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Original Article

Multiparametric MRI Evaluation of Cervical Cancer with Histopathological Correlation

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ABSTRACT

Introduction: Carcinoma cervix is the most common carcinoma in the developing countries and the choice of treatment is completely dependent on its staging and hence accurate pretreatment staging is essential. MRI is the choice of imaging for carcinoma cervix for tumor location, extensions and staging. The increased knowledge in surgical techniques, radiation treatment and recent advances in chemotherapy requires a clearer staging of the disease. Hence, a study was done to evaluate Multiparametric Magnetic Resonance Imaging [MRI] including regular MRI, Diffusion weighted imaging [DWI], Dynamic contrast-enhanced MR [DCE-MR] and MR spectroscopy [MRS] in clinically diagnosed and staged cases of carcinoma cervix to give definitive diagnosis with histopathological correlation.

Objectives:

- To assess the role of Multiparametric MRI in evaluation of cervical cancer.
- To evaluate the DWI, DCE and MRS for tumor size detection, staging and characteristic of cervical cancer with histopathological correlation.

Materials and methods: A clinically diagnosed and staged 42 cases of untreated patients with carcinoma cervix, aged 30-60 years, underwent MR examination and biopsy of the lesion. The images were analyzed for the tumor detection, characterization, microenvironment and its metabolic changes, then it is correlated with histopathology.

Results: On histopathology, 32 patients were proven case of squamous cell carcinoma and 10 cases were of adenocarcinoma. Among 42 patients, all the patients showed high signal intensity on DWI. The ADC values were calculated and showed late stage [1092x10-6 mm/s] had higher ADC value than early stage [962x10-6 mm/s]. The mean ADC values of adenocarcinoma [1072x10-6 mm/s] was mildly higher than squamous cell carcinoma [1065x10-6 mm/s] and in the subtypes of squamous cell carcinoma, poorly differentiated squamous cell [993x10-6 mm/s] was lower than the moderately differentiated [1035x10-6 mm/s] and well-differentiated [1101x10-6 mm/s] squamous cell carcinoma.

On DCE, the enhancement was seen at 20-30 sec with a steep slope. Plotted graph curves showed type II in 71% of the cases showed type II curve and type III curve in 29%.

On MRS, choline and lipid peaks were seen irrespective of the tumor subtypes.

Conclusion: Traditional MR sequences [T1W and T2W] images are mainly useful for anatomical details. DWI and ADC values are useful in assessment of the tumor and its subtype as well as grading of the lesions. DCE is helpful for the assessment of the tumor visualization, its enhancing time and planning for radiotherapy whereas MRS is helpful in assessment of the tumor location, extension and possibly tumor grading.

***Keywords**: Cervix, DWI, ADC values, DCE, MRS.*

INTRODUCTION

Cervical cancer is one of the leading causes of death among women in developing country. It is the second leading cancer in worldwide, whereas in India also it is the second most common cancer among women next to breast cancer [1] with a survival rate of 5 years in stage 0 is 93% and approximately 15% in stage IV.[2] Hence, accurate diagnosis and staging of the tumor is crucial for determining the mode of treatment. Recent advances in the clinical imaging enable us to stage the carcinoma precisely and could lead to improvement of the treatment.[3]

MRI with high contrast resolution and multiplanar capability helps in delineating the cervix and its relationship with other pelvic organs better.[4]. Magnetic resonance imaging (MRI) plays an important role in the detection and staging of malignancy because of its precise soft tissue resolution. But conventional T1 and T2 sequences cannot provide information about the microenvironment of the tumors.

The changes of microenvironment of the tumors can be detected by diffusion weighted imaging [DWI] and dynamic contrast-enhanced [DCE] MRI.

