THE ACCURACY OF TRU-CUT NEEDLE BIOPSY IN DETECTION OF PROSTATE CANCER IN RELATION TO PROSTATIC SCREENING TESTS (PSA, DRE, AND TRUS)

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ABSTRACT

Background

Prostate carcer is the second most common cancer in men. The causes of the disease are essentially unknown, although hormones are involved, diet may exert an indirect influence, some genes potentially involved in hereditary prostate cancer (HPC) have been identified. Suspicion of prostate cancer may derive from elevated prostate-specific antigen (PSA) and/or a suspicious Digital Rectal Examination (DRE) and suspicious Transrectal Ultrasound TRUS. However, for a definite diagnosis prostate biopsy is indicated.

Objective

To determine the efficacy of various diagnostic tests (PSA, DRE, and TRUS) for detection of prostate cancer in comparison with prostate biopsy.

Material and Methods

Eighty six patients underwent PSA measurement, DRE, TRUS and prostate biopsy in the urological department of the Sulaimani Surgical Teaching Hospital between April, 2005 and February, 2006.

Results

Twenty four out of 86 patients who underwent biopsy were found to have a prostate cancer. Majority of patients (40) were between (70-79 years).

Conclusion

Adenocarcinoma of prostate is the commonest histological type. The combined use of different tests (PSA, DRE, and TRUS) is better in early diagnosis of prostate cancer. The definitive diagnosis is achieved by prostate biopsy.

Keywords: *True-cut biopsy, Prostatic carcinoma, Digital rectal examination, Transrectal ultra sound, Prstatic specific antigen, Positive predictive value.*

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INTRODUCTION

Prostate cancer is the most common solid malignant tumor in men and second to lung cancer as the leading cause of death in USA [1]. Almost all prostate cancer arise from the secretory glandular cell in the prostate [2]. Prostate cancer is diagnosed in very few people aged younger than 50 years [3].

Digital rectal examination (DRE) is the primary method of examination of the prostate it allows the examiner to appreciate the glands morphology, mobility, including any irregular, nodular, firm, hard or indurated area that might be suspicious for malignancy [4, 5, 6].

Prostatic specific antigen (PSA), is exclusively secreted by prostate epithelial cell, has a number of application in the management of men with prostatic cancer, it is widely recognized that elevated PSA correlates with presence of carcinoma [7, 8], However serum PSA is also increased in most patient with BPH, after DRE, prostatitis, prostatic biopsy, after TURP. So the measurement lacks specificity as a test for cancer [8, 9].

Approximately 50% of organ confined tumor and 30% with extra prostatic extension are associated with normal serum PSA level [10]. To improve the ability of PSA testing to detect early prostatic cancer age-adjusted reference interval has been used [11].

Clinical trans rectal ultra sound (TRUS) was pioneered in the early 1980 which is known to be operator dependant diagnostic procedure which requires expertise to obtain good sensitivity and specifity [12] for cancer diagnosis TRUS on its own has a positive predictive value of 6% if PSA and DRE are normal [13].

Described appearance of prostatic cancer ranges from hypoechoic to hyperechoic lesions, but the vast majority are isoechoic or distinguished only by non-specific echo irregularity. A further factor that limits the diagnostic ability of TRUS is the inevitable back ground benign prostatic hyperplasia in the target population. The mixed echo-pattern of BPH may mask any concurrent cancer [14].

Even Increased vascularity within a region of the gland, or the presence of a focal bulge or irregularity of the capsule are not sufficiently reliable. The sensitivity of TRUS in identifying tumor less than 5 mm is only approximately 60% [15].

Combination of DRE, serum PSA and TRUS are useful for the detection of organ confined prostate cancer and prostatic biopsy should be performed in patients with abnormal finding for both DRE and PSA[16].

The detection rate in a screened population depends on the three major diagnostic tools; PSA, DRE and TRUS. The PPV(positive predictive value) for biopsy could ranges from about 20-80%. It depends on the number of positive findings and operator experience (DRE, PSA and TRUS); in which if one of these tests was abnormal PPV will range from 5-25%, while the PPV will reach 15-60% for two out of three, 55-70% for three of three i.e. when all the tests were positive [17].

