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Evaluation of Diagnostic Accuracy of Diffusion Weighted Imaging Sequences in Comparison with Other Sequences of Multi-parametric Imaging for Diagnosis of Peripheral Zone Prostate Cancer

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Abstract

Objectives: Prostate cancer is among the most prevalent cancers between elder men. Accurate and reliable diagnosis and staging are crucial factors in planning the treatment. A number of indicators have been developed in order to help with better diagnosis of prostate cancers ranging from trans-rectal ultrasonography, assessing the PSA antigen, magnetic resonance imaging, MRI guided or Ultrasonography guided biopsy. Multi-parametric magnetic resonance imaging is a new trend in diagnosis and differentiating of prostatic lesions. It uses the cutting edge technology to make reliable and optimized diagnosis about focal lesions of prostate. Current study aims to compare the efficacy of mp-MRI compared with TRUS biopsy results with focus on diffusion weighted imaging.

Methods: 42 patients were examined between 2017 and 2018 prior to doing TRUS biopsy. The mp-MRI and TRUS biopsy findings were cross-referenced. Both mp-MRI and biopsy findings were analyzed. Sensitivity, specificity, positive predictive value and negative predictive value were assessed for each MRI sequence and biopsy.

Results: Overall sensitivity, specificity, PPV and NPV for mp-MRI were 72.72%, 88.89%, 96% and 47.06%.

Conclusion: Mp-MRI can be quite helpful in diagnosis and staging of PCa especially when it comes to using DWI in combination with other sequences. High sensitivity is a major advantage but adequate studies are needed to be done in order to benefit from efficacy and reliability of mp-MRI.

Keywords: Prostate cancer; Multi-parametric imaging; Mp-prostate MRI; Prostate peripheral zone

Introduction

Prostatic cancer holds the highest prevalence, 25% in men amongst all probable cancers. One in every six men experience prostatic cancer in their life time but only 3% of them lead to death [1,2]. Almost 30% of men in their forties, 50% in their fifties and 75% above 85 years of old, experience prostatic cancer [3,4].

In 99% of PC patients, they live at least for five years and it is worth to mention that 93% of them will live at least 10 and 79% of them will live on at least for 15 years. A huge portion of PC patients die because of other causes rather than prostatic cancer [5]. Thus in few cases there are no need for active treatment [1].

Men in 50 and above this age are referred to take PSA antigen and DRE examinations because they are complaining about their inferior urinary systems. Low specificity is the disadvantage of PSA antigen examination which can lead to unnecessary biopsy. Meanwhile, 25% of PC patients show normal range of PSA antigen and 50% of them seem normal in DRE [6]. Patient is referred to multi-parametric MRI when at least one of these examinations indicates the presence of PC and he will be referred to TRUS biopsy if the mp-MRI indicates the signs of PC. TRUS biopsy has its downsides among which are the risk of septicemia and low sensitivity due to impossibility of taking samples from anterior and apex of prostate. But 70% of metastatic tumors' belong to peripheral zone and this zone is available for TRUS biopsy sampling thus TRUS biopsy has a preferable sensitivity in PZ. Multi-parametric MRI is also a preferable method for PZ and it demonstrated a key role in diagnosis and staging of tumors in prostate. Current study is focused on the efficacy of mp-MRI in diagnosis of PC in PZ comparing to TRUS biopsy [7,8].

Method and Materials

Patients

Between May of 2017 and January of 2018 in an eight months period, 42 patients were selected for this study. Their rectal examination and prostate specific antigen assessment suggested further examination of prostate.

They referred to imaging department of Payambaran hospital. Patients' age ranged between 49 And 85 (mean ± 62 y). A consent form was filled and signed by every participating patient and approved by research committee of Payambaran hospital.

MR techniques

MRI pulse sequences were performed on a 1.5 Tesla closed magnet MRI machine, Siemens (avanto) using 8 channel Body Coil as well as endo-rectal coil.

