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Original Article

Diagnostic Accuracy of Apparent Diffusion Coefficient in Differentiating Malignant from Benign Endometrial Lesions, Taking Histopathology as Gold Standard

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ABSTRACT

Endometrial cancer is the cancer of the inner lining of the uterus. Histopathology is considered a gold standard invasive diagnostic test for it. However, Magnetic Resonance Imaging (MRI) based Diffusion-Weighted Imaging (DWI) and apparent diffusion coefficients (ADC) values are non-invasive tests that can differentiate malignant endometrial lesions from benign conditions. **Objective:** To assess the diagnostic accuracy of MR DWI in differentiating benign from malignant endometrial lesions taking histopathology as a gold standard. **Methods:** This cross sectional study was carried out at Radiology Ward Lahore General Hospital Lahore for six months. A total of 132 women between 25-55 years of age, with abnormal vaginal bleeding were included. In all patients, diffusion-weighted MRI (DE-MRI) of the pelvis was done followed by histopathology. DW-MRI and histopathology findings were compared. Data were analyzed on SPSS 20.0. The Sensitivity, Specificity, Positive Predictive Value (PPV), Negative Predictive Value (NPV) and diagnostic accuracy were measured using 2×2 contingency table. P-value of <0.001 was taken as significant. **Results:** DW-MRI diagnosed endometrial cancer in 75 patients while 57 patients didn't show any malignant lesion. Histopathology confirmed endometrial cancer in 79 cases and benign lesion in 53. Out of 75 positive DW-MRI patients, 72 were True Positive (TP). Out of 57 negative DW-MRI patients, 07 were True negative (TN). Sensitivity, Specificity, PPV, NPV and diagnostic accuracy were 91.14%, 94.34%, 96.0%, 97.72% and 92.42% respectively. **Conclusions:** DWI based apparent diffusion coefficients (ADC) can more accurately diagnose endometrial cancers than benign lesions. Hence it can be useful adjunct for diagnosis of endometrial lesions.

INTRODUCTION

Worldwide, endometrial cancers are the commonest gynecological malignancy of females around the age of 60 years. Around 3.4% newer cancer cases are attributed to it. Other benign lesions are polyps, hyperplasia, fibroid and adenomyosis [1]. As per USA cancer registry statistics 2010-2014, annually the new cases of endometrial cancer were 25.7 per 100,000 deaths were 4.6 per 100,000 women and 2.8% new diagnosis during the entire life of women [2]. The organization of International Gynecology and Obstetrics Federation (FIGO) states the surgical staging of the endometrial lesion. Histological grading and lymphovascular and cervical invasion should always be recorded [3]. Endometrial histopathology is gold standard for diagnosis its lesions however it is difficult to perform in cervical or vaginal stenosis patients [4]. MRI is the noninvasive radiological entity of choice for the uterine lesions. Conventional MRI tells about size and extent of the disease but not about lymphovascular penetration [5, 6]. DWI and ADC shows decrease values for various tumors and increased for benign lesions. The endometrial cancers assessment has been reported using DWI and 1.5T MRI [7, 8]. Another study on 119 patients showed lower ADC values

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for malignant than benign lesions and sensitivity and specificity of ADC for detecting endometrial carcinoma as 100% and 90.2% respectively [9]. Similarly, in another study, the sensitivity and specificity of apparent diffusion coefficient taken 88.9% and 100.0% respectively [10]. DWI is a form of MRI that measures the free diffusion of water molecules in body tissues. Recently DWI has got significant value in treating gynecological lesions [11]. Theoretically malignant endometrial lesions show lower ADC values and this low value is associated with histological parameters and vice versa. However, there were other studies that show low ADC values association with prognosis of the cancer [12].

This study aimed to find out DWI based ADC diagnostic accuracy in differentiating benign from malignant endometrial lesions taking Histopathology as a gold standard.

