

## Original Research Article

# Evaluation of apparent diffusion coefficient in endometrial carcinoma compared to normal endometrium: a retrospective study

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## ABSTRACT

**Background:** To determine whether diffusion-weighted imaging (DWI) with measurement of apparent diffusion coefficient (ADC) will help in differentiating endometrial cancer from normal endometrium and to determine whether the grades of endometrial cancer will show significant difference in ADC values.

**Methods:** This is a retrospective study done in MOSC medical college hospital Kolencherry. on patients on whom preoperative MRI was done before hysterectomy. Cases from July 2017 to March 2021 were included. Study cases included 40 females with pathologically confirmed endometrial cancer and 30 females with pathologically proven normal endometrium in cases of uterine leiomyoma and cervical cancer. The exclusion criteria for the study were patients with endometrial cancer in whom surgery was not done within 2 weeks of MRI, patients who were treated with chemotherapy or radiotherapy before surgery, patients who had hydrometra or pyometra.

**Results:** The mean ADC value ( $10^{-3} \text{ mm}^2/\text{second}$ ) of endometrial cancer was  $0.77 \pm 0.04$ , which was significantly lower ( $p < 0.05$ ) than that of normal endometrium ( $1.323 \pm 0.05$ ). The ADC values of different grades of endometrial cancers did not show any statistically significant difference ( $p > 0.05$ ).

**Conclusions:** Our study showed that ADC measurement can differentiate between normal endometrium and endometrial cancer. The ADC values of different grades of endometrial cancers did not show any statistically significant difference.

**Keywords:** Endometrial cancer, Diffusion weighted imaging, ADC, Endometrial thickening

## INTRODUCTION

Endometrial cancer is the most common gynaecologic malignancy in developed countries.<sup>1</sup> However, in developing countries, it is the second most common gynaecologic malignancy.<sup>2</sup> Patients present with abnormal uterine bleeding in more than 80% of cases. Endometrial carcinoma is more common during the 6th and 7th decades of life, with the mean age of patients being 65 years.<sup>3</sup> Obesity, unopposed oestrogen intake, nulliparity, diabetes mellitus, Stein-Leventhal syndrome, Lynch syndrome, and tamoxifen therapy are the known risk factors for the development of endometrial carcinoma.<sup>3</sup> Definitive diagnosis of endometrial carcinoma is generally made by

endometrial biopsy or dilatation and curettage. Although the grade and histological subtype of endometrial cancer can be diagnosed through endometrial sampling, tumour staging is performed intraoperatively, according to the International Federation of Gynaecology and Obstetrics (FIGO) guidelines, which include the use of total abdominal hysterectomy, bilateral salpingo-oophorectomy, peritoneal lavage, and pelvic/para-aortic lymphadenectomy, depending on the findings at intraoperative staging.<sup>4</sup>

Preoperative assessment of the extent of the tumour is important in planning the surgical procedure and to determine whether to perform sampling of lymph node.

MRI has proven to be an important tool to evaluate local stage of endometrial cancer, which includes myometrial invasion and cervical involvement.<sup>5-7</sup> The most important morphologic prognostic factor is depth of myometrial invasion which correlates with grade of tumour, metastases to lymph nodes and survival of patients. The lymph node metastases vary from 3% with superficial myometrial invasion to 46% with deep myometrial invasion.<sup>8,9</sup> In various studies diffusion-weighted and dynamic contrast enhanced MR imaging have been shown to improve the accuracy of MRI in determining the depth of myometrial invasion and can be used to assess tumour response to therapy and to differentiate tumour recurrence from posttreatment changes.<sup>10-12</sup>

