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Trans-rectal ultrasound guided twelve core prostate biopsy in evaluating prostate cancer with histopathological evaluation, total prostate specific antigen and percentage of free-to-total prostate specific antigen correlation

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Abstract:
Background*: Trans-rectal ultrasound guided twelve core prostate biopsy in evaluating prostate cancer with histopathological evaluation, total prostate specific antigen and percentage of free-to-total prostate specific antigen correlation.*
Materials and Methods*: This study was done on 28 patients who were referred to department of Radio-Diagnosis at Yenepoya Medical College Hospital, Mangalore. TRUS guided 12 core prostate biopsy was performed and samples were sent to department of pathology for histopathological evaluation and results were documented.*
Results: *Prostate diseases were more common in the older age group and the incidence increases with age. 43% of malignancy were detected in patients with grade I prostatic enlargement. Detection of malignancy in this group was significantly increased by 12 core biopsy.*
On HPE 14 (50%) patients were found to be benign and 14 (50%) malignant. 83% in patients with total PSA levels of >51 ng/ml and cancer detection rate was 22%, 43% and 75% for total PSA levels ranging between 4-10 ng/ml, 10.1-20 ng/ml, and 20.1-30 ng/ml respectively.
Conclusion: *TRUS guided twelve core prostate biopsy is a safe and effective procedure which can be performed under local anaesthesia with good patient compliance and almost nil complications in diagnosing prostate cancer in patients with elevated total PSA levels.*
Significance of percentage of free PSA to total PSA was not demonstrated in our study. This may be due to lesser number of study participants or due to confounding factors such as significantly elevated total PSA in study participants.

Key Word*: TRUS, Prostate Biopsy, Prostate Carcinoma, Prostate Specific Antigen*

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I. Introduction

Prostate cancer is a common cause of cancer related death among men. Although it is a common disease, it is slow to manifest clinical signs. Unfortunately, anatomic location of prostate does not lend itself to straight forward examination. Digital rectal examination has been the principal method of examination of prostate. However, this technique has its own limitations. The advent and refinement of ultrasound technology have provided a new method.

Trans-rectal ultrasound with prostate biopsy, which is correlated with histopathological examination in conjunction with development of serum assays for Prostate specific antigen PSA, has resulted in an impressive change in manner of diagnosis of prostate cancer.

Trans-rectal ultrasonography (TRUS) is the most commonly used modality for imaging the prostate gland. It enables accurate determination of prostate size. When a cancer is visualized by ultrasonography, it is usually hypoechoic relative to normal tissue. However the majority of hypoechoic foci detected by TRUS are not malignant; therefore, both its sensitivity and specificity are low. TRUS is mainly used to guide prostate biopsies.

At present TRUS-guided biopsy is the most reliable method for accurate sampling of prostatic tissue in men who are considered at high risk for prostatic cancer. It is utilized in patients with clinical suspicion of having prostate cancer on the the basis of digital rectal examination (DRE), serum assays of prostate specific antigen (PSA) and free-to-total prostate specific antigen (PSA) ratio.

Trans-rectal ultrasound (TRUS) was initially described as a technique to evaluate rectal pathology[1]. In 1963, Takahashi and Ouchi[2] were the first to describe the use of TRUS to evaluate the prostate. However, medical ultrasound was rather primitive at this time, so the images created with this array were of such poor quality that they carried little medical utility. The first clinically applicable images of the prostate obtained with TRUS were described in 1967 by Watanabe[3]. They used a 3.5 MHz transducer, which at that time was considered to be state of the art, to obtain images that were clinically meaningful. As ultrasound technology has become more refined, the use of TRUS in the evaluation of prostatic disease has increased. By the mid1980s[1], the 7 MHz ultrasound probe, which more clearly delineated the architecture of the prostate, had become a standard diagnostic instrument.

Astraldi[4] performed the first trans-rectal biopsy in 1937. In the mid 1980s[1], a trans-perineal ultrasound array was fitted with biopsy apparatus to allow direct correlation of the sonographic appearance of focal prostatic lesions with the histology of these lesions. Several years later, a spring-loaded core biopsy device was developed that operated via a TRUS probe.

In 1987[1], the first literature appeared describing the use of TRUS with trans-rectal biopsy. Since then, as ultrasound technology has become more refined, this technique has been described as a superior method of performing a core biopsy of the prostate.

