PREDICTING RESPONSE TO CHEMO RADIOTHERAPY IN HEAD AND NECK SQUAMOUS CELL CARCINOMA: DOES APPARENT DIFFUSION COEFFICIENT (ADC) ADD VALUE?

1Prof.Dr.S.Kalpana MD, DMRD, Dip NB,
2Dr.Mohideen Ashraf A.MBBS, DMRD
3Prof.Dr.N.Kailasanathan MD, DMRD
1,2,3Barnard Institute of Radiology, Medical College, Chennai-600003.

Abstract

BACKGROUND AND PURPOSE: Apparent Diffusion Coefficient (ADC) provides a measure of diffusion of water molecules in tissues. The aim of the study was to evaluate the role of ADC values in predicting response of the primary tumor, to concurrent chemoradiotherapy in head and neck squamous cell carcinoma.

MATERIALS AND METHODS: Thirty patients underwent Diffusion Weighted MR imaging at pretreatment and at 3 weeks after the start of treatment. The pre-treatment ADC value and the fractional change in ADC value following treatment of the primary tumor as well as of the nodal deposits were compared with Loco regional control (LRC) and loco regional failure (LRF) and were analyzed using Receiver operating characteristic analysis. Other parameters that were tested similarly include pretreatment gross tumor volume, TNM Stage and tumor regression rate.

RESULTS: The fractional change in ADC of the primary tumor at 3weeks was found to have significant association with loco regional control/failure. A cut off value for fractional change in ADC of primary below 0.194 correlated with treatment failure. Another parameter that correlated strongly with loco regional failure / control is pretreatment mean ADC of the primary. A cutoff value for pretreatment mean ADC of the primary below 1.21 x 10^{-3} mm^2/s correlated with LRC. However, the fractional change in ADC of the node did not show association with LRF/LRC. Similarly the pretreatment gross tumor volume, TNM Stage and tumor regression rate did not show significant association with LRF/LRC.

CONCLUSIONS: The pretreatment mean ADC and fractional change in ADC of the primary tumor at 3weeks were found to have significant association with loco regional control/failure. However the positive predictive value/negative predictive value was not high with both these parameters. This highlights the need for further studies, before fractional change in ADC values and pre-treatment mean ADC of the primary, can be used in decision making.

Keywords: Head and neck squamous cell carcinoma(HNSCC), concurrent chemoradiotherapy(CCRT), Diffusion weighted imaging(DWI), Apparent diffusion coefficient(ADC), fractional change, Locoregional control/failure(LRC/LRF)

I. INTRODUCTION:

In India, cancers of the head and neck are the most common cancer of males and the fifth most common among females. Over ninety percent of head and neck cancers are squamous cell carcinomas. Around 75% to 80% of patients with cancers present in the late stages when the disease is incurable with a high mortality rate. Organ-preserving treatment strategies are becoming the norm for patients with locally advanced tumors. Organ-preserving implies use of radiotherapy and/or chemotherapy, either singly or in combination. Since up to 30% of patients with head and neck squamous cell carcinoma subject to concurrent chemoradiotherapy (CRT), present with loco regional failure, the need to identify non-responders before treatment or very early in the course of treatment, becomes important. This will spare eventual non responders the unwanted toxicity from ineffective treatment and allow the physician to select alternative treatment strategies. The search is on for a reliable prognostication indicator at the tissue level that can be useful in this regard. The quest for imaging based biomarkers (1) has led us to the realm of functional imaging and Diffusion weighted MR imaging seems to have the answer. Diffusion weighted imaging (DWI) uses information from diffusion of water molecules that is quantified using Apparent Diffusion coefficient (ADC). Hatakenaka et al. demonstrated the use of pretreatment ADC, to predict local failure in head and neck cancer patients on follow up after chemo radiotherapy. Vandecaveye et al. noted that the change in ADC values at 2 and 4 weeks of treatment had significant correlation with LRC and was more accurate than changes in gross tumor volume for the prediction of treatment outcome. But no consensus has been reached on the timing of ADC measurement. The aim of the study is to evaluate whether fractional change in ADC of the primary tumor and or node, during concurrent chemo radiotherapy can be used as a valid predictive indicator of treatment response in HNSCC (IMAGING BIO MARKER) and to identify cut off value.
for fractional change in ADC in the event of statistical significance. We also wish to evaluate whether pre-treatment ADC values of the primary and pre-treatment primary gross tumor volume correlate independently with loco-regional control/failure.

