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Validity of Multiparametric MRI (mpMRI) and Magnetic Resonance Spectroscopy (MRS) in diagnosis of Prostatic Cancer

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ABSTRACT

Background: Current methods for detection of Prostate cancer have limited accuracy for most early prostate cancers. Moreover, diagnosing carcinoma prostate in patients in grey zone of PSA [4 to 10 ng/ml] and patients with normal digital rectal examination is still difficult.

Objectives: To assess the validity of multiparametric magnetic resonance imaging (MRI) in detection and local staging of prostatic cancer and to review current evidence on the diagnostic performance of prostatic metabolites in detection and assessment of severity of prostatic cancer.

Materials and methods: A prospective study included 36 patients suspected to have prostatic cancer having high prostatic specific antigen examined with 1.5 Tesla MRI machine. We used different sequence Time 2 weighted (T2W) axial, coronal ,sagittal, Time1weighted (T1W) sagittal, T1W with contrast , diffusion weighted Image (DWI) b0 and b1000, and apparent diffusion coefficient (ADC) as well as Magnetic Resonant Spectroscopy (MRS) to assess prostatic metabolites.

Results: Biopsy proved prostatic cancer in 72.2% of cases. mpMRI sensitivity, specificity and accuracy were 96.2%, 70% and 88.9% respectively. MRS sensitivity was 88.5%, specificity of 90% and accuracy was 89.5%. When both MRS and MRI combined higher sensitivity, specificity and accuracy were obtained, 96.2%, 70%, and 88.9%, respectively.

Conclusion: mpMRI has excellent sensitivity for diagnosis of cancer, & can be used to localize csPCa before biopsy. MRSI has good sensitivity and specificity in assessment of prostatic cancer volume. Combination of both mpMRI and MRSI has higher sensitivity and specificity than each mpMRI and MRSI separately.

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Keywords: Prostatic Cancer, Diagnosis, Histopathology, Multiparametric MRI, Magnetic Resonance Spectroscopy.

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1. INTRODUCTION

The Prostate cancer is common and remains the second leading cause of cancer death among elderly men. Current methods for its detection, like Digital rectal examination, Transrectal ultrasound, Prostate Specific Antigen assay and even sextant biopsy have limited accuracy for most early prostate cancers (1). Moreover, diagnosing carcinoma prostate in patients in grey zone of PSA [4 to 10 ng/ml] and patients with normal Digital rectal examination is still difficult (2). There is much overlap between Benign prostatic hyperplasia[BPH] and carcinoma prostate in this diagnostic grey zone of Prostate specific antigen. The histologic diagnosis of prostate cancer is made, in the majority of cases, by prostate needle biopsy (3). Prostate cancer rarely causes symptoms until it is advanced. Thus, suspicion of prostate cancer resulting in a recommendation for prostatic biopsy is most often raised by abnormalities found on digital rectal examination [DRE] or by elevations of PSA. Although there is controversy regarding the benefits of early diagnosis, it has been demonstrated that an early diagnosis of prostate cancer is best achieved using a combination of DRE and PSA (4). Transrectal ultrasound (TRUS)-guided, systematic needle biopsy is the most reliable method, at present, to ensure accurate sampling of prostatic tissue in men considered at high risk for harboring prostatic cancer on the basis of DRE and PSA findings (5). This challenge in diagnosis, localization and staging of potentially curable early disease has prompted further research into radiological imaging which could be more specific and sensitive, and also noninvasive that provides good positive and negative predictive value(PPV and NPV)(6). Magnetic Resonance Imaging [MRI] is well known for its diagnostic potential, primarily due to its capability to noninvasively generate high-resolution anatomical images based on various inherent tissue characteristics (7). With ongoing research on ways of data acquisition during MRI and their analysis, newer sequences and strategies have been developed that provide more specific information like diffusion imaging, functional imaging, metabolic imaging, etc., faster image generation and higher resolution (8). With these newer technologies, the diagnostic potential of MR techniques is improving further, and its indications are also developing. Magnetic Resonance spectroscopic imaging (MRSI) is one of these new promising techniques, and uses the regular MRI machine, requiring only software upgrades as an