Prostatic biopsy is the mainstay of definitive diagnosis of prostate cancer, is used to confirm the diagnosis of cancer as well as to identify tumour aggressiveness (grading) [14]. Biopsy is performed either transrectaly or transperinealy. Finger guidance or trans-rectal ultrasound guided prostatic biopsy is usually done using 18 gauge needle loaded in a spring action automated device which was introduced since late 1980 [18]. As the disease is often multi-centric, areas throughout the whole gland are sampled. In other words ultrasound imaging is used to guide the biopsy needle into different areas of the gland, rather than to identify lesions [14].

Sextant multiple random biopsy was quickly accepted by urologists and become gold standard for the procedure [19a]. Extended biopsy protocols(8, 10, 12, >12 and saturation biopsy protocols) are increasingly being used to improve diagnostic accuracy especially in those patients who require repeated biopsy. This trend has been facilitated by the ongoing improvement in safety and acceptability of the procedure, particularly with the use of antibiotic prophylaxis and local anaesthesia [14, 19a].

Morbidity of trans-rectal prostate biopsy is low and increasing number of cores correlated with minor and statistically not significant increase in the rates of the side effects.

The main complications of prostate biopsy include pain, infection, haematuria, rectal bleeding and haemospermia[19b].

The aim of our study is to determine the results of True Cut needle biopsies in Prostate cancer detection in patients which are clinically or sonographically suspicious and/or with normal or high PSA. Moreover, we aim to determine the efficacy of various combinations of diagnostic tests for detection of prostate cancer (PSA, DRE, TRUS and prostate biopsy). Finally, current study

aims to determine the most affected age group in our locality determine the most frequent histological type of prostate cancer.

MATERIAL AND METHODS

Between April 2005 and February 2006, 86 patients admitted to the urological department of the Sulaimaniyah Surgical Teaching Hospital who were suspected to have prostate cancer.

Full history and physical examinations including DRE, serum PSA estimation has been done using VIDAS TPSA which is an automated quantitative test for use on the VIDAS instrument, for the quantitative measurement of PSA level in human serum and plasma (Lithium heparinate or EDTA), using the ELFA technique (Enzyme Linked Fluorescent Assay).

Trans-rectal U/S was done by sono Line–Versa instrument with a transrectal probe of 7.5 Mhz by single operator.

The indication for the Trans-rectal TRU-CUT biopsy of the prostate was abnormal findings suggesting prostate cancer on any one of the following tests; digital rectal examination and / or trans-rectal U/S and / or increased level of PSA (4ng/ml as a cut off value). Digitally guided systematic sextant random biopsy regimen plus another 2 lateral pieces to mount to 8 pieces finally with the use of 18 gauge needle driven TRU-CUT gun device. This procedure is done under local anaesthesia in the theatre with the use of prophylactic antibiotics. Immediately the pieces were put in a container filled with 10% formalin for histopathological examination and staining using Haematoxylin and Eosin (H&E)

For the statistical analysis alfa 2 (chi square test) was used and for determination of cancer detection rate the following formula was used: DR = number of cancer cases / total number of cases X 100

Calculation of Sensitivity, Specificity, positive predictive value, Negative predictive value and Accuracy was done as the following;

Sensitivity = true positive/ true positive+ false negative X100

Specificity = true negative / true negative + false positive X100

Positive predictive value = true positive/ true positive + false positive X 100

Negative predictive value = true negative/ true negative + false negative X 100

Accuracy = true positive +true negative/ true positive +true negative +false positive +false negative X100.

RESULTS

Between April, 2005 to February, 2006, 86 patients with lower urinary tract problem underwent the diagnostic triad test (i.e Digital Rectal Examination, PSA, Transrectal Ultrasound) for prostate cancer detection and digitally guided transrectal prostate biopsy.

The mean age of patients was 68 years, ranging from (40-90) years. Majority of patients (40) were between (70-79 years), from which 13 patients were cancer. Second most frequent encountered patients (19 patients) were between (60-69 years), from which 3 patients found to have cancer. Fifteen patients were in the age group of (50-59 years), and 3 of them were cancer patients. Seven patients belong to age group (80-89years), from which 3 patients confirmed to have cancer. Four patients were in the group (40-49years) and half of them were cancer. Finally, only one patient was in the group (90 and above) as shown in Table .1.