II. MATERIALS AND METHODS:

This prospective observational study was carried out after obtaining clearance from the Ethics committee in our institution and with written informed consent from all the participants. The study included thirty four patients having histopathologically proven HNSCC with no previous treatment history. Patients with non-squamous histology (Tumors of the nasal cavity, paranasal sinuses, nasopharynx, salivary glands.), T4b disease, distant metastasis or other serious comorbidities were excluded from the study. Four patients were excluded from the data analysis: in one of them, there was degradation of image quality due to motion artifacts, the other 3 patients died within one month of completing treatment with unknown disease status. Eventually a total of 30 patients were eligible for the study. They included 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 to 2 weeks before start of treatment. Eligible patients received concurrent chemo-radiotherapy (66Gy in 20Gy per fraction; 5 days a week along with weekly Inj. Cisplatin 30mg/m2 and daily Tab Gefitinib 250mg once daily) over a SIX week period.

After treatment, patients were on follow up and examined for loco regional control/failure by means of clinical examination, supplemented by pan endoscopy. Contrast-enhanced CT /MR imaging and biopsy were carried out when required. The response to treatment was defined at the primary and nodal site by using the RECIST 1.1 criteria.

Follow up period refers to the period from treatment completion until tumor recurrence or last contact with patient. Tumor recurrence any persistent or recurrent mass at either primary or nodal site was considered recurrence, when there was supporting histopathologic evidence or when definite increase in lesion size could be demonstrated on successive imaging examinations.

MR IMAGING:

MR Imaging was done on 3 T system (Skyra, Siemens, Erlangen, Germany) with neck coil. All the sequences extended from the skull base to the thoracic outlet.

<table>
<thead>
<tr>
<th>Table 1: MR imaging parameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>MR IMAGING PROTOCOL</td>
</tr>
<tr>
<td>T1 GRE</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>T2 TSE</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>DWI</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>FOV</td>
</tr>
<tr>
<td>Section thickness</td>
</tr>
<tr>
<td>Intersection gap</td>
</tr>
</tbody>
</table>
IMAGING ANALYSIS:

All the primary tumors and lymph nodes identified to harbor metastatic deposits on pre-treatment clinical and imaging examination were subsequently evaluated on MR imaging with DWI performed 1 to 2 weeks before starting treatment. MR imaging was repeated at 3 weeks after the start of treatment. In this study the mean ADC of the primary tumor and node is measured. First the lesion is outlined on consecutive axial sections using the freehand Region of Interest (ROI) tool available on the Syngovia workstation(Fig.3 & 4) The individual values are added and then divided by the number of sections, to arrive at the mean ADC of the tumor. While placing ROI tracings on the lesions, care was taken to include only the solid portions after carefully excluding necrotic or cystic portions. The contrast enhanced MR images were reviewed to identify intrasional non enhancing areas that correspond to the necrotic areas. The necrotic areas can also be identified by looking for areas with decreasing signal intensity on increasing b value DW images. Considering the complex anatomy and irregular shape of tumors in the head and neck, tumor size estimation using single longest dimension was done away with. Instead the gross tumor volume was used for this purpose. The ROI s used for ADC calculations were also used for gross tumor volume calculations. The cross sectional area of the tumor on each axial slice was multiplied by the section thickness and these were added together to arrive at gross tumor volume. The mean ADC value of the whole tumor was used in this study, to avoid sampling errors inherent with taking the measurements on a single axial slice.

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

\[
\text{Fractional change in ADC} = \frac{\text{ADC}_{3w} - \text{ADC}_{pre}}{\text{ADC}_{pre}}
\]

where,
- \(\text{ADC}_{pre}\) represents the pretreatment ADC values,
- \(\text{ADC}_{3w}\) represents the ADC values at 3 weeks after the start of treatment.

\[
\text{Tumor regression rate} = \frac{\text{TV}_{pre} - \text{TV}_{3w}}{\text{TV}_{pre}}
\]

where,
- \(\text{TV}_{pre}\) represents the pretreatment tumor volume,
- \(\text{TV}_{3w}\) represents the tumor volume at 3 weeks.