The following pulse sequences were performed:

T2-WI (TSE, 3000-4800/132 repetition time msec/echo time msec-, 160 flip angle, 15-20 sections, 3-mm section thickness, 190 field of view, 256*256 matrix) which images were taken in axial, sagittal and coronal planes from prostate and seminal vesicles. Normal peripheral zone is characterized by uniform high signal intensity due to the water content of glandular structures in PZ. Typically, tumors are low in signal intensity compared to glandular PZ. It is not a solid diagnosis and should be differentiated from hemorrhage, prostatitis and BPH. T2WI is the most useful sequence to determine whether tumor is confined to the prostate or extending beyond the capsule. The presence of extra-capsular extension (ECE) is quite helpful for risk stratification of PC patients.

DWI: (echo planar sequence) TR 3900/TE 99, field of view 230, Matrix 150 150 (±10), slice thickness 3.5 mm, gap 0 , and using three b values including (50, 800, 1200). DW-MRI deals with the quantity of Brownian motion of free water protons by applying b values. Most common b values for prostate cancer are 0-800 and 1200 sec/mm^2. The characteristic of prostate cancer is having a low signal in ADC maps images compared with different hyper signal intensity of normal tissue in background. DW-MRI is considered to be quantitative because ADC values can be calculated based upon DW-MRI. Short acquisition time and high contrast resolution between tumor and normal tissue are among its major advantages. DW-MRI has its limitations because of poor spatial resolution and the risk of image distortion due to post-biopsy hemorrhage. Post-biopsy hemorrhage can lead to magnetic field inhomogeneity.

Csi 3D MR spectroscopy from the entire prostate by inserting the selected boxes all around it. The FOV (real-phase) AP»100-RL»100-FH»100, the repetition time was 690 ms. Volume of interest (VOI) aligned to axial T2WI; the prostate was covered by the VOI entirely; field of view was chosen approximately 1.5 voxels larger than VOI in all directions; using Spectral selective suppression to remove signal from water and lipid; using at least six fat saturation bands near the margin of prostate. Proton magnetic resonance spectroscopic imaging (MRSI) measures the intra-cellular concentration of choline and citrate. Areas under metabolite peaks represent metabolite concentrations. Normal prostate tissue contains citrate whereas in PC the citrate levels decrease. Concurrently, the level of choline increases in PC. Although the level of choline also increases in BPH, PC can be differentiated from BPH because MRSI is carried out after T2W anatomic imaging. MRSI has its own disadvantages e.g. long acquisition time, sophisticated techniques and it needs proper magnetic resonance shimming, experienced readers. MRSI does not provide any direct visualization of prei-prostatic anatomy.

Dynamic contrast-enhanced imaging (3D T1-VIBE) with the parameters including (4.9/1.7 flip angle, 20 transverse positions on a 3D slab, 3.6 mm section thickness, 250 mm field of view, 192 140 matrix) acquired and a bolus of paramagnetic gadolinium chelate 0.1 mmol/kg body weight of gadobutrol (Gadovist, Bayer® AG, Leverkusen, Germany), was injected intravenously *via* a power injector at 3 ml/sec followed by a 20 ml saline flush. 3D volume was obtained every 17.5 sec including 25 measurements in 7.29 min, Post-processing was determined by locating regions of interest (ROI) upon the suspected lesions as well as the normal gland. As for suspected areas, the TIC curve was drawn by mean Curve® application in LEONARDO® advanced post-processing-® by Siemens. DCE-MRI evaluates the vascularity of tumors by using the fast T1W-MRI scanning sequence before, during and after the rapid administration of GBCAs. Genetic mutation in cancers leads to production and release of angiogenesis factors such as the vascular permeability factor or vascular endothelial growth factor. As a consequence, the number of vessels in cancerous tissue increases thus tumor vessels have higher permeability than normal vessels. Detection and localization of PC can be done based on evaluating wash out rate and tumor permeability.

