Value of Diffusion-Weighted and Perfusion-Weighted MR Imaging in Differentiation of Recurrent Tongue Carcinoma from Post-Treatment Changes

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Abstract

Background: Tongue carcinoma is characterized by high recurrence rate. Thus, post-treatment follow-up imaging is critically important. Advanced Magnetic Resonance Imaging (MRI) techniques can be employed for this purpose due to the limited accuracy of conventional MRI.

Aim of Study: Evaluation of the value of Diffusion Weighted (DW) and perfusion weighted MRI implementation in the post-treatment follow-up of tongue carcinoma.

Patients and Methods: This study was conducted on 23 patients on post-treatment follow-up of tongue carcinoma. They underwent DW-MRI and Dynamic Contrast Enhanced (DCE) perfusion T1-weighted MRI to differentiate between recurrent tumor and post-treatment changes. Apparent Diffusion Coefficient (ADC) was estimated, perfusion MR qualitative and semiquantitative assessment was performed. Resulting data were compared to histopathologic characterization (n=18) and further clinical and radiological follow-up (n=5) which were considered as the reference standards.

Results: The mean ADC value of recurrent tongue carcinoma (1.029±0.207 X 10⁻³ mm²/s) was significantly lower (p<0.001) than the mean ADC value of post-treatment changes (1.425±0.238 X 10⁻³ mm²/s). The ADC threshold used for differentiating recurrent tumor from post-treatment changes was 1.175 X 10⁻³ mm²/s with Area Under the Curve (AUC) of 0.938 and diagnostic accuracy of 82.6%. Among the DCE perfusion weighted MR parameters, the wash in rate and Area Under Gadolinium Curve (AUGC) displayed the highest diagnostic accuracy (73.9%) with thresholds of 18.65a.u/s and 126826.7m.M.s respectively. The combined use of both DW-MRI and perfusion weighted MRI showed the highest diagnostic accuracy.

Conclusion: The DW MRI is a non-invasive technique providing accurate post-treatment follow-up assessment of tongue carcinoma. The perfusion weighted MRI provides lower diagnostic accuracy than DWI. The combined use of both techniques provides superior differentiation of tumor recurrence from post-treatment changes.


Introduction

TONGUE carcinoma is the most common malignancy of the oral cavity, it represents about 30-40% of the oral cavity cancers [1,2]. The management of tongue carcinoma usually involves multidisciplinary treatment including surgery, radiation and chemotherapy [2-8]. Despite the constant advancement of surgery and radiation therapy, the treatment of tongue carcinoma is difficult due to the localization and the invasive nature of the available treatment methods, thus, post-treatment follow-up is crucial [3,6].

Many cross-sectional imaging modalities are used for post-treatment follow-up of the tongue

List of Abbreviations:

MRI : Magnetic Resonance Imaging.
DW-MRI : Diffusion Weighted Magnetic Resonance Imaging.
ADC : Apparent Diffusion Coefficient.
AUC : Area Under Curve.
AUGC : Area Under Gadolinium Curve.
a.u/s : Arbitrary unit/second.
m.M.s : Millimole. Second.
CT : Computed Tomography.
18-FFDG-PET : 18-F-Fluorodeoxyglucose Positron Emission Tomography.
TR/TE/NEX : Repetition time/echo time/number of excitation.
FOV : Field of View.
TIC : Time signal intensity curve.
TTP : Time-to-Peak.
ROC : Receiver Operator Characteristic.
PPV : Positive Predictive Value.
NPP : Negative Predictive Value.
DSC : Dynamic Susceptibility Contrast.
cancers, such as Computed Tomography (CT), Magnetic Resonance Imaging (MRI) and 18-F-Fluorodeoxyglucose Positron Emission Tomography (18-FFDG-PET) \[3,7\]. MRI is regarded the preferred imaging modality in diagnosis of oral area tumor detection and follow-up as well. However, surgery and radiation can cause significant inflammation, fibrosis and distortion of the anatomy preventing accurate differentiation between residual or recurrent tumor and post-treatment changes by conventional MRI sequences \[1,2,7-10\].

