THE ROLE OF DIFFUSION WEIGHTED MAGNETIC RESONANCE IMAGING IN GRADING OF CERVICAL AND ENDOMETRIAL CARCINOMA

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ABSTRACT:

Background: *Histological grade is one of the main prognostic factors in patients with endometrial and cervical carcinoma. DW-MRI provides important new information non-invasively.*

Aim of the Work: *to investigate if there is a correlation between qualitative (visual) and quantitative (ADC value) provided by the diffusion weighted imaging and the pathological grade of endometrial and cervical carcinoma in order to reach the appropriate treatment options.*

Patients and Methods: *Our study was conducted on twenty patients with pathologically proven endometrial (n=10) and cervical (n=10) carcinoma. It stressed on the role of Diffusion MRI in preoperative grading, aiming to emphasize its role in proper selection of patient's management plan. We performed DWI using different b-values, and quantitative analysis, named apparent diffusion coefficient (ADC). Areas of restricted water diffusion of uterine malignancy demonstrated high signal intensity on DWI and lower ADC values on ADC map.*

Results: *There was a significant difference (b < 0.01) between grades (1 and 2) from grade 3 in measuring the ADC values of both endometrial and cervical carcinoma, while there was no statistically significant difference between grade 1 and grade 2 or between grade 2 and grade 3. The mean ADC value of well differentiated tumors was (> 0.9 x 10^{-3} mm^2/ sec), while that of poor differentiated tumors was (< 0.7 x 10^{-3} mm^2/ sec). We also included in our analysis the size of the proved uterine cancer and aimed to establish another item that could reflect the tumor grading, but we haven't reached a statistical significance in the current research; which could be due to the limited sample size.*

Conclusion: *Lower ADC values were associated with poorly differentiated endometrial and cervical tumors. Therefore, the ADC value may represent a useful marker for assessing the biological features and grading of the uterine cancers.*

Key words: *Diffusion, Magnetic Resonance Imaging, cervical and endometrial, carcinoma*

INTRODUCTION:

Uterine cervical cancer is the fourth most common female malignancy and has a high mortality rate. Most women with cervical cancer are diagnosed before the age of 50**(1)**.

Endometrial carcinoma is the most common gynecological malignancy and the

sixth most common neoplasm worldwide. It typically presents with abnormal uterine bleeding in 75% to 90% of patients [(2)].

Transvaginal Ultrasound has advantage of being readily available and with low costs , but sensitivities and specificities of TVU for the detection of deep myometrial invasion and cervical stroma invasion are 71–85 % , Due to the small field of view and limited depth of penetration using high-frequency vaginal ultrasound probes, TVU is not considered suited for valid assessment of pelvic and paraaortic lymph node metastases[(3)].

CT's poor soft tissue differentiation limits its use in the local staging of Endometrial carcinoma. CT is less sensitive and less specific

in accurately visualizing myometrial invasion and cervical involvement than MRI. The sensitivity and specificity of CT in evaluating myometrial invasion range from 40% to 83% and from 42% to 75%, respectively [(4)].

DW MR imaging with reference to ADC mapping in detecting cervical stromal invasion of endometrial cancer. Type 1 cancer: well or moderately differentiated endometrioid adenocarcinoma; type 2 cancer: poorly differentiated endometrioid, clear cell, serous papillary or undifferentiated carcinoma [(5)].

We used image processing software on a MR post-processing ,Myometrial invasion and staging were analyzed using T2WI and fused T2WI-DWI. To assesse the following parameters: 1) invasion depth, 2) cervical stromal involvement, 3) bilateral adnexa and vaginal or other pelvic organ involvement, 4) presence of enlarged lymph nodes, and 5) presence of distant metastatic disease [(6)].

The International Federation of Gynaecology and Obstetrics (FIGO) for the first time use of MR imaging techniques,to update cervical carcinoma staging and assess the important prognostic factors , MRI is the imaging modality of choice for staging the primary cervical tumour [(7)].

Recently new magnetic resonance imaging (MRI) technology provide functional, tissue-specific, molecular information; beyond the excellent anatomical and contrast resolution with the aid of high resolution morphological measu rements as well as quantification can also be performed[(8)].

-Patients with cervical cancer FIGO IB1–IVBunderwent chemoradiation, laparoscopic staging led to an upstaging of 83% of cases, improves the prognosis of the primary chemoradiation [(9)].

According to the staging system developed by the Féderation Internationale de Gynécologie et d'Obstétrique (FIGO), a locally advanced cervix cancer in down-staging, The standard treatment is Concurrent chemoradiotherapy (CCRT), showed survival benefits , when compared with radiotherapy alone [(9)].

-DWI and ADC values provide additional information to routine pelvic MRI and improve the specificity of MRI for myometrial invasion and detecting tumour extension and thus increasing the radiologist's confidence in image interpretation which will finally reflect on the patients' outcome and prognosis [(10)].

When DW-MRI is used in gynecologic applications, areas characterized by "restricted' diffusion or by low values of the apparent diffusion coefficient generally correspond with foci of hypercellularity. By performing DWI using different b-values, quantitative analysis by calculating the apparent diffusion coefficient (ADC) values, it is possible to display the ADC values as a parametric map (ADC map). Restricted water diffusion demonstrates high signal intensity on DWI and lower ADC values on ADC map [(11)].

AIM OF THE WORK:

The aim of this study is to investigate if there is a correlation between qualitative (visual) and quantitative (ADC value) provided by the diffusion weighted imaging and the pathological grade of endometrial and cervical carcinoma in order to reach the appropriate treatment options.

PATIENTS AND METHODS:

The current study is a prospective analysis that included 20 cases with uterine malignancy (10 patients with endometrial carcinoma and 10 cases with cervical carcinoma) after initial biopsy confirmation for pre-management.