Since the initial reports of TRUS of the prostate by Wild and Reid[5], substantial technologic advances have improved the diagnostic capabilities of this modality. The current state of the art TRUS probe is a 5-8 MHz hand-held, high-resolution probe with multi-axial planar imaging capabilities, which has the capacity for both transverse and sagittal imaging of the prostate in real time. This probe can be fitted with an adapter that accepts the needle of a spring-loaded biopsy gun, thus allowing multiple cores of tissue to be easily obtained. The visualization provided by the new higher resolution transducers, coupled with the ability to direct the biopsy needle into various regions of interest and to provide uniform spatial separation of the areas to be sampled, has helped to make TRUS-guided prostate biopsy a standard technique in the diagnosis of prostate cancer.

Hodge et al[6] published the landmark paper demonstrating the efficacy of systemic sampling of prostate during TRUS-guided biopsy. They were the first to report that systemic sampling of the prostate the prostate guided by TRUS improved the detection rate of prostate cancer over merely sampling hypo-echoic or other lesions. By taking sextant (six-core) biopsies from the mid-lobe (parasagittal) of each side of prostate at the apex, middle and base, the cancer detection rate was superior to lesion directed biopsies.

However, with wider experience, it was found that even the sextant technique was inadequate, this was because it under-samples the peripheral zone. Keetch et al.[7] showed a 20% positive rate on re-biopsy (missed cancers on initial biopsy) and all subsequent studies have confirmed this high false-negative rate of the classical sextant method. With a better understanding of the origin of prostate cancers within the gland, a modified protocol was introduced to improve the detection rate in which the biopsy trajectories were angled more antero-laterally.

With time, this 'modified protocol' was also shown to miss some tumors. Chen et al.[8] showed that midline and apico-lateral peripheral zone tumors were being missed, this lead to an increase in the number of cores biopsied, and also to the inclusion of the transitional zone into the area biopsied.

In a systemic review done by Eichler *et al*[9], which included 87 studies with a total of 20,698 patients, it was concluded that schemes with 12 cores that took additional laterally directed cores detected 31% more cancers (95% CI 25 to 37) than the sextant scheme and schemes with 18 to 24 cores did not detect significantly more cancers. Adverse events for schemes up to 12 cores were similar to those for the sextant pattern.

Elevated levels of total PSA is not very specific to prostate cancer. A lower free/total prostate-specific antigen (PSA) ratio (%fPSA) is a more reliable predictor of prostate cancer and helps avoid unnecessary biopsy in subjects with intermediate PSA levels. Djavan *et al.*[10] demonstrated the

detection rate of prostate cancer was 10% on repeat biopsy in subjects with a negative initial biopsy and showed that %fPSA was a significantly better predictor of repeat biopsy results than total PSA, PSA density, or transition zone PSA density.

The objective of our study was to evaluate the role of trans-rectal ultrasound (TRUS) guided twelve core prostate biopsy with histopathological evaluation (HPE) in the detection of prostate cancer on the basis of elevated prostate-specific antigen levels (PSA) and decreased percentage of free-to-total prostate specific antigen (PSA) correlation.

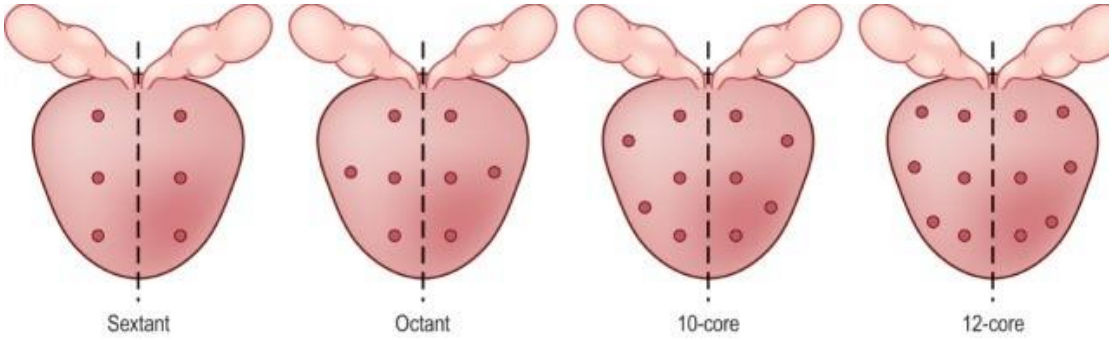


Figure 1: The various biopsy schemes used, in the coronal plane. The first is the classic sextant pattern, which misses about 25% of cancers. The next three schemes illustrate the octant, 10-core and 12-core regimes, respectively. In current practice the 10- or 12-core regime is favoured.[11]

