

## ROLE OF DIFFUSION WEIGHTED IMAGING IN GYNAECOLOGICAL DISEASE

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**Abstract**

**Background:** Diffusion weighted imaging [DWI] and ADC have a potential ability in diagnosing endometrial, cervical, myometrial and ovarian lesions. Purpose of our study was to determine the applicability and feasibility of DWI using multiple b values and accuracies of various respective Apparent Diffusion Coefficient [ADC] values for examining the female pelvic region and characterizing normal and pathological tissues. **Material and Methods:** Present study was single-center, comparative, observational study, conducted in women with various gynaecological diseases referred for MRI evaluation were considered for this study. **Results:** In our study, ADC values of both b 600 and 800 had the highest accuracy in differentiating normal endometrium from cancerous tissues. On increasing b values, progressive decrease in ADC values was noted i.e. mean ADC 800 was lesser than ADC 300 as shown in the example given below for endometrial cancer. For cervical cancer, best accuracy ie highest area under the curve was noted for ADC 800. Additionally efficacy of routine MR sequences and DWI in detection of early cancers [Stage I] was poor [only three cases were detected in five early cancers], however had a good accuracy in the detection of parametrial involvement and late stage of cancers. In myometrial cancers, fair accuracy was noted for ADC of b 300 and good accuracy for ADC values of b 600 and 800 in differentiating normal myometrium from fibroids. In ovarian lesions, good accuracy was noted for ADC values of all the three b values in differentiating normal ovary from solid ovarian lesions with the highest accuracy for ADC value of b 300. **Conclusion:** Use of DWI is complimentary to routine MRI sequences in characterization of various gynaecological lesions with best results in cervical and endometrial pathologies.

### INTRODUCTION

MRI has evolved as an essential tool in the examination of female pelvis due to its ability to visualize pelvic organs with excellent soft tissue contrast. Its role as a problem solving tool and as an aid for therapeutic decision is now well established.<sup>[1]</sup> Diffusion weighted imaging [DWI] is a recently introduced MRI sequence that allows observation of differences in molecular diffusion caused by random and microscopic motion of molecules, also known as Brownian motion.<sup>[2]</sup> Recent developments in parallel imaging techniques have improved the quality of abdominal DWI by reducing the acquisition time and by minimizing the echoplanar imaging- related susceptibility artifact.<sup>2</sup> Diffusion-weighted imaging and ADC have a potential ability in diagnosing endometrial, cervical, myometrial and ovarian lesions.<sup>[3,4,5]</sup>

Since there are only few studies available on the utility of DWI for gynaecological imaging especially in Indian subcontinent, the purpose of our study was to determine the applicability and feasibility of DWI using multiple b values [300, 600 and 800] and accuracies of various respective Apparent Diffusion Coefficient [ADC] values for examining the female pelvic region and characterizing normal and pathological tissues.

### MATERIAL AND METHODS

Present study was single-center, comparative, observational study, conducted in department of Radiodiagnosis and Imaging in KMC, Manipal, India. Study duration was of 2 years. Study approval was obtained from institutional ethical committee.

Women with various gynaecological diseases referred for MRI evaluation were considered for

this study. Women having contraindications for MRI (Brain Aneurysm Clip, Implanted neural stimulator, Implanted cardiac pacemaker or defibrillator, Cochlear implant, Ferromagnetic Ocular foreign body, Other implanted medical devices: (eg Swan Ganz catheter), Insulin pump, Metal shrapnel or bullet) & pregnant women were excluded.

Study was explained to patients in local language & written consent was taken for participation &

study. The study was conducted with GE ‘Signa HDxt’ 1.5 T MRI machine. Conventional MR sequences and DWI was performed on 1.5 tesla GE MR machine. b values used were 0, 300, 600 and 800. Phased array body coil [16 channel] was used with adequate padding anteriorly. In each patient, ADC values of lesions and normal tissues was calculated and the role of ADC in characterisation of gynaecological lesions into benign and malignant was studied.