The study was conducted at Ain Shams University Hospital. The patients were referred from the gynecology department to the radiology department (Women's imaging unit) in the period from December 2015 to March 2022.

Study population:

Patients presented with a histologic diagnosis of endometrial or cervical carcinoma. MR imaging and DWI suggested pathology whether benign or malignant had been correlated with the pathological specimen. They presented with pre-menopausal abnormal vaginal bleeding, postmenopausal bleeding and/ or vaginal discharge. The standard reference for the histological grade was the complete pathologic specimen following hysterectomy or curettage samples in patients not fit for surgery.

MR Imaging:

MR imaging was performed on two devices (FUJIFILM medical system) using a 1.5-T magnet. All the patients were imaged in the supine position with the aid of pelvic phased-array coil. (SENSE XL Torso coil 16 channels).

Imaging Protocol:

Pre-contrast imaging:

Axial T1WI data were obtained in the axial plane with the following parameters: repetition time msec/echo time msec, 500/10 msec; field of view, 260x 216 mm; matrix, 263 x171; section thickness, 6 mm with a 1.3-mm intersection gap ; **w**hich is useful for observing extrauterine disease and any other structural anatomical detail that may influence the extent of primary surgery.. **Axial T2Wis** data were obtained with the following parameters: repetition time msec/echo time msec, 3300/100 msec; field of view, 288x350 mm; matrix, 292x180; section thickness, 6 mm with a 1.3-mm intersection gap; ; **w**hich is useful for observing extrauterine disease and any other structural anatomical detail that may influence the extent of primary surgery **Sagittal T2WI** data were obtained with the following parameters: repetition time msec/echo time msec, 3000/90 msec; field of view, 290x290 mm; matrix, 208x205; section thickness, 4 mm with a 1.5-mm intersection gap ; **w**hich is sensitive to distinguish superficial from deep myometrial invasion related to the incidence of nodal metastasis and for presurgical prognostication of patients who may be suitable for more conservative treatment **Coronal T2Wis** data were obtained with the following parameters: repetition time msec/echo time msec, 5000/90 msec; field of view, 300 x300 mm; matrix, 272x200; section thickness, 5 mm with a 1 -mm intersection gap ; **w**hich is suited to detect and evaluate endometrial cancer within the endometrial cavity; tumor infiltration into myometrium, endocervix, and gross extension into the parametria; and other pelvic tumor deposits **.**

Diffusion study:

- Axial oblique DWI was performed. Data acquisition was obtained by

applying three different b factors of 0, 500, and 1000 s/mm^2.

- DW Diffusion weighted images were utilized for calculation of the ADC values.
- ADC measurements were automatically calculated by drawing the largest possible region of interest (ROI) with focus on the solid component of the uterine carcinomas. ADC value was usually expressed in (× 10^{-3}) square millimeters per second.

Image Analysis:

MR images were analyzed for the following:

a) Tumor signal intensity on T1-, T2-weighted images.

b) Tumor size on T2-weighted images: The diameter-based calculation was done by measuring the largest tumor diameter in T2 sequences. The longitudinal diameter (d1) along the long axis of the endometrial cavity on the sagittal images and the antero-posterior diameter (d2: orthogonal to the longitudinal diameter) was measured on the sagittal images**.**

c) Areas of persistent diffusion restriction on DW MR Images (b-value of 1000 seconds/mm2): diffusion weighted imaging (DWI) MR sequences with b=0, b=500 and b=1000, is usually performed at two or more b values including low b values (0 or 50 sec/mm^2) and a very high b value (usually ~1000 sec/mm^2 or 1500 sec/ mm^2), according to that a higher b value can result in stronger diffusion-weighting. And it has an important role in assess response qualitatively by increasing image contrast between the cancer lesion and benign tissues.

Therefore, Examinations with low b values suffer significantly from T2 effects (shine through)**.** By contrast, high b values mostly overcome this effect. However, measurements performed with b value greater than 1,000s/mm^2 provide low-quality images, with an unfavorable signal-to-noise ratio and a low spatial resolution**.**

d) ADC values measurement of the tumor: The ADC maps were calculated and mapped by the imaging system software. To measure normal ADC values, a circular region of interest (ROI) was placed on each uterine zone. The measurements were obtained from the same parts of each zone. The calculation of the endometrium was performed at the fundus level.

The areas of the ROI in my patient groups of the myometrium, endometrium, junctional zone, and cervix were 1.4–3.6, 0.7–8.6, 0.6–1, and 0.7–4.3 cm2, respectively.

Regarding relation between tumor grade and ADC values in endometrial carcinoma: the results showed that the mean ADC value for each histologic grade, which was 0.99±0.03 (G1), 0.92±0.02 (G2), and 0.66±0.04 (G3). Which indicated the inverse relationship between ADC values and tumor cellularity in endometrial cancer. the lower the tumor grade, the wider the SD. While in the cervical carcinoma show the mean ADC value for each histologic grade, which was 1.02±0.07 (G1), 0.97±0.07 (G2), and 0.67±0.05 (G3).

Statistical Analysis:

- Computer software package SPSS (version 12 windows) was used in the analysis.
- Results are expressed as mean (as a measure of central tendency) ± standard deviation (as measures of variability) or number (%).
- Comparison between mean values of ADC in the studied groups was performed using T test.

- P value ≤ 0.05 was considered significant and < 0.01 was considered highly significant.

MRI can accurately assess prognostic indicators in patients who were treated by assessing: the tumor size, parametrial invasion, pelvic sidewall, and lymph node invasion.

