Apparent diffusion coefficient value in evaluating types, stages and histologic grading of cancer cervix

Doaa Ibrahim Hasan a,*, Mones M. Enaba a, Hossam M. Abd El-Rahman a, Shrin El-Shazely b

a Diagnostic Radiology Department, Zagazig University, Egypt
b Obstetric and Gynecology Department, Zagazig University, Egypt

Received 28 January 2015; accepted 9 April 2015
Available online 18 May 2015

Abstract  Aim: To determine whether the apparent diffusion coefficient (ADC) measurements calculated values were significantly different between cervical tumors with different histological characteristics (type, degree of differentiation, and stage of malignancy).
Patients and methods: MRI and DWI scans performed in 26 pathologically proved cancer cervix patients. ADC values of different pathological types of cervical cancer were compared. Student’s t test was used for statistical analysis.
Results: There were 18 squamous cell carcinoma and 8 adenocarcinomas showed with biopsy results. Early stage (FIGO-Ib–IIa, n = 7), (FIGO-IIb–IIIb–IVa, n = 19). The mean ADC values for squamous cell carcinoma (n = 18), and adenocarcinoma (n = 8) were $0.88 \times 10^{-3}$, and $0.91 \times 10^{-3}$ mm$^2$/s, respectively. Statistical analysis showed significant difference in ADC value between both tumor types ($P < 0.05$). There was also significant difference between the mean ADC values of the tumor grade I and the other grades (II, III) ($p < 0.05$). The mean ADC values in early stage cervical cancer ($0.83 \pm 0.05 \times 10^{-3}$ mm$^2$/s) were significantly lower than the mean ADC values in late stage disease ($0.98 \pm 0.06 \times 10^{-3}$ mm$^2$/s) ($p < 0.05$).
Conclusion: ADC value measurements can provide useful information in diagnosis of cervical cancer as well as in preoperative assessment of the tumor stage.

1. Introduction

Uterine cervical cancer is the third most common malignancy affecting the female genital tract in middle age group between 45 and 55 years (1,2). Its incidence is increasing rapidly in developing countries. The International Federation...
Table 1  FIGO staging for carcinoma of cervix (3). International Federation of Gynecology and Obstetrics (FIGO) Staging Systems.

- **Stage 0:**
  Cervical intraepithelial neoplasia (CIN III)

- **Stage I**
  Confined to cervix
  Ia: Invasive carcinoma only diagnosed by microscopy
  Ia1: Stromal invasion < 3 mm in depth and < 7 mm in extension
  Ia2: Stromal invasion > 3 mm depth and not > 5 mm and extension > 7 mm

- **Stage Ib:**
  Clinically visible lesions limited to the cervix or pre-clinical cancers > stage 1a
  Ib1: Clinically visible tumor > 4 cm in greatest dimension
  Ib2: Clinically visible tumor > 4 cm in greatest dimension

- **Stage II:**
  Beyond cervix though not to the pelvic sidewall or lower third of the vagina
  IIa: Involves upper 2/3rd of vagina without parametrial invasion
  IIa1: Clinically visible tumor > 4 cm in greatest dimension
  IIa2: Clinically visible tumor > 4 cm in greatest dimension
  IIb: With parametrial invasion

- **Stage III**
  Stage IIIa:
  Tumor involves the lower third of the vagina with no extension to pelvic sidewall
  Stage IIIb:
  Extension to pelvic side wall or causing obstructive uropathy

- **Stage IV**
  Extension beyond pelvis or biopsy proven to involve the mucosa of the bladder or the rectum
  IVa: Extension beyond pelvis or rectal/bladder invasion
  IVb: Distant organ spread

Fig. 1  Staging of uterine cervix carcinoma according to FIGO (4).
of Gynecology and Obstetrics (FIGO) staging system updated in 2009 (Table 1 and Fig. 1) is commonly used for treatment planning but is inadequate in the evaluation of prognostic factors such as tumor volume and nodal status (3,4). Among the imaging modalities used in the preoperative evaluation of cervical cancer, MRI is an excellent modality for depicting invasive cervical cancer: it can provide objective measurement of tumor size and provides a high negative predictive value for parametrical invasion and stage IVa disease (5). Diffusion weighted imaging (DWI) is a recent approach for evaluating malignancies. Although it is widely used in the detection and evaluation of acute stroke (6), with improving MRI technology, it has also been used in the diagnosis of malignancies. Although it is widely used in the detection and evaluation of acute stroke (6), with improving MRI technology, it has also been used in the diagnosis of malignancies.

