ORIGINAL ARTICLE

Changes in Magnetic Resonance Imaging Parameters and Chemo-Radiotherapy Response among Cervical Cancer Patients Attending a Regional Cancer Center of North India

Divya Gupta, Rajiv Kumar Seam1, Manoj Gupta2, Sanjeev Sharma3, Mitasha Singh4, Shikha Sood4

Introduction

Cancer of the cervix uteri is the fourth most common cancer among women worldwide, with an estimated 527,624 new cases and 265,672 deaths in 2012. About 122,844 new cervical cancer cases are diagnosed annually in India (estimations for 2012). Cervical cancer ranks as the second leading cause of female cancer in India. The North Indian states have also reported carcinoma cervix as the most common gynecological malignancy in the fairer sex. At the Regional Cancer Centre, Shimla, carcinoma of uterine cervix accounts for approximately 58.66% of all gynecological malignancies, with about 80–90% patients presenting in advanced stage with bulky central disease.

Objective: This study was planned to evaluate the effectiveness of dynamic contrast-enhanced magnetic resonance and diffusion-weighted imaging techniques in evaluating tissue hypoxia and thus develop an early predictor of treatment response in cervical cancer. Materials and Methods: This prospective study was conducted at a regional cancer center of North India from 2013 to 2014. It was conducted among locally advanced carcinoma cervix patients. Magnetic resonance imaging (MRI) was carried out at three time points, namely, prior to commencement of, after 2 weeks of start, and after 4–5 weeks of chemo-radiotherapy. A total of 48 MRI scans were performed. Change in dynamic contrast perfusion parameters ($K_{trans}$, $K_{ep}$, $V_e$, and $I_{AUC}$) and values of apparent diffusion coefficient (ADC) between different time points was calculated. Results: A total of 19 patients underwent 48 MRI scans. The percentage tumor volume regression (PTR) between the first and third MRI volumes ranged from 36.9% to 100%. The percentage diameter regression calculated between the first and third MRI ranged from 10% to 100%. The tumor volume and diameter reduced significantly from pre- to post-treatment. As compared to pretreatment parameters, it was observed that the values of $V_e$, IAUC, and ADC demonstrated an increase from baseline to the subsequent MRI; however, $K_{ep}$ and $K_{trans}$ showed an opposite trend. Conclusion: A higher value of $K_{trans}$ is associated with a better tumor response to treatment. These changes can help in predicting response to therapy.

Keywords: Cervical cancer, magnetic resonance imaging parameter, predictors, treatment
Biologic factors such as low levels of oxygen in cells prevent them from being killed by radiation. The tumors with a significant amount of hypoxic cells are therefore resistant to radiation therapy.

There are a wide range of methods for determining the existence and/or extent of tumor hypoxia. These methods include radiobiological assays, pimonidazole experiments, oxygen electrodes, magnetic resonance imaging (MRI) techniques (e.g., dynamic contrast-enhanced MRI [DCE-MRI] and diffusion-weighted imaging [DWI]), electron paramagnetic resonance, positron emission tomography, and single photon emission spectroscopy (SPECT).[9]

Thus, this study was planned to evaluate the effectiveness of DCE-MRI and DWI techniques in evaluating tissue hypoxia and thus develop an early predictor of treatment response in cervical cancer. We also tried to assess the MRI parameters such as tumor volume, \( K_{\text{trans}} \), \( K_e \), \( V_e \), \( J_{\text{ADC}} \), and apparent diffusion coefficient (ADC) or their combination, which can correctly predict tumor response in cervical cancer. These methods estimate changes in tissue contrast agent concentration following intravenous injection. Between 12% and 45% contrast leaks into the extravascular extracellular space (\( V_e \)) during the first pass and results in measurable T1 shortening of tissues. The transfer constant (\( K_{\text{trans}} \)) describes the transendothelial transport of contrast medium by diffusion from the vascular space to the tumor interstitium and provides a measure of vascular permeability. Over time, gadolinium diffuses back into the vasculature, which can be measured by the rate constant (\( K_e \)). These parameters are related by the equation \( K_{\text{ep}} = K_{\text{trans}}/V_e \). Thus, pretreatment (\( K_{\text{ep}} \)) values are also high but decrease after successful treatment.[9]

**Materials and Methods**

**Study design and setting**

This prospective study was conducted at a regional cancer center of North India.

**Study duration**

The patients were enrolled and followed up from 2013 to 2014. The study was designed with an aim of detecting early response only.