Numbers of cases with prostatic cancer were 24 (27.9%), 62 cases (72.1%) diagnosed with BPH; all malignant cases were of adenocarcinoma as shown in the Table 2.

DRE were positive in 61 cases (in the form indurations, firmness, nodularity, and mass), 21 of them were cancer; proved by biopsy, while the remaining 40 cases diagnosed as BPH.

DRE were negative in the remaining 25 cases of the total 86 in which 3 of them were found to be carcinoma proved by biopsy. The other 22 cases were diagnosed by biopsy as BPH (Table 2.3).

Sensitivity of DRE was (87.5%), specificity (35.5%), PPV (34.4%), NPV (88%), Accuracy (50%).

PSA level: 26 cases were below 4 ng/ml in which 2 of them were malignant, the other 24 cases proved to be BPH by biopsy. Table 4. The other 60 cases with level of more than 4 ng/ml.22 were malignant, while the remaining 38 cases were BPH as shown in the Table 4.

PSA Sensitivity was (91.7%), specificity (38.7%), PPV (36.7%), NPV (92-3%), Accuracy (53.5%).

Table 1. Frequency of cases with age groups.

Age group	No. of cases	No. of malignant cases.	%
40-49	4(4.65%)	2	8.3
50-59	15(17.44%)	3	12.5
60-69	19(22.09%)	3	12.5
70-79	40(46.51%)	13	54.1
80-89	7(8.13%)	3	12.5
90 and above	1(1.16%)	-	-
Total	86	24	100

Table 2. Histopathological diagnosis of cases with prostatic biopsy (Cancer detection rate is 27.9%).

Diagnosis	No. of cases	%
BPH	62	72.1%
Cancer	24	27.9%
Total	86	100%

Table 3. Relation of DRE with results of biopsy.

DRE	No. & % of cases	Biopsy	
		CA	BPH
Negative	25(29.1%)	3	22
Positive	61(70.9%)	21	40
Total	86(100%)	24	62

Table 4. Relation of PSA with biopsy.

PSA	No. %	Biopsy	
		CA	BPH
4 ng/ml and below	26 (30.2%)	2	24
Above 4 ng/ml	60(69.8%)	22	38
Total	86(l00%)	24	62

Regarding the TRUS of the 86 cases, 32 of them were normal in which (1) malignant case was found, other cases were proved to be BPH by biopsy. Table 5.

The remaining 54 cases were associated with abnormal TRUS (in the form of enlargements with increased echogenesity or presence of a mass or with distorted architectures) 23 of them were malignant, while the other 31 were BPH as shown in the Table 2.5

TRUS sensitivity (95.9%), specificity (48.4%), PPV (41.8%), NPV (96.8%), Accuracy (61-6%).

Number of cases in which both PSA and DRE were abnormal is 17 in which (1) case detected as cancer, so cancer detection rate for both PSA and DRE is (4.1%).

Number of cases in which both PSA and TRUS were abnormal is 18, in which (3) cancer cases were detected i.e. cancer detection rate for both PSA and TRUS is (12.5%). Number of cases in which both DRE and TRUS were abnormal is (13) cases in which (2) cases were found to be cancer, so cancer detection rate for both DRE and TRUS is (8.3%). Number of cases in which all 3 tests were abnormal is 21 and 18 detected (75%). See Table 6.

By using Chi-square test the result was 22.41, Df=6, P-value=0.0010, and since the P-value is less than 0.01, were can say that the test is significant with 99% confidence level.

Table 5. Relation of TRUS with biopsy.

TRUS	No%	Biopsy	
		CA	BPH
Negative	32(37.2%)	1	31
Positive	54(62.7%)	23	31
Total	86(100%)	24	62

Table 2.6 Cancer detection rate of each test alone and in combinations.

Positive tests	No.	Cancer	Cancer detection rates%
PSA	4	0	0
DRE	10	0	0
TRUS	3	0	0
PSA+DRE	17	1	4.1
PSA+TRUS	18	3	12.5
DRE+TRUS	13	2	8.3
DRE+PSA+TRUS	21	18	75
Total	86	24	100%

Table 7. List of Sensitivity, Specificity, PPV, NPV, Accuracy of each test alone and in different combinations.

