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Original article:

The role of apparent diffusion coefficient as imaging bio marker in head and neck squamous cell carcinoma

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Abstract:

Objective: Apparent Diffusion Coefficient (ADC) serves as a measure of diffusivity of water molecules within tissues. The aim of our study is to evaluate the relevance of ADC values in predicting treatment response of the primary tumor, to chemo radiotherapy in head and neck squamous cell carcinoma.

Materials and Methods: We conducted a prospective study with thirty patients who underwent Diffusion Weighted MR imaging once prior to treatment initiation and at 3 weeks following the start of treatment. The ADC value prior to treatment initiation and the fractional change in ADC value 3 weeks after starting treatment of the primary tumor including the nodal deposits were compared with patients classified clinically as Loco regional control (LRC) and loco regional failure (LRF), which were analyzed using Receiver operating characteristic analysis. Pretreatment gross tumor volume, tumor regression rate and TNM Stage were the other parameters that were evaluated.

Results: There is significant association of the fractional change in ADC of the primary tumor 3weeks after treatment initiation with loco regional control/failure. The cut off value for fractional change in ADC of the primary tumour below 0.189 correlated with treatment failure . Pretreatment mean ADC of the primary is yet another parameter that correlated strongly with loco regional failure / control. A cut off value for pretreatment mean ADC of the primary below 1.19 x 10^{-3} mm^2 /s correlated strongly with LRC. However, the fractional change in ADC of the involved nodes did not show similar association with LRF/LRC. So also the TNM Stage, pretreatment gross tumor volume, and tumor regression rate were not found to show significant association with LRF/LRC.

Conclusions: The pre treatment mean ADC and fractional change in ADC of the primary tumor mass at 3 weeks after initiation of treatment , had significant association with loco regional control/failure. But the positive predictive value / negative predictive value was low with both these parameters. This underscores the need for further studies, before fractional change in ADC values and pre-treatment mean ADC of the primary tumor , can serve as useful tools for decision making.

Keywords: Head and neck squamous cell carcinoma (HNSCC), Diffusion weighted imaging (DWI)

Introduction:

Head and neck cancers are the most common cancer of males and the fifth most common among females in India. Upto ninety percent of head and neck cancers are squamous cell carcinomas. A vast majority of the patients with cancers present in the late stages when the disease becomes incurable with a high mortality rate. Organ-preserving treatment strategies are becoming the standard for patients with locally advanced tumors. This is made possible thanks to the widespread use of radiotherapy and/or chemotherapy. Since up to 30% of patients with head and neck

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squamous cell carcinoma undergoing chemo radiotherapy (CRT), present with loco regional failure, it becomes imperative to identify non-responders before treatment or early during treatment. This will protect eventual non responders from the unwanted toxicity of ineffective treatment and permit the physician to choose alternative treatment strategies.The search continues for a reliable prognostication indicator at tissue level that can address this issue.The search for imaging based biomarkers [(1)] leads us to the world of functional imaging and Diffusion weighted MR imaging may have the solution. Diffusion weighted imaging (DWI) uses information from diffusion of water molecules that can be quantified using Apparent Diffusion co- efficient (ADC).Hatakenaka et al, suggested the use of pretreatment ADC, to predict local failure in head and neck cancer patients on follow up after chemo radiotherapy. Vandecaveye et al , observed that the change in ADC values at 2 and 4 weeks of treatment had significant correlation with LRC and was more precise than changes in gross tumor volume for the prediction of treatment outcome . But there is no consensus on the timing of ADC measurement.The aim of our study is to evaluate whether fractional change in ADC of the primary tumor and or the metastatic node,during chemo radiotherapy can be used as a valid imaging bio marker for treatment response in HNSCC and to identify cut off value for change in ADC ,in the event of statistical significance.

Materials and methods:

The prospective observational study was done out after obtaining necessary clearance from the Ethics committee in our institution and after written informed consent from all the participants.The study included thirty four patients having histopathologically proven HNSCC without prior treatment history ,referred for Magnetic resonance imaging . Based on the imaging and after clinical consideration, these patients were subjected to chemoradiotherapy and followed up over 12 months .Patients with non squamous histology (Tumors of the nasal cavity, paranasal sinus, nasopharynx, salivary glands.),T 4 b disease, distant metastasis or other serious comorbidities were excluded from the study. A total of 30 patients were eligible for the study , comprising of 24 male and 6 female patients, in the age group of 34 to 72 years (mean age 55.7 years; median age, 55 years)

Treatment And Follow-Up:

Pre - treatment MR was done 1 week before start of treatment.Eligible patients received chemoradiotherapy over a SIX week period. After treatment, patients were on follow up and examined for loco regional control/failure by means of clinical examination, and if needed pan endoscopy. Contrast- enhanced CT /MR imaging and biopsy were done when needed.