**Ethical consideration**

The study was approved by the institute’s ethical committee, and a signed informed consent was obtained from all the patients enrolled in this study.

**Study population**

It was conducted among patients suffering from locally advanced carcinoma of cervix.

**Inclusion criteria**

The cases included in this study were locally advanced carcinoma cervix belonging to Stages IIa, IIb, IIIa, and IIIb according to the FIGO 2009 staging[10] and histologically proven invasive squamous cell carcinoma (SCC), adenocarcinoma, and adenosquamous carcinoma.

**Exclusion criteria**

The following patients were excluded from the study:

1. Stage – IA, IB, IV-A, and IV-B
2. Age >70 years and <18 years
3. Patients who have had prior pelvic surgery for cancer and pelvic RT or prior chemotherapy within 5 years
4. Those with contraindications to MRI, for example, metal prosthesis, pacemakers, and claustrophobia
5. Deranged kidney function tests (blood urea nitrogen or creatinine twice above the normal limit)
6. Deranged liver function tests (bilirubin twice above the normal limit)
7. Karnofsky performance status ≤60 and
8. Distant metastasis (disease beyond true pelvis).

**Sample size**

Each patient underwent complete physical examination, including pelvic examination (under anesthesia if needed), for clinical staging. Other investigations included complete hemogram, blood biochemistry, urine routine and microscopic examination, chest X-ray (posteroanterior [PA] view), ultrasound, and computed tomography scan of the abdomen and pelvis. To exclude the bladder involvement, urine cytology and/or cystoscopy was done.

Nineteen patients met the inclusion and exclusion criteria and hence were enrolled in the study.

**Administration of treatment**

RT was given at a dose of 2 Gy in 20-25 fractions. The total RT dose given in 4–5 weeks was 45–50 Gy.[11] Injection cisplatin 40 mg/m² on day 1 of every week was administered as concurrent chemotherapy. After 2–3 weeks, intracavitary RT (ICRT) was given. If patient was not fit for ICRT, then supplement external beam radiation therapy (EBRT) at 20 Gy per fraction in 2 weeks at a dose of 2 Gy per fraction with injection cisplatin was given. EBRT was given by Teletherapy Theratron 780 E, MDS Nordian and Equinox Cobalt 60 machines (Theratron). After 2–3 weeks, Low dose rate (LDR) intracavitary brachytherapy was done, and 36–50 Gy to point A was given.

**Treatment portals**

Pelvic radiation was delivered by anteroposterior and PA parallel ports or a four-field box technique (anteroposterior, PA, and two lateral fields). The
irradiated volume included the whole uterus, paracervical and parametrium uterosacral regions, as well as external iliac, hypogastric, and obturator lymph nodes.

**Imaging protocol**

MRI was carried out at three time points, namely, prior to commencement of Chemo-radiotherapy after 2 weeks of the start of CRT, and after completion of 4–5 weeks of CRT. A total of 48 MRI scans were performed.

**Technique/data collection**

MRI studies were performed using a 1.5-T whole-body MRI unit (Magnetom Avanto, Siemens, Malvern, USA). MRI was performed using two body coils covering the abdomen and pelvis.

Gadopentetate dimeglumine was used for contrast enhancement. The contrast was given using a pressure injector at a dose of 0.1 mmol/kg body weight and at a rate of 1.5 ml/s, followed by a saline flush of 10 ml.

**Image analysis/data variables**

Postprocessing was done using Siemens Tissue 4D. Visible tumor was outlined by a radiologist on the sagittal T2-weighted (T2W) images and the T1-weighted dynamic sections. The relative position of the region of interest (ROI) was manually adjusted for motion artifact if necessary. Tumor volume was obtained by multiplying the area of tumor outlined on each T2W section by the slice thickness. The volumes from the first and third scans for each patient were used to calculate percentage tumor regression (PTR). Maximum tumor diameter (MTD) was also outlined in these images. Similar to the calculation of PTR, MTD from the first and third scans for each patient was calculated and used to categorize patients as responders and nonresponders (Response Evaluation Criteria in Solid Tumors -1.1). Patients with complete and partial responses were categorized as responders, whereas the rest as nonresponders.

Change in dynamic contrast perfusion parameters ($K_{trans}$, $K'_e$, $V'_e$, and $J_{AUC}$) and values of ADC between different time points was calculated. For all semi-quantitative and quantitative parameters, a single value was obtained for each tumor by averaging the values across all the corresponding ROIs. A correlation was then sought between these parameters and PTR.

