ORIGINAL ARTICLE

Role of diffusion weighted MRI in the initial diagnosis and follow-up of pharyngeal squamous cell carcinoma

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KEYWORDS
Pharyngeal neoplasm; DWI; Squamous cell carcinoma

Abstract  Background and purpose: Pharyngeal squamous cell carcinoma is a unique disease, and early initial diagnosis and follow-up after treatment are areas in which DWI may be very helpful. The purpose of our study was to evaluate the role of diffusion weighted MRI in initial diagnosis and post treatment follow-up of pharyngeal carcinoma.

Material and methods: 25 patients with 58 lesions were included in this study, and patients were classified into two groups according to their clinical situation: pretreatment group coming for initial diagnosis or pretreatment staging and post treatment group coming for follow-up. All patients were submitted to MRI including DWI with measurement of ADC value and correlation with histopathological data.

Results: In pretreatment group which includes 10 patients with 30 lesions DWI shows sensitivity of 89% compared to 71% and 82% for conventional and contrast enhanced (CE) MRI respectively. In post treatment group DWI shows PPV of 95% as compared to 81% and 87% for conventional and CE MRI respectively.

Conclusion: Diffusion weighted imaging shows high sensitivity in terms of detection, staging and follow-up of pharyngeal carcinoma.

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who present with locally advanced disease at diagnosis, combined modality therapy is generally recommended (2).

Differentiation of malignant head and neck tumors from benign lesions and accurate definite diagnosis are essential for treatment planning as well as for prognosis of malignant tumors (3) (see Figs. 1–9).

Anatomical data provided by imaging techniques e.g. CT and conventional MRI are not always enough for assessment of the behavior of the head and neck lesions, and the use of intravenous contrast increases the diagnostic accuracy of these techniques (4).

The differentiation between post treatment changes and residual/recurrent tumors is a common diagnostic dilemma (2). DWI is an established imaging technique that was primarily used in the early detection of acute cerebrovascular stroke yet now it is gaining increasing importance in several oncologic applications (5).

DWI is based on the Brownian motion of water protons in the tissue, which is affected by the microstructure of tissue (6).

The advantages of DW-MRI include the ability to objectively measure indicators of normal biological processes and pathological changes helping in tumor grading and response to therapy but it also has some limitations such as image degradation due to motion artifacts (7); yet, many of these limitations have recently been overcome (8).

Many recent studies reported that apparent diffusion coefficient (ADC) measurement in diffusion weighted (DW) MRI was useful in the differentiation of benign and malignant lesions; low ADCs indicate limited diffusion of water molecules in the tissue. Theoretically, therefore, a tumor or area within a tumor with low ADC contains a greater number of cells than one with high ADC. So, malignant masses have lower ADCs than benign lesions (9), this means the presence of a clinically validated inverse correlation between the ADC value and tumor cellularity (3); however, other variables such as perfusion, tortuosity of the extra cellular space and integrity of cellular membranes affect diffusivity (10).

In this study, the hypothesis that diffusion weighted imaging and ADC evaluation can play a role in initial diagnosis, staging and post-treatment evaluation of pharyngeal carcinoma was assessed.

2. Material and methods

2.1. Study population

The institutional ethics committee approved this study and waived informed consent. All data were reviewed prospectively.

Fig. 1 16-year old male patient presented with right neck lump. (A) Coronal T2WI of the neck reveals multiple malignant looking cervical nodes. (B) Axial T2WI shows nasopharyngeal soft tissue mass centered on the right fossa of Rosenmullar. (C) Axial T1 postcontrast shows homogenous postcontrast enhancement (pathologically proven nasopharyngeal carcinoma). (D) ADC map demonstrates soft tissue mass with significant low signal Low ADC value keeping with packed cellularity (arrows).
Inclusion criteria were as follows: (a) pathologically proven pharyngeal mucosal SCC with or without treatment; (b) clinical suspicion as neck lump, dysphagia, recurrent otitis media, tongue fixation, and visible lesion in endoscopy; (c) previous radiological investigation with suspected pharyngeal mucosal space mass or malignant cervical LN for the post treatment surveillance we added; (d) the term between the end of treatment and post treatment imaging was longer than 6 weeks, to avoid very early post-treatment changes; (e) newly developed or increased enhancing portion on post-contrast T1-weighted images where recurrence was highly suspected or indeterminate; and (f) the lesion was large enough to measure on MR imaging (diameter ≥5 mm).