Gold standard for the diagnosis of lymph node metastases, surgical lymph node assessment is the gold standard for the diagnosis of lymph node metastases, however, it is an important factor in the choice of adjuvant radiation therapy in cervical cancer. Surgical lymph node assessment is the gold standard for the diagnosis of lymph node metastases, yet it is not incorporated in the FIGO staging system, however, it is an important factor in the choice of adjuvant radiation therapy in cervical cancer. Surgical lymph node assessment is the gold standard for the diagnosis of lymph node metastases, yet it is not incorporated in the FIGO staging system, however, it is an important factor in the choice of adjuvant radiation therapy in cervical cancer.

Lymph node involvement is an important factor in the choice of adjuvant radiation therapy in cervical cancer. Surgical lymph node assessment is the gold standard for the diagnosis of lymph node metastases, yet it is not incorporated in the FIGO staging system, however, it is an important factor in the choice of adjuvant radiation therapy in cervical cancer.

2. Patients and methods

This study was conducted following ethics approval from the local institutional review boards and all patients gave informed consent. From December 2012 to November 2014, we evaluated 26 histopathologically proved cervical cancer patients with early and late stage locally advanced cancer cervix. All examinations were performed on a 1.5-T MRI system (Achieva, Philips Healthcare, Best, the Netherlands) using a dedicated torso coil. The standard sequences included high-resolution sagittal T2-weighted turbo spin-echo (TR/TE = 4000/80 ms, turbo factor = 14, field of view = 240 × 240 mm, matrix size = 400 × 392, slice thickness = 4 mm, intersection gap = 0 mm), axial T2-weighted turbo spin-echo (TR/TE = 2800/100 ms, turbo factor = 12, field of view = 405 × 300 mm, matrix size = 787 × 600, slice thickness = 4 mm, intersection gap = 0 mm) and T1-weighted turbo-field-echo contrast-enhanced acquisition (TR/TE = 2.4/1.2 ms, field of view = 350 × 350 mm, matrix size = 212 × 211, slice thickness = 3.0 mm, intravenous bolus injection of 0.1 mmol/kg body weight gadopentetate dimeglumine at 3.0 ml/s), to allow accurate evaluation of the parametrium.

2.2. DW-MRI

DW-MRI was performed using single-shot spin-echo echoplanar imaging, immediately after the axial T2-weighted imaging and before intravenous contrast injection. It was acquired in free breathing with background body signal suppression (per-saturation inversion recovery fat suppression) using the following parameters: TR/TE = 2000/54 ms, field of view = 403 × 300 mm, matrix size = 168 × 124, slice thickness = 4 mm, intersection gap = 0 mm, parallel imaging with sensitivity encoding factor of 2, receiver bandwidth = 1382.5 Hz per pixel. We acquired b values (0, 500 and 1000 s/mm²) in the axial plane covering 20 slices to include the entire cervical body.

Table 2 The patient age, number of each FIGO stage and detected pelvic LNs.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total n = 26</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)*</td>
<td>59.7 ± 4.6 years (35-71 years)</td>
</tr>
<tr>
<td>Premenopause/postmenopause ratio</td>
<td>20:6</td>
</tr>
<tr>
<td>FIGO stageb</td>
<td></td>
</tr>
<tr>
<td>Early</td>
<td></td>
</tr>
<tr>
<td>Ib</td>
<td>2 (7.9%)</td>
</tr>
<tr>
<td>Ha</td>
<td>5 (19%)</td>
</tr>
<tr>
<td>Late</td>
<td></td>
</tr>
<tr>
<td>Iib</td>
<td>9 (34.6%)</td>
</tr>
<tr>
<td>IIb</td>
<td>7 (26.9%)</td>
</tr>
<tr>
<td>Iva</td>
<td>3 (11.4%)</td>
</tr>
<tr>
<td>Pelvic LN + metastasis</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>9 (47.3%)</td>
</tr>
<tr>
<td>No</td>
<td>10 (52.6%)</td>
</tr>
</tbody>
</table>

* P value shows statistically significant (P > 0.05).

Table 3 Comparison between the histopathologic subtypes, tumor stage, tumor grades and the mean ADC values.