II. Material And Methods

This was a prospective study carried out on 28 patients over a period of 2 years. The study synopsis was presented to the ethical committee of Yenepoya (deemed to be university) and ethical clearance was obtained; after it was present to the scientific review board and approved by them.

Study Design: Prospective study

Study Location: This was a tertiary care teaching hospital based study done in Department of radio diagnosis, at Yenepoya medical college hospital, Mangalore, Karnataka .

Study Duration: November 2016 to November 2018.

Sample size: 28 patients.

Sample size calculation:

Total sample size is calculated using G power software

'n' = 28

With a level of significance 'α' = 5%

Power 'β' = 80%

Effect size = 0.55

Subjects & selection method: Patient selection was done from the patients who were referred with urinary symptoms suggestive of prostatic disease were diagnosed using voluson E8 ultrasound machine. This study includes patients with elevated PSA levels (>4 ng/ml), decreased percentage of free-to-total prostate specific antigen (PSA) <25% and prostatic lesions noted on TRUS. Informed consent was obtained from all participants, and a full explanation about the procedure, risks involved & post procedure complications were explained to the patients.

Inclusion criteria:

1. Prostate specific antigen (PSA) > 4 ng/ml
2. Percentage of free-to-total prostate specific antigen (%fPSA) <25%
3. Nodule visible on TRUS

Exclusion criteria:

1. Known case of Prostatitis.
2. Un-correctable bleeding diathesis (abnormal coagulation indices).
3. Uncooperative patient.

Procedure methodology

All patients were subjected to DRE, serum PSA, percentage of free-to-total PSA, coagulation profile, trans-abdominal ultrasound examination and TRUS, as well as TRUS guided biopsy.

Before the procedure, the patients were given antibiotics to protect them against infection, they also underwent rectal enema to empty the rectum before the procedure to obtain clear images, and intra-rectal instillation of local anaesthetic gel (lidocaine) was used to alleviate pain and discomfort during the procedure.

A trans-rectal ultrasound probe (6-12 MHz range) with a combination of end-viewing and side-viewing transducer attached to voluson E8 ultrasound machine was used. Ultrasound gel was applied over a latex condom applied onto the probe. All patients were examined in the left lateral decubitus position because it is well tolerated.