**Table 1: MRI routine sequences**

Sequence	FLIP [degree]	TE[ms]	TR[ms]	Thickness/Interval	FOV [cm]	Matrix	NEX
Sag T2FRFSE	90	100	4820	4/1	24	320 x 256	4
Axial T2FRFSE	90	100	3825	4/1	26	288 x 224	4
Coronal T2 FRFSE	90	100	3825	4/1	24	288 x 224	4
AX T1+CCOR T1+C	90	11.4	600	4.4/1	24	256 X 192	2

**Table 2: DWI acquisition parameters**

b-value (s/mm <sup>2</sup> )	0, 300,600 and 800
TR (ms)	5600.0
TE (ms)	70.7
Slice orientation	Axial
Slice thickness/gap (mm)	4/0
FOV (mm)	320
Matrix	128 x 172
Diffusion gradient directions	3
No. of excitations	4
Scan time	b-300- 1.30mins b- 600 and 800- 3.00 mins each

## IMAGE ANALYSIS AND POST PROCESSING

- Signal intensity of the lesions on DWI were compared with signal intensity of outer myometrium and accordingly classified as hyperintense if signal intensity of lesion was greater than that of outer myometrium and vice versa.
- ADC was calculated using post processing software, FUNCTOOL
- The circular ROI was kept as large as possible within the target lesion on the T2 weighted EPI image [b=0], while referring to the sagittal and axial contrast enhanced sequences [where available] and T2 weighted images for verification of the lesion boundaries.
- The ROI was then copied to the corresponding ADC map.

Accuracy of ADC values of various b values were analysed using Receiver operating characteristic curves to obtain most accurate ADC for particular gynaecological lesion under study. For comparison of the results, statistical differences among the case and control groups with respect to the ADC values were assessed by independent Student ‘t’ test.

Significant statistical difference was considered when p value was < 0.05.

## RESULTS

**ENDOMETRIAL CANCER-**A total of 22 subjects (11 women with histopathologically proven. endometrial cancer lesions and 11 normal lesions) were analysed. In the present study mean age group of cancer group was 50.9 years and that of control group was 36.4 years.

In our study, ADC values of both b 600 and 800 had the highest accuracy in differentiating normal endometrium from cancerous tissues. ADC of b 800 was chosen to compare the means between the two entities and the difference in the means obtained was found to be statistically significant. [Normal endometrium is  $1.22 \pm 0.17$ , and that for endometrial cancer is  $0.8 \pm 0.21$ ]. On increasing b values, progressive decrease in ADC values was noted i.e. mean ADC 800 was lesser than ADC 300 as shown in the example given below for endometrial cancer.

**Table 1: Variation of ADC values with increasing b values in endometrial cancers**

	ADC 300	ADC 600	ADC 800
Mean	1.26195	1.12368	1.01764
Std. Deviation	.339638	.312853	.278728

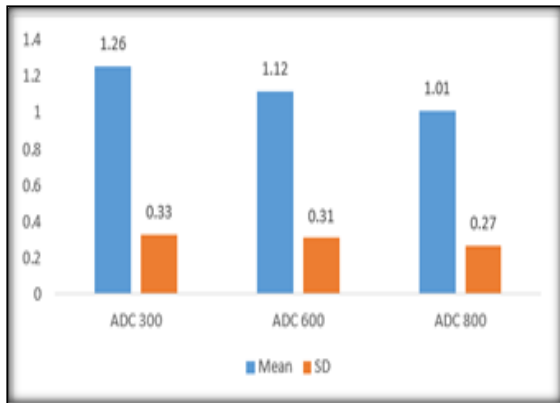


Figure 1:

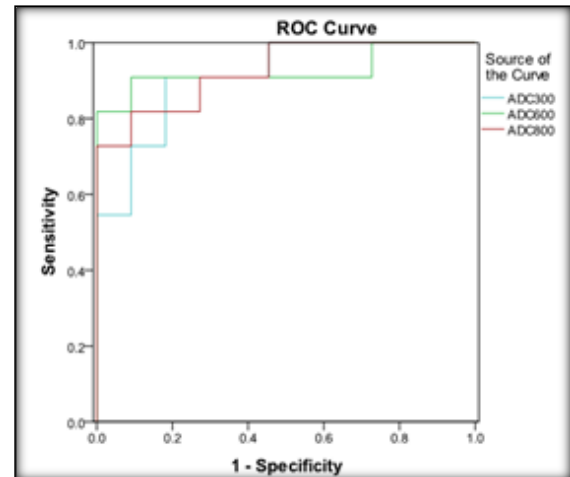


Figure 1

Figure 1: Receiver operating characteristics curve showing relationship between sensitivity and specificity of various ADC values for each cut-off value. Best accuracy ie highest area under the curve was noted for ADC 800. Deeper myometrial involvement was noted in eight patients, which were also detected by routine MR sequences and DWI.

Table 2: Best ADC value with their sensitivity and specificity (ENDOMETRIAL CANCER)

VARIABLES	BEST ADC VALUE	SENSITIVITY	SPECIFICITY
ADC 300	1.285	90.9	81.8
ADC 600	1.16	90.9	90.9
ADC 800	1.003	81.8	90.9

**CERVICAL CANCER-** A total of 33 subjects [21 histopathologically proven. cervical cancer lesions and 12 normal lesions] were analysed. Mean age of cancer group was 43.9 years and that of control group was 35.0 years.