<table>
<thead>
<tr>
<th>Histopathology</th>
<th>No (%)</th>
<th>Mean ADC value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Squamous cell cancer</td>
<td>18 (69.2%)</td>
<td>0.88 × 10⁻³ mm²/s*</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>8 (30.7%)</td>
<td>0.91 × 10⁻³ mm²/s</td>
</tr>
<tr>
<td>Tumor stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early stage (stages Ib–IIa)</td>
<td>7 (26.9%)</td>
<td>0.83 × 10⁻³ mm²/s*</td>
</tr>
<tr>
<td>Late stage (stages II–III–IV)</td>
<td>19 (73%)</td>
<td>0.98 × 10⁻³ mm²/s</td>
</tr>
<tr>
<td>Tumor grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade I</td>
<td>11 (42.3%)</td>
<td>0.90 × 10⁻³ mm²/s*</td>
</tr>
<tr>
<td>Grade II</td>
<td>8 (30%)</td>
<td>0.94 × 10⁻³ mm²/s</td>
</tr>
<tr>
<td>Grade III</td>
<td>7 (26.9%)</td>
<td>0.97 × 10⁻³ mm²/s</td>
</tr>
<tr>
<td>Pelvic LN + metastasis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>9 (47.3%)</td>
<td>0.77 × 10⁻³ mm²/s*</td>
</tr>
<tr>
<td>No</td>
<td>10 (52.6%)</td>
<td>1.70 × 10⁻³ mm²/s</td>
</tr>
</tbody>
</table>

* P value shows statistically significant (P > 0.05).

b FIGO = International Federation of Gynecology and Obstetrics. Numbers in parenthesis are percentage.
cancer, using motion-probing gradients in three orthogonal axes. We ensured that the field of view, slice thickness and intersection gap were the same as the anatomical axial T2-weighted imaging to allow image overlay and co-registration.

ADC maps were calculated from DW images that were previously assessed. In the patient group, ADC measurements were executed on reconstructed ADC maps with the largest region of interest (ROI) within the tumor. Equal-sized ROIs (each 5 mm$^2$) that excluded macroscopic necrotic areas (fluid signal on T2), large vessels and areas with susceptibility artifact caused by air–water interface. The greatest dimension of the tumor was measured. ROIs were set up three times and the average of them was used for each ADC value measurement in the malignant masses and detected pelvic L.Ns (>10 mm in the longitudinal diameter).

2.3. Statistics

Descriptive statistics were used to describe clinical demographics using range, means and standard deviation (mean ± SD). A $t$-test was used to analyze comparisons and a $p$ value < 0.05 was accepted as statistically different. Comparisons of mean ADC values between histopathological subtypes, tumor grades and stages were made. Rare cervical cancer subtypes like small-cell carcinoma were excluded from the study because of insufficient numbers. Comparisons of mean ADC values between enlarged metastatic pelvic L.Ns and nonmetastatic one.

3. Results

Twenty-six patients, their average age 35–71 years old (mean was 59.7 ± 4.6 years). They were premenopause/postmenopause (20:6) (Table 2).

Pathological diagnoses: Early stage (FIGO-Ib–IIa, $n = 7$), (FIGO-IIb–IIIb–IVa, $n = 19$). According to the International Federation of Gynecology and Obstetrics (FIGO), classification stages I–IIa are considered early stage and stages IIb or more are considered late stage (3). Seven patients were in the early stage with 2 patients in stage Ib and 5 in stage IIa, whereas 19 patients were in the late stage, nine patients in stage IIb, 7 patients in stage IIIb and 3 patients in stage IVa (Table 2). Enlarged L.Ns found in 19/26 of the patients, nine of them were malignant, while the other 10 patients were hyperplastic lymph nodes.

There were squamous cell cancer in 18 (69.2%) patients and adenocarcinoma in 8 (30.7%) patients, with mean ADC values of $0.88 \times 10^{-3}$ mm$^2$/s and $0.91 \times 10^{-3}$ mm$^2$/s, respectively. Apparent diffusion coefficient value of squamous carcinoma was statistically significant lower than that of adenocarcinoma ($P < 0.05$) (Table 3).

Fig. 2  37 years old female with cervical carcinoma, FIGO stage Ib2. (A and B) Axial and sagittal T2WI show well defined isointense cervical mass involving the posterior lip of the cervix with clear upper vagina as well as preserved peripheral hypointense stromal ring denoting the absence of parametrial invasion. (C and D) DWI and ADC maps show restricted diffusion of the cervical mass with low ADC measures $0.687 \times 10^{-3}$ mm$^2$/s. Pathologically proved as moderately differentiated squamous cell carcinoma grade I.
According to the FIGO classification stages: seven patients (26.9%) were in the early stage with 2 patients in stage Ib (Fig. 2) and 5 in stage Ila (Fig. 3), whereas 19 (73%) patients were in the late stage, 9 patients in stage IIb (Fig. 4), 7 patients in stage IIIb (Fig. 5) and 3 patients in stage IVa (Fig. 6).

