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## Can Diffusion weighted MR imaging add diagnostic information in the evaluation of uterine tumor?

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# ABSTRACT

**Purpose:** to evaluate the role of DW imaging in the detection of cervical and endometrial cancers and correlate the histopathological grading and ADC values.

**Materials and Methods:**

53 women with positive biopsy for cervical and endometrial cancer enrolled in the study underwent MR examination; based on biopsy 34/53 patients had cervical cancer and 19/53 patients had endometrial cancer.

MR study protocol included DWI sequence obtained with a single-shot echo-planar sequence (EPI) in the axial or sagittal plane, with b value of 500s/mm2.

MR protocol also included fast spin-echo T2w.i. sequences acquired in the sagittal and axial planes. Lesions' signal intensity and ADC values were evaluated on DWI images. Lesions' signal intensities on T2w.i and maximum diameter were also collected.

Student's $t$ test was applied for statistical analysis of collected data; a two tailed p-value of less than 0.05 was considered as significant.

**Results:**

On DWI, only 30/53 tumors were appreciable , in particular 29/30 lesions (96.7%) were cervical cancers; 1/19 was an endometrial cancer; 18/19 endometrial cancers and 5/34 cervical cancers were not detectable on DWI images.

No relationship was found between cervical cancers' size and lesions' signal intensity on DWI nor lesions' signal intensity on T2w.i. ($p>.05$).

Mean ADC values of G1 graded cervical cancers resulted to be significantly higher than ADC values of G2 and G3 graded neoplasms ($p<.05$).

**Conclusion:** DWI can help in detecting the presence of cervical tumor, while it does not result useful in assessing the presence of endometrial neoplasms.

ADC values of well differentiated cervical cancers are higher than relative values of more de-differentiated neoplasms

## INTRODUCTION

Diffusion-weighted imaging (DWI) is a functional imaging technique, applied in Magnetic Resonance imaging, whose contrast derives from the random motion of water molecules within explored tissues.

Since image contrast is derived from inherent differences in the restriction of the movement of water molecules, no exogenous contrast medium administration is required, so that DWI sequences can now be included in routine patient assessment.

DWI uses the measurement of Brownian movements of water molecules by applying symmetric pairs of equally weighted diffusion sensitizing gradients about the 180°refocusing pulse of a spin-echo T2-weighted sequence. Static water molecules develop additional phase incoherencies from the application of the first diffusion gradient, but these incoherencies are eliminated by the application of the second gradient, resulting in no additional net loss of signal (aside from normal T2 decay) [1]. However, mobile water is not completely rephased by the second gradient owing to movement to a different microenvironment during the application of the first gradient, so that a subsequent reduction in signal intensity is observed. DWI sensitivity to water motion is dependent on three main parameters: the gradient amplitude, the duration, and the time interval (b-value) between paired diffusion gradients [2]. Tissues containing water that is moving the most freely (eg, within blood vessels, ducts, or the bladder) will demonstrate greater signal losses after the application of the smallest diffusion gradients (<100 sec/mm2). Signal losses caused by water motion in the extracellular space of tumors occur at higher b values because water motion is modified by interactions with hydrophobic cell membranes

and macromolecules (increased extracellular space tortuosity) [3]. In solid tumors of high cellularity, there are additional significant reductions in extracellular space, resulting in further restrictions to free water movement.

When DWI is used in gynecologic applications, cervical cancers have been shown to have significantly lower apparent diffusion coefficient (ADC) values than normal cervical tissue [4]. Similar findings have been noted in endometrial cancers, with a tendency toward lower ADC values in higher-grade lesions.

## ADC value

The ADC value (measured in mm2/sec) is usually calculated by the slope of the line of the natural logarithm of signal intensity (y axis) versus b values (x axis) [5].


## DWI imaging: applications in female pelvic neoplasms

## Cervical cancer

Cervical cancer is the second most common female cancer in the world and it occurs predominantly in women between the age of 30 and 44 years [6]. The American Cancer Society provides the following list of risk factors for cervical cancer: Human Papillomavirus (HPV) infection, smoking, HIV infection, chlamydia infection, dietary factors, hormonal contraception, multiple pregnancies, exposure to the hormonal drug diethylstilbestrol (DES) and a family history of cervical cancer [7].