MR images assessment

All the MR images were inspected and assessed by a radiologist. Then radiologist decided whether TRUS biopsy is needed or not? Since biopsy proceeded after MR imaging, during MR examination radiologist was blind to biopsy results. Radiologist assessed all the images carefully and judged each case by comparing results from all 4 protocols. In each case, If 3 out of 4 protocols were in favor of prostatic cancer, radiologist considered it as a positive case and vice versa. There was neither only one case in which the results of 4 protocols were 2 *vs* 2 in favor of neither positive nor negative. In that particular case, radiologist decided based on protocols with better sensitivity and specificity. All the results returned back to radiologist in order to comparison the MP MRI and TRUS biopsy results and reach a conclusion. Biopsy was the golden standard to which all the results' accuracy was assessed.

Histopathologic examinations

MR/ultrasound fusion guided biopsy was done on each patient. The total number of 12 or in some cases more samples were taken from suspicious areas of prostate according to MR sequences and ultrasound images. Biopsy procedures were done by my lab, Eight®, Esaote®, Geno, Italy. This device provides the fusion of MRI and Ultrasound images at the same time and satisfying precision for procedure prior to biopsy, suspected areas for prostatic cancer were outlined by radiologists. Then, the prostate was biopsied by the help of the fusion of MR images and transrectal ultrasound images. Samples were fixed in 4% buffered formaldehyde for 48 hours. Clinical pathology laboratory of Payambaran hospital received the samples according to lab routines. A pathologist who was blind to MR results evaluated the hematoxylin-eosin and saffron stained slides. He outlined cancer foci, determined its location and grade. Pathologist used tumor Gleason score for biopsy using score 4 or higher in case of prostate cancer.

Data analysis

Data analysis was done with the help of MedCal online calculator. Descriptive statistics are presented as count and percentage for categorical variables. Data from pre-biopsy was cross referenced to results of TRUS biopsy in order to calculate the positive and negative predictive value and accuracy. Four main a, b, c, d variables were given to true positive, false negative, false positive and true negative as in mentioned order. Sensitivity, specificity, positive and negative

predictive value and accuracy were assessed. P<0.05 was considered statistically significant.

Results

42 patients with suspicious case of prostatic cancer participated in this study (mean age=66.3) among whom 33 cases were approved to be prostatic cancer by TRUS biopsy (true positive). Other 9 cases approved to be negative by TRUS biopsy (true negative). Results from multi factor magnetic resonance imaging diagnosed 26 positive cases and 16 negative cases of prostatic cancer. Comparing mp-MRI results to TRUS biopsy results, 25 cases were true positive, 8 cases were true negative and there were 1 false positive and 8 false negative. As shown in Table 1. Biopsy-proved adenocarcinoma in a 68 years old man results shown in Figures 1-3.

Sequence	True Positive	True Negative	False Positive	False Negative
MRS multi-voxel	25	8	1	8
DCE-MR	21	9	0	12
T2WI	20	8	1	13
DWI	31	4	5	2
Multi-parametric MR	24	8	1	9

Table 1: Detailed results from each MR protocols.