Tests	Sensitivity%	Specificity%	PPV%	NPV%
DRE	87.5	35.5	34.4	88
PSA	91.7	38.7	36.7	92.3
TRUS	95.9	48.4	41.8	96.8
PSA+DRE	100	13.63	50	50
TRUS+DRE	100	17.64	60.6	100
PSA+TRUS	100	35.7	53.8	100
PSA+DRE+TRUS	100	91.1	75	100

DISCUSSION

In the present study cancer detection rate was (27.9%) which is lower than the results of (Kiat et al, 2005) [20] 52%; and that of (Thompson and Fielding, 1991) [22] 30%.

This difference may be because of the small samples. Additionally biopsy was performed on symptomatic cases as prostate cancer has a little tendency to cause symptoms, which brings the patients to clinicians.

They are also seen when they have abnormal (DRE, PSA and TRUS).

In other studies lower values were reported as (26%) by (Elem and Patil, 1991) [23], (14.6%) by (Gohiji et al, 1995) [16], (16.4%) cancer detection rate by (Kapoor et al, 2004) [24].

The mean age of 86 patients was (68.12), which is nearly equal to the mean of (66.7) reported by (Akdas et al, 1995) [25] and (65.7) by (Lee wan sangtong et al, 2000) [26].

In the present study younger patients were affected, as men who fall in group 40-59 years were affected by 20.6% which is higher than 13.7% of the same age group reported by (Crawford, 2003) [27], this difference may be due to the change in lifestyle and diet.

In our study 71% of cases were over 65 years, while in another study by (Bracarda et al, 2005) [28] 81% of men over ages of 65 years were affected, this difference may be in our locality the life expectancy is lower. Older patients die of other diseases especially heart problem, the visits to physician will be decreased with advances in age.

The affection rate increased with advanced age as 42.85% of men aged 80 and above was affected with prostate cancer as its go with the result of (Crawford, 2003) [27]. Sensitivity, Specificity, PPV, NPV, Accuracy, of DRE was as the following: 87.5%, 35.48%, 34.42%, 80%, and 50% respectively.

Table 8.

Researches	Sensitivity%	Specificity%	PPV%	NPV%	Accuracy%
Present study	87.5	35.48	34.42	80	50
Richie et al [29]	75	69			
Martinez et al [30]	94	20.5			
Akdas et al [25]			57.5	73.22	79.9
Mistry et al [31]			17.8		
Mettlin et al[32]			28		

The present findings may meet some and differs from the results of other reports, in which the Sensitivity of DRE was 75% by (Richie et al, 1994) [29] which is lower than that of the present study. Specificity of 69% was reported by (Richie et al, 1994) [29] as it is higher may be because of the fact that many cases other than cancer show the same finding on DRE.

The study of (Martinez et al, 1995) [30] shows a Sensitivity of 94%, Specificity of 20.5%, and accuracy of 79.9% by (Akdas et al, 1995) [25], which is higher than the present result. DRE depends on the individual experience. It has a positive predicted value of 17.8% by (Mistry and Cable, 2003)[31] and of 28% was reported by (Mettlin et al, 1991)[32] in which both are lower than the present value. Positive predicted value of 57.5% and a negative predicted value of 73.22% were reported by (Akdas et al, 1995) [25]). Although the present PPV was low, most of patients diagnosed with cancer have an abnormal DRE.

It is clear that the risk of over diagnosis is high because it has reported that for every patient who dies of prostate cancer, at least 380 cases with prostate cancer will be missed clinically. [33, 34].

Table 9. A comparison between the results of the present study and of others regarding PSA sensitivity, specificity, PPV, NPV and Accuracy.

Researches	Sensitivity%	Specificity%	PPV%	NPV%	Accuracy%
Present study	91.66	38.7	36.66	92.3	53.48
Martinez et al	84	31			
Iqbal et al	87	70.8		85.22	
Richie et al	75				
Crawford et al,1996 [35]	34.9		27.7		
Crawford et al,1999 [36]		61.1			
Mistry et al		93.2	25.1		

In other studies PSA Sensitivity was 87% by (Iqbal and Husain, 2003) [37], 84% by (Martinez et al, 1995) [30] or 75% by (Richie et al, 1994) [29] 34.9% by (Crawford et al, 1999) [27], all are lower than the present result. Specificity of 31% was reported by (Martinez et al, 1995) [30] approaches our value although higher Specificity was reported by (Iqbal and Husain, 2003) [37] as 70.8%, 61.1% by (Crawford et al, 1999) [27] and as much high as 93.2% by (Mistry and Cable, 2003) [31]. Raising PSA cut-off value can elevate its Sensitivity. Positive Predicted Value of PSA as 27.7% by (Crawford et al, 1999) [27], 25.1% by (Mistry and Cable, 2003) [31] was reported which generally approaches the present value; also higher PPV can be achieved by increasing the cut-off value which decreases its Sensitivity.