DWI sequence gives information about the microstructural changes and hence reflects on the changes of oxygenation, perfusion and tissue physiology of the tumor microstructure and yields quantitative and semi-quantitative parameters. DWIMRI generates tissue contrast from the difference in mobility of water molecules of the tumor during the sequence. The impedance of water molecules diffusion is determined by tissue cellularity and intact cell membrane which can be quantitatively assessed by apparent diffusion coefficient [ADC] value. Dense cellular tissue or those with cellular swelling exhibit lower diffusion coefficient and thus diffusion is particularly useful for tumor characterization.[5, 6]

DCE MR gives information about the neo angiogenesis and morphology of the tumors. DCE-MRI is a technique where it requires intravenous injection of MRI contrast [Gadodiamide]. This contrast agent reduces the T1 and T2 relaxation time but its effects is greater on T1, hence the area of uptake is brighter on T1 weighted imaging. The tumors appear brighter after contrast due to its neo angiogenesis and leaky capillary membranes of the tumors.[7] Hence, they can assess the tumor tissue perfusion and oxygenation within the tumor microenvironment.[7]

MRI spectroscopy [MRS] is used to study the chemical and metabolic changes of the tumors. The electron cloud surrounding the different chemical compounds shields the resonant atoms of spectroscopic interest to varying degree depending upon the specific compound and specific position of the compound. This electron shielding causes the observed resonance slightly different and therefore identifiable with MRS. The choline metabolite is associated with membrane turnover and increase cell division. Increase choline indicates increase in cell production or membrane breakdown that suggests demyelination or presence of malignant tumor. [8]

AIM OF THE STUDY

To assess the role of Multiparametric MRI in evaluation of cervical cancer.

OBJECTIVES OF THE STUDY

1. To evaluate the DWI [Diffusion weighted imagining] MRI in tumor size detection, characterization and staging of cervical cancer with histopathological correlation.
2. To evaluate the DCE [Dynamic contrast-enhanced] MRI in tumor size detection, characterization and staging of cervical cancer with histopathological correlation.
3. To evaluate the MR Spectroscopy in in tumor size detection, characterization and staging of cervical cancer with histopathological correlation.

MATERIAL AND METHODS

Patients were clinically staged by oncologist from Department of Oncology and referred to Department of Radiology for cross sectional imaging. Forty-two women with primary untreated uterine ((delete) cervical carcinoma were examined by MRI. The Study (small) was done in tertiary care centers over a period of 18months.

Inclusion criteria - All patients with clinically staged cervical carcinoma

Exclusion criteria - Recurrent cervical carcinoma, - (delete) Severely (small) debilitated patient, renal impairment, allergic to contrast media.

Methodology

Pelvic examination was under anaesthesia, including bimanual palpation. Chest x-ray, cystoscopy and proctoscopy were also done and clinical stage was assigned based on FIGO system. Following (spacing) which the patients were referred to Department of Radiodiagnosis and Imaging for MRI. MR examination were performed on a 1.5 Tesla GE Signa. The pulse

sequences were acquired contrast and non-contrast. ADC measurement was performed on reconstructed ADC maps with the largest ROI with in the tumour. For each ADC value measurement three ROIs were placed and the average of them was used for the analysis. Mean ADC values were compared between tumour grades, stages and histopathologic subtypes.

DCE-MRI was done with intravenous injection of paramagnetic contrast agent (Omniscan, Gadodiamide) as bolus injection. The SI values were recorded before; during and after contrast administration and dynamic time signal intensity curves were generated using a fixed ROI. MRI findings and stage were compared with clinical staging and histopathological correlations.

Study design: Prospective, Observational and comparative study

Statistical sample size collection: Assuming an expected population of true cervical cancer patients as 70% [out of total suspected cases sent to MRI], with a power of 80%, level of 5% a sample size of 42 has been calculated.

Sampling collection: Convenience sampling.

Statistical methods: Data was entered in MS Excel and analyzed in SPSS V22 (IBM, Chicago, Illinois). Quantitative data were represented with Mean and Standard deviation. Qualitative Data were represented with percentage. Logistic regression analysis was applied. Cross tabs with chi square test analysis were done for comparison of parameters of different modality. Statistically significant differences were indicated with $p < 0.05$.

