Role of apparent diffusion coefficient as a biomarker in the evaluation of cervical cancer

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Abstract

Background: Diffusion-weighted magnetic resonance imaging (DW-MRI) has evolved as a major diagnostic and prognostic tool in cervical cancer. The aim of our study was to compare the change in mean apparent diffusion coefficient (ADC) value before and after concurrent chemoradiation therapy (CCRT) in carcinoma cervix thereby establishing its role as a cancer biomarker. Materials and Methods: A hospital-based prospective study was conducted in 35 patients diagnosed with cervical cancer. All 35 patients underwent pelvic MRI before and after 6 months of CCRT. The study was done over a period of 12 months. Conventional axial and sagittal T2 imaging was followed by DW-MRI. In the axial DW/ADC images at “b-value” of 800 s/mm², a circular region of interest was drawn covering more than 60% of the tumor volume to calculate the ADC values. Statistical Package for the Social Sciences (version 21.0) was used for statistical evaluation. Chi-square test, independent samples t-test, and analysis of variance were used to analyze the data. The results are depicted as frequencies (number), proportion (percentages), and mean ± standard deviation. Results: Pre-CCRT mean ADC value was $0.814 \times 10^{-3}$ mm²/s. Post-CCRT mean ADC value was $1.294 \times 10^{-3}$ mm²/s. Mean ADC value of patients having lymph node involvement and parametrial extension was significantly lower when compared with those without lymph node involvement and parametrial extension ($P = 0.001$). Nonresponders with residual lesion had lower ADC values than responders with no residual lesion. An interesting and unique observation was that pre-CCRT mean ADC value of responders was higher than nonresponders. Conclusion: An increase in mean ADC value of $0.480 \times 10^{-3}$ mm²/s after CCRT was found to be statistically significant ($P < 0.001$) thereby proving its role as an imaging biomarker in cancer cervix.

Key words: Apparent diffusion coefficient; cervical cancer; concurrent chemoradiation therapy; diffusion-weighted magnetic resonance imaging

Introduction

Every year in India, 122,844 women are diagnosed with cervical cancer, of which 67,477 succumb to the disease. India has a population of 432.2 million women, age 15 years and above, who are at risk of developing cancer.[1] It is the second most common cancer in women age 15-44 years. India also has the highest age-standardized incidence of cervical cancer in South Asia at 22, compared with 19.2 in Bangladesh, 13 in Sri Lanka, and 2.8 in Iran.[1] This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

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The Federation of Gynecology and Obstetrics (FIGO) system for staging of cervical carcinoma (classification IIB–IVB), which is based on clinical examination, is widely used for treatment planning and for standardization of epidemiological and treatment results. It is important to assess the extent of the disease before planning surgical treatment or chemoradiation therapy which is not possible by conventional clinical or histopathological evaluation.\(^2,^3\) The prognosis of cervical cancer depends on tumor type, tumor volume, grade, absence or presence of lymphovascular space invasion, and locoregional lymph node status; for which magnetic resonance imaging (MRI) is the ideal radiological tool.\(^4,^5\) It is also useful in assessing the efficiency of chemoradiation therapy and in the evaluation of tumor recurrence.\(^6\)

Diffusion-weighted (DW)-MRI is being explored as a noninvasive and noncontrast-based alternative in oncological imaging\(^7\) for the detection of cancers and for monitoring their response to concurrent chemoradiation therapy (CCRT). It demonstrates the “property of diffusivity” in each voxel, and based on their difference it attempts to distinguish pathological tissue from normal tissue. The technique uses the image contrast arising from the thermally driven water molecules within tissue in different microenvironments.\(^8,^9\) Tumor-affected cells exhibit an anomalous microenvironment characterized by dense interstitial structure, high cellularity, and accumulated solid stress.\(^10\) It has the potential to highlight these characteristics of tumors and have been recognized as cancer biomarkers. DW-MRI studies of cervical cancer have been shown to have significantly lower apparent diffusion coefficient (ADC) values compared with normal tissue. In tumor tissue, the increased cellularity compared with nontumor tissue restricts water movement between cells so that the tumor retains signal intensity on DW images with corresponding low ADC values. ADC is derived from this variation in diffusivity of movement of water molecules within biological tissue.\(^11,^12\) The change in ADC value before and after CCRT can be used in assessing the response of tumors to chemoradiation therapy.\(^8,^13\) Apart from cervical cancer, it is also being tested in liver, breast, and prostate malignancies.\(^14,^16\) “b-value” is the strength of the diffusion gradient.