Exclusion criteria were as follows: (a) primary origin outside pharyngeal mucosal space; (b) pathologically proven neoplasm other than carcinoma; (c) pathologically proven non-neoplastic process such as inflammation; (d) negative imaging result; and (e) degradation of image quality (e.g., susceptibility artifacts that distort the area of concern partly or completely).

Twenty-three patients were enrolled in this study: 10 males (43%) and 13 females (57%). Patients’ age was ranging from 40 to 76 years with the mean age of 57.5 (±9.7) years. Five patients (21.7%) were coming for initial diagnosis. Eighteen patients (78.3%) were pathologically proven pharyngeal mucosal space carcinoma, 5 of them were coming for initial staging and 13 patients were coming for post-treatment follow-up. The anatomical distribution of pharyngeal SCC consisted of nasopharyngeal carcinoma (14 cases), hypopharyngeal SCC (5 cases) and oropharyngeal SCC (4 cases). For post-treatment group, various surgical procedures or re-irradiation (if recurrence occurred >6 months from end of treatment) was performed according to the disease extent and location.

2.2. Acquisition of MR images

A 1.5 MR unit (Achieva XR; Philips Medical System, The Eindhoven, the Netherlands) was used with a 200-mm Synergy Flex L Coil, a 140 × 170 mm Synergy Flex M Coil, or a Synergy Head/Neck Coil (Philips). The following sequences were acquired: T1-weighted sequences before and after intravenous administration of paramagnetic contrast material (repetition time msec/echo time msec, 593/15) and T2-weighted (4200/130) imaging. DWI images were obtained by using a multisection single-shot spin-echo echo planar imaging sequence, with short inversion time inversion-recovery fat suppression (5872/70, inversion time of 180 ms, four signals

Fig. 2 Post treatment follow-up (after 3 months): no changes of the conventional images or diffusion restriction and ADC value. Malignant cervical LNs are stable (not shown) keeping with poor response to treatment.
Fig. 3 47-year old male patient complaining of tongue fixation. (A) DWI: soft tissue mass with significant diffusion restriction (blue arrows). (B) ADC shows low ADC signal and value. Notice central T2 Shine through (red arrows) corresponding to central breaking down. (C) Axial T2WI shows tongue base Infiltrative soft tissue mass (oropharynx) invading the floor of mouth. (D) Axial T1 postcontrast shows the enhancing solid component and central non-enhancing necrosis. 3-month follow-up study (E to H). Shown lower ADC value keeping with more packed cellularity. Feature which is confirmed by conventional images that show increased extension, more solid component and postcontrast enhancement. Progressive disease and no response to treatment.
acquired, field of view of $25 \times 20\, \text{cm}^2$, section thickness of 4 mm, acquisition matrix of $121 \times 101\, \text{mm}^2$, intersection gap of 0 mm, and $b$ values of 0, 300, and 800 s/mm$^2$).

Fig. 4 57-year old female patient received XRT for nasopharyngeal carcinoma developed abnormal enhancing soft tissue mass in the left pterygopalatine fossa and retro-antral regions (dotted line) in Axial T2WI (A) and postcontrast axial T1WI (B). In DWI (C) only central focus with diffuse restriction and low ADC signal and value in ADC map (D) (blue arrows) keeping with recurrent tumor and surrounding desmoplastic reaction.

Fig. 5 Sensitivity of conventional MRI, CE MRI and DW MRI in pretreatment group with DWI MRI has the highest value (89%).

Fig. 6 Sensitivity, PPV and PABAK of conventional MRI, CE MRI and DW MRI in pretreatment group with DWI MRI have the highest values (89%, 93% and 67% respectively).

2.3. Analysis of conventional images

Two experienced radiologists in MRI of head and neck interpretation with 14 and 11 years experience reviewed the
conventional MR images of pharyngeal mucosal space in consensus. All images were evaluated at a 2000 × 2000 PACS monitor with adjustment of the optimal window setting in each case. MR studies were reviewed for the presence of any malignant pharyngeal mass lesion and malignant cervical LN. When a lesion was detected, the maximum diameter, shape, and signals intensities (T1-weighted, T2-weighted and enhancement) were determined.

Lymph nodes were assumed to be suspicious for metastatic involvement if they showed one of the following features: (a) oval in shape with a maximum transverse diameter greater than 10 mm, (b) round shaped and exceeded 8 mm in diameter, (c) any size and shape with internal central or eccentric necrotic areas, and (d) any size and shape with speculated or indistinct borders and heterogeneous signal intensity (SI) on T2 weighted images.