RESULTS

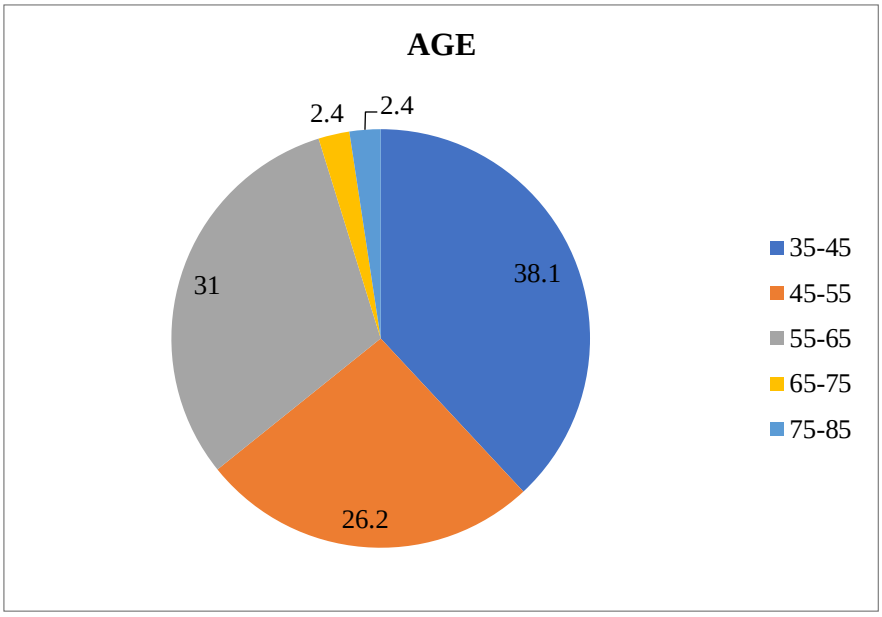

Figure 1: Pie diagram showing age wise distribution of cervical cancer.

Forty-two women ranging from 35 to 85 years with mean age of 51 years presented with cervical cancer and maximum of the cervical cancer was found to be in between 35-45 years. Most the patients were of low socio-economic status.

In all the 42 patients, lesions were isointense on T1W, hyperintense on T2W and high signal in all the 42 patients, lesion was isointense on T1W, hyperintense on T2W and high signal intensity on DWI.