## Cervical cancer: Histopathology

The World Health Organization (WHO) recognizes two main histological types of invasive cervical cancer.

- Squamous carcinoma (which constitute about 85% of all cases)
- Adenocarcinoma (which constitute about 10-12% of all cases)

Several other types of carcinoma (eg adenosquamous carcinoma, adenoid cystic carcinoma, metastatic carcinoma) make up the remaining 3-5% of all cases.

Squamous carcinomas are further typed according to whether they are keratinizing or not keratinizing carcinomas. Keratinizing carcinomas may be well differentiated or moderately differentiated and are composed of large tumour cells. Non-keratinizing carcinomas (poorly differentiated carcinomas) may be of large cell or small cell type [8].

Most cervical squamous cell carcinomas grow at the squamocolumnar junction (SCJ). In young women, the SCJ is located outside the external uterine os, and the tumor tends to grow outward (exophytic growth pattern). In contrast, in elderly patients, the SCJ is located within the cervical canal. In these patients, cervical cancer tends to grow inward along the cervical canal (endophytic growth pattern) [9].

Adenocarcinomas are less commonly found and although each type is histologically distinct, it is not uncommon to find two or more histological forms of adenocarcinoma in a single tumour .The frequent coexistence of glandular and squamous carcinoma suggest that they may have a common origin in the reserve cells of the cervix as well as a common etiology. The most frequent type of adenocarcinoma to be found in the cervix is the endocervical type of mucinous adenocarcinoma. Three grades of endocervical carcinoma are recognized -well differentiated, moderately differentiated and poorly differentiated - depending on the similarity of the tumour cell to the glandular epithelial lining the endocervix. In fact, in endocervical adenocarcinoma, endocervical type, different subtypes can be found (endometrioid type, clear cell type, papillary serous type, intestinal type, mixed type) [10].

## Cervical cancer: MR features

At baselineT2 w.i MR examination, cervical cancers appear as slightly hyperintense masses, while their predominantly signal intensity on baseline T1 w.i is hypointensity. On vascular dynamic study, cervical cancers can show no enhancement or slighly marginal enhancement on arterial phase.

## Endometrial cancer

Endometrial cancer is the most common malignancy of the genital tract and overall the endometrium is the fourth most frequent cancer site. Risk factor for endometrial cancer include obesity, diabetes, oestrogen therapy, polycystic ovarian syndrome and westernization of lifestyle.[11]. Approximately 75% of cases occur in postmenopausal women, with the median age at diagnosis being 70 years.

## Endometrial cancer: Histopathology

Endometrial tumors can be have different histology: endometrial carcinoma (with its histopathologic subtypes: villoglandular  or papillary, secretory, ciliated cell, adenocarcinoma with squamous differentiation), adenocarcinoma (serous, mucinous, clear cell), squamous cell carcinoma; undifferentiated carcinoma; mixed carcinoma, metastatic carcinoma and carcinosarcoma.

Adenocarcinomas account for 90% of endometrial neoplasms, whereas uterine sarcomas are relatively rare and account for only 2%–6%; the remaining histologic types include adenocarcinoma, with squamous cell differentiation and adenosquamous carcinoma [12].

**Endometrial cancer: MR features**

At MR examination, endometrial cancer is iso-hypointense in respect to the surrounding normal endometrium on baseline T1w.i -weighted images, while it does most commonly show heterogeneous, iso up to hyperintensity on baseline T2wi.

Neoplasms are usually mildly hyperintense on baseline T2w.i. in respect to myometrium.

Endometrial cancer can have different pattern of appearances on baseline T2 w.i.: hypointense pseudonodular lesions, diffuse endometrial thickening, hypointense vegetations, or infiltrative endometrial plaques with heterogeneous signal intensity.

Endometrial carcinomas are divided into two types: one shows as a well-demarcated exophytic mass (Type I), while the other shows as an invasive, endophytic growth toward the myometrium (Type II). The former subtype is considered to be malignant with favorable prognosis [13].

# MATERIALS AND METHOD

**Patients**

The present retrospective study received institutional ethics committee approval, and all patients provided informed written consent.

Study group consisted of 53 women (mean age: 54.5 years; range 30–83) years with biopsy positive for cervical and endometrial cancer and enrolled from March 2008 to January 2012.