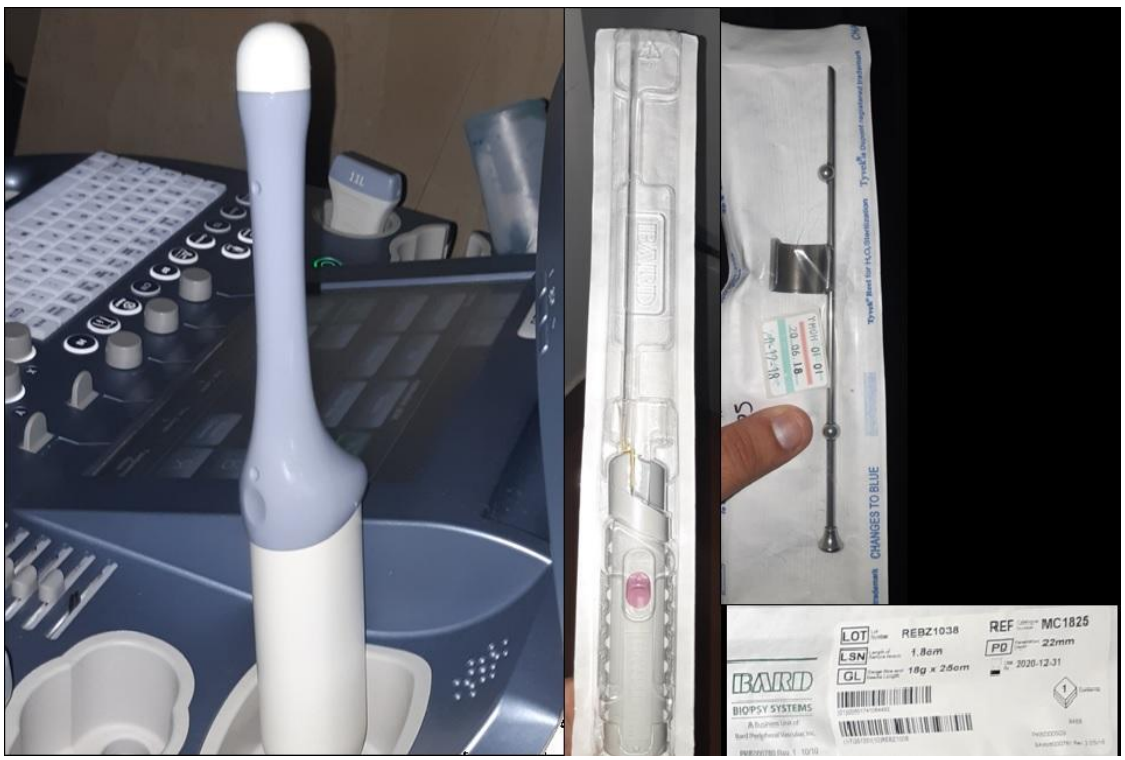
The prostate was imaged in both axial and sagittal planes with assessment of volume, echogenicity, surface, calcification, and the presence of nodules. Each nodule was assessed for size, location in the gland, morphology, echogenicity, margin, and extent. Colour Doppler ultrasonography was then performed to assess colour mapping of the nodules and the surrounding prostate tissue. Sampling of the prostate was performed in the sagittal plane. Biopsies were obtained using: automatic biopsy gun needle (18G×25cm). The most commonly used protocol was the "targeted plus systematic" twelve-core biopsy protocol.

After biopsy samples were obtained, they were persevered in formaldehyde solution and were sent to the pathology centre for cytological analysis. The patients rectum was then packed with lidocaine gel coated gauze packs to achieve haemostasis.

After the procedure the patient was assessed for any complications & appropriate action was taken if necessary. Any acute emergency associated post procedure was recognised & was responded with immediate management. Post procedure the patient was transferred to the urology / surgery ward for further observation and management.

Statistical analysis

The data was entered and analysed in SPSS statistics. Frequency and percentages of the variables were computed. The chi-square test was used to compare the association of serum PSA levels and percentage of free PSA to total PSA. The results were considered statistically significant if the p-value was <0.05