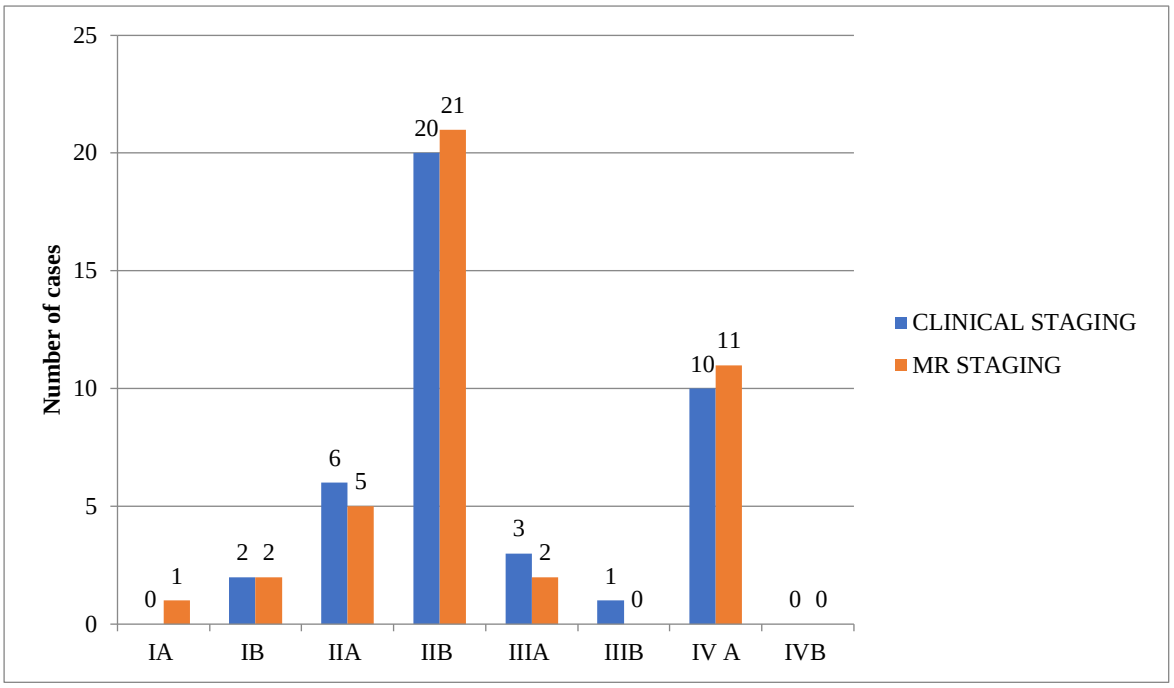

Figure 2: Bar diagram showing Clinical Staging and MR staging

On clinical staging, majority of the patients in our study were staged IIb [20 cases], followed by IVa [10 cases] and IIa [6 cases]. On clinical examination, 20 patients showed parametrial involvement, 1 patient showed lateral pelvic wall infiltration, 3 patients showed involvement of the lower third of the vagina and 10 patients showed infiltration into adjacent pelvic organ.(Figure 2)

On MRI, majority of the patients were staged under stage IIb [21 cases]. One patient who was diagnosed with cervical intraepithelial neoplasia, on MR imaging showed no abnormal signal intensity or enhancement. 11 patients showed parametrial involvement and 11 patients staged under IVa (urinary bladder/rectum involvement).

On comparing clinical staging with MR staging, it was revealed that only 3 cases were over staged clinically, 1 case was under staged clinically and the rest that is 38 cases were staged correctly.(Figure 2)

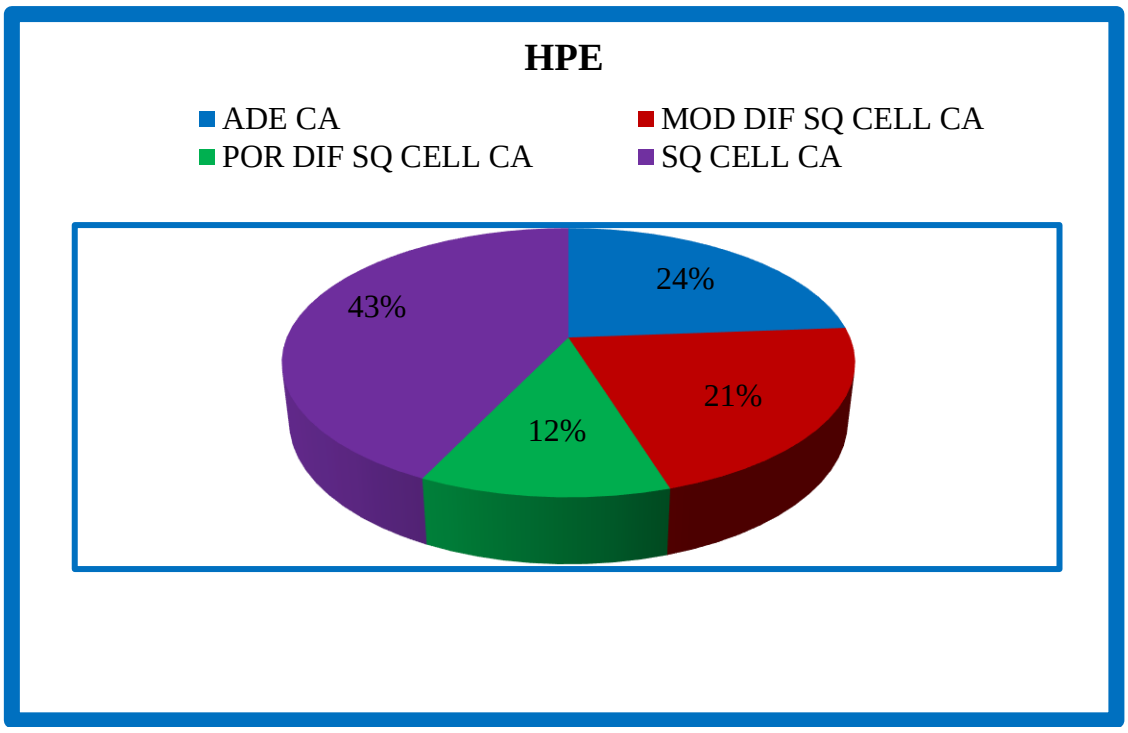

Figure 3: Pie diagram showing histopathology subtypes of the cervical cancer.