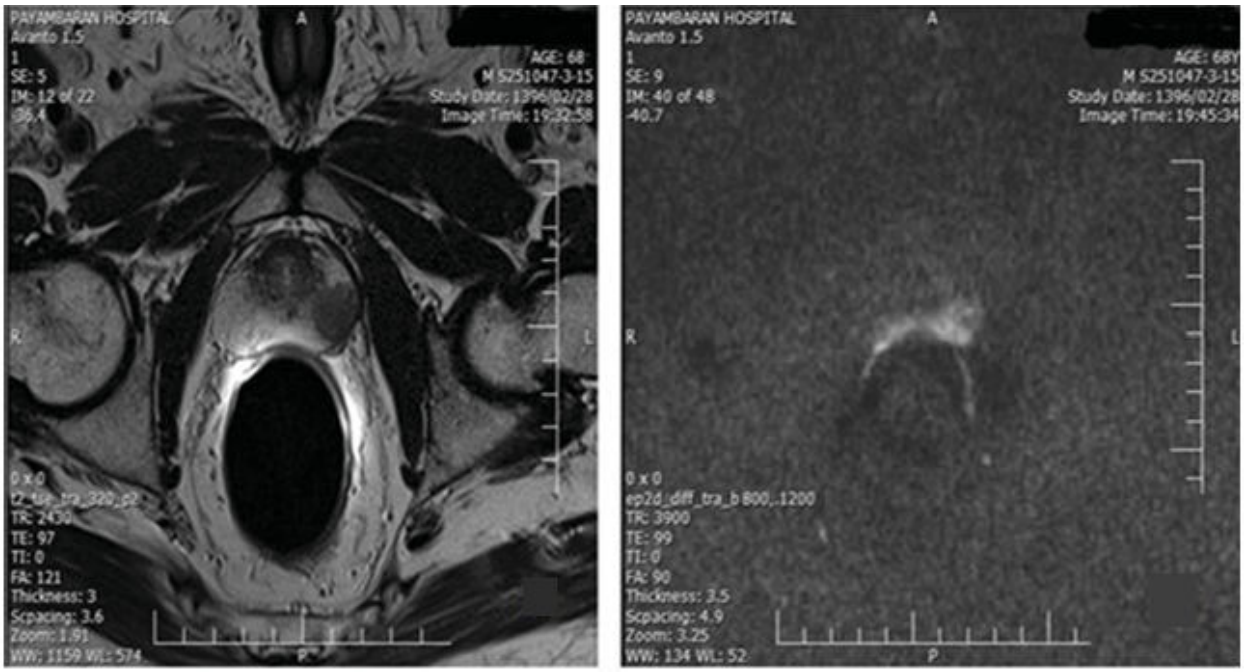

Figure 1: Biopsy-proved adenocarcinoma in a 68-years-old man; Axial T2-weghted images shows a well-defined oval shape hypo-signal mass lesion with 19*15 mm diameter is evident in peripheral zone in Lt. base of prostate; Axial diffusion-weighted image shows high signal intensity in the same area.

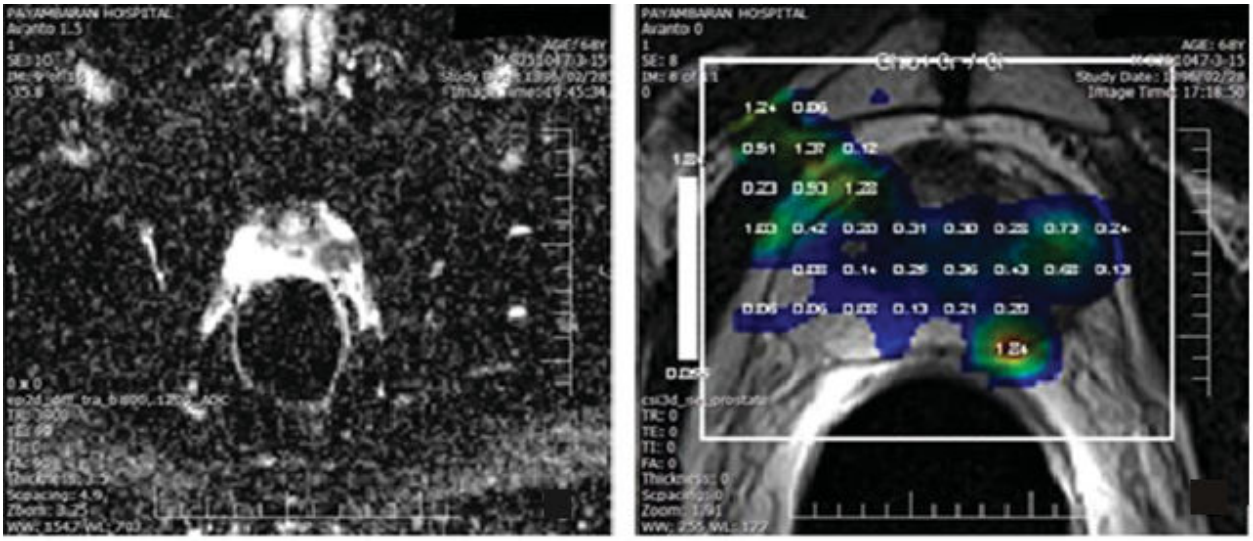

Figure 2: ADC map shows low signal intensity in the same area.