The mean ADC values in early-stage cervical cancer (0.83 ± 0.05 × 10⁻³ mm²/s) were significantly lower than the mean ADC values in the late stage of the disease (0.98 ± 0.06 × 10⁻³ mm²/s) (p < 0.05).

Comparison of mean ADC values for early and late stage cervical cancer according to FIGO classification (Table 3). There was a significant difference between early and late stage cervical cancer (p < 0.05).

With regard to tumor grades, there were statistical differences found between the mean ADC values, grade I (n:11), and other grades (grade II n:8 and grade III n:7) (p < 0.05). The mean ADC value of grade I cases was 0.90 × 10⁻³ mm²/s, while in grade II and III the mean ADC values were 0.94 × 10⁻³ mm²/s and 0.97 × 10⁻³ mm²/s, respectively. There was no statistically significant difference between grade II and grade III (Table 3, Fig. 7).

In the study group the mean ADC values (0.77 × 10⁻³ mm²/s) for metastatic enlarged L.Ns (Fig. 5E and G), which were statistically significant (p < 0.05) than that of the hyperplastic enlarged L.Ns (1.70 × 10⁻³ mm²/s) (Table 3).

4. Discussion

Magnetic Resonance Imaging with high soft-tissue resolution is the most valuable imaging modality in the assessment of tumor size, depth of cervical invasion and extent of locoregional spread in the treatment planning of cervical cancer (12,13). DWI which has recently been used in the diagnosis of malignant lesions, can distinguish the normal uterine cervix from cervical cancer and benign lymph nodes from malignant ones (14).

In our study the mean ADC values in squamous carcinoma were statistically lower than those of adenocarcinoma (p < 0.05). Similar findings had reported by Lui et al. (15) in their studying 42 patient group. The different pathological characteristics are of these two tumor types. Cell of squamous carcinoma tends to be more compact and crowded, while adenocarcinoma gives out more tube-like structures which mimic adeno-tissues. These tube-like structures have a large intercellular space which will lead to higher ADC value. DWI, as a classification methodology applied successfully in gliomas...
(16) could probably also been used in pathological subtype classification of cervical tumor.

On contrary Tuna et al. (17) had reported no significant difference between mean ADC values of squamous cell cancer and adenocarcinoma (0.95 \times 10^{-3} \text{mm}^2/\text{s} and 0.91 \times 10^{-3} \text{mm}^2/\text{s}, respectively) ($p > 0.05$). They explained that may be related to the smaller patient group of their study. Mangal et al. (18) found in their study, preoperative estimation of histologic type based on the ADC values still seems difficult because there is a considerable overlap between them.

In the present study, according to the FIGO classification stages: the mean ADC values in early-stage cervical cancer (0.83 $\pm$ 0.05 $\times 10^{-3}$ \text{mm}^2/\text{s}) were significantly lower than the mean ADC values in the late stage of the disease (0.98 $\pm$ 0.06 $\times 10^{-3}$ \text{mm}^2/\text{s}) ($p < 0.05$). Several researches showed potential clinical value of ADC value in differentiating FIGO stage or pathological grade. Patrick et al. (19) analyzed relationship between FIGO stage and ADC value. They found that ADC was significantly lower in FIGO stage T1b/T2a than that in T2b and T3/T4. This may indicate disease prognosis or help in treatment planning.

McVeigh et al. (9) reported that mean ADC values of patients with cervical cancer were lower than normal cervix ADC values. Also, with regard to FIGO classification, mean ADC values were found to be lower in stages Ib/Iia than in stage IIb and stages III/IV, as we found in this study. The significant difference between the FIGO stages may be a useful factor in treatment planning, especially for cases in which the extent of the disease is undetermined. In a study by Kuang et al. (20), they concluded that in the evaluation of cervical cancer, the diagnostic accuracy of ADC values for the distinction of cancers from normal tissue was high.

In our study the ADC values of cervical cancers of higher pathological grade showed tendency to decrease compared to those of lower grade, with significant difference between grade I and other grades (II, III). On the other hand, a negative correlation between tumor grade and mean ADC values was reported in many studies (15,17). While in Ken’s study, the ADC values of endometrial cancers of higher pathological grade showed tendency to decrease compared to those of lower grade, although estimation of histological grade based on ADC values seems difficult because of considerable overlap (21).