Total 42 cases in our study were squamous carcinoma out of which 5 cases were poorly differentiated, 9 cases were moderately differentiated and 18 cases were well-differentiated squamous cell carcinoma. 10 cases were adenocarcinoma.(Figure 3)

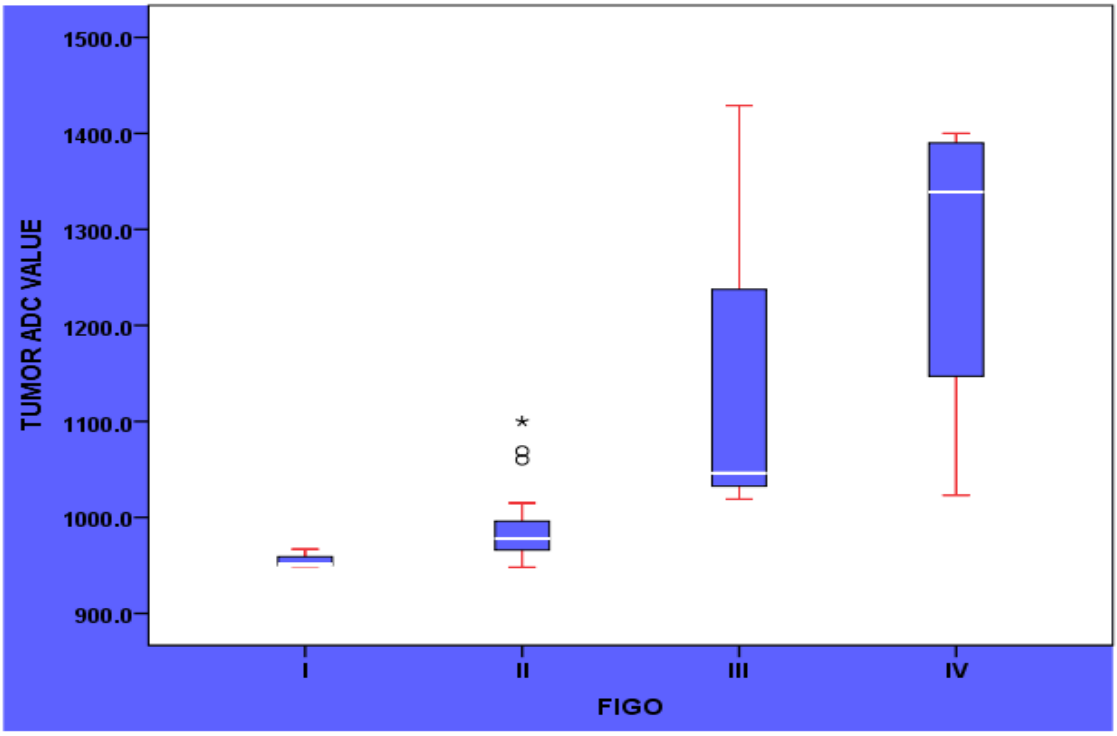

Figure 4: ADC value of the tumor according to FIGO Stage

With regards to ADC mean values of the tumor stages, that is Ia-b is 955X10 $^{-6}$mm2/s, IIa-b is988X10 $^{-6}$mm2/s, IIIa-b is 1032X10 $^{-6}$mm2/s and IVa-b is 1292X10 $^{-6}$mm2/s, there was increase in ADC values as the grade increases.