RESULTS:

The study group consisted of 20 patients with uterine malignancy (10 cases endometrial carcinoma & 10 cases cervical carcinoma) and the results were analyzed as follows:

(Endometrial carcinoma)

Fifteen patients with pathologically proven endometrial carcinoma with their age ranged between 65 to 92 years (mean age 78.5±9.76 SD) **(Diagram 1)**. 7 patients (70%) complain of post-menopausal bleeding, while 3 patients (30%) complain of menometrorrhagia.

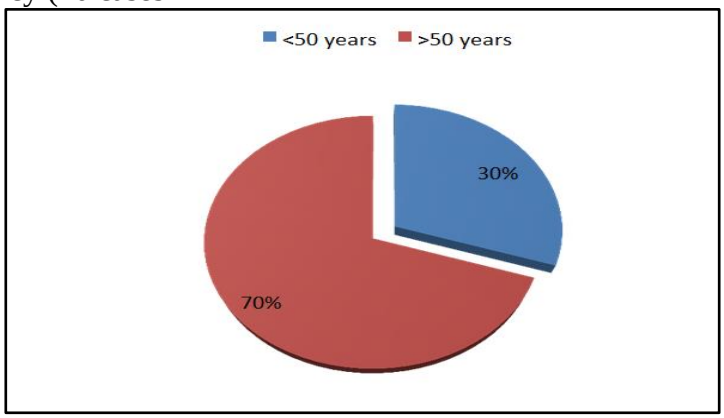

Diagram (1): Age distribution of endometrial carcinoma.

Histopathological types of endometrial carcinoma in the studied group: (Diagram 2)

- 8 patients with endometrioid adenocarcinoma.
- 1 patient with clear cell carcinoma.
- 1 patient with undifferentiated carcinoma.

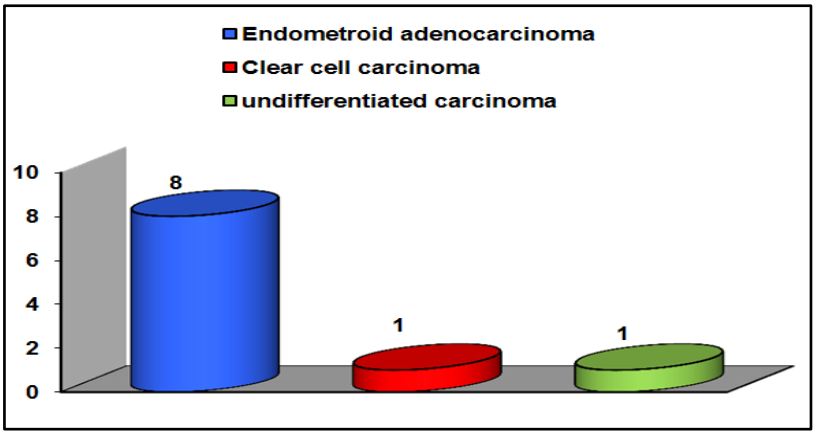

Diagram (2): Histological types of endometrial carcinoma.

In all cases, the tumor intensity was iso to hypointense on T1WIs, of intermediate signal intensity (SI) on T2WIs, showed restricted diffusion of persistent bright SI on Diffusion WIs, and low SI on ADC map. The mean ADC value ($10^{-3}mm^2$/second) of the included endometrial cancer in our study was 0.84±0.17.

Table (1): Endometrial carcinoma grades.

Tumor Grade	Endometrial Ca	
	No	%
Grade I	2	20%
Grade II	2	20%
Grade III	6	60.0%

(Table 1) This table shows that the different tumor grades among the 10 endometrial carcinoma patients was highest in grade III by 60% ,and lower by 20% in both grade I and grade II.

Table (2): Relation between tumor grade and ADC values in endometrial Carcinoma.

Endometrial carcinoma grades		Grade I	Grade II	Grade III
ADC Value ($x10^{-3}$) expressed in mm^2/second	Mean±SD	0.99±0.03	0.92±0.02	0.66±0.04
	Range	0.96 – 1	0.9 – 0.93	0.62 – 0.7

This table shows that the mean ADC value for each histologic grade, which was 0.99±0.03 (G1), 0.92±0.02 (G2), and 0.66±0.04 (G3). Which indicated the inverse relationship between ADC values and tumor cellularity in endometrial cancer. the lower the tumor grade, the wider the SD.

Table 3 shows relation between ADC values in well and poor differentiated endometrial carcinoma, which was >0.9 $x10^3$ in well differentiated tumors with mean ADC value 0.95±0.05 $x10^{-3}$, while it was usually ≤0.9 $x10^{-3}$ in poor differentiated tumors with mean ADC value 0.66±0.04$x10^{-3}$. Which indicated the inverse relationship between ADC values and tumor cellularity

Table (3): Comparison between well and poor differentiated endometrial carcinoma according to their ADC values.

		Well differentiated	Poor differentiated	Chi Square test	
				X^2 / F	P value
ADC category	≤0.9	0 (0%)	4 (100%)	15.00 0	0.0001
	>0.9	6 (100%)	0 (0%)		
ADC Value ($x10^{-3}$) expressed in mm^2/second	Mean±S D	0.95±0.05	0.66±0.04	15.31 1	0.0001
	Range	0.9 – 1	0.62 – 0.7		

Statistical analysis of the ADC values of different tumor grades showed that there was no statistically significant difference between grade 1 and grade 2 (P>0.05) , and between grade 2 and grade 3 (P>0.05), while there was significant difference between grades (1 and 2) from grade 3. i.e.: there was significant difference (P>0.01) between well differentiated & poor differentiated tumors.

Cervical carcinoma:

Fifteen patients with pathologically proven cervical carcinoma with their age ranged between 44 to 92 years (mean age 51.40±15.90 SD). 3 patients (30%) complain of post-menopausal bleeding, while 7 patients (70%) complain of menometrorrhagia.