**Statistical analysis**

Continuous variables were presented as median and categorical as proportions. Chi-square test was used to test the difference between proportions. Due to nonnormality of distribution of continuous variables (tumor and MRI parameters), nonparametric tests were applied to test the significance of difference between the two variables. SPSS version 21 (IBM SPSS software version 21.0, IBM Corp., Armonk, NY, USA) was used for statistical analysis. Wilcoxon signed-rank test was applied to evaluate the temporal changes in DCE-MRI measurements. Correlations between variables were assessed using Pearson’s correlation coefficient ($r$). The statistical significance was defined as $P < 0.05$.

**RESULTS**

A total of 19 patients underwent 48 MRI scans. The proposed three MRI scans per patient could not be performed in all, due to technical and resource constraints. Out of the 48 scans done, 6 scans had suboptimal parametric studies, due to hand injection of the contrast and hence were not included in the multiparametric analysis.

Majority of the study participants (42.1%) were in the age group of 51–60 years and 31.6% in 41–50 years’ age group. Out of the total 19 patients enrolled, 11 had Stage IIb disease (57.9%), one had Stage IIIa disease, and seven had Stage IIIb (36.8%) [Table 1]. Seventeen patients had SCC on cervical biopsy, one had adenocarcinoma, and one had adenosquamous histology. Out of the 17 patients with SCC, 14 had moderately differentiated carcinoma, whereas in the rest, the histological grade was not specified.

The Percentage tumor regression (PTR) calculated by subtracting the first and third MRI volume ranged from 36.9% to 100%. The percentage diameter regression (PDR) calculated between the first and third MRI ranged from 10% to 100%. The tumor volume and diameter reduced significantly from pretreatment to posttreatment (4 weeks) [Table 2]. According to PDR, 16 patients were categorized as responders (complete response and partial response) and 3 as nonresponders.

The second parametric study was done for seven patients only, and the third study was done for 16 patients. As compared to pretreatment parameters, it was observed that the values of $V'_e$, AUC, and ADC demonstrated an increase from baseline to the subsequent MRI (posttreatment at 4 weeks); however, $K'_e$ and $K_{trans}$ showed an opposite trend. The change in

| Table 1: Age-wise distribution of stages of tumor |
|-----------------------------------------------|
| Age groups (year) | Stage of tumor (%) | Total |
|-------------------|-------------------|-------|
|                   | IIb               | IIIa  | IIIb  |       |
| 31–40             | 2 (66.7)          | 0 (0.0) | 1 (33.3) | 3 (100.0) |
| 41–50             | 4 (66.7)          | 1 (16.7) | 1 (16.7) | 6 (100.0) |
| 51–60             | 4 (50.0)          | 0 (0.0) | 4 (50.0) | 8 (100.0) |
| >60               | 1 (50.0)          | 0 (0.0) | 1 (50.0) | 2 (100.0) |
| Total             | 11 (57.9)         | 1 (5.3) | 7 (36.8) | 19 (100.0) |

Pearson’s $\chi^2$=3.54, $P=0.74$
the pretreatment values of ADC to the posttreatment (at 2 weeks) was statistically significant. The values of $V_e$ and $K_{ep}$ from pretreatment to posttreatment (4 weeks) were also statistically significant. Similar trend was observed among responders also [Tables 3 and 4].

$K_{trans}$, $K_{ep}$, $I_{UAC}$ and ADC had positive correlation with the PTR, but this was not statistically significant. Pretreatment $V_e$ had moderate negative correlation with tumor regression ($r = 0.53$). However, all the parameters had negative correlation with PTR except $I_{UAC}$ in the posttreatment (2 weeks) MRI. At 4 weeks post treatment, MRI parameters $K_{trans}$ and $V_e$ remained weakly positively correlated with PTR, $K_{ep}$ and $I_{UAC}$ remained weakly negatively correlated with tumor regression, and ADC had almost no correlation with PTR [Table 5].

**DISCUSSION**

A high value of $K_{trans}$ and $K_{ep}$ observed in cervical carcinoma during RT indicates a considerable amount of vascular elements combined with a high endothelial permeability. In addition, in the responder group, pretreatment $K_{trans}$ was higher in comparison to that of the nonresponder group, which again supports the concept that tumors with higher vascularity have better response to treatment. The increase in $K_{trans}$ during early 2–3 weeks of irradiation could be due to increased endothelial permeability of contrast media and/or vascularity.

