose of third generation cephalosporin (injection ceftriaxone 1 g) was administered 1 hour prior to the intervention. The patient was placed in left-lateral decubitus position. One ampoule of injection atropine (6 mg) was also administered intravenous (IV) just before starting the procedure. A DRE was performed with adequate lubrication using lignocaine (2%) jelly. TRUS study of the prostate was performed by Hitachi HI VISION Avius scanner (Hitachi Ltd. Tokyo, Japan) (**Fig. 1A**) using 7.5 MHz bi-planar probe. A biopsy guide was attached to the TRUS-probe and 18-gauge \times 18 cm spring-loaded automatic biopsy needle (**Fig. 1B**) (BARD MAX-CORE Disposable Core biopsy instrument, Bard Peripheral Vascular Inc. Tempe, Arizona, United States) was used to obtain a 12-core prostate biopsy (**Fig. 2B**), each of 22 mm core length. The samples were submitted for histopathological examination in separate containers with 10% formalin solution.

Statistical Analysis

Continuous variables were indicated either as mean \pm standard deviation or median (interquartile range). Categorical variables were reported as number of occurrences and frequency. Statistical comparison of continuous variables was performed using Student *t*-test and Pearson Chi-square test/Fisher exact test was used for comparison of means of



Fig. 1 (a) Hitachi HI VISION Avius ultrasound scanner (Hitachi Ltd. Tokyo, Japan). (b) 7.5 MHz transrectal probe CC531T/CC531L, with a biopsy guide (yellowish white) and an 18-gauge \times 18 cm BARD MAX-CORE disposable core biopsy needle (Bard Peripheral Vascular Inc. Tempe, Arizona, United States).

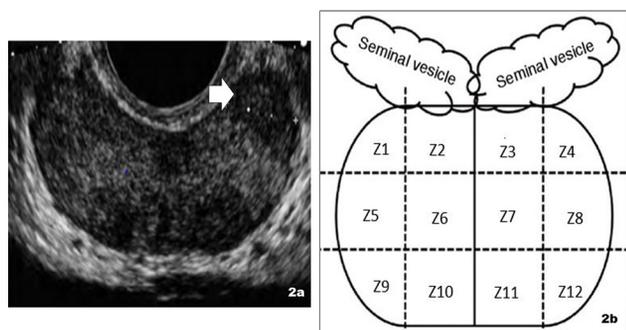


Fig. 2 (a) Transrectal ultrasound image showing a hypoechoic lesion (white arrow) in the peripheral zone (left lobe) of the prostate. (b) Schematic diagram showing template of 12-core biopsy labeled as zones (Z1 to Z12).

categorical variables. The positive and negative predictive values were used to examine the predictive accuracy of TRUS lesions in predicting PCa. The Gleason grades were compared between two groups of CaP patients classified according to presence or absence of hypoechoic lesion on TRUS study. Age, DRE findings, prostate volume (in mL), serum PSA, PSAD, and hypoechoic lesion on TRUS were the factors evaluated for risk of harboring clinically significant PCa. Logistic regression analysis of the factors predicting presence of clinically significant PCa was also performed. The outcomes were presented as the odds ratio and 95% confidence interval based on a two-sided test. All the statistical analyses were performed using SPSS v20.0 software (IBM Corp. Chicago, United States). A p -value <0.05 was considered as statistically significant.

Results

Among the 151 men included in the study, 68 (45.03%) were diagnosed with PCa. The mean age at presentation was 69.81 ± 6.49 years with mean and median serum PSA levels were 56.85 ± 217.23 ng/mL and 9.62 ng/mL,

respectively. Hypoechoic lesion on TRUS imaging (**Fig. 2A**) was noted in 58 patients (38.41%) and the cancer detection rate amongst them was 68.96%. This was significantly higher than the cancer detection rate in normal TRUS group (30.10%, $p < 0.0001$) (**Table 1**). A comparative analysis was performed in 68 patients diagnosed with PCa according to the Gleason Grade Groups (**Table 2**). More number of patients (i.e., 65.78%) had hypoechoic lesion on TRUS among the patient with a higher grade cancer (Grade Group \geq III, **Fig. 3**) as compared with those with lower Gleason Grade (36.6%, $p < 0.05$). Patients who were diagnosed with higher grade disease also had significantly older age at presentation, abnormal DRE findings, significantly elevated PSA levels, and PSAD ($p < 0.05$).