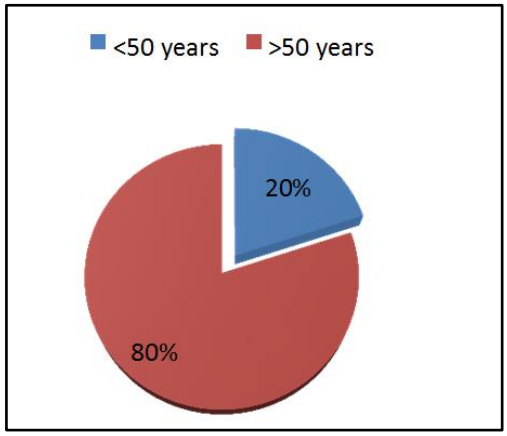

Diagram (3): Age distribution of cervical carcinoma.

Histopathological types of cervical carcinoma in the studied group: (Diagram 4)

- 7 patients with squamous cell carcinoma.
- 2 patients with Adenocarcinoma. 1 patient with spindle cell tumor.

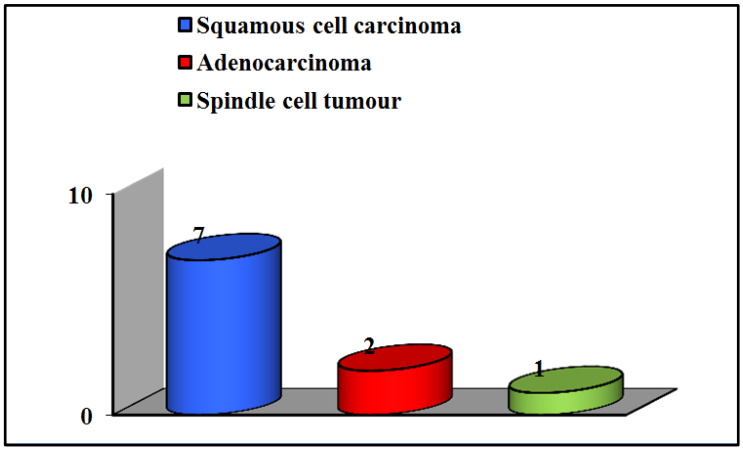

Diagram (4): Histological types of cervical carcinoma.

Studied cervical carcinoma displayed comparable MR signal intensity to those described earlier with endometrial carcinoma in T1, T2 and Diffusion weighted images. The appearance of noninvasive endometrial carcinoma on MRI is characterized by a normal or thickened endometrium, with an intact junctional zone and a sharp tumor-myometrium interface. Invasive endometrial carcinoma is characterized disruption or irregularity of the junctional zone by intermediate signal intensity mass on T2-weighted images .The mean ADC value ($10^{-3}mm^2$/second) of cervical cancer in cases included in our study was 0.90±0.18.

Table (4): Cervical carcinoma grades.

Tumor Grade	Cervical Ca	
	No	%
Grade I	2	20%
Grade II	6	60%
Grade III	2	20%

Table (4) This table shows that the different tumor grades among the 10 cervical carcinoma patients was highest in grade 2 by 60%, and lower by 20% in both grade 1 and grade 3.

Table (5): Relation between tumor grade and ADC values in cervical Carcinoma

Cervical carcinoma grades		**Grade I**	**Grade II**	**Grade III**
ADC Value ($x10^{-3}$) expressed in mm^2/second	Mean±SD Range	1.02±0.07 0.98 – 1.1	0.97±0.07 0.9 – 1.1	0.67±0.05 0.62 – 0.7

Table (5) and Diagram (5) show the mean ADC value for each histologic grade, which was 1.02±0.07 (G1), 0.97±0.07 (G2), and 0.67±0.05 (G3).

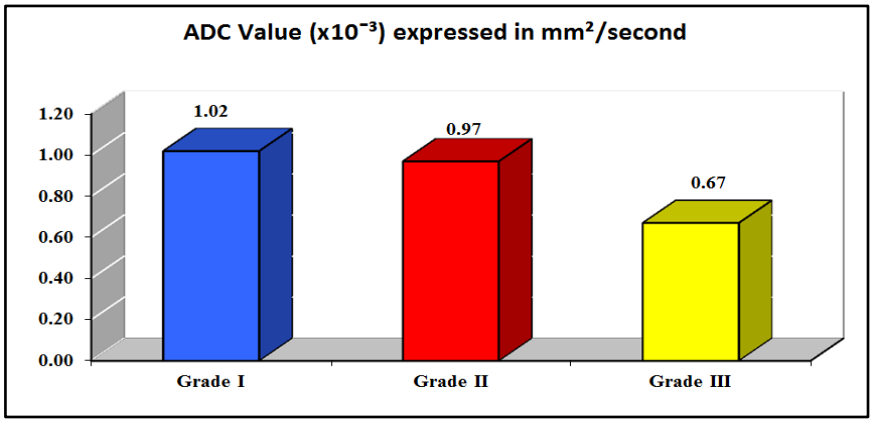

Diagram (5): ADC values of different cervical carcinoma grades

Table 6 and Diagram 6 show relation between ADC values in well and poor differentiated cervical carcinoma, which was $>0.9x10^{-3}$ in well differentiated tumors with mean ADC value 0.99±0.07 $x10^{-3}$, while it was usually $\leq 0.9x10^{-3}$ in poor differentiated tumors with mean ADC value $0.67\pm0.05x10^{-3}$.

Table (6): Comparison between well and poor differentiated cervical carcinoma according to their ADC values.