METHODS

This was a cross sectional study done at Radiology ward, Lahore General Hospital, Lahore from 20th August 2018 to 19th February 2019 after taking institutional review board approval vide letter No. AMC/PGMI/LGH/Article/Research No/176/2018. 132 patients were taken, with 95% confidence level, 41.67% endometrial carcinoma prevalence and 86.67% sensitivity and 91.0% specificity of ADC to differentiate between malignant and benign lesions [7]. All females between 25-55 years of age having abnormal vaginal bleeding for more than 3 months without any obvious cause were taken in the study by non-probability, consecutive sampling technique. All patients consent was taken before enrolment. Abnormal vaginal bleeding was defined as heavy regular cycle that occurred every 21-35 days and lasts longer than 7 days and endometrium thickness > 14 mm on ultrasonography. All patients had overnight fast of 8hrs and inj. azithromycin for gut clearance for better MR image visualization The major exclusions were pregnant or lactating women, history of uterine procedure in last 6 months, history of previous other cancers, chemotherapy or radiation, patients with hypertension or bleeding disorders and patients with pacemakers, metallic plates attached or having claustrophobia. All patients undergone DW MRI pelvis on 1.5Tesla MR unit. The total scan time was 3-4 minutes and Images were made with an 8-channel body array coil with the help of lower configuration in supine position with single breath hold to take all sequences at two b values (0 mm2/s, 1000mm2/s). The sequences were T1-weighted fast spin-echo axial plane (T1W FSE), T2-weighted fast relaxation fast spin-echo sagittal, coronal and axial planes (T2W FR FSE), T2- weighted fast relaxation fast spin-echo short tau inversion recovery (T2W STIR FSE) and DWI in the axial plane as shown in table I. Manufacturer's software was used to generate the ADC maps. The T1, T2 and DWI images for endometrial lesions were analyzed by a single radiologist on the MR system monitor. Malignant lesions showed high signal intensity on DWI images with the b value of 1000 mm2 /s and low signal intensity on ADC maps. In benign lesions high signal intensity on DWI corresponded to high signal intensity on ADC maps. The ADC values of all endometrial lesions were calculated manually by drawing a circular region of interest (ROI) on T2 weighted image to include the maximum solid part of the endometrial lesion. The ROI was then manually copied to its ADC map, which automatically generated ADC values. The mean ADC value of the patient was calculated by drawing three individual ROIs at different sections of each lesion. After MRI biopsy of all the patients was done in the concerned oncology department and specimen slides were evaluated for endometrial histopathology (HP) by a single histopathologist. Final diagnosis was established on the basis of HP report and DW-MRI and HP results were compared. Demographic details like age, parity, BMI, menopausal status and marital status) were noted on a predesigned proforma. Data were analyzed by using SPSS 20.0. Descriptive statistics (mean, standard deviation, frequency, percentage) used to summarize, organize, and present data meaningfully and concisely. Age, BMI and disease duration were plotted as mean and standard deviation. Maritalstatus (married/unmarried/widow/divorced), parity (primiparous/multiparous), menopausal status (pre-menopause/post-menopause) and endometrial lesions on ADC and histopathology were plotted as frequencies and percentages. 2×2 contingency table was made to calculate above parameters taking histopathology as gold standard. Stratification for age, disease duration, BMI, marital status (married/unmarried), parity (primiparous/ multiparous) and menopausal status (pre-menopause/post-menopause) was done followed by above mentioned parameters calculation. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and ADC diagnostic accuracy were measured. P-value of <0.001 was taken significant.

RESULTS

In table 1 the MRI parameters used for pelvic examinations in the assessment of endometrial lesions.

Table 1: MRI Parameters for pelvis examination for endometrial Lesions

S. No	Sequence	T1W FSE	T2W FR FSE	T2W FSE STIR	DWI
1	Plane	Axial	Axial, Coronal ,Sagittal	Oblique	Axial
2	Field of view	25x25	25x25,28x28 27x27	23x23	35x35
3	Matrix Size	328x212	328x212,368x 212,356x232	232x212	78x120
4	No of slices	39	39,34,30	25	39
5	Slice Thickness	3mm	4,4,4mm	3mm	4mm
6	Band Width	25.31Hz	22,27.32, 37.63Hz	22Hz	--
7	Rep/Echo Time	398min	1800/170,6100/ 170,1890/170	4001/170	9800/62

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8	Excitations	1.50	2.50,1.50,1.50	3.0	--
9	Scan Time	3.32min/s	4,3.45,3.20 min/s	4min/s	0.27min/s
10	b Values	--	--	--	00,1000s/mm^2

The mean patient's age was 42.70 ± 8.41 years. The mean disease duration was 5.54 ± 1.32 months. The mean BMI was 28.11±2.50 kg/m^2. Out of 132 patients, 42 were primiparous and 90 patients were multiparius.73 patients were premenopausal and 69 were post-menopausal as shown in table 2.