Endometrial carcinomas are divided into two subtypes by histopathology. Type I is the endometrioid adenocarcinoma is the most common endometrial cancer (accounts for 90% of the tumours) and is linked to estrogenic excess and obesity. Type I endometrial cancers are, generally low grade, and have a good prognosis and occur in early perimenopausal age group. Based on the degree of differentiation, endometrioid adenocarcinomas are divided into three grades: Grade 1, well differentiated; grade 2, moderately differentiated; and grade 3, poorly differentiated tumors.<sup>13</sup> Type II endometrial cancers (including the clear-cell, serous papillary subtypes and carcinosarcomas) have no association with oestrogen excess, generally occur in older women, carry a worse prognosis, All type II cancers and grade 3 endometrioid tumours are grouped as high-grade tumours and are associated with a poor prognosis.<sup>14</sup> Endometrial cancers are staged by revised FIGO staging system (2009).<sup>15,16</sup> Endometrial cancer is usually seen as thickened endometrium on imaging. However, conventional MRI does not always clearly show the focus of the tumour, since the signal intensity of the endometrial cancer can vary and sometimes cannot be distinguishable from normal endometrium or adjacent myometrium.<sup>17</sup> Diffusion-weighted (DW) MRI is used to show tissue characteristics based on diffusion motion of water molecules. The DW imaging can also provide apparent diffusion coefficient (ADC) value of tissue, which is considered to be influenced by nuclear-to-cytoplasm ratio and cellular density.<sup>18,19</sup> In cases of malignant tumours, the ADC value has been reported to correlate with histologic grade of the tumours, in which high grade tumours tended to show low ADC values.<sup>20</sup>

The purpose of this study was to assess role of DW imaging with ADC in the differentiation of endometrial cancer from normal endometrium and to determine whether the ADC values help in differentiating grades of endometrial cancer.

## METHODS

This is a retrospective study done in MOSC medical college hospital Kolencherry on patients on whom preoperative MRI was done before hysterectomy. Cases

from July 2017 to March 2021 was included. 40 cases of histopathologically proven endometrial cancer and 30 patients of histopathologically proven normal endometrium for whom hysterectomy were done for cervical carcinoma and uterine leiomyoma were included in this study.

The exclusion criteria for our study were patients diagnosed with endometrial cancer in whom surgery was not performed, patients who were given preoperative chemotherapy or radiotherapy and patients having hydrometra or pyometra.

MR examinations were done using a 3T MR scanner (Philips Ingenia) with a Dstream architecture body coil having 60cm coverage and with 32 channels. MR sequences done routinely in preoperative evaluation included fast spin-echo T2-weighted images (TR/TE=3655 msec/100 msec) in the sagittal, coronal and axial plane and spin-echo T1-weighted images (TR/TE=522 msec/8 msec) in the axial plane were obtained in all cases. After the acquisition of these sequences, DW images were obtained in the same axial plane using a single-shot echo-planar imaging sequence (TR/TE=4500 msec/80 msec, flip angle=90°, excitations=3, matrix size=112×81, bandwidth=2202.2 Hz/pixel) and sensitivity encoding (SENSE) technique (SENSE factor of 2.5). The corresponding b-values to the diffusion sensitizing gradient were 0, 800, and 1000 seconds/mm<sup>2</sup>. All the axial images, including DW images, were taken with a slice thickness of 3 mm, intersection gap of 1 mm, and field of view (FOV) of 260 mm. ADC maps were automatically generated on a pixel-by-pixel basis from the DW images for quantitative analysis. Dynamic Contrast-enhanced fat-suppressed T1-weighted images were also taken in the axial plane.

Assessment of the following parameters were done in the endometrial cancer group i.e., the endometrial thickness on T2-weighted images; the signal intensity of the tumour and the myometrium on DW images with a b-value of 1000 seconds/mm<sup>2</sup> the signal intensity of the tumour relative to that of the adjacent myometrium on T2-weighted images; and ADC values of the tumour. In the cases with the histopathologically proven normal endometrium, the following were assessed; the signal intensity of the normal endometrium was evaluated on T2-weighted images, also assessment made about any restricted diffusion ADC of the normal endometrium was also assessed. For the accurate identification of anatomical structures that shows abnormal signal on DW images, the fusion images (with DW images with a b-value of 1000 seconds/mm<sup>2</sup> onto T2-weighted images), were generated using the workstation IntelliSpace Portal 8.0 Philips. Circular ROI was kept on the suspicious area in the case of endometrial cancer for determining the ADC. ROI was kept excluding any area showing obvious necrosis.