additional cost factor. It is not only useful in diagnosing the disease but also useful in assessing the local extant of disease which is also important in cure of the disease (9). So this study is intended to assess the role of MR DWI and MRS in addition to the routine MRI sequences in diagnosing carcinoma prostate in suspicious patients. Currently the combination of digital rectal examination (DRE) and prostate–specific antigen (PSA) testing is the primary diagnostic procedure. Typically, an elevated PSA or a nodule detected on physical examination prompts an evaluation and an eventual TRUS biopsy may reveal cancer (10). However, in most cases, positive identification of Prostatic Carcinoma only becomes evident when malignancy has been established and the cancer has metastasized beyond the capsular region of the prostate (11). In recent years, magnetic resonance spectroscopy of the prostate has shown to provide very useful metabolic information of the prostate. The combined used of MRI and MRSI has shown to increase the sensitivity and specificity in the detection of prostate cancer (12). In imaging of Prostate, recent development in ultrasonography technology, have made ultrasonography one of the most useful modality in evaluation of the prostate (13,14). Transrectal US of the prostate provides excellent visualization of the prostate in the axial and sagittal planes(15). Color Doppler TRUS, including the use of contrast agents , may provide the necessary improvements to specifically identify cancer sites in the future (16). Although techniques for registration and fusion of images obtained from separate PET and CT scanners have been available for several years, the readily apparent and documented advantages of having PET and CT in a single device have resulted in the rapid dissemination of this technology in the United States. This Procedure Guideline pertains only to combined PET/CT devices (17,18). Recent progress in imaging, and particularly in magnetic resonance imaging (MRI). multi-parametric MRI (mpMRI) that combines T2-weighted imaging (T2WI) with functional pulse sequences such as diffusion-weighted imaging (DWI) or dynamic contrast-enhanced (DCE) imaging has shown excellent results in PCa detection. As a consequence, biopsies targeting suspicious lesions seen on mpMRI are increasingly used in addition to systematic biopsy (18,19). The mpMRI play different roles in the evaluation and management of clinically localized PCa , local staging and active surveillance (AS) (20,21).

Magnetic Resonance Spectroscopy MRSI is a powerful tool that can provide useful biological information associated with many different metabolites. A standardized scoring method was

developed by Jung et al,which. MRI/MRSI may be of great value for patients who are at increased risk for prostate cancer (22).

2. METHODOLOGY

This prospective study was carried out at Al Ameer Diagnostic Center of Radiology in Al Najaf. During the period between October 2020 and October 2021. All patients gave their written informed consent for taking part in this study. The study was approved by Ethical Committee of Faculty of Medicine, University of Kufa. It included 36 patients who were referred for MRI study firstly from Urologist by clinical exam and high PSA, due to suspicion of prostatic cancer. The study included all patients who had suspicion of prostatic cancer and performed prostatic biopsy. Patients with inconclusive MRI images, renal impairment and missed biopsy result were excluded

Data collection:

Data collected through full history taking and thorough clinical examination in addition to laboratory and imaging data. Prostatic Specific Antigen (PSA) Measurement done by sandwich procedure. The normal value of PSA in this procedure is 2.5 - 4 ng/ ml.

MRI Technique:

Magnetic resonance imaging (MRI) of the prostate include the use of magnet with high field strength, 1.5 tesla wide pore ALTECH machine with spine coil, using novel set of imaging sequences

Multiparametric Imaging:

Three individual imaging sequences were obtained during a prostatic MRI examination; diffusion-weighted imaging (DWI) with an apparent diffusion coefficient (ADC), T2-weighted (T2W) imaging, and dynamic intravenous contrast-enhanced (DCE) imaging in addition to the T2 fat suppression and T1W sequences.

Magnetic Resonance Spectroscopy Imaging:

It was performed with 1.5 Tesla (ALTECH machine figure 2.1). In each patient we calculate the ratio of choline + creatine to citrate and we consider a ratio less than 0.5 was normal, more than 0.5 is suspicious for prostatic cancer & more than 2 is abnormal, highly suspicious.

MRS spectrum with good sensitivity and signal to noise (S/N) ratio was obtained in all included subjects.

Prostate Imaging Reporting and Data System (PI-RADS):

We applied PI-RAD v2.1, which was published in 2019, revises the technical parameters for image acquisition and modifies the interpretation criteria for MRI data, among other changes (23). The PI-RADS system categorizes prostate lesions based on the likelihood of cancer according to a five-point scale. All focal lesions are evaluated on all sequences, and the parameters can be assessed and scored by PI-RADS (24).