2.4. Analysis of DWI

The overall ADCs for each lesion were determined as follows: Gray-scale ADC map images (3 middle images from each tumor) were saved in DICOM format. Free hand ROIs along the margins of the lesions were manually placed onto the ADC maps by using the corresponding fat-suppressed T2-weighted MR images as references for placing the ROIs. Then, average ADC of the whole lesion was determined (overall ADC). We classified the lesions into 2 categories on the basis of ADC level: lesions with low ADC values <1.2 × 10⁻³ mm²/s and lesions with high ADC values ≥1.2 × 10⁻³ mm²/s, and this method of DWI analysis and the used ADC limit values are in concordance with the study done by Ichikawa et al. (17).

ADC value was determined for suspicious cervical lymph nodes, and analysis was performed in region of interests (ROIs) placed in each lymph node manually to include largest solid component excluding obviously cystic/necrotic components. The ADC was expressed as means ± standard deviation.

According to Lee et al., authors considered ADC value of 1.086 ± 0.222 × 10⁻³ ± mm²/s for benign lymph nodes and 0.705 ± 0.118 × 10⁻³ ± mm²/s for malignant lymph nodes (12).

2.5. Histologic analysis

Histologic findings of excised specimens obtained at endoscopic biopsy and/or at surgery were compared with ADC levels in the pharyngeal lesions and cervical LN. Direct comparison between histologic sections and the corresponding DWI maps of tumors was not achievable because in most cases, the specimens were obtained at biopsy and the planes of MR images and those of histologic sections in each tumor were not identical. The final estimation was made by consensus of 2 observers.

2.6. Statistical analysis

Data were analyzed using MedCalc© version 14 (MedCalc© Software bvba, Ostend, Belgium) and the DAG Stat spreadsheet.

Skewed numerical data were presented as median (interquartile range) and between-group comparisons were done using the Mann–Whitney test.

Inter-observer and inter-method agreement was assessed by calculation of the weighted kappa statistic (κ) and the prevalence-adjusted and bias-adjusted kappa (PABAK) (13).

3. Results

55 lesions were detected clinically and radiologically in 23 patients (including primary lesions and metastatic lymph nodes), 48 of them were proven to be malignant (either pharyngeal neoplasm or metastatic lymph nodes), 2 lesions were proven to be benign conditions (one is pleomorphic adenoma of the minor salivary glands and the second one is palatine tonsil lymphoid hyperplasia) and the remaining 5 lesions were proven to be post treatment changes.

3.1. The patients were divided into two groups

3.1.1. Pretreatment group

It includes 10 patients with 30 lesions; 28 of these lesions were diagnosed as malignant lesions.
Of these 28 malignant lesions 25 lesions show malignant criteria by DW MRI.

The results of conventional MRI, CE MRI and DWI MRI in pretreatment group are summarized in Table 1.

Comparison between the sensitivities of conventional MRI, CE MRI and DW MRI in pretreatment group showed that although DW MRI has the highest sensitivity as compared to conventional and CE MRI, the difference is statistically nonsignificant.

### Table 1 Diagnostic value of conventional MRI, CE MRI and DWI MRI for identification of malignant lesion in pretreatment group.

<table>
<thead>
<tr>
<th></th>
<th>Conventional MRI</th>
<th>CE MRI</th>
<th>DWI MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>0.71</td>
<td>0.82</td>
<td>0.89</td>
</tr>
<tr>
<td>Specificity</td>
<td>0.50</td>
<td>0.50</td>
<td>Undefined</td>
</tr>
<tr>
<td>PPV</td>
<td>0.95</td>
<td>0.96</td>
<td>0.93</td>
</tr>
<tr>
<td>NPV</td>
<td>0.11</td>
<td>0.17</td>
<td>0.00</td>
</tr>
<tr>
<td>LR +</td>
<td>1.43</td>
<td>1.64</td>
<td>0.89</td>
</tr>
<tr>
<td>LR –</td>
<td>0.57</td>
<td>0.36</td>
<td>Undefined</td>
</tr>
<tr>
<td>Cohen’s kappa (κ)</td>
<td>0.08</td>
<td>0.17</td>
<td>-0.09</td>
</tr>
<tr>
<td>PABAK</td>
<td>0.40</td>
<td>0.60</td>
<td>0.67</td>
</tr>
</tbody>
</table>

Of these 28 malignant lesions 25 lesions show malignant criteria by DW MRI.