Data Collection:

Pre-treatment MR with DWI was done 1 to 2 weeks before the start of treatment. Another MR imaging with DWI was done 3 weeks after the initiation of chemo radiotherapy. The ADC values were measured at baseline and 3 weeks after starting treatment.

MR Imaging:

MR imaging was done on 3 T system with neck coil. All the sequences extended from the skull base to the thoracic outlet.

Image Analysis:

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The lesion is initially outlined on consecutive axial sections using the freehand Region of Interest (ROI) tool available on the Syngovia workstation. While drawing ROI on the lesions, were included only the solid portions after carefully excluding necrotic or cystic portions. The non enhancing areas on contrast enhanced correspond to the necrotic areas. Given the irregular shape of tumours and complex anatomy of the head and neck ,tumor size measurement using the largest two measurements was not followed.Instead the cross sectional area of the tumor on each axial slice was multiplied by the section thickness and when these were added together ,we were able to arrive at gross tumor volume. The mean ADC value of the whole tumor was used, thus avoiding sampling errors that may occur while taking the measurements on a single axial slice.The same ROI s used for tumour volume were also used for ADC calculation.

Data Analysis:

The fractional change in ADC for each primary tumor and node was calculated using the following formula:

Fractional change in ADC = (ADC $_{3\,w}$ - ADC pre) / ADC pre

where, ADC pre represents the pretreatment ADC values, and ADC_{3W} represents the ADC values at 3 weeks after the start of treatment.

Tumor regression rate = (TV pre TV $_{3w}$) / TV pre

where, TV pre represents the pretreatment tumor volume TV_{3w} represents the tumor volume at 3 weeks.

Results:

Patient characteristics:

During follow up LRC was observed in 18 of 30 patients (65.3%). Five of 30 patients (14.3%) developed an isolated local recurrence. Three of 35 patients (6.7%) developed a regional recurrence without primary tumor recurrence. Five of 35 patients (15.2%) developed a simultaneous loco regional tumor recurrence.

In the present study, when a cut-off value for pre-treatment primary tumor volume of 16 cc was used, sensitivity and specificity were 60 % for prediction of control. Patients with pre - treatment primary tumor volume < 16 cc. showed less chance of recurrence. (*Table 1).*Since patients with locally advanced disease were included in the present study, the mean gross tumor volume was high and measured 24 cc. This could account for the increased cut off values.*(Table 2)*

DISCUSSION:

Highly cellular tumors have diffusion restriction and hence low ADC values. Cancer treatments result in cell death, cause increased water diffusion and lead to elevation in ADC values. In the past, clinical studies on the role of DW-MR in response prediction, have focused on two main parameters namely, pre-treatment ADC and the change in ADC after treatment completion. Both these ADC related parameters have been found to be useful. Kim et al noticed that pre-treatment ADC values could be used to predict response to treatment in cervical lymphadenopathy [(3).] In addition King et al, found that serial change in ADC correlated strongly with LRF.

In the present study, rise in primary tumor ADC correlated strongly with chemo radiotherapy. Although the reason for early elevation in ADC value following treatment is clearly understood , it is postulated that treatment induced apoptosis and necrosis, lead to disruption of tissue architecture with resultant increase in fractional volume and increased diffusion tendencies. Therefore fractional change in ADC of primary tumor early into treatment, is

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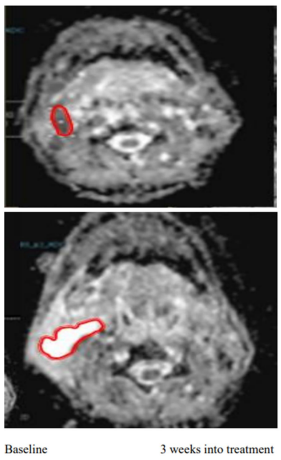
reflective of the extent of damage to tumor cells. Since it is known that differences in tumor aggressiveness or treatment protocol can influence treatment response, a single pre-treatment ADC value may be inadequate in predicting response. Therefore calculation of the fractional change in ADC may be needed for predicting response. Ideally, repeat scan should be performed before changes in tumor size become apparent. In this study, time for repeat scan was chosen at 3 weeks. Matoba et al observed that an interval of three weeks is required for changes to be apparent on DW-MRI. Foci of intratumoral liquefaction necrosis arising from treatment may influence ADC calculation. [(4)] This may result in spuriously elevated ADC values, while viable tumor components still be present. This was the reason for using the mean ADC of the whole tumor during calculations of ADC.