Biopsy of the Prostate:

The procedure done by urologists with general pre biopsy preparation. Transrectal ultrasound guided biopsy was performed for all patients and specimens sent for histopathology study.

Statistical Analysis:

Data entered and managed using the statistical package for social sciences (SPSS) version 27. Appropriate statistical tests were applied accordingly. Receiver Operating Characteristic (ROC) curve used to assess the validity of MRS finding choline /Creatine to citrate ratio in detection of prostate cancer according to histopathology. Cross-tabulation used in comparison of combined MRS and MRI vs. histopathology .

Bivariate Spearman's and Pearson's correlation tests used to assess the correlation between Choline /creatine to citrate ratio and Prostatic specific Ag titer against Gleason score. Regression Curve Estimation used to demonstrate the correlation of Choline /creatine to citrate ratio with Gleason score. Level of significance set at 0.05, two tailed P. value as cutoff point below which the difference or correlation considered significant.

3. RESULTS

There were 36 patients enrolled in this study with a mean age of 65.9 ± 8.6 (range : 45 – 80) years and 72.2% of patients were older than 60 years. Urine retention was the main complaint of the patients contributed for 27/36 (75%) while other complaints including backache in 4 patients, dysuria 4 patients, and drippling in only one patient all represented 25%. Digital rectal examination revealed, hard prostate in 29 (80.6%) patients, irregular

surface in 3 patients (8.3%) and it was soft in 4 patients (11.1%). Histopathology was abnormal (Adenocarcinoma) in 26 (72.2%) patients and negative, non-malignant, in 10 (27.8%) patients. Capsule was involved in 19.4% of cases, seminal vesicle in 19.4%, lymphadenopathy reported in 11.1% and bone deposit (metastasis) in 13.9%. All these findings are shown in (**Table 1**). No significant difference was found in mean age between cases with adenocarcinoma and those with negative findings. On the other hand, the mean choline + creatine to citrate was significantly higher in patients with prostate cancer compared to those with negative findings, the mean choline + creatine to citrate ratio was 1.6 vs. 0.5, respectively. The Prostatic specific antigen (PSA) level was significantly higher in cancer cases compared to negative group, 31.5 vs. 8.9, respectively, (P=0.029). No significant difference in volume of prostate between cancer and normal cases, (P>0.05) as shown in (**Table 2**). Comparison of mpMRI vs. histopathology revealed that out of the 26 cases with abnormal histopathology, MRI correctly identified (true positive) 24 cases as abnormal (cancer cases) and correctly identified 8 cases as normal out of the 10 cases with normal histopathology, giving a sensitivity, specificity, accuracy, Positive predictive value (PPV) and Negative predictive value (NPV) of 92.3%, 80%, 88.9%, 92.3% and 80%, respectively, as shown in (**Table 3**). Receiver Operating Characteristic (ROC) curve for the validity of MRS finding choline Creatine/ citrate in detection of abnormal histopathology revealed that choline Creatine/ citrate ratio was excellent predictor of prostate cancer with an area under the curve of 0.923. At an optimal cutoff point of 0.78, choline Creatine/ citrate ratio produces a sensitivity of 88.5%, specificity of 90% , accuracy of 89.5%, PPV of 89.8% and NPV of 89%, (**Figure 1**). When MRS at cutoff point of 0.78 categorized into two categories (< 0.78 and > 0.78) as normal and abnormal MRS combined with MRI findings and compared against histopathology, a sensitivity of 96.2%, specificity of 70%, accuracy of 88.9%, were obtained, with a PPV of 89.3% and NPV of 87.5%, as shown in (**Table 4**). Bivariate correlation analysis for Choline + creatine to citrate ratio and Prostatic specific Ag titer against Gleason score revealed a positive (direct) significant correlations between Gleason score and each of Choline + creatine to citrate ratio(R = 0.533, P = 0.013) and PSA (R = 0.558, P = 0.011) from the other side, as shown in (**Table 5**).