The results of conventional MRI, CE MRI and DWI MRI in pretreatment group are summarized in Table 1.

Comparison between the sensitivities of conventional MRI, CE MRI and DW MRI in pretreatment group showed that although DW MRI has the highest sensitivity as compared to conventional and CE MRI, the difference is statistically nonsignificant.

#### 3.1.2. Post treatment group

It includes 13 patients with 25 lesions, 20 of these lesions were diagnosed as malignant lesions.

Using DWI the lesions were classified into 2 groups according to the ADC value: (a) post treatment granulation/scar (5 lesions) and (b) recurrent tumor (20 lesions).

Only one false positive lesion was detected by DW MRI resulting in PPV of 95% as compared to 80% and 86% for conventional and CE MRI respectively.

Also DW MRI showed the highest PABAK being 84% as compared to that of conventional and of CE MRI (60% of each).

The results of conventional MRI, CE MRI and DW MRI in post treatment group are summarized in Table 2.

### Table 2 Diagnostic value of conventional MRI, CE MRI, or DWI MRI for identification of malignant lesion in post-treatment group.

<table>
<thead>
<tr>
<th></th>
<th>Conventional MRI</th>
<th>CE MRI</th>
<th>DWI MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>1.00</td>
<td>0.90</td>
<td>0.95</td>
</tr>
<tr>
<td>Specificity</td>
<td>0.80</td>
<td>0.86</td>
<td>0.95</td>
</tr>
<tr>
<td>PPV</td>
<td>Undefined</td>
<td>0.50</td>
<td>0.80</td>
</tr>
<tr>
<td>NPV</td>
<td>1</td>
<td>1.50</td>
<td>4.75</td>
</tr>
<tr>
<td>LR +</td>
<td>Undefined</td>
<td>0.25</td>
<td>0.06</td>
</tr>
<tr>
<td>LR –</td>
<td>0</td>
<td>0.32</td>
<td>0.75</td>
</tr>
<tr>
<td>Cohen’s kappa (κ)</td>
<td>0.60</td>
<td>0.60</td>
<td>0.84</td>
</tr>
</tbody>
</table>

PPV: positive predictive value; NPV: negative predictive value; LR +: positive likelihood ratio; LR –: negative likelihood ratio; PABAK: prevalence and bias adjusted kappa.

### Table 3 Comparison of the sensitivities of conventional MRI, CE MRI, and DWI MRI in pre-treatment and post-treatment groups.

<table>
<thead>
<tr>
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<th>Conventional MRI</th>
<th>CE MRI</th>
<th>DWI MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity in pretreatment group</td>
<td>0.71</td>
<td>0.82</td>
<td>0.89</td>
</tr>
<tr>
<td>Sensitivity in post treatment group</td>
<td>1.00</td>
<td>0.90</td>
<td>0.95</td>
</tr>
<tr>
<td>P-value</td>
<td>0.024</td>
<td>0.720</td>
<td>0.834</td>
</tr>
</tbody>
</table>

z-Test.

The difference in sensitivity of each individual imaging modality between pre and post treatment groups is shown in Table 3.

These results showed that although DW, conventional and CE MRI have higher sensitivity in post treatment group than
that in pretreatment group, this difference is statistically nonsignificant.

The median ADC value for benign lesions in both pre and post treatment groups was $1.28 \times 10^{-3}$ (1.21 $\pm 10^{-3}$ to $1.3 \times 10^{-3}$) mm$^2$/s, while the median ADC value for the malignant lesions in both the groups was $0.9 \times 10^{-3}$ (0.81 $\pm 10^{-3}$ to $0.96 \times 10^{-3}$) mm$^2$/s and the median ADC value for lymph nodes was $0.74 \times 10^{-3}$ (0.69 $\pm 10^{-3}$ $\pm 0.81 \times 10^{-3}$) mm$^2$/s.

Receiver-operating characteristic (ROC) curve analysis for discrimination between benign and malignant lesions in both pre and post treatment groups using the ADC value revealed that a cutoff value equal to $0.978 \times 10^{-3}$ mm$^2$/s gives sensitivity of 85.7% while this type of analysis was not applicable for lymph nodes as all of them in our study were malignant.

4. Discussion

Pharyngeal squamous cell carcinoma (SCC) is one of the most frequent tumors in the head and neck region for which chemoradiotherapy (CRT) and surgery are curative treatment options, and CT and MRI are the primary diagnostic modalities for locoregional staging of pharyngeal SCC. However, their reliance on morphological and size-related criteria bears some inherent disadvantages (14).