III. Image gallery

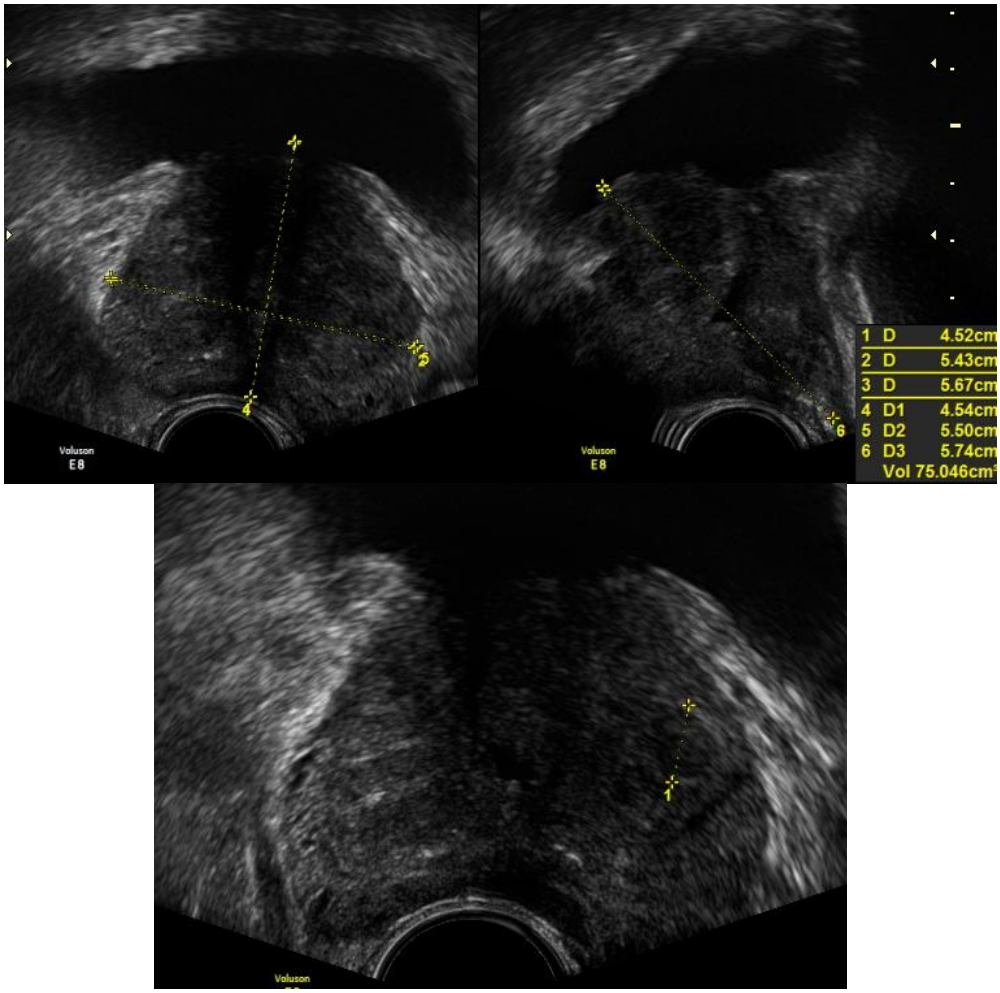


Image 1: TRUS image of 65 years old showed enlarged prostate with focal hypoechoic lesion in the left lobe, biopsy was suggestive of adenocarcinoma.

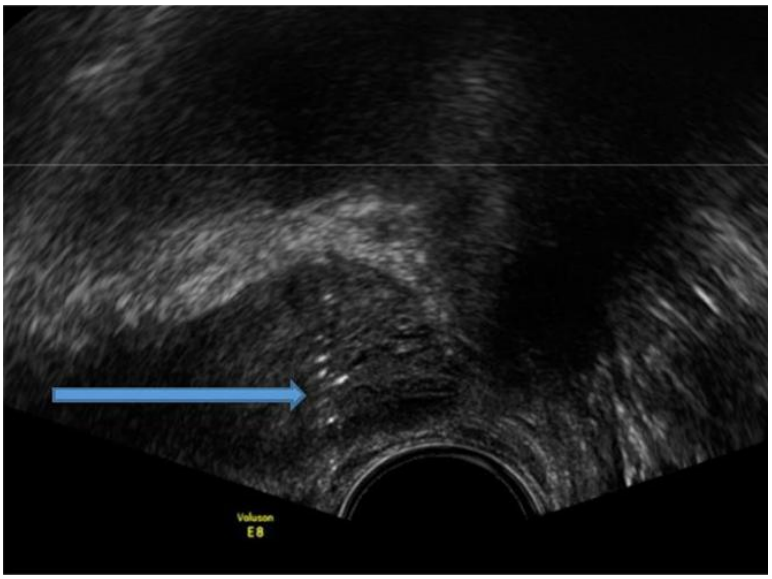


Image 2: Post TRUS biopsy image of 48 year old patient shows the path of the biopsy needle.

IV. Result

A. Demographic Data

Out of 28 patients studied the mean age of the group was 66.8 years (48-83 years). Maximum number of patients was in the age group of 61-70 years (14) and least was in 41-50 years (1)

B. Clinical Data and Diagnosis

Clinical data revealed that prevalence of symptoms of voiding difficulties and dysuria was almost similar with a slight predominance of voiding difficulty at 54%; and clinically suspected to have carcinoma prostate.

C. Serum PSA levels and Percentage of Free PSA to Total PSA

In our study the PSA levels ranged from 5.28 to >100 ng/ml. Maximum number of patients (9) had a PSA range of 4-10 ng/ml and 6 patients had a PSA of >50 ng/ml. We have taken 25% as a cut-off for significant level of percentage %fPSA.

We had 2 patients who had grossly elevated total PSA and the percentage free PSA was not calculable. In rest of our 26 patients, % free PSA was less than 25%. However, within the 26 patients studied only 12 patients had a positive (malignant) histopathological report; which is 46% of all the patients.