Table 1. Baseline characteristics of the studied group

Variable		No.	%
Age (year)	≤ 60	10	27.8
	61 - 70	16	44.4
	71 - 80	10	27.8
	Mean (SD)	65.9 (8.6)	-
	Range	45 – 80	-
Complain	Urine retention	27	75.0
	Others*	9	25.0
Clinical finding on DRE	Hard	29	80.6
	Irregular surface	3	8.3
	Soft	4	11.1
Histopathological findings	Adenocarcinoma	26	72.2
	Normal (negative)	10	27.8
Involvement of other organs	Capsule Involved	7	19.4
	Seminal vesicle Involved	7	19.4
	Lymphadenopathy	4	11.1
	Bone deposit (metastasis)	5	13.9

SD: standard deviation of mean, DRE: Digital rectal examination
*Others: Backache 4, Dysuria 4, Drippling 1

Table 2. comparison of mean age , choline + creatine to citrate ratio, PSA and prostate volume according to histopathology findings

Variable	Histopathology (biopsy)				P. value
	Adenocarcinoma		Negative		
	Mean	SD	Mean	SD	
Age (year)	66.5	9.1	64.4	7.3	0.535 ns
choline + creatine to citrate ratio	1.6	0.7	0.5	0.06	<0.001 sig
PSA titer	31.5	30.9	8.9	6.8	0.029 sig
Prostate Volume (ml)	74.0	70.6	97.0	71.7	0.338 ns

SD: standard deviation of mean , ns: not significant, sig: significant, PSA: Prostatic specific antigen

Table 3. Comparison and validity of Multiparametric MRI in detection of prostate cancer

Multiparametric MRI		Histopathology				Total	
		Abnormal		Normal			
		No.	%	No.	%	No.	%
Abnormal		24	92.3	2	20	26	72.2
Normal		2	7.7	8	80	10	27.8
Total		26	100.0	10	100.0	36	100.0
Validity parameters	Sensitivity	92.3%					
	Specificity	80.0%					
	Accuracy	88.9%					
	PPV	92.3%					
	NPV	80.0%					

PPV: Positive predictive value, NPV: Negative predictive value

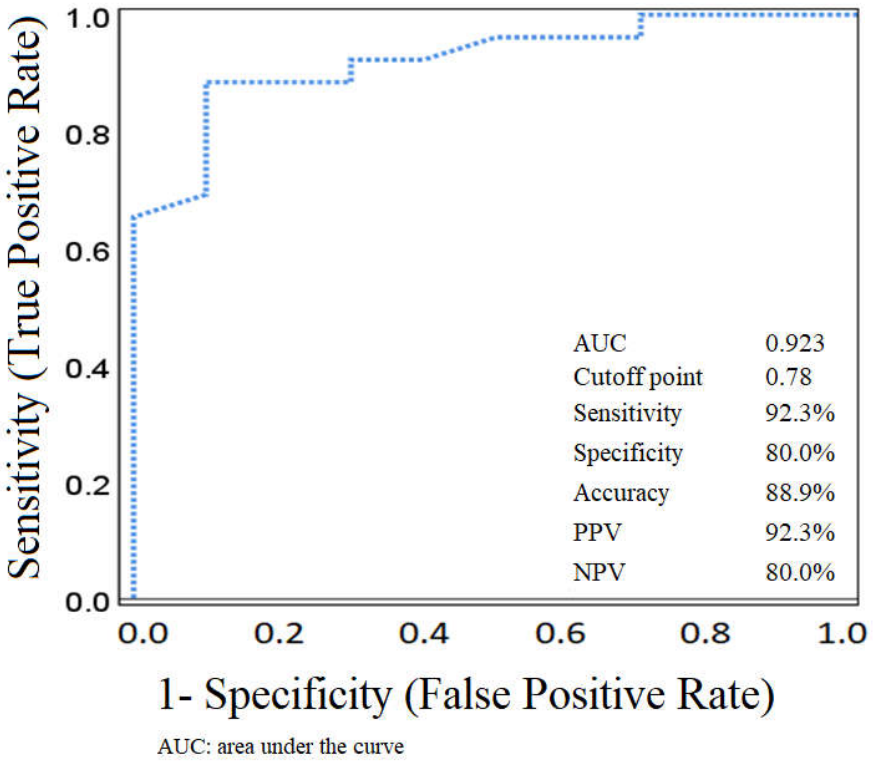

Figure 1. Receiver Operating Characteristic (ROC) curve for the validity of MRS finding choline+ Creatine to citrate in detection of abnormal histopathology