New functional imaging technologies nowadays are employed in oncologic post-treatment follow-up due to the limited accuracy of conventional MRI. Diffusion Weighted Imaging (DWI) is an MR technique that has been suggested as noninvasive imaging biomarker to predict tumor response. The obvious advantage of DW-MRI, which uses water molecules motion in intracellular and extra-cellular space to reflect biological changes in tumor microenvironment, is that it is useful for accurately distinguishing recurrent disease from radiation-induced soft-tissue changes. The DW-MRI derived parameter of Apparent Diffusion Coefficient (ADC) represents direction independent water displacement. In tissues with high cellularity, free water motion is restricted, and the measured ADC is low, whereas in tissues with low cellularity, the corresponding ADC is high. This inverse correlation between ADC and cellularity may serve as a method to differentiate between recurrent tumors and post-treatment changes. DW-MRI should detect the disease before the recurrence of clinical symptoms \[3,5,7,11-13\].

Another advanced MRI technique that can be useful in the same purpose is perfusion-weighted Dynamic Contrast-Enhanced (DCE) MRI using T1-weighted sequence. This technique has been reported to be able to characterize perfusion and vascularization of tissues. Therefore, it can play a key role as a beneficial biomarker for tumor angiogenesis. It has also been demonstrated that DCE MRI can be helpful in differentiation between malignant and benign lesions as well as prediction of response to therapy in different tumors. It involves serial MR image acquisition after injection of gadolinium-based contrast agent, thus, tissue perfusion and permeability can be assessed based on the signal enhancement kinetics \[6,13-19\].

This study aimed at assessment of the value of DW-MRI and perfusion-weighted DCE MRI as well as their combined use in the post-treatment follow-up of tongue carcinoma.

### Patients and Methods

#### Study design and patients:

The Institutional review board approved this longitudinal study and informed consents were obtained from participating patients. From July 2018 to January 2020, this study was conducted in Mansoura University Hospital, Radiology Department upon 23 consecutive patients (14 males, 9 females) with their mean age of 52.5 years, ranging from 38 to 63 years. All patients were referred from Clinical Oncology Department, they were on follow-up after ending the treatment of pathologically confirmed tongue carcinoma. All cases had been treated surgically with post-operative radiation therapy.

#### Inclusion criteria:

Patients with treated histopathologically-proven tongue squamous cell carcinoma, the term between the end of treatment and post-treatment imaging was 6 months or longer.

#### Exclusion criteria:

Patients with tongue carcinoma who were still having radiotherapy or had less than 6 months duration since the end of their treatment, contraindications to gadolinium contrast administration such as renal impairment or known allergic reaction to gadolinium, contraindication to MR examination like having artificial pacemakers and uncooperative patients.

The final diagnosis was obtained with histopathologic characterization (n=18) and further clinical and radiological follow-up (n=5) which were considered the reference standards in this study.

#### MR image acquisition:

All patients underwent MR studies using a 1.5-Tesla scanner (Ingenia, Philips, Philips Medical Systems, Netherland). Dedicated multichannel head and neck coil was applied. Non-contrast MRI examination included the following sequences: Axial T1 weighted Turbo Spin Echo (TSE) without and with fat suppression with the following parameters: Repetition time/echo time/number of excitation (TR/TE/NEX)=(600/20/2), axial T2 TSE without and coronal T2 weighted sequence with fat suppression with the following parameters: (TR/TE/NEX)=(4000/90/4); field of view (FOV)=18cm; section thickness, 2mm; section gap, 1mm; matrix, 256 X 256.

The DW-MRI was carried out using multi-slice single shot spin echo planar imaging sequence in
the axial plane with the following parameters: TR/TE of 1700/100msec; FOV of 25cm; section thickness of 5mm; inter-slice gap of 2mm and acquisition matrix of 256 X 128. Diffusion gradients were applied in the three orthogonal directions (x, y and z) with the same strength. DW-MR images were acquired with two diffusion weighted factors, factor b of 0 and 1000s/mm² in the axial plane. The acquisition time for the diffusion-weighted sequence was 1 minute and 45 seconds. Apparent Diffusion Co-efficient (ADC) maps were generated for all images, an ADC maps were obtained.