In our study, fractional change in ADC value of primary was significantly lower for LRF compared with control. Also out of all the variables that were measured, fractional change in ADC of primary correlated strongly with control. In previous studies done on HNSCC using DWI, ADC map were generated using a minimum of 3 b-values. Although b-values as high as 1000 s/mm ^{2} have been used in the past, the maximum b-value in this study was kept at 800s/mm ^{2} .This was done to reduce the influence of susceptibility artifacts and low signal to noise ratio on calculated ADC maps. Since primary tumors occur at air - tissue interfaces, they are prone to susceptibility artifacts. Motion artifacts from swallowing and breathing also cause image degradation. These issues will not be encountered when ADC calculations are performed on metastatic nodes. However since most of the patients had bulky nodal disease, meaningful ADC calculation was not possible. There are instances ,where an increase in nodal volume early during treatment ,may be erroneously interpreted as disease progression. *(Fig.1).*



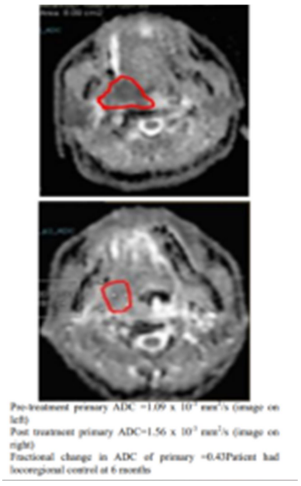


Fig 1. ADC map of Ca.tongue and right level II node.

Fig 2.Right tonsil Ca.

At 3 wks,node becomes cystic and increases in volume; this may erroneously suggest progressive disease.

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Area under the curve			
Test Result Variable(s): Pre Mean ADC Primary			
Area	P value	Asymptotic 95% C I	
		L B	U B
0.801	0.007	0.642	0.96

When a cutoff value of< **1.21 x 10^{-3} mm^2/s** (Pretreatment mean ADC primary) is used,

Sensitivity= 63.6% Specificity =68.4%

Table 1: Prediction of LRC using pre treatment tumor volume AUC is 0.737

Area Under the Curve			
Test Result Variable(s): Fractional change in mean ADC Primary			
Area	P value	Asymptotic 95% C I	
		L B	U B
0.916	0.0005	0.814	1

When Cut off value <0.143 (fractional change in mean ADCprimary) is used for predictinfailure,

Table 2:Prediction of LRC using Fractional change in ADC of primary AUC is 0.916 and p value < 0.01

Despite being easy to use ,MR DWI poses some challenges in certain clinical situation.Treatment induces increased mucosal secretions producing swallowing artifacts,image distortion occurring near tracheostomy tube placement sites posing difficulties in the case of subglottic tumors and artifacts due to air tumor interfaces in the superficial tumors of lip , can interfere with image interpretation. The small sample size along with the short follow up period also pose major limitations to this study.

Conclusion:

The use of DWI in head and neck cancer as a possible predictive biomarker has been investigated since long. To avoid the toxicity associated with chemo radiation as a whole and the financial costs of some treatment protocols, it is preferable to identify and stop ineffective therapy as early as possible, and change over to alternative treatment options whenever available. The fractional change in ADC of the primary tumor at 3weeks was found to have significant association with LRC/LRF. A cut off value for fractional change in ADC of primary below 0.189 correlated with LRF. *(Fig.2)* But the positive predictive value/negative predictive value was not high in the present study. Pre treatment mean ADC of the primary is another parameter that correlated strongly with LRC/LRF . A cutoff value for pre-treatment mean ADC of the primary below 1.19 x 10^{-3} mm^2 /s correlated with LRC. However this parameter also did not show high positive predictive value/negative predictive value. This underscores the need for further studies, before fractional change in ADC values and pretreatment mean ADC of the primary, can be used in decision making.

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