The patients were grouped according to PSA intervals based on presence or absence of PCa on histopathology examination reports. The overall sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of hypoechoic lesion for detecting PCa were 70.59, 87.95, 82.76, 78.49, and 80.13%, respectively. The predictive efficacy also varied amongst different PSA intervals, showing a trend toward increasing accuracy in the higher PSA interval (>20 ng/mL) (**Table 3**). Similarly, the relationship between hypoechoic lesion and Gleason Grade group in different PSA intervals was presented (**Table 4**). The existence of hypoechoic lesion on TRUS was significantly associated with higher grade cancer in patient with PSA interval of >20 ng/mL ($p < 0.05$). Simple logistic regression analysis of the factors predicting presence of clinically significant PCa in PCa patients revealed that age, abnormal DRE findings, prostate volume, serum PSA, PSAD, and hypoechoic lesion on TRUS were significant factors ($p < 0.05$), whereas, abnormal DRE findings (nodule on DRE or hard consistency of prostate) and hypoechoic lesion on TRUS were identified as significant predictors of clinically significant cancer on multiple logistic regression analysis ($p < 0.05$) (**Table 5**).

Table 1 Clinical characteristics of the study group and differences between the groups based on transrectal ultrasound findings

Variable	All cases (n = 151)	TRUS without visible lesion (n = 93)	Hypoechoic lesion on TRUS (n = 58)	p-Value
Age (years)	69.81 \pm 6.49	68.09 \pm 7.93	71.12 \pm 7.88	0.0235
Abnormal DRE	35 (23.17)	12 (12.90)	23 (39.65)	0.0002
Prostate volume (cc)	57.09 \pm 19.13	56.72 \pm 15.12	57.26 \pm 20.61	0.85
Serum PSA	56.85 \pm 217.23	22.05 \pm 68.38	134.79 \pm 365.5	0.004
Median serum PSA	9.62 (6.1–19.1)	7.21 (5.1–13.3)	18.94 (12.5–64.8)	<0.0001
PSA density	0.17 (0.09–0.35)	0.12 (0.07–0.24)	0.32 (0.17–1.11)	<0.0001
BPH	83 (54%)	65 (69.9%)	18 (31.04%)	<0.0001
Ca prostate	68 (46.03%)	28 (30.10%)	40(68.96%)	<0.0001
Gleason grade				
Group I/II	30	20	10	0.0039
Group \geq III	38	12	26	

Abbreviations: DRE, digital rectal examination; BPH, benign prostatic hyperplasia; PSA, prostate-specific antigen; TRUS, transrectal ultrasound. Note: Values are presented as mean \pm SD, number (%), or median (interquartile range).

Table 2 Clinical characteristics of patients with prostate cancer (n = 68) according to Gleason grade groups

Variable	Gleason grade Group I/II (n = 30)	Gleason grade Group ≥III (n = 38)	p-Value
Age (years)	65.52 ± 6.94	70.48 ± 4.88	0.001
Abnormal DRE (%)	10 (33.33%)	24 (63.15%)	0.015
Prostate volume (cc)	54.47 ± 7.87	59.55 ± 6.97	0.006
Serum PSA (ng/mL)	10.14 (4.80–20.46)	40.88 (12.48–108.97)	0.001
PSA Density	0.22 (0.14–0.47)	0.96 (0.38–2.84)	0.001
Hypoechoic lesion on TRUS	11 (36.66)	25 (65.78)	0.017

Abbreviations: DRE, digital rectal examination; PSA, prostate-specific antigen; TRUS, transrectal ultrasound.
Note: Values are presented as mean ± SD, number (%), or median (interquartile range).

Table 3 Predictive efficacy of hypoechoic lesion for prostate cancer in different PSA intervals

PSA interval		CaP (n = 68)	BPH (n = 83)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)	p-Value
4–10 ng/mL	Hypoechoic lesion	10	5	66.67	76.19	66.67	76.19	72.22	0.01
	No visible lesion	5	16						
>10–20 ng/mL	Hypoechoic lesion	17	3	62.96	86.36	85.00	65.52	73.47	0.0004
	No visible lesion	10	19						
>20 ng/mL	Hypoechoic lesion	21	2	80.77	95.00	91.30	88.37	89.39	<0.0001
	No visible lesion	5	38						

Abbreviations: BPH, benign prostatic hyperplasia; CaP, cancer prostate; NPV, negative predictive value; PPV, positive predictive value; PSA, prostate-specific antigen.