Statistical analysis was done in R studio software. Comparison of the ADC values of the endometrial cancers

and ADC value of the normal endometrium was done. The statistical difference was determined by Two Sample t-test and P value of less than 0.05 was considered statistically significant. ADC values of different grades of endometrial cancers were compared to assess any statistical significance. i.e., comparison of ADC of grade 1 and grade 2, ADC of grade 2 and grade 3, ADC of grade 3 and Grade 1 using two sample t test.

## RESULTS

Mean age of the patients in the endometrial cancer group was 67 years. Pathologic findings in the 40 patients with endometrial carcinoma are as follows. The cases were mostly endometrioid carcinomas, 2 cases with clear cell adenocarcinomas, 1 case with serous papillary carcinoma, and 1 case with mixed endometrioid adenocarcinoma and serous papillary carcinoma.

**Table 1: Pathology of endometrial carcinoma cases.**

Type of tumor	Number	Percentage
<b>Endometrioid adenocarcinoma</b>	36	90
<b>Grade 1</b>	14	35
<b>Grade 2</b>	13	32.5
<b>Grade 3</b>	9	22.5
<b>Clear cell carcinoma</b>	2	5
<b>Serous papillary</b>	1	2.5
<b>Mixed endometrioid and clear cell carcinoma</b>	1	2.5
<b>Total</b>	40	

**Table 2: Surgical FIGO stage of endometrial carcinoma cases.**

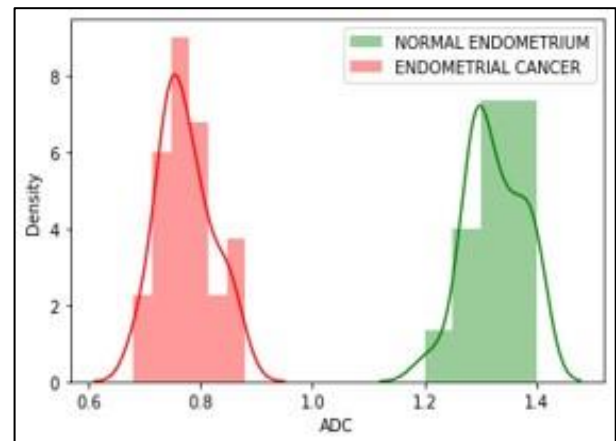
FIGO stage	Number	Percentage
<b>IA</b>	23	57.5
<b>IB</b>	11	27.5
<b>II</b>	4	10
<b>III</b>	1	2.5
<b>IV</b>	1	2.5
<b>Total</b>	40	

The histologic grades of endometrioid cancer were grade 1 (N=14), grade 2 (N=13), and grade 3 (N=9) (Table 1). The endometrial thickness in the endometrial carcinoma group ranged from 1 cm to 4 cm. Surgically, the FIGO stages were stage IA (23 cases), stage IB (11 cases), stage II (4 cases), and stage III (1 case) and stage IV (1 case) (Table 2).

Endometrial cancer in T2W images appeared as either a diffuse endometrial thickening or as a focal mass. The number of patients with diffuse thickening was 35. Only in 5 cases focal thickening was noted. On T2 w images the thickened endometrium showed varying signal intensity including diffusely hyperintense, heterogeneously hyperintense and isointense to myometrium. All cases of

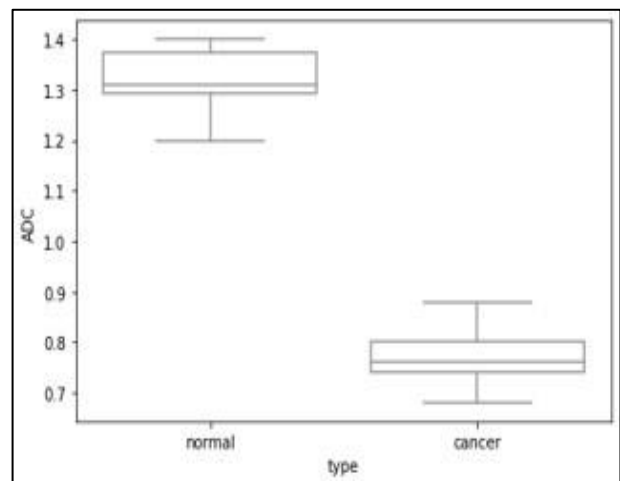
endometrial cancer showed hyperintensity on DWI at B value of 800 and 1000. All cases of endometrial cancer appeared hypointense on ADC.