All the patients performed MR examination after biopsy . Mean time between biopsies and MR examination resulted to be 2 weeks.

**MRI study**

All MRI examinations were performed with a 1.5 T unit (Excite,Twin Speed, GE Healthcare) with an 8 channel phased-array coil.

MRI protocol included fast spin-echo T2wi.i sequences acquired in the sagittal and axial planes [repetition time/echo time (TR/TE), 4000 ms/85 ms; echo-train length 17; matrix size 320 # 224; band width 31.25 Hz/pixel; field of view 36 cm; NEX: 2; slice thickness: 6 mm; gap: 1 mm); when needed a sagittal or axial FSE T2w.i sequence with fat saturation was performed.

DWI sequence was acquired using single-shot echo-planar imaging (EPI) and array spatial sensitivity encoding technique (ASSET; TR/TE 4000 ms/58.5 ms; matrix size 128x128-

224; field of view 26-34 cm; nex 4; section thickness 6 mm; gap 1 mm; R factor 2) in the

axial or sagittal plane with b values of 0 and 500 s/ mm2. The DWI examination time was

1-2 min.

**Statistical analysis**

The Student's *t*-distribution was used for the two arm comparison and *p* value acquisition.

Receiver operating characteristic analysis and relationship between cervical cancers' size

and lesions' signal intensity on DWI  nor  lesions' signal intensity on T2w.i. or between

cervical cancers' size and lesions' signal intensity on T2w.i were calculated. Finally we

searched relationship between  mean ADC values and histological grading. A p-value of

less than 0.05 was considered as significant.

# RESULTS

At histology, 53 patients had a bioptical diagnosis of a uterine cancer.  34 patients had a

cervical cancer and 19 an endometrial cancer.

Out of 34 cervical cancers, 19 were non keratinizing squamous cell carcinomas, 10

keratinizing squamous cell carcinomas, 4 endocervix adenocarcinomas and 1 cancer with

mucinous aspects.

Out of 19 endometrial cancers, 12 patients were endometrioid adenocarcinoma, 1

neuroendocrine tumor, 2 were adenocarcinoma with squamous cell differentiation, 1 was a

endometrioid serous adenocarcinomas; 1 patient with endometrioid mucinous

adenocarcinoma;1 case of endometrial metastasis of urotelial cancer and 1 patient with a

carcinosarcoma.

Well differentiated cervical cancer G1 had increased ADC value from 1,30 to 1,40  e-9; in

mildly differentiated cervical cancers (G2) ADC value could range from 0,82 to 1,24 e -9.

In poorly differentiated tumors (G3) ADC value could range from 0,43 to 1,24 e-9. (Table. 2).

On DWI, only 30/53 tumors were appreciable, in particular 29/30 lesions (96.7%) were cervical cancers; 1/19 was an endometrial cancer; 18/19 endometrial cancers and 5/34 cervical cancers were not detectable on DWI images.

No relationship was found between cervical cancers' size and lesions' signal intensity on DWI nor lesions' signal intensity on T2w.i. (p>.0.5).(Table. 3- 4).

Mean ADC values of G1 graded cervical cancers resulted to be significantly higher than ADC values of G2 and G3 graded neoplasms (p<.0.5). (Table. 5)

## DISCUSSION

### Cervical cancer

With increasing tumor cellularity and architectural distortion, there is a reduction in extracellular space, which also becomes increasingly tortuous. These changes are reflected by a reduced ADC value. High-grade adenocarcinomas typically have high cellular density and so would be expected to have lower ADC values. A trend toward lower ADC values in higher-grade endometrial cancers was noted by Tamai et al [14].

Our study confirms that high-grade adenocarcinomas typically have high cellular density and lower ADC values.

Well differentiated cervical cancer G1 had increased ADC value from 1,30 to 1,40 e-9; in mildly differentiated cervical cancers (G2) ADC value could range from 0,82 to 1,24 e -9. In poorly differentiated tumors (G3) ADC value could range from 0,43 to 1,24 e-9.

A limit of DWI in discovering cervical cancer was correlate to exclusive localization in the uterine fornix (anterior or posterior) or to uterine atrophic structure. In the most of case cervical cancers exhibited a ovalar morphology. Cervical cancers appeared hyperintense

on T2 w.i in 25 patients; isointense in 6 patients and hypointense in 1 patient.