Table 4. Comparison of combined MRS and MRI vs. histopathology

MRS+MRI		Histopathology				Total	
		Abnormal		Normal			
		No.	%	No.	%	No.	%
Abnormal		25	96.2	3	30.0	28	77.8
Normal		1	3.8	7	70.0	8	22.2
Total		26	100.0	10	100.0	36	100.0
Validity parameters	Sensitivity	96.2%					
	Specificity	70.0%					
	Accuracy	88.9%					
	PPV	89.3%					
	NPV	87.5%					

PPV: Positive predictive value, NPV: Negative predictive value

Table 5. Bivariate correlation analysis for Choline + creatine to citrate ratio and Prostatic specific Ag titer against Gleason score

Parameter	Statistics for Correlations with Gleason score	
Choline+ creatine to citrate ratio	R	0.533
	P. value	0.013 sig
Prostatic specific Ag titer	R	0.558
	P. value	0.011 sig

R: correlation coefficient, sig: significant

4. DISCUSSION

Multiparametric magnetic resonance imaging (mpMRI) is increasingly being used for the detection and risk stratification of clinically significant prostate cancer (csPCa), and there are continued requirements to standardize techniques and train radiologists in its optimal application (25). In this prospective study we enrolled 36 patients with a mean age of 65.9 ± 8.6 (range 45 – 80) years and 72.2% of patients were older than 60 years. No significant difference in the mean age of patients with prostatic cancer and those free from cancer, this consistent with Kaneko et al. 2019 (26). Also consistent with Anunobi et al. 2011 (27),

common age group of adenocarcinoma 40 to 98 years with a mean age of 66 years. Urine retention was the main complaint of the patients contributed for (41.6%), drippling (16.6%), Hematospermia (11.1%), other patient presented with backache, dysuria, and erectile dysfunction, the clinical presentation of our patients were comparable with other studies (26-28). Digital rectal examination revealed, hard prostate in (80.6%) of patients, irregular surface (8.3%) and soft in (11.1%), which consistent with the findings of Hoeks et al. 2011 (28). The distribution of patients according to involvement of other organs, capsule was involved in 19.4% of cases, seminal vesicle in 19.4%. Lymphadenopathy reported in 11.1% and bone deposit in 13.9% while none of patients had bladder base or rectum involvement. These findings were in line with other (28,29). In the current study histopathology was abnormal and confirmed prostatic cancer in 26 patients (72.2%) in all these patients the histopathology was adenocarcinoma, this finding was consistant with other studies that adenocarcinoma contributed for about 95-99% (30).

In the present study there was no correlation between prostatic volume and patient age, this may be due to small sample size and the included age group between 45-80 years, this finding is mismatched with findings of Grossman et al. 2018 (34) and Khalid et al. 2020 (13), who found significant correlation between the prostate volume and age.

The mean value of PSA in prostatic cancer patients was 31.5 ng/ml which is significantly higher than in patients free of cancer 8.9 ng/ml this finding consistent with other studies (35-37). The mean ratio of Choline+Creatine/ Citrate was significantly higher in patients with prostatic cancer than in patients free from cancer 1.6 vs.0.5, this was consistent with Coode-bate 2017 (38) as well as with Peng et al 2021 (39), by using MRI spectroscopy , although it is difficult to separate the individual metabolite signals due to overlapped choline, polyamine (mainly spermine), and citrate spectral lines between 3 and 3.2 ppm. Cho/(Cit+Spm) ratio, was found to discriminate between PCa and healthy tissue.

In the current study choline/Creatine to citrate ratio produced a sensitivity of 88.5%, specificity of 90% , accuracy of 89.5%, PPV of 89.8% and NPV of 89%, and matched with the study that conducted by the Litjens et al. 2015 (40), in their study the sensitivity and specificity was found (0.93 to 0.98, p=0.029, 0.37 to 0.59, p=0.013). Our study found a significant correlation between Gleason score histopathology and ratio of Choline +Creatine