Table 2: Demographics of study participants(n=132)

Variables	Category	N (%)	ADC Mean ± SD
Age in years	25-40	48 (36.6)	42.70 ± 8.41
	41-55	84 (63.4)	
Disease Duration in months	< 6	99 (75)	5.54 ± 1.32
	>6	33 (25)	
BMI (Kg/m^2)	≤27	54 (40.91)	28.11 ± 2.50
	>27	78 (59.09)	
Parity	Primiparous	42 (31.82)	-
	Multiparous	90 (68.18)	
Menopausal status	Pre-menopause	73 (55.30)	-
	Post-menopause	69 (44.70)	

In table presented the histopathological findings of both malignant and benign endometrial lesions in a sample of 132 cases.

Table 3: Histopathological findings of malignant and benign endometrial Lesions(n= 132)

S.No.	Endometrial Lesions	N (%)	Endometrial Lesions Catagory	ADC Mean ± SD
1	Serous Carcinoma	11(8.34%)	Malignant 79 (59.85%)	0.676 ± 0.06
2	Endometroid Carcinoma	59 (44.69%)		0.518 ± 0.19
3	Adenocarcinoma	6 (4.55%)		0.756 ± 0.09
4	Undiferentiated Carcinoma	3 (2.27%)		0.891 ± 0.17
5	Endometrial Hyperplasia	21 (15.91%)	Benign 53 (40.15%)	1.398 ± 0.24
6	Adenomyoma	4 (3.03%)		1.361 ± 0.19
7	Endometrial Polyp	28 (21.21%)		1.424 ± 0.30

Histopathological slide of endometrial carcinoma shown in figure 1(a).

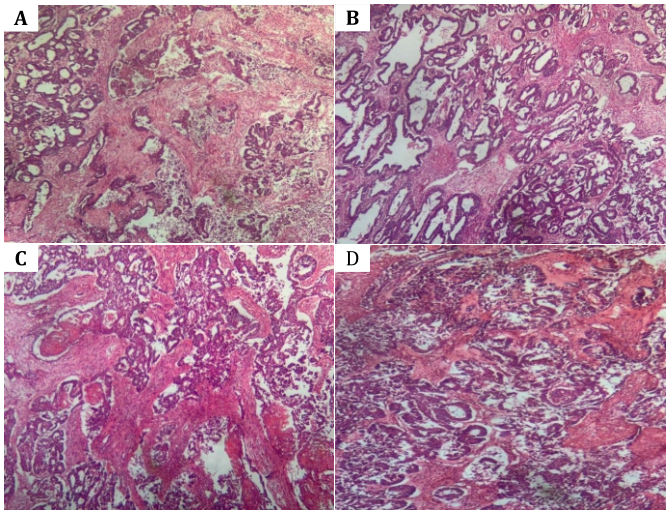

Figure 1(a): Histopathological Images of Low Grade Endometroid Adenocarcinoma (A-D) Confluent Atypical Glands with Very Little Intervening Stroma at High Magnification with H and E Stain

The MRI images in various planes of the patient were shown in figure 1(b).

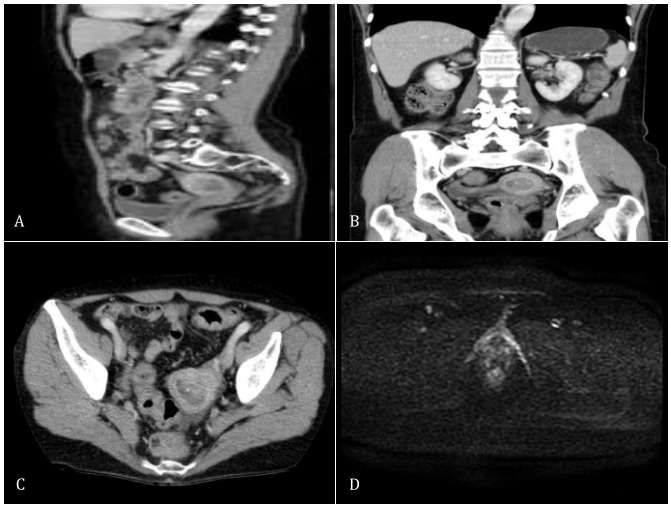

Figure 1 (b): MRI Images of endometrial carcinoma (A) Sagittal section of MRI showing Endometrial Carcinoma (B) Coronal sectional of MRI showing Endometrial Carcinoma (C) Axial section of MRI showing Endometrial Carcinoma (D) DWI Axial section showing endometrial carcinoma.