Statistical calculations were performed by using statistical analysis software (Statistical Package for the Social Sciences, Version 15.0 IBM, Armonk, New York), and \(P\) values < 0.05 were considered statistically significant and \(P\) values < 0.01 were considered highly significant.

RESULTS:

**Table 2:** Prediction of loco regional control by using pre mean ADC primary

<table>
<thead>
<tr>
<th>Area under the curve</th>
<th>Test Result Variable(s): Pre Mean ADC Primary</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Area</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>0.801</td>
<td>0.007</td>
</tr>
</tbody>
</table>

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

**Sensitivity = 63.6% Specificity = 68.4%**

**Table 3:** Prediction of locoregional control using pretreatment primary tumor volume

<table>
<thead>
<tr>
<th>Area under the curve</th>
<th>Test Result Variable(s): Pre primary tumor volume</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Area</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>0.737</td>
<td>0.033</td>
</tr>
</tbody>
</table>

When Cut off value <16.29 cc is used for identification of control, based on pretreatment primary tumor volume.

**Sensitivity = 63.20% Specificity = 63.60%**

**Table 4:** Prediction of locoregional control by using fractional change in mean ADC primary

<table>
<thead>
<tr>
<th>Area under the curve</th>
<th>Test Result Variable(s): Fractional change in mean ADC Primary</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Area</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>0.916</td>
<td>0.0005</td>
</tr>
</tbody>
</table>

When Cut off value <0.143 (fractional change in mean ADC primary) is used for predictin failure,
Sensitivity = 81.8% Specificity = 78.9%
Positive predictive value = 51.9 and Negative predictive value = 48.7

During the follow-up period, complete LRC was achieved in 19 of 30 patients (63.3%). Four of 30 patients (13.3%) developed an isolated local recurrence. Two of 35 patients (5.7%) developed a regional recurrence without primary tumor recurrence. Five of 35 patients (14.2%) developed a simultaneous loco regional tumor recurrence. Patients with loco regional recurrence were treated with salvage surgery and/or neck dissection with or without adjuvant chemotherapy.

Since the tumors were inoperable in all but one patient with recurrence, only chemotherapy was performed. Four of 35 patients (11.4) died during the early follow-up period (within two months of completing treatment due to unrelated causes. (Three patients developed aspiration pneumonia; one had myocardial infarction) because of the extent of local recurrent tumor. These patients were excluded when performing the calculations as the extent of disease could not be assessed.

III. DISCUSSION

As a matter of fact, highly cellular tumors have diffusion restriction and hence low ADC values. Cancer treatments cause cell death, increase water diffusion and lead to elevation in ADC values. ADC values are measured pre& post treatment (i.e. 3wks after start of CRT) and the fractional change in ADC values will be calculated.

In the past, clinical studies evaluating 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. The nasopharyngeal carcinomas were excluded because of their better treatment response profiles and their more complex cellular make-up. A significant proportion of well differentiated adenocarcinomas are known to occur in the nasopharynx. These tumors because of their tendency to glandular formation may result in elevated ADC values and thus hamper statistical calculations.

Kim et al observed that pre-treatment ADC values could be used to predict response to treatment in cervical denopathy (3). In addition King et al, found that serial change in ADC correlated strongly with LRF.

Baseline 3 weeks into treatment

Fig 2: Graph showing treatment induced changes in cell population.

A rise in ADC values following successful therapy has been noted in several anatomic sites, namely breast cancers, hepatocellular carcinoma, liver metastasis, primary sarcomas of bone, and in malignant brain tumors (4). 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 not fully known, it has been postulated that treatment induced apoptosis and necrosis, will lead to disruption of the existing microarchitecture with resultant increase in fractional volume and increased diffusion in the extracellular space. Therefore fractional change in ADC of primary tumor early into treatment, is 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. By this time, a cumulative dose of 30 Gray would have been accumulated.