		Well differentiated	**Poor differentiated**	**Chi Square test**	
				X^2	**P value**
ADC category	≤0.9	0 (0%)	3 (100%)	15.000	<0.001**
	>0.9	7 (100%)	0 (0%)		
ADCValuex10^{-3} expressedinmm^2second	Mean±SD Range	0.99±0.07 0.9 – 1.1	0.67±0.05 0.62 – 0.7	9.551	<0.001**

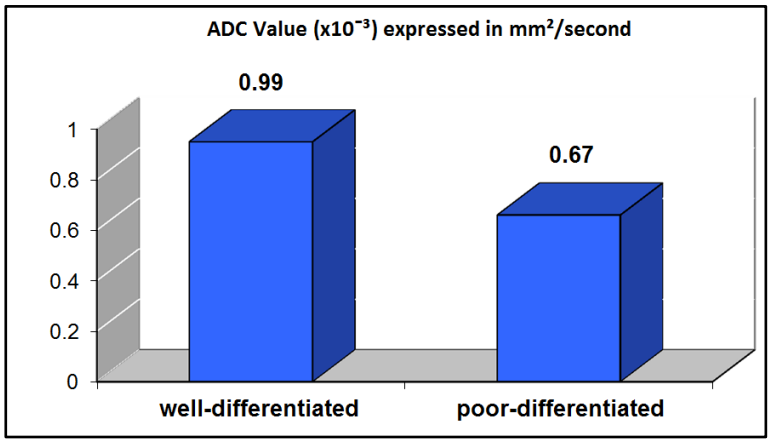

Diagram (6): Comparison between well and poor differentiated cervical carcinoma according to their ADC values.

Statistical analysis of the ADC values of different tumor grades showed that there was no statistically significant difference between grade 1 and grade 2 (P>0.05), and between grade 2 and grade 3 (P>0.05), while there was significant difference between grades (1 and 2) from grade 3. i.e.: there was significant difference (P<0.01) between well differentiated & poor differentiated tumors.

Uterine carcinoma (endometrial and cervical):

When dividing the 20 patients into 3 groups according to their pathologic grade, (G1, n=9; G2, n=11; G3, n=10) the higher grade tumors tend to have lower ADC values, while lower grade tumors tend to have higher ADC values. **Table (7)** shows the mean ADC values in different grades in uterine carcinoma (Endometrial & Cervical) with mean ADC value 1.0±0.05 for Grade I, 0.95±0.07 for Grade II and 0.66±0.04 for Grade III. Therefore, well differentiated tumors (Grade I & II) usually have ADC values >0.9, while poor differentiated tumors (Grade III) usually have ADC values ≤0.9.

Table (7): Relation between ADC values and different tumor grades in both Endometrial & Cervical Carcinomas.

		Grade I	**Grade II**	**Grade III**	**Chi-square test**	
		n = 4	**n = 8**	**n = 8**	**X^2**	**P-value**
ADC category	≤0.9	0 (0.0%)	0 (0.0%)	8 (100.0%)	30.000	<0.001**
	>0.9	4 (100.0%)	8 (100.0)%	0 (0.0%)		
ADC	Mean±SD	1.0±0.04	0.95±0.06	0.66±0.03	158.045	<0.001**
	Range	0.96 - 1.1	0.9 - 1.1	0.62 - 0.7		

When dividing the 20 patients into 2 groups well-differentiated (n=13) & poor differentiated (n=7) according to their pathologic grade, well differentiated tumors tend to have higher ADC values, while poor differentiated tumors tend to have lower ADC values. Table (8) shows the different mean ADC values of well and poor differentiated tumors in uterine carcinoma (Endometrial & Cervical) which was 0.94±0.07 in well differentiated tumors and 0.66±0.04 in poor differentiated tumors.

Table (8): Mean ADC values of well and poor differentiated tumors in uterine carcinoma (Endometrial & Cervical).

		Well differentiated	Poor differentiated	Chi-square test	
		n = 13	n = 7	X^2	P value
ADC category	≤0.9	0 (0.0%)	7 (100.0%)	30.000	<0.001**
	>0.9	13 (100.0%)	0 (0.0%)		
ADC	Mean±SD	0.94±0.07	0.66±0.04	16.415	<0.001**
	Range	0.9 - 1.1	0.62 - 0.7		

ADC Value ($x10^{-3}$) expressed in mm^2/second:

Statistical analysis of the ADC values of different tumor grades in uterine carcinoma (Endometrial & Cervical) showed that there was no statistically significant difference between grade 1 and grade 2 (P>0.05), and between grade 2 and grade 3 (P>0.05), while there was significant difference between grades (1 and 2) from grade 3. i.e.: there was significant difference (P>0.01) between well differentiated & poor differentiated tumors.

Correlation between uterine Tumor size & grading:

Tumor size is an important prognostic factor that is particularly helpful in directing adjuvant radiation therapy. During the study analysis; an extra attention was drawn to find out if there is a correlation between tumor size and the tumor grade, according to

us; the tumor size for endometrial and cervical cancer showed a trend to be larger in grade 3 tumors than grade 1& 2; however, this did not reach a statistical significance. The 10 cases were included in that assessment and findings were presented in (Table 9).

Table (9): Correlation between Tumor size and Tumor grade in the studied patients.

		Grade I	Grade II	Grade III
		n = 2	n = 3	n = 5
Tumor Size	Mean±SD	1.5±2.5	1.5±2.0	4±2
	Range	1 - 2	2 - 3	2 - 6

Relation between Parametrial invasion & ADC value:

When dividing the 20 patients into 2 groups invasion (n=6) & non-invasion (n=14) according to their ADC value, Non-invasion have higher ADC values, while Invasion have lower ADC values, there was highly statistically significant with p-value (p<0.001). **(Table 10 and Diagram 12)** show the different mean ADC values of non-invasion and invasion in uterine carcinoma (Endometrial & Cervical) which was 0.98±0.08 in non-invasion and 0.69±0.05 in invasion.