Perfusion weighted MRI was obtained with dynamic 3D (axial contrast-enhanced T1WI with fat suppression) fast spoiled gradient recalled sequence was performed using the following parameters: TR/TE=5.1/1.1msec; flip angle 30 degrees; FOV 18cm; section thickness 4mm; section gap 1mm; matrix 256 X 128, total acquisition time of 300 seconds during bolus injection of a single dose contrast agent (gadolinium-DTPA) at a concentration of 0.1mmol/kg at a rate of 2.5ml/s given intravenously, followed by 20ml saline flush using an automatic injector. Sequential images were obtained through the lesion in axial plane and at different time intervals (at 30, 60, 90, 120, 150, 180, 240 and 300s following injection).

After dynamic Contrast-Enhanced (CE) image acquisition, conventional CE T1-weighted fat suppressed MR sequence was acquired in the axial, sagittal, and coronal planes with the same parameters as non-contrast axial T1 weighted sequence.

**MR image analysis:**

The MR images were analyzed on a Philips extended work space release 2.6 workstation. Conventional MR images were analyzed for abnormal signal intensity lesions and contrast enhancement on contrast-enhanced T1 weighted images.

Qualitative assessment of DW-MRI study was performed, diffusion restriction was decided as high signal intensity lesions on high b-value (1000) diffusion weighted images with hypointense signal on corresponding ADC map. Quantitative analysis of ADC values of the lesions was performed on ADC map. Circular Region of Interest (ROI), measuring 10-15 mm in diameter, was placed in the lesion (avoiding cystic parts in mixed lesion by correlation with T2 and post contrast T1weighted images) and three ADC values were automatically measured in $X \times 10^{-3} \text{mm}^2/\text{sec}$, then their mean ADC value was calculated.

Dynamic contrast enhanced images were assessed qualitatively and semiquantitatively. Region of Interest (ROI) was placed within an area of the tumor measuring 10mm² (avoiding cystic parts, vessels, necrosis, calcifications, and hemorrhages). Qualitative assessment was concerned with visual assessment of time signal intensity curve (TIC), it was referred to as type I (persistent), type II (plateau) or type III (washout) curves. Semi-quantitative parameters: Wash-in rate, wash-out rate, Area Under Gadolinium Curve (AUGC) and Time-to-peak (TTP) were automatically calculated.

**Statistical analysis:**

Data were analysed using Statistical Package for Social Science version 22 (IBM SPSS Inc. released 2013, Chicago, Ill, USA). Qualitative data were described using number and percent. Quantitative data were declared using median (minimum and maximum) for non-parametric data and mean, standard deviation for parametric data. Significance of the obtained results was judged at $p \leq 0.05$. Fischer Exact test was used for comparison of qualitative data (diffusion restriction, type of DCE TIC) in comparison to the reference standard results. Parametric and non parametric data were compared using Student $t$-test & Mann-Whitney U-test respectively. Receiver Operator Characteristic (ROC) curve analysis was performed to detect validity of ADC & perfusion parameters in differentiating recurrent tongue carcinoma from post-treatment changes. Sensitivity and specificity were detected from the curve, Positive Predictive Value (PPV), Negative Predictive Value (NPV) and accuracy were calculated through cross tabulation.

**Results**

This study comprised 23 patients on follow-up 6-24 months after completion of treatment of tongue carcinoma, 14 males and 9 females, their mean age was 52.52±7.71 SD. The treated tumors had been pathologically diagnosed as squamous cell carcinoma and located in the oral tongue (n=16) and at the tongue base (n=7).

The final diagnosis was acquired with histopathologic characterization (n=18) and further clinical and radiological follow-up (n=5). The final diagnosis was tumor recurrence in 13 patients and post-treatment changes in 10 patients. The time of tumor recurrence was 6-12 months after completion of therapy (n=4), 12-18 months after completion of therapy (n=7), 18-24 months after completion of therapy (n=2).
Restricted diffusion was detected in 11 (84.6%) of recurrent tumor cases, non-restricted diffusion was predicted in 90.0% of post-treatment change cases. The mean ADC value for tumor recurrence was $1.029 \pm 0.207 \times 10^{-3}$ mm$^2$/s Fig. (1) and for post-treatment changes was $1.425 \pm 0.238 \times 10^{-3}$ mm$^2$/s Fig. (2) with statistically significant difference between them ($p<0.001$) (Table 1). The Receiver-Operator Characteristics (ROC) analysis declared that the threshold of ADCs used to differentiate between tumor recurrence and post-treatment changes was $1.175 \times 10^{-3}$ mm$^2$/s. With diagnostic accuracy of 82.6%, sensitivity of 84.6% and specificity of 80% (Table 2) Fig. (3).