Regarding the accuracy of ADC, out of 132 cases, DW-MRI supported the diagnosis of endometrial cancer in 75 cases while histopathology (HP) confirmed endometrial cancer in 79 cases. On the other hand, DW-MRI supported the diagnosis of endometrial benign lesions in 57 cases while histopathology (HP) confirmed endometrial benign lesions in 53 cases. Out of 75 positive DW-MRI patients, 72 were true positive (TP) and 03 were false positive (FP). Out of 57 negative DW-MRI patients, 07 were true negative (TN) and 50 were false negative (FN). P value was significant (0.0001). Sensitivity, specificity, PPV, NPV and ADC diagnostic accuracy was 91.14%, 94.34%, 96.0%, 87.72% and 92.42% respectively as shown in table 4.

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Table 4: Diagnostic accuracy of ADC taking histopathology as Gold Standard (n=132)

Results	Negative Histopathology	Positive Histopathology	P-Value
Positive DWI Results	72 (TP)*	03 (FP)***	0.0001
Negative DWI Results	07 (FN)**	50 (TN)****	

The diagnostic accuracy of the ADC was demonstrated by its impressive metrics: a sensitivity of 91.14% indicated that the test correctly identified 91.14% of true positive cases, reflecting its ability to detect the presence of the condition when it was actually present. With a specificity of 94.34%, the ADC effectively identified 94.34% of true negative cases, showcasing its ability to confirm the absence of the condition. The Positive Predictive Value (PPV) of 96% meant that 96% of individuals who tested positive genuinely had the condition, while the Negative Predictive Value (NPV) of 87.72% confirmed that 87.72% of those who tested negative were truly free of the condition. Overall, the diagnostic accuracy of 94.42% signified that the ADC correctly identified the condition in 94.42% of all cases, reflecting its high reliability and effectiveness in clinical settings (Figure 2).

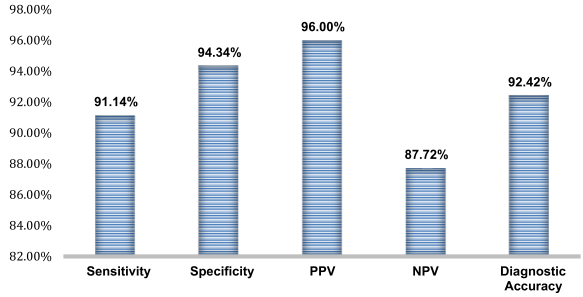

Figure 2: Diagnostic Accuracy of ADC

In table 5 stratification of diagnostic accuracy with respect to age groups, duration of symptoms, BMI, marital status, parity and menopausal status was also done. The post stratification diagnostic accuracy for age group 25-40 and 41-55 years were 97.92% and 89.29% respectively. The post stratification diagnostic accuracy for duration of symptoms in less than 6 and more than 6 months were 90.91% and 96.97% respectively. Similarly post stratification diagnostic accuracy with BMI below 27 and above 27 groups were 98.15% and 88.46% respectively. Post stratification diagnostic accuracy for all married females was 92.42% primparous and multiparous groups had a post stratification diagnostic accuracy of 97.62% and 90%. Similarly, premenopausal and postmenopausal groups post stratification diagnostic accuracy was 97.26% and 86.44% respectively as shown in table 5 all had p value of <0.001.