/ Citrate in MRS (R = 0.533, P = 0.013) as well as a significant correlation with PSA (R = 0.558, P = 0.011). Our data indicate that MR metabolic profiling is a potentially useful tool for the assessment of cancer aggressiveness. This finding was compatible with *Zakian* et al 2005 (41), they found an overall sensitivity of MR spectroscopic imaging was 56% for tumor detection, increasing from 44% in lesions with Gleason score of 3 + 3 to 89% in lesions with Gleason score greater than or equal to 4 + 4. Other studies showed significant correlation between prostatic cancer volume and Choline+Creatine/Citrate ratio, they found that MR metabolic profiling is a potentially useful tool for the assessment of cancer aggressiveness study which matched with our finding regarding validity of MRSI in assessment of prostatic cancer aggressiveness (Gleason grade) (40-42). There was a significant difference in the mean ratio of choline +creatine to Citrate in patients with prostatic cancer and patient free from cancer P > 0.05. A cut off point 0.78 gave an AUC 0.923 with 88.5%sensitivity, 90% specificity, 89.5% accuracy, 89.8% PPV and 89.0% NPV, these findings compatible with studies (1,42),they mentioned an important role of MRS in assessment effect of therapy of prostatic cancer, where there was high choline and low citrate before therapy and the loss of all metabolites (metabolic atrophy) has been associated with effective therapy, while residual prostate cancer has been identified based on the presence of 3 or more voxels having Choline+Creatine/Citrate > 1.5 with an accuracy of 80%. In recent years, mpMRI has emerged as the most sensitive and specific imaging tool for PCa staging Boesen et al. 2017. Our finding regarding comparison of multiparametric MRI vs. histopathology revealed that out of the 26 cases with abnormal histopathology, MRI correctly identified 24 cases as abnormal (cancer cases) and correctly identified 8 cases as normal out of the 10 cases with normal histopathology, giving a sensitivity, specificity, accuracy, PPV and NPV of 92.3%, 80%, 88.9%, 92.3% and 80%, respectively. The overall validity parameters of MRI in detection of abnormal histopathology indicated that MRI was good sensitive, specific and accurate, in detection of abnormal histopathology. Estimation of the sensitivity of MRI in the detection of the prostate cancer vary widely depending on method of analysis used and the definition of significant disease. Recent estimation using T2-weighted sequences and endo rectal coils vary from 60% to 96%. Several groups have convincingly shown that dynamic contrast enhancement and spectroscopy each improve detection and that the sensitivity of MRI is

comparable to and may exceed that of trans rectal biopsy. Specificity is not yet good enough to consider the use of MRI in screening. Large tumors and high grade are detected significantly more often with both T2 sequences and spectroscopy. Size estimation is improved by dynamic contrast and spectroscopy, but errors of >25% are common. In the current study the MRS finding is high sensitivity about 88.5%, and specificity 90%. and when combined MRS and MRI and compared against histopathology, higher sensitivity, specificity were obtained, 96.2%, and 70%, respectively. The result from both MRI and MRSI indicated the presence of tumor with high specificity (91%) while high sensitivity (95%) for localization of the tumor, and incompatible with the study that conducted by Hoeks et al. 2011 (36), MR spectroscopic imaging has shown higher specificity (68%–99%) and lower sensitivity (25%–80%) for prostate cancer localization, and when compared with anatomic T2-weighted MR imaging (specificity, 61%–90%; sensitivity, 68%–87%). Hoeks et al. 2011 (28), found the correlation of MRI and MRSI to histopathological finding sensitivity 96.2% and specificity 70%. Limitations of the study The Corona Virus pandemic (COVID – 19) was the strongest limit to the study of prostatic carcinoma. Some of patients refused to perform a biopsy, and others didn't bear the cost of the examination of MRI, and some of patients had a claustrophobia for that didn't complete the MRI examination.

5. CONCLUSIONS

mpMRI has excellent sensitivity for aggressive cancer, can be used to localize csPCa before biopsy. MRSI has good sensitivity and specificity in assessment of prostatic cancer aggressive . Combination of both mpMRI and MRSI has higher sensitivity and specificity than each study separately. Hence we recommend to use mpMRI and MRSI as a imaging of choice in diagnosis of prostatic cancer before biopsy and in assessment of its aggressiveness and to reduce no. of true cut biopsies. However, further studies with large sample volume and multicenter with interobserver analysis are recommended.

Ethical Approval:

All ethical issues were approved by the author. Data collection and patients enrollment were in accordance with Declaration of Helsinki of World Medical Association , 2013.

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