ADC value at b 500 correlated with histological grading and therefore with prognosis. In fact ADC value from 0,43 to 1,24 e-9 were correlate to a bad prognosis instead a ADC value from 1,30 to 1,40 e-9 was correlate to a good prognosis.

**Endometrial cancer.**

The use of a high b-value makes images more sensitive to water diffusion; it thus increases contrast enhancement between normal and cancerous tissue, but this is offset by decreased signal intensity and anatomic detail in the adjacent structures [15]. DWI can demonstrate uterine endometrial cancer and ADC measurement can provide useful information for differentiating malignant from benign uterine endometrial cavity lesions. Higher-grade endometrial cancers exhibit a tendency towards decreased values compared to those of lower-grade lesions. In our study, using a b value (500), DWI was not useful to reveal endometrial cancer (DWI failed in detection in 18 patients (94,73%). DWI allowed to reveal size of lesion in 1 patient. Generally endometrial tumor appeared as a slightly hypointense lesion on DWI in contrast with marked hyperintensity of normal endometrium, without revealing margin and tumoral size or as hypointense line in thickened endometrium. Rarely, as in one case of our study, endometrial tumor appeared as hyperintense lesion on DWI.

Endometrial cancers is better revealed on T2 w.i where tumor can exhibit a focal hypontensity in endometrial cavity or a decreased hyperintensity in a thickened

endometrium.

Meanwhile, we confirm as noted by Sachi Kaneda [17] that endometrial cancer appears more elongated than cervical cancer and tends to form a longitudinal shape while cervical cancer tends to appear round or ovoid because in growth endometrial cancer is

sandwiched by the strong uterine muscular wall. Therefore endometrial cancer is forced to migrate in a cranio-caudal direction rather than a lateral direction, thus resulting in an elongated configuration.

Some limitations of this study need to be taken into consideration. First, this was a retrospective study, and the readers knew the diagnosis of endometrial and cervical carcinoma when they reviewed the images, which may have influenced the readers. Second, the study was also limited by the relatively small number of patients included. Third, small cancers' (<1cm) were excluded from study.

**TABLES**

**Table1:** MR protocol- T2 w.i Technical parameters.

| Parameters  T2w.i | |
|---|---|
| TR/TE | 4000 ms/85 ms |
| Echo-train length | 17 |
| Matrix size | 320 # 224 |
| Band width | 31.25 Hz/pixel |
| Field of view | 36cm |
| gap | 1mm |

**Table 2:** Histological grading and ADC value calculated in cervical cancer

| Histological grading | ADC values (e-9 mm2/s) |
|---|---|
| G1 | 1.30-1.40 |
| G2 | 0.82-1.24 |
| G3 | 0.45-1.24 |

**Table 3:** no relationship between cervical cancers' size and lesions' signal intensity on DWI

| Signal Intensity DW | Number | Mean of Area | Std Dev | P value |
|---|---|---|---|---|
| Hyperintense | 27 | 1833,41 | 1506,16 | 0,13 |
| Hypointense | 5 | 306,00 | 200,95 | 0,03 |
| Isointense | 2 | 2138,00 | 1558,46 | 0,77 |

**Table 4:** no relationship between cervical cancers' size and lesions' signal intensity on T2 w.i.

| Signal Intensity T2 | Number | Mean of Area | Std Dev | P value |
|---|---|---|---|---|
| Hyperintense | 26 | 1696,65 | 1611,37 | 0,57 |
| Hypointense | 2 | 1062,50 | 1219,76 | 0,71 |
| Isointense | 6 | 1511,67 | 972,18 | 0,78 |