Foci of intratumoral liquefaction necrosis arising from treatment may influence ADC calculation. (4) This may contribute to spuriously elevated ADC values, even though viable tumor components may still be present. In this study the 89 freehand ROIs were drawn on the ADC map after assessing for tumor heterogeneity on T2w images. These tiny necrotic foci may be beyond the resolution of conventional morphologic imaging and may be inadvertently included within the freehand ROIs drawn on the ADC map. This was the reason behind taking the mean ADC of the whole tumor during calculations of ADC. However the heterogeneous nature of the lesion may be obscured when a single average value like mean ADC is used. This may be circumvented by applying a technique called functional diffusion mapthat is being currently used to quantify diffusion changes in brain tumors. But we have to bear in mind that applying the functional ADC map for tumors outside the brain will pose its own challenges. Physiologic motion induced by swallowing may interfere with acquiring slices and generating co-registered data sets, which are the basis of this technique.

In the present study, fractional change in ADC value of primary was significantly lower for LRF compared with control. Also among all the variables considered, fractional change in ADC of primary correlated strongly with control.

In large volume primary tumors, Ohnishi et al (5) have shown that pre-treatment primary gross tumor volume was useful for response prediction. They established a cut off value of 10 cc for primary gross tumor volume, with patients having primary tumor volume more than 10 cc along with high ADC values, showing higher chance of local recurrence. In the present study, when a cut-off for pre-treatment primary tumor volume of 16.29 cc. was used, sensitivity and specificity were 60% for prediction of control. Patients with pre–treatment primary tumor volume < 16.29 cc. showed less chance of recurrence. Since patients with locally advanced disease were included in the present study, the mean gross tumor volume was high and measured 23.77 cc. This could account for the increased cut off values.

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/mm² have been used in the past, the maximum b-value in this study was kept at...
This was done to reduce the influence of susceptibility artifacts and low signal to noise ratio on calculated ADC maps. Though it is known that the quality of ADC maps improves with increase in the number of b-values, only three b-values (b=0, b=100 & b=800 s /mm²) were used in this study. Increasing the number of b-values will result in increased imaging times.

In their study on metastatic neck nodes, Kim et al noted that the change in ADC values in the first week of treatment was a better predictor of response when compared with pre-treatment ADC. It is well known that primary tumors occur at air – tissue interfaces, making them prone to susceptibility artifacts. Motion artifacts from swallowing and breathing pose another problem. These issues will not be encountered when ADC calculations are performed on metastatic nodes. However in the present study, considering the bulky metastatic nodal disease, most of the involved nodes went in for macroscopic necrosis with treatment initiation, precluding meaningful ADC calculation (Fig. 5). Also in some cases, there was an increase in nodal volume early during treatment, which could be erroneously interpreted as disease progression.

Despite the ease of application of the technique in routine MRI examinations, certain practical issues merit consideration. Early treatment induced increases in mucosal secretions producing swallowing artifacts, image distortion near tracheostomy tube placement sites posing difficulties in the case of subglottic tumors and artifacts arising from air tumor interfaces in the case of external component of lip tumors can interfere with image interpretation.

The small sample size along with the short follow up period may be considered major limitations of this study.

IV. CONCLUSION

The role of DWI in head and neck cancer as an important predictive biomarker has been known for long. Given the high toxicity associated with chemo radiation as a whole and the financial burden incurred from some treatment protocols, it is desirable to identify and stop ineffective therapy as early as possible, and switch over to alternative treatment options whenever available. The fractional change in ADC of the primary tumor at 3 weeks was found to have significant association with LRC/LRF. A cut off value for fractional change in ADC of primary below 0.194 correlated with LRF. However the positive predictive value/negative predictive value was not high in the present study.

Another parameter that correlated strongly with LRC/LRF is pre-treatment mean ADC of the primary. A cutoff value for pre-treatment mean ADC of the primary below 1.21 x 10⁻³ mm²/s correlated with LRC. However the positive predictive value/negative predictive value was not high, with this parameter as well. This highlights the need for further studies, before fractional change in ADC values and pre-treatment mean ADC of the primary, can be used in decision making.
Pre-treatment primary ADC = $1.39 \times 10^{-3}$ mm$^2$/s (image on left)

Post treatment primary ADC = $1.51 \times 10^{-3}$ mm$^2$/s (image on right)

Fractional change in ADC of primary = 0.079

Patient developed locoregional failure at 5 months.

**REFERENCES**