Table (10): Relation between ADC value (x10^{-3}) expressed in mm^2/second and parametrial invasion in both Endometrial & Cervical Carcinomas.

		Parametrial invasion		Chi-square test	
		Invasion	Non-Invasion		
		n = 6	n = 14	X^2	P-value
ADC category	≤0.9	6 (100%)	0 (0%)	15.522	<0.001**
	>0.9	0 (0%)	14 (100%)		
ADC	Mean±SD	0.69±0.05	0.98±0.08	8.151	<0.001**
	Range	0.62 - 0.75	0.91-1.1		

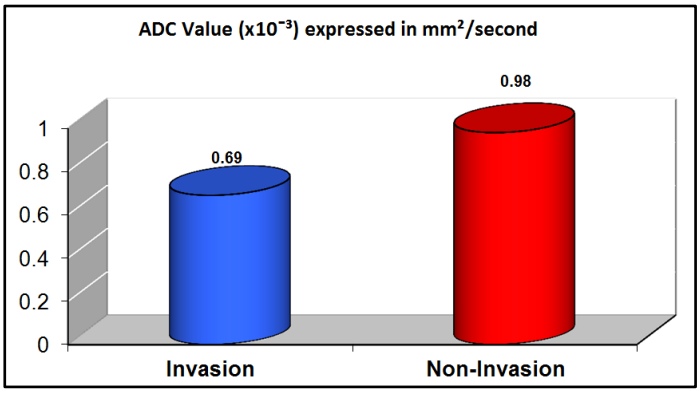

Diagram (7): Relation between ADC value (x10^{-3}) expressed in mm^2/second and parametrial invasion in both Endometrial & Cervical Carcinomas.

Relation between Tumor size & ADC value:

When dividing the 20 patients into 2 groups Tumor size <4cm (n=13) & Tumor size ≥4cm (n=7) according to their ADC value, Tumor size <4cm have higher ADC values, while Tumor size ≥4cm have lower ADC values, there was highly statistically significant with p-value (p<0.001). Table (11) shows the different mean ADC values of Tumor size <4cm and Tumor size ≥4cm in uterine carcinoma (Endometrial & Cervical) which was 0.96±0.08 in Tumor size <4cm and 0.68±0.05 in Tumor size ≥4cm.

Table (11): Relation between ADC value ($x10^{-3}$) expressed in mm^2/second and Tumor size "cm" in both Endometrial & Cervical Carcinomas.

		Tumor Size		Chi-square test	
		<4 cm	≥4 cm		
		N=13	N=7	X^2	P-value
ADC category	≤0.9	0 (0%)	7 (100%)	15.848	<0.001**
	>0.9	13 (100%)	0 (0%)		
ADC	Mean±SD	0.96±0.08	0.68±0.05	8.662	<0.001**
	Range	0.91-1.1	0.62 - 0.8		

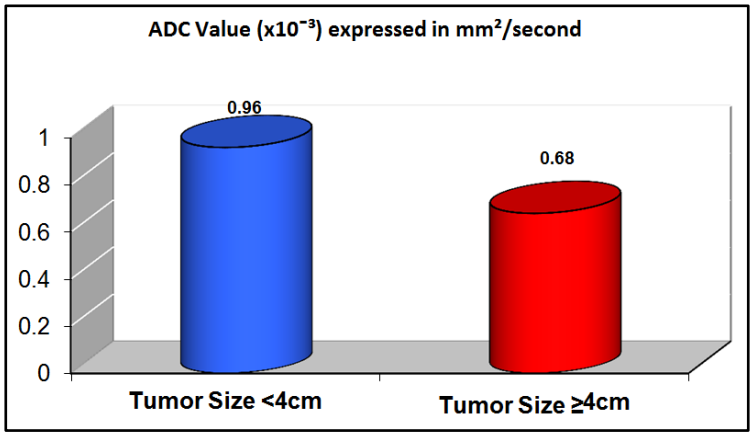

Diagram (8): Relation between ADC value (x10-3) expressed in mm2/second and Tumor size "cm" in both Endometrial & Cervical Carcinomas.

Relation between Tumor Stage & ADC value.

Statistical analysis of the ADC values of different tumor stage in uterine carcinoma (Endometrial & Cervical) showed that there is no statistically significant difference between stage 1, stage 2 and Stage 3 (P>0.05), while there was significant difference between stage (I, II and II) compared to grade IV. i.e.: there was significant difference (P<0.01).

Table (12): Relation between ADC value (x10-3) expressed in mm2/second and Tumor Stage in both Endometrial & Cervical Carcinomas.

			Tumor Stage			Chi-square test	
		Stage I	Stage II	Stage III	Stage IV		
		N=7	N=7	N=4	N=2	X^2	P-value
ADC category	≤0.9	0 (0%)	0 (0%)	2 (50%)	2 (100%)	13.750	0.003*
	>0.9	7 (100%)	7 (100%)	2 (50%)	0 (0%)		
ADC	Mean±SD	1.02±0.05	0.97±0.07	0.89±0.08	0.67±0.04	69.681	<0.001**
	Range	0.94 - 1.1	0.91 - 1.1	0.67-0.84	0.62 - 0.7		

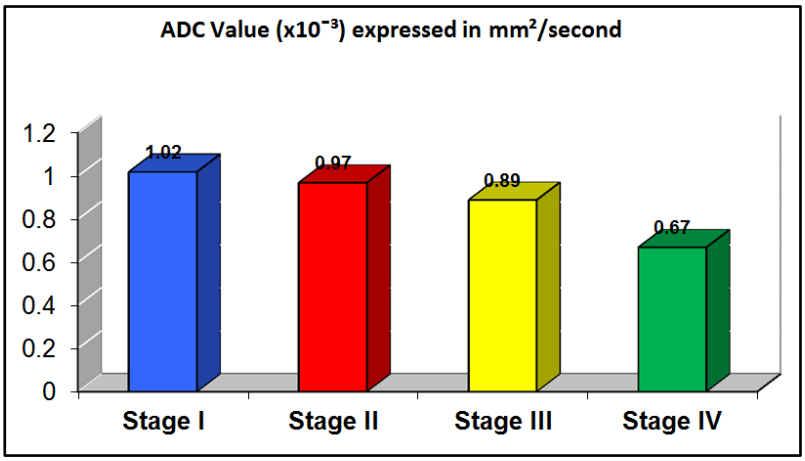

Diagram (9): Relation between ADC value (x10^{-3}) expressed in mm^2/second and Tumor Stage in both Endometrial & Cervical Carcinomas.