**Table 5:** significantly relationship between histological grading and mean ADC value in G1 cervical cancer (p<.0.5).

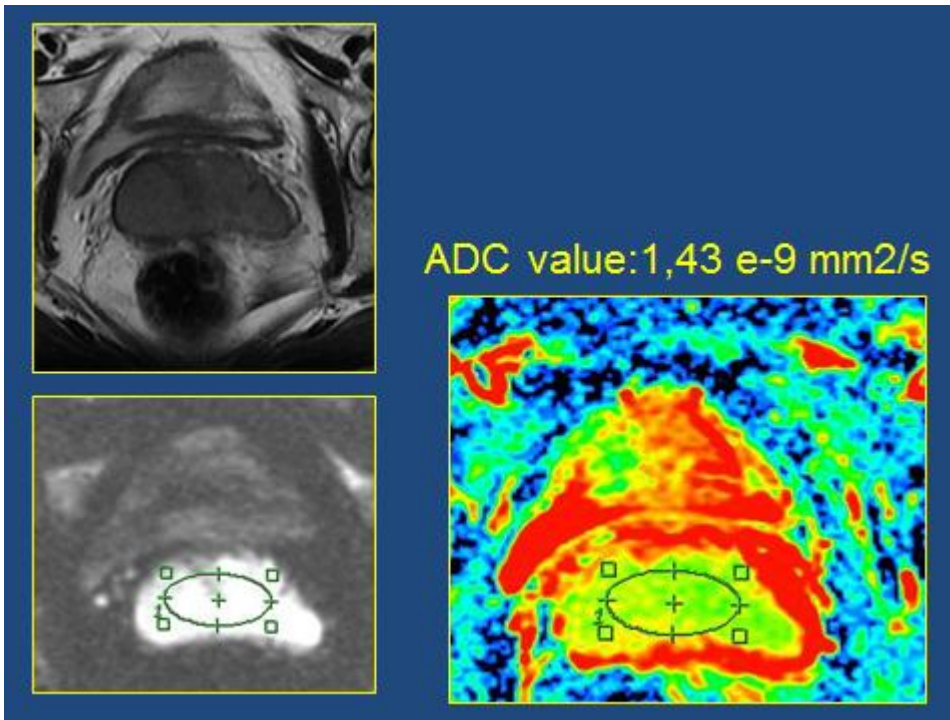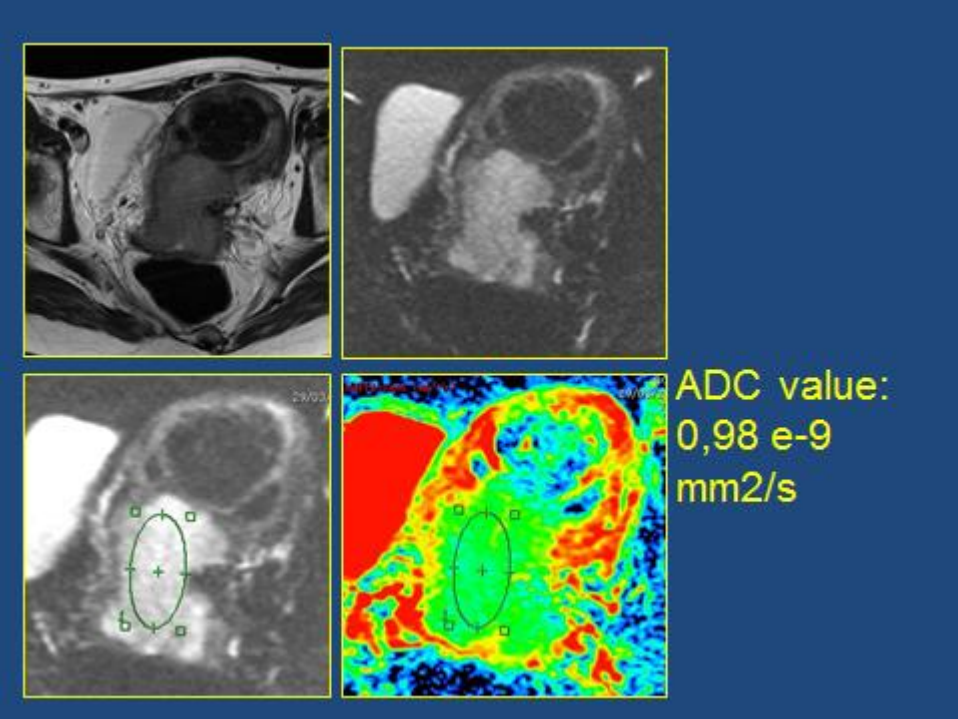| Histological grading | Number | Mean ADC value | Std Dev | P value |
|---|---|---|---|---|
| G1 | 5 | 1,32 | 0,07 | 0,02 |
| G2 | 14 | 0,78 | 0,46 | 0,04 |
| G3 | 15 | 0,85 | 0,44 | 0,67 |