In our study, ADC value of b 800 had the highest accuracy in differentiating normal cervix from cancerous tissues and was used to compare the statistical difference between the mean ADC values of the two entities [Normal cervix:  $1.42 \pm 0.27$ , Cervical cancers:  $0.98 \pm 0.23$ ]. Difference was found to be statistically significant [ $p < 0.05$ ], thus establishing role of ADC in characterization of normal and cancerous tissues.

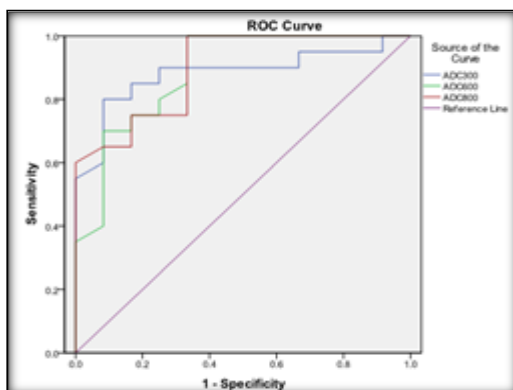


Figure 2:

Figure 2: Receiver operating characteristics curve showing relationship between sensitivity and specificity of various ADC values for each cut-off value. Best accuracy ie highest area under the curve was noted for ADC 800. Additionally efficacy of routine MR sequences and DWI in detection of early cancers [Stage I] was poor [only three cases were detected in five early cancers], however had a good accuracy in the detection of parametrial involvement and late stage of cancers.

Among the five early cancers [one case of stage Ia, four cases of stage Ib] only three cases were detected by routine MRI sequences as well as DWI. One case of stage IA2 and one case of stage IB were missed on both routine MRI sequences and DWI. However all cases of parametrial involvement were excellently detected by both routine MRI sequences and DWI.

**Table 3: Best ADC value with their sensitivity and specificity (CERVICAL CANCER)**

VARIABLES	BEST ADC VALUE	SENSITIVITY	SPECIFICITY
ADC 300	1.64	85	83.3
ADC 600	1.49	100	67.7
ADC 800	1.37	100	67.7

**MYOMETRIAL CANCER**-Total no of cases: 25 [24 fibroids and 1 leiomyosarcoma], Total no of controls: 22. Mean age of cancer group was 44.9 years and that of control group was 43.9 years. Fair accuracy was noted for ADC of b 300 and good accuracy for ADC values of b 600 and 800 in differentiating normal myometrium from fibroids. Difference in the mean ADC values of b 600 and 800 between the two entities was statistically significant. [Mean ADC value of b 600 for normal tissue is  $-1.48 \pm 0.25$  and that for fibroids is  $-1.16 \pm 0.33$  and that for b 800 is  $1.32 \pm 0.29$  for normal tissue and for fibroids is  $0.99 \pm 0.29$ .]

Myometrial lesions were classified based on T2 weighted image into homogeneously hypointense [n =16] and heterogenous lesions [n=9]. Low signal intensity and ADC values of ordinary leiomyomas on DW images can be explained with “T2 blackout effect”, which indicates hypointensity on DW images caused by hypointensity on T2-weighted images since DW images are inherently T2-weighted.

In our study early endometrial cancers [stage I] were noted in three patients, which were detected using both routine MR sequences and DWI in all these cases. Deeper myometrial involvement was noted in eight patients, which were also detected by routine MR sequences and DWI.

**Table 4: Shows best ADC value with their sensitivity and specificity**

VARIABLES	BEST ADC VALUE	SENSITIVITY	SPECIFICITY
ADC 300	1.51	75.0	72.7
ADC 600	1.295	75.0	81.8
ADC 800	1.008	66.7	86.4

**MYOMETRIAL LESIONS**-A total of 47 subjects [24 cases of fibroids, 1 case of leiomyosarcoma and 22 normal myometrium] including 7 external controls were analyzed. Accuracy of three ADC values were calculated using receiver operating characteristics curve. Fair accuracy was noted for ADC 300 and good accuracy for ADC 600 and 800. Best accuracy ie highest area under the curve was noted for ADC 600.