**Aim**

The aim of this study was to prove the role of quantitative ADC value as an imaging biomarker by comparing its change before and after CCRT.

**Materials and Methods**

The prospective study included 35 patients confirmed histopathologically as carcinoma cervix and referred to the Department of Radiology and Imaging of a tertiary care hospital for further evaluation. The study was done over a period of 12 months after obtaining approval and ethical clearance from the Institutional Ethical Committee. Claustrophobic patients and those with cardiac pacemakers and metallic implants were excluded from the study. All 35 patients subsequently underwent both pre- and post-CCRT MRI evaluation after obtaining informed written consent.

**MRI protocol**

Axial and sagittal T2-weighted images and axial DW images were acquired using Siemens Magnetom Avanto MR Machine, Germany with a 1.5-Tesla scanner. Imaging parameters for T2-weighted fast spin echo were the following: repetition time (TR) 4225–6200 ms, echo time (TE) 15–100 ms, bandwidth 20.83 kHz, echo train length 15 kHz, slice thickness 4 mm, gap 1 mm, field of view (FOV) 22 cm, matrix 256 × 256, number of excitations four, and acquisition time of 4 min. Once the tumor had been visualized on conventional T2-weighted imaging, axial DW images were obtained using b-values of 0, 90, and 800 s/mm\(^2\). Imaging parameters for these were TR 5200 ms, TE 69 ms, FOV 32 cm, bandwidth 62.5 kHz, slice thickness 6 mm, gap 0 mm, number of excitations 16, matrix 128 × 128, and acquisition time of 5 min. All patients were imaged before commencement of chemoradiation therapy and after 6 months of concurrent chemoradiotherapy. For localization of the tumor, measurement of its dimensions and assessment of morphological response sagittal and axial T2-weighted images were used.

In the axial ADC images, a circular region of interest (ROI) was drawn on low-signal intensity area representing the tumor, covering more than 60% of its volume. The ADC value (×10\(^{-3}\) mm\(^2\)/s) was determined by the workstation. Diagnostic efficacy of ADC was evaluated in terms of sensitivity, specificity, positive predictive, negative predictive, and accuracy values.
Results

The mean age of the study group was 60.71 years as depicted in Figure 1 and Table 1. Of 35 cases enrolled in the study, 33 (94.3%) were diagnosed histopathologically as squamous cell carcinoma, and of the remaining two cases, one (2.9%) each was diagnosed as papillary adenocarcinoma and small cell carcinoma, respectively. Hence, the most common type of carcinoma cervix was squamous cell carcinoma. Among 33 cases diagnosed as squamous cell carcinoma, 16 were well-differentiated, 12 were moderately differentiated, and 5 were poorly differentiated [Figure 2] according to FIGO, 2009 standards. In the majority of cases, cervical cancer extended to involve lower uterine segment and vagina [Figure 3 and Table 2]. Of 35 diagnosed cases, 22 had parametrial extension and 19 showed lymph node involvement [Table 3]. Among those having lymph node involvement, inguinal lymph nodes were the most commonly involved (n = 9) followed by iliac lymph node (n = 8).

All 35 patients underwent both pre- and post-CCRT MRI evaluation. Of 35 patients, 4 were nonresponders who had increase in size or less than 40% reduction in tumor volume after 6 months of CCRT, and the remaining 31 of them were termed as responders who showed more than 40% reduction in tumor volume after CCRT.

On pre-CCRT imaging, all the cases revealed restricted diffusion with low ADC values on DWI/ADC maps [Figure 4]. Pre-CCRT ADC values ranged from 0.331 to 1.021 × 10⁻³ mm²/s [Figure 5]. The mean pre-CCRT ADC value was 0.814 × 10⁻³ mm²/s with an SD of 0.133. The median mean ADC value was 0.836 × 10⁻³ mm²/s [Table 3].

The mean ADC value of patients having lymph node involvement was significantly lower (0.770 ± 0.143 × 10⁻³ mm²/s) when compared with those with no lymph node involvement (0.868 ± 0.099 × 10⁻³ mm²/s) (P = 0.027). The mean ADC value of patients showing parametrial extension was significantly lower (0.762 ± 0.133 × 10⁻³ mm²/s) when compared with those with no parametral extension (0.902 ± 0.073 × 10⁻³ mm²/s) (P = 0.001) [Table 3].