**PICTURES**

**Figure. 1:** T2w.i, DWI and DWI with color map of G1 cervical cancer.

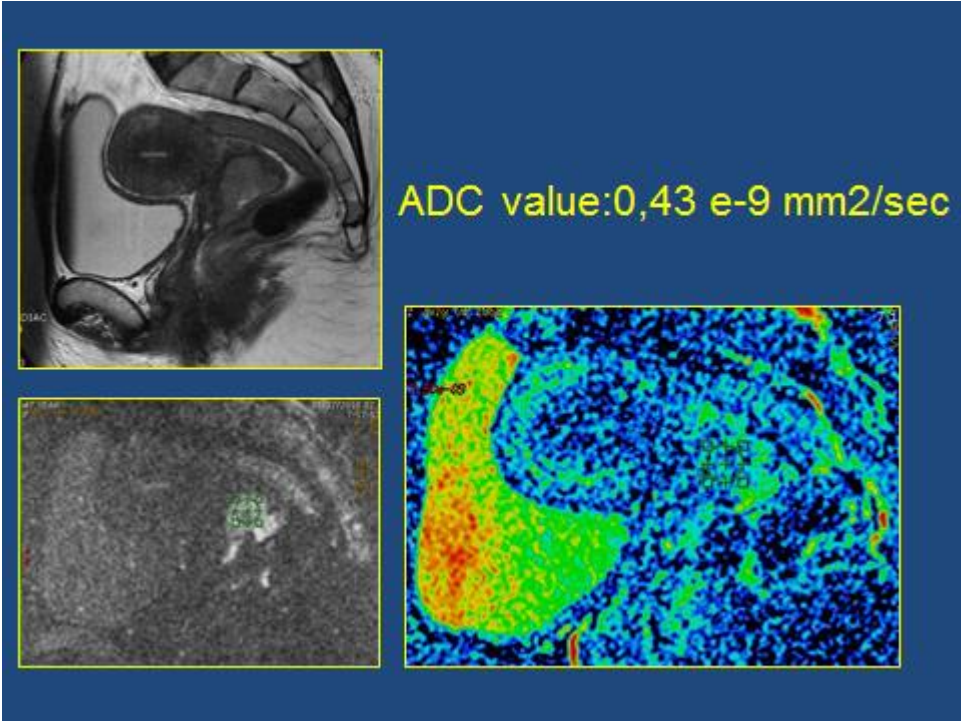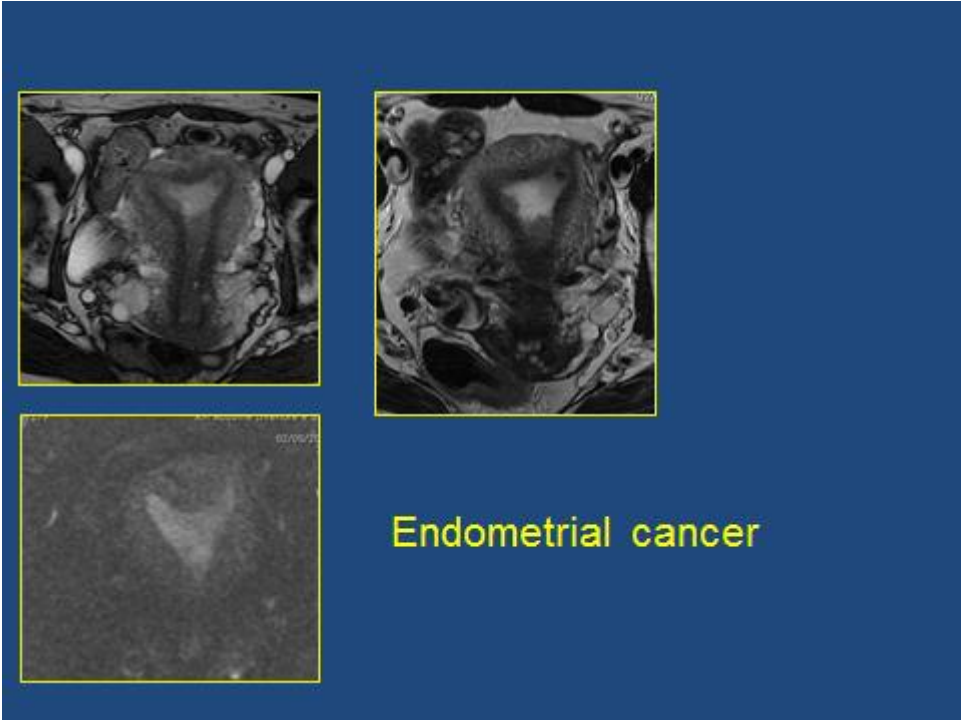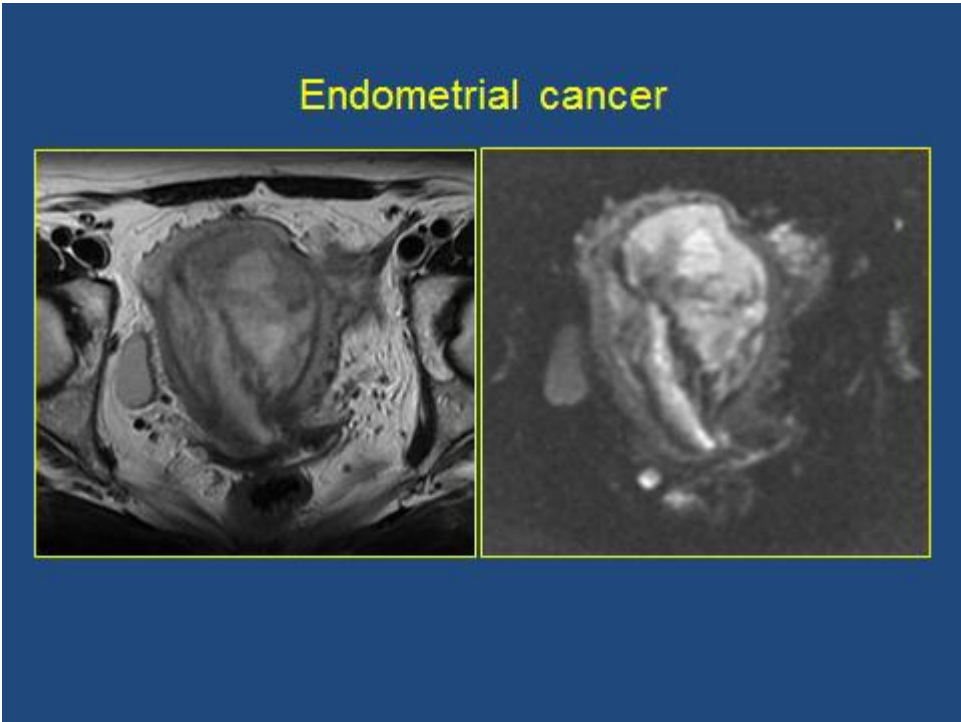**Figure.2:** T2w.i, DWI and DWI with color map of G2 cervical