Table 5: Stratification of Diagnostic Accuracy with Various Parameters

Variables	Category	Positive on both DW-MRI and Histopathology (TP) n	Negative on both DW-MRI and Histopathology (TN) n	Sensitivity %	Specificity %	PPV %	NPV %	Diagnostic Accuracy %
Age (Years)	25-40	15	32	100.0	96.97	93.75	100.0	97.92
	41-55	57	18	89.06	90.0	96.61	72.0	89.29
Duration of Symptoms in Months	< 6	57	33	89.06	94.29	96.61	82.50	90.91
	>6	15	17	100.0	94.44	93.75	100.0	96.97
BMI Kg/m^2	≤27 (N=54)	36	17	100.0	94.44	97.30	100.0	98.15
	>27 (N=78)	36	33	83.72	94.29	94.74	82.50	88.46
Married	N=132	72	50	91.14	94.34	96.0	87.72	92.42
Parity	Primiparous (N=42)	26	15	100.0	93.75	96.30	100.0	97.62
	Multiparous (N=90)	46	35	86.79	94.59	95.83	83.33	90.0
Menopause	Pre menopause (N=73)	32	39	96.97	97.50	96.97	97.50	97.26
	Post menopause (N=59)	40	11	86.96	84.62	95.24	64.71	86.44%

Note: P-value for all of above mentioned parameters is <0.000

DISCUSSION

Our study emphasized the diagnostic accuracy of ADC (92.42%) in differentiating benign from malignant endometrial lesions keeping histopathology as gold standard. This has been supported by a number of studies. Yamada and their colleagues studied that ADC had significantly higher diagnostic performance for predicting histopathology grade and was a more useful indicator predicting survival in patients with endometrial lesions. [13]. Similarly, Deng L *et al.*, studied ADC value enhances confidence in preoperative endometrial cancer evaluation [14]. ADC values in another study was correlated with histologic tumor grade and it was concluded that ADC on MRI is a useful predictor of endometrial malignancy [15]. Quan Q *et al.*, in their study concluded similar findings that ADC values were important to diagnose endometrial lesions, grade risk and prognosis [16]. In another study it was concluded that ADC is a non-invasive technique that has the potential to preoperatively differentiate between

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low-grade and high-grade endometrial tumors [17]. Mean age in our cohort was 42.70 ± 8.41 years and diagnostic accuracy of ADC of 92.42% while Abdel-Latif M and Mosaad HS in their study have reported a little higher age group i.e. 56.15 years (± 8.229) in their study with a diagnostic accuracy of 84.6% for endometrial carcinomas [18]. Çavuşoğlu M *et al.*, have studied 52 post-menopausal cases with mean age of 57 ± 10 and found the diagnostic accuracy of 92.9% for DW1 images in cases of endometrial lesions [5]. Derbyshire AE *et al.*, in their study on 74 women reported that obesity (BMI34-81) is a risk factor for endometrial carcinoma, which increases further with increase in BMI. In our cohort we found 59.09% cases of high BMI [19]. Bae H *et al.*, in their study on 175 patients reported different tumor diameter ($p < 0.001$), signal intensity and heterogeneity on DWI ($p = 0.003$) for disease risk. They concluded that DWI can differentiate different levels of malignant lesions in endometrial lesions [20]. Keriakos NN and Darwish E *et al.*, reported that DWIs with ADC had sensitivity and specificity of 80% each in endometrial lesions and mean ADC value was 0.8×10^{-3} mm^2/s. Our values of sensitivity and specificity (91.14%, 94.34% respectively) show even better results than this. We could not record the mean ADC values in our study [21]. Moharamzad Y et al., reported in their systemic review and meta-analysis on 269 malignant and 208 benign lesions that combined (95% CI) sensitivity and specificity of mean ADC values were 93% and 94% respectively which was comparable to the values i.e. sensitivity: 91.14%, specificity: 94.34% [21]. Gharibvand MM et al., concluded in their study on 22 patients of abnormal vaginal bleeding the mean ADC value was lower for endometrial cancer than those with benign endometrial lesions, the difference was not significant ($P = 0.13$) however ADC values equaled 90.91 and 9.09 for sensitivity and specificity to differentiate benign from malignant lesions, with an equal of 50% for positive and negative predictive values. In our cohort we found the PPV of 96.0% and NPV of 87.72% [22]. Petrila O et al., in their study concluded that out of 92 cases 77 cases ADC values showed similar results as that of histopathology of endometrial carcinoma showing a diagnostic accuracy of 83.69% for endometrial cancers [23].

CONCLUSIONS

It was concluded that ADC has high diagnostic accuracy to differentiate malignant from benign endometrial lesions. Hence in future it can be used as non-invasive adjunct diagnostic tool.

Authors Contribution

Conceptualization: SS[1]
Methodology: SS[2], FS
Formal Analysis: FS, ZN
Writing, review and editing: SS[2], FS, SHD, ZN, FA

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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