The values of $K_{ep}$ decreased after successful treatment, whereas for nonresponders, the values increased. Although not significant, these findings support that after successful treatment, the tumor vascularity and permeability return to normal in some patients. The values of $V_e$ were lower before the start of therapy as compared to post treatment values. During the early 2–3 weeks of RT, the $V_e$ increased, which may reflect a larger interstitial space. Although this change was seen in nonresponders as well, in our study, this change was significant for responders when the pretreatment values were compared to post treatment values. The increase in permeability of contrast media and/or vascularity.

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**Table 2: Change in tumor volume and diameter from pre- to post-treatment (4 weeks)**

| MRI parameters | Median (IQR) (cm$^3$ or cm) | Pretreatment | Posttreatment | $P^*$ |
|----------------|----------------------------|--------------|---------------|------|
| Among all patients (19) | | | | |
| Median tumor volume (IQR) | 41.13 (47.57) | 3.86 (11.9) | <0.001 |
| Median of MTD (IQR) | 5.00 (1.40) | 2.50 (1.60) | <0.001 |
| Among responders (16) | | | | |
| Median tumor volume (IQR) | 55.80 (59.17) | 7.05 (23.07) | <0.001 |
| Median of mean tumor diameters (IQR) | 5.00 (1.60) | 2.00 (2.43) | <0.001 |

*Wilcoxon signed rank test. IQR: Interquartile range, MTD: Maximum tumor diameter

**Table 3: Change in parameters on magnetic resonance imaging from pre- to post-treatment (at 2 and 4 weeks)**

| MRI parameters | Median (IQR) | Pretreatment | Posttreatment | $P^*$ |
|----------------|--------------|--------------|---------------|------|
| $K_{trans}$ | 0.27 (0.75) | 0.48 (0.40) | 0.61 | |
| $K_{ep}$ | 1.88 (5.98) | 1.01 (3.16) | 0.31 | |
| $V_e$ | 0.17 (0.16) | 0.31 (0.32) | 0.06 | |
| IAUC | 9.78 (7.54) | 8.67 (16.05) | 0.87 | |
| ADC | 690.00 (235.60) | 171.30 (217.00) | 0.02 | |

At 2 weeks

| MRI parameters | Median (IQR) | Pretreatment | Posttreatment | $P^*$ |
|----------------|--------------|--------------|---------------|------|
| $K_{trans}$ | 0.27 (0.75) | 0.48 (0.40) | 0.61 | |
| $K_{ep}$ | 1.88 (5.98) | 1.01 (3.16) | 0.31 | |
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*Wilcoxon signed rank test. IQR: Interquartile range, IAUC: Initial area under curve, ADC: Apparent diffusion coefficient, MRI: Magnetic resonance imaging, $K_{trans}$: Transfer constant, $K_{ep}$: Rate constant, $V_e$: Extravascular extracellular space

**Table 4: Temporal changes in the magnetic resonance imaging parameters from pre- to post-treatment (at 2nd week and 4th week) among responders**

| MRI parameters | Median (IQR) | Pretreatment | Posttreatment | $P^*$ |
|----------------|--------------|--------------|---------------|------|
| $K_{trans}$ | 0.53 (0.69) | 0.52 (0.60) | 0.61 | |
| $K_{ep}$ | 2.41 (6.73) | 1.41 (3.11) | 0.31 | |
| $V_e$ | 0.20 (0.18) | 0.29 (0.32) | 0.06 | |
| IAUC | 9.19 (7.99) | 7.98 (9.56) | 0.87 | |
| ADC | 640.70 (194.20) | 916.15 (223.6) | 0.02 | |

At 2 weeks

| MRI parameters | Median (IQR) | Pretreatment | Posttreatment | $P^*$ |
|----------------|--------------|--------------|---------------|------|
| $K_{trans}$ | 0.53 (0.69) | 0.34 (0.57) | 0.64 | |
| $K_{ep}$ | 2.41 (6.73) | 0.64 (1.28) | 0.02 | |
| $V_e$ | 0.20 (0.18) | 0.48 (0.21) | <0.001 | |
| IAUC | 9.19 (7.99) | 12.40 (12.30) | 0.83 | |
| ADC | 640.70 (194.20) | 634.10 (1055.20) | 0.79 | |

At 4 weeks

*Wilcoxon signed rank test. IQR: Interquartile range, IAUC: Initial area under curve, ADC: Apparent diffusion coefficient, MRI: Magnetic resonance imaging, $K_{trans}$: Transfer constant, $K_{ep}$: Rate constant, $V_e$: Extravascular extracellular space
authors observed little change in tumor size during irradiation while showing a significant decrease in the cellularity of irradiated tumors, resulting in a larger interstitial space.