cancer.

**Figure. 3:** T2w.i, DWI and DWI with color map of G3 cervical cancer.

**Picture 4:** T2 w.i. and DWI in endometrial cancer.



Endometrial cancer

**Picture 5:** T2 w.i. and DWI in endometrial cancer.

# CONCLUSIONS

DW image can help to detect the presence of cervical tumor; DWI image by means of ADC values, can be helpful to discriminate poorly differentiated from well differentiated cervical tumors. Based on our results, higher ADC values (from 1,30 to 1,40e-9) were noted in G1 tumors while lower values (0,43-1,24 e-9) were observed in G3 tumors. In the cases of cervical cancer with G2 the ADC were values were variable and therefore controversial 0,82 -1,47 e-9.

Before we analyzed which possible limits Diffusion could have in detection cervical cancer and after this retrospective study. We noticed that DWI failed when cancer was placed only in fornix or if cervical tumor arise from an atrophic structure.

We also analyze which factor could influence the ADC values as: the keratinizing and mixoid or solid components. Keratinizing let reduce ADC value because in deed this element is present in the well differentiated  tumors. Mixoid or solid components, instead, let increase ADC value.

In endometrial tumors we considered that DWI is not useful in detection. We arrived to diagnosis and staging only with T2 w.i and T1 w.i after injection of contrast media.

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