Table 1: ADC value of the tumor according to histopathology

HPE	Tumor ADC Value				
	N	Mean	SD	Minimum	Maximum
Adenocarcinoma	10	1072×10^{-6}	181×10^{-6}	963×10^{-6}	1429×10^{-6}
Moderately Differentiated Squamous Cell Carcinoma	9	1035×10^{-6}	105×10^{-6}	960×10^{-6}	1304×10^{-6}
Poorly Differentiated Squamous Cell Carcinoma	5	993×10^{-6}	86×10^{-6}	948×10^{-6}	1147×10^{-6}
Squamous Cell Carcinoma	18	1101×10^{-6}	173×10^{-6}	949×10^{-6}	1392×10^{-6}

Among 32 patients of squamous cell carcinoma and 10 patients of adenocarcinoma, the mean ADC value of adenocarcinoma [$1072x10^{-6}$ mm^2/s] was mildly lower than squamous cell carcinoma and in the subtypes of squamous cell carcinoma, poorly differentiated squamous cell carcinoma [$993x10^{-6}$ mm^2/s] was lower than the moderately differentiated [$1035x10^{-6}$ mm^2/s] and well differentiated [$1101x10^{-6}$ mm^2/s] squamous cell carcinoma.

30 (71.4%) cases showed II curve and 12 (28.6%) cases showed III curve [Figure 5]. In our study we observed the most of the tumor showed lipid and choline peak [Figure 6].

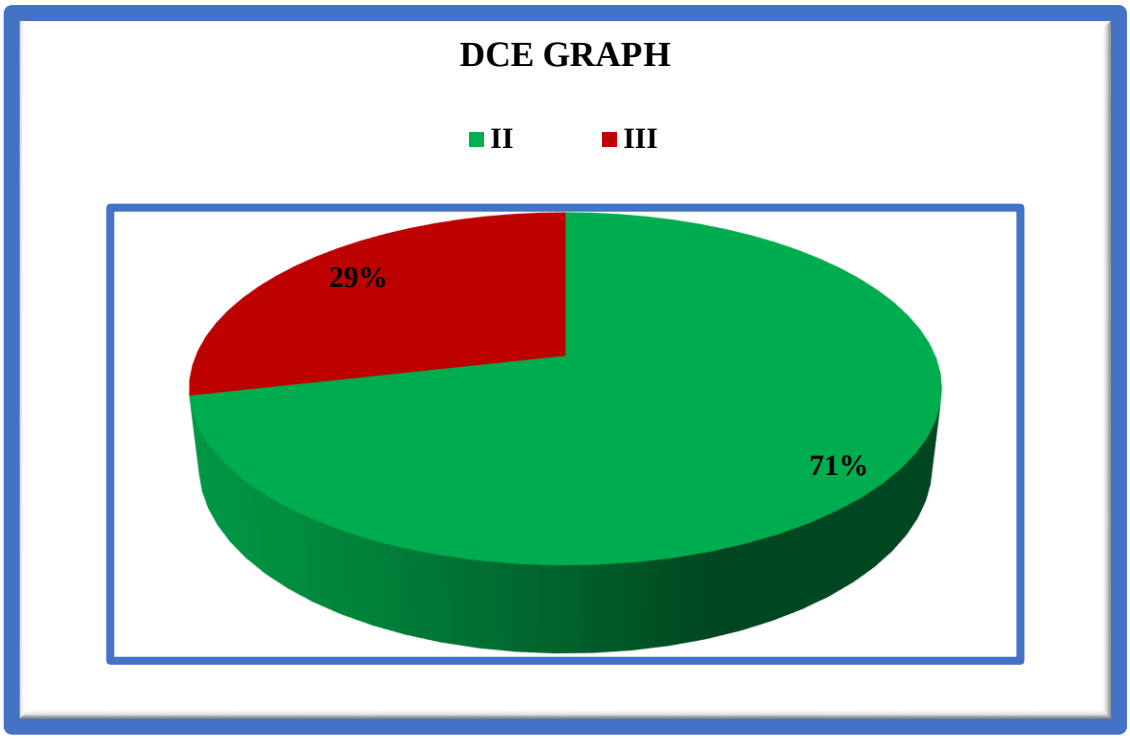

Figure 5: Pie diagram showing distribution based on DCE.