The values of $I_{AUC}$ increased from pretreatment to posttreatment. There was no significant difference between the values in responders and nonresponders. This is explained by the study by Walker-Samuel et al., which shows that $I_{AUC}$ is a mixed parameter in terms of $K_{\text{trans}}$ and $V_e$ and hence, we did not find a significant trend over different time periods.\textsuperscript{[15]}

DWI has been shown to be feasible as an early marker of treatment response because cell death and vascular alterations typically occur before size changes.\textsuperscript{[16]} Increases in ADC values with treatment reflect decreases in cellularity and thus provide an indirect assessment of treatment-induced cell death. It has been reported that transient decreases in ADC may occur early in treatment related to cellular swelling, reduction in blood flow, or reduction in the extravascular–extracellular space due to dehydration (the latter particularly so after antiangiogenic treatment).\textsuperscript{[17,18]} However, early decreases in ADC values are not consistently seen, and it has recently been reported that increases in ADC value with therapy response occur within 3–7 days in responding patients treated with chemotherapy.\textsuperscript{[19]} In our study, the responders had a significant increase in the values of ADC after 2–3 weeks of treatment as compared to pretreatment values. In primary rectal tumors, both Dzik-Jurasz et al.\textsuperscript{[20]} and DeVries et al.\textsuperscript{[21]} have shown that pretreatment ADC correlated with tumor response after chemotherapy and chemoradiation (CRT). In our study, responders had a lower ADC at presentation than nonresponders. Higher pretreatment ADC values in nonresponders may reflect necrotic tumors that are more resistant to therapy because of concomitant hypoxia.

**Limitations and recommendations**

The main limitation of this study is the small number of patients. Collaborative studies are necessary to achieve significantly higher numbers, further emphasizing the need for quantitative DCE-MRI measurements that would allow direct comparisons between centers. Larger studies are needed for studying the effect of other factors which affect tumor response (hemoglobin levels, histopathology types, overall treatment time, etc.). In addition, the current study with few patients cannot conclude upon definitive criteria before dynamic MRI. Larger multicentric studies can give definitive criteria for clinical decision-making where nonresponders can be treated aggressively from beginning as compared to responders.

There are also technical limitations of DCE-MRI that need to be considered. The choice of imaging sequence involves a trade-off between temporal and spatial resolution, depending to a certain extent on tumor site. For tumors such as cervical cancers for which there is rapid uptake of contrast, fast sequences are necessary to characterize the change in signal intensity over time, but this will result in a corresponding decrease in spatial resolution. Although there have been various attempts to standardize the parameters used in DCE-MRI,\textsuperscript{[22,23]} the lack of standardized and independently validated analysis packages makes comparisons between different studies difficult. This is particularly relevant for quantitative measurements, particularly as they are increasingly used to evaluate antiangiogenic and antivascular therapies.

**Conclusion**

Our study has shown that a higher value of $K_{\text{trans}}$ is associated with a better tumor response to CRT. Furthermore, $K_{\text{ep}}$ decreased after successful therapy. In responders, a significant increase in the values of $V_e$ and ADC was seen with treatment. These changes can help in predicting response to therapy.

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Nil.

**Conflicts of interest**

There are no conflicts of interest.

**Table 5: Correlation of magnetic resonance imaging parameters with percentage tumor regression during pre- and post-treatment (2 and 4 weeks)**

| Pretreatment | Posttreatment (2 weeks) | Posttreatment (4 weeks) |
|--------------|-------------------------|-------------------------|
|              | Correlation coefficient | $P$                     | Correlation coefficient | $P$                     | Correlation coefficient | $P$                     |
| $K_{\text{trans}}$ | 0.13                    | 0.60                    | $-0.34$                | 0.45                    | $0.17$                | 0.52                    |
| $K_{\text{ep}}$    | 0.18                    | 0.46                    | $-0.28$                | 0.55                    | $0.19$                | 0.48                    |
| $V_e$          | $-0.53$                | 0.83                    | $-0.03$                | 0.95                    | 0.14                  | 0.60                    |
| IUAC           | 0.23                    | 0.35                    | 0.22                    | 0.63                    | $-0.13$                | 0.64                    |
| ADC            | 0.11                    | 0.69                    | $-0.01$                | 0.98                    | 0.01                  | 0.98                    |

PTR: Percentage tumor regression, ADC: Apparent diffusion coefficient, IUAC: Initial area under curve, $K_{\text{trans}}$: Transfer constant, $K_{\text{ep}}$: Rate constant, Ve: Extravascular extracellular space.
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