It's well-known that PSA values for prostate cancer and BPH overlaps considerably, in which 21-47% of men with proved BPH histologically have a high PSA (more than 4ng/ml) [36] and this overlap can be differentiated just by biopsy. It is reported by (Tprnblom et al, 1999) [39] and (Lodding et al, 1998) [40] that 62% of prostate cancers have PSA level of more than 4ng/ml and 38% with level less than 4ng/ml, which means that cancer can be detected in 62% of cases by the use of PSA 4ng/ml, or more as a cut-off value. In the present study, 90% of cancer cases were associated with high PSA (more than 4ng/ml) so 10% of prostate cancer will be missed if PSA 4ng/ml is used as a cut-off value, and this is proving that the present PSA sensitivity is high. The NPV of 85.22% by (Iqbal et al, 2003) [37] was reported, as low PSA level can be seen in malignant cases.

When a patient has abnormal finding in DRE or high PSA level, the chance of cancer is 1:4-5 [36] in the present study approximately 1in3 cases with abnormal PSA or DRE have the chance of cancer. Conversely when the PSA level or finding on DRE was normal the chance of missing cancer is 10% [36], while in our study approximately 8-12% is the chance of missing cancer, that's why our tests may tends to over diagnose so as to overcome cancer missing. Of (86) cases only 4 of them underwent biopsy depending on the abnormality of PSA alone and none of them were malignant, so cancer detection rate of PSA alone was 0%.

Results of TRUS were Sensitivity (95.83%), Specificity (48.38%), PPV (41.81%), NPV (96.77%) and Accuracy (61.62%) which can be compared with that of other studies in table 3.3. a comparison between the results of the present study and those of other regarding TRUS.

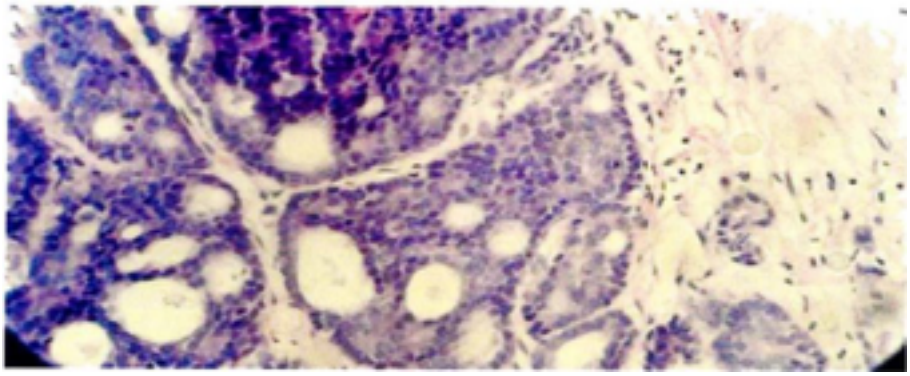

Image 1. Prostatic adenocarcinoma /HE staining x 400

Table 10.

Researches	Sensitivity%	Specificity%	PPV%	NPV%	Accuracy%
Present	95.83	48.38	41.81	96.77	61.62
Seijii et al	88	77			80
Mettlin et al [32]	77.2	89.4	15.2		
TetTis et al	53.3				
Song et al [38]		61.3			
Martinez et al			77.8	87.7	

Sensitivity of TRUS by (Seijii et al, 1988) [39] study was 88% by (Mettlin et al, 1991) [32] 77.2%, and only 53.3% by (Terris et al, 1991) [40] so the present value was higher than others (as TRUS is a sensitive diagnostic method).