Qualitative assessment of DCE MR study revealed washout (type III) curve in 69.2% of tumor recurrence cases Fig. (1), while plateau curve was depicted in 60% of cases of post-treatment changes Fig. (2). Regarding quantitative DCE MR parameters, no detected significant difference of between tumor recurrence and post-treatment changes (Table 1). The ROC analysis revealed that among the DCE MR parameters, the wash in and wash out rates showed the highest sensitivity to differentiate between tumor recurrence and post-treatment changes (69.2% for each), the thresholds of wash in rate and washout rates for differentiation between both entities were 18.65a.u/s and 2.25a.u/s respectively. Meanwhile, the AUGC displayed the highest specificity for differentiation between tumor recurrence and post-treatment changes (90%) with a threshold of 126826.7m.M.s for differentiation of both entities (Table 2) Fig. (4).

The ROC analysis of results of combined implementation of DWI and DCE MR for differentiation of tongue carcinoma post-treatment recurrence and post-treatment changes revealed the highest sensitivity, specificity and accuracy (Table 2), Fig. (5).

Table (1): ADC value & perfusion MR parameters in recurrent tongue carcinoma from post-treatment changes.

<table>
<thead>
<tr>
<th></th>
<th>Post radiation change N=10</th>
<th>Recurrent tumor N=13</th>
<th>Test of significance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DWI n (%):</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No restriction</td>
<td>9 (90.0%)</td>
<td>2 (15.4%)</td>
<td>FET</td>
</tr>
<tr>
<td>Restriction</td>
<td>1 (10.0%)</td>
<td>11 (84.6%)</td>
<td>$p&lt;0.001$ *</td>
</tr>
<tr>
<td><strong>ADC ($10^{-3}$ mm$^2$/s):</strong></td>
<td>Mean ± SD</td>
<td></td>
<td>$t=4.249, p&lt;0.001$ *</td>
</tr>
<tr>
<td>Wash in (a. u/s):</td>
<td>1.425±0.238</td>
<td>1.029±0.207</td>
<td></td>
</tr>
<tr>
<td>Wash out (a.u/s):</td>
<td>17.1 (14.0-20.6)</td>
<td>21.0 (12.2-78.9)</td>
<td>$Z=1.83, p=0.067$</td>
</tr>
<tr>
<td>AUGC (m.M.s):</td>
<td>94358.0 (33100-132000)</td>
<td>140590 (17800-203000)</td>
<td>$Z=1.426, p=0.154$</td>
</tr>
<tr>
<td>Time to peak (s):</td>
<td>99.0 (51.6-125.2)</td>
<td>118.0 (51.6-231.8)</td>
<td>$Z=2.14, p=0.094$</td>
</tr>
<tr>
<td>Types of curve:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type II (Plateau)</td>
<td>6 (60.0)</td>
<td>4 (30.8)</td>
<td>FET</td>
</tr>
<tr>
<td>Type III (Washout)</td>
<td>4 (40.0)</td>
<td>9 (69.2)</td>
<td>$p=0.222$</td>
</tr>
</tbody>
</table>


Table (2): Validity of ADC value, perfusion MR parameters and their combined implementation in differentiating recurrent tongue carcinoma from post-treatment changes.