Results from assessment of sensitivity, specificity, positive predictive value, negative predictive value and accuracy for each MR protocol can be found in Table 2.

Looking through Table 2 and comparing results from all 4 protocols, DWI sequences stand out for higher sensitivity, accuracy and negative predictive value while DCE-MRI possesses the highest results for positive predictive value. Moreover, we notice that T2W is related with lowest results for sensitivity, accuracy and negative predictive value while DWI has the lowest specificity and positive predictive value results.

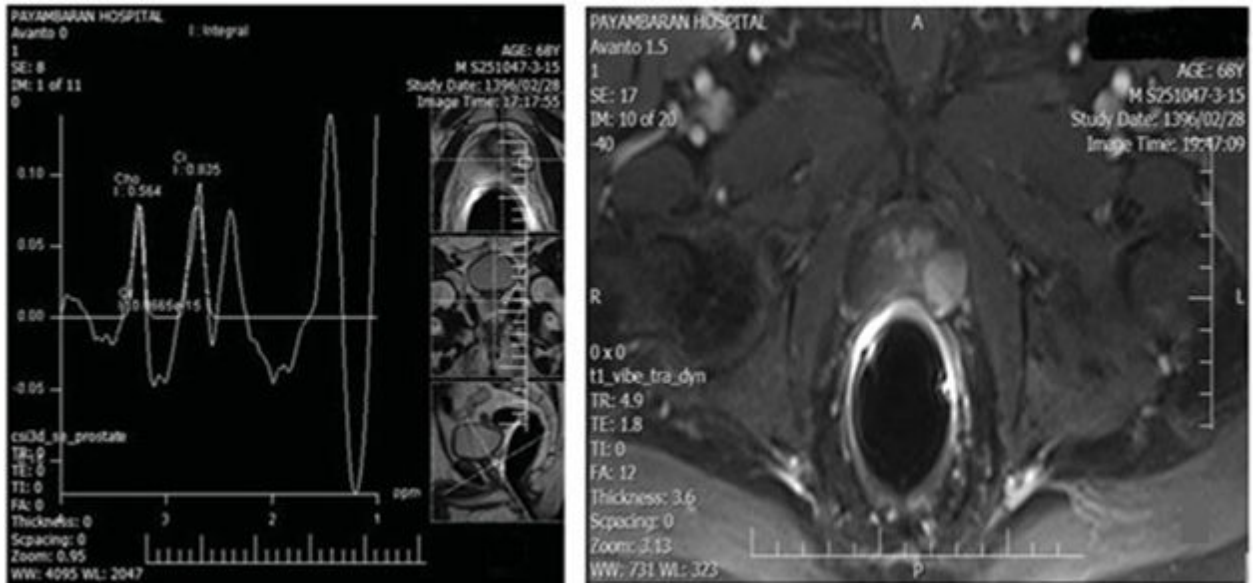

Figure 3: At H1 spectroscopy, choline/citrate ratio in the mass lesion is elevated; DCE-MRI showing enhancement after contrast injection.

Sequence	Sensitivity (%)	Specificity (%)	Accuracy (%)	PPV (%)	NPV (%)
MRS multi-voxel	75.76	88.89	78.57	96.15	50
DCE-MR	63.64	100	71.43	100	42.86
T2WI	60.61	88.89	66.67	95.24	38.1
DWI	93.94	44.44	83.33	86.11	66.67
Multi-parametric MR	72.73	88.89	76.19	96	47.06

Table 2: The comparisons of all 4 MR protocols by their sensitivity, specificity, positive predictive value, negative predictive value and accuracy.