TRUS Specificity which was reported in other studies 89.4% by (Mettlin et al, 1991) [32], 77% by (Seijii et al, 1988) [41], 61.3% by (Song et al, 2005) [38] were higher than our present results. This may be because the changes which are seen on TRUS and produced by cancer can be seen in other cases such as calculi, BPH, and infection. To avoid the possibility of missing any suspected cases). The PPV of TRUS, which was reported in other study, is 77.8% by (Martinez et al, 1995) [31] which is higher than the present study, although lower PPV of 15.2% by (Mettlin et al, 1991) [32] was also reported. The NPV of TRUS was 87.7% by (Martinez et al, 1995) [31] which is slightly lower than the present result, as sometime cancer cases may be missed by TRUS examination especially in diffuse tumours. Accuracy of 80% was reported in a study by (Seijii et al, 1988) [41], which is higher than the present value this may be due to that TRUS needs more experience.

Ten per cent of men older than 50 years are likely to develop clinically serious disease. Therefore it needs early detection depending on the tests for diagnosis of prostate cancer and the definitive diagnosis is made up by TRU-CUT needle biopsy (Scardino, 1989) [43]. Of (86) cases only 3 of them underwent biopsy depending on the abnormality of TRUS alone and none of them were malignant, so cancer detection rate of TRUS alone was 0%.[39]

Sensitivity, Specificity, PPV and NPV of PSA and DRE combination was: 100%, 13.63%, 50% and 100% respectively. Values of other results show a Specificity of 87.9% which is higher than the present value and Sensitivity of 38% reported by (Crawford et al, 1999) [36]. This is different from ours, may be due to over diagnosis so as not to miss any suspected cases. On the other hand if we raise the cut-off value of PSA to 10 ng/ml then the Specificity will be increased but the Sensitivity will decrease. PPV of combined PSA and

DRE was reported to be 56.6% by (Crawford et al, 1999) (36) which is similar to ours. Although value of 80% was also reported by (Galic et al, 2003) [44] Cancer detection rate for both PSA and DRE is (4.1%), value of 4% was reported by (Crawford et al, 1996) [35] as this shows that the detection rate is better when both tests were used together.

Sensitivity, Specificity, Positive Predicted Value and Negative Predicted Value of DRE and TRUS combination was: 100%, 17.64%, 60.6% and 100% respectively with cancer detection rate of 8.3%, which shows that the efficacy of the use of DRE with TRUS is better than its combination with PSA.

Sensitivity, Specificity, PPV and NPV of TRUS and PSA combination was: 100%, 35.71%, 53.84% and 100% respectively with cancer detection rate of 12.5% as this shows that the efficacy of combination of PSA and TRUS is better than the combination of any one of them with DRE. (Song et al, 2005) [38] reported that cancer detection rate is 16-34% when 2 of the tests will be abnormal, in the present study is lower may be because the finding tends to be less specific and more sensitive as the detection rate depends on the balance between the Sensitivity and Specificity of the tests.

Sensitivity, Specificity, PPV and NPV of the combination of all the tests together were 100%, 91.1%, 75%, 100% and Accuracy of 100% respectively. These high values may be due to the fact that in the present study biopsy were performed only on symptomatic cases when one or more of the three parameters were abnormal and there is no case which underwent biopsy if all of the parameters were normal. Values of 84.2%, 91.2%, and 71.4% for Accuracy, Specificity and Sensitivity respectively were reported by (Akdas et al, 1995) [25] PPV of 65% was reported by (Gohiji et al, 1995) [16], and 83% by (Ciatto et al, 2001) [45].

Cancer detection rate of the three parameters combination was 75%, which is similar to 76% detection rate by (Song et al, 2005) [38]. Generally, the Sensitivity of all parameters were better than their Specificity, and those of TRUS were better than Sensitivity and Specificity of DRE and PSA. When each test was used alone, as TRUS can detect more cases which may be missed by DRE or PSA, and TRUS and PSA combination gives us a better Specificity, PPV, Accuracy and cancer detection rate. Therefore, these combinations are highly sensitive but not specific for prostate cancer. Combination of all parameters together gives us a better efficacy for prostate cancer detection.

Conclusion

The most affected age is men at their seventies and early detection was a finding in younger age.Adenocarcinoma of prostate is the commonest histological type.

Accuracy of the triad diagnostic tests is much better when they are used in combinations.

Cancer detection rate is better in combination than when each test used alone. Accuracy and sensitivity of TRUS is better than other tests. For definitive diagnosis of prostate cancer, prostate TRU-CUT biopsy is mandatory.

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