On post-CCRT imaging (after 6 months), 31 (81.8%) cases (responders) [Figure 6] showed no residual lesion, while 4 (18.2%) cases (nonresponders) showed residual lesion [Table 4].

The mean pre-CCRT ADC value of cases showing residual lesion (nonresponders) was found to be significantly lower (0.770 ± 0.143 × 10⁻³ mm²/s) when compared with those with no residual lesion (responders) (0.868 ± 0.099 × 10⁻³ mm²/s) (P = 0.027).

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Table 1: Age-wise distribution of cases

<table>
<thead>
<tr>
<th>S. No</th>
<th>Age group</th>
<th>No. of cases</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>≤50 years</td>
<td>2</td>
<td>5.7</td>
</tr>
<tr>
<td>2.</td>
<td>51-60 years</td>
<td>15</td>
<td>42.9</td>
</tr>
<tr>
<td>3.</td>
<td>61-70 years</td>
<td>17</td>
<td>48.6</td>
</tr>
<tr>
<td>4.</td>
<td>&gt;70 years</td>
<td>1</td>
<td>2.8</td>
</tr>
</tbody>
</table>

Mean age in years 60.71

Table 2: Distribution of cases according to pre CCRT extent of cervical cancer

<table>
<thead>
<tr>
<th>Extent of cervical cancer</th>
<th>No.</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Involving lower uterine segment and upper 1/3 of vagina</td>
<td>22</td>
<td>62.9</td>
</tr>
<tr>
<td>Involving lower uterine segment and upper 2/3 of vagina</td>
<td>5</td>
<td>14.3</td>
</tr>
<tr>
<td>Involving lower uterine segment with no vaginal extension</td>
<td>2</td>
<td>5.7</td>
</tr>
<tr>
<td>Confined to cervix</td>
<td>2</td>
<td>5.7</td>
</tr>
<tr>
<td>Involving mid-lower uterine segment and upper 1/3 of vagina</td>
<td>2</td>
<td>5.7</td>
</tr>
<tr>
<td>Involving lower uterine segment, upper 1/3 of vagina, and urinary bladder</td>
<td>1</td>
<td>2.9</td>
</tr>
<tr>
<td>Involving upper 1/3 of vagina</td>
<td>1</td>
<td>2.9</td>
</tr>
</tbody>
</table>
lower (0.641 ± 0.214 × 10⁻³ mm²/s) when compared with that of cases showing no residual (responders) lesion (0.796 ± 0.089 × 10⁻³ mm²/s) [Table 4] [Figure 7]. The area under curve (AUC) value was found to be 0.819, thus showing the predictive efficacy to be close to 81.9%.

On evaluating different coordinates generated by ROC analysis, pre-CCRT ADC <0.799 was projected to be 100% sensitive and 61.1% specific in prediction of residual lesion [Figure 8]. Following CCRT, on DWI/ADC maps, responders showed high ADC values and hypointense signal on T2WI and nonresponders revealed lower ADC values and heterogeneously hyperintense signal on T2WI. Nonresponders (four cases) with residual lesion had lower ADC values (1.092 ± 0.214 × 10⁻³ mm²/s) when compared with responders with no residual lesion (31 cases).

Table 3: Association of pre-CCRT Mean ADC values with lymph node involvement, parametrial extension & HPE grading

<table>
<thead>
<tr>
<th>Condition</th>
<th>n</th>
<th>Pre-CCRT mean ADC value (10⁻³ mm²/s)</th>
<th>SD</th>
<th>Statistical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymph node involvement</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>19</td>
<td>0.770</td>
<td>0.143</td>
<td>t=2.315; P=0.027</td>
</tr>
<tr>
<td>No</td>
<td>16</td>
<td>0.868</td>
<td>0.099</td>
<td></td>
</tr>
<tr>
<td>Parametrial extension</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>22</td>
<td>0.762</td>
<td>0.133</td>
<td>t=3.471; P=0.001</td>
</tr>
<tr>
<td>Absent</td>
<td>13</td>
<td>0.902</td>
<td>0.073</td>
<td></td>
</tr>
<tr>
<td>HPE grade of squamous cell carcinoma (n=33)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Well differentiated</td>
<td>16</td>
<td>0.817</td>
<td>0.178</td>
<td>F=0.338; P=0.716</td>
</tr>
<tr>
<td>Moderately differentiated</td>
<td>12</td>
<td>0.831</td>
<td>0.070</td>
<td></td>
</tr>
<tr>
<td>Poorly differentiated</td>
<td>5</td>
<td>0.772</td>
<td>0.064</td>
<td></td>
</tr>
</tbody>
</table>

CCRT: concurrent chemoradiation therapy; ADC: apparent diffusion coefficient; SD: standard deviation; HPE: Histopathological examination

Figure 3 (A and B): Conventional pre CCRT T2W sagittal (A) and axial image (B) shows malignant cervical lesion (Red arrow) with nodular margins involving corpus uteri (Blue arrow) and vagina (Green arrow) as well as posterior wall of the urinary bladder (Yellow arrow).