A study by Chen et al. (22) reported lower mean ADC values for cervical cancer than for a normal cervix. Also, they reported that there was an increase in ADC values after radiotherapy, which indicated that DWI might be used to monitor the response to therapy. Moreover in patients with cervical
A 73 years old patient presented with postmenopausal bleeding with cancer cervix FIGO stage IIIb. (A and B) Sagittal and axial T2WIs show the large cervical mass involving both anterior and posterior cervical wall distending the cervical canal and extending to the upper vagina. It displays intermediate SI with interruption of the low-signal-intensity cervical stromal ring. (C) Axial T2-weighted image on higher level shows bilateral enlarged deep external iliac pelvic LNs. (D and E) DWI shows restricted diffusion in the cervical mass and LNs (arrow). (F and G) Gray ADC map shows low ADC value of the cervical mass and within the enlarged L.N, which were $0.866 \times 10^{-3}$ mm$^2$/s and $0.733 \times 10^{-3}$ mm$^2$/s respectively. Pathologically proved as invasive well poor differentiated squamous cell carcinoma grade III.
cancer, the measurement of ADC values could be an important factor for assessing response to chemoradiotherapy (23,24).

Within the pelvis, cervical cancer spreads first to the parametrial nodes, then to the obturator and iliac nodes. Although not incorporated in the FIGO staging system, the presence of lymph node metastases has significant prognostic and treatment consequences. The 5 year survival for node-positive patients is 39–54%, compared with 67–92% in patients without nodal involvement (25).

Among our studying group, the mean ADC of metastatic lymph nodes was significantly lower than in benign lymph nodes, which were $0.77 \times 10^{-3}$ mm$^2$/s for metastatic enlarged LNs compared to $1.70 \times 10^{-3}$ mm$^2$/s for enlarged hyperplastic LNs. Similar results had reported by Lei et al. (11) and Nakai et al. (26). Moreover, use of DWI in conjunction with T2-weighted images identified 85% of metastatic nodes, while only 25% were identified on the T2-weighted images alone (26). DWI sequence increased the sensitivity for identifying lymph nodes, meaning the information could be used as a map to aid surgical planning, avoiding extensive lymphadenectomy and refining radiotherapy fields (11).

Fig. 6 60 years old female presented by postmenopausal bleeding with cancer cervix FIGO stage IVa. (A) Sagittal T2WI Large ill defined cervical mass involving both anterior and posterior cervical lips, displaying intermediate SI on T2WI, following contrast it shows homogenous enhancement. Interruption of the T2 hypointense ring. Invasion of the upper 2/3 as well as lower 1/3 of the vagina. (B and C) DWI at the cervical region and more higher level shows invasion of the posterior UB wall, right pelvic side and enlarged right deep pelvic LN. (D) Restricted diffusion with ADC value $0.877 \times 10^{-3}$ mm$^2$/s. Pathologically proved as of squamous cell carcinoma grade III.

Fig. 7 Box-whisker plots for the mean ADC values of the histological grades of uterine cervical cancer. The ADC values of uterine cervical cancer grade I were significantly lower than those of grades II and III.

Although not incorporated in the FIGO staging system, the presence of lymph node metastases has significant prognostic and treatment consequences. The 5 year survival for node-positive patients is 39–54%, compared with 67–92% in patients without nodal involvement (25).

Among our studying group, the mean ADC of metastatic lymph nodes was significantly lower than in benign lymph nodes, which were $0.77 \times 10^{-3}$ mm$^2$/s for metastatic enlarged LNs compared to $1.70 \times 10^{-3}$ mm$^2$/s for enlarged hyperplastic LNs. Similar results had reported by Lei et al. (11) and Nakai et al. (26). Moreover, use of DWI in conjunction with T2-weighted images identified 85% of metastatic nodes, while only 25% were identified on the T2-weighted images alone (26). DWI sequence increased the sensitivity for identifying lymph nodes, meaning the information could be used as a map to aid surgical planning, avoiding extensive lymphadenectomy and refining radiotherapy fields (11).

The limitation of our study was that it did not encompass all of the cervical cancer subtypes.

5. Conclusion

Use of ADC value measurements may provide convenient data for the diagnosis of cervical cancer as well as for preoperative assessment of the tumor and nodal staging.
Conflict of interest

The authors declare that there are no conflict of interest.

References