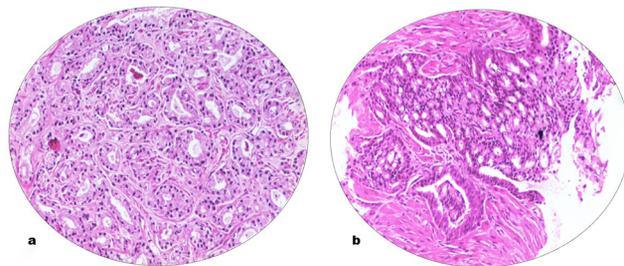


Fig. 3 (a) H & E staining 40x, showing Gleason pattern 3. Well formed, individual glands of varying sizes. (b) H&E staining 40x, showing Gleason pattern 4. Cribriform pattern, neoplastic cells running across the core.

Discussion

PCa incidence in the Indian subcontinent is still lower as compared with the western countries.³ However, the incidence is on the rise perhaps due to stressful lifestyle, increased public awareness, and the misuse of serum PSA testing during general health check-up of middle aged and elderly men. The PSA threshold for subjecting a patient to prostatic biopsy is a topic of widespread dispute. At present, it is clear that different populations need to have a different cut-off levels of PSA. According to Prostate Cancer Screening trial (PLCO study) in the United States, a PSA level ≥ 4 ng/mL was used as

a threshold for biopsy,¹⁰ whereas European Prostate Cancer Screening Trial (ERSPC) had set a PSA level of ≥ 3.0 ng/mL as a trigger for biopsy.¹¹ These recommendations led to an unnecessarily high number of prostatic biopsies and an increase in the diagnosis of clinically insignificant PCa. In a study from India, Dubey questioned the routine use of serum PSA testing and advocated against it owing to a low incidence of PCa in India.¹² The author appropriately states that if a patient requests PSA testing, he should be informed about its benefits and harms and shared decision should be taken in the patients' best interest. We would like to differ with this report as we have noticed a rise in the incidence of PCa in our own clinical experience.⁵ This can possibly be attributed to the improvement in health care availability and better imaging modalities.

Once the decision to perform a biopsy is made, TRUS-guided biopsy is given consideration. It allows visualization of the prostate and suspicious lesions which can then be targeted for biopsy under real-time guidance.¹³ Onur et al reported the contemporary impact of TRUS in the diagnosis of PCa; they found 25.5% cancer detection rate in targeted biopsy of hypoechoic lesions.¹⁴ Similarly, Toi et al described that biopsy obtained from a lesion on TRUS was two times more likely to reveal malignancy when compared with normal TRUS imaging biopsy sample.¹⁵ Several studies in literature support the role of biopsy performed from a visible

Table 4 Association between hypoechoic lesion and Gleason grade groups in different PSA intervals

PSA interval	TRUS Finding	Grade I/II (n = 30)	Grade ≥III (n = 38)	p-Value
4–10 ng/mL	Hypoechoic lesion	3	2	>0.05
	No visible lesion	4	1	
>10–20 ng/mL	Hypoechoic lesion	4	5	>0.05
	No visible lesion	6	4	
>20 ng/mL	Hypoechoic lesion	4	18	0.029
	No visible lesion	9	8	

Table 5 Logistic regression analysis of the factors predicting presence of clinically significant prostate cancer (Gleason Grade Group ≥III) in 68 patients

Variables	Simple logistics regression			Multiple logistics regression		
	OR	95% CI	p-Value	OR	95% CI	p-Value
Age	1.47	1.45–1.49	0.001			
Abnormal DRE	5.88	3.87–8.94	0.001	2.98	1.69–4.97	0.001
Prostate volume	0.98	0.97–0.99	0.004			
Serum PSA	1.05	1.04–1.06	<0.001			
PSA density	6.48	4.57–9.87	0.001			
Hypoechoic lesion on TRUS	4.14	3.18–6.12	<0.001	1.87	1.34–2.67	0.028

Abbreviations: CI, confidence interval; DRE, digital rectal examination; OR, odds ratio; PSA, prostate-specific antigen; TRUS, transrectal ultrasound.

lesion on TRUS to increase the yield and reduce the rate of false negative biopsies. In our study, 58 patients (38.41%) had presence of hypoechoic lesion on TRUS and the cancer detection rate amongst them was 68.96%. This was significantly higher than the rate in normal TRUS imaging group (30.10%, $p < 0.0001$). This is in consensus with the cancer detection rate reported in literature (62.9–67.2%).