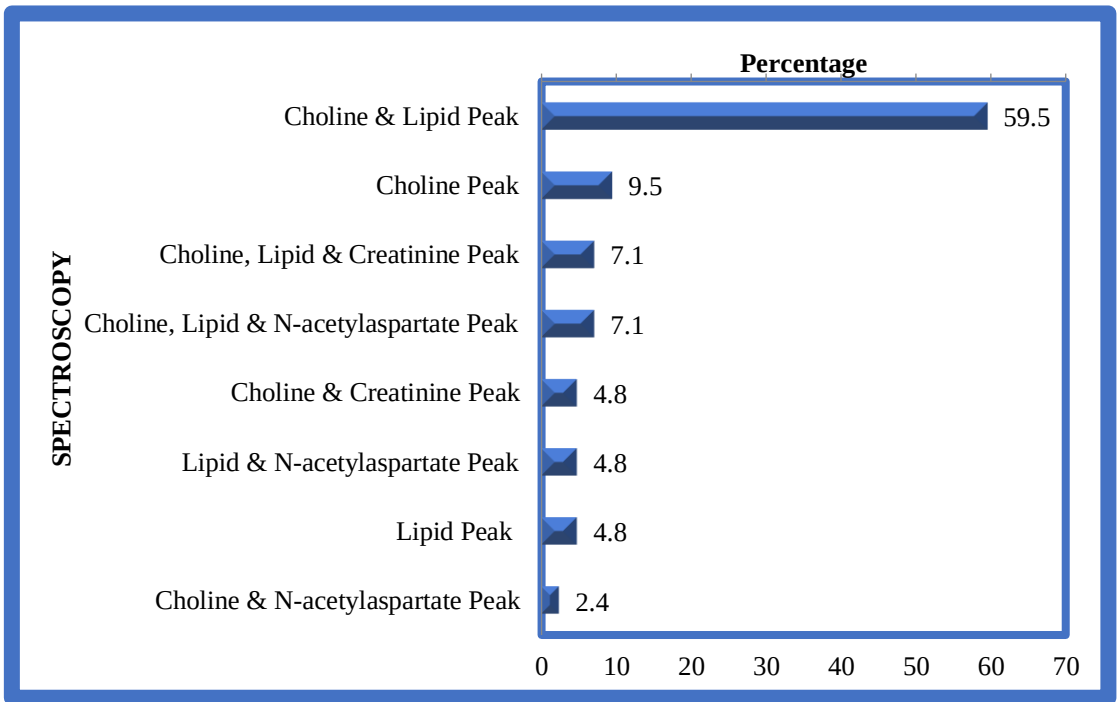

Figure 6: Bar diagram showing distribution based on spectroscopy.

DISCUSSION

MRI with high soft tissue resolution is the most valuable modality in the assessment of the tumor size, cervical invasion and extent of local regional spread in the treatment planning of cervical cancer [9,10]. Among the 42 patients with age ranging from 35 to 85 years, the mean age of carcinoma cervix was found to be 51 years and maximum frequency was found to be in between 35-45 years and 25 cases (59.52%) were post-menopausal and 17 (40.48%) were pre-menopausal status.(Figure 1)

All 42 cases showed isointense on T1W and hyperintense on T2W with 69.05% showing homogenous enhancement and 30.95% showing heterogeneous enhancement on post contrast sequences. All stage IVa cases were squamous cell carcinoma and maximum of the adenocarcinoma were stage IIb likely due to slow growing rate of the adenocarcinoma. Most of the squamous cell carcinoma were between age group of 45-55 years and adenocarcinoma were 55-65 years.