Figure 4 (A and B): Pre CCRT DW (A) and ADC (B) images of a patient with cervical carcinoma illustrates restricted diffusion (Red arrow) with low ADC value of 0.938 × 10⁻³ mm²/s (Yellow arrow).

Figure 6 (A and B): Conventional sagittal pre CCRT (A) and post CCRT (B) T2W images of a patient with cervical carcinoma involving corpus uteri (Red arrow) showing complete response as evident by significant reduction in tumor size and extent (Yellow arrow) indicative of a responder.
(1.212 ± 0.214 × 10⁻³ mm²/s) [Figures 9 and 10]. Post-CCRT ADC values ranged from 0.983 to 1.563 × 10⁻³ mm²/s. The mean post-CCRT ADC value was 1.294 × 10⁻³ mm²/s with an SD of 0.142. The median mean ADC value was 1.320 × 10⁻³ mm²/s [Figure 11].

Pre-CCRT mean ADC value was 0.814 ± 0.129 × 10⁻³ mm²/s which increased to 1.294 ± 0.142 × 10⁻³ mm²/s after CCRT, thus showing a change of 0.480 × 10⁻³ mm²/s which was found to be statistically significant (P < 0.001). The mean pre- and post-CCRT ADC value in responders was 0.796 and 1.43 × 10⁻³ mm²/s, respectively. The mean pre- and post-CCRT ADC value in nonresponders was 0.641 and 1.12 × 10⁻³ mm²/s, respectively [Table 5].

Discussion

Histopathologically, a total of 33 (94.3%) cases were diagnosed as squamous cell carcinoma. Hasan et al.⁹ in their study showed 69.2% of squamous cell carcinoma and 30.7% of adenocarcinoma cases. Atram et al.¹⁰ in their series, showed 82.8% of squamous cell carcinoma, 15.8% of adenocarcinoma, and 1.4% of adenosquamous carcinoma cases. Karunya et al.¹¹ revealed 88% of squamous cell, 6% of adenocarcinoma, 4% of adenosquamous carcinoma, and 2% of undifferentiated types. McVeigh et al.¹² in their study found 37 of 47 (78.7%) as squamous cell carcinoma, and Chen et al.¹³ found all their 33 cases diagnosed with squamous cell carcinoma. Hence, in concordance with other similar major studies, squamous cell carcinoma was found to be the most common type of cervical cancer.

In this study, the majority of cervical cancers (62.9%) had involvement of lower uterine segment and upper one-third portion of vagina. Lymph node involvement was seen in 19 (54.3%) cases and parametrial extension was seen in 22 (62.9%) cases. Similar findings were seen in a study conducted by Hasan et al.¹⁴ Atram et al.¹⁵ reported lymph
node involvement in 34% and Karunya et al.[19] reported lymph node involvement in 31% of cases.

In this study, pre-CCRT ADC values ranged from 0.331 to 1.021 × 10⁻³ mm²/s. The mean ADC value was 0.814 ± 0.133 × 10⁻³ mm²/s. Hasan et al.[17] in their series reported the mean ADC values for both squamous cell carcinoma and adenocarcinoma cases to be less than 1 × 10⁻³ mm²/s (0.88 and 0.91 × 10⁻³ mm²/s, respectively), Atiram et al.[18] reported a mean ADC value of 0.8827 × 10⁻³ mm²/s, and Karunya et al.[19] reported a mean ADC value of 0.72 ± 0.168 × 10⁻³ mm²/s. In the series by McVeigh et al.[20] the mean ADC value of cervical cancer cases was reported to be 1.09 × 10⁻³ mm²/s, and Kuang et al.[21] reported a mean ADC value of 0.910 ± 0.15 × 10⁻³ mm²/s for cervical cancer. As observed in various studies cited above, the mean pre-CCRT ADC value of cervical cancer in our study was also found to be less than 1.