The mean ADC value ( $10-3 \text{ mm}^2/\text{second}$ ) of endometrial cancer was  $0.77 \pm 0.048$ , which was significantly lower ( $p < 0.05$ ) than that of normal endometrium ( $1.32 \pm 0.051$ ). Distribution of values of ADC in the cases studied shows no overlap between ADC values of endometrial cancer group and normal endometrium group (Figure 1).



**Figure 1: Distribution of values of ADC values in the cases of endometrial cancers and cases of normal endometrium studied.**

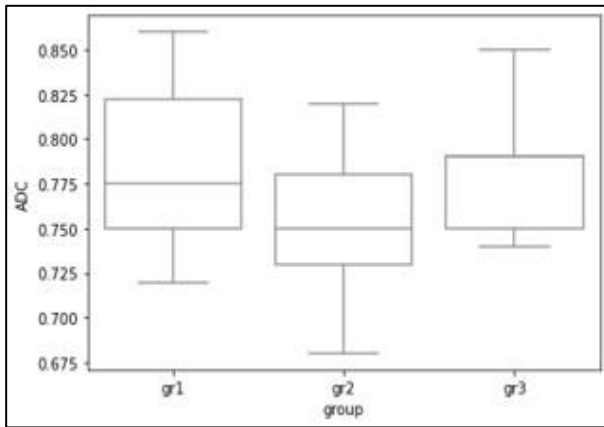
The range of ADC values of endometrial cancer and normal endometrium is depicted in box plots (Figure 2).



**Figure 2: Box plots of ADC values in endometrial carcinoma and in normal endometrium.**

Box plots of ADC values in endometrial carcinoma and in normal endometrium, in which edge of boxes near to zero is 25th percentile, line within boxes marks median, and edge of boxes away from zero is 75th percentile. Errors bars above and below boxes indicate maximum and minimum values, respectively (Figure 2).

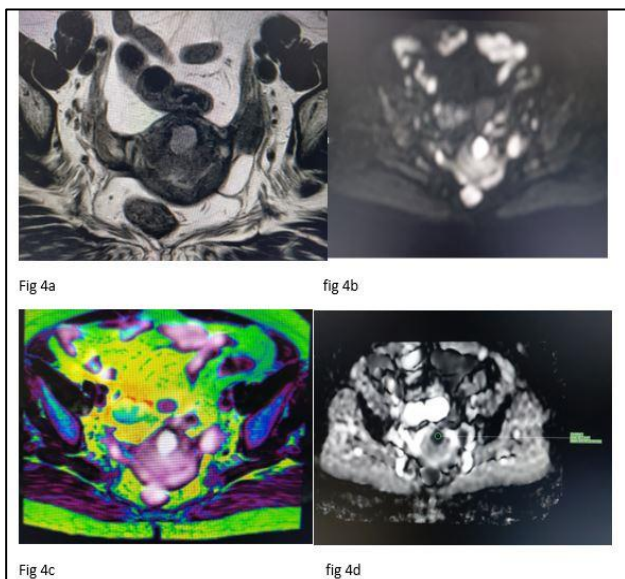
In the endometrial cancer group, the ADC values for each grade was not statistically different ( $p>0.05$ ). The range of ADC values in different grades of endometrial cancer is depicted in box plots (Figure 3).



**Figure 3: Box plots of ADC values of different grades of tumors in endometrial carcinoma.**

Box plots of ADC values of different grades of tumors in endometrial carcinoma in which edge of boxes near to zero is 25th percentile, line within boxes marks median, and edge of boxes away from zero is 75th percentile. Errors bars above and below boxes indicate maximum and minimum values, respectively (Figure 3).

A sample case of MRI pelvis of a 70-year-old female with pathologically proven endometrial carcinoma, with thickened endometrium appearing isointense to myometrium on T2W images and showing restriction of diffusion noted on DWI with ADC value of  $0.6 \times 10^{-3} \text{ mm}^2/\text{second}$  (Figure 4).