A total of 24 fibroids were analysed, mean ADC 600 calculated and their statistical difference with mean ADC600 value of 22 normal myometrium compared using Student’s independent t test. The difference was found to be statistically significant. [Normal myometrium:  $1.48 \pm 0.25$ ; Fibroids:  $1.16 \pm 0.33$ ]

**Table 5: Difference between mean ADC 600 values of normal myometrium and fibroids**

	MEAN ADC VALUE	STD DEVIATION
NORMAL MYOMETRIUM	1.48	0.25
FIBROIDS	1.16	0.33

[P =0.001]

**OVARIAN LESIONS**-In our study, 67 lesions were assessed among 48 study population [Benign lesions: 26, Malignant lesions: 14, Normal ovary: 27]. In the present study Mean age group of cancer group was 39.6 years and that of control group was 49.6 years.

Good accuracy was noted for ADC values of all the three b values in differentiating normal ovary [n=27] from solid ovarian lesions [n =18] with the highest accuracy for ADC value of b 300. Hence ADC of b 300 was chosen to compare the means between the two entities and the difference in the means obtained was found to be statistically significant. [Normal ovary:  $2.33 \pm 0.98$ ; solid ovarian lesions:  $1.4 \pm 0.5$ ]

Accuracy of three ADC values were calculated using receiver operating characteristics curve. Good accuracy was noted for all three ADC values. Best accuracy ie highest area under the curve was noted for ADC 600.

**Table 19: Shows best ADC value with their sensitivity and specificity**

VARIABLES	BEST ADC VALUE	SENSITIVITY	SPECIFICITY
ADC 300	1.79	85.7	81.5
ADC 600	1.43	78.6	88.9
ADC 800	1.32	78.6	88.9

## DISCUSSION

DWI can demonstrate abnormal signals emitted by pathologic foci based on differences in molecular diffusion and can delineate malignant lesions displaying hyperintense signal because of water

diffusion being restricted in tissues of high cellularity with excellent tissue contrast.<sup>[2]</sup> It also permits the quantitative evaluation by using apparent diffusion coefficient [ADC] that provides analysis of microscopic water diffusibility in target tissues which is mainly influenced by the tissue

cellularity and hence may be useful for distinguishing between malignant and benign tissues and for monitoring therapeutic outcomes.<sup>[3]</sup> In present study we observed that as the b value increased, there was a fall in ADC value. Our findings were in consensus with study by Reiko *et al.*<sup>[6]</sup> Since ADC includes both the effects of real diffusion and perfusion (pseudo diffusion), calculation of ADC on the maps obtained at lower b values contains a significant amount of non-diffusional intravoxel incoherent motion, often derived from perfusion, hence a higher ADC value is obtained. By contrast, high b values overcome this effect.

In the present study, all endometrial cancer and the normal endometrium showed increased signal intensity on DW images with a b-value of 800 seconds/mm<sup>2</sup>. This was in consensus with study by Tamai *et al.*<sup>[7]</sup> The reason why the normal

endometrial tissue shows increased intensity on DW images could be due to high cellularity and abundant cytoplasm [with abundant intracellular water molecules] of endometrial glands and stromal cells as explained by Tamai K *et al.*<sup>[7]</sup> Thus, DW imaging is feasible in demonstrating endometrial cancer. Although the degree of signal intensity on DW images may be different between endometrial cancers and normal endometrium, quantitative comparison is difficult since the signal intensity on MRI may be subjective and can be influenced by the adjustment of window level and width. In contrast, the ADC value calculated from DW images can provide quantitative analysis of microscopic water diffusibility in the target tissues. Mean ADC values of our study was in consensus with other studies and best correlated with that of Chen Y *et al.*<sup>[8]</sup> as both studies were done on a 1.5T magnet using b value of 800.

**Table 6: Comparison of mean ADC values between cases and controls with other studies**

	OUR STUDY	Chen Y <i>et al.</i> <sup>8</sup>	Tamai <i>et al.</i> <sup>7</sup>	Bharwani <i>et al.</i> <sup>9</sup>	Junping Wang <i>et al.</i> <sup>10</sup>
CASES	0.90 [0.23]	0.86 [0.31]	0.88 [0.16]	0.97 [0.31]	0.878 [0.185]
CONTROLS	1.35 [0.20]	1.27 [0.22]	1.53 [0.1]	1.50 [0.14]	1.446 [0.246]

DWI is complimentary to routine MRI sequences in analyzing depth of myometrial invasion by endometrial cancer which is an important prognostic factor and is also important in pre operative assessment.<sup>[11,12]</sup> In our study, myometrial involvement could be detected equally on both DWI and routine MRI sequences which was in consensus with study by Chen Y *et al.*<sup>[8]</sup>

Squamous cell carcinoma was the most common histopathological variety among cervical cancers in

our study. There was no statistically significant difference among mean ADC values of various histopathological types of cervical cancers in our study. However, study by Liu *et al.*<sup>[13]</sup> showed significant difference between mean ADC values of squamous cell carcinoma and adenocarcinoma, but they also observed significant overlap between the two groups.