Post-CCRT assessment was done in all 35 cases. Of 35 cases, 4 had residual lesion (nonresponders). Post-CCRT ADC values ranged from 0.983 to 1.563 × 10⁻³ mm²/s with a mean of 1.294 ± 0.142 × 10⁻³ mm²/s. On comparing them with pre-CCRT ADC values, there was a mean increase of 0.480 ± 0.134 × 10⁻³ mm²/s which was statistically significant. Similar observations were also made by other authors[22–30] and few recent studies [Table 6].

Nonresponders (4 cases) with residual lesion had lower ADC values (1.092 ± 0.214 × 10⁻³ mm²/s) when compared with responders (31 cases) with no residual lesion (1.212 ± 0.214 × 10⁻³ mm²/s). These findings are in agreement with the observations made by Fu et al.[23] who on the basis of a metaanalysis of 16 studies that included 517 patients with cervical cancer, reported that the mean ADC value in patients without residual tumor post-CCRT was significantly higher than in patients with residual tumors. Chopra et al.[21] in their ROC analysis identified volume of 25 cm³ or higher (sensitivity = 80%, specificity = 80%, AUC = 0.76, P = 0.04) and ADC more than 1 × 10⁻³ mm²/s predicted partial response with high sensitivity (85.7%) and specificity (100%) (AUC = 0.96, P = 0.05). In our study, the AUC value was found to be 0.819, thus showing the predictive efficacy to be close to 81.9%; and on evaluating different coordinates generated by ROC analysis, pre-CCRT ADC <0.799 was projected to be 100% sensitive and 61.1% specific in prediction of residual lesion. However, due to low volume and insufficient data, we were not able to determine the exact cut-off ADC values for cervical cancer at the end of treatment. An interesting and unique observation was that pre-CCRT ADC values of nonresponders were lower than responders.

The findings of this study within its limitations, that is limitation of sample size and duration, showed that DW imaging and ADC values are helpful in characterizing the cervical cancer and can also play a role in predicting response to chemoradiotherapy and in posttreatment assessment. Further studies on larger sample size with longer duration of follow-up are recommended to reconfirm the findings especially in context with tumor stage, grade, stromal invasion, and recurrence pattern.

**Conclusion**

The pre-CCRT mean ADC value of cases with lymph node involvement and parametrial extension were lower when compared with those without lymph node involvement and parametrial extension. On post-CCRT imaging, nonresponders (4 cases) with residual lesion had lower

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**Table 4: Responders vs Non-responders**

<table>
<thead>
<tr>
<th>Responders vs nonresponders</th>
<th>No. of cases (%)</th>
<th>Mean pre-CCRT ADC (10⁻³ mm²/s)</th>
<th>Mean post-CCRT ADC (10⁻³ mm²/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responders with no residual lesion</td>
<td>31 (81.8)</td>
<td>0.796</td>
<td>1.43</td>
</tr>
<tr>
<td>Nonresponders with residual lesion</td>
<td>04 (8.2)</td>
<td>0.641</td>
<td>1.12</td>
</tr>
</tbody>
</table>

CCRT: concurrent chemoradiation therapy; ADC: apparent diffusion coefficient

**Table 5: Evaluation of Change in Mean ADC values before and after CCRT (n = 35)**

<table>
<thead>
<tr>
<th>Time interval</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-CCRT</td>
<td>0.814</td>
<td>0.129</td>
</tr>
<tr>
<td>Post-CCRT</td>
<td>1.294</td>
<td>0.142</td>
</tr>
<tr>
<td>Mean change</td>
<td>0.480</td>
<td></td>
</tr>
<tr>
<td>Standard deviation of change</td>
<td>0.134</td>
<td></td>
</tr>
<tr>
<td>t-value (paired t-test)</td>
<td>18.410</td>
<td></td>
</tr>
<tr>
<td>P-value</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

SD: standard deviation; CCRT: concurrent chemoradiation therapy

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**Figure 11:** Histogram showing dispersion of post-CCRT mean ADC values
ADC values when compared with responders (31 cases) with no residual lesion. The pre-CCRT mean ADC value of responders was found to be higher than nonresponders. Although this study had limitations of sample size, duration, and absence of control, still the quantitative ADC values obtained from focal areas of restricted diffusion show promising role of ADC as a potential imaging cancer biomarker in cervical cancer, prediction of CCRT outcome, and post-CCRT response evaluation.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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