**Figure 4: MRI pelvis of a 70-year-old female. (a) T2W axial image, (b) DWI axial, (c) DWI and T2W fusion image axial and (d) ADC axial.**

MRI pelvis of a 70-year-old female showing thickened endometrium appearing isointense to mildly hyperintense to myometrium on T2W images. Restriction of diffusion noted on DWI with ADC value of  $0.6 \times 10^{-3} \text{ mm}^2/\text{second}$ . Mixed type of carcinoma i.e., endometrioid adenocarcinoma (grade 3) and clear cell adenocarcinoma. Histological grade-G3 poorly differentiated (Figure 4).

## DISCUSSION

The mean ADC value ( $10^{-3} \text{ mm}^2/\text{second}$ ) of endometrial cancer was  $0.77 \pm 0.048$ , which was significantly lower ( $p<0.05$ ) than that of normal endometrium ( $1.32 \pm 0.051$ ). There was no overlap between them. In the endometrial cancer group, the mean ADC value for each histologic grade was not statistically different. ( $p>0.05$ )

Normal endometrium can appear hyperintense on DWI even at high B values. This is due to T2-shine through effect and also suggested to be due to cellular endometrial glands in reproductive age group.<sup>21</sup>

In the study by Tamai et al there was a significant difference in ADC value between normal endometrium and in endometrial cancer. They also further reported a significant difference in ADC values between different grades of tumours especially between grade 1 and grade 3 tumors. The mean ADC values were  $0.88 \pm 0.10 \times 10^{-3} \text{ mm}^2/\text{sec}$  in endometrial cancer, and  $1.53 \pm 0.10 \times 10^{-3} \text{ mm}^2/\text{sec}$  in normal endometrium in their study. which was significant ( $p<0.01$ ).<sup>21</sup>

In the study by Reichichi et al mean ADC values of endometrial cancer were significantly lower than those of normal endometrium and myometrium ( $p<0.0001$ ), but no significant difference existed between grades of endometrial cancer.<sup>22</sup>

Woo et al in their study on 33 patients with endometrial cancer, for ADC values showed a significant difference among various cancer grades ( $p<0.03$ ) and between high and low grades ( $p<0.024$ ).<sup>23</sup>

In the study by Nougaret et al, there was no significant difference in the ADCs between grades 1 and 2 tumors ( $p>0.05$ ). However, ADCs were significantly lower in grade 3 tumors than in grades 1 and 2 tumors ( $p<0.02$ ).<sup>24</sup>

In our study, the ADC values of endometrial cancers were significantly lower ( $p<0.05$ ) than those of the normal endometrium, without any overlap. This result suggests that ADC measurement has a potential ability to differentiate between normal and cancerous tissue in the endometrium. Our study concurred with the studies of Tamai and Reichichi et al in the ability of ADC to differentiate normal and cancerous endometrium.<sup>21,22</sup>

However, in our study endometrial cancers of different grades did not show any statistically significant difference in ADC values. Our study findings were similar to



Reichichi et al, who also reported no significant difference in ADC values in different grades of endometrial carcinoma.<sup>22</sup> However studies by Tamai et al, Woo et al, Nougaret et al and Seo et al reported a significant difference in ADC values in different grades of endometrial cancers.<sup>21-25</sup>

Fujii et al and Kilikesmez et al, have reported low values of ADC in endometrial cancers, however in their studies, they have included benign endometrial pathologies in their studies.<sup>26,27</sup> Seo et al has also reported low values of ADC in endometrial cancers but in their study they are comparing with ADC of normal myometrium.<sup>25</sup> However in our study comparison was made between endometrial cancer and normal endometrium and ADC of benign pathologies or of normal myometrium were not included.

Limitations in our study are as follows. In our study benign endometrial pathologies, were not included. Thus, the ability of ADC values in differentiating between malignant and benign endometrial lesions is not assessed. The ADC values of the normal endometrium may vary according to menstrual cycle in premenopausal women, and this was not considered in our study

## CONCLUSION

ADC values of endometrial cancer are significantly lower than those of normal endometrium and so has the potential to differentiate normal endometrium and endometrial cancers. However, no significant association between ADC and histologic tumour grade, was found in our study.

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