DISCUSSION:

Histological grade is one of the main prognostic factors in patients with uterine cancer; preoperative prediction of the grade using histographic analysis of ADC maps may provide necessary clinical information and guide clinicians with more accurate staging and subsequent management **(12).**

MR imaging plays an important role in the patient's journey from the initial evaluation of disease extent to treatment selection and follow-up **(4).**

Though MRI not included in FIGO clinical staging system, the FIGO staging committee in 2009 has advised the incorporation of cross-sectional imaging techniques (MR imaging & CT) into the evaluation and treatment planning of patients**(13).**

Diffusion weighted magnetic resonance imaging (DW-MRI) is now part of the standard imaging protocols for accurate diagnosis of uterine malignancies**(14).**

Recently, Quantitative analysis of maximum ADC (difference) value of uterine cervical cancer was considered for the assessment of the grade of tumor differentiation since it provides valuable information on tumor microcirculation and perfusion **(15).**

The aim of our study was to investigate whether the apparent diffusion coefficient (ADC) values of uterine cancer differ according to the histologic grade of the tumor and to find out whether diffusion weighted imaging is needed to assess the grade of endometrial or cervical carcinoma.

In this study we prospectively evaluated 20 cases presented with different grades of endometrial (n=10) and cervical (n=10) carcinoma. Results were correlated to the pathologic grading.

Until now, several investigators have explored the value of diffusion-weighted magnetic resonance imaging (DWI) for preoperative tumor grading of endometrial Carcinoma.

Our results showed that uterine cancer of higher grade tended to have lower ADC values as compared with cancer of lower grade.

Murakami et al.(16) stated that ADC value is inversely related to the tumor cellularity and consequently may suggest tumor grading and aggressiveness**(16).**

Similarly in **2007, Tamai et al.(17)** performed a study on 30 female patients and

concluded that The ADC values of endometrial cancers of higher grade showed tendency to decrease compared to those of lower grade. According to their results; the mean ADC value of endometrial cancer was (0.88 +/- 0.16), which was significantly lower (P < 0.01) than that of normal endometrium (1.53 +/- 0.10). The mean ADC value for each histologic grade was 0.93 +/- 0.16 (G1), 0.92 +/- 0.13 (G2), and 0.73 +/- 0.09 (G3)**(17).**

Going in the same path; another study was performed in 2013 and stated that The standard deviation for ADC values was found to be significantly different between the grades of endometrial carcinoma (P=0.03). It was significantly different between grades 1 and 3 (P=0.03), and between grades 2 and 3 (P=0.018), but not between grades 1 and 2 (P=0.818)**(12).**

However, the diagnostic value of DWI with quantitative ADC in grading of the endometrial carcinoma has been controversial **(18).**

In 2011 Rechichi et al. (19) observed that the ADC value in endometrial cancers did not show a significant relationship with tumor grade.

Also **in 2011, Bharwani et al. (20)** performed a study on 23 female patients with histologically proved endometrial cancer aiming to correlate the ADC value with the histological tumor grade. The study concluded that there was considerable overlap and no statistically significant difference between tumor grades for mean ADC or minimal ADC values.

In my study, the results were similar to finding of **Tamai et al. (17)** and **Woo et al. (12)** with the mean ADC value of endometrial cancer of (0.84 ± 0.15 x10^{-3}) mm^2/sec. The mean ADC value for each histologic grade was 0.99 ± 0.02 (G1), 0.92 ± 0.01 (G2), and 0.66 ± 0.03 (G3).

I observed that; there was no statistically significant difference between grade 1 and grade 2, and between grade 2 and grade 3, while there was significant difference between grades (1 and 2) from grade 3. i.e.: there was significant difference (P < 0.01) between well differentiated & poor differentiated tumors.

Several factors may be the cause of discrepant results as the selection and positioning of the ROIs, therefore, I believe the presence of macroscopic cystic or necrotic areas within the tumor which are more frequently seen in higher grade uterine cancers could justify the higher frequency of voxels with high ADC values within the tumor bulk **(21)**.

In 2009, Lin et al,(22), performed a study on 32 female patients with pathologically proven cervical cancer and concluded that The ADC value of cervical cancer represents tumor cellular density, thus evaluating the pathologic grading of tumor and presented mean ADC value of cervical cancer (0.88 +/- 0.15 x 10^{-3} mm^2/sec). Higher grade tumors tend to have lower ADC values and higher cellular density. The apparent diffusion coefficient value of different pathologic grade varied significantly (b = 0.000); the ADC value of grade 3 tumors was statistically lower than that of grade 1 tumors (b = 0.000) and also grade 2 tumors (b = 0.014), and the ADC value of grade 2 tumors was statistically lower than that of grade 1 tumors (b = 0.000). The mean ADC value for each histologic grade was 1.09 +/- 0.16 (G1), 0.86 +/- 0.10 (G2), and 0.71 +/- 0.05 (G3).