<table>
<thead>
<tr>
<th></th>
<th>AUC (95% CI)</th>
<th>Cut off point</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>Accuracy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ADC ($10^{-3}$ mm$^2$/s):</strong></td>
<td>0.938 (0.842-1.10)</td>
<td>$\leq 1.175$</td>
<td>84.6</td>
<td>80.0</td>
<td>84.6</td>
<td>80.0</td>
<td>82.6</td>
</tr>
<tr>
<td>Wash in (a.u/s):</td>
<td>0.727 (0.505-0.949)</td>
<td>$\geq 18.65$</td>
<td>69.2</td>
<td>80.0</td>
<td>68.7</td>
<td>81.8</td>
<td>73.9</td>
</tr>
<tr>
<td>Wash out (a.u/s):</td>
<td>0.565 (0.322-0.809)</td>
<td>$\geq 22.25$</td>
<td>69.2</td>
<td>60.0</td>
<td>69.2</td>
<td>60.0</td>
<td>65.2</td>
</tr>
<tr>
<td>AUGC (m.M.s):</td>
<td>0.677 (0.438-0.915)</td>
<td>$\geq 126826.7$</td>
<td>61.5</td>
<td>90.0</td>
<td>88.9</td>
<td>64.3</td>
<td>73.9</td>
</tr>
<tr>
<td>Time to peak (s):</td>
<td>0.708 (0.491-0.925)</td>
<td>$\geq 111.5$</td>
<td>61.5</td>
<td>50.0</td>
<td>61.5</td>
<td>50.0</td>
<td>56.5</td>
</tr>
<tr>
<td>Combined ADC &amp; perfusion MRI parameters</td>
<td>1.0 (1.0-1.0)</td>
<td>0.99</td>
<td>100.0</td>
<td>100.0</td>
<td>100.0</td>
<td>100.0</td>
<td>100.0</td>
</tr>
</tbody>
</table>

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Fig. (1): MRI of a 44 years old male on post-treatment follow-up of tongue squamous cell carcinoma after 24 months termination of post-operative radiation therapy, with recurrent tumor (Pathologically proved): Axial T1 (A), axial T2 (B) showed abnormal signal intensity soft tissue mass at the surgical bed on the left side of tongue, with heterogeneous enhancement on contrast-enhanced axial T1 (C) and area of diffusion restriction DWI-MRI (D) and ADC map (E), with mild enhancement on DCE MR subtraction image (F) (arrow). DCE MR perfusion colored map (G), time intensity curve (TIC) (H) displayed type III (washout) curve.

- Time to peak = 231.8 s.
- Wash-in rate = 21.0 1/s.
- Wash-out rate = 9.2 1/s.
- Brevity of enhancement = 14.6 s.
- Area under curve = 187737.3
Fig. (2): MRI of a 59 year old female on post-treatment follow-up of tongue squamous cell carcinoma after 10 months termination of postoperative radiation therapy, with post-treatment changes (confirmed by further follow-up): Axial T1 (A), axial T2 (B) show abnormal signal intensity lesion at the surgical bed on the right side of tongue, enhancing on contrast-enhanced axial T1 (C), False diffusion restriction on DWI-MRI (D) and no diffusion restriction on ADC map (E), with mild enhancement on DCE MR subtraction image (F) (arrow). DCE MR perfusion colored map (G), time intensity curve (TIC) (H) shows type II (plateau) curve.
Discussion

The present study investigated the value of diffusion weighted MRI and perfusion weighted MRI using DCE T1-weighted MRI in post-treatment evaluation of tongue carcinoma. The quantitative diffusion weighted MRI reported high sensitivity, specificity and accuracy of ADC study in differentiation between post-treatment changes and tumor recurrence. Among the perfusion parameters, the wash in and wash out rates showed moderate sensitivity and the AUGC displayed the highest specificity to differentiate between tumor recurrence and post-treatment changes. However, combined use of both diffusion and perfusion MR techniques revealed excellent sensitivity, specificity and accuracy.

Due to the high recurrence rate of tongue carcinoma, post-treatment surveillance is critically important. Magnetic resonance imaging is the most preferable technique in this issue. However, post-treatment morphological findings from conventional MRI has limited accuracy because of complexity of the surgeries performed and the post-irradiation changes. Therefore, new functional imaging technologies are being employed [3,5,7,20].

Diffusion-weighted MRI and its related ADC have been reported to be useful tool to differentiate tumor recurrence from normal post-treatment changes, it has been considered one of the promising recently developed techniques for functional assessment of tumors as well as characterization of regional lymph nodes if present, detection of cancer recurrence and, more recently, assessment of treatment response in different organs or tissues. Nevertheless, its use is still limited in the clinical practice of head and neck oncology [5,11,13,21,22].