On comparing clinical staging with MR staging, it was revealed that only 3 cases were over staged Clinically, 1 case was under staged and the rest, that is 38 cases were staged correctly.(Figure 2)

Diffusion Weighted Imaging

DWI enables the assessment of the morphologic and physiologic changes in a single examination. DWI allows quantitative evaluation of ADC from the images with different b-values and can provide excellent tissue contrast and scanning time is relatively short.[11, 12,]

In our study, it was found that all the 42 patients showed high signal intensity on DWI. (Figure 4)

With regards to ADC mean values of the tumor stages, that is Ia-b is 955X10 $^{-6}$mm2/s, IIa-b is988X10 $^{-6}$mm2/s, IIIa-b is 1032X10 $^{-6}$mm2/s and IVa-b is 1292X10 $^{-6}$mm2/s, there was increase in ADC values as the grade increases. (Figure 3)

In our study, according to the FIGO classification, stage Ia to IIa were grouped as early stage and IIb to IVb as late stage and it has been observed that the mean ADC values of the late stage [1092X10 $^{-6}$mm2/s] were higher than the early stage [962X10 $^{-6}$mm2/s] ($p<0.05$). In McVeigh et al. [13] with regard to FIGO classification, mean ADC values were found to be lower in stages Ib/IIa than in stage IIb and stage III/IV, as is found in our study.

There were 32 patients of squamous cell carcinoma and 10 patients of adenocarcinoma, the mean ADC value of adenocarcinoma [1072x10-6 mm2/s] was mildly higher than squamous cell carcinoma [1065X10 $^{-6}$ mm/s] and in the subtypes of squamous cell carcinoma, poorly differentiated squamous cell carcinoma [993x10-6 mm2/s] was lower than the moderately differentiated [1035x10-6 mm2/s] and well differentiated [1101x10-6 mm2/s] squamous cell carcinoma. (Table. 1) Liu et al. [14] stated that the mean ADC value of squamous cell carcinoma was lower than adenocarcinoma and the reason is squamous cell carcinoma tends to be more compact and crowded, while adenocarcinoma gives out more tube-like structures which mimics adeno-tissues. This tube-like structure has a large intercellular space which lead to higher ADC values. (Table 1)

On contrary, Levy et al. [15] has reported that no significant difference between mean ADC values of squamous cell carcinoma and adenocarcinoma ($p>0.05$). However, in our study there is no significant statistical significance ($p=0.5$) between the mean ADC value of squamous cell carcinoma and adenocarcinoma likely due to a smaller number of adenocarcinoma patient as compared to squamous differentiated squamous cell carcinoma ($p=0.016$).

Dynamic Contrast Enhanced MRI

On DCE MRI in our study a graph was plotted and was found that 71% of the cervical patients showed type II curve [Breast curve] and 29% of the cases showed type II curve [Breast curve]. In our study, it is found to have early intense enhancement with late washout in most of the cases. This intense enhancement is due to hypervascularity of the lesions.(Figure 5)

Seki et al,[16] have suggested, imaging is a more reliable technique for detecting invasive lesions with more than 3 mm of stromal invasion than is either T2-weighted or contrast-enhanced TI -weighted MR imaging and believe that dynamic MR imaging is helpful in assessing the depth of stromal invasion by carcinoma of the cervix.

Magnetic Resonance Spectroscopy

In our study we observed the most of the tumor showed lipid and choline peak. Lee et al,[17] in their study to diagnose cervical carcinoma and categorize the spectrum according to histologic type and found that choline and lipid peaks were present in both squamous cell carcinoma and adenocarcinoma with lipid peak at 1.3 ppm in squamous cell carcinoma and 2ppm in adenocarcinoma. Mahon et al. [18] study stated that lipid levels which are measured by MRS doubles in malignant as compared normal cervical tissue due to the triglyceride's levels in the tumor. Lipid peak in MRS suggests areas of necrosis and choline peak suggest increase cell turn over. Cytoplasmic(small) lipids can also give rise to MR visible signals. (Figure 6)

CONCLUSION:

MRI is emboldened for cervical cancer staging and there is a good correlation between histological and tumor bulk. Conventional MRI sequences, T1W and T2W provides normal anatomical details whereas DWI and ADC histogram provides suitable data for the diagnosis of the cervical cancer as well as for preoperative assessment and distinguishing histologic types and grades of cervical cancer non-invasively, although there might be some overlap. DCE helps indistinguishing tumor from normal cervical stroma, whereas MRS helps in the assessment of the tumor location and extension of the tumor.

Multiparametric MRI for carcinoma cervix eludes conventional MRI by reporting different aspects of the tumor, characteristics and staging.

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