Although FDG PET/CT can be useful in diagnosis, staging and follow-up of pharyngeal SCC, the low spatial resolution of this technique may lead to false negative results in cases of small lesions or small lymph nodes (less than 1 cm).

Tanvetyanon et al. (15), in a retrospective study, tried to define which patients with recurrent tumors might benefit from re-irradiation and who most likely will not. They studied potential prognostic factors for survival after re-irradiation. In the multivariate analysis, tumor bulk at re-irradiation was one of independent prognostic factors. These results indicated the need for early diagnosis of recurrence.

In cases of suspected recurrent tumors, most investigators perform endoscopy with biopsy under general anesthesia. Recurrent carcinomas are often present with multiple tumor foci dispersed in different regions. Furthermore, recurrent tumors may develop beneath an intact mucosa and therefore be missed on endoscopy leading to false negative results. The differentiation between radionecrosis and tumor recurrence is difficult by computed tomography scan and magnetic resonance imaging in many cases after radiotherapy (11-12).

Thus an ideal diagnostic imaging technique able to assess the cancer burden avoiding radiation exposure and to fulfill some essential prerequisites such as accuracy, availability, reproducibility, cost effectiveness, and efficiency is needed and DW-MRI seems to fulfill these requirements (14).

The use of DWI to characterize head and neck lesions with higher sensitivity and specificity than anatomical imaging modalities has been investigated in only a limited number of studies (16).

The hypothesis of this study was that adding DWI to the routine MRI protocol used in patients with clinically suspected, pathologically proven or treated pharyngeal SCC will result in increase in its diagnostic performance, and to prove this hypothesis we compared the results of conventional, CE and DW MRI in the same patients (25 patients) after dividing them into two groups (pre and post treatment groups).

We classified the lesions according to their overall ADC values based on cutoff values previously used by Ichikawa et al. (17).

In both groups (pre and post treatment), DW MRI showed sensitivity and PPV of 89% and 93% (for pretreatment group) and 95% and 95% (for post treatment group).

When we use the cutoff value obtained by ROC analysis the sensitivity falls to about 85.7%, which is likely due to smaller number of cases involved in our study compared to the study of Ichikawa et al. (17).

These results indicate that malignant lesions have higher ADC value than benign lesions which is more or less in agreement with the studies done by Hwang et al. and Zheng et al. (18,19).

Regarding the analysis of the ADC value of suspicious lymph nodes we use cutoff values based on the study done by Lee et al. (20), and our results were in agreement with their results although 3 T MR machine was used in their study in comparison with 1.5 T MR machine used in our study; Sumi et al. (21), showed different results, yet this can be explained by the necrotic metastatic lymph nodes used in their study that we avoided by placing the ROI into the solid part of the lymph node.

In the pretreatment group, the sensitivities of the conventional, CE and DW MRI were 71%, 82% and 89% respectively showing that there is a noticeable positive trend, which was also noticed in the post treat group in which conventional, CE and DW MRI showed specificity of 0%, 40% and 80% respectively, and this positive trend did not show a statistically significant $P$ value; yet, this could be explained by small number of cases enrolled in this study, and for our knowledge no studies compared the results of conventional, CE and DW MRI to correlate our results with their results.

To compare the role of DW MRI in the pre and post treatment groups, the comparison of the sensitivity of DW MRI in the two groups showed higher sensitivity in post treatment group (95% as compared to 89% respectively) indicating that DW MRI tends to be more useful in follow-up of post treatment cases in spite of $P$ value of 0.821 (>0.005) indicating non-significant difference which can be explained again by the small number of cases.

4.1. Limitations

Anatomic distortion was due to magnetic-susceptibility artifact, yet they did not hinder adequate evaluation of DWI image.

We found that ADC value assessment requires relatively large target areas to obtain reliable ADC values with high signal-to-noise ratios (SNR). ADC value measurements on smaller lesions in our study would be hampered by low signal-to-noise ratios.

The sample size available in this analysis is somewhat small; thus, we use PABAK which is prevalence and bias adjusted parameters.

5. Conclusion

The study showed that DW MRI has a noticeable positive trend in improving the diagnostic accuracy of MRI in initial diagnosis and post treatment follow-up of pharyngeal...
carcinoma, yet more studies with larger number of cases are needed to prove this.

Conflict of interest

We have no conflict of interest.

References