In the current study, DW-MRI study revealed that the ADC value of recurrent tongue carcinomas was significantly lower than that of post-treatment changes ($p<0.001$). The ADC cutoff value between the two groups was $1.175 \times 10^{-3}$ mm$^2$/s. With accuracy of 82.6%. These results matched with previous studies conducted on role of DW-MRI in post-treatment follow-up of squamous cell carcinoma in the head and neck region [21,23-25].

In a study concerned with patients laryngeal and hypopharyngeal malignancy treated with chemo/radiotherapy, the mean ADC value of residual/recurrent tumors were significantly lower than that of post-radiation changes ($p<0.0002$) and ROC analysis provided an ADC threshold measuring $1.3 \times 10^{-3}$ mm$^2$/s with sensitivity of 67%, specif-
Perfusion weighted MRI permits the detection of the contrast kinetics within the tumors. The perfusion weighted MRI methods include T1-weighted DCE MRI and T2*-weighted Dynamic Susceptibility Contrast (DSC) perfusion weighted MRI which uses echo-planar sequence. The T1-weighted DCE MRI has higher spatial resolution than the T2*-weighted DSC MRI which may be associated with susceptibility artifact at the air/tissue interface [19,28]. The DCE MRI has been reported to be useful for various applications in head and neck oncology, such as differentiating squamous cell carcinoma from lymphoma, detecting metastatic lymph nodes, assessing tumor cell proliferation, predicting early treatment response and treatment outcome [14,15,19,29,30].

In the present study, qualitative assessment of DCE MRI revealed type III (washout curve) in 69.2% of recurrent tumor cases, while type II (plateau curve) in 60% of post-treatment changes cases. This result was explained that the small amount of interstitium in between the malignant cells may result in decreased leakage from blood vessels. While, the post-treatment inflammatory and fibrotic changes result in a large capacity of the interstitium which may drive contrast medium leakage from the blood vessels [28,31].

In the semi-quantitative assessment of this study, the wash in and wash out rates of recurrent tumor were higher than those of post-treatment changes, among the measured perfusion MR parameters, the wash in and wash out rates showed the highest sensitivity. These results were attributed to the nature of malignant tissue which was reported by showing early enhancement and early washout out of gadolinium contrast [28]. In agreement with previous studies, the AUGC of recurrent malignancy was reported to be more than of the post-treatment changes, with the highest specificity among the measured DCE parameters. The AUGC reflects the accumulation and/or depletion of contrast media within the cancer regardless of curve shape, but it has no direct correlation with the contrast circulation pathway and it is not able to reflect any specific physiological processes such as perfusion or permeability [28,32]. The recurrent malignant tumors displayed longer TTP than those of post-treatment changes, agreeing with Furukawa et al., who stated that benign lesions had faster TTP and washout times, indicating rather intact microvascular circulation with limited permeability. Also, this is likely due to leakiness of blood vessels in malignant tumors, thus taking longer time to reach the maximum [28]. Nevertheless, it was noticed in the present study that TTP parameter revealed the least sensitivity and specificity among the calculated perfusion parameters. The addition of DW-MRI to DCE MRI increased the confidence of prediction of differentiation of recurrent tongue carcinoma from post-treatment changes.

Our study had many advantages, including the combined study of two advanced MR techniques and their role in follow-up of tongue carcinoma, also the choice of the long term follow-up of cases after the resolution of early post-treatment reactions. However, there were some drawbacks in this study, including the small number of patients, the heterogeneity of the DCE MRI studies in terms of used sequences and reference standards, making it difficult to have reliable standardized quantitative results.

**Conclusion:**

Diffusion weighted MRI was declared to be a reliable fast non-invasive technique to differentiate recurrent tongue carcinoma from post-treatment changes. Perfusion weighted MRI showed less accuracy for this purpose. The combined use of both techniques increased the confidence of post-treatment follow-up of tongue carcinoma.

**References**


5. MARTINS E., CHONJIAK R., KOWALSKI L., NICOLAU U., LIMA E. and BITENCOURT A.: Diffusion-