**Table 7: Comparison of mean ADC value of various histologic subtypes with others**

	Our study	Liu <i>et al.</i> <sup>5</sup>
SCC	0.95	0.85
Others	1.05	0.98

Eleven among these patients were freshly diagnosed cases while ten were already known cases of cervical cancer on treatment. No statistical significant difference was noted between the mean ADC values of freshly diagnosed cervical cancer cases and already known cases on treatment. In our study, all cervical cancers showed increased intensity on DWI as compared to the stroma correlating with studies by Naganawa *et al.*<sup>[14]</sup> This is because of greater cellularity of cervical cancer compared with the normal hypointense fibroelastic cervical stroma.<sup>[15,16]</sup>

**Table 8: Comparison of mean ADC values between cases and controls with other studies**

	Our Study	Naganawa <i>et al.</i> <sup>14</sup>	McVeigh <i>et al.</i> <sup>17</sup>	Liu <i>et al.</i> <sup>13</sup>
CASES	0.98 [0.23]	1.09 [0.20]	1.09 [0.2]	0.88 [0.31]
CONTROLS	1.42 [0.27]	1.79 [0.24]	2.09 [0.2]	1.50 [0.14]

Mean ADC values [b 600] of ordinary fibroids and normal myometrium in the present study was comparable to the values in the study by Tamai *et al.*<sup>[7]</sup> As higher b value [1000] was used in study by Tamai *et al.*<sup>[7]</sup> mean ADC value of ordinary fibroids in their study was slightly lower as compared to that in the present study. [Mean ADC value of b 800 for ordinary Leiomyomas was 0.97 ± 0.28 in our study].

**Table 9: Comparison of mean ADC values between cases and controls of our study with other studies for ordinary leiomyomas and normal myometrium**

b 600	OUR STUDY	Tamai <i>et al.</i> <sup>7</sup>
ORDINARY LEIOMYOMAS	1.05 [0.28]	0.88 [0.2]
NORMAL MYOMETRIUM	1.48 [0.25]	1.62 [0.2]

Lesions which were heterogenous on T2 weighted sequence were considered equivocal and included four cases of degenerated leiomyomas and one case of leiomyosarcoma. Leiomyosarcoma showed increased signal intensity on DWI. Variable signal intensities was noted among degenerated leiomyomas. Also difference between mean ADC values [b 800] of the two groups was found to be statistically insignificant. Hence DWI and ADC has limited role in differentiating such equivocal lesions. Our study was in consensus with study by Bakir *et al.*<sup>[18]</sup>.

**Table 10: Comparison of mean ADC values with other studies for myometrial lesions and normal myometrium**

	OUR STUDY [b value 800]	Tamai <i>et al.</i> , <sup>7</sup>	B Bakir <i>et al.</i> , <sup>18</sup>
FIBROIDS	0.84	0.88	0.84
CONTROLS	1.22	1.62	-
LEIOMYOSARCOMA	1.13	1.17	0.96
DEG FIBROID	1.11	1.7	1.19

All the solid malignant ovarian tumors showed increased signal intensity on diffusion and low ADC values suggesting restricted diffusion. No statistical significant difference was noted between that of malignant mucinous and serous cystadenocarcinoma cases and between that of primary ovarian malignant lesions and metastatic lesion of ovary. This was in consensus with study by Bakir *et al.*<sup>[18]</sup> [Mean ADC of mucinous cystadenocarcinoma : 1.01 ; serous cystadenocarcinomas : 1.22] [Mean ADC of primary ovarian lesion  $1.4 \pm 0.5$  and that of metastatic lesion  $1.78 \pm 0.32$ ]

Limitations of this study, were smaller study population. Endometrial cancer patients and those with normal endometrium were not age matched. There was lack of good frequency of benign solid ovarian and malignant myometrial lesions to compare. In endometrial and cervical pathologies, study population was limited to normal and malignant tissues. Benign pathologies like endometrial hyperplasia, endometrial and cervical polyps were not included. Thus, the ability of ADC values in differentiating between malignant and non-malignant endometrial and cervical lesions is not assessed. Menstrual phase of the patients was not taken into consideration in analyzing the ADC values of the normal tissues in the control group which may vary according to menstrual cycle in premenopausal women.

## CONCLUSION

Our study concludes that use of DWI is complimentary to routine MRI sequences in characterization of various gynaecological lesions with best results in cervical and endometrial pathologies. DWI can be easily added to MR study

protocols with no significant increase in overall scan time. However DWI and ADC value have limited role in evaluation of myometrial and ovarian lesions.

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