Also, another study was done in 2015 showed that the mean ADC value of cervical cancer was (0.849 +/- 0.157). The mean ADC value for each histologic grade was 1.091 +/- 0.37 (G1), 0.859+/-0.133 (G2), and 0.807 +/- 0.11 (G3). Thus there was a significant difference between G1 and G2 (P = 0.03) and G1 and G3 (P = 0.001) but no significant difference between G2and G3 (P = 0.56) **(23).**

My results were similar to **Liu Y, et al.** [15] in finding no statistically significant difference between grade 1 and grade 2, and between grade 2 and grade 3, while there was significant difference between grades (1 and 2) from grade 3.

i.e.: there was significant difference ($b < 0.01$) between well differentiated & poor differentiated tumors with mean ADC value of cervical cancer (0.90 ± 0.16). The mean ADC value for each histologic grade was 1.02 ± 0.06 (G1), 0.97 ± 0.06 (G2), and 0.67 ± 0.04 (G3).

We have to admit that our patient population was relatively small, yet this did not limit us from deriving the inclusion, exclusion criteria and differentiating high from low-grade uterine carcinoma, further investigation that includes a larger population is warranted to strengthen the statistical power.

Although imaging of the female pelvis with the echo planar sequences is limited by many artifacts, however these artifacts were not an obstacle during our performance of pelvic DWI. We used a pelvic phase array body coil to improve the imaging quality. Thus, for all cases, the artifacts and deformation of the DW imaging were low; hence, the imaging fulfilled the requirements needed to make the diagnosis.

Tumor size is an important prognostic factor that is particularly helpful in directing adjuvant radiation therapy in patients without staging lymph node biopsies[24].

Cranio-caudal tumor extension is particularly important for determining the feasibility of organ-sparing surgery of early cervical cancer, and for potential sparing of the uterine corpus in radiation therapy[25].

In 2014, Berretta, et al.[26] stated that grading and endometrial tumor dimension is related. In particular, a maximum correlation was noted between well differentiated and highly undifferentiated cancer in relation to tumor size.

In patients selected for trachelectomy, it is preferable to leave some healthy cervical stroma in situ so that the risks of cervical incompetence, infection, premature rupture of membranes and premature delivery in subsequent pregnancies are reduced [27].

Most surgeons require 1 cm of tumor free cervix proximal to the tumor but some will accept 5–7 mm. Therefore, pre-operative assessment with MRI to determine the maximum tumor diameter, volume and degree of endocervical extension is of major importance [28].

In 2014, Downey, et al. [29] stated that tumor size correlates with histopathological cervical grade ($b < 0.0001$) using a combined T2- and diffusion-weighted endo-vaginal MRI technique at 3.0 T.

Conclusion

Lower ADC values were associated with poorly differentiated endometrial and cervical tumors. Therefore, the ADC value may represent a useful marker for assessing the biological features and grading of the uterine cancers.

Conflicts of Interest: The authors state that the publishing of this paper is free of any conflicts of interest.

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دور التصوير بالرنين المغناطيسى بخاصية الانتشار فى تحديد درجات سرطان عنق وبطانة الرحم

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المقدمة: الدرجة النسيجية هي أحد العوامل الإنذارية الرئيسية في المرضى الذين يعانون من سرطان بطانة الرحم وعنق الرحم. يوفر التصوير بالرنين المغناطيسى بمعامل الانتشار معلومات جديدة مهمة غير جراحية.

الهدف من الدراسة: التحقق مما إذا كان هناك ارتباط نوعي (بصري) وكمي (قيمة ADC) التي يوفرها التصوير الموزون بالانتشار ودرجة سرطان الرحم وسرطان عنق الرحم من أجل الوصول إلى خيارات العلاج المناسبة.

المرضى وطريقة البحث: أجريت دراستنا على عشرين مريضًا مصابات بسرطان بطانة الرحم (بعدد 10) وسرطان عنق الرحم (ن = 10). وشدد على دور التصوير بالرنين المغناطيسي المنتشر في التصنيف قبل الجراحة ، بهدف التأكيد على دوره في الاختيار المناسب لخطة معالجة المريض. أجرينا التصوير بالرنين المغناطيسى باستخدام قيم b مختلفة ، وتحليل كمي ، يسمى معامل الانتشار الظاهري. أظهرت مناطق انتشار المياه المقيد للأورام الخبيثة في الرحم كثافة إشارة عالية على التصوير بالرنين المغناطيسى وقيم معامل الانتشار الظاهرى.

النتائج: كان هناك اختلاف ذو دلالة إحصائية (عند نقطة دلالة إحصائية < 0,01 بين الصفين (1 و 2) من الصف الثالث في قياس قيم معامل الانتشار الظاهرى لكل من سرطان بطانة الرحم وعنق الرحم ، بينما لم يكن هناك فرق ذو دلالة إحصائية بين الصفين الأول والثاني أو بين الصفين. 2 والدرجة 3. كان متوسط قيمة ADC للأورام المتمـــايزة جيـــدًا (< 0.9 × 10-3 مم 2 / ثانية) ، بينما كانت قيمة الأورام المتمايزة الفقيرة (<0.7 × 10-3 مم 2 / ثانية). قمنا أيضًا بتضمين تحليلنا حجم سرطان الرحم المثبت وهدفنا إلى إنشاء عنصر آخر يمكن أن يعكس تصنيف الورم ، لكننا لم نصل إلى أهمية إحصائية في البحث الحالي ؛ والتي يمكن أن تكون بسبب حجم العينة المحدود.

الخلاصة: ارتبطت قيم معامل الانتشار الظاهري المنخفضة بأورام بطانة الرحم وعنق الرحم سيئة التمايز. لذلك، قد تمثل قيمة ADC علامة مفيدة لتقييم السمات البيولوجية وتصنيف سرطانات الرحم.