Discussion

Multi-parametric MRI can be of a great help with assisting in diagnosis of prostatic cancer and making sound treatment decisions. Our overall results from MP-MRI were close to what Portalez et al. [9] achieved during their prospective study on 129 patients. Their numbers for Sensitivity and specificity were 74%, 82%. Our results depict 72%, 88%.

TRUS biopsy was the gold standard technique and MRI results were compared with it. This study depicted the high sensitivity of DWI technique. In other word, DWI was the prominent technique for diagnosis of true positives with 93.94%. This study agrees with Ioannis Papadopoulosa et al. [10], Hoda et al. [11], that DWI has the dominant role in diagnosis of prostatic cancer. Ioannis Papadopoulosa et al. discuss that combination of DWI and T2W allows us the better differentiate between suspicious and normal tissue. Our results also demonstrate that the combination of DWI and T2W increases the sensitivity, specificity, NPV and PPV. They also mention that dropping DCE and MRS significantly reduce the acquisition time, 25-55 min, and would make mp-MRI more efficient.

b values in this study were optimized. In order to have our DWI sequences optimized, we have two options; first option was to do the sequences with a 3 Tesla scanner which was not practical for this study. Second option was to use high and ultra-high b values which have some limitations. Applying ultra-high b values increases the acquisition time and reduces the comfort and collaboration of patients. Thus, we optimized our b values to have best DWI sequences in a sensible time.

DCE and T2W results were inferior in sensitivity and NPV compared with DWI and MRS. Our results correlates with Portalez et al. results. Moreover, our results suggest that the combination of DWI and DCE-MRI can be really helpful since their combination excels the sensitivity and specificity. Sensitivity and specificity for DWI were 93.94% and 44.44% whereas for DCE were 63% and 100%. DCE-MRI and MRS are time consuming and DCE technique requires GBCAs injected *via* IV line. Time consumption and GBCAs could be determining factors while considering patients comfort and safety. Delongchamps et al. [12] discuss that DCE-MRI does not significantly improve the accuracy of DWI and T2W in peripheral zone whereas Baur et al. [13] discuss that redefining the criteria for evaluating the DCE-MRI might improve performance and interpretation of mp-MRI.

Borofsky et al. in a retrospective study [14] demonstrates that 26% of the PC cases were missed by MP-MRI. Being multifocal and 2 to 3 times lower in volume are the major contributing factors in missing the lesions explained by them. We also have 9 false negative cases in current study. Lesion could be missed due to similar reasons. Borofsky et al. also discuss that this missing could be because of 'satisfaction of search' phenomenon which means missing a clinically important finding hindered by another clinically important one.

Oto et al. [15] Discuss that DWI/ACD is a preferable sequence for characterization of lesion in peripheral zone but not for central zone due to its low specificity. Our results correlate with their study since the specificity is relatively low in our study. De Rooji et al. [16] in a diagnostic meta-analysis discuss that ESUR recommendation on using T2WI, DWI and DCE-MR for detection of prostate cancer is based upon expert opinion. They included 7 studies among which 4 studies recommend DWI and DCE-MR as additional techniques rather than alone and 3 studies demonstrate no significant advantage or disadvantage between using T2WI, DWI and DCE-MR or just T2WI and DWI. They believe further prospective studies should be done to fully evaluate the advantages of each combination. Our current results are also in agreement with this meta-analysis since the combination of DWI, T2WI and DCE-MR can be of a great help due to high sensitivity and specificity.

Conclusion

Multi-parametric-MRI is a helpful non-invasive tool to help with diagnosis of prostatic cancerous lesions in peripheral zone of prostate. Diffusion weighted imaging can be really functional due to its high sensitivity. Some combinations like DWI plus DCE-MRI and DWI, T2WI and DCE-MRI can be great in increasing the sensitivity, specificity and accuracy of mp-MRI in order to be more reliable and optimized.

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