We must highlight that not all hypoechoic lesions on TRUS imaging suggest the presence of malignancy, contrariwise, not all cancerous lesions appear hypoechoic. It is known that approximately 60 to 70% of PCa lesions appear hypoechoic on TRUS; the rest may be isoechoic (30–40%)¹⁶ or rarely hyperechoic (<2%).^{17,18} Presence of hypoechoic lesions in the prostate can also be noted in case of prostatic lymphoma, granulomatous prostatitis, and rarely prostatic infarction.¹⁹ Some reports suggest that a limited sextant biopsy (six cores) could also be sufficient provided that the hypoechoic areas if present, are adequately sampled.²⁰ However, there is now a clear consensus that a sextant biopsy is insufficient; a 10- or 12-core biopsy should be routinely employed including the targeting of suspicious lesions on TRUS.²¹ We performed a systematic 12-core prostate biopsy including a core from suspicious hypoechoic lesion.

Patients who had hypoechoic lesions in our series were also found to have an aggressive disease. There were 38 patients with high-grade tumor (Gleason grade group ≥III) of which 25 (65.78%) cases had hypoechoic lesions. Similar findings were reported by Noh et al, as 64.2% of their patients in the higher Gleason group (Gleason score >7) were found to have hypoechoic lesion on TRUS.²² To evaluate the relationship between cancer and hypoechoic lesion, we also subdivided the patients as per their PSA levels. This revealed

that hypoechoic lesions were associated with PCa among all the PSA intervals with the highest predictive efficacy in cases with PSA levels >20 ng/mL. Patients with highest PSA levels (>20 ng/mL) were also found have significant association with occurrence of high-grade tumor ($p < 0.05$). Similar findings were reported by Yang et al.²³ Numerous investigators have presented that abnormal DRE findings were associated with aggressive cancer^{24–26}; our study also confirmed these findings. Nodules on DRE or hard consistency of prostate was independent variable associated with high-grade cancer ($p < 0.05$).

There have been arguments about the benefits and limitations of TRUS even though it is currently being widely utilized for the diagnosis of PCa. TRUS carries poor accuracy in the detection of small lesions, is highly operator dependent, and cannot be applied for local staging, detection of extracapsular spread, and seminal vesicle infiltration.²⁷ Multiparametric MRI hence acts as an important tool which is now being increasingly utilized in the diagnosis of PCa. It has a high sensitivity and specificity for cancer staging, 91 and 96%, respectively.⁶ The introduction of MRI-guided biopsy has altered the paradigm regarding prostate biopsies. Even though it has similar overall PCa detection rates compared with TRUS-guided biopsies, it has higher detection rate of clinically significant PCa.²⁸ In spite of this, TRUS continues to play a key role in PCa diagnosis. It provides dynamic imaging, has virtually no contraindications, and is less time consuming. It also imparts less financial burden on patients which makes it an attractive option suitable for our country.

The results of the present study are promising; however, they are not without limitations. The primary limitation to generalization of our results is a single institutional study

with a relatively small study cohort. It can be addressed in future research. Inclusion of factors like number of biopsy cores positive for malignancy and the percentage of core involved can help us identify clinically significant PCa in a more objective manner. This can act as a valuable tool in making treatment-related decisions.

Conclusion

Diagnosis of PCa has experienced a stage migration due to extensive use of serum PSA testing. It raises the concern about the overdiagnosis of clinically insignificant cancers. Patients with prostate cancer harboring a hypoechoic lesion on TRUS had more aggressive disease as compared with those without any abnormal findings. Hypoechoic lesion can improve the predictive efficacy of diagnosis of prostate cancer based on different PSA intervals. We conclude that hypoechoic lesion on TRUS can be considered as an indicator of clinically significant prostate cancer in the background of suspicious DRE findings and elevated serum PSA.

Conflict of Interest

None declared.

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