D. Histopathological Diagnosis

On histopathological correlation 14 patients were found to have malignant features and 14 were found to have benign features. 11 of the patients with malignancy had adenocarcinoma and 3 had PIN. 6 patients had benign prostatic hyperplasia and 3 patients had features of prostatitis.

E. Complications Post TRUS Guided Biopsy

Out of 28 patients who had TRUS guided 12 core prostate biopsy under local anaesthetic, none of the patients had post procedure complications like rectal bleeding, need for anaesthesia or prolongation of hospitalization; similar to results showed by Tobiume et al[12].

STATISTICAL ANALYSIS

The data was entered and analysed in SPSS statistics. Frequency and percentages of the variables were computed. The chi-square test was used to compare the association of serum PSA levels and percentage of free PSA to total PSA. The results were considered statistically significant if the p-value was <0.05.

1. CORRELATION BETWEEN TOTAL PSA AND HISTOPATHOLOGY

A study done by Lojanapiwat,et al[13] demonstrated specificity of PSA levels of 4-10,10.1-20,21-50,50-100 and >100 ng/ml in the diagnosis of prostate cancer as 9.3, 55.5, 87.5, 98.2 and 99.7 respectively. And another study by Ahmed Alghazo et al [14] showed PSA levels between 4-10 ng/ml, between 10-20 ng/ml and above 20ng/ml, the cancer detection rate by TRUS guided biopsy was 20.6%, 32.4 % and 47 % respectively. These show a statistically significant correlation between total PSA levels and detection of malignancy.

Our data also showed a strong correlation of total PSA level with detection of malignancy having a very high statistical significance with p value of 0.002.

Serum PSA levels			Histopathology		Total
			Benign	Malignant	
	4-10 ng/ml	Count	7	2	9
		%	78%	22%	100.0%
	10.1-20 ng/ml	Count	4	3	7
		%	57%	43%	100.0%
	20.1-30 ng/ml	Count	1	3	4
		%	25%	75%	100.0%
	30.1-40 ng/ml	Count	0	1	1
		%	0%	100%	100.0%
	40.1-50 ng/ml	Count	1	0	1
		%	100%	0%	100.0%
	>50 ng/ml	Count	1	5	6
		%	17%	83%	100.0%
Total		Count	14	14	28
		%	50%	50%	100.0%

X^2 test , p valve = 0.002

Table 1: Correlation between PSA levels and HPE

2. CORRELATION BETWEEN PERCENTAGE OF FREE-PSA TO TOTAL-PSA AND HISTOPATHOLOGY

In the 28 patients who were send for TRUS guided biopsy after having clinically suspicion of prostate carcinoma, all 28 patients had %FPSA <25% (which was considered significant).
Out of the 28 patients, 50% of them had malignancy detected on HPE.

In our study there was no significant statistical relation between %FPSA and detection of malignancy on HPE.

		Levene's Test for Equality of Variances		t-test for Equality of Means						
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
									Lower	Upper
FPSA (percentage)	Equal variances assumed	2.320	.141	-.167	24	.868	-.432	2.581	-5.758	4.894
	Equal variances not assumed			-.164	20.371	.871	-.432	2.636	-5.925	5.061

Table 2: Independent Samples Test

LIMITATIONS

- ❖ It's a short term study hence long term changes in the prostate are not studied in the younger population.
- ❖ The size of the study population is small.
- ❖ Long term follow up of those patients with elevated serum PSA and normal HPE was not done.

V. Conclusion

TRUS guided twelve core prostate biopsy is a safe and effective procedure in diagnosing prostate cancer under local anaesthesia with no significant post procedural complications and has high diagnostic rates, even for patients with mild prostatomegaly and moderate elevation of total PSA levels.

It has been shown that twelve core prostate biopsy is the ideal amount of core for TRUS guided prostate biopsy in terms of detection rate to biopsy related complications. In our study also the detection rate for malignancy was 50% with nil biopsy related complications.

We also recommend considering MRI evaluation of the prostate in patients clinically suspected of having prostate cancer and targeting lesions detected on MRI via TRUS guided biopsy.

Percentage of free PSA to total PSA also needs further detailed assessment with larger number of participants and clear cut-off for %fPSA levels to establish a relationship between % free PSA